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(54) Title: FLUORINATED ESTROGEN RECEPTOR MODULATORS AND USES THEREOF

(57) Abstract: Described herein are compounds that are estrogen receptor modulators. Also described are pharmaceutical compositions and medicaments that include the compounds described herein, as well as methods of using such estrogen receptor modulators, alone and in combination with other compounds, for treating diseases or conditions that are mediated or dependent upon estrogen receptors.

FLUORINATED ESTROGEN RECEPTOR MODULATORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/570,756 entitled "ESTROGEN RECEPTOR MODULATORS AND USES THEREOF" filed on December 14, 2011, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, including pharmaceutically acceptable salts, solvates, metabolites, prodrugs thereof, methods of making such compounds, pharmaceutical compositions comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases or conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated.

BACKGROUND OF THE INVENTION

[0003] The estrogen receptor ("ER") is a ligand-activated transcriptional regulatory protein that mediates induction of a variety of biological effects through its interaction with endogenous estrogens. Endogenous estrogens include 17β-estradiol and estrones. ER has been found to have two isoforms, ER-α and ER-β.

[0004] Estrogens and estrogen receptors are implicated in a number of diseases or conditions, such as breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, uterine cancer, as well as others diseases or conditions.

SUMMARY OF THE INVENTION

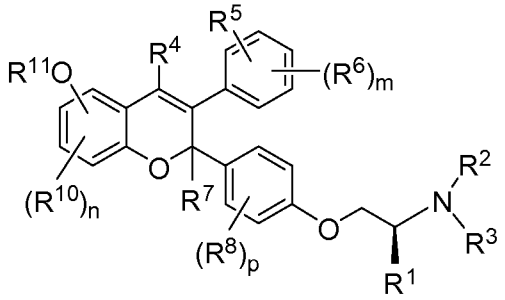
[0005] In one aspect, presented herein are compounds of Formula (I), (II), (III), (IV), (V), and (VI) that diminish the effects of estrogens with estrogen receptors and/or lower the the concentrations of estrogen receptors, and therefore, are useful as agents for the treatment or prevention of diseases or conditions in which the actions of estrogens and/or estrogen receptors are involved in the etiology or pathology of the disease or condition or contribute to at least one symptom of the disease or condition and wherein such actions of estrogens and/or estrogen receptors are undesirable. In some embodiments, compounds disclosed herein are estrogen receptor degrader compounds.

[0006] In one aspect, a compound of Formula (I), (II), (III), (IV), (V), or (VI) is useful for the treatment of ER-related diseases or conditions including, but not limited to, ER-α dysfunction associated with cancer (bone cancer, breast cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer), central nervous system (CNS) defects (alcoholism, migraine), cardiovascular system defects (aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension), hematological system defects (deep vein thrombosis), immune and inflammation diseases (Graves' Disease, arthritis, mulitple

sclerosis, cirrhosis), susceptibility to infection (hepatitis B, chronic liver disease), metabolic defects (bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis), neurological defects (Alzheimer's disease, Parkinson's disease, migraine, vertigo), psychiatric defects (anorexia nervosa, attention deficity hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis), uterine diseases (e.g. leiomyoma, uterine leiomyoma, endometrial hyperplasia, endometriosis), and reproductive defects (age of menarche, endometriosis, infertility).

[0007] In one aspect, described herein are compounds of Formula (I), (II), (III), (IV), (V), and (VI), pharmaceutically acceptable salts, solvates, metabolites and prodrugs thereof. Compounds described herein are estrogen receptor modulators. In some embodiments, the compound of Formula (I), (II), (III), (IV), (V), or (VI) is an estrogen receptor antagonist. In some embodiments, the compound of Formula (I), (II), (III), (IV), (V), or (VI) is an estrogen receptor degrader. In some embodiments, the compound of Formula (I), (II), (III), (IV), (V), or (VI) is an estrogen receptor antagonist as well as an estrogen receptor degrader. In some embodiments, the compound of Formula (I), (II), (III), (IV), (V), or (VI) displays miminal or no estrogen receptor agonist activity. In some embodiments, in the context of treating cancers, the compound of Formula (I), (II), (III), (IV), (V), or (VI) may offer improved therapeutic activity characterized by complete or longer-lasting tumor regression, a lower incidence or rate of development of resistance to treatment, and/or a reduction in tumor invasiveness.

[0008] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

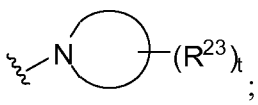
wherein,

R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form



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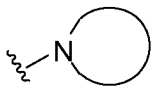


is a monocyclic C_2-C_{10} heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

t is 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl or C_3-C_6cycloalkyl;

R^5 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -S(=O)$_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -S(=O)$_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

R^7 is H or C_1-C_4alkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

each R^{10} is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -S(=O)$_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{11} is independently selected from H, -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

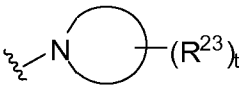
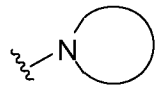
m is 0, 1, 2, 3 or 4;

n is 0, 1, or 2;

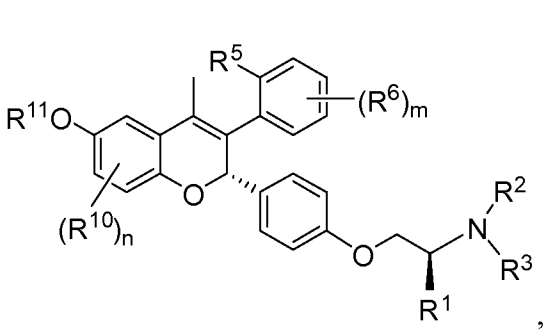
p is 0, 1, or 2;

provided that the compound is not 2-(4-((S)-2-((R)-3-fluoropyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol.

[0009] For any and all of the embodiments described herein, substituents are selected from among a subset of the listed alternatives. For example in some embodiments, R^7 is H or $-CH_3$. In other embodiments, R^7 is H.

[0010] In some embodiments, R^1 is H or C_1-C_6alkyl; R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl; R^3 is C_1-C_6fluoroalkyl; or R^2 and R^3 are taken together with the N atom to which they are attached to form  ;  is a 4-, 5-, 6- or 7-membered monocyclic C_2-C_6heterocycloalkyl; each R^{23} is independently F or C_1-C_6fluoroalkyl; t is 1 or 2; R^4 is $-CH_3$; R^7 is H; p is 0 or 1.

[0011] In some embodiments, the compound has one of the following structures: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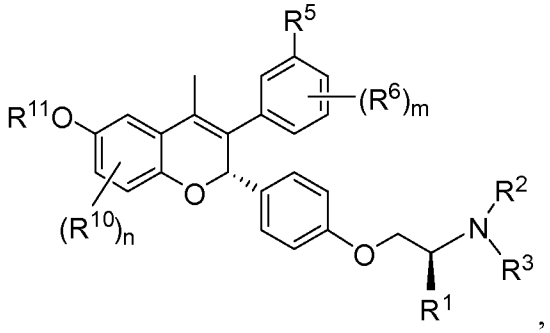
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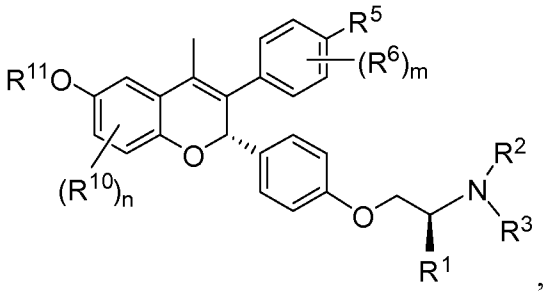
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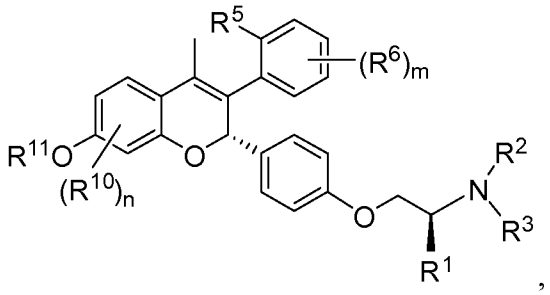
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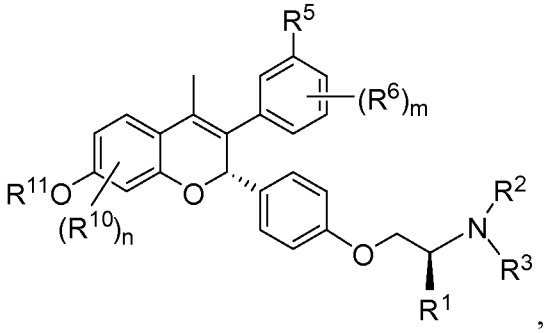
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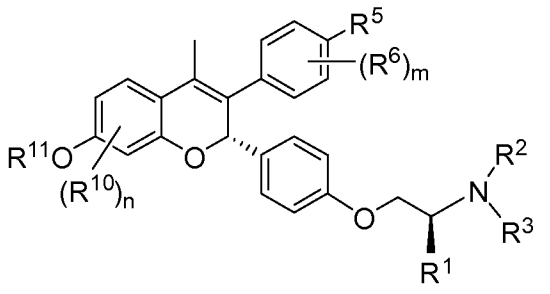
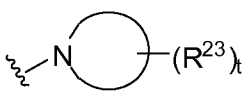
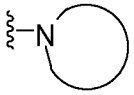
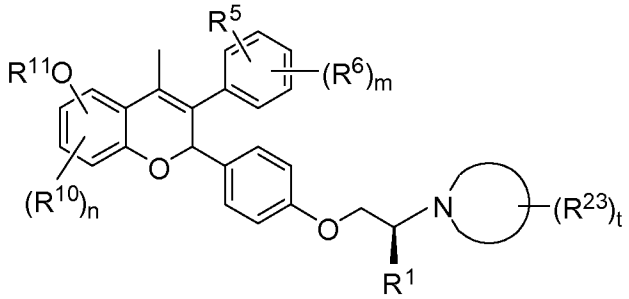


or is a pharmaceutically acceptable salt, or solvate thereof.

[0012] In some embodiments, R^5 is -OH; each R^{10} is independently selected from H, halogen, -CN, -OH, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; R^{11} is H.

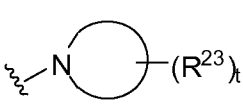
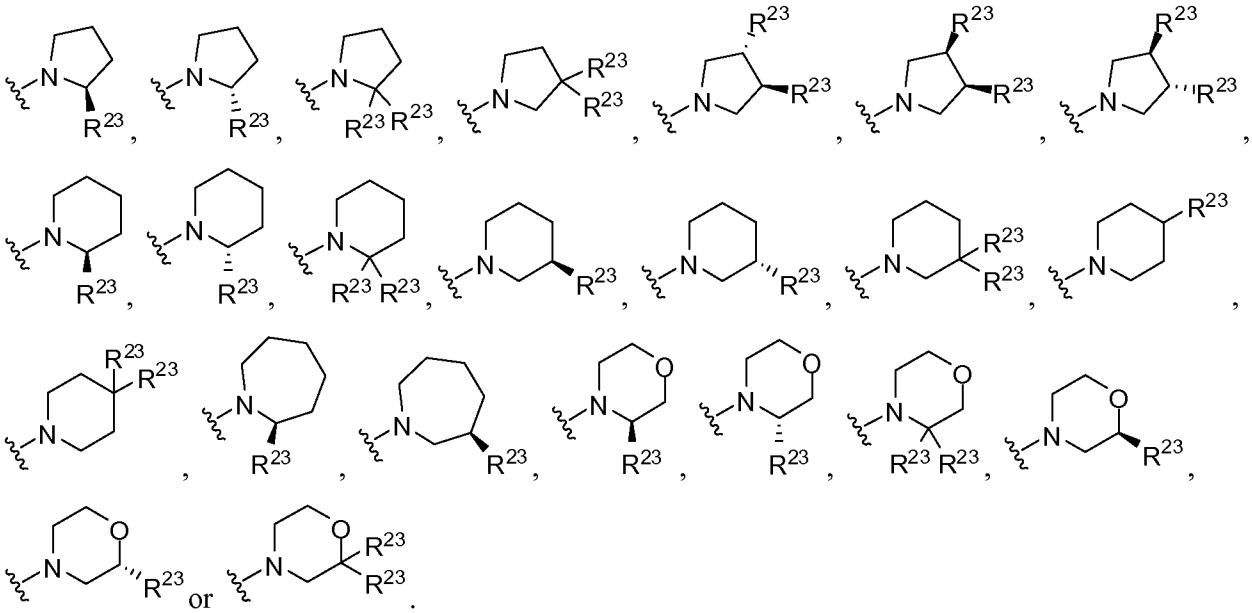
[0013] In some embodiments, R^1 is H, or $-CH_3$; R^2 and R^3 are taken together with the N atom to which they are attached to form  ;  is azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, morpholinyl, or piperazinyl; each R^{23} is independently F, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$.

[0014] In some embodiments, the compound of Formula (I) has the structure of Formula (II):

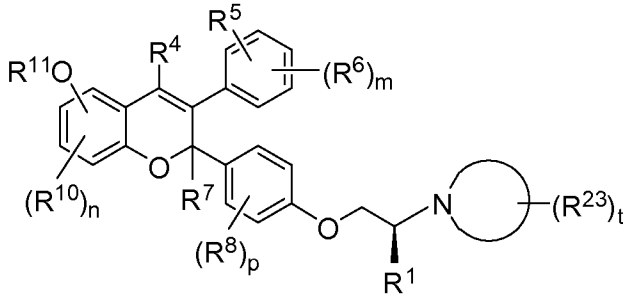


Formula (II)

or is a pharmaceutically acceptable salt, or solvate thereof.

[0015] In some embodiments,  is  .

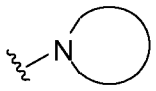
[0016] In another aspect, described herein is a compound of Formula (III), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (III)

wherein,

R^1 is C_1-C_6fluoroalkyl;

 is a monocyclic C_2-C_{10}heterocycloalkyl;

each R^{23} is independently F, C_1-C_6alkyl or C_1-C_6fluoroalkyl;

t is 0, 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl or C_3-C_6cycloalkyl;

R^5 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

each R^{10} is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

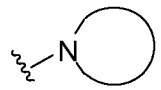
each R^{11} is independently selected from H, -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

m is 0, 1, 2, 3 or 4;

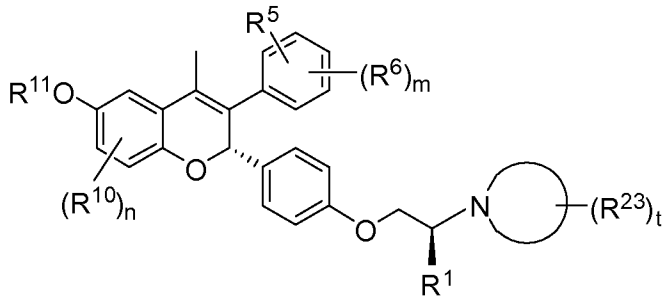
n is 0, 1, or 2;

p is 0, 1, or 2.

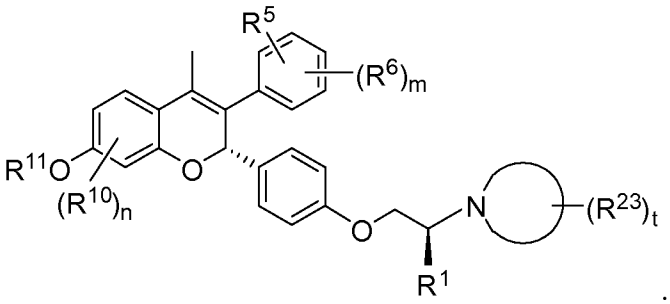
[0017] In some embodiments, R^1 is -CH_2F, -CHF_2, or -CF_3;  is an azetidinyl, pyrrolidinyl, piperidinyl, or azepanyl; each R^{23} is independently F, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -$CHFCH_3$,

$-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$; t is 0, 1 or 2; R^4 is $-CH_3$; R^7 is H; p is 0 or 1.

[0018] In some embodiments, the compound has one of the following structures:

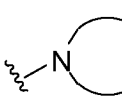
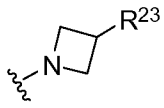
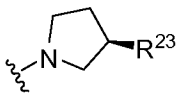
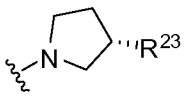
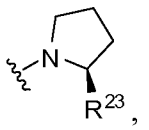
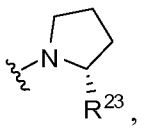
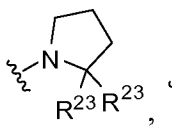
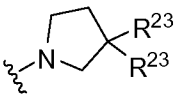
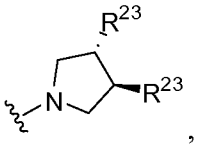
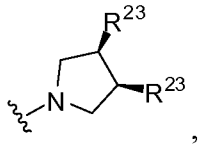
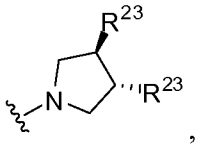
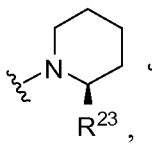
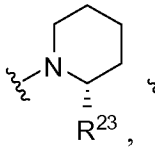
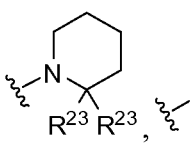
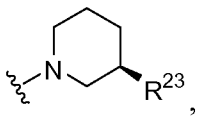
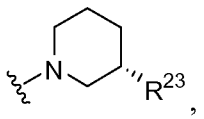
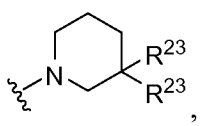
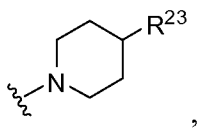
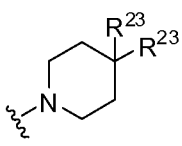
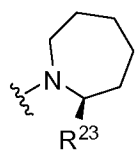
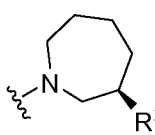


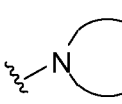
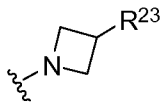
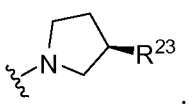
or

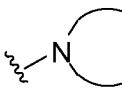
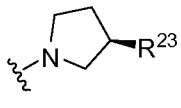


.

[0019] In some embodiments, R^5 is -OH; each R^{10} is independently selected from H, halogen, -CN, -OH, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; R^{11} is H.

[0020] In some embodiments,  is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

[0021] In some embodiments,  is  or  .

[0022] In some embodiments,  is  .

[0023] In some embodiments, each R^{23} is independently F, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$. In some embodiments, each R^{23} is independently F, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^{23} is independently F, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^{23} is independently $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^{23} is independently $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^{23} is independently $-CH_3$.

[0024] In some embodiments, R^2 and R^3 are taken together with the N atom to which they are attached to form substituted or unsubstituted pyrrolidinyl.

[0025] In some embodiments, R^1 is $-CH_3$. In some embodiments, R^1 is $-CH_3$; R^4 is $-CH_3$.

[0026] Compounds disclosed herein are estrogen receptor modulators. In some embodiments, compounds disclosed herein have high specificity for the estrogen receptor and have desirable, tissue-selective pharmacological activities. Desirable, tissue-selective pharmacological activities include, but are not limited to, ER antagonist activity in breast cells and no ER agonist activity in uterine cells. In some embodiments, compounds disclosed herein are estrogen receptor degraders that display full estrogen receptor antagonist activity with negligible or minimal estrogen receptor agonist activity.

[0027] In some embodiments, compounds disclosed herein are estrogen receptor degraders. In some embodiments, compounds disclosed herein are estrogen receptor antagonists. In some embodiments, compounds disclosed herein have minimal or negligible estrogen receptor agonist activity.

[0028] In some embodiments, presented herein are compounds selected from active metabolites, tautomers, pharmaceutically acceptable solvates, pharmaceutically acceptable salts or prodrugs of a compound of Formula (I), (II), (III), (IV), (V), or (VI).

[0029] Also described are pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition also contains at least one pharmaceutically acceptable inactive ingredient. In some embodiments, the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration. In some embodiments, the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a suspension, a solution, an emulsion, an ointment, or a lotion.

[0030] In some embodiments, the pharmaceutical composition further comprises one or more additional therapeutically active agents selected from: corticosteroids, anti-emetic agents, analgesics, anti-cancer agents, anti-inflammatories, kinase inhibitors, antibodies, HSP90 inhibitors, histone deacetylase (HDAC) inhibitors, poly ADP-ribose polymerase (PARP) inhibitors, and aromatase inhibitors.

[0031] In some embodiments, provided herein is a method comprising administering a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, to a human with

a diseases or condition that is estrogen sensitive, estrogen receptor meditated or estrogen receptor dependent. In some embodiments, the human is already being administered one or more additional therapeutically active agents other than a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof. In some embodiments, the method further comprises administering one or more additional therapeutically active agents other than a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof.

[0032] In some embodiments, the one or more additional therapeutically active agents other than a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are selected from: corticosteroids, anti-emetic agents, analgesics, anti-cancer agents, anti-inflammatories, kinase inhibitors, antibodies, HSP90 inhibitors, histone deacetylase (HDAC) inhibitors, and aromatase inhibitors.

[0033] Pharmaceutical formulations described herein are administered to a mammal in a variety of ways, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), buccal, topical or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[0034] In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are administered orally.

[0035] In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are administered systemically.

[0036] In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), or (VI), are administered intravenously.

[0037] In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are administered subcutaneously.

[0038] In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are administered topically. In such embodiments, the compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, shampoos, scrubs, rubs, smears, medicated sticks, medicated bandages, balms, creams or ointments. In some embodiments, the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are administered topically to the skin of mammal.

[0039] In another aspect is the use of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease,

disorder or conditions in which the activity of estrogen receptors contributes to the pathology and/or symptoms of the disease or condition. In one aspect, the disease or condition is any of the diseases or conditions specified herein.

[0040] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) adminstered non-systemically or locally to the mammal.

[0041] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[0042] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[0043] Also provided is a method of reducing ER activation in a mammal comprising administering to the mammal at least one compound having the structure of F Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof. In some embodiments, the method comprises reducing ER activation in breast cells, lung cells, ovarian cells, colon cells, prostate cells, endometrial cellls, or uterine cells in the mammal. In some embodiments, the method comprises reducing ER activation in breast cells, ovarian cells, colon cells, prostate cells, endometrial cellls, or uterine cells in the mammal. In some embodiments, the method of reducing ER activation in the mammal comprises reducing the binding of estrogens to estrogen receptors in the mammal. In some embodiments, the method of reducing ER activation in the mammal comprises reducing ER concentrations in the mammal.

[0044] In one aspect is the use of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of diseases or conditions of the uterus in a mammal. In some embodiments, the disease or condition of the uterus is leiomyoma, uterine leiomyoma, endometrial hyperplasia, or endometriosis. In some embodiments, the disease or condition

of the uterus is a cancerous disease or condition of the uterus. In some other embodiments, the disease or condition of the uterus is a non-cancerous disease or condition of the uterus.

[0045] In one aspect is the use of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of diseases or conditions that are estrogen sentitive, estrogen receptor dependent or estrogen receptor mediated. In some embodiments, the disease or condition is breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, or uterine cancer. In some embodiments, the disease or condition is described herein.

[0046] In some cases disclosed herein is the use of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in the treatment or prevention of diseases or conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated. In some embodiments, the disease or condition is described herein.

[0047] In any of the embodiments disclosed herein, the mammal is a human.

[0048] In some embodiments, compounds provided herein are used to diminish, reduce, or eliminate the activity of estrogen receptors.

[0049] Articles of manufacture, which include: packaging material; a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, or composition thereof, within the packaging material; and a label that indicates that the compound or pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, or composition thereof, or composition thereof, is used for reducing, diminishing or eliminating the effects of estrogen receptors, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from a reduction or elimination of estrogen receptor activity, are provided.

[0050] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description

DETAILED DESCRIPTION OF THE INVENTION

[0051] Estrogen receptor alpha (ER-α; NR3A1) and estrogen receptor beta (ER-β; NR3A2) are steroid hormone receptors, which are members of the large nuclear receptor superfamily. Nuclear receptors share a common modular structure, which minimally includes a DNA binding domain (DBD) and a ligand binding domain (LBD). Steroid hormone receptors are soluble, intracellular proteins that act as ligand-regulated transcription factors. Vertebrates contain five closely related steroid hormone receptors (estrogen receptor, androgen receptor, progesterone receptor, glucocorticoid receptor, mineralcorticoid

receptor), which regulate a wide spectrum of reproductive, metabolic and developmental activities. The activities of ER are controlled by the binding of endogenous estrogens, including 17β-estradiol and estrones.

[0052] The ER-α gene is located on 6q25.1 and encodes a 595 AA protein. The ER-β gene resides on chromosome 14q23.3 and produces a 530 AA protein. However, due to alternative splicing and translation start sites, each of these genes can give rise to multiple isoforms. In addition to the DNA binding domain (called C domain) and ligand binding domain (E domain) these receptors contain an N-terminal (A/B) domain, a hinge (D) domain that links the C and E domains, and a C-terminal extension (F domain) (Gronemeyer and Laudet; Protein Profile 2: 1173-1308, 1995). While the C and E domains of ER-α and ER-β are quite conserved (95% and 55% amino acid identity, respectively), conservation of the A/B, D and F domains is poor (below 30% amino acid identity). Both receptors are involved in the regulation and development of the female reproductive tract but also play various roles in the central nervous system, cardiovascular systems and bone metabolism.

[0053] The ligand binding pocket of steroid hormone receptors is deeply buried within the ligand binding domain. Upon binding, the ligand becomes part of the hydrophobic core of this domain. Consequently most steroid hormone receptors are instable in the absence of hormone and require assistance from chaperones, such as Hsp90, in order to maintain hormone-binding competency. The interaction with Hsp90 also controls nuclear translocation of these receptors. Ligand-binding stabilizes the receptor and initiates sequential conformational changes that release the chaperones, alter the interactions between the various receptor domains and remodel protein interaction surfaces that allow these receptors to translocate into the nucleus, bind DNA and engage in interactions with chromatin remodeling complexes and the transcriptional machinery. Although ER can interact with Hsp90, this interaction is not required for hormone binding and, dependent on the cellular context, apo-ER can be both cytoplasmic and nuclear. Biophysical studies indicated that DNA binding rather than ligand binding contributes to the stability of the receptor (Greenfield *et al.*, Biochemistry 40: 6646-6652, 2001).

[0054] ER can interact with DNA either directly by binding to a specific DNA sequence motif called estrogen response element (ERE) (classical pathway), or indirectly via protein-protein interactions (nonclassical pathway) (Welboren *et al.*, Endocrine-Related Cancer 16: 1073-1089, 2009). In the nonclassical pathway, ER has been shown to tether to other transcription factors including SP-1, AP-1 and NF-κB. These interactions appear to play critical roles in the ability of ER to regulate cell proliferation and differentiation.

[0055] Both types of ER DNA interactions can result in gene activation or repression dependent on the transcriptional coregulators that are recruited by the respective ER-ERE complex (Klinge, Steroid 65: 227-251, 2000). The recruitment of coregulators is primarily mediated by two protein interaction surfaces, the AF2 and AF1. AF2 is located in the ER E-domain and its conformation is directly

regulated by the ligand (Brzozowski *et al.*, Nature 389: 753-758, 1997). Full agonists appear to promote the recruitment of co-activators, whereas weak agonists and antagonists facilitate the binding of co-repressors. The regulation of protein with the AF1 is less well understood but can be controlled by serine phosphorylation (Ward and Weigel, Biofactors 35: 528-536, 2009). One of the involved phosphorylation sites (S118) appears to control the transcriptional activity of ER in the presence of antagonists such as tamoxifen, which plays an important role in the treatment of breast cancer. While full agonists appear to arrest ER in certain conformation, weak agonists tend to maintain ER in equilibrium between different conformations, allowing cell-dependent differences in co-regulator repertoires to modulate the activity of ER in a cell-dependent manner (Tamrazi *et al.*, Mol. Endocrinol. 17: 2593-2602, 2003). Interactions of ER with DNA are dynamic and include, but are not limited to, the degradation of ER by the proteasome (Reid *et al.*, Mol Cell 11: 695-707, 2003). The degradation of ER with ligands provides an attractive treatment strategy for disease or conditions that estrogen-senstitive and/or resistant to available anti-hormonal treatments.

[0056] ER signaling is crucial for the development and maintenance of female reproductive organs including breasts, ovulation and thickening of the endometrium. ER signaling also has a role in bone mass, lipid metabolism, cancers, etc. About 70% of breast cancers express ER-α (ER-α positive) and are dependent on estrogens for growth and survival. Other cancers also are thought to be dependent on ER-α signaling for growth and survival, such as for example ovarian and endometrial cancers. The ER-α antagonist tamoxifen has been used to treat early and advanced ER-α positive breast cancer in both pre- and post-menopausal women. Fulvestrant (Faslodex™) a steroid-based ER antagonist is used to treat breast cancer in women which has have progressed despite therapy with tamoxifen. Steroidal and non-steroidal aromatase inhibitors are also used to treat cancers in humans. In some embodiments, the steroidal and non-steroidal aromatase inhibitors block the production of estrogen from androstenedione and testosterone in post-menopausal women, thereby blocking ER dependent growth in the cancers. In addition to these anti-hormonal agents, progressive ER positive breast cancer is treated in some cases with a variety of other chemotherapeutics, such as for example, the anthracylines, platins, taxanes. In some cases, ER positive breast cancers that harbor genetic amplication of the ERB-B/HER2 tyrosine kinase receptor are treated with the monoclonal antibody trastuzumab (Herceptin™) or the small molecule pan-ERB-B inhibitor lapatinib. Despite this battery of anti-hormonal, chemotherapeutic and small-molecule and antibody-based targeted therapies, many women with ER-α positive breast develop progressive metastatic disease and are in need of new therapies. Importantly, the majority of ER positive tumors that progress on existing anti-hormonal, as well as and other therapies, are thought to remain dependent on ER-α for growth and survival. Thus, there is a need for new ER-α targeting agents that have activity in the setting of metastatic disease and acquired resistance. In one aspect, described herein are compounds that are selective estrogen receptor modulators (SERMs). In specific embodiments, the SERMs described herein are selective estrogen receptor degraders (SERDs). In some

embodiments, in cell-based assays the compounds described herein result in a reduction in steady state ER-α levels (i.e. ER degradation) and are useful in the treatment of estrogen sensitive diseases or conditions and/or diseases or conditions that have developed resistant to anti-hormonal therapies.

[0057] Given the central role of ER-α in breast cancer development and progression, compounds disclosed herein are useful in the treatment of breast cancer, either alone or in combination with other agent agents that can modulate other critical pathways in breast cancer, including but not limited to those that target IGF1R, EGFR, erB-B2 and 3 the PI3K/AKT/mTOR axis, HSP90, PARP or histone deacetylases.

[0058] Given the central role of ER-α in breast cancer development and progression, compounds disclosed herein are useful in the treatment of breast cancer, either alone or in combination with other agent used to treat breast cancer, including but not limited to aromatase inhibitors, anthracylines, platins, nitrogen mustard alkylating agents, taxanes. Illustrative agent used to treat breast cancer, include, but are not limited to, paclitaxel, anastrozole, exemestane, cyclophosphamide, epirubicin, fulvestrant, letrozole, gemcitabine, trastuzumab, pegfilgrastim, filgrastim, tamoxifen, docetaxel, toremifene, vinorelbine, capecitabine, ixabepilone, as well as others described herein.

[0059] ER-related diseases or conditions include ER-α dysfunction is associated with cancer (bone cancer, breast cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian and uterine cancer), central nervous system (CNS) defects (alcoholism, migraine), cardiovascular system defects (aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery disease, hypertension), hematological system defects (deep vein thrombosis), immune and inflammation diseases (Graves' Disease, arthritis, mulitple sclerosis, cirrhosis), susceptibility to infection (hepatitis B, chronic liver disease), metabolic defects (bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis), neurological defects (Alzheimer's disease, Parkinson's disease, migraine, vertigo), psychiatric defects (anorexia nervosa, attention deficity hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis) and reproductive defects (age of menarche, endometriosis, infertility.

[0060] In some embodiments, compounds disclosed herein are used in the treatment of an estrogen receptor dependent or estrogen receptor mediated disease or condition in mammal.

[0061] In some embodiments, the estrogen receptor dependent or estrogen receptor mediated disease or condition is selected from cancer, central nervous system (CNS) defects, cardiovascular system defects, hematological system defects, immune and inflammation diseases, susceptibility to infection, metabolic defects, neurological defects, psychiatric defects and reproductive defects.

[0062] In some embodiments, the estrogen receptor dependent or estrogen receptor mediated disease or condition is selected from bone cancer, breast cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian cancer, uterine cancer, alcoholism, migraine, aortic aneurysm, susceptibility to myocardial infarction, aortic valve sclerosis, cardiovascular disease, coronary artery

disease, hypertension, deep vein thrombosis, Graves' Disease, arthritis, mulitple sclerosis, cirrhosis, hepatitis B, chronic liver disease, bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis, Alzheimer's disease, Parkinson's disease, migraine, vertigo, anorexia nervosa, attention deficity hyperactivity disorder (ADHD), dementia, major depressive disorder, psychosis, age of menarche, endometriosis, and infertility.

[0063] In some embodiments, compounds disclosed herein are used to treat cancer in a mammal. In some embodiments, the cancer is breast cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer. In some embodiments, the cancer is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is a hormone dependent cancer. In some embodiments, the cancer is an estrogen receptor dependent cancer. In some embodiments, the cancer is an estrogen-sensitive cancer. In some embodiments, the cancer is resistant to anti-hormonal treatment. In some embodiments, the cancer is an estrogen-sensitive cancer or an estrogen receptor dependent cancer that is resistant to anti-hormonal treatment. In some embodiments, the cancer is a hormone-sensitive cancer or a hormone receptor dependent cancer that is resistant to anti-hormonal treatment. In some embodiments, anti-hormonal treatment includes treatment with at least one agent selected from tamoxifen, fulvestrant, steroidal aromatase inhibitors, and non-steroidal aromatase inhibitors.

[0064] In some embodiments, compounds disclosed herein are used to treat hormone receptor positive metastatic breast cancer in a postmenopausal woman with disease progression following anti-estrogen therapy.

[0065] In some embodiments, compounds disclosed herein are used to treat a hormonal dependent benign or malignant disease of the breast or reproductive tract in a mammal. In some embodiments, the benign or malignant disease is breast cancer.

[0066] In some embodiments, the compound used in any of the methods described herein is an estrogen receptor degrader; is an estrogen receptor antagonist; has minimial or negligible estrogen receptor agonist activity; or combinations thereof.

[0067] In some embodiments, methods of treatment with compounds described herein include a treatment regimen that includes administering radiation therapy to the mammal.

[0068] In some embodiments, methods of treatment with compounds described herein include administering the compound prior to or following surgery.

[0069] In some embodiments, methods of treatment with compounds described herein include administering to the mammal at least one additional anti-cancer agent.

[0070] In some embodiments, compounds disclosed herein are used to treat cancer in a mammal, wherein the mammal is chemotherapy-naïve.

[0071] In some embodiments, compounds disclosed herein are used in the treatment of cancer in a mammal. In some embodiments, compounds disclosed herein are used to treat cancer in a mammal,

wherein the mammal is being treated for cancer with at least one anti-cancer agent. In one embodiment, the cancer is a hormone refractory cancer.

[0072] In some embodiments, compounds disclosed herein are used in the treatment or prevention of diseases or conditions of the uterus in a mammal. In some embodiments, the disease or condition of the uterus is leiomyoma, uterine leiomyoma, endometrial hyperplasia, or endometriosis. In some embodiments, the disease or condition of the uterus is a cancerous disease or condition of the uterus. In some other embodiments, the disease or condition of the uterus is a non-cancerous disease or condition of the uterus.

[0073] In some embodiments, compounds disclosed herein are used in the treatment of endometriosis in a mammal.

[0074] In some embodiments, compounds disclosed herein are used in the treatment of leiomyoma in a mammal. In some embodiments, the leiomyoma is a uterine leiomyoma, esophageal leiomyoma, cutaneous leiomyoma, or small bowel leiomyoma. In some embodiments, compounds disclosed herein are used in the treatment of fibroids in a mammal. In some embodiments, compounds disclosed herein are used in the treatment of uterine fibroids in a mammal.

Compounds

[0075] Compounds of Formula (I), (II), (III), (IV), (V), or (VI), including pharmaceutically acceptable salts, prodrugs, active metabolites and pharmaceutically acceptable solvates thereof, are estrogen receptor modulators. In specific embodiments, the compounds described herein are estrogen receptor degraders. In specific embodiments, the compounds described herein are estrogen receptor antagonists. In specific embodiments, the compounds described herein are estrogen receptor degraders and estrogen receptor antagonists with minimal or no estrogen receptor agonist activity.

[0076] In some embodiments, compounds disclosed herein are estrogen receptor degraders and estrogen receptor antagonists that exhibit: no estrogen receptor agonism; and/or anti-proliferative activity against breast cancer, ovarian cancer, endometrial cancer, cervical cancer cell lines; and/or maximal anti-proliferative efficacy against breast cancer, ovarian cancer, endometrial cancer, cervical cell lines in-vitro; and/or minimal agonism in the human endometrial (Ishikawa) cell line; and/or no agonism in the human endometrial (Ishikawa) cell line; and/or no agonism in the immature rat uterine assay in-vivo; and/or inverse agonism in the immature rat uterine assay in-vivo; and/or anti-tumor activity in breast cancer, ovarian cancer, endometrial cancer, cervical cancer cell lines in xenograft assays in-vivo or other rodent models of these cancers.

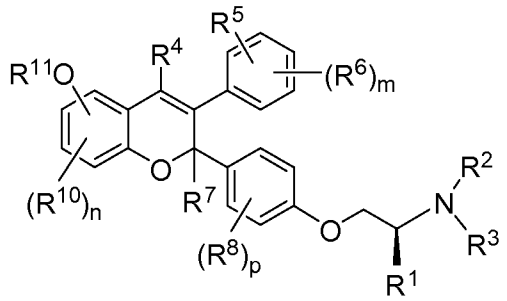
[0077] In some embodiments, compounds described herein have reduced or minimal interaction with the hERG (the human Ether-à-go-go-Related Gene) channel and/or show a reduced potential for QT prolongation and/or a reduced risk of ventricular tachyarrhythmias like torsades de pointes.

[0078] In some embodiments, compounds described herein have reduced or minimal potential to access the hypothalamus and/or have reduced or minimal potential to modulate the Hypothalamic-Pituitary-

Ovarian (HPO) axis and/or show a reduced potential to cause hyper-stimulation of the ovaries and/or show a reduced potential for ovary toxicity.

[0079] In some embodiments, compounds described herein for use in the treatment of a disease or condition in a pre-menopausal woman have reduced or minimal potential to access the hypothalamus and/or have reduced or minimal potential to modulate the Hypothalamic-Pituitary-Ovarian (HPO) axis and/or show a reduced potential to cause hyper-stimulation of the ovaries and/or show a reduced potential for ovary toxicity. In some embodiments, the disease or condition in the pre-menopausal woman is endometriosis. In some embodiments, the disease or condition in the pre-menopausal woman is an uterine disease or condition.

[0080] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

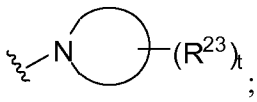
wherein,

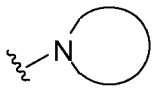
R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form

 ;

 is a monocyclic C_2-C_{10} heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

t is 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl or C_3-C_6cycloalkyl;

R^5 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

R^7 is H or C_1-C_4alkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

each R^{10} is independently selected from H, halogen, -CN, -OH, $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{11} is independently selected from H, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)NHR^{12}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C_1$-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), $-C_1$-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), $-C_1$-C_2alkylene-(substituted or unsubstituted aryl), and $-C_1$-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C_1$-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), $-C_1$-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), $-C_1$-C_2alkylene-(substituted or unsubstituted aryl), and $-C_1$-C_2alkylene-(substituted or unsubstituted heteroaryl);

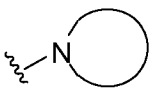
m is 0, 1, 2, 3 or 4;

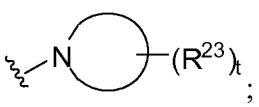
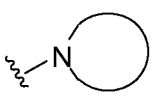
n is 0, 1, or 2;

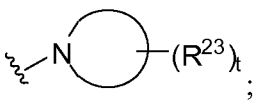
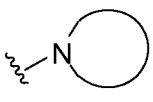
p is 0, 1, or 2;

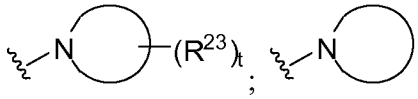
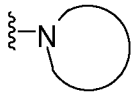
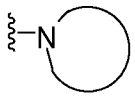
provided that the compound is not 2-(4-((S)-2-((R)-3-fluoropyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol.

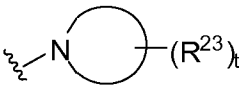
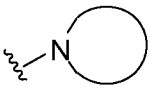
[0081] For any and all of the embodiments described herein, substituents are selected from among a subset of the listed alternatives. For example in some embodiments, R^7 is H or $-CH_3$. In other embodiments, R^7 is H.

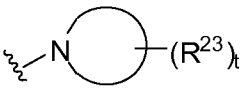
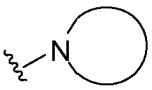
[0082] In some embodiments,  is a monocyclic C_2-C_{10} heterocycloalkyl; each R^{23} is independently C_1-C_6fluoroalkyl; t is 1, 2, 3, or 4.

[0083] In some embodiments, R^2 and R^3 are taken together with the N atom to which they are attached to form  ;  is a monocyclic C_2-C_{10} heterocycloalkyl

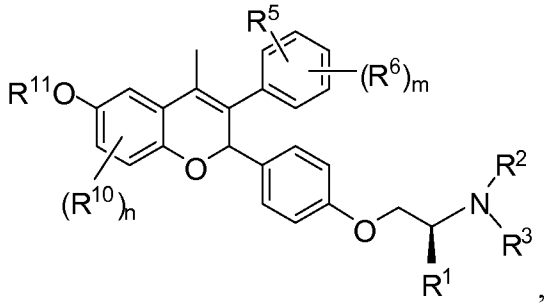
[0084] In some embodiments, R^2 and R^3 are taken together with the N atom to which they are attached to form  ;  is a monocyclic C_2-C_6 heterocycloalkyl.

[0085] In some embodiments, R^2 and R^3 are taken together with the N atom to form  ; is a 4-, 5-, 6- or 7-membered monocyclic C_2-C_6 heterocycloalkyl. In some embodiments,  is azetidinyl, pyrrolidinyl, piperidinyl, or azepanyl. In some other embodiments,  is pyrrolidinyl.

[0086] In some embodiments, R^1 is H or C_1-C_6alkyl; R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl; R^3 is C_1-C_6fluoroalkyl; or R^2 and R^3 are taken together with the N atom to which they are attached to form  ;  is a 4-, 5-, 6- or 7-membered monocyclic C_2-C_6heterocycloalkyl; each R^{23} is independently F or C_1-C_6fluoroalkyl; t is 1 or 2; R^4 is $-CH_3$; R^7 is H; p is 0 or 1.

[0087] In some embodiments, R^1 is H or C_1-C_6alkyl; R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl; R^3 is C_1-C_6fluoroalkyl; or R^2 and R^3 are taken together with the N atom to which they are attached to form  ;  is a 4-, 5-, 6- or 7-membered monocyclic C_2-C_6heterocycloalkyl; each R^{23} is independently C_1-C_6fluoroalkyl; t is 1 or 2; R^4 is $-CH_3$; R^7 is H; p is 0 or 1.

[0088] In some embodiments, the compound has one of the following structures:



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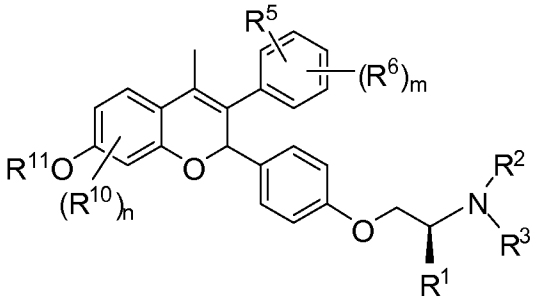
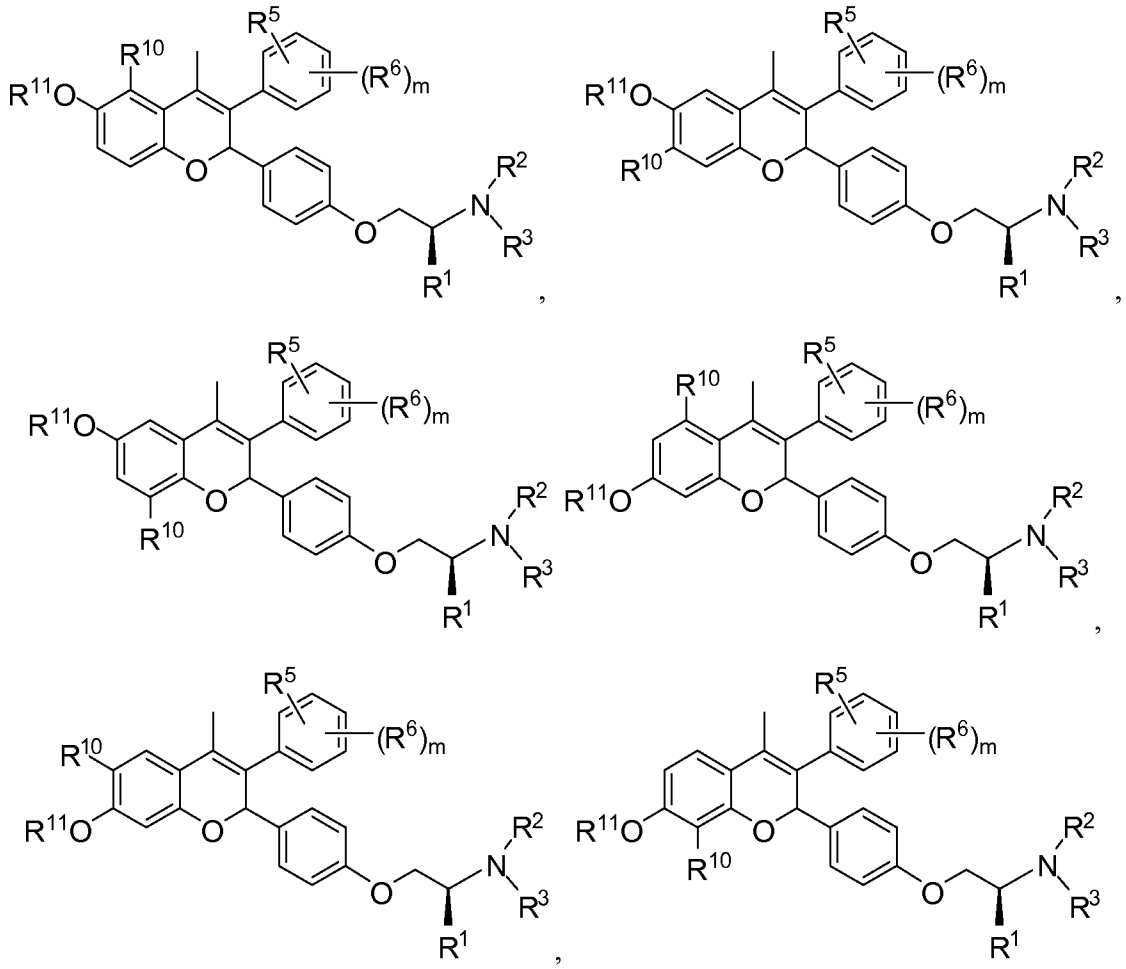


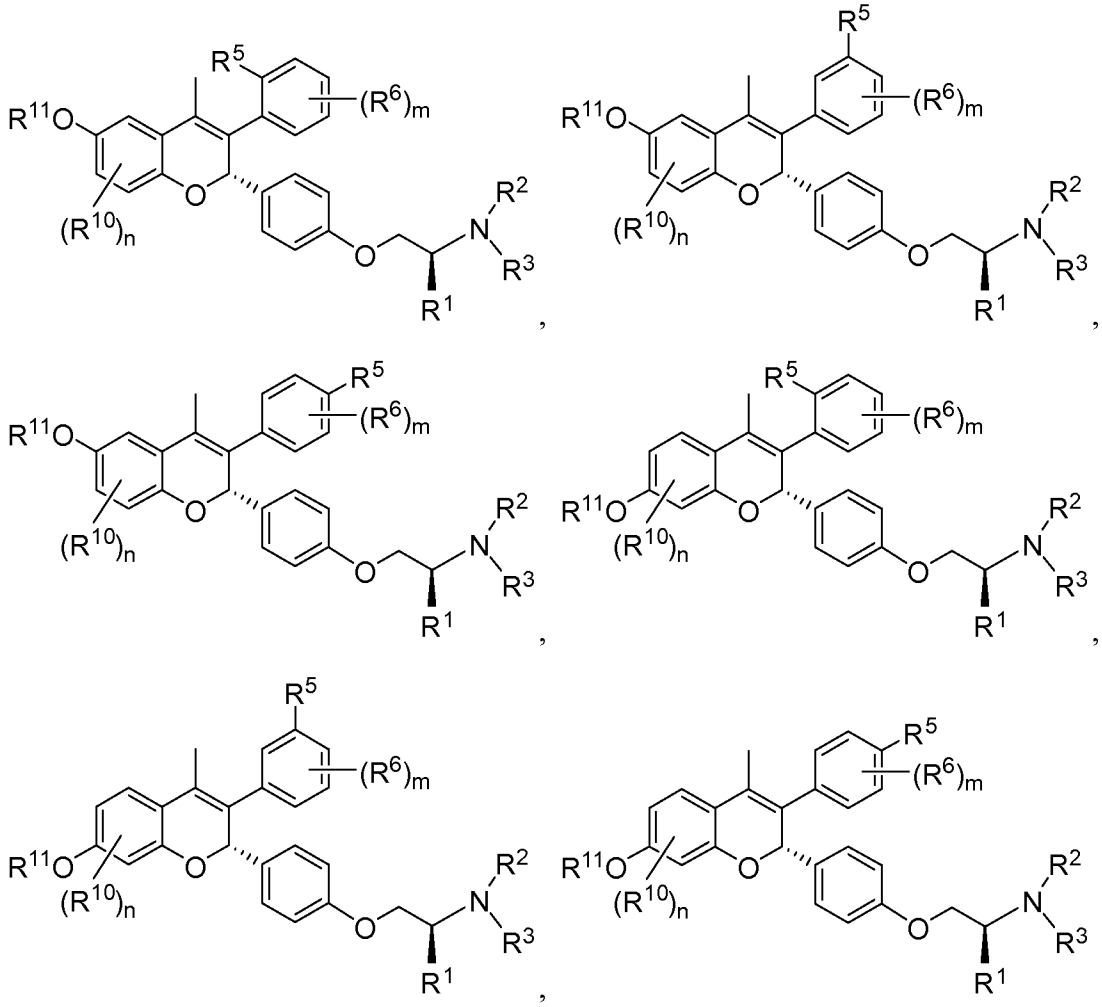
or is a pharmaceutically acceptable salt, or solvate thereof.

[0089] In some embodiments, the compound has one of the following structures:



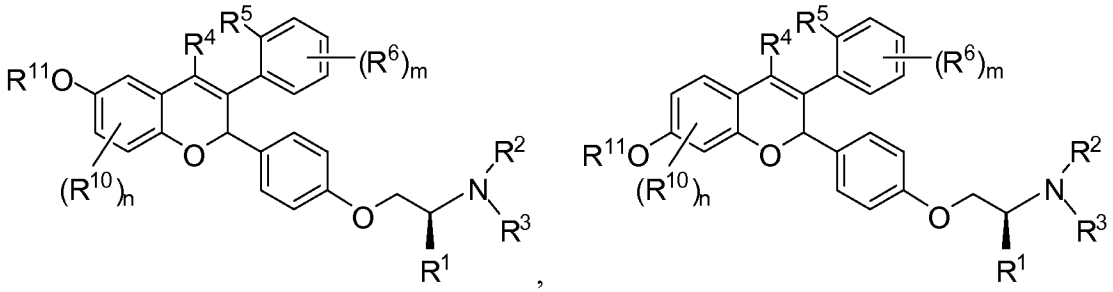
or is a pharmaceutically acceptable salt, or solvate thereof.

[0090] In some embodiments, the compound has one of the following structures:



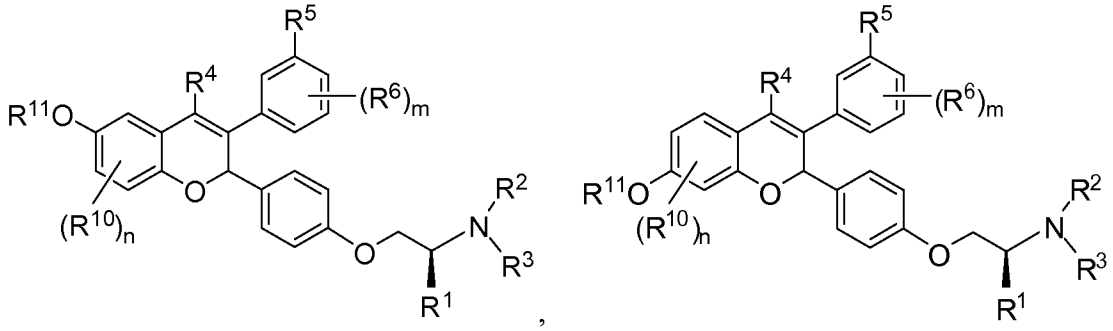
or is a pharmaceutically acceptable salt, or solvate thereof.

[0091] In some embodiments, the compound has one of the following structures:



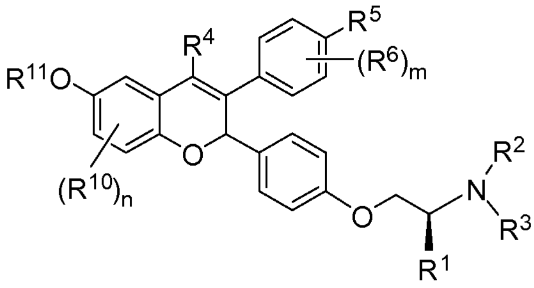
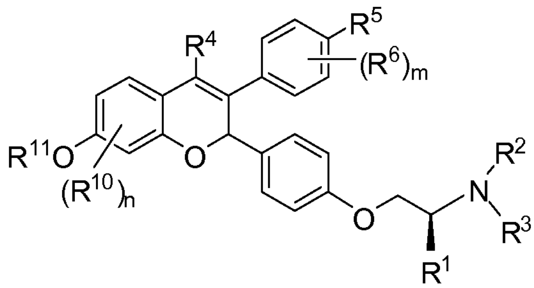
or is a pharmaceutically acceptable salt, or solvate thereof.

[0092] In some embodiments, the compound has one of the following structures:



or is a pharmaceutically acceptable salt, or solvate thereof.

[0093] In some embodiments, the compound has one of the following structures:


,


or is a pharmaceutically acceptable salt, or solvate thereof.

[0094] In some embodiments, each R^{10} is independently selected from -CN, -OH, $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl. In some embodiments, each R^{10} is independently selected from H, halogen, -CN, -OH, $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl. In some embodiments, each R^{10} is independently selected from H, F, Cl, -CN, $-CH_3$, and $-CF_3$. In some embodiments, each R^{10} is independently selected from H and F.

[0095] In some embodiments, n is 0 or 1. In some embodiments, n is 0.

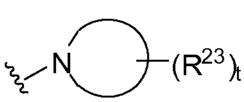
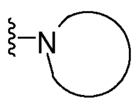
[0096] In some embodiments, R^5 is $–OR^{11}$. In some embodiments, R^{11} is H. In some embodiments, R^5 is -OH; R^{11} is H.

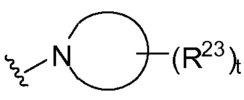
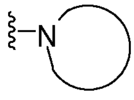
[0097] In some embodiments, R^5 is -OH; each R^{10} is independently selected from H, halogen, -CN, -OH, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; R^{11} is H.

[0098] In some embodiments, each R^6 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy. In some embodiments, each R^6 is independently selected from H, halogen, and –CN. In some embodiments, each R^6 is H, F, Cl, -CN, $-CH_3$, and $-CF_3$. In some embodiments, m is 0 or 1. In some embodiments, m is 0.

[0099] In some embodiments, R^4 is $-CH_3$.

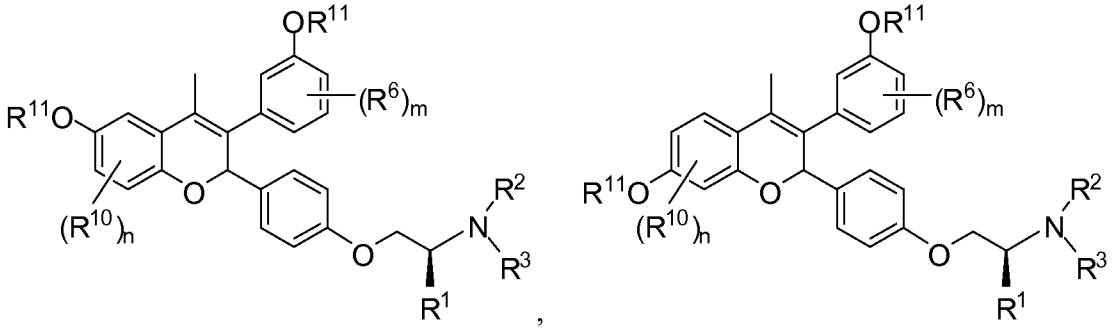
[00100] In some embodiments, R^1 is H or $-CH_3$. In some embodiments, R^1 is $-CH_3$.

[00101] In some embodiments, R^1 is H, or $-CH_3$; R^2 and R^3 are taken together with the N atom to which they are attached to form  ;  is azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, morpholinyl, or piperazinyl; each R^{23} is independently F, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $–CF(CH_3)_2$.

[00102] In some embodiments, R^1 is H, or $-CH_3$; R^2 and R^3 are taken together with the N atom to which they are attached to form  ;  is azetidinyl, pyrrolidinyl, piperidinyl,

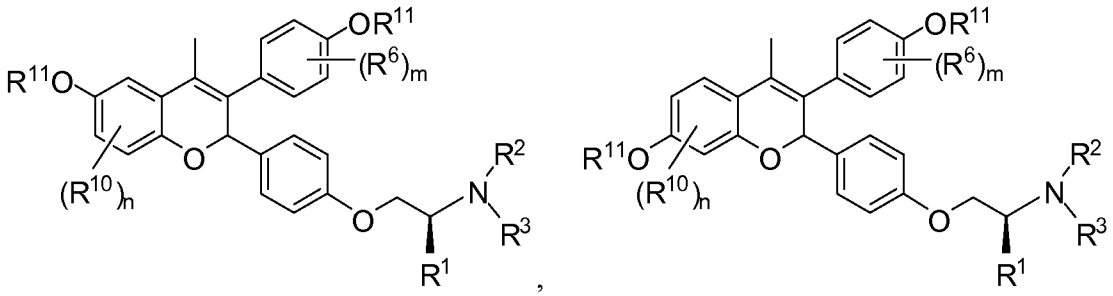
azepanyl, morpholinyl, or piperazinyl; each R^{23} is independently $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$.

[00103] In some embodiments, the compound has one of the following structures:



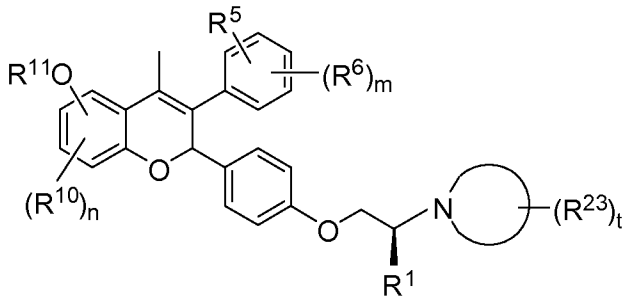
or is a pharmaceutically acceptable salt, or solvate thereof.

[00104] In some embodiments, the compound has one of the following structures:



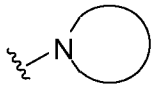
or is a pharmaceutically acceptable salt, or solvate thereof.

[00105] In some embodiments, the compound of Formula (I) has the structure of Formula (II):

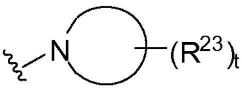
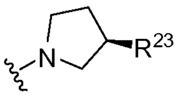


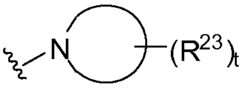
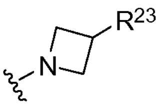
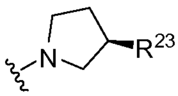
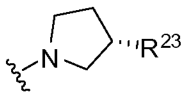
Formula (II)

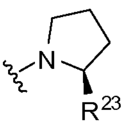
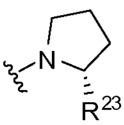
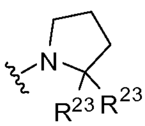
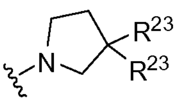
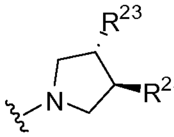
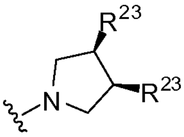
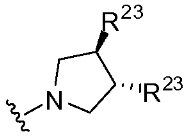
or is a pharmaceutically acceptable salt, or solvate thereof.

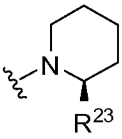
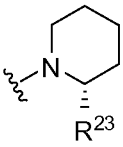
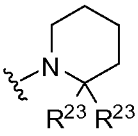
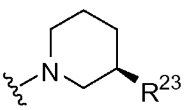
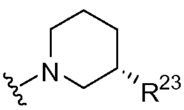
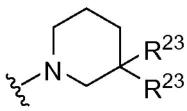
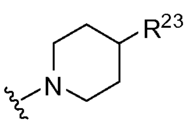
[00106] In some embodiments of the compound of Formula (II), R^1 is H or $-CH_3$;  is a monocyclic C_2-C_6heterocycloalkyl; each R^{23} is independently C_1-C_6fluoroalkyl; t is 1 or 2; R^5 is $-OR^{11}$; each R^6 is independently selected from H, halogen, -CN, -OH, $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; each R^{10} is independently selected from H, halogen, -CN, -OH, $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; each R^{11} is independently

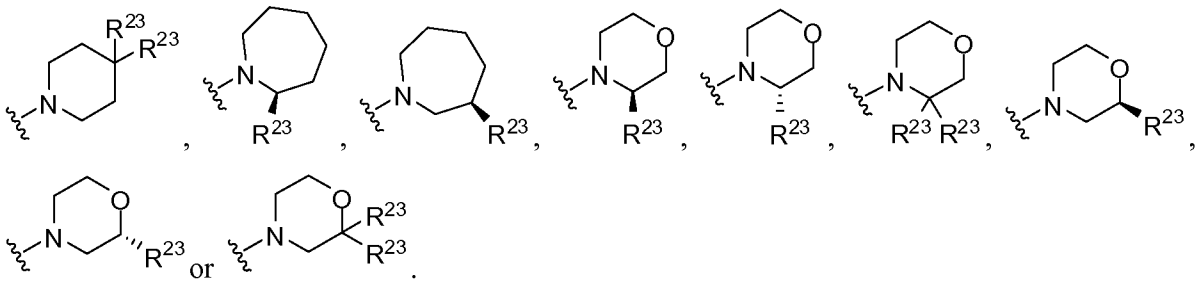
selected from H, -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl); each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl); m is 0 or 1; n is 0 or 1. In some embodiments, m is 0. In some embodiments, n is 0. In some embodiments, each R^{11} is H.

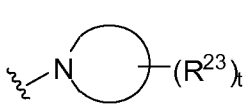
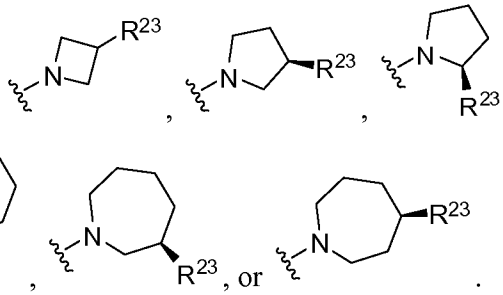
[00107] In some other embodiments of the compound of Formula (II), R^1 is H or -CH_3;  is  ; R^{23} is C_1-C_4fluoroalkyl; R^5 is -OR^{11}; each R^6 is independently selected from H, halogen, and -CN; each R^{10} is independently selected from H, halogen and -CN; each R^{11} is independently selected from H, -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, and C_1-C_6alkyl; each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl); m is 0 or 1; n is 0 or 1. In some embodiments, each R^{11} is H. In some embodiments, m is 0. In some embodiments, n is 0.

[00108] In some embodiments,  is  ,  ,  ,

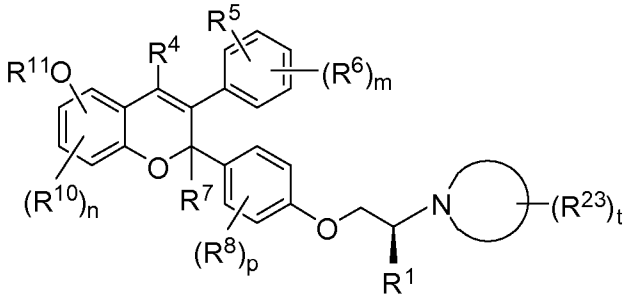
 ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,



[00109] In some embodiments,  is 

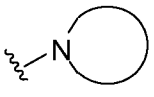
[00110] In another aspect, described herein is a compound of Formula (III), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (III)

wherein,

R^1 is C_1-C_6fluoroalkyl;

 is a monocyclic C_2-C_{10}heterocycloalkyl;

each R^{23} is independently F, C_1-C_6alkyl or C_1-C_6fluoroalkyl;

t is 0, 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl or C_3-C_6cycloalkyl;

R^5 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

each R^{10} is independently selected from H, halogen, -CN, -OH, $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

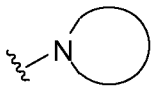
each R^{11} is independently selected from H, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)NHR^{12}$, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C_1$-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), $-C_1$-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), $-C_1$-C_2alkylene-(substituted or unsubstituted aryl), and $-C_1$-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C_1$-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), $-C_1$-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), $-C_1$-C_2alkylene-(substituted or unsubstituted aryl), and $-C_1$-C_2alkylene-(substituted or unsubstituted heteroaryl);

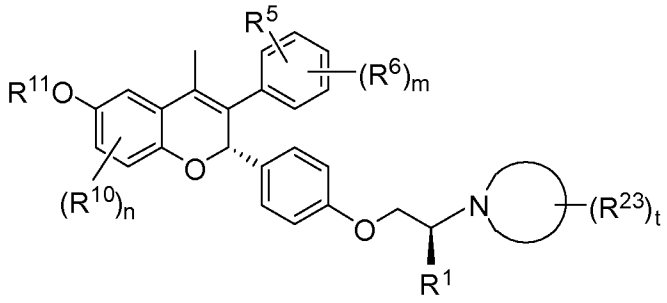
m is 0, 1, 2, 3 or 4;

n is 0, 1, or 2;

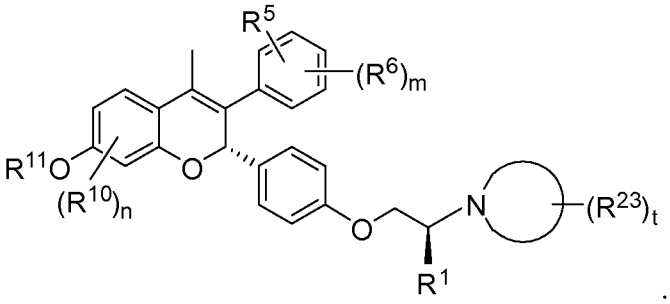
p is 0, 1, or 2.

[00111] In some embodiments, R^1 is $-CH_2F$, $-CHF_2$, or $-CF_3$;  is an azetidinyl, pyrrolidinyl, piperidinyl, or azepanyl; each R^{23} is independently F, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$; t is 0, 1 or 2; R^4 is $-CH_3$; R^7 is H; p is 0 or 1.

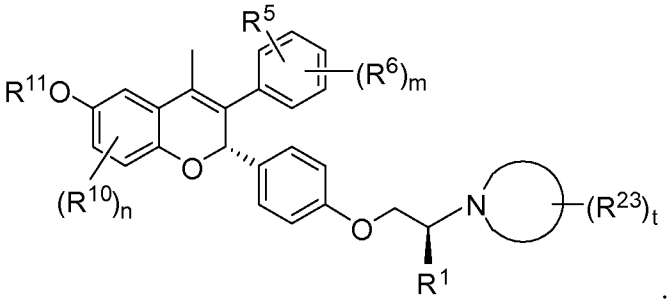
[00112] In some embodiments, the compound of Formula (I), (II) or (III) has one of the following structures:



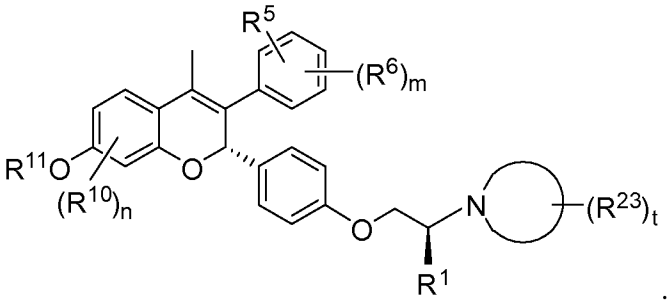
or



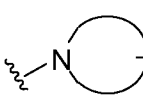
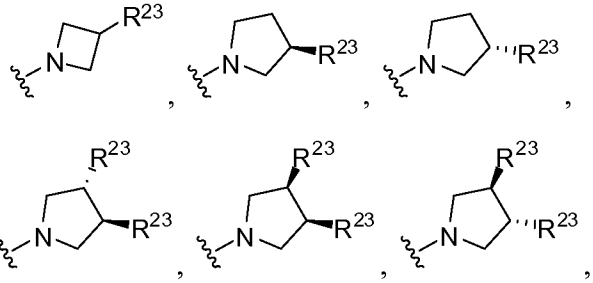
[00113] In some embodiments, the compound of Formula (I), (II) or (III) has the following structure:

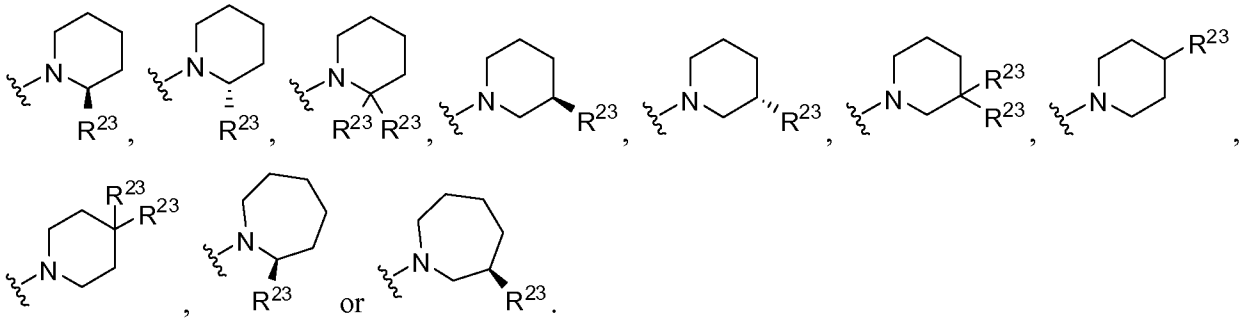


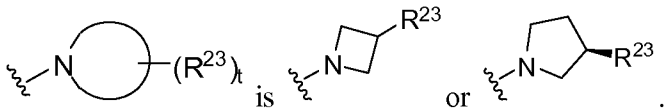
[00114] In some embodiments, the compound of Formula (I), (II) or (III) has the following structure:

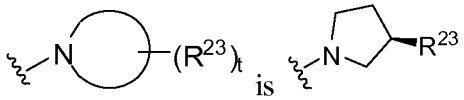


[00115] In some embodiments, R^5 is -OH; each R^{10} is independently selected from H, halogen, -CN, -OH, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; R^{11} is H. In some embodiments, R^5 is -OH; each R^6 is independently selected from H and halogen; each R^{10} is independently selected from H and halogen; R^{11} is H.

[00116] In some embodiments,  is 



[00117] In some embodiments,  .

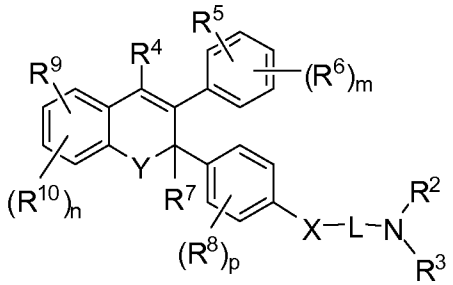
[00118] In some embodiments,  .

[00119] In some embodiments, each R^{23} is independently F, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$. In some embodiments, each R^{23} is independently F, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^{23} is independently F, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^{23} is independently $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^{23} is independently $-CH_2F$. In some embodiments, each R^{23} is independently $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, each R^{23} is independently $-CH_3$.

[00120] In some embodiments, R^2 and R^3 are taken together with the N atom to which they are attached to form substituted or unsubstituted pyrrolidinyl.

[00121] In some embodiments, R^1 is $-CH_3$. In some embodiments, R^1 is $-CH_3$; R^4 is $-CH_3$.

[00122] In some embodiments, described herein is a compound of Formula (IV), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (IV)

wherein,

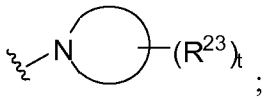
L is a substituted or unsubstituted C_1-C_6flouroalkylene, where if L is substituted, then L is substituted with 1 or 2 R^1;

R^1 is C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_6cycloalkyl, C_3-C_6fluorocycloalkyl, or C_1-C_6heteroalkyl;

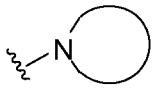
R^2 is H or R^{12};

R^3 is -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, -S(=O)$_2R^{12}$, or R^{12};

or R^2 and R^3 are taken together with the N atom to which they are attached to form



;



is a monocyclic heterocycloalkyl or a bicyclic heterocycloalkyl;

each R^{23} is independently selected from F, Cl, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -S(=O)$_2R^{12}$, -C(=O)R^{12}, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6fluoroalkoxy, substituted or unsubstituted C_1-C_6alkoxy, and substituted or unsubstituted C_1-C_6heteroalkyl;

or two R^{23} on the same carbon atom are taken together with the carbon atom to which they are attached to form –C(=O)-;

or two R^{23} on adject carbon atoms are taken together with the carbon atoms to which they are attached to form a C_3-C_6cycloalkyl;

or 1 R^{23} is taken together with R^1 and the intervening atoms connecting R^{23} to R^1 to form a 5-7 membered ring;

t is 0, 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, C_3-C_6cycloalkyl, C_3-C_6fluorocycloalkyl, C_3-C_6heterocycloalkyl, C_1-C_6heteroalkyl, -C_1-C_4alkylene-C_3-C_6cycloalkyl, -SR^{11}, -S(=O)R^{12}, -S(=O)$_2R^{12}$, -C(=O)R^{12}, -C(=O)NHR^{12}, or -C(=O)N(R^{12})$_2$;

R^5 is H, halogen, -CN, -NHR^{11}, -N$R^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -S(=O)$_2R^{12}$, -C(=O)R^{12}, -C(=O)OH, -C(=O)OR^{12}, -C(=O)NHR^{12}, -C(=O)N(R^{12})$_2$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6fluoroalkoxy, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or a substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^6 is independently selected from H, halogen, -CN, -SR^{11}, -S(=O)R^{12}, -S(=O)$_2R^{12}$, -C(=O)R^{12}, -C(=O)OH, -C(=O)OR^{12}, -C(=O)NHR^{12}, -C(=O)N(R^{12})$_2$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6fluoroalkoxy, substituted or unsubstituted C_1-C_6alkoxy, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl;

R^7 is H or C_1-C_4alkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6fluoroalkoxy, substituted or unsubstituted C_1-C_6alkoxy, and substituted or unsubstituted C_1-C_6heteroalkyl;

R^9 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6fluoroalkoxy, substituted or unsubstituted C_1-C_6alkoxy, and substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^{10} is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6fluoroalkoxy, substituted or unsubstituted C_1-C_6alkoxy, and substituted or unsubstituted C_1-C_6heteroalkyl;

each R^{11} is independently selected from H, -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

Y is -O-, -S-, -S(=O)-, -$S(=O)_2$-, or –NR^{13}-; R^{13} is H, -C(=O)R^{12}, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl;

X is -O-, -S-, -S(=O)-, -$S(=O)_2$-, -CH_2-, -NH- or –N(C_1-C_6alkyl)-;

m is 0, 1, 2, 3 or 4;

n is 0, 1, or 2;

p is 0, 1, or 2.

[00123] In some embodiments, p is 0, 1, or 2. In some embodiments, p is 0 or 1. In some embodiments, p is 1. In some embodiments, p is 0.

[00124] In some embodiments, n is 0, 1, or 2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 1 or 2.

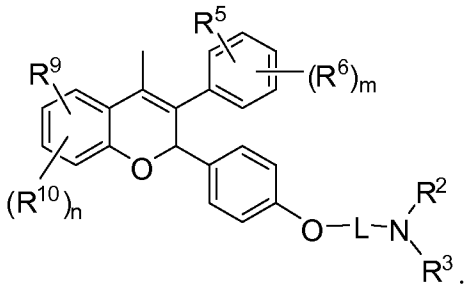
[00125] In some embodiments, m is 0, 1, 2, 3 or 4. In some embodiments, m is 1, 2, 3 or 4. In some embodiments, m is 0, 1, 2, or 3. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0, or 1. In some embodiments, m is 1, 2, or 3. In some embodiments, m is 1, or 2. In some embodiments, m is 1. In some embodiments, m is 0 or 1. In some embodiments, m is 0.

[00126] In some embodiments, Y is -O-. In some embodiments, X is -O-.

[00127] In some embodiments, L is a substituted or unsubstituted flouroethylene, where if L is substituted, then L is substituted with 1 or 2 R^1; R^4 is C_1-C_4alkyl; R^5 is halogen, -CN, $-NHR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl; each R^6 is independently selected from H, halogen, -CN, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-C(=O)R^{12}$, -C(=O)OH, $-C(=O)OR^{12}$, $-C(=O)NHR^{12}$, $-C(=O)N(R^{12})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl; R^7 is H; R^9 is H, halogen, -CN, -OH, $-OR^{11}$, $-NHR^{11}$, $-NR^{11}R^{12}$, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-C(=O)R^{12}$, -C(=O)OH, $-C(=O)OR^{12}$, $-C(=O)NHR^{12}$, $-C(=O)N(R^{12})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, or a substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl; each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy; each R^{10} is independently selected from H, halogen, -CN, $-SR^{11}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; Y is -O-; X is -O-; p is 0 or 1.

[00128] In some embodiments, R^5 is –OH or $-OR^{11}$; R^9 is –OH or $-OR^{11}$; p is 0 or 1.

[00129] In some embodiments, the compound of Formula (IV) has the following structure:



[00130] In some embodiments, R^2 is H, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, or substituted or unsubstituted C_1-C_6fluoroalkyl; R^3 is $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)NHR^{12}$, $-S(=O)_2R^{12}$, or R^{12}; R^4 is C_1-C_4alkyl; R^7 is H; Y is -O-; X is -O-.

[00131] In some embodiments, R^4 is C_1-C_4alkyl. In some embodiments, R^4 is C_1-C_4fluoroalkyl. In some embodiments, R^4 is H, halogen, -CN, C_1-C_4fluoroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, C_3-C_6cycloalkyl, C_3-C_6fluorocycloalkyl, C_3-C_6heterocycloalkyl, C_1-C_6heteroalkyl, -C_1-C_4alkylene-C_3-C_6cycloalkyl, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$C(=O)R^{12}$, -$C(=O)NHR^{12}$, or -$C(=O)N(R^{12})_2$. In some embodiments, R^4 is halogen, -CN, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, C_3-C_6cycloalkyl, C_3-C_6fluorocycloalkyl, C_3-C_6heterocycloalkyl, C_1-C_6heteroalkyl, -C_1-C_4alkylene-C_3-C_6cycloalkyl, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, -$C(=O)R^{12}$, -$C(=O)NHR^{12}$, or -$C(=O)N(R^{12})_2$.

[00132] In some embodiments, R^9 is –OH or -OR^{11}. In some embodiments, R^9 is –OH. In some embodiments, R^9 is –OH or -OR^{11}; p is 0 or 1.

[00133] In some embodiments, R^5 is –OH. In some embodiments, R^5 is –OH or -OR^{11}; p is 0 or 1.

[00134] In some embodiments, R^9 is –OR^{11}. In some embodiments, R^9 is –OH. In some embodiments, R^5 is –OR^{11}. In some embodiments, R^5 is –OH. In some embodiments, R^9 is –OR^{11}; and R^5 is –OR^{11}. In some embodiments, R^{11} is H. In some embodiments, R^9 is –OH; and R^5 is –OH.

[00135] In some embodiments, R^4 is C_1-C_4alkyl; each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; R^7 is H; each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy; Y is -O-; X is -O-; p is 0 or 1.

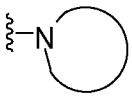
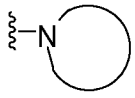
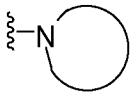
[00136] In some embodiments, R^9 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl; each R^{10} is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

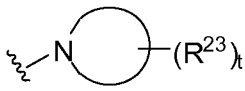
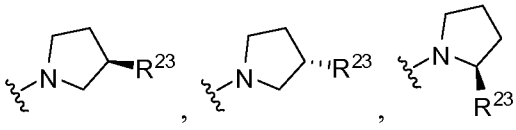
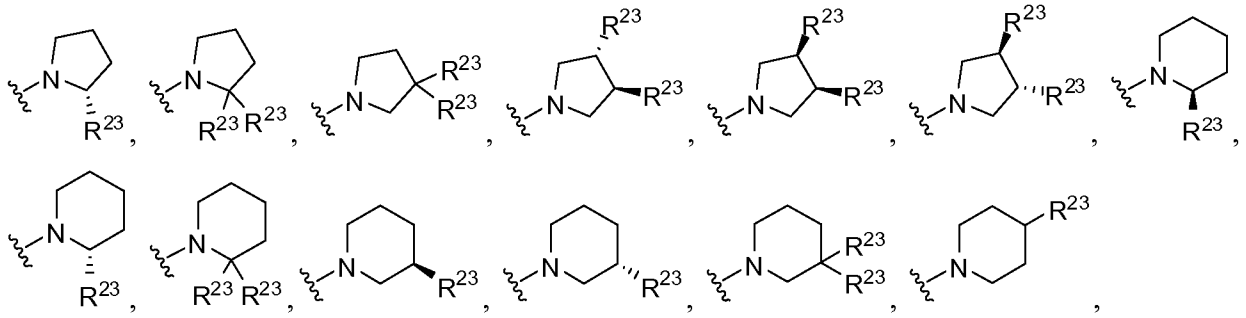
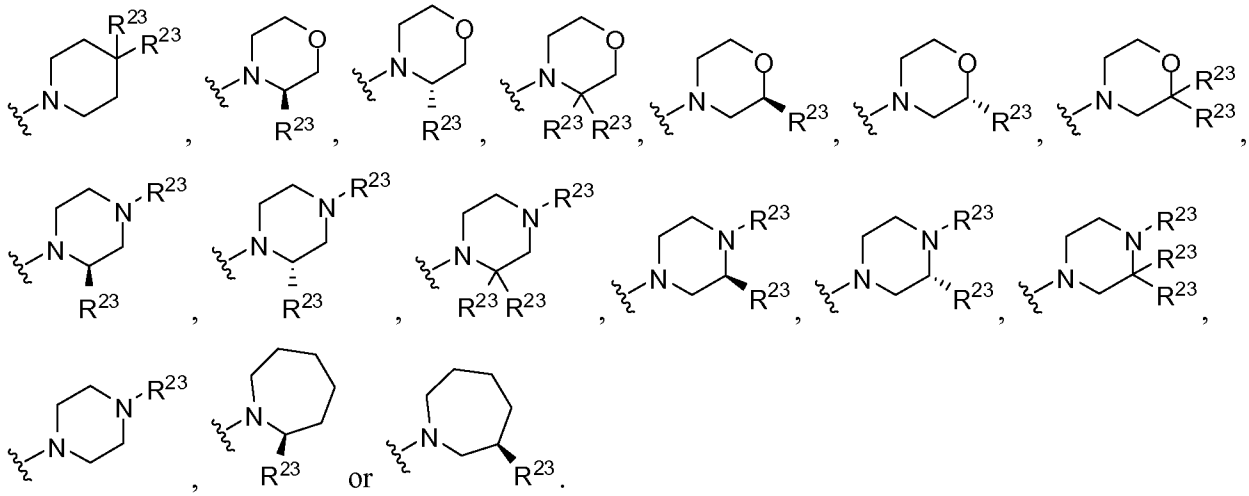
[00137] In some embodiments, R^4 is C_1-C_4alkyl; R^5 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl; each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; R^7 is H; Y is -O-; X is -O-.

[00138] In some embodiments, R^4 is C_1-C_4alkyl; each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl; R^7 is H; each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy; Y is -O-; X is -O-; p is 0 or 1.

[00139] In some embodiments, R^9 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic

heteroaryl; each R^{10} is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -$S(=O)R^{12}$, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl.

[00140] In some embodiments,  is azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, morpholinyl, piperazinyl, 3-azabicyclo[3.1.0]hexan-3-yl, 3-azabicyclo[3.2.0]heptan-3-yl, or octahydrocyclopenta[c]pyrrolyl. In some embodiments,  is azetidinyl, pyrrolidinyl, piperidinyl, or azepanyl. In some embodiments,  is pyrrolidinyl.

[00141] In some embodiments,  is    or .

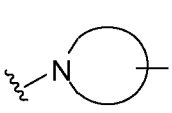
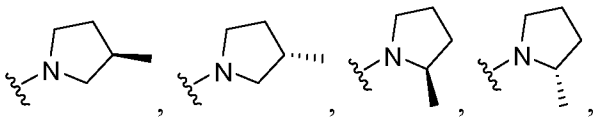
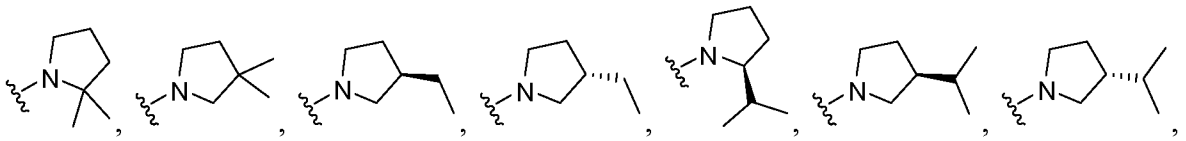
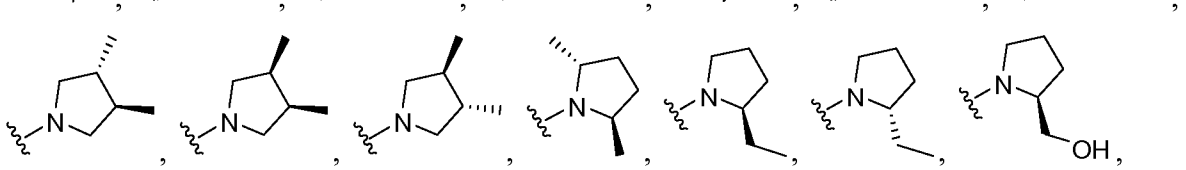
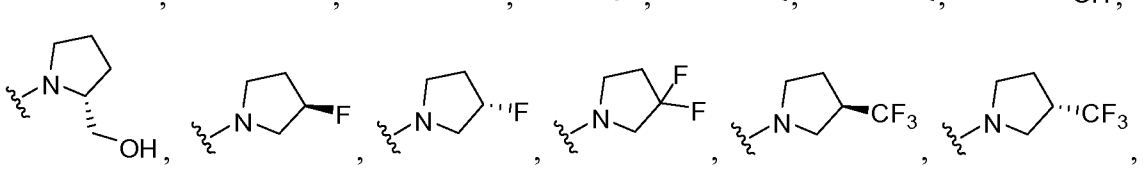
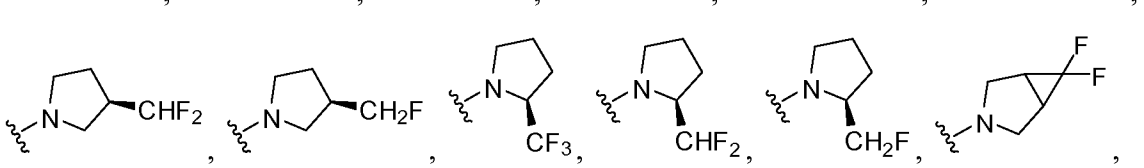
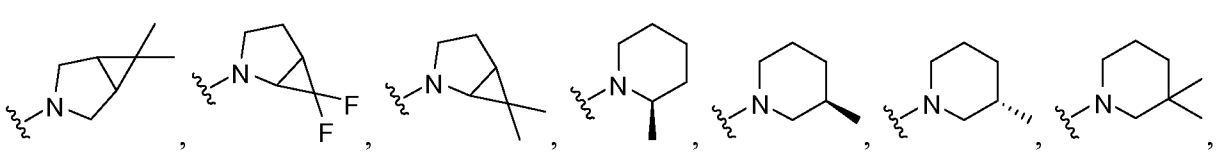
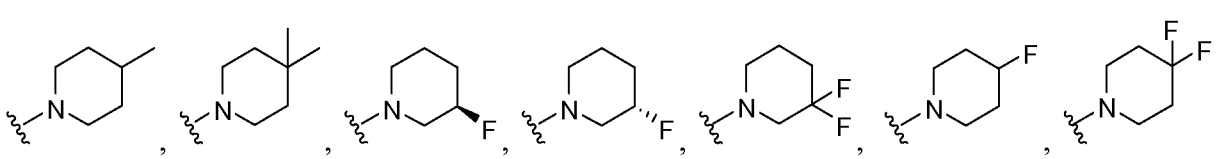
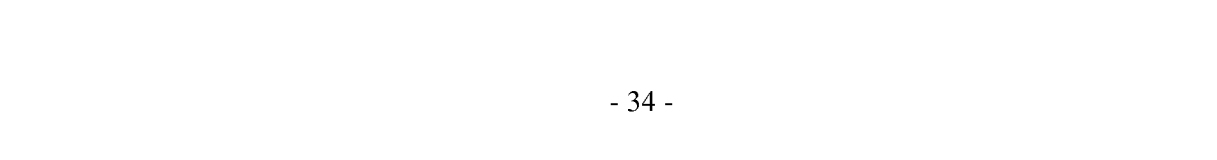
[00142] In some embodiments, each R^{23} is independently selected from F, Cl, -CN, -OH, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -CH_2F, -CHF_2, -CF_3, -$CHFCH_3$, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -$CH_2CH_2CF_3$, -$CH_2CH_2CH_2CF_3$, -$CHCH_3CF_3$, -$CH(CF_3)_2$,–$CF(CH_3)_2$, -OCF_3, -OCH_2CF_3, -OCH_3, -OCH_2CH_3, -CH_2OCH_3, -$CH_2OCH_2CH_3$, and -CH_2OH. In some embodiments, each R^{23} is independently selected from F, Cl, -CN, -OH, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -CH_2F, -CHF_2, -CF_3, -$CHFCH_3$, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -$CH_2CH_2CF_3$, -$CH_2CH_2CH_2CF_3$, -$CHCH_3CF_3$, -$CH(CF_3)_2$,–$CF(CH_3)_2$, -OCF_3, -

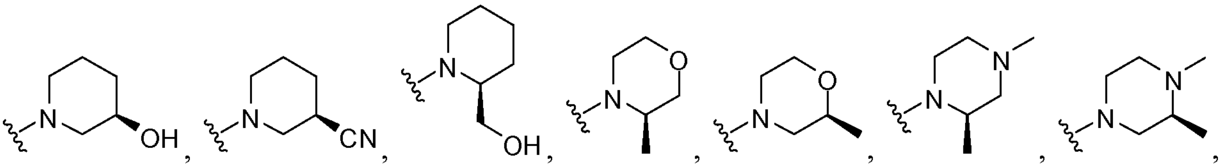
OCH_2CF_3, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OH$, provided that at least one R^{23} is a F or a fluoroalkyl.

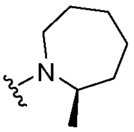
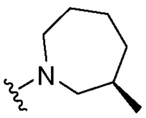
[00143] In some embodiments, each R^{23} is independently selected from F, Cl, -CN, -OH, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CF_3$, $-CH_2CF_3$, $-OCF_3$, $-OCH_2CF_3$, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2OH$.

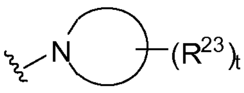
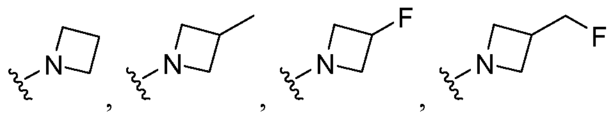
[00144] In some embodiments, each R^{23} is independently selected from F, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$. In some embodiments, each R^{23} is independently selected from $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$.

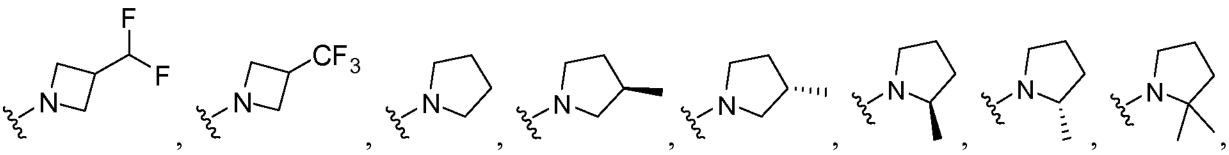
[00145] In some embodiments, each R^{23} is independently selected from F, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$. In some embodiments, each R^{23} is independently selected from $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$. In some embodiments, each R^{23} is independently selected from $-CH_2F$.

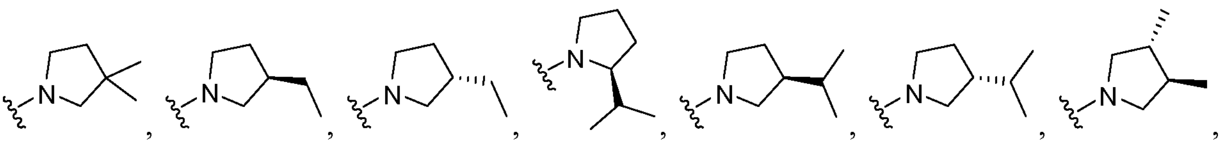
[00146] In some embodiments,  is 








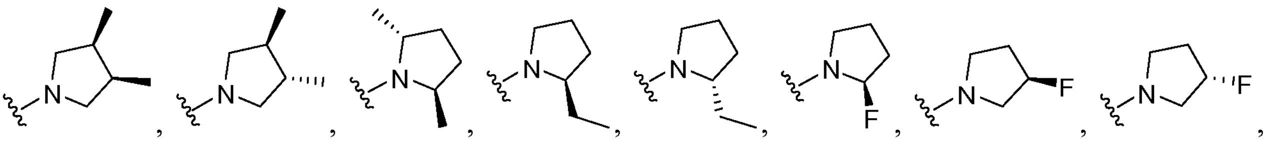


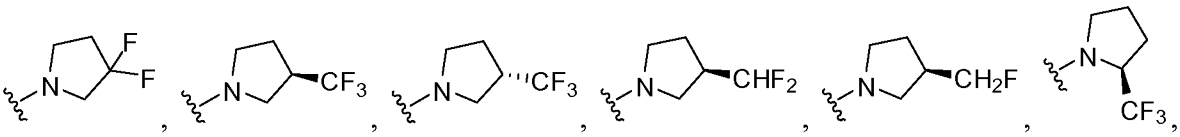
 , or  .

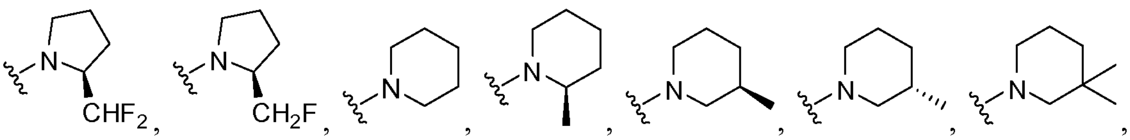
[00147] In some embodiments,  is  ,

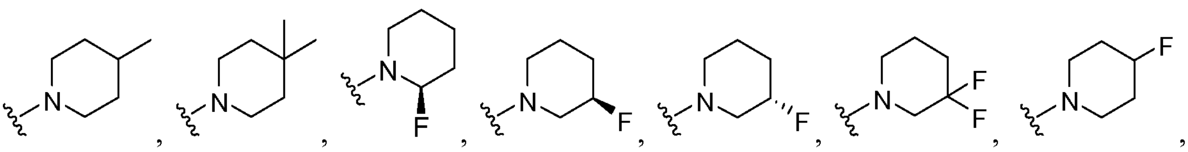
 ,

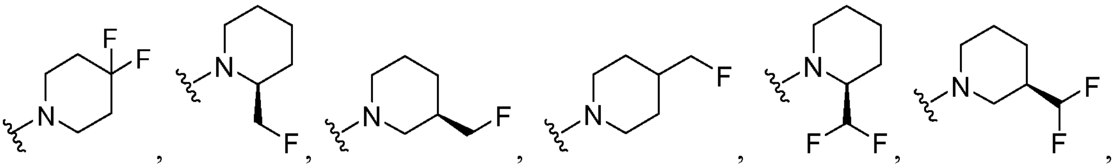
 ,

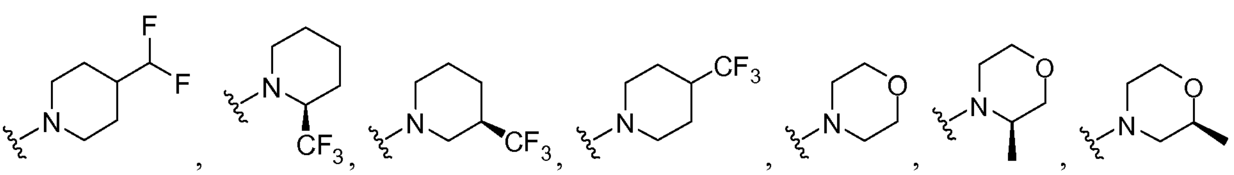
 ,

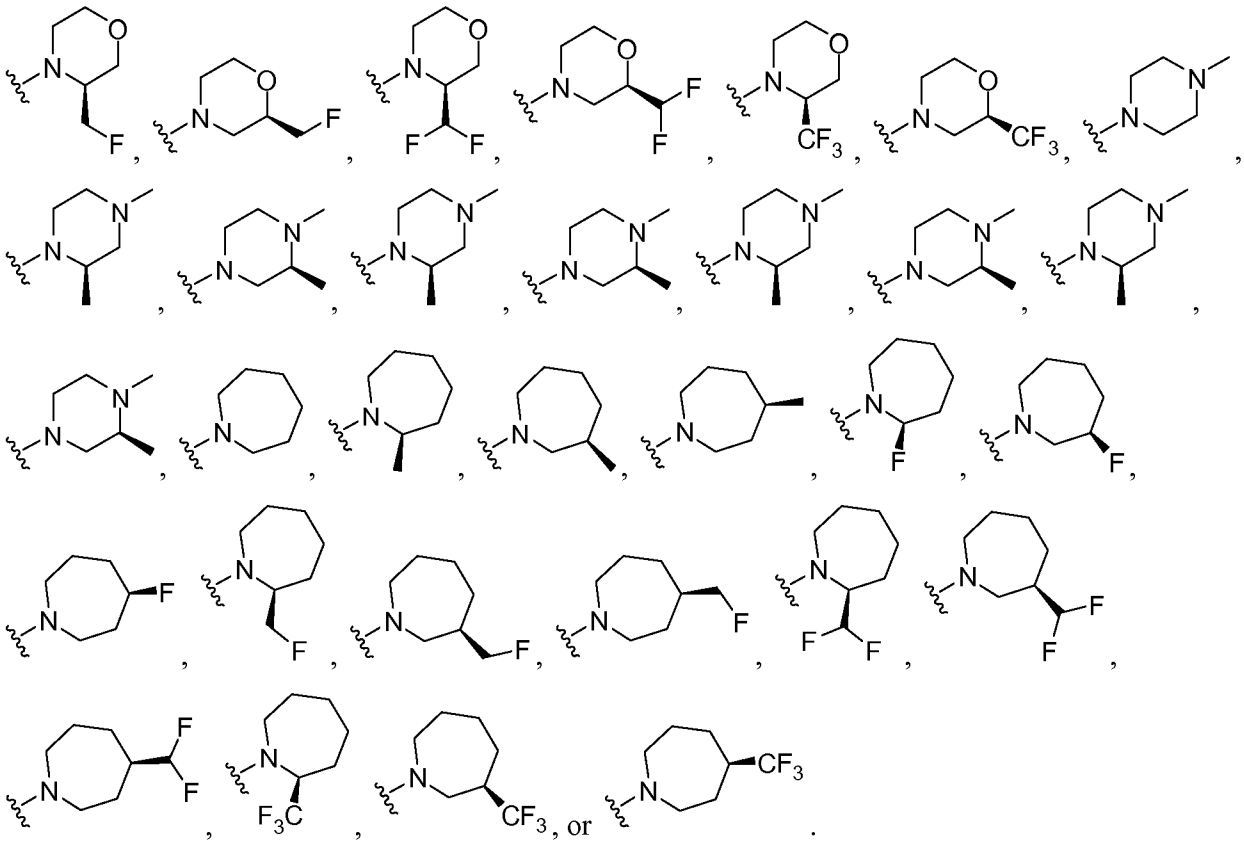
 ,

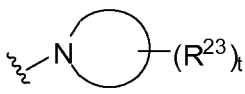
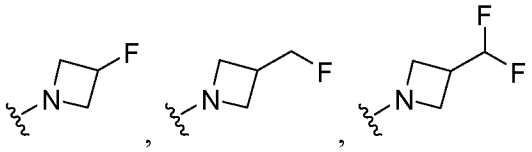
 ,

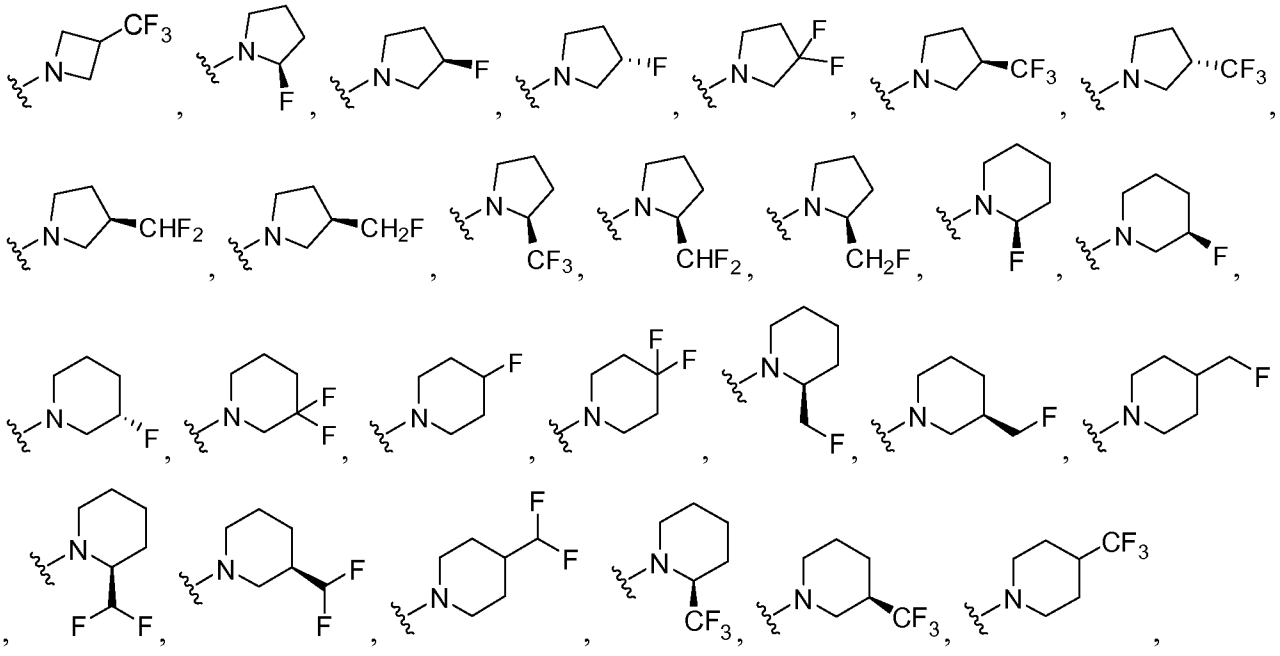
 ,

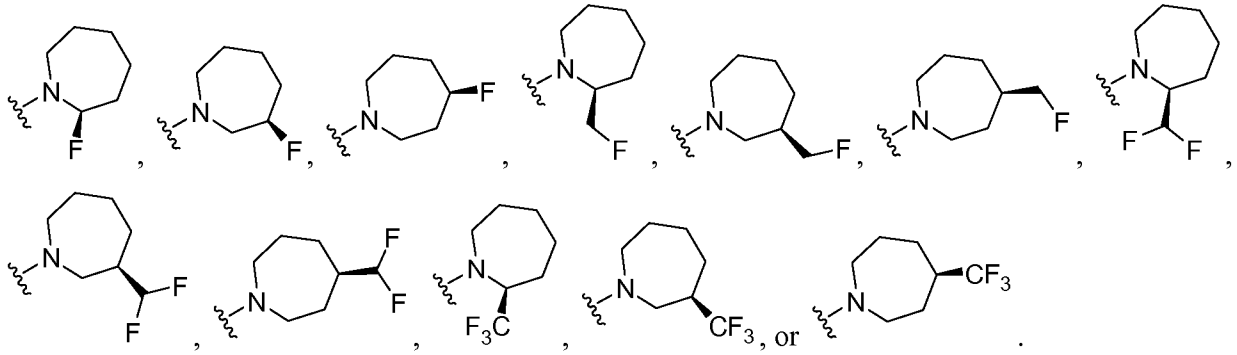
 ,

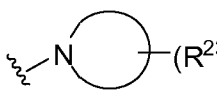
 ,

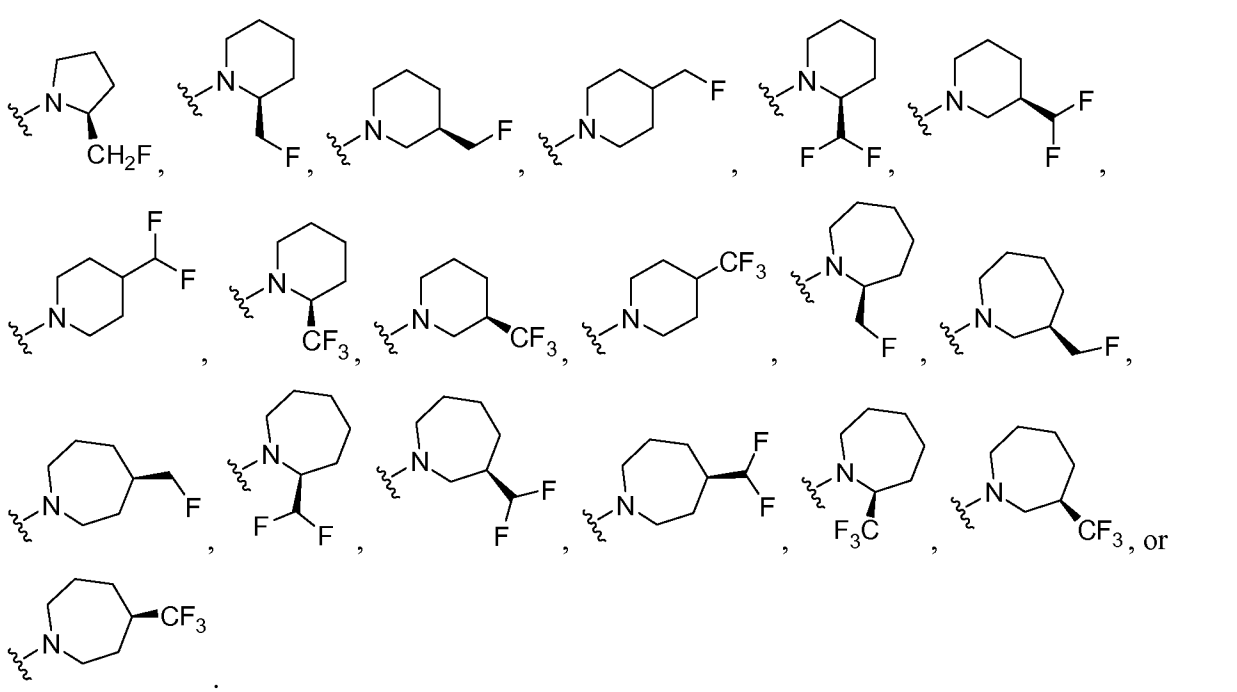


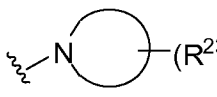
[00148] In some embodiments,  is 

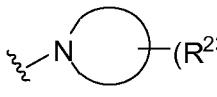
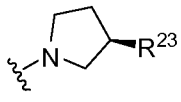




[00149] In some embodiments,  is



[00150] In some embodiments,  is

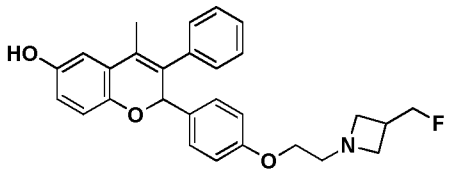
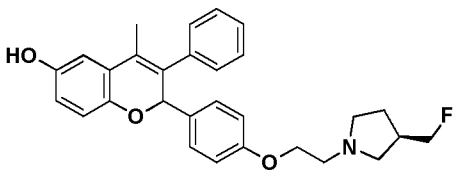
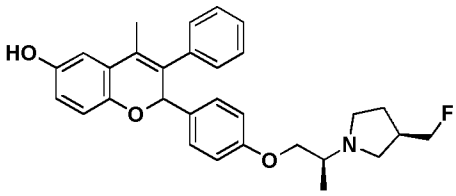
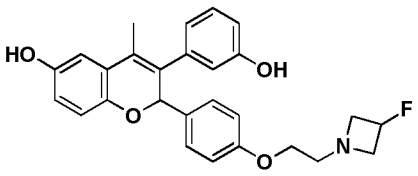
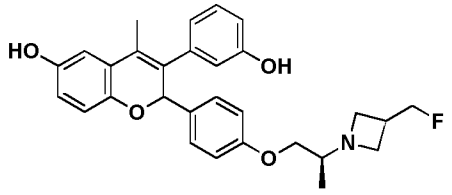
[00151] In some embodiments,  is  . In some embodiments, R^{23} is -CH_3. In some embodiments, R^{23} is –CH_2F.

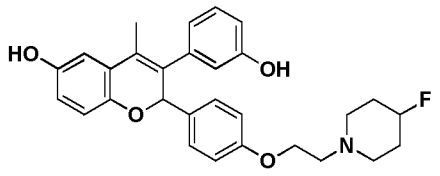
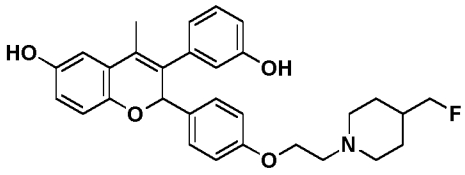
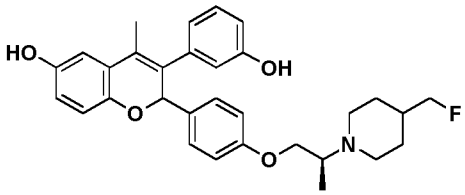
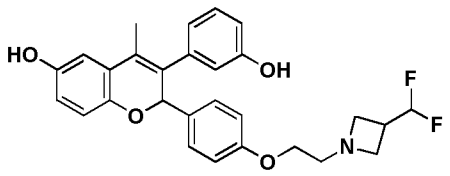
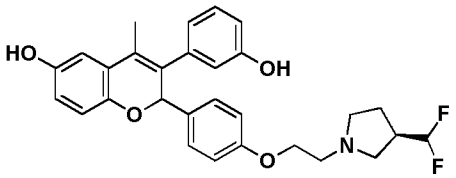
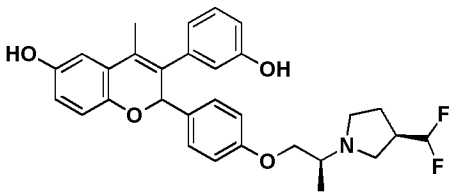
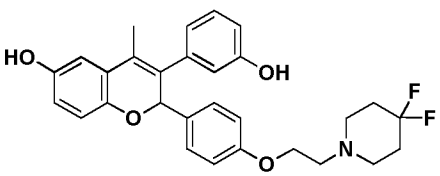
[00152] In some embodiments, R^2 and R^3 are taken together with the N atom to which they are attached to form substituted or unsubstituted pyrrolidinyl.

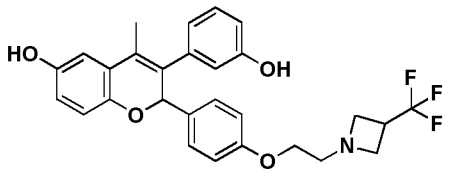
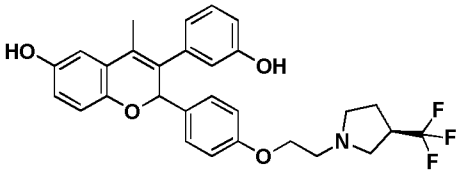
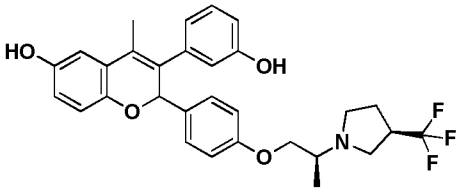
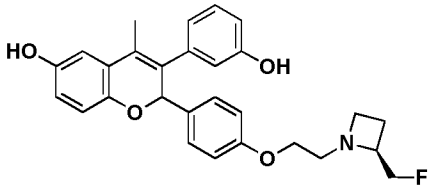
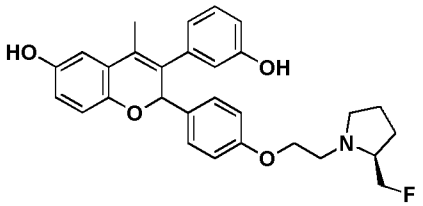
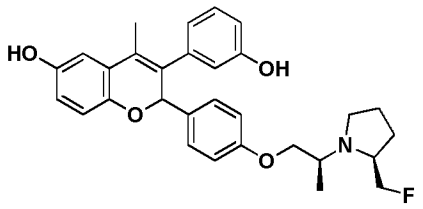
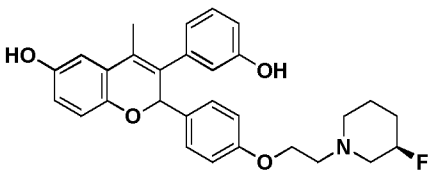
[00153] In some embodiments, R^1 is H or $-CH_3$; R^4 is $-CH_3$. In some embodiments, R^1 is $-CH_3$; R^4 is $-CH_3$.

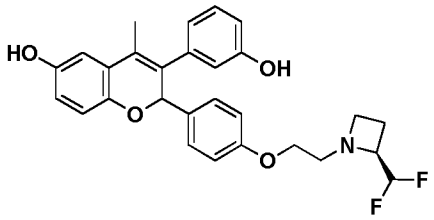
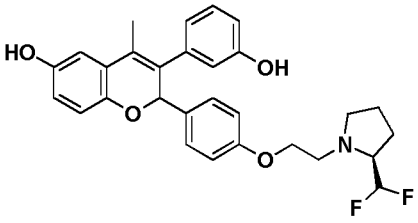
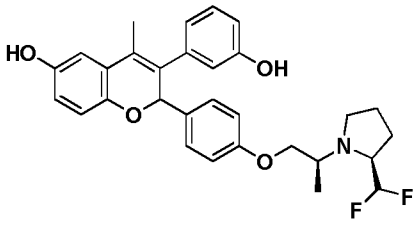
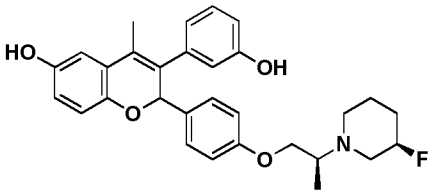
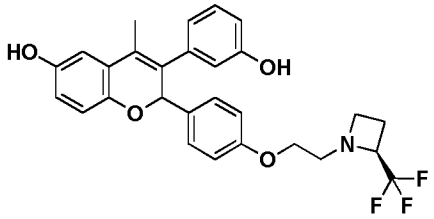
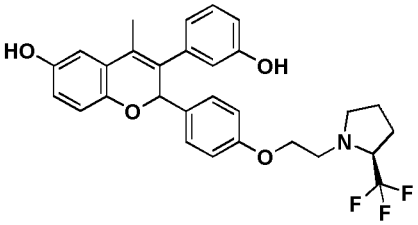
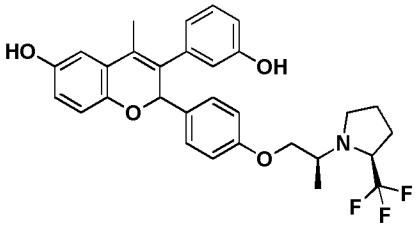
[00154] Compounds of Formula (I), (II), (III), or (IV), include, but are not limited to, compounds in the following table.

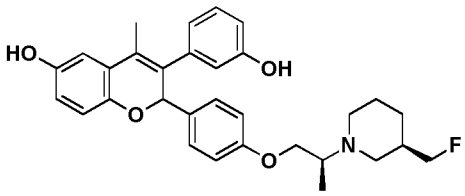
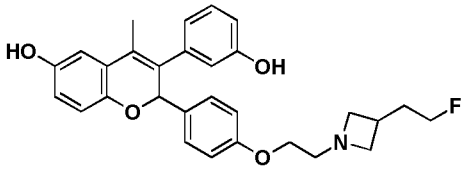
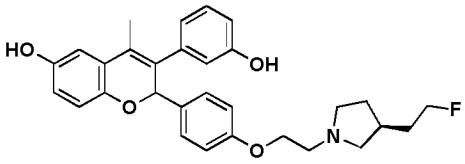
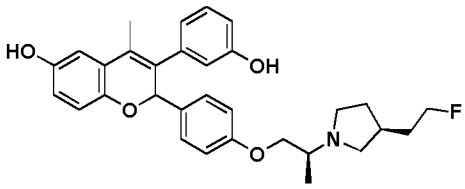
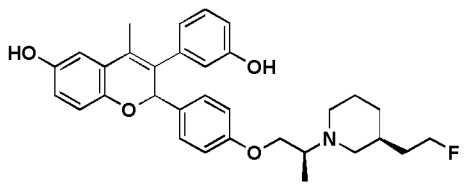
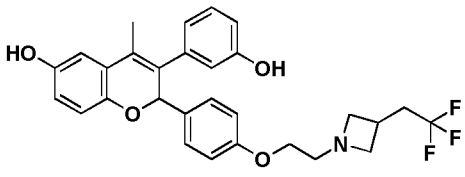
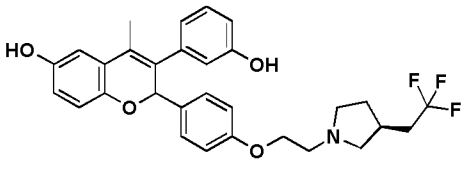
Table 1.

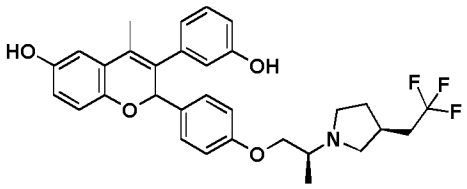
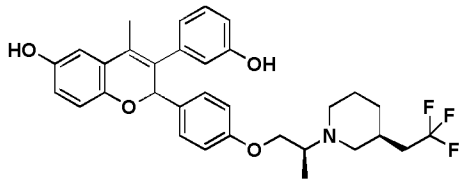
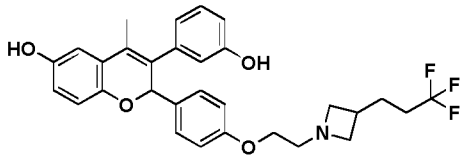
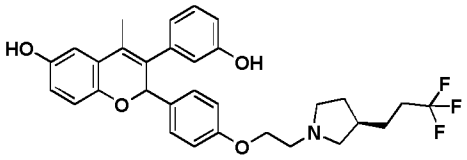
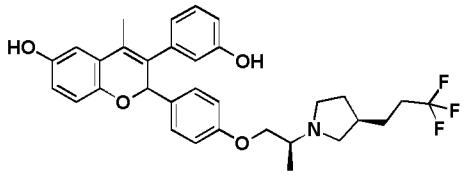
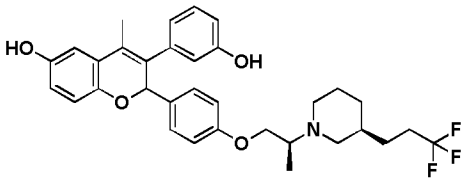
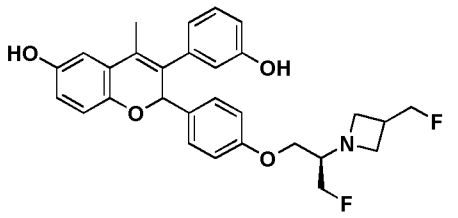
Structure	Name
	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-3-phenyl-2H-chromen-6-ol
	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-3-phenyl-2H-chromen-6-ol
	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-3-phenyl-2H-chromen-6-ol
	2-(4-(2-(3-fluoroazetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-(3-(fluoromethyl)azetidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

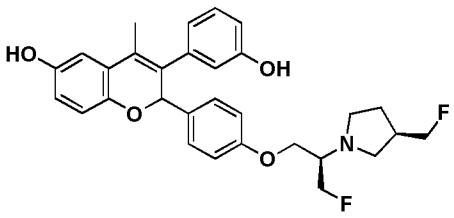
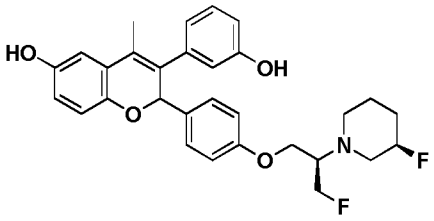
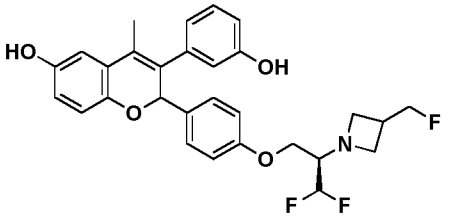
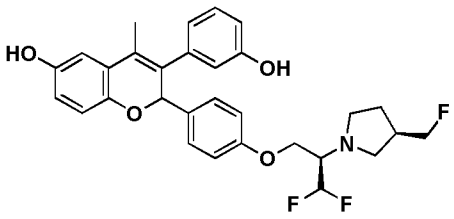
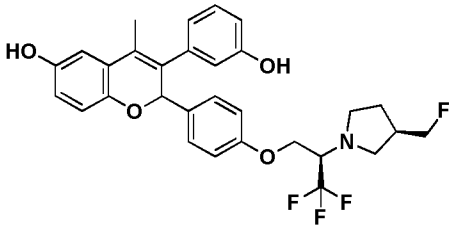
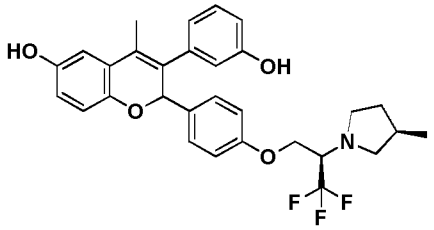
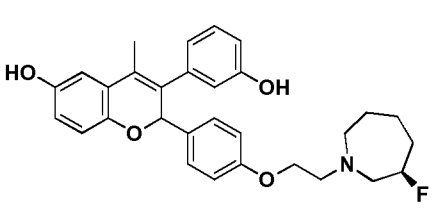
Structure	Name
	2-(4-(2-(4-fluoropiperidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(4-(fluoromethyl)piperidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-(4-(fluoromethyl)piperidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(3-(difluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((R)-3-(difluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((R)-3-(difluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(4,4-difluoropiperidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

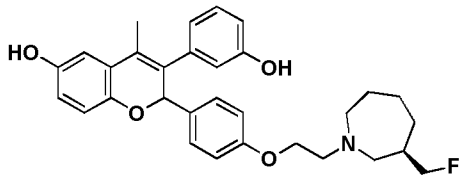
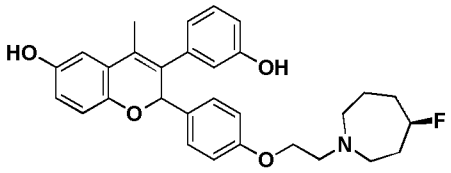
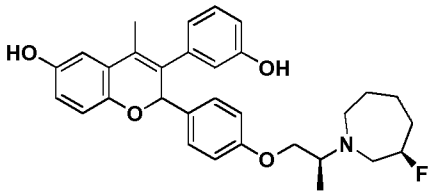
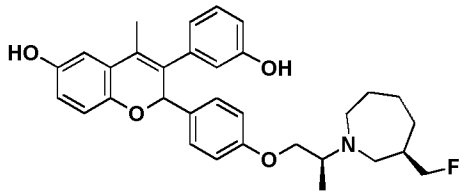
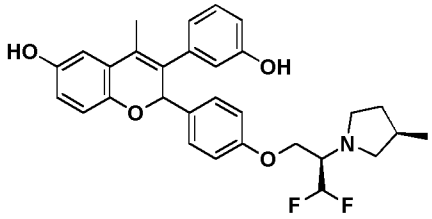
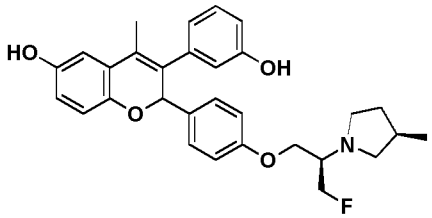
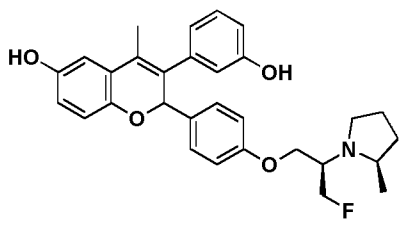
Structure	Name
	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-(3-(trifluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-((R)-3-(trifluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-(trifluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	2-(4-(2-((S)-2-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((S)-2-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((S)-2-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((R)-3-fluoropiperidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

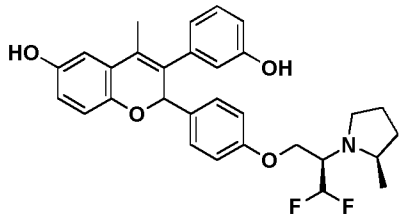
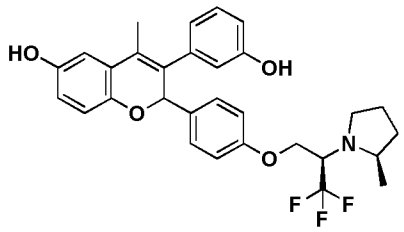
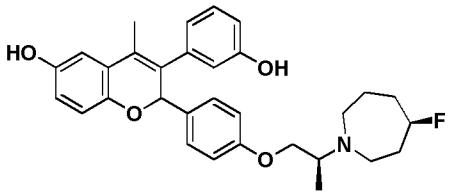
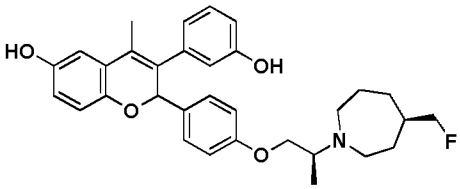
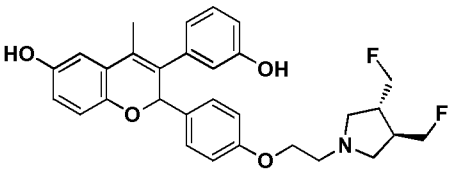
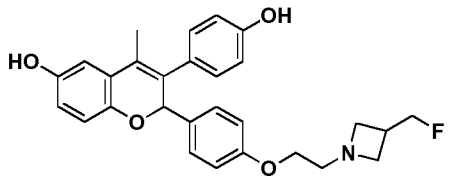
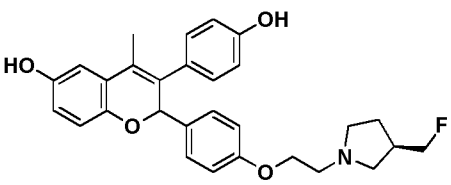
Structure	Name
	2-(4-(2-((S)-2-(difluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((S)-2-(difluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((S)-2-(difluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((R)-3-fluoropiperidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-((S)-2-(trifluoromethyl)azetidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-((S)-2-(trifluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((S)-2-(trifluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol

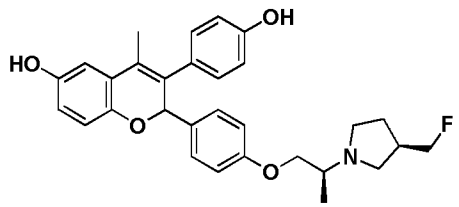
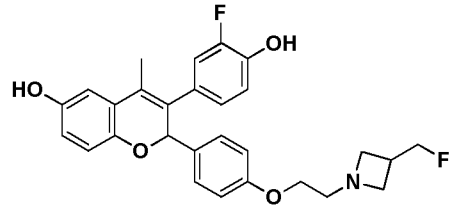
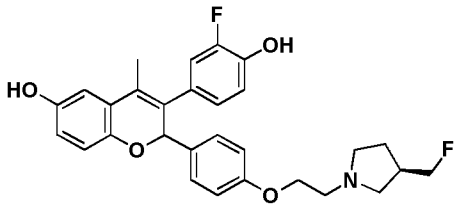
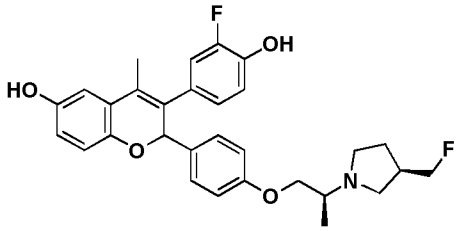
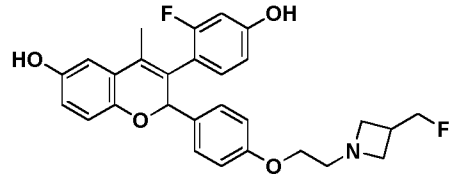
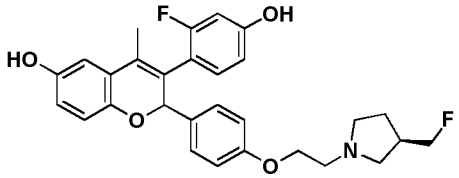
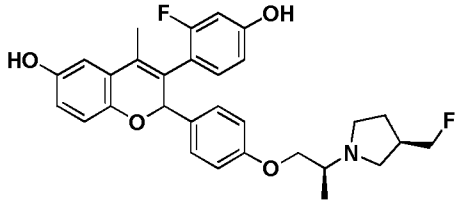
Structure	Name
	2-(4-((S)-2-((R)-3-(fluoromethyl)piperidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(3-(2-fluoroethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((S)-3-(2-fluoroethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((S)-3-(2-fluoroethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((S)-3-(2-fluoroethyl)piperidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-(3-(2,2,2-trifluoroethyl)azetidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-((S)-3-(2,2,2-trifluoroethyl)pyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol

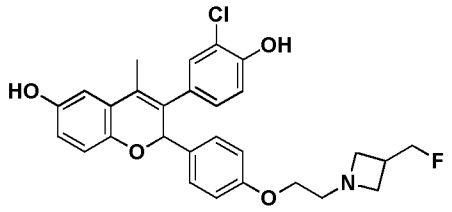
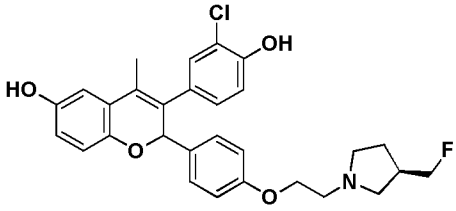
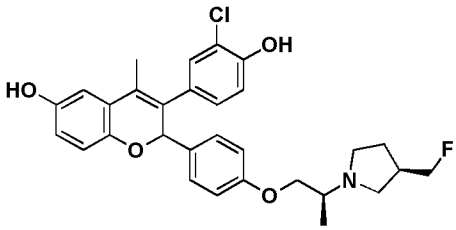
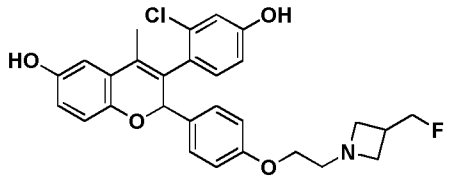
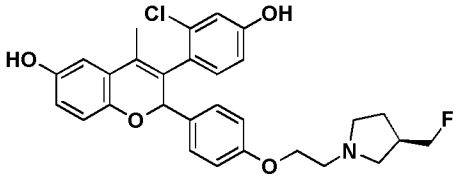
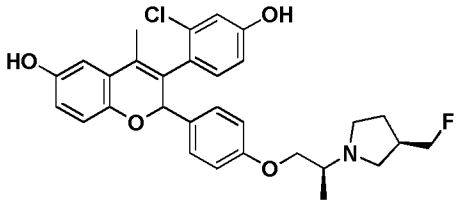
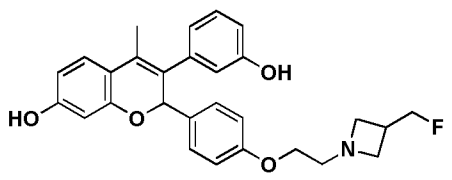
Structure	Name
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((S)-3-(2,2,2-trifluoroethyl)pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((S)-3-(2,2,2-trifluoroethyl)piperidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-(3-(3,3,3-trifluoropropyl)azetidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-(2-((R)-3-(3,3,3-trifluoropropyl)pyrrolidin-1-yl)ethoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((R)-3-(3,3,3-trifluoropropyl)pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((S)-3-(3,3,3-trifluoropropyl)piperidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	2-(4-((R)-3-fluoro-2-(3-(fluoromethyl)azetidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

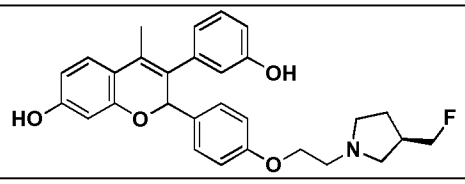
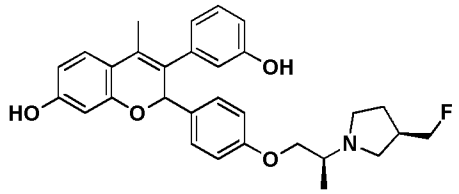
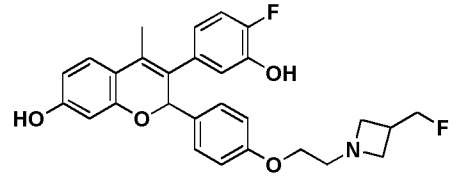
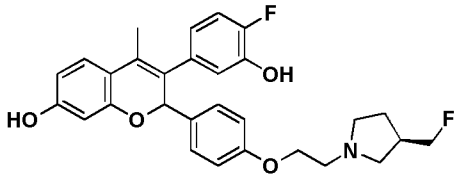
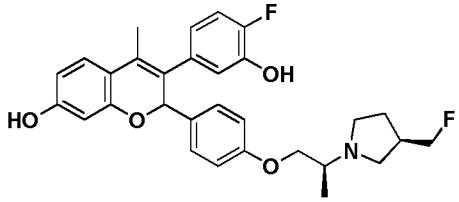
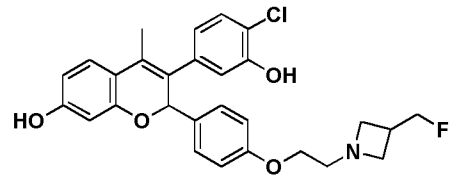
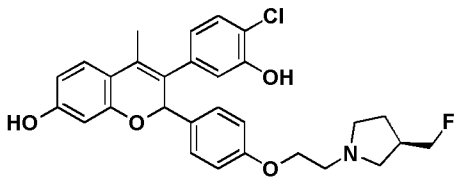
Structure	Name
	2-(4-((R)-3-fluoro-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((R)-3-fluoro-2-((R)-3-fluoropiperidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((R)-3,3-difluoro-2-(3-(fluoromethyl)azetidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((R)-3,3-difluoro-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((R)-3,3,3-trifluoro-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((R)-3,3,3-trifluoro-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	2-(4-(2-((R)-3-fluoroazepan-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

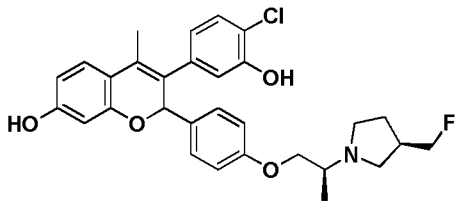
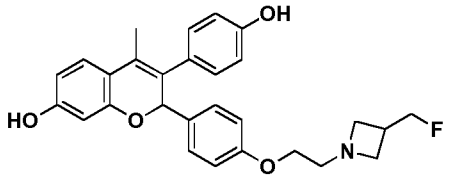
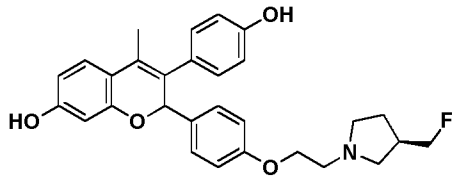
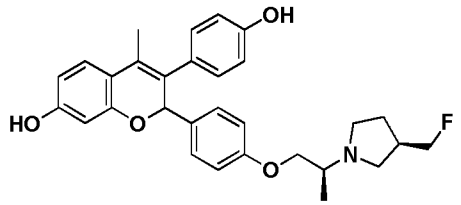
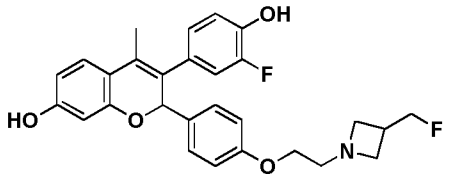
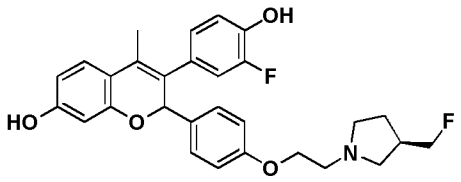
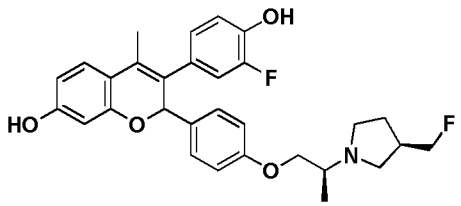
Structure	Name
	2-(4-(2-((R)-3-(fluoromethyl)azepan-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((R)-4-fluoroazepan-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((R)-3-fluoroazepan-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((R)-3-(fluoromethyl)azepan-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((R)-3,3-difluoro-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((R)-3-fluoro-2-((R)-3-methylpyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((R)-3-fluoro-2-((R)-2-methylpyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

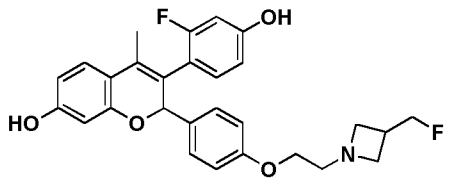
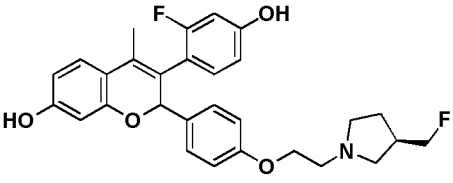
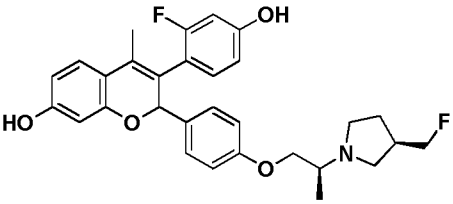
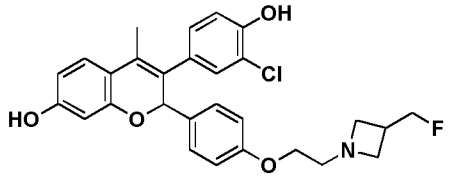
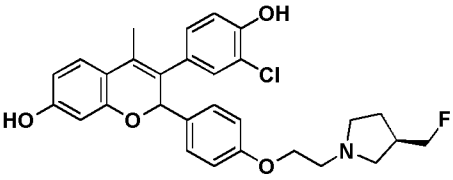
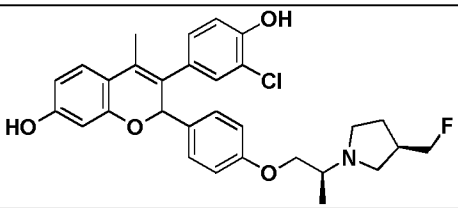
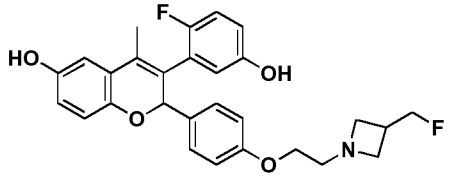
Structure	Name
	2-(4-((R)-3,3-difluoro-2-((R)-2-methylpyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((R)-3,3,3-trifluoro-2-((R)-2-methylpyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	2-(4-((S)-2-((R)-4-fluoroazepan-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((R)-4-(fluoromethyl)azepan-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((3R,4R)-3,4-bis(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(4-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(4-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

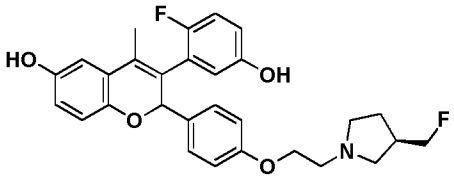
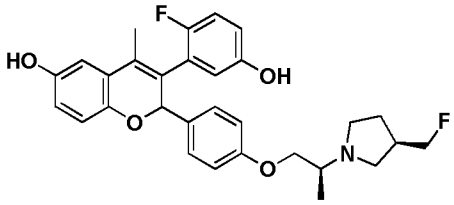
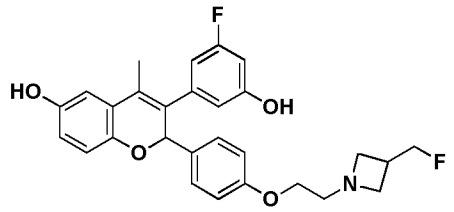
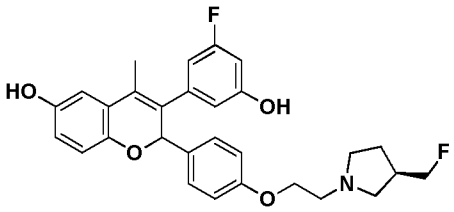
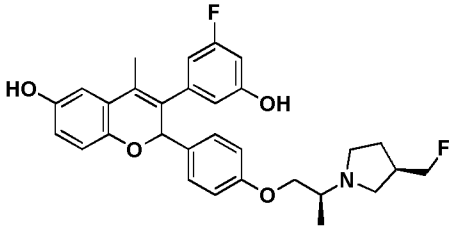
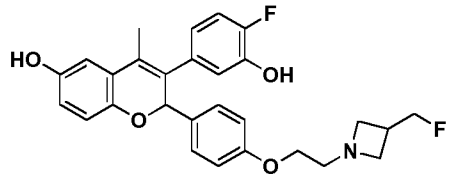
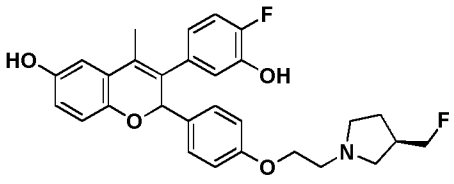
Structure	Name
	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(4-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	3-(3-fluoro-4-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-fluoro-4-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-fluoro-4-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-fluoro-4-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-fluoro-4-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-fluoro-4-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol

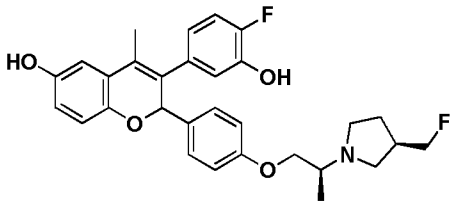
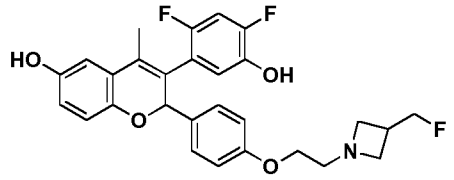
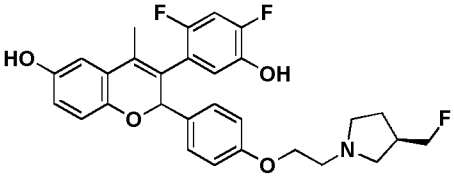
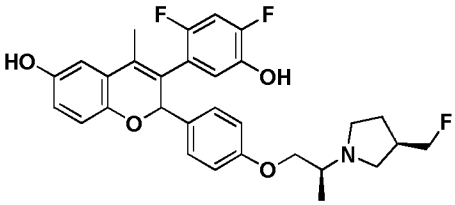
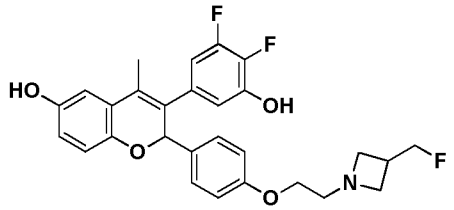
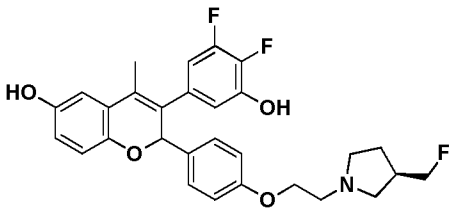
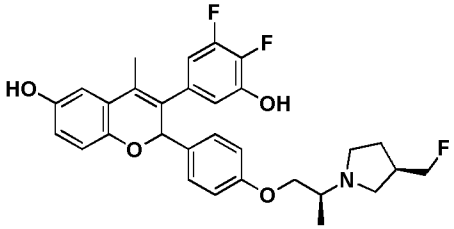
Structure	Name
	3-(3-chloro-4-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chloro-4-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chloro-4-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-chloro-4-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-chloro-4-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-chloro-4-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-7-ol

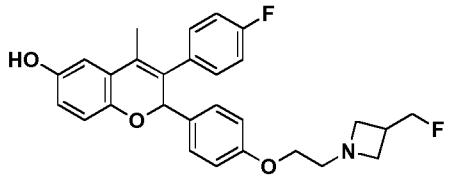
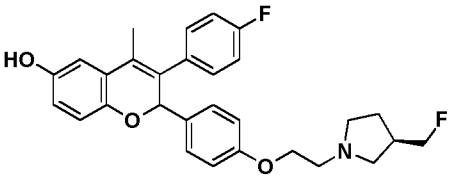
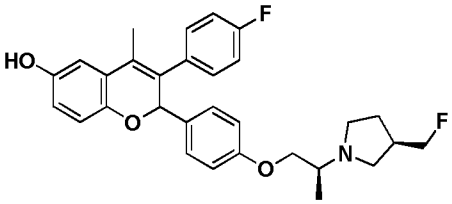
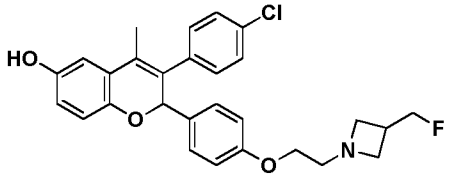
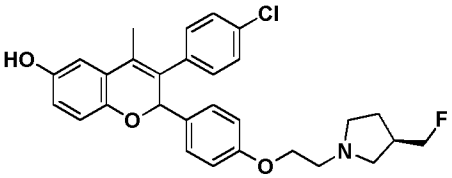
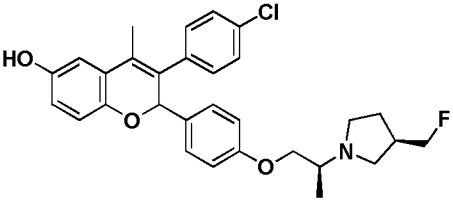
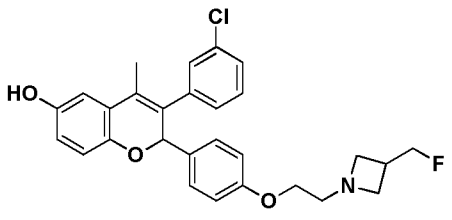
Structure	Name
	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-7-ol
	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-7-ol
	3-(4-fluoro-3-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(4-fluoro-3-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(4-fluoro-3-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(4-chloro-3-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(4-chloro-3-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol

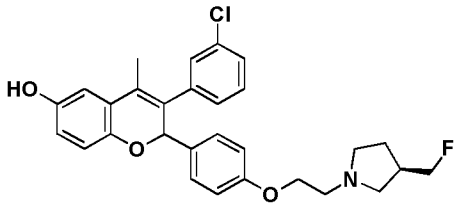
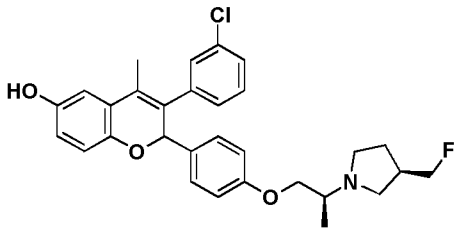
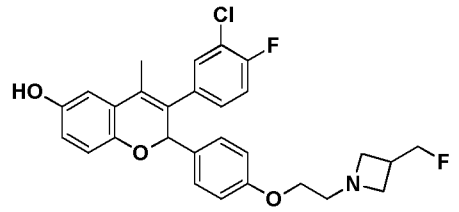
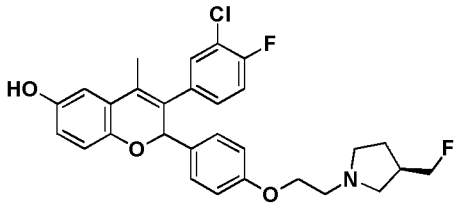
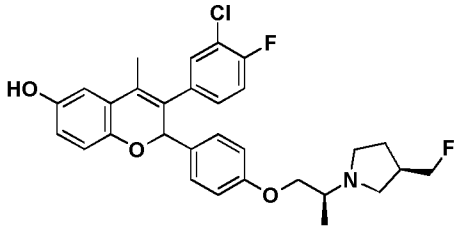
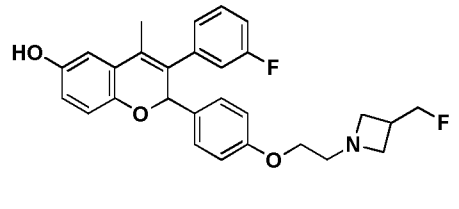
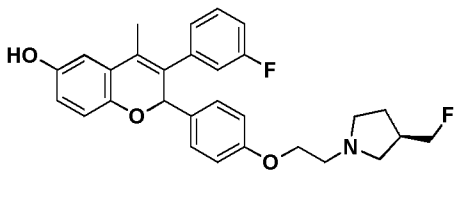
Structure	Name
	3-(4-chloro-3-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-7-ol
	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(4-hydroxyphenyl)-4-methyl-2H-chromen-7-ol
	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(4-hydroxyphenyl)-4-methyl-2H-chromen-7-ol
	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(4-hydroxyphenyl)-4-methyl-2H-chromen-7-ol
	3-(3-fluoro-4-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(3-fluoro-4-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(3-fluoro-4-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-7-ol

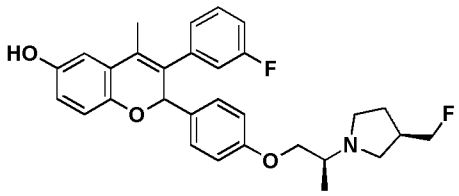
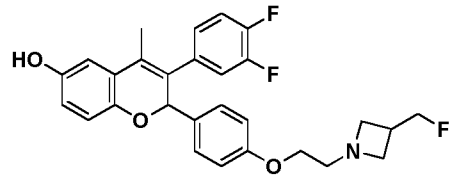
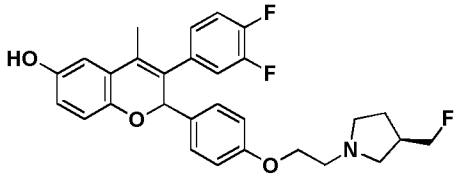
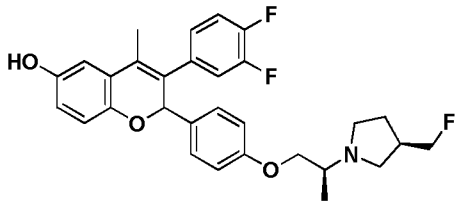
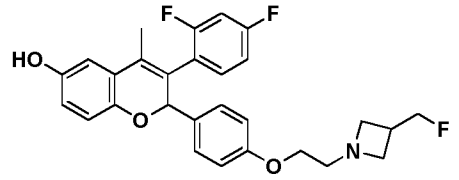
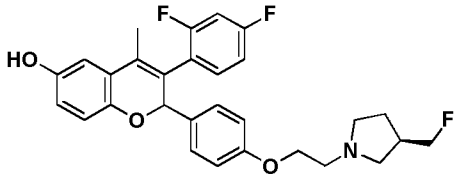
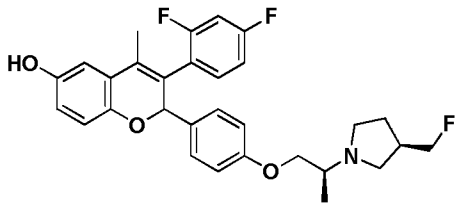
Structure	Name
	3-(2-fluoro-4-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(2-fluoro-4-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(2-fluoro-4-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(3-chloro-4-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(3-chloro-4-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(3-chloro-4-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-7-ol
	3-(2-fluoro-5-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol

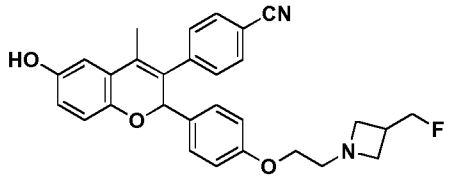
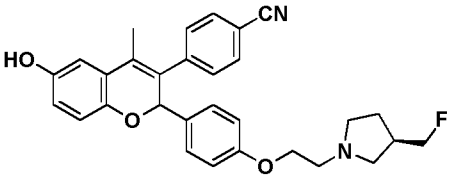
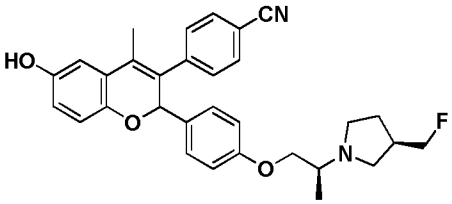
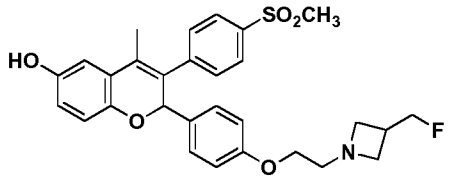
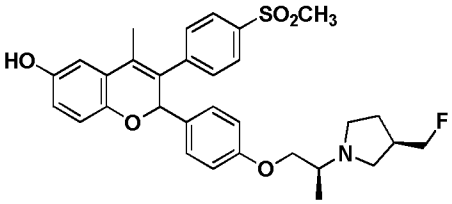
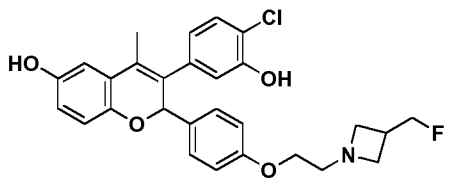
Structure	Name
	3-(2-fluoro-5-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-fluoro-5-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-fluoro-5-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-fluoro-5-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-fluoro-5-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(4-fluoro-3-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(4-fluoro-3-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol

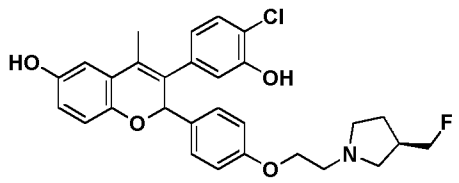
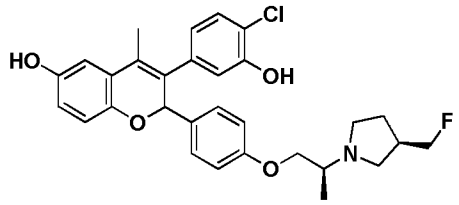
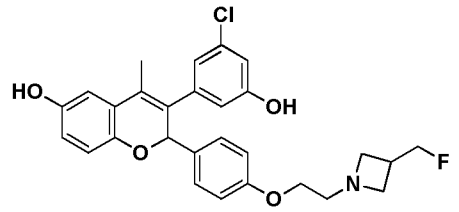
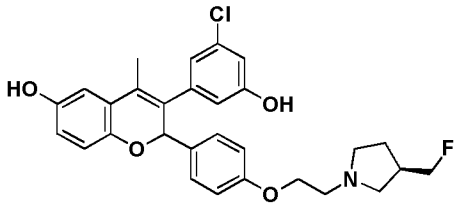
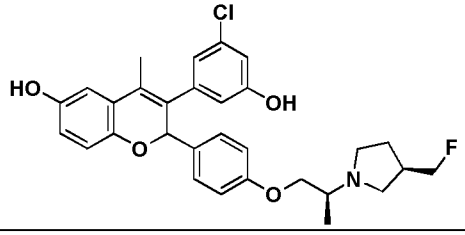
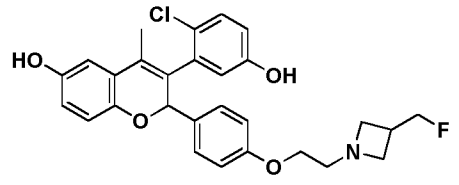
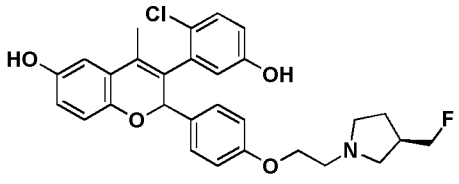
Structure	Name
	3-(4-fluoro-3-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2,4-difluoro-5-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2,4-difluoro-5-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2,4-difluoro-5-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3,4-difluoro-5-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3,4-difluoro-5-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3,4-difluoro-5-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol

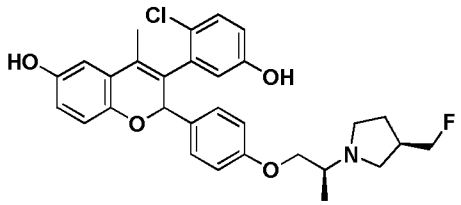
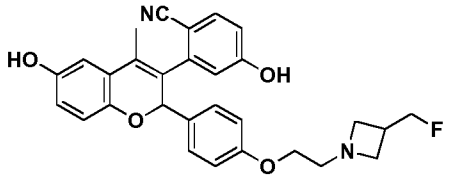
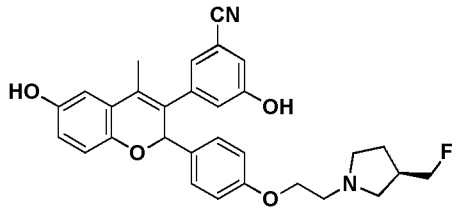
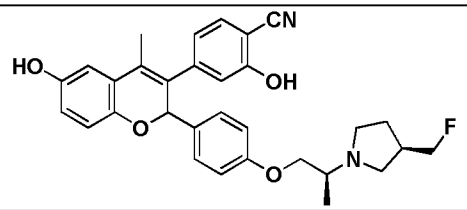
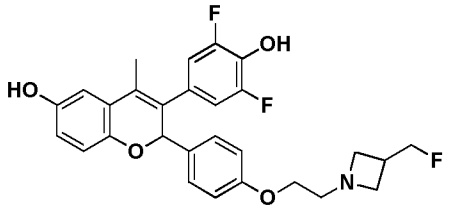
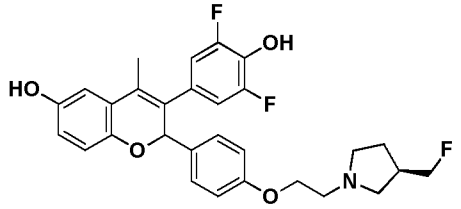
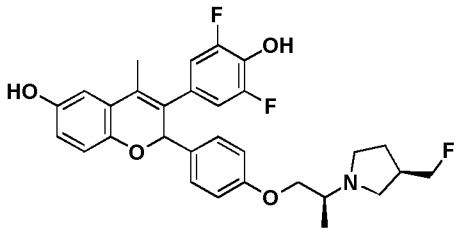
Structure	Name
	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol
	3-(4-chlorophenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(4-chlorophenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(4-chlorophenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chlorophenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol

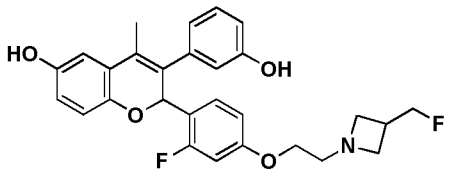
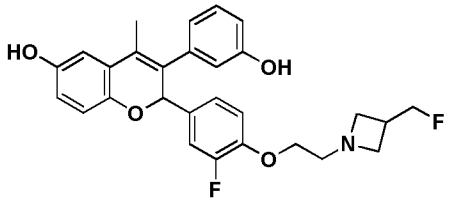
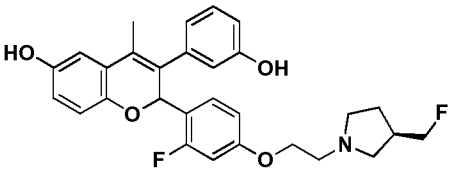
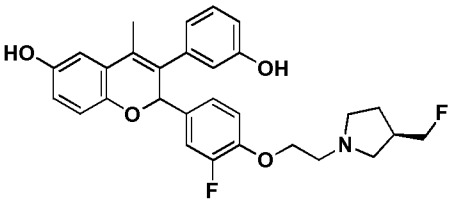
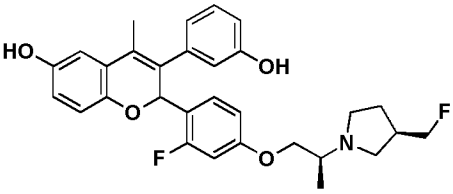
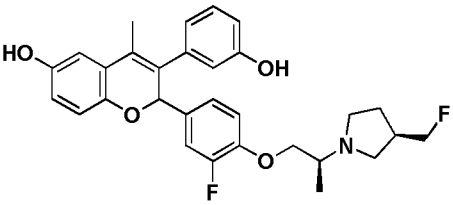
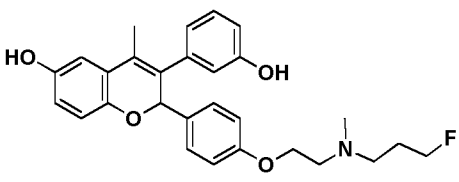
Structure	Name
	3-(3-chlorophenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chlorophenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chloro-4-fluorophenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chloro-4-fluorophenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chloro-4-fluorophenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-fluorophenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-fluorophenyl)-4-methyl-2H-chromen-6-ol

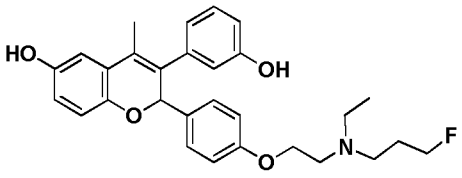
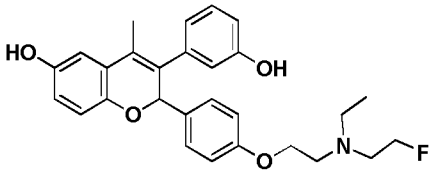
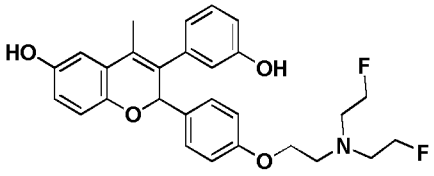
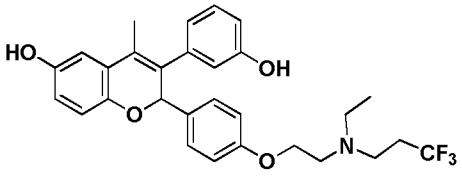
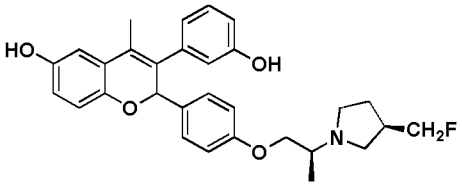
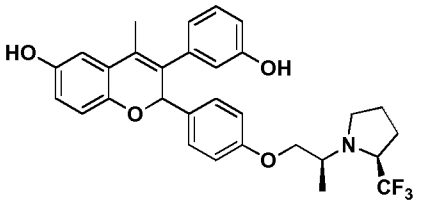
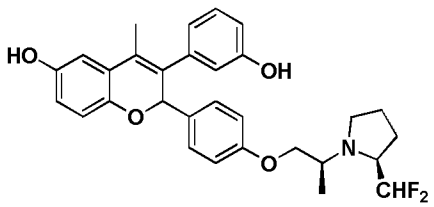
Structure	Name
	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-fluorophenyl)-4-methyl-2H-chromen-6-ol
	3-(3,4-difluorophenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3,4-difluorophenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3,4-difluorophenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2,4-difluorophenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2,4-difluorophenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2,4-difluorophenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol

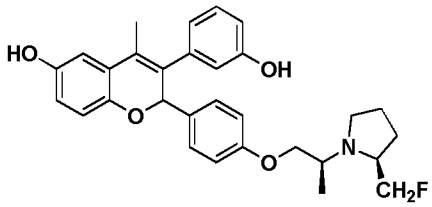
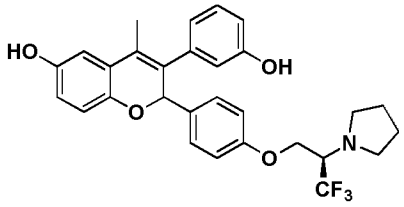
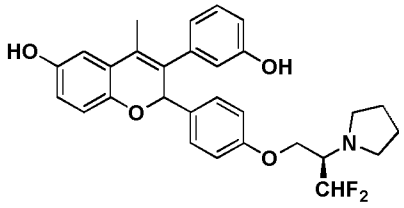
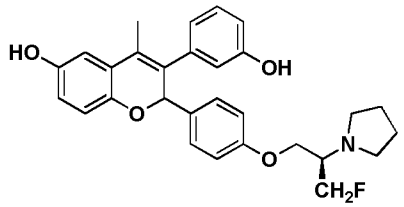
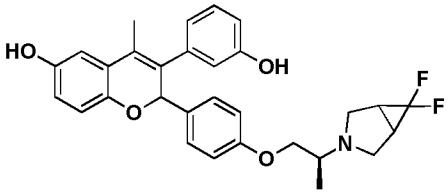
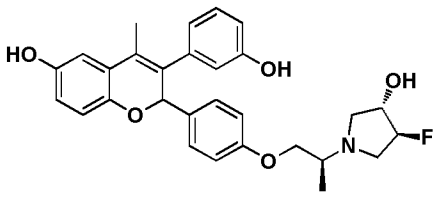
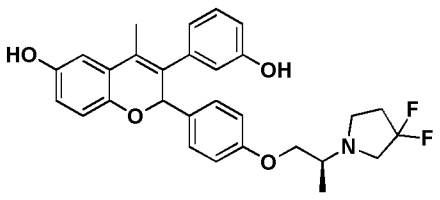
Structure	Name
	4-(2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)benzonitrile
	4-(2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)benzonitrile
	4-(2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)benzonitrile
	2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2H-chromen-6-ol
	2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2H-chromen-6-ol
	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-3-(4-(methylsulfonyl)phenyl)-2H-chromen-6-ol
	3-(4-chloro-3-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol

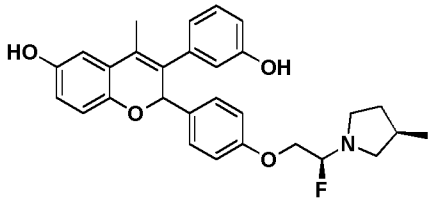
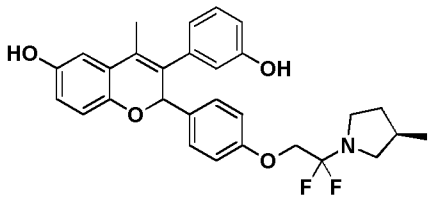
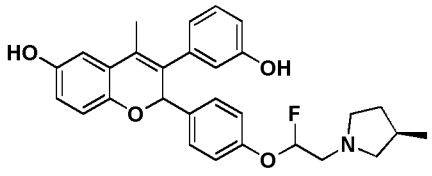
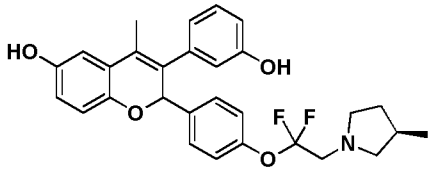
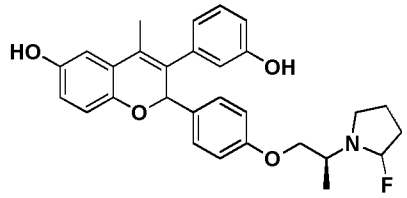
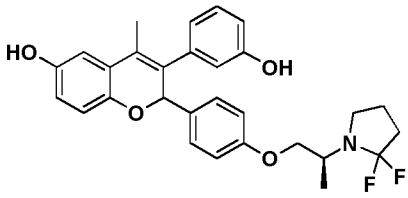
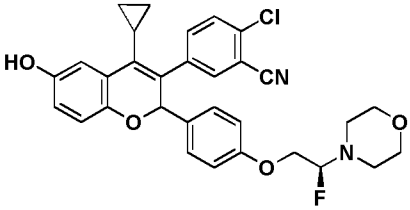
Structure	Name
	3-(4-chloro-3-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(4-chloro-3-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chloro-5-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chloro-5-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-chloro-5-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-chloro-5-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-chloro-5-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol

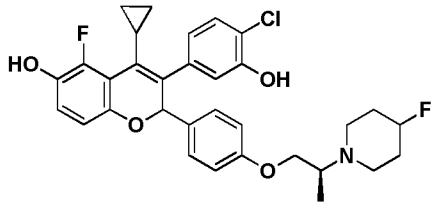
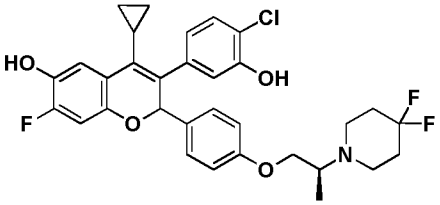
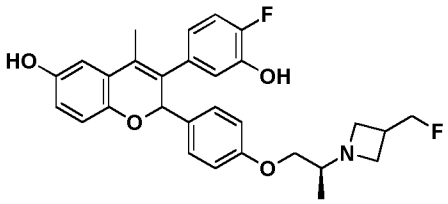
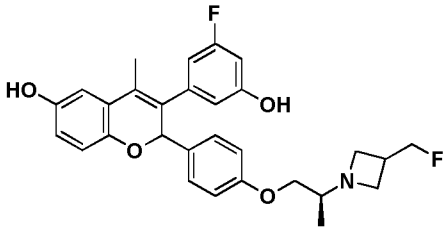
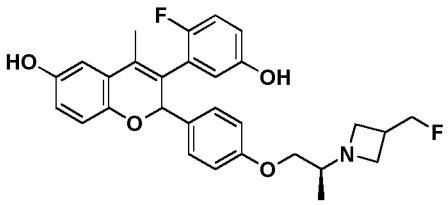
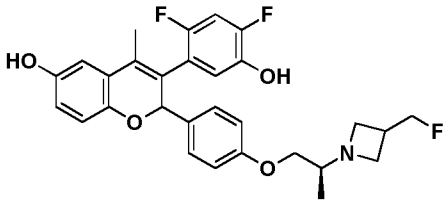
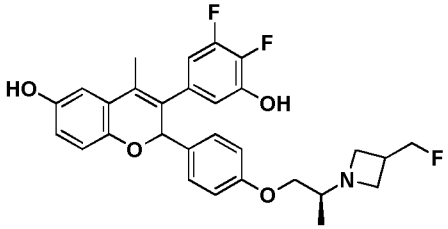
Structure	Name
	3-(2-chloro-5-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	2-(2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)-4-hydroxybenzonitrile
	3-(2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)-5-hydroxybenzonitrile
	4-(2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)-2-hydroxybenzonitrile
	3-(3,5-difluoro-4-hydroxyphenyl)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3,5-difluoro-4-hydroxyphenyl)-2-(4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3,5-difluoro-4-hydroxyphenyl)-2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol

Structure	Name
	2-(2-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(3-fluoro-4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(2-fluoro-4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(3-fluoro-4-(2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(2-fluoro-4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(3-fluoro-4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-((3-fluoropropyl)(methyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

Structure	Name
	2-(4-(2-(ethyl(3-fluoropropyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(ethyl(2-fluoroethyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(bis(2-fluoroethyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2-(ethyl(3,3,3-trifluoropropyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-((R)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((S)-2-((S)-2-(trifluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	2-(4-((S)-2-((S)-2-(difluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

Structure	Name
	2-(4-((S)-2-((S)-2-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	3-(3-hydroxyphenyl)-4-methyl-2-(4-((R)-3,3,3-trifluoro-2-(pyrrolidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	2-(4-((R)-3,3-difluoro-2-(pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((R)-3-fluoro-2-(pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((2S)-2-(6,6-difluoro-3-azabicyclo[3.1.0]hexan-3-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	(3S,4S)-4-fluoro-1-((2S)-1-(4-(6-hydroxy-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-2-yl)phenoxy)propan-2-yl)pyrrolidin-3-ol
	2-(4-((S)-2-(3,3-difluoropyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

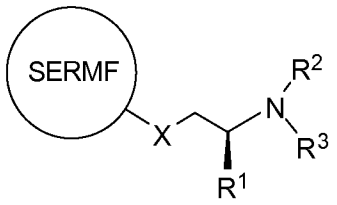
Structure	Name
	2-(4-((S)-2-fluoro-2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(2,2-difluoro-2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(1-fluoro-2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-(1,1-difluoro-2-((R)-3-methylpyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((2S)-2-(2-fluoropyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-(4-((S)-2-(2,2-difluoropyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol
	2-chloro-5-(4-cyclopropyl-2-(4-((S)-2-fluoro-2-morpholinoethoxy)phenyl)-6-hydroxy-2H-chromen-3-yl)benzonitrile

Structure	Name
	3-(4-chloro-3-hydroxyphenyl)-4-cyclopropyl-5-fluoro-2-(4-((S)-2-(4-fluoropiperidin-1-yl)propoxy)phenyl)-2H-chromen-6-ol
	3-(4-chloro-3-hydroxyphenyl)-4-cyclopropyl-2-(4-((S)-2-(4,4-difluoropiperidin-1-yl)propoxy)phenyl)-7-fluoro-2H-chromen-6-ol
	3-(4-fluoro-3-hydroxyphenyl)-2-(4-((S)-2-(3-(fluoromethyl)azetidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3-fluoro-5-hydroxyphenyl)-2-(4-((S)-2-(3-(fluoromethyl)azetidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2-fluoro-5-hydroxyphenyl)-2-(4-((S)-2-(3-(fluoromethyl)azetidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(2,4-difluoro-5-hydroxyphenyl)-2-(4-((S)-2-(3-(fluoromethyl)azetidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol
	3-(3,4-difluoro-5-hydroxyphenyl)-2-(4-((S)-2-(3-(fluoromethyl)azetidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol

[00155] In some embodiments, any one of the 2H-chromene compounds described herein exists as a racemic mixture with respect to the stereochemistry at the 2-position of the 2H-chromene compound. In other embodiments any one of the 2H-chromene compounds described herein exists as a single stereoisomer with respect to the stereochemistry at the 2-position of the 2H-chromene compound. In some embodiments, any one of the 2H-chromene compounds described herein exists as a (S)-isomer with respect to the stereochemistry at the 2-position of the 2H-chromene compound. In some other embodiments, any one of the 2H-chromene compounds described herein exists as a (R)-isomer with respect to the stereochemistry at the 2-position of the 2H-chromene compound.

[00156] In some embodiments, a pharmaceutically acceptable salt of a compound of Formula (I), (II), (III), or (IV) includes a pharmaceutically acceptable salt of any one of the compound in the preceding table of compounds.

[00157] In another aspect, described herein is a compound with the structure of Formula (V), or a pharmaceutically acceptable salt thereof:



Formula (V)

wherein

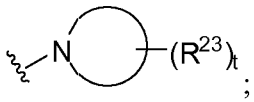
SEMF is a selective estrogen receptor modulator fragment;

R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

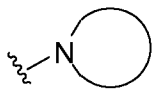
R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form



;



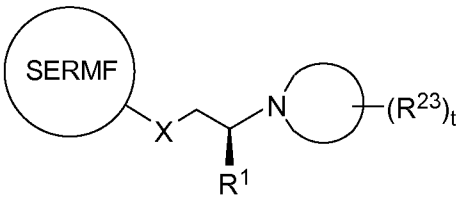
is a monocyclic C_2-C_6heterocycloalkyl;

each R^{23} is independently C_1-C_6fluoroalkyl, or F;

t is 1, 2, 3, or 4;

X is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -C(=O)-, -CH_2-, -NH- or –N(C_1-C_6alkyl)-.

[00158] In another aspect, described herein is a compound with the following structure of Formula (VI), or a pharmaceutically acceptable salt thereof:

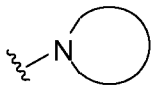


Formula (VI)

wherein,

SEMF is a selective estrogen receptor modulator fragment;

R^1 is C_1-C_6fluoroalkyl;

 is a monocyclic C_2-C_{10}heterocycloalkyl;

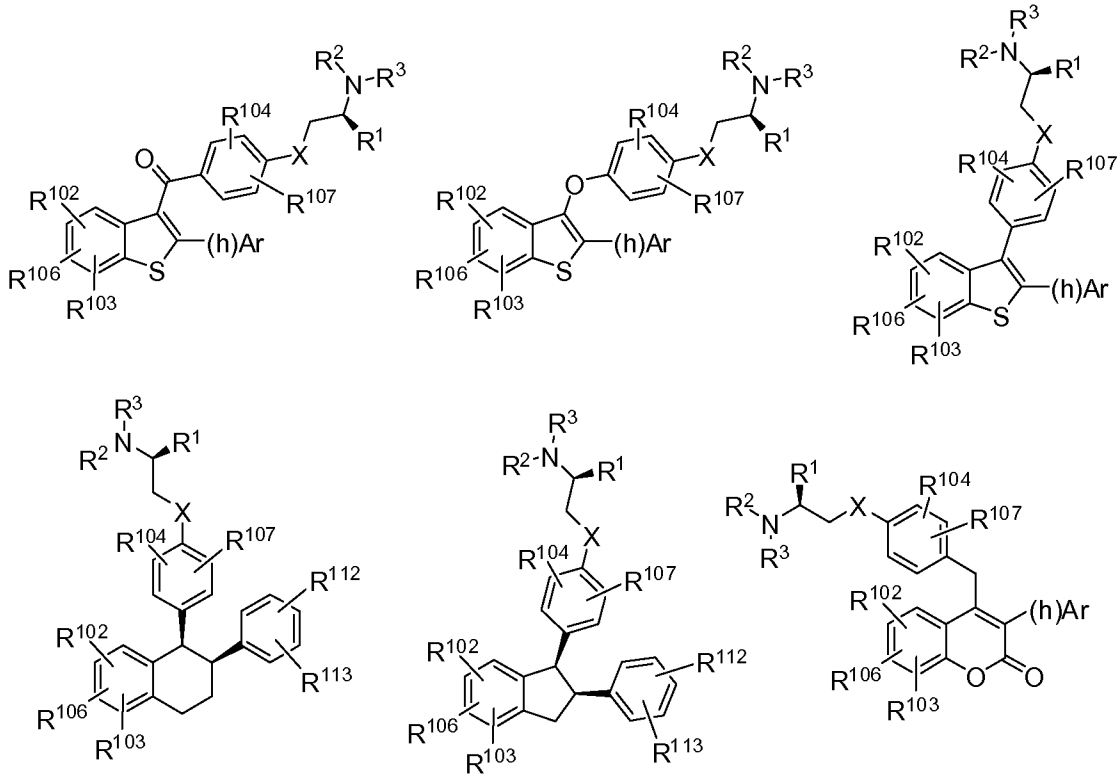
each R^{23} is independently F, C_1-C_6alkyl or C_1-C_6fluoroalkyl;

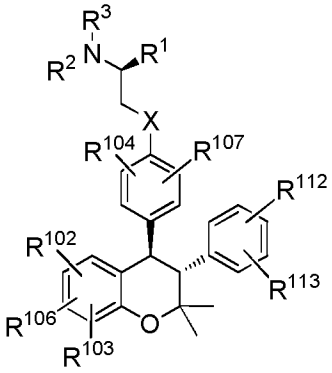
t is 0, 1, 2, 3, or 4;

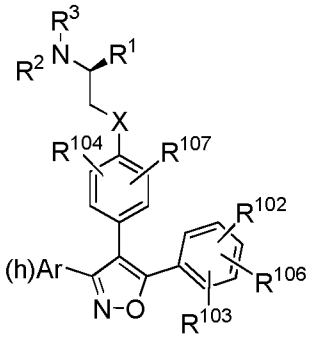
X is absent, -O-, -S-, -S(=O)-, -S(=O)$_2$-, -C(=O)-, -CH_2-, -NH- or –N(C_1-C_6alkyl)-.

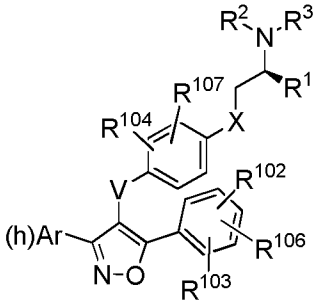
[00159] In some embodiments, X is absent, O, S, -CH_2-, -C(=O)-, -NH-, or –N(C_1-C_4alkyl)-. In some other embodiments, X is O.

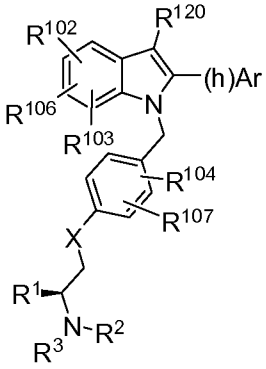
[00160] In some embodiments, the compound of Formula (V) has one of the following structures:

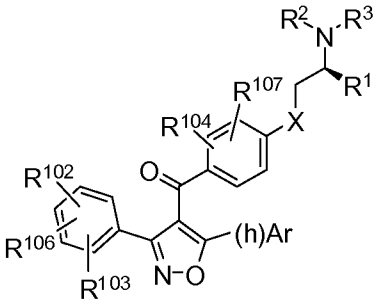


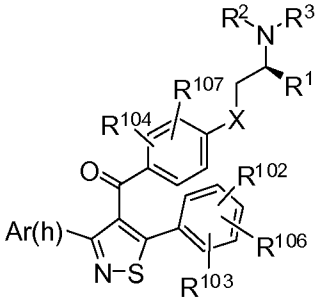


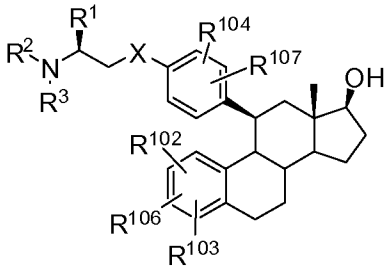


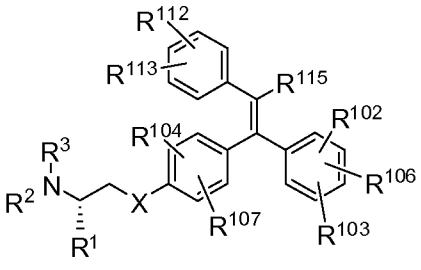


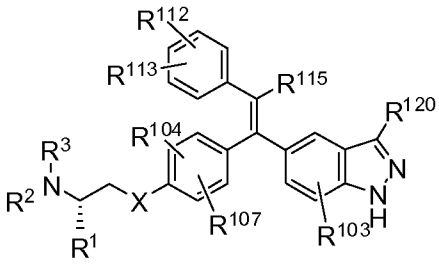


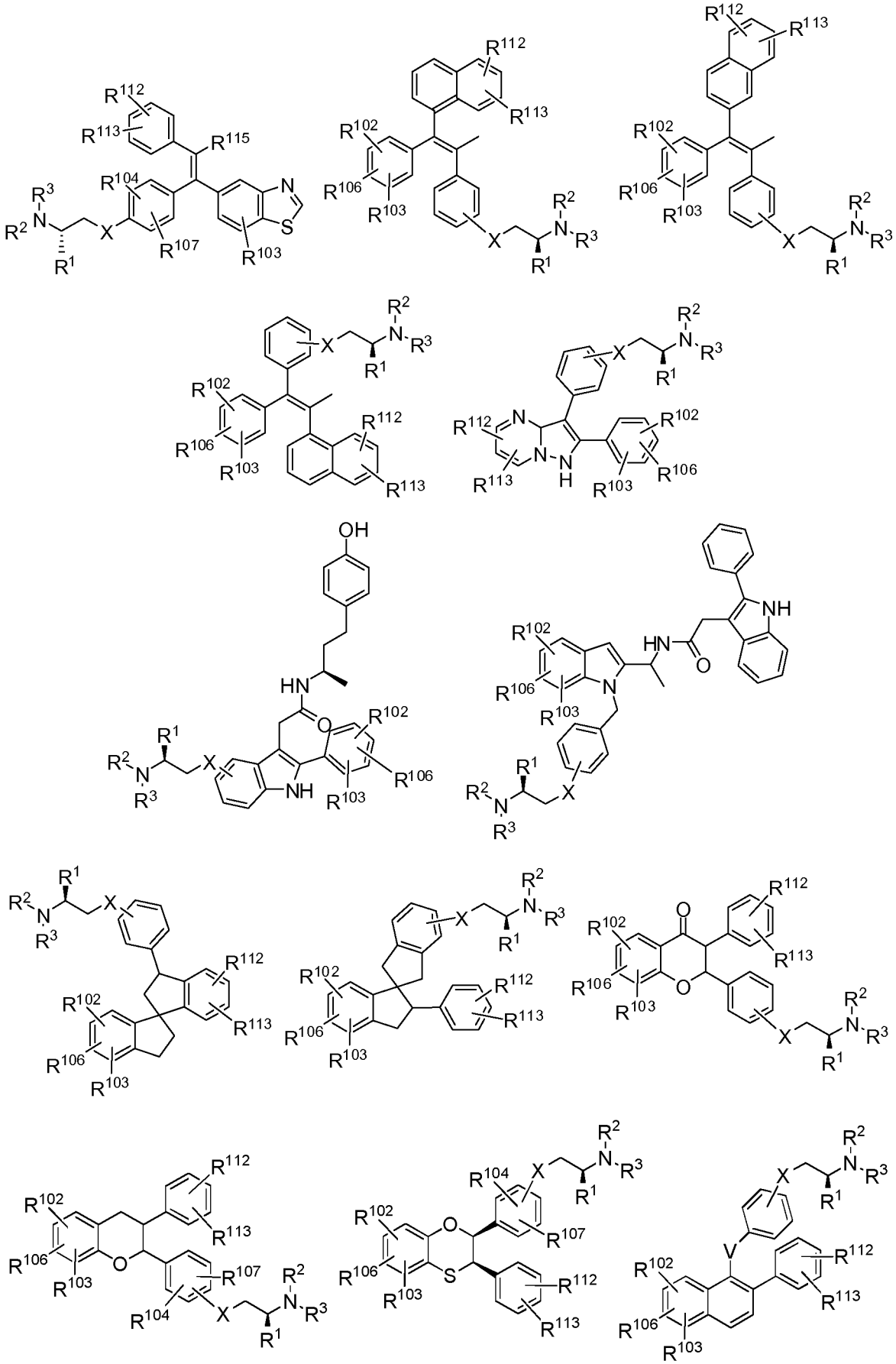


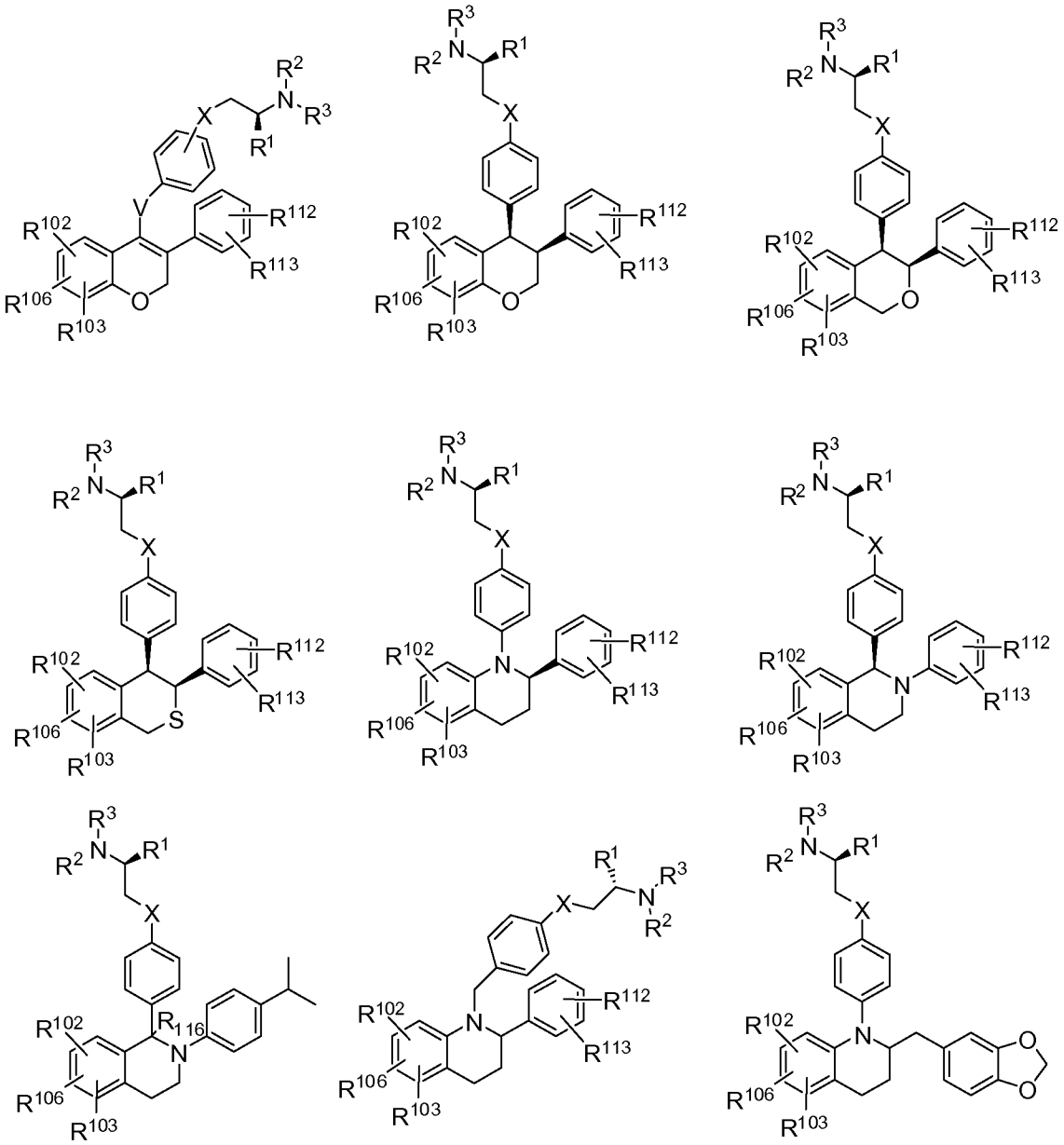


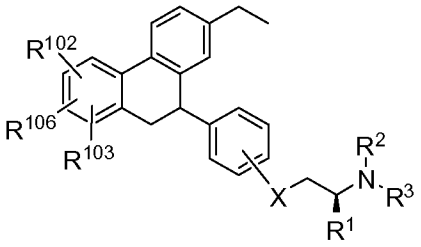
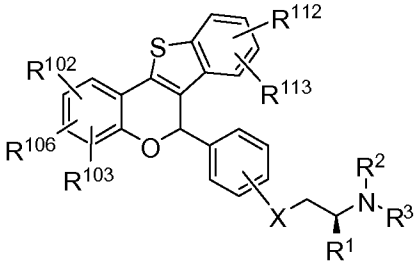
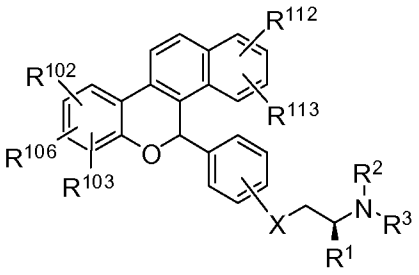
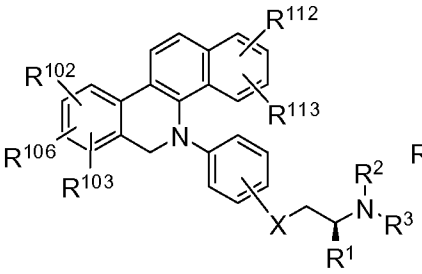
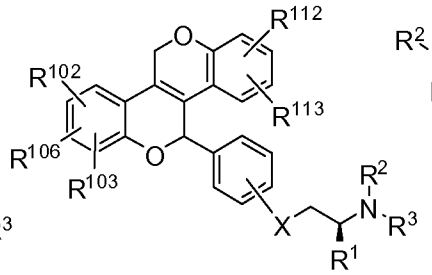
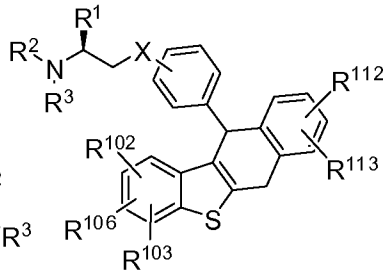
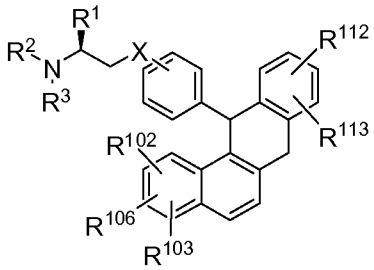
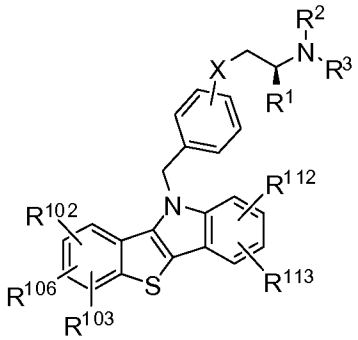
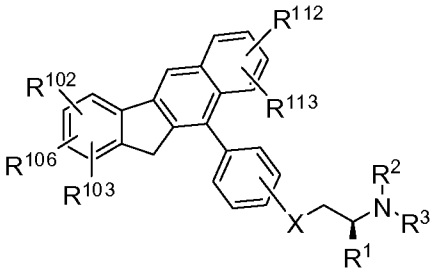
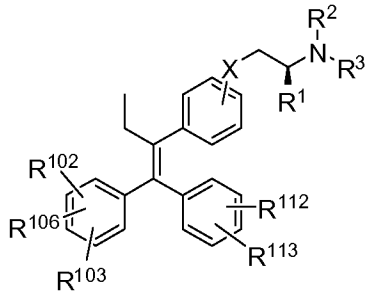
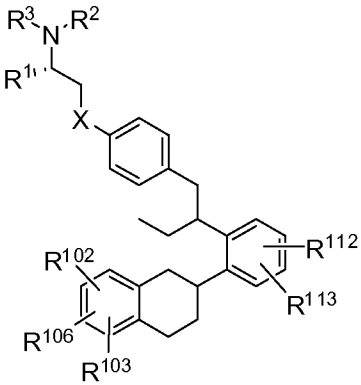
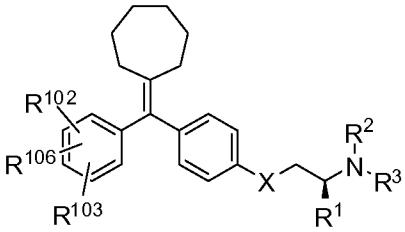


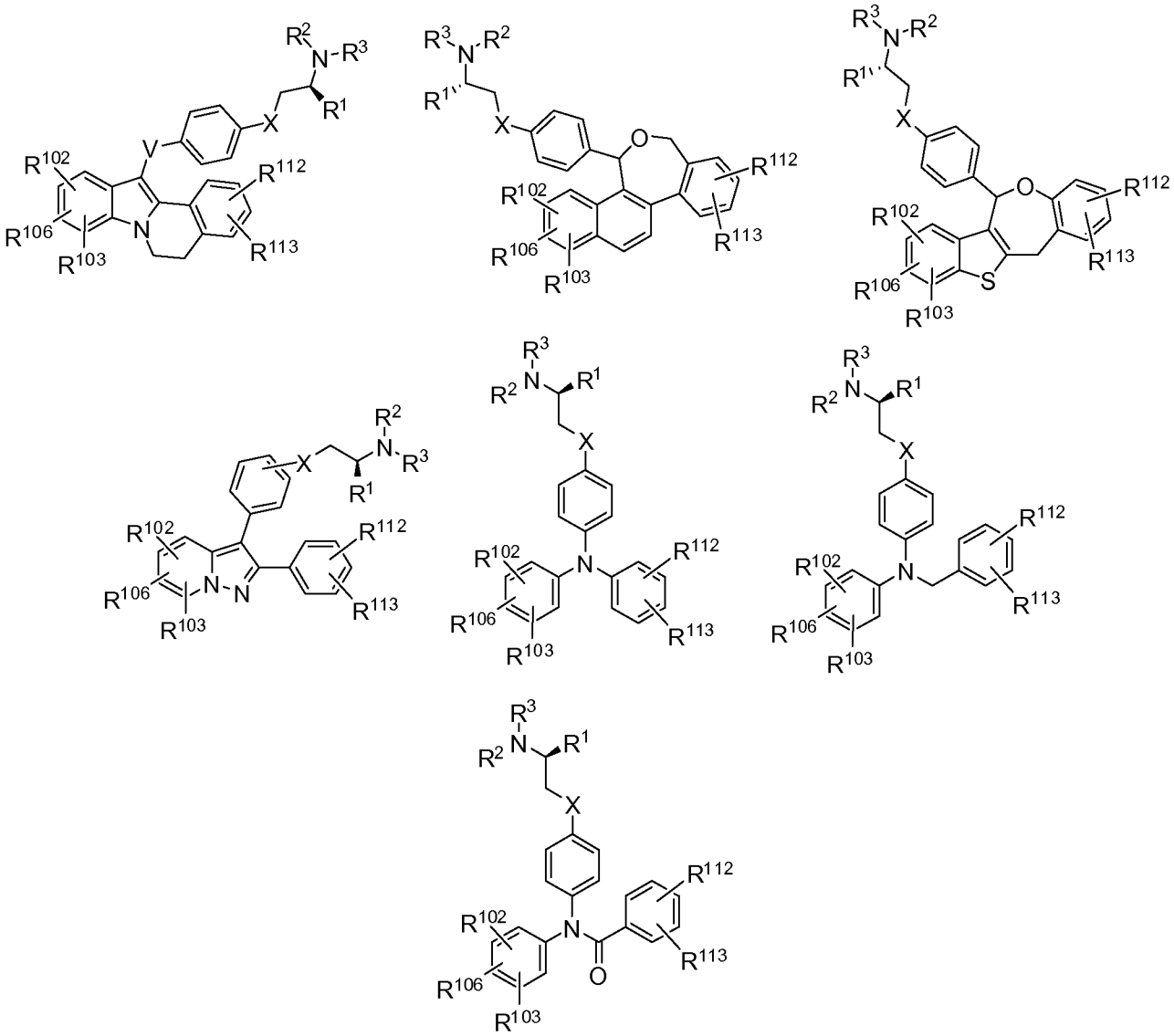










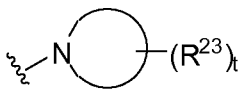
wherein

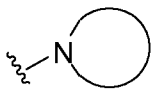
R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form

 ;

 is a monocyclic C_2-C_6heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

t is 1, 2, 3, or 4;

X is absent, O, S, -CH_2-, -C(=O)-, -NH-, or –N(C_1-C_4alkyl)-;

(h)Ar is a (hetero)aromatic ring, optionally substituted with R^{112} and R^{113};

R^{102} and R^{103} are independently selected from H, F, Cl, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, -CF_3 or -CN;

R^{104} and R^{107} are independently selected from H, fluorine, chlorine, C_1-C_2alkyl, -CF_3, or -CN;

R^{112} is H, fluorine, chlorine, C_1-C_2alkyl, C_1-C_2alkoxy, -CN or hydroxyl;

R^{113} is H, fluorine, chlorine, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, -CF_3 or -CN;

R^{106} is H, hydroxyl, amine or C_1-C_6alkoxy;

R^{106} and R^{102} may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or C_1-C_3alkyl;

R^{105} is H, C_1-C_3alkyl, optionally substituted with one or more fluorine;

Vis -O-, -S-, -CH_2-, -CH(OH)-, -CH(C_1-C_3alkoxy)-, -C=CH_2, carbonyl, -N-R^{116};

R^{115} is H, halogen, nitro, nitrile or C_1-C_6alkyl, C_1-C_6cycloalkyl, optionally substituted with one or more halogen;

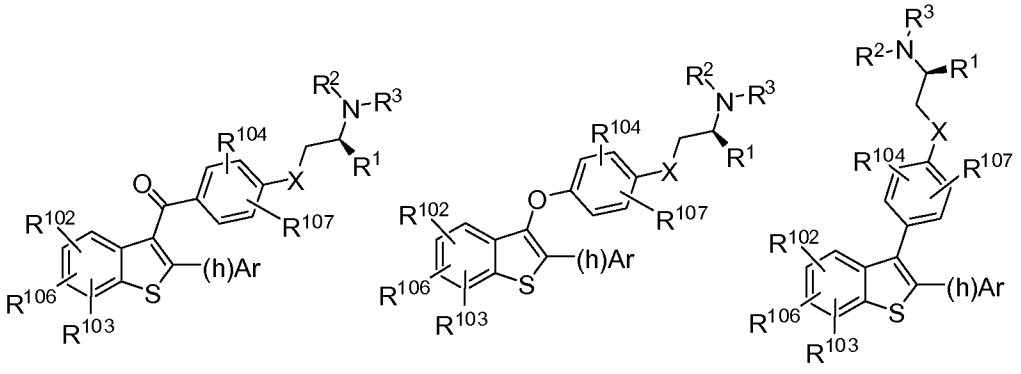
R^{116} is H, C_1-C_4alkyl, C_1-C_4alkenyl, optionally substituted with one or more halogen;

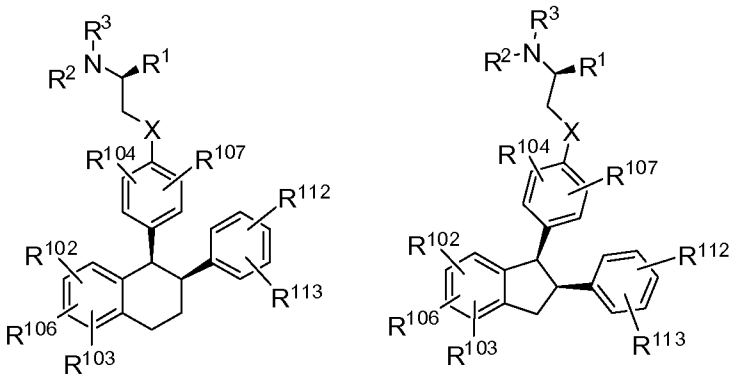
R^{120} is C_1-C_3alkyl, optionally substituted with one or more fluorine;

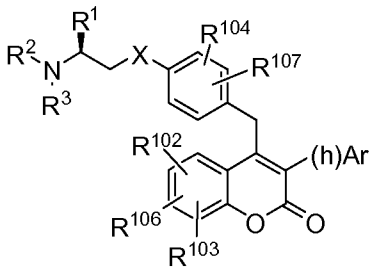
or a pharmaceutically acceptable salt thereof.

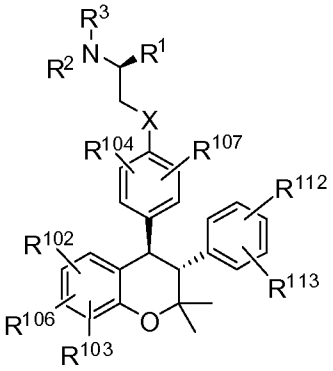
[00161] The term (h)Ar or (hetero)aromatic ring means an aromatic or heteroaromatic ring system, the aromatic skeleton of which contains five to ten atoms of which zero to four atoms other than carbon, are selected from oxygen, nitrogen or sulfur. Examples are phenyl, naphthyl, pyridyl, thienyl, furanyl, thiazolyl, oxazolyl, pyrrolyl, thiadiazolyl, tetrazolyl, benzopyrrolyl and benzopyrrazolyl.

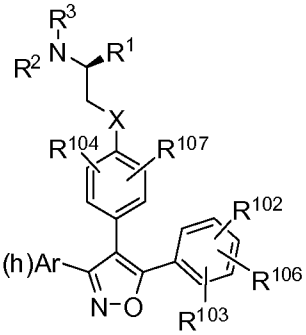
[00162] In another embodiment, the compound of Formula (V) has one of the following structures:

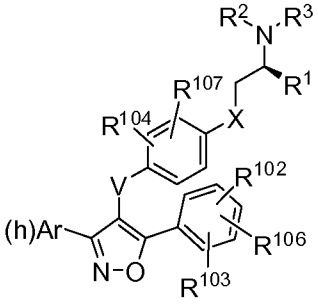












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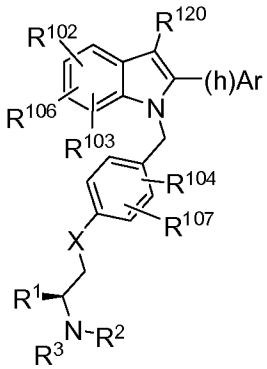
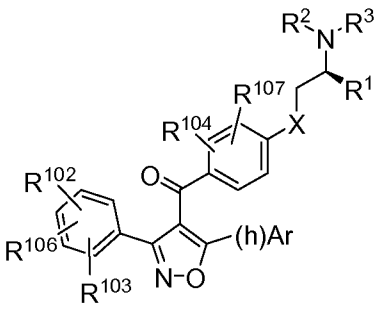
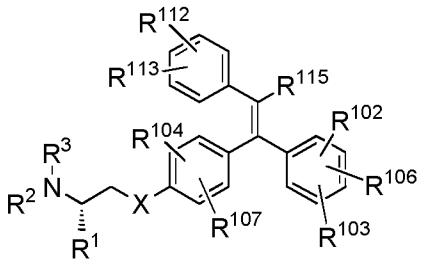
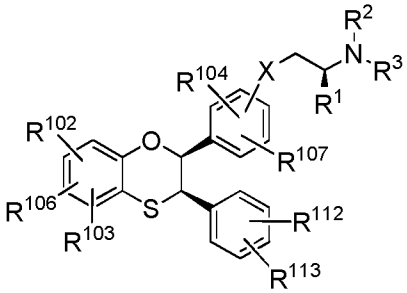
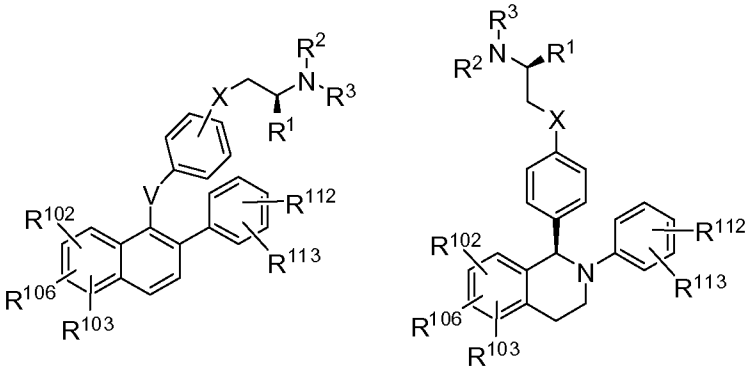










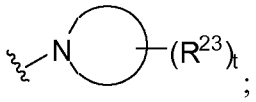
wherein

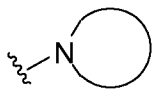
R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form

 ;

 is a monocyclic C_2-C_6heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

t is 1, 2, 3, or 4;

X is absent, O, S, $-CH_2-$, -C(=O)-, -NH-, or $-N(C_1$-C_4alkyl)-;

(h)Ar is a (hetero)aromatic ring, optionally substituted with R^{112} and R^{113};

R^{102} and R^{103} are independently selected from H, F, Cl, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, $-CF_3$ or -CN;

R^{104} and R^{107} are independently selected from H, fluorine, chlorine, C_1-C_2alkyl, $-CF_3$, or -CN;

R^{112} is H, fluorine, chlorine, C_1-C_2alkyl, C_1-C_2alkoxy, -CN or hydroxyl;

R^{113} is H, fluorine, chlorine, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, $-CF_3$ or -CN;

R^{106} is H, hydroxyl, amine or C_1-C_6alkoxy;

R^{106} and R^{102} may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or C_1-C_3alkyl;

R^{105} is H, C_1-C_3alkyl, optionally substituted with one or more fluorine;

Vis -O-, -S-, $-CH_2-$, -CH(OH)-, $-CH(C_1$-C_3alkoxy)-, $-C{=}CH_2$, carbonyl, $-N-R^{116}$;

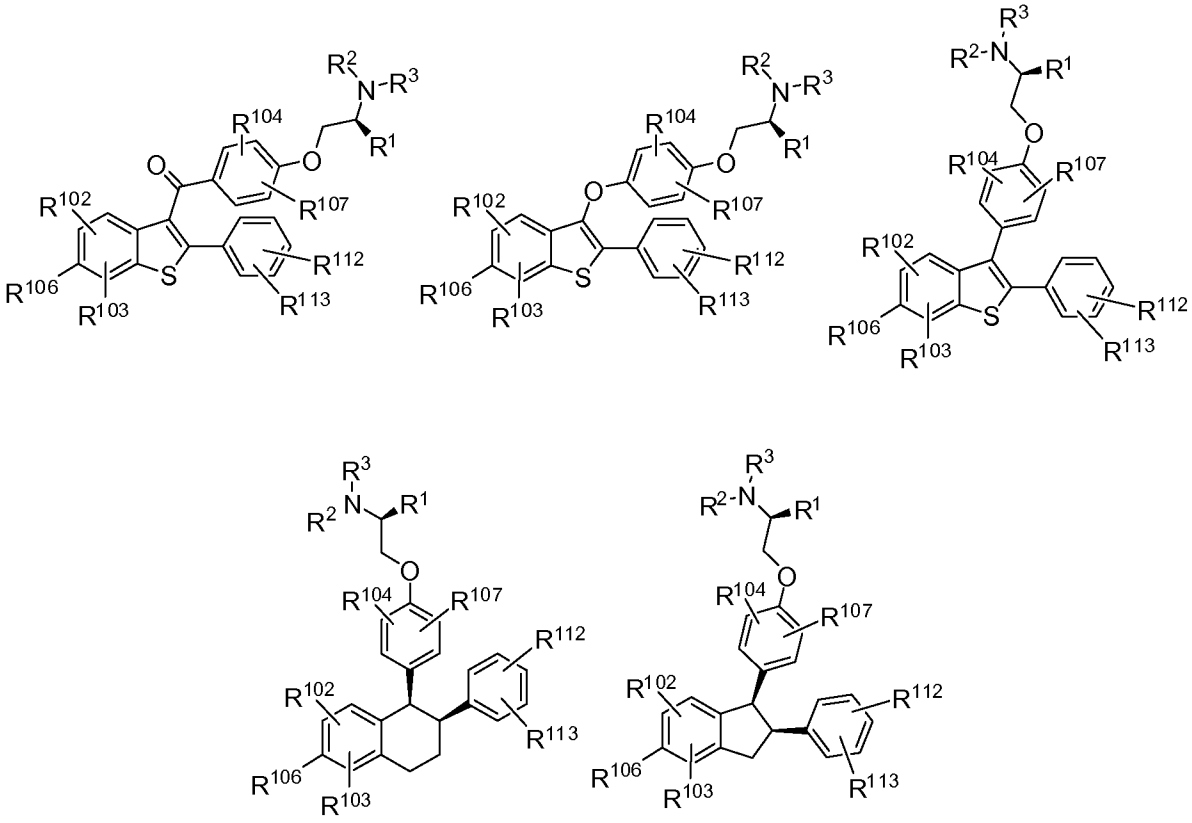
R^{115} is H, halogen, nitro, nitrile or C_1-C_6alkyl, C_1-C_6cycloalkyl, optionally substituted with one or more halogen;

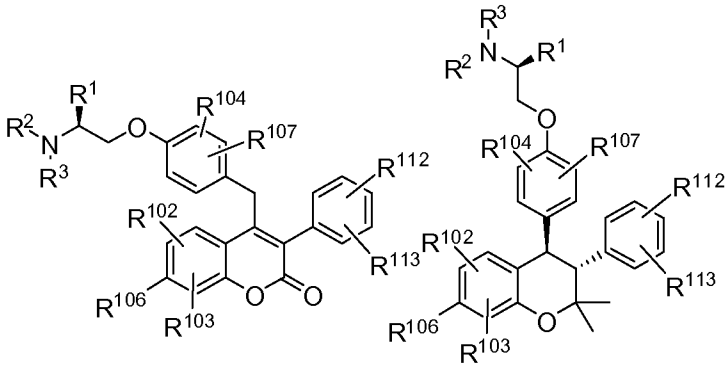
R^{116} is H, C_1-C_4alkyl, C_1-C_4alkenyl, optionally substituted with one or more halogen;

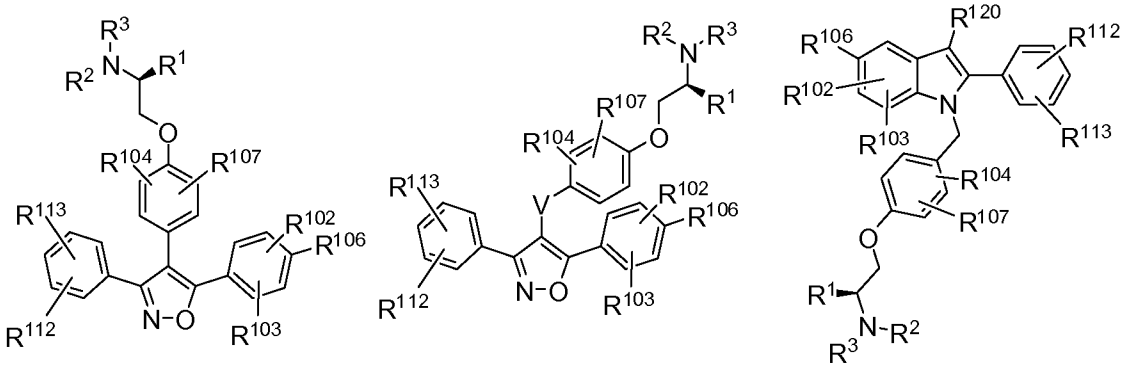
R^{120} is C_1-C_3alkyl, optionally substituted with one or more fluorine;

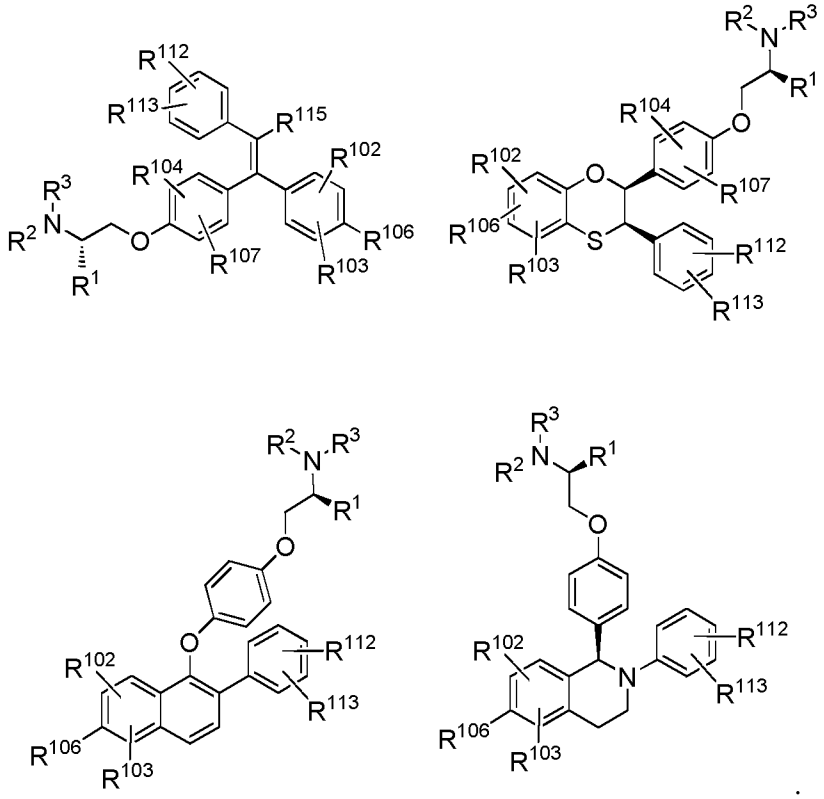
or a pharmaceutically acceptable salt thereof.

[00163] In another embodiment, the compound of Formula (V) has one of the following structures:









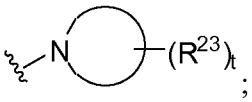
wherein

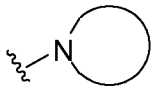
R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form

 ;

 is a monocyclic C_2-C_6heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

t is 1, 2, 3, or 4;

X is absent, -O-, -S-, $-CH_2-$, -C(=O)-, -NH-, or $-N(C_1$-C_4alkyl)-;

R^{102} and R^{103} are independently selected from H, F, Cl, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, $-CF_3$ or -CN;

R^{104} and R^{107} are independently selected from H, fluorine, chlorine, C_1-C_2alkyl, $-CF_3$, or -CN;

R^{112} is H, fluorine, chlorine, C_1-C_2alkyl, C_1-C_2alkoxy, -CN or hydroxyl;

R^{113} is H, fluorine, chlorine, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, $-CF_3$ or -CN;

R^{106} is H, hydroxyl, amine or C_1-C_6alkoxy;

R^{106} and R^{102} may be linked to form a (hetero)aromatic ring which is optionally substituted with fluorine, chlorine or C_1-C_3alkyl;

R^{105} is H, C_1-C_3alkyl, optionally substituted with one or more fluorine;

Vis -O-, -S-, -CH_2-, -CH(OH)-, -CH(C_1-C_3alkoxy)-, -C=CH_2, carbonyl, -N-R^{116};

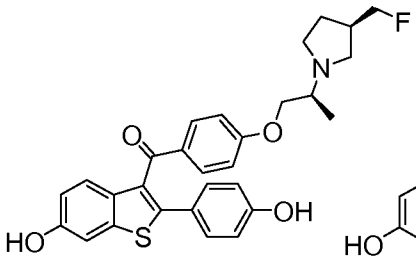
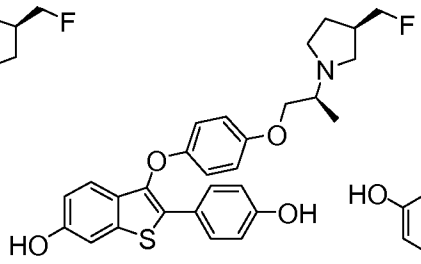
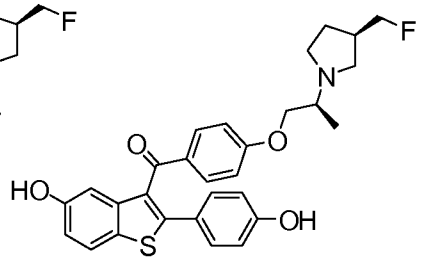
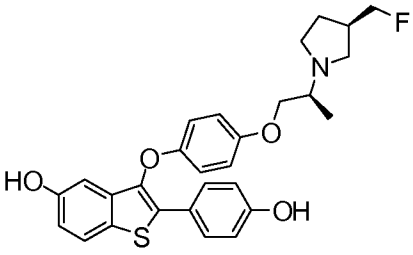
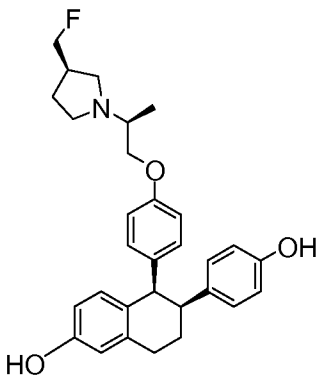
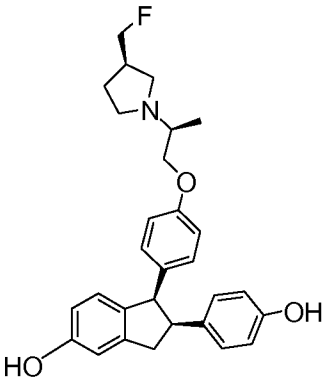
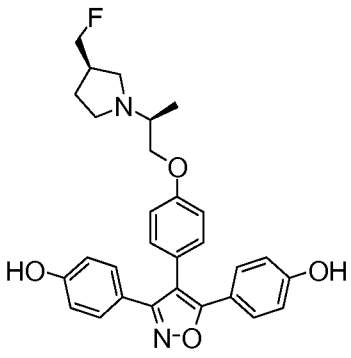
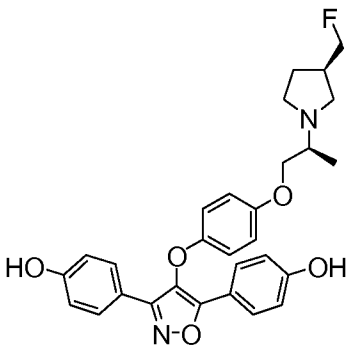
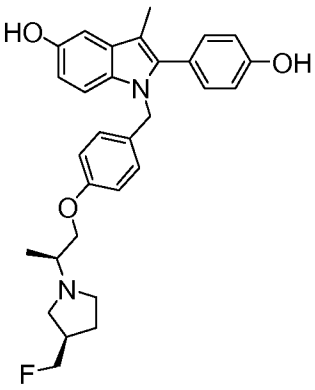
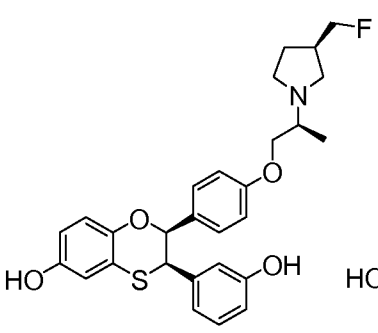
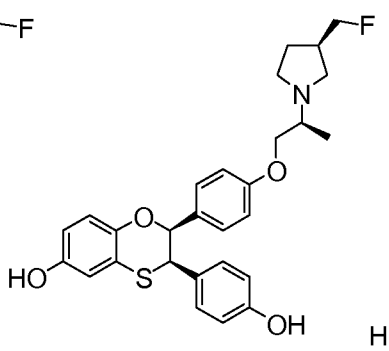
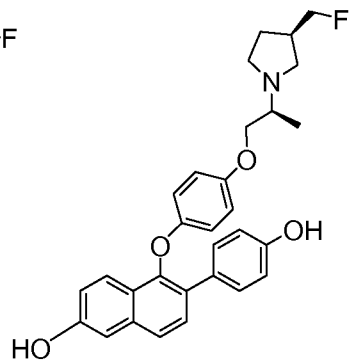
R^{115} is H, halogen, nitro, nitrile or C_1-C_6alkyl, C_1-C_6cycloalkyl, optionally substituted with one or more halogen;

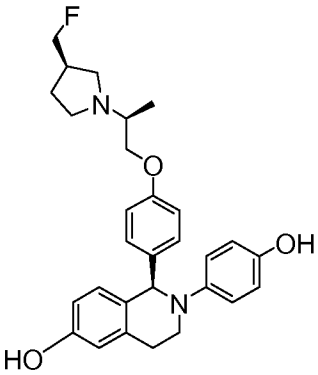
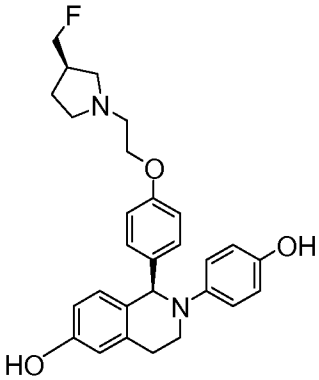
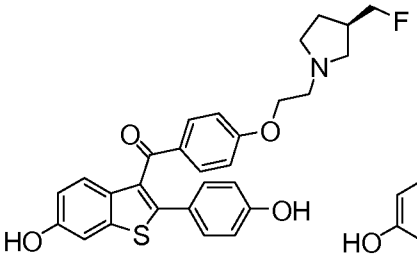
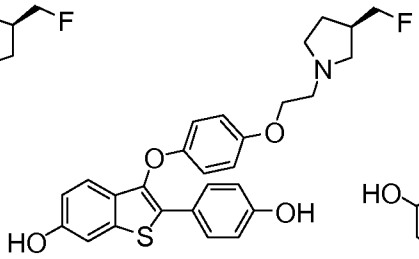
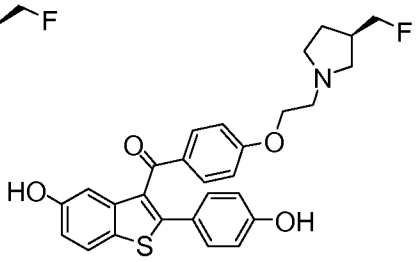
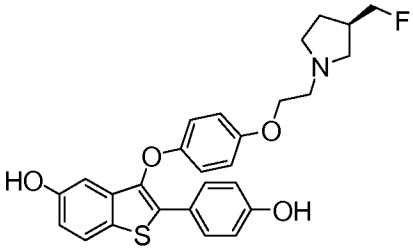
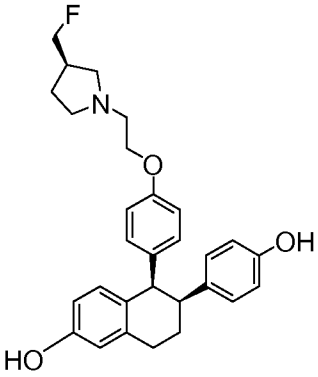
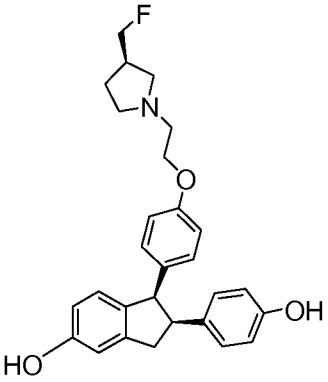
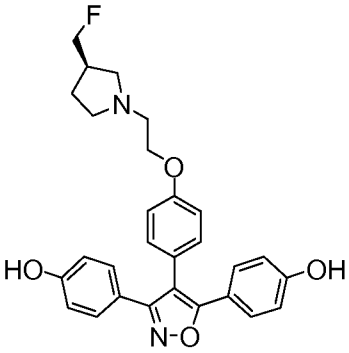
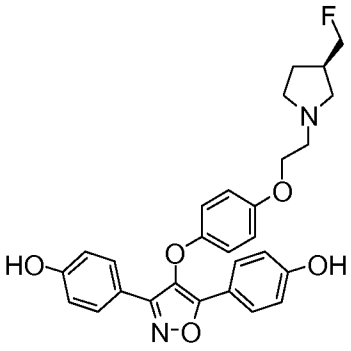
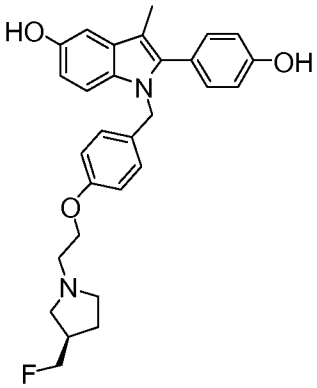
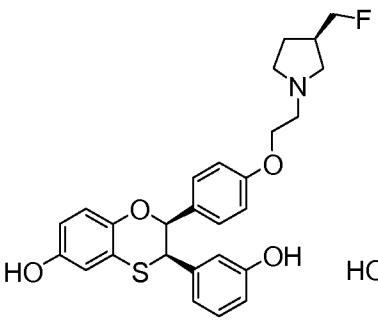
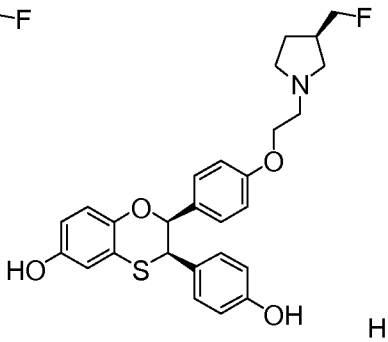
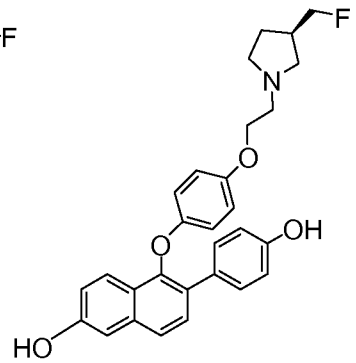
R^{116} is H, C_1-C_4alkyl, C_1-C_4alkenyl, optionally substituted with one or more halogen;

R^{120} is C_1-C_3alkyl, optionally substituted with one or more fluorine;

or a pharmaceutically acceptable salt thereof.

[00164] In some embodiments, the compound of Formula (V) has one of the following structures:

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or is a pharmaceutically acceptable salt, or solvate, or prodrug thereof.

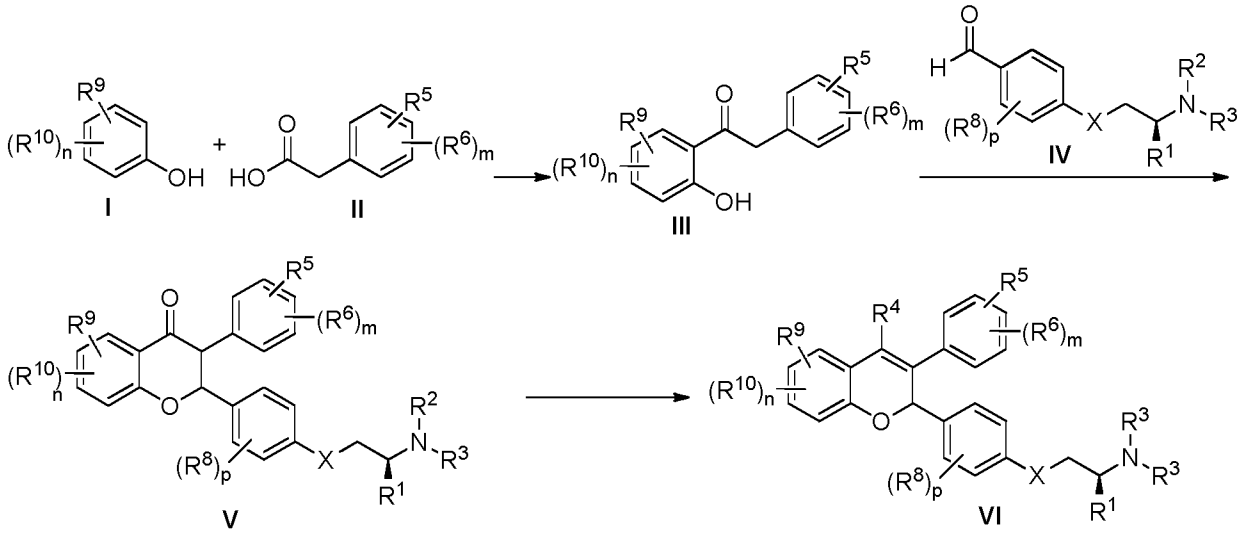
Synthesis of Compounds

[00165] Compounds described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein. In additions, solvents, temperatures and other reaction conditions presented herein may vary.

[00166] The starting material used for the synthesis of the compounds described herein are either synthesized or obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Fluka, Acros Organics, Alfa Aesar, and the like. The compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein or otherwise known, including those found in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999). General methods for the preparation of compounds can be modified by the use of appropriate reagents and conditions for the introduction of the various moieties found in the formulae as provided herein.

[00167] In some embodiments, the compounds described herein are prepared as outlined in the following Schemes.

Scheme 1:

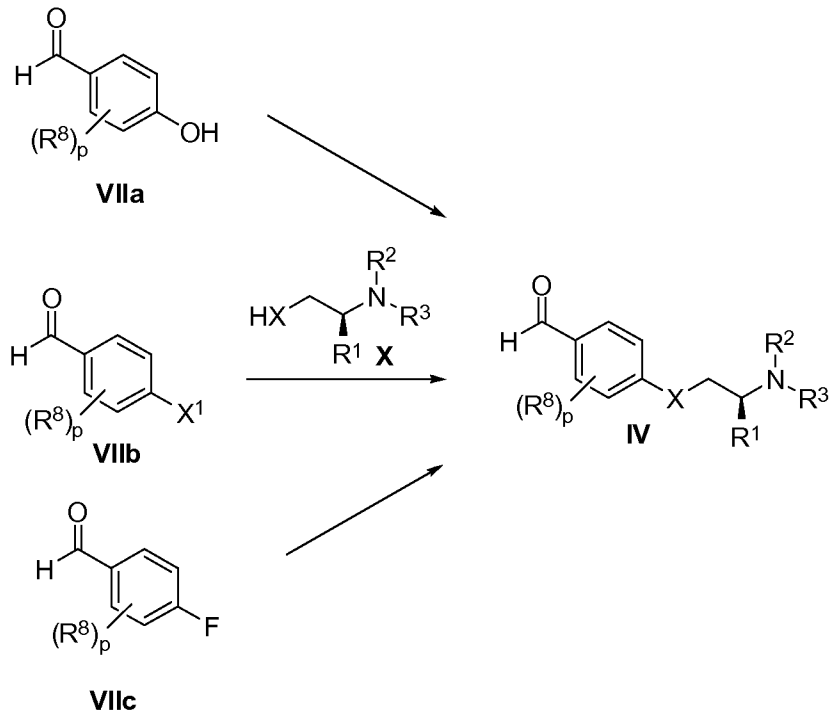


[00168] Treatment of phenols of structure **I** with phenylacetic acids of structure **II** in the presence of a suitable Lewis Acid in a suitable solvent provides ketones of structure **III**. In some embodiments the suitable Lewis Acid is BF_3-Et_2O. In some embodiments, the suitable solvent is toluene. In some embodiments, the reaction is heated. In some embodiments, the reaction is heated to 90 °C for 2 hours. Ketones of structure **III** are reacted with benzaldehydes of structure **IV** in the presence of a suitable base and suitable solvent to provide compounds of structure **V**. In some embodiments, the suitable base is piperidine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In some embodiments, the suitable solvent is *s*-butanol and/or *i*-propanol. In some embodiments, ketones of structure **III** are reacted with benzaldehydes of structure **IV** in the presence of piperidine, DBU in s-butanol at reflux for 3 hours and

then i-propanol is added and the reaction is stirred at room temperature for 1-3 days. Compounds of structure **V** are treated with suitable organometallic reagents to provide tertiary alcohols that are then dehydrated to provide chromenes of structure **VI**. In some embodiments, the suitable organometallic regaent is R^4-Li or R^4-MgCl. In some embodiments, the suitable organometallic regaent is methyl lithium, methyl magnesium chloride or methyl magnesium bromide. In some embodiments, compounds of structure **V** are dissolved in tetrahydrofuran and treated with methyl lithium at -78 °C to room temperature for 1 hour or methyl magnesium chloride at 0 °C to room temperature for 2 hours. The tertiary alcohol that is produced is then treated with acetic acid/water to eliminate to the chromene.

[00169] In some embodiments, benzaldehydes of structure **IV** are prepared as outlined in Scheme 2.

Scheme 2.



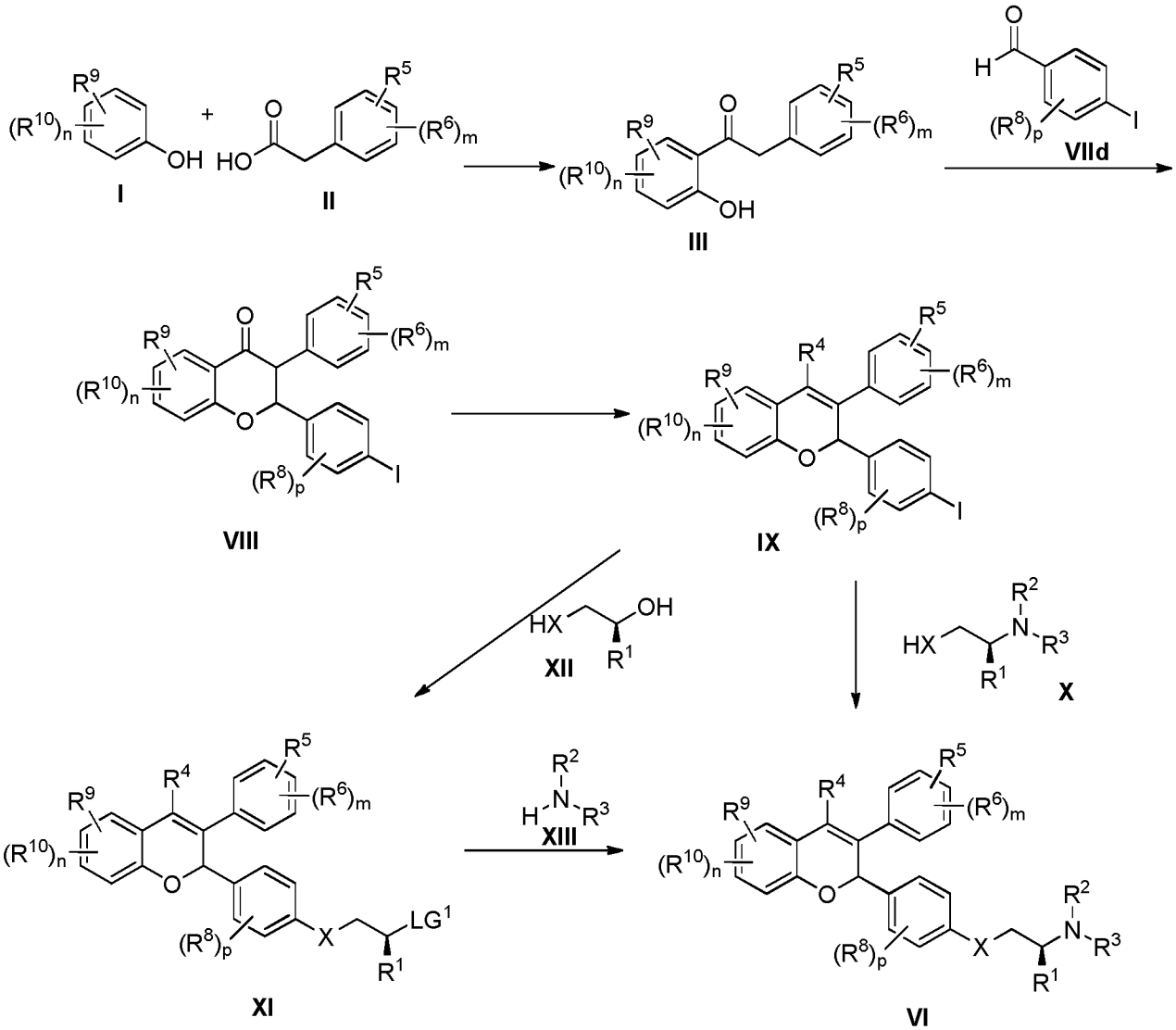
[00170] In some embodiments, 4-hydroxybenzaldehydes of structure **VIIa** are coupled with amino compounds of structure **X** under suitable coupling conditions. In some embodiments, the suitable coupling conditions include the use of triphenylphosphine, diisopropyl azodicarboxylate and tetrahydrofuran. In some embodiments, the coupling is performed at room temperature.

[00171] In some embodiments, 4-halobenzaldehydes of structure **VIIb** (e.g. where X1 is Br or I) or 4-fluorobenzaldehydes of structure **VIIc** are coupled with amino compounds of structure **X** under suitable coupling conditions. In some embodiments, when X^1 is I and X is O then the suitable reaction condition include the use of CuI, potassium carbonate, butyronitrile with heating to about 125 °C. In an alternative embodiment, when X^1 is I and X is O then the suitable reaction condition include the use of CuI, cesium carbonate, m-xylenes, with heating to about 125 °C. In some embodiments, phenanthroline is used in these copper mediated coupling reaction conditions. In some embodiments, when X^1 is Br and X is N then the suitable reaction condition include the use of $Pd_2(dba)_3$, BINAP, cesium carbonate,

and toluene, with heating to about 100 °C. In some embodiments, when X^1 is Br and X is S then the suitable reaction condition include the use of sodium hydride and dimethylformamide or cesium carbonate and N-methylpyrrolidinone with heating. In some embodiments, 4-fluorobenzaldehydes of structure **VIIc** are coupled with amino compounds of structure **X** (where X is O) with the use of sodium hydride and dimethylformamide or potassium *tert*-butoxide in dimethylformamide. In some embodiments, 4-fluorobenzaldehydes of structure **VIIc** are coupled with amino compounds of structure **X** (where X is N) with the use of potassium carbonate and dimethylformamide with heating to reflux or potassium carbonate in ethanol with heating to reflux or the reaction is perfomed heated with heating. In some embodiments, 4-fluorobenzaldehydes of structure **VIIc** are coupled with amino compounds of structure **X** (where X is S) with the use of sodium hydride and dimethylformamide at room temperature.

[00172] In some embodiments, compounds are prepared as outlined in Scheme 3.

Scheme 3:



[00173] In some embodiments, ketones of structure **III** are prepared as outlined in Scheme 1 and then reacted with 4-halobenzaldehydes of structure **VIId** in the presence of a suitable base and suitable

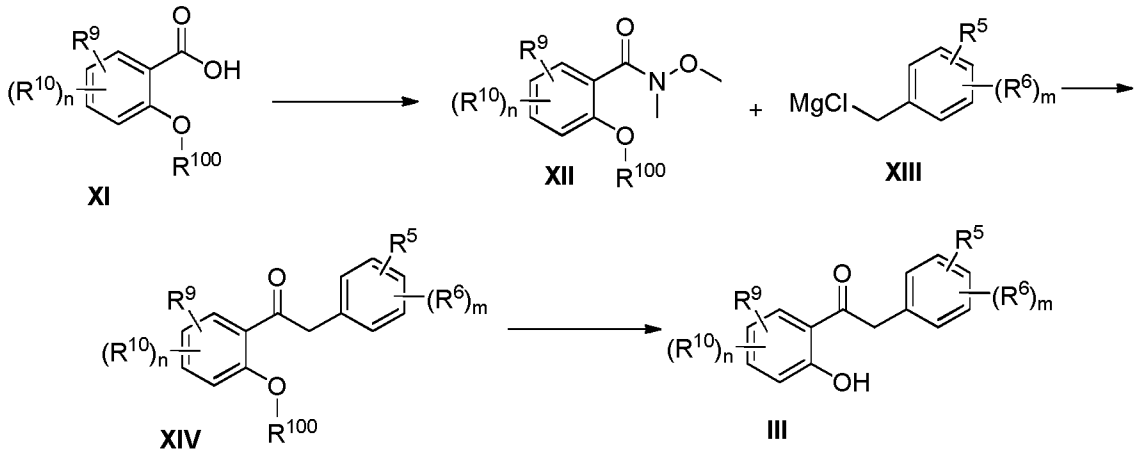
solvent to provide compounds of structure **VIII**. In some embodiments, the suitable base is piperidine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In some embodiments, the suitable solvent(s) is s-butanol and i-propanol. Compounds of structure **VIII** are then treated with suitable organometallic reagents, followed by dehydration of the tertiary alcohol to provide chromenes of structure **IX**. In some embodiments, the suitable organometallic reagent is R^4-Li or MgCl-R^4. In some embodiments, compounds of structure **VIII** are reacted with CsF and CF_3TMS in a suitable solvent at room temperature, followed by deprotection of the TMS protecting group and then dehydration of the resulting tertiary alcohol to provide chromenes of structure **IX** where R^4 is $-CF_3$. Chromenes of structure **IX** are then reacted with amino compounds of structure **X** under Ullmann reaction conditions to provide chromenes of structure **VI**. Ullmann reaction conditions include the use of copper salts. In some embodiments, the Ullmann reaction conditions include the use of CuI, Cs_2CO_3, and butyronitrile with heating to about 125 °C. In some embodiments, the Ullmann reaction conditions include the use of CuI, bipyridine, and K_2CO_3 with heating to about 140 °C. In some other embodiments, Ullmann reaction conditions include the use of CuI, potassium carbonate, and butyronitrile with heating to about 125 °C for about 5 days.

[00174] In an alternative embodiment, chromenes of structure **IX** are reacted with compounds of structure **XII** under Ullmann reaction conditions, followed by conversion of the –OH to a suitable leaving group (LG^1) to provide chromenes of structure **XI**. In some embodiments, X is O in the compounds of structure **XII** and the Ullmann reaction conditions include the use of CuI, potassium carbonate, and butyronitrile with heating to about 125 °C. Examples of suitable leaving groups (LG1) include -Cl, -Br, -I, -OTf, -OMs, and –OTs. In some embodiments, the –OH is converted to –OMs by treating the –OH with MsCl and triethylamine in dichloromethane at about 0 °C. In some embodiments, the –OH is converted to –OTf by treating the –OH with Tf_2O and triethylamine in dichloromethane at about -78 °C with warming to room temperature.

[00175] Chromenes of structure **XI** are then treated with amines of structure **XIII** under suitable reaction conditions to provide chromenes of structure **VI**. In some embodiments, when LG^1 is –OMs then the suitable reaction conditions include the use of potassium carbonate, acetonitrile with heating to about 80 °C. In some embodiments, when LG^1 is –OTf then the suitable reaction conditions include the use of diisopropylethylamine, dichloromethane at about -78 °C with warming to room temperature.

[00176] In some embodiments, ketones of structure **III** are prepared as outlined in Scheme 4:

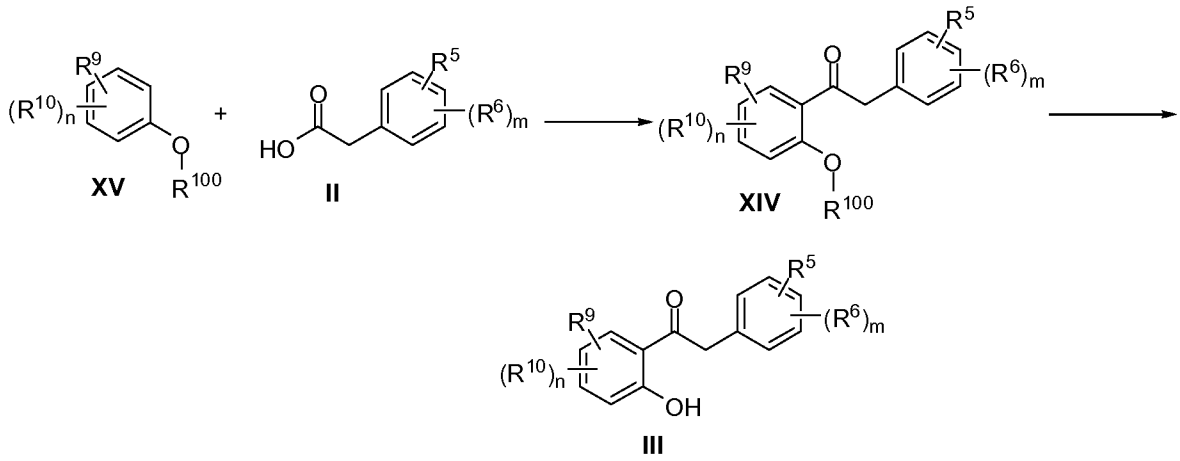
Scheme 4:



[00177] Benzoic acid compounds of structure **XI** are converted to Weinreb amides of structure **XII**. In some embodiments, benzoic acid compounds of structure **XI** are treated with oxalyl chloride, dimethylformamide (DMF), dichloromethane (DCM), at room temperature for 2 hours followed by treatments with triethylamine (Et_3N), N,O-dimethylhydroxylamine-HCl, DCM, at 0 °C to rt for 1 hour to provide Weinreb amides of structure **XII**. Weinreb amides of structure **XII** are then treated with suitable organometallics reagents of structure **XIII** to provide ketones of structure **XIV**. In some embodiments, R^{100} is a phenol protecting group. In some embodiments, R^{100} is methyl. In some embodiments, when R^{100} is methyl then ketones of structure **XIV** are treated with BBr_3, DCM, -78 °C to 0 °C for about 30 minutes to provide ketones of structure **III**.

[00178] In some embodiments, ketones of structure **III** are prepared as outlined in Scheme 5:

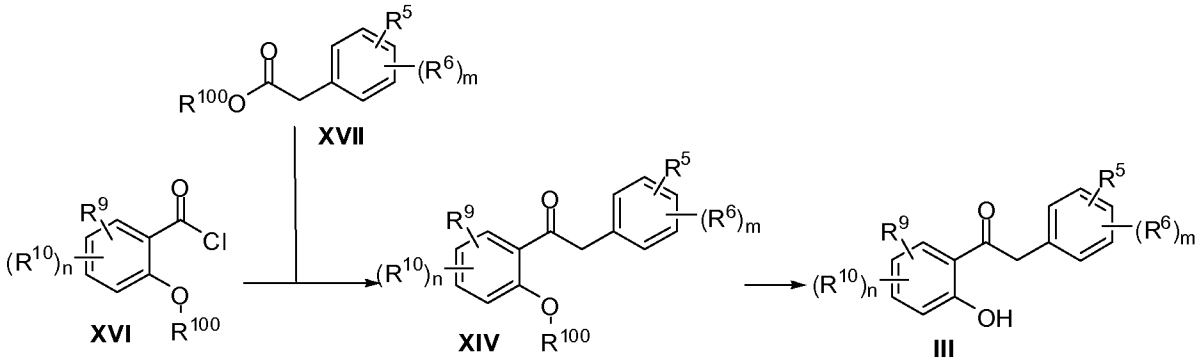
Scheme 5:



[00179] In some embodiments, suitably protected phenols of structure **XV** are treated with polyphosphoric acid and phenyl acetic acids of structure **II** to provide ketones of structure **XIV**. In some embodiments, R^{100} is a phenol protecting group. In some embodiments, R^{100} is methyl. Ketones of structure **XIV** are then converted to ketones of structure **III** as outlined in Scheme 4.

[00180] In some embodiments, ketones of structure **III** are prepared as outlined in Scheme 6:

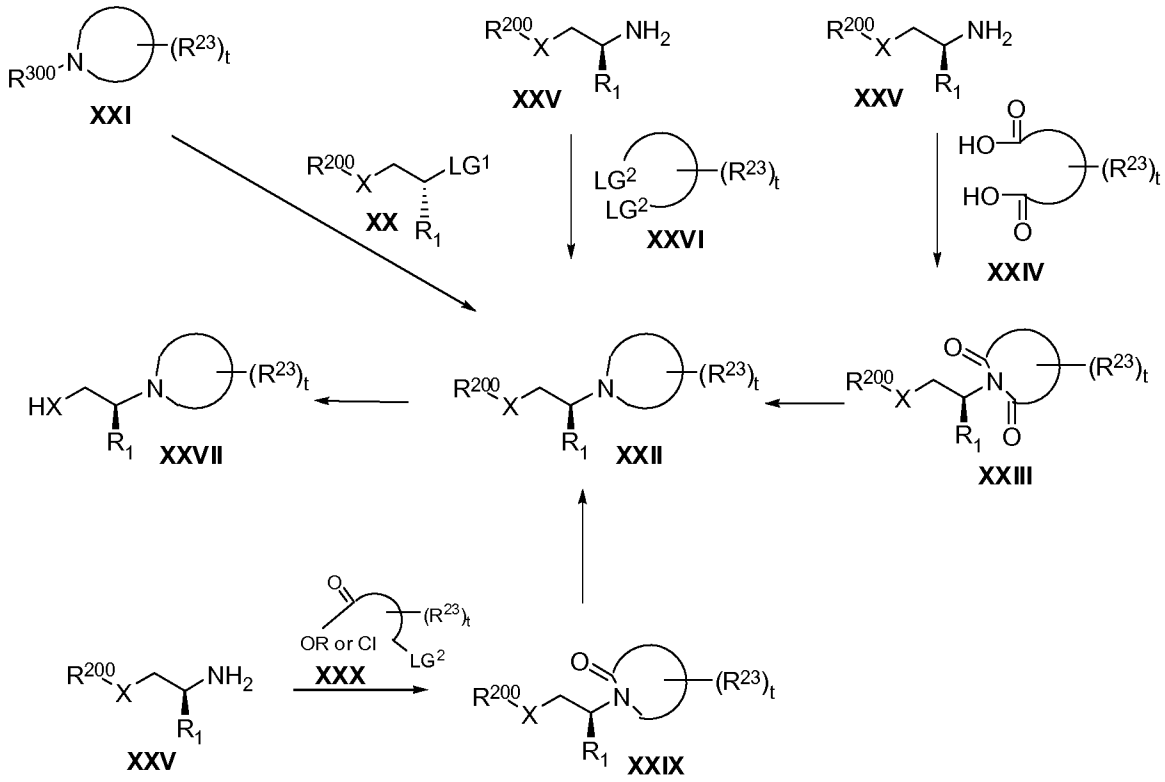
Scheme 6:



[00181] Alkyl esters of phenylacetic acids, such as compounds of structure **XVII**, are treated with a suitable base and then reacted with acid chlorides of structure **XVI** to provide keto-esters that are decarboxylated to provide ketones of structure **XIV**. In some embodiments, R^{100} is alkyl. In some embodiments, R^{100} is methyl. In some embodiments, the suitable base is lithium bis(trimethylsilyl)amide (LiHMDS). In some embodiments, compounds of structure **XVII** are treated with LiHMDS in tetrahydrofuran at -78 °C for about 15 minutes and then reacted with acid chlorides of structure **XVI** at -78 °C for about 1 hour. In some embodiments, decarboxylation of the keto-ester is accomplished using Krapcho decarboxylation condition. In some embodiments, Krapcho decarboxylation conditions include dimethylsulfoxide, brine with heating to about 150 °C for about 5 hours. Other decarboxylation conditions include the use of concentrated hydrochloric acid in ethanol at 130 °C for about 3 hours. R^{100} is then removed from ketones of structure **XIV** as described in Scheme 4 to provide ketones of structure **III**.

[00182] In some embodiments, when R^2 and R^3 are taken together with the N atom to which they are attached to form a substituted or unsubstituted heterocycle, the substituted or unsubstituted heterocycle is prepared as outlined in Scheme 7.

Scheme 7:



[00183] In some embodiments, substituted or unsubstituted heterocycles of structure **XXI**, where R300 is a protecting group such as t-BOC or Cbz, are first deprotected and then reacted with compounds of structure **XX**, where LG^1 is a leaving group, under suitable reaction conditions to provide compounds of structure **XXII**. In some embodiments, when R300 is t-BOC then the deprotection is perfomed using hydrochloric acid in dioxane at room temperature. In some embodiments, when LG^1 is –OMs then the suitable reaction conditions include the use of potassium carbonate (or cesium carbonate), acetonitrile (or methanol, ethanol, isopropanol, or tetrahydrofuran) with optional heating. In some embodiments, when LG^1 is –OMs then the suitable reaction conditions include perfoming the reaction neat (i.e. amine as solvent) with heating. In some embodiments, when LG^1 is -OTf then the suitable reaction conditions include the use of diisopropylethylamine, dichloromethane, with the reaction initial performed at -78 °C then warming to room temperature. In some embodiments, R^{200} is a suitable protecting group for X. In some embodiments, X is oxygen. In some embodiments, R^{200} is trityl or benzyl. In some embodiments, R^{200} is removed from compounds of structure **XXII** to provide compounds of structure **XXVII**. In some embodiments, the suitable deprotection conditions include the use of hydrochloric acid in dioxane (or tetrahydrofuran); or formic acid in diethylether; or acetic acid ether (for when R^{200} is trityl).

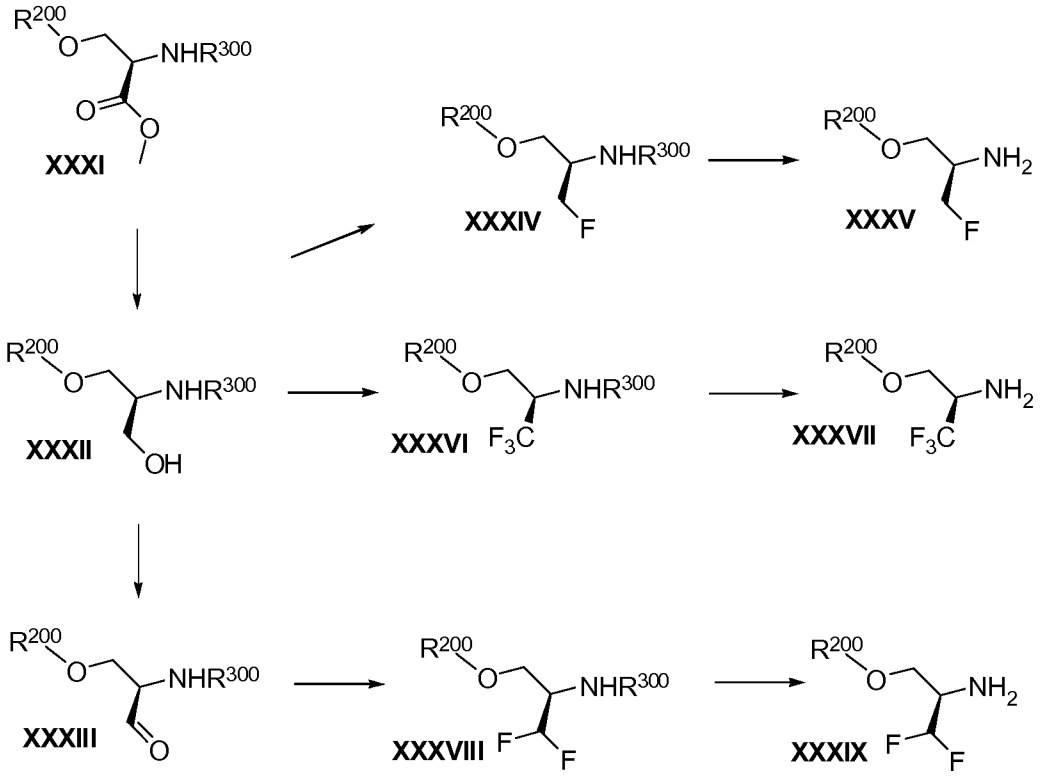
[00184] Alternatively, reaction of amines of structure **XXV** with activated alkanes of structure **XXVI**, where LG^2 is a suitable leaving group, under suitable reaction conditions provides compounds of structure **XXII**. Suitable leaving groups include, chloro, bromo, iodo, tosylate, mesylate, and triflate. In some embodiments, suitable reaction conditions include potassium carbonate, acetonitrile or neat, at room temperature.

[00185] Alternatively, reaction of diacids of structure **XXIV**, with acetic anhydride at about 85 °C for about 30 minutes provides an anhydride which is then treated with amines of structure **XXV** followed by acetic anhydride to provide amides of structure **XXIII**. Amides of structure **XXIII** are then reduced to provide amines of structure **XXII**. In some embodiment, the reduction is performed with lithium aluminum hydride in tetrahydrofuran$LiAlH_4$, THF or DIBAL, THF.

[00186] In some embodiments, amines of structure **XXV** are reacted with compounds of structure **XXX** under suitable reaction conditions to provide compounds of structure **XXIX**. In some embodiments, the suitable reaction conditions include the use of potassium carbonate in tetrahydrofuran or dimethylformamide. In some embodiment, amides of structure **XXIX** are then reduced to provide amines of structure **XXII** as described above.

[00187] In some embodiments, fluorinated R^1 groups are introduced as outlined in Scheme 8.

Scheme 8.



[00188] R^{200} is a suitable protecting group for the oxygen atom. In some embodiments, R^{200} is trityl. R^{300} is a suitable protecting group for the nitrogen atom. In some embodiments, R^{300} is mesyl, tosyl or Cbz. In some embodiments, R^{200} and R^{300} are taken together with oxygen and nitrogen atoms to which they are attached to form a cyclic protecting group. In some cases the protected amino-alcohol is an oxazolidine such as that in Garner's aldehyde.

[00189] In some embodiments, esters of structure **XXXI** are reduced under suitable reaction conditions to provide alcohols of structure **XXXII**. In some embodiments, the suitable reduction reaction conditions include the use sodium borohydride in tetrahydrofuran or DIBAL-H in tetrahydrofuran.

Oxidation of the alcohol under suitable oxidation conditions provides aldehydes of structure **XXXIII**. Exemplary oxidation conditions include Dess-Martin periodinane, Swern oxidation, or PDC.

[00190] Treatment of alcohols of structure **XXXII** with a suitable fluorinating agent provides monofluoro compounds of structure **XXXIV**. In some embodiments, such suitable fluorinating conditions include the use of diethylaminosulfur trifluoride (DAST) in dichloromethane at about -78 °C with warming to room temperature. Alternatively, the suitable fluorinating reaction conditions include the use of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-fluor) in dichloromethane at about -78 °C with warming to room temperature. In yet in another alternative embodiment, the suitable fluorinating reaction conditions include the use of SF_4, HF. In yet another embodiment, the suitable fluorinating reaction conditions include the use methane sulfonyl chloride, triethylamine, in dichloromethane at about 0 °C followed by tetrabutyammonium fluoride.

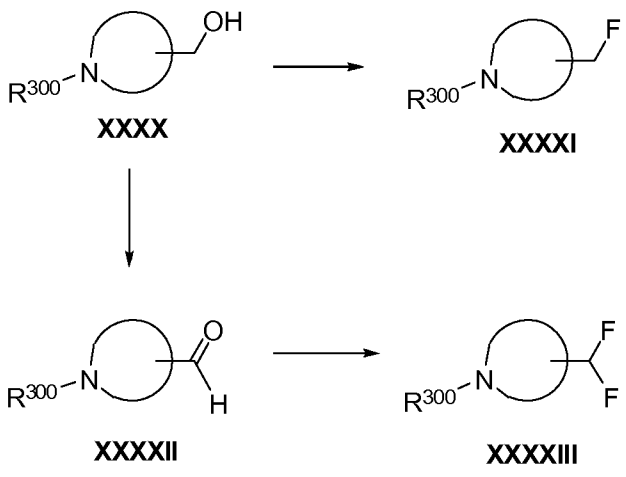
[00191] In some embodiments, alcohols of structure **XXXII** are used to prepare trifluoro compounds of structure **XXXVI**. In some embodiments, alcohols of structure **XXXII** are oxidized with PDC or potassium permanganate and then treated with SF_4, HF to provide trifluoro compounds of structure **XXXVI**.

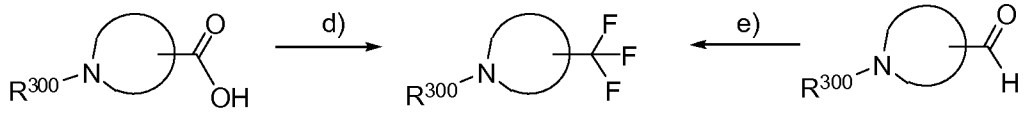
[00192] In some embodiments, aldehydes of structure **XXXIII** are used to prepare difluoro compounds of structure **XXXVIII**. In some embodiments, aldehydes of structure **XXXIII** are treated with diethylaminosulfur trifluoride (DAST) in dichloromethane at about -78 °C with warming to room temperature. In some other embodiments, aldehydes of structure **XXXIII** are treated with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-fluor) in dichloromethane at about -78 °C with warming to room temperature.

[00193] R^{300} is removed under suitable deprotection reaction conditions. In some embodiments, when R^{300} is Ms or Ts then the suitable deprotection reaction conditions include the use of sodium hydroxide, and water with heating. In some embodiment, when R^{300} is Cbz then the suitable deprotection reaction conditions include the use of hydrogen gas and palladium on carbon.

[00194] In some embodiments, fluorinated R^{23} groups are introduced as outlined in Scheme 9.

Scheme 9.





XXXXIV XXXXV XXXXII

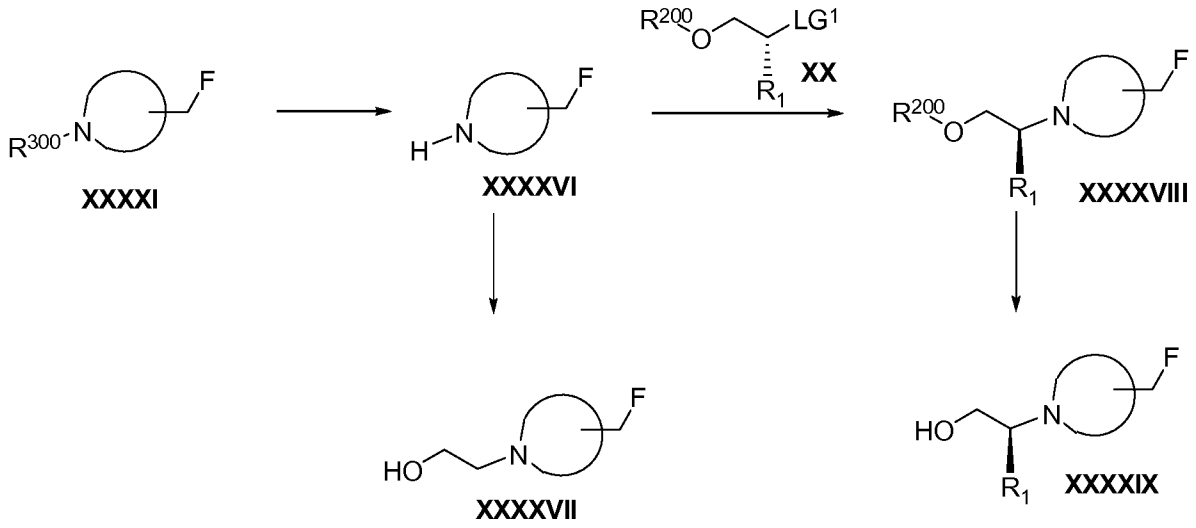
[00195] Treatment of alcohols of structure **XXXX** with a suitable fluorinating agent under suitable reaction conditions provides monofluoro compounds of structure **XXXXI**. In some embodiments, the suitable fluorinating is diethylaminosulfur trifluoride (DAST) and the suitable reaction conditions includes the use dichloromethane at about -78 °C with warming to room temperature. In some other embodiments, the suitable fluorinating is SF_4, HF. In an alternative embodiment, alcohols of structure **XXXX** are treated with methane sulfonyl chloride and triethylamine in dichloromethane at about 0°C followed by tetrabutyammonium fluoride to provide monofluoro compounds of structure **XXXXI**.

[00196] Oxidation of alcohols of structure **XXXX** provides aldehydes of structure **XXXXII**, which are then treated with diethylaminosulfur trifluoride (DAST) in dichloromethane at about -78 °C with warming to room temperature to provide difluoro compounds of structure **XXXXIII**. In some other embodiments, aldehydes of structure **XXXXII** are treated with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-fluor) in dichloromethane at about -78 °C with warming to room temperature to provide difluoro compounds of structure **XXXXIII**.

[00197] Trifluoro compounds of structure **XXXXV** are prepared from acids of structure **XXXXIV** or aldehydes of structure **XXXXII**. In some embodiments, acids of structure **XXXXIV** are treated with diethylaminosulfur trifluoride (DAST) in dichloromethane at about -78 °C with warming to room temperature to provide trifluoro compounds of structure **XXXXV**. In some other embodiments, acids of structure **XXXXIV** are treated with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-fluor) in dichloromethane at about -78 °C with warming to room temperature to provide trifluoro compounds of structure **XXXXV**. In some embodiments, aldehydes of structure **XXXXII** are treated with propane-1,3-dithiol, BF_3-OEt_2 in dichloromethane followed by pyridine, hydrofluoride (1:9), dibromodimethylhydantoin in dichloromethane at 0 °C to provide trifluoro compounds of structure **XXXXV**.

[00198] In some embodiments, monofluoro compounds of structure **XXXXI** are elaborated into compounds of structure **XXXXVII** or **XXXXIX** as shown in Scheme 10. Although monofluoro compounds are shown, it is understood that the same transformation could be used for other fluorinated compounds.

Scheme 10.



[00199] In some embodiment, when R^{300} is t-Boc, then monofluoro compounds of structure **XXXXI** are treated with hydrochloric acid in dioxane at room temperature to provide amines of structure **XXXXVI**. Amines of structure **XXXXVI** are then coupled with compounds of structure **XX** and the R^{200} protecting group is removed as outlined in Scheme 7. In some embodiments, amines of structure **XXXXVI** are treated with bromoethanol and potassium carbonate in acetonitrile with heating to about 80 °C. In other embodiments, amines of structure **XXXXVI** are treated with bromoethanol and potassium carbonate in ethanol with heating to about 80 °C.

[00200] In one aspect, compounds described herein are synthesized as outlined in the Examples.

[00201] Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[00202] A detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure.

Further Forms of Compounds

[00203] In one aspect, compounds described herein possess one or more stereocenters and each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. In certain embodiments, compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are seprated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of steroisomers is

performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[00204] The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). In one aspect, compounds described herein are in the form of pharmaceutically acceptable salts. As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00205] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the "prodrug") but then is metabolically hydrolyzed to provide the active entity. In some embodiments, the active entity is a phenolic compound as described herein. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00206] Prodrugs of the compounds described herein include, but are not limited to, esters, ethers, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, and sulfonate esters. See for example Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 and Method in Enzymology, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein by reference. In some embodiments, a hydroxyl group in the compounds disclosed herein is used to form a prodrug, wherein the hydroxyl group is incorporated into an acyloxyalkyl ester, alkoxycarbonyloxyalkyl ester, alkyl ester, aryl ester, phosphate ester, sugar ester, ether, and the like.

[00207] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound of Formula (I), (II), (III), (IV), (V), or (VI), as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00208] In some embodiments, sites on the aromatic ring portion of compounds described herein are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the aromatic ring structures will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium or an alkyl group.

[00209] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00210] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl. In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. In some embodiments, one or more hydrogen atoms that are present in the compounds described herein is replaced with one or more deuterium atoms.

[00211] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00212] "Pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00213] The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, pharmaceutically acceptable

salts are obtained by reacting a compound described herein with acids. Pharmaceutically acceptable salts are also obtained by reacting a compound described herein with a base to form a salt.

[00214] Compounds described herein may be formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid to form a salt such as, for example, a hydrochloric acid salt, a hydrobromic acid salt, a sulfuric acid salt, a phosphoric acid salt, a metaphosphoric acid salt, and the like; or with an organic acid to form a salt such as, for example, an acetic acid salt, a propionic acid salt, a hexanoic acid salt, a cyclopentanepropionic acid salt, a glycolic acid salt, a pyruvic acid salt, a lactic acid salt, a malonic acid salt, a succinic acid salt, a malic acid salt, a maleic acid salt, a fumaric acid salt, a trifluoroacetic acid salt, a tartaric acid salt, a citric acid salt, a benzoic acid salt, a 3-(4-hydroxybenzoyl)benzoic acid salt, a cinnamic acid salt, a mandelic acid salt, a methanesulfonic acid salt, an ethanesulfonic acid salt, a 1,2-ethanedisulfonic acid salt, a 2-hydroxyethanesulfonic acid salt, a benzenesulfonic acid salt, a toluenesulfonic acid salt, a 2-naphthalenesulfonic acid salt, a 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid salt, a glucoheptonic acid salt, a 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid) salt, a 3-phenylpropionic acid salt, a trimethylacetic acid salt, a tertiary butylacetic acid salt, a lauryl sulfuric acid salt, a gluconic acid salt, a glutamic acid salt, a hydroxynaphthoic acid salt, a salicylic acid salt, a stearic acid salt, a muconic acid salt, a butyric acid salt, a phenylacetic acid salt, a phenylbutyric acid salt, a valproic acid salt, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion (e.g. a lithium salt, a sodium salt, or a potassium salt), an alkaline earth ion (e.g. a magnesium salt, or a calcium salt), or an aluminum ion (e.g. an aluminum salt). In some cases, compounds described herein may coordinate with an organic base to form a salt, such as, but not limited to, an ethanolamine salt, a diethanolamine salt, a triethanolamine salt, a tromethamine salt, a N-methylglucamine salt, a dicyclohexylamine salt, or a tris(hydroxymethyl)methylamine salt. In other cases, compounds described herein may form salts with amino acids such as, but not limited to, an arginine salt, a lysine salt, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[00215] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms.

Certain Terminology

[00216] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. In this application, the use of "or" or "and" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00217] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl group is saturated or unsaturated. The alkyl moiety, whether saturated or unsaturated, may be branched or straight chain. The "alkyl" group may have 1 to 6 carbon atoms (whenever it appears herein, a numerical range such as "1 to 6" refers to each integer in the given range; *e.g.*, "1 to 6 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). In one aspect the alkyl is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary butyl, pentyl, neopentyl, hexyl, allyl, vinyl, acetylene, but-2-enyl, but-3-enyl, and the like. In some embodiments, 1 or more hydrogen atoms of an alkyl are replaced with 1 or more deuterium atoms.

[00218] The term "alkylene" refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. Typical alkylene groups include, but are not limited to, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and the like.

[00219] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00220] The term "alkylamine" refers to the $-N(alkyl)_xH_y$ group, where x and y are selected from the group x=1, y=1 and x=2, y=0.

[00221] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. Aromatics are optionally substituted. The term "aromatic" includes both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[00222] The term "carbocyclic" or "carbocycle" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon.

[00223] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl groups are optionally substituted. In one aspect, an aryl is a phenyl or a naphthalenyl. In one aspect, an aryl is a phenyl. In one aspect, an aryl is a C_6-C_{10}aryl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group). In some embodiments, 1 or more hydrogen atoms of an aryl are replaced with 1 or more deuterium atoms

[00224] The term "cycloalkyl" refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Cycloalkyl groups may be substituted or unsubstituted. Depending on the structure, a cycloalkyl group can be a monoradical or a diradical (i.e., an cycloalkylene group, such as, but not limited to, cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, cyclopentan-1,1-diyl, cyclohexan-1,1-diyl, cyclohexan-1,4-diyl, cycloheptan-1,1-diyl, and the like). In one aspect, a cycloalkyl is a C_3-C_6cycloalkyl.

[00225] The term "halo" or, alternatively, "halogen" or "halide" means fluoro (F), chloro (Cl), bromo (Br) or iodo (I). In some embodiments, halogen is F or Cl. In some embodiments, halogen is F.

[00226] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoralkyl is a C_1-C_6fluoroalkyl. In some embodiments, a fluoroalkyl is a monofluoroalkyl, wherein one hydrogen atom of the alkyl is replaced by a fluorine atom. In some embodiments, a fluoroalkyl is a difluoroalkyl, wherein two hydrogen atoms of the alkyl are replaced by a fluorine atom. In some embodiments, a fluoroalkyl is a trifluoroalkyl, wherein three hydrogen atom of the alkyl are replaced by a fluorine atom. In some embodiments, a fluoroalkyl is a monofluoroalkyl, difluoroalkyl, or trifluoroalkyl. In some embodiments, a monofluoroalkyl is $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$.

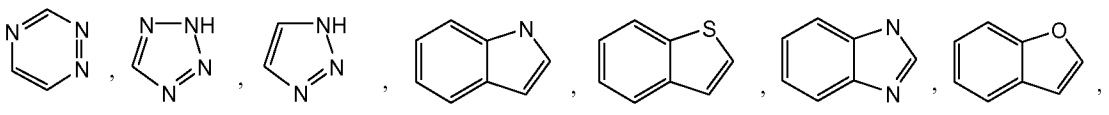
[00227] The term "fluoroalkylene" refers to a divalent fluoroalkyl radical. Any of the above mentioned monovalent fluoroalkyl groups may be an fluoroalkylene by abstraction of a second hydrogen atom from the fluoroalkyl. Typical alkylene groups include, but are not limited to, $-CF_2-$, CHF-, $-CH(CF_3)-$, $-C(CF_3)_2-$, $-CHFCH_2-$, $-CH_2CHF-$, $-CF_2CH_2-$, $-CH_2CF_2-$, $-CH_2CH(CF_3)-$, $-CH_2CH(CHF_2)-$, $-CH_2CH(CFH_2)-$ and the like.

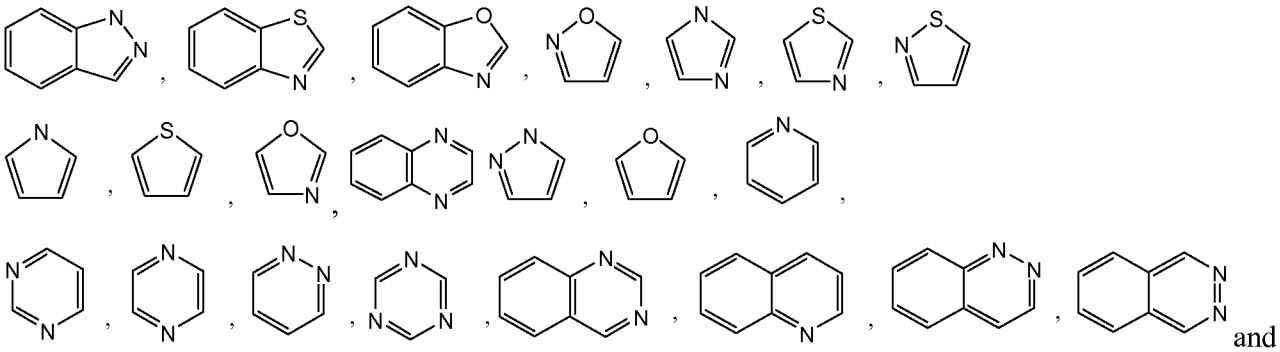
[00228] The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (e.g. –NH-, -N(alkyl)-), sulfur, or combinations thereof. In one aspect, a heteroalkyl is a C_1-C_6heteroalkyl. In some embodiments, a

heteroalkyl is a C_1-C_4heteroalkyl. In some embodiments, a heteroalkyl is an alkyl group in which one or more skeletal atoms of the alkyl is oxygen (e.g. a hydroxyalkyl or an alkoxyalkyl).

[00229] The term "heterocycle" or "heterocyclic" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include groups having only 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3-membered heterocyclic group is aziridinyl. An example of a 4-membered heterocyclic group is azetidinyl. An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups may be C-attached (or C-linked) or *N*-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles may ber substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one.

[00230] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryl groups include the following moieties:





and the like. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. In some embodiments, a heteroaryl contains 0-3 N atoms in the ring. In some embodiments, a heteroaryl contains 1-3 N atoms in the ring. In some embodiments, a heteroaryl contains 0-3 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl is a monocyclic or bicyclic heteroaryl. In some embodiments, heteroaryl is a C_1-C_9heteroaryl. In some embodiments, monocyclic heteroaryl is a C_1-C_5heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, bicyclic heteroaryl is a C_6-C_9heteroaryl. Depending on the structure, a heteroaryl group can be a monoradical or a diradical (i.e., a heteroarylene group).

[00231] A "heterocycloalkyl" or "heteroalicyclic" group refers to a cycloalkyl group wherein at least one of the carbon atoms of the cycloalkyl is relaced with nitrogen (unsubstituted or substituted, e.g. –NH-, -NR^{23}-), oxygen (-O-), or sulfur (e.g. –S-, -S(=O)- or –$S(=O)_2$-). The radicals may be fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is selected from oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and indolinyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[00232] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[00233] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00234] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl,

cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, nitro, haloalkyl, fluoroalkyl, fluoroalkoxy, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. In some embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(alkyl)$, $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic, saturated or unsaturated carbon atoms, excluding aromatic carbon atoms) includes oxo (=O).

[00235] In certain embodiments, the compounds presented herein possess one or more stereocenters and each center independently exists in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns.

[00236] The methods and formulations described herein include the use of *N*-oxides (if appropriate), crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having the structure of Formula (I), (II), (III), (IV), (V), or (VI), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In specific embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In other embodiments, the compounds described herein exist in unsolvated form.

[00237] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00238] The term "modulate" as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00239] The term "modulator" as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an antagonist. In some embodiments, a modulator is a degrader.

[00240] "Selective estrogen receptor modulator" or "SERM" as used herein, refers to a molecule that differentially modulates the activity of estrogen receptors in different tissues. For example, in some embodiments, a SERM displays ER antagonist activity in some tissues and ER agonist activity in other tissues. In some embodiments, a SERM displays ER antagonist activity in some tissues and minimal or no ER agonist activity in other tissues. In some embodiments, a SERM displays ER antagonist activity in breast tissues, ovarian tissues, endometrial tissues, and/or cervical tissues but minimal or no ER agonist activity in uterine tissues.

[00241] The term "antagonist" as used herein, refers to a small -molecule agent that binds to a nuclear hormone receptor and subsequently decreases the agonist induced transcriptional activity of the nuclear hormone receptor.

[00242] The term "agonist" as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently increases nuclear hormone receptor transcriptional activity in the absence of a known agonist.

[00243] The term "inverse agonist" as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently decreases the basal level of nuclear hormone receptor transcriptional activity that is present in the absence of a known agonist.

[00244] The term "degrader" as used herein, refers to a small molecule agent that binds to a nuclear hormone receptor and subsequently lowers the steady state protein levels of said receptor. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95%. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 65%. In some embodiments, a degrader as described herein lowers steady state estrogen receptor levels by at least 85%.

[00245] The term "selective estrogen receptor degrader" or "SERD" as used herein, refers to a small molecule agent that preferentially binds to estrogen receptors versus other receptors and subsequently lowers the steady state estrogen receptor levels.

[00246] The term "ER-dependent", as used herein, refers to diseases or conditions that would not occur, or would not occur to the same extent, in the absence of estrogen receptors.

[00247] The term "ER-mediated", as used herein, refers to diseases or conditions that would not occur in the absence of estrogen receptors but can occur in the presence of estrogen receptors.

[00248] The term "ER-sensitive", as used herein, refers to diseases or conditions that would not occur, or would not occur to the same extent, in the absence of estrogens.

[00249] The term "cancer" as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but is not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, uterus, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid),

prostate, skin (melanoma or basal cell cancer) or hematological tumors (such as the leukemias and lymphomas) at any stage of the disease with or without metastases.

[00250] Additional non-limiting examples of cancers include, acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenström macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sézary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, Wilms tumor.

[00251] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00252] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00253] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00254] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00255] The terms "kit" and "article of manufacture" are used as synonyms.

[00256] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Metabolites of the compounds disclosed herein are optionally identified either by administration of compounds to a host

and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

[00257] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[00258] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Routes of Administration

[00259] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00260] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

Pharmaceutical Compositions/Formulations

[00261] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack

Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00262] Provided herein are pharmaceutical compositions that include a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable inactive ingredient. In some embodiments, the compounds described herein are administered as pharmaceutical compositions in which a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is mixed with other active ingredients, as in combination therapy. In other embodiments, the pharmaceutical compositions include other medicinal or pharmaceutical agents, carriers, adjuvants, preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In yet other embodiments, the pharmaceutical compositions include other therapeutically valuable substances.

[00263] A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, with other chemical components (i.e. pharmaceutically acceptable inactive ingredients), such as carriers, excipients, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, or one or more combination thereof. The pharmaceutical composition facilitates administration of the compound to a mammal.

[00264] A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[00265] The pharmaceutical formulations described herein are administered to a subject by appropriate administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00266] Pharmaceutical compositions including a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are manufactured in a conventional manner, such as, by

way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00267] The pharmaceutical compositions will include at least one compound of Formula (I), (II), (III), (IV), (V), or (VI), as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides (if appropriate), crystalline forms, amorphous phases, as well as active metabolites of these compounds having the same type of activity. In some embodiments, compounds described herein exist in unsolvated form or in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00268] The pharmaceutical compositions described herein, which include a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, solid oral dosage forms, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00269] Pharmaceutical preparations that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In some embodiments, the push-fit capsules do not include any other ingredient besides the capsule shell and the active ingredient. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

[00270] All formulations for oral administration are in dosages suitable for such administration.

[00271] In one aspect, solid oral soage forms are prepared by mixing a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, with one or more of the following: antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[00272] In some embodiments, the solid dosage forms disclosed herein are in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder, a capsule, solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, beads, pellets, granules. In other embodiments, the pharmaceutical

formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet. In other embodiments, pharmaceutical formulation is in the form of a capsule.

[00273] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing particles of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutical excipients to form a bulk blend composition. The bulk blend is readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. In some embodiments, the individual unit dosages include film coatings. These formulations are manufactured by conventional formulation techniques.

[00274] Conventional formulation techniques include, e.g., one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

[00275] In some embodiments, tablets will include a film surrounding the final compressed tablet. In some embodiments, the film coating can provide a delayed release of the compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, from the formulation. In other embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). Film coatings including Opadry® typically range from about 1% to about 3% of the tablet weight.

[00276] A capsule may be prepared, for example, by placing the bulk blend of the formulation of the compound described above, inside of a capsule. In some embodiments, the formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the formulation is placed in a sprinkle capsule, wherein the capsule is swallowed whole or the capsule is opened and the contents sprinkled on food prior to eating.

[00277] In various embodiments, the particles of the compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the formulation into the gastrointestinal fluid.

[00278] In still other embodiments, effervescent powders are also prepared. Effervescent salts have been used to disperse medicines in water for oral administration.

[00279] In some embodiments, the pharmaceutical solid oral dosage forms are formulated to provide a controlled release of the active compound. Controlled release refers to the release of the active compound from a dosage form in which it is incorporated according to a desired profile over an

extended period of time. Controlled release profiles include, for example, sustained release, prolonged release, pulsatile release, and delayed release profiles. In contrast to immediate release compositions, controlled release compositions allow delivery of an agent to a subject over an extended period of time according to a predetermined profile. Such release rates can provide therapeutically effective levels of agent for an extended period of time and thereby provide a longer period of pharmacologic response while minimizing side effects as compared to conventional rapid release dosage forms. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations.

[00280] In some embodiments, the solid dosage forms described herein are formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to affect release in the small intestine or large intestine. In one aspect, the enteric coated dosage form is a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. In one aspect, the enteric coated oral dosage form is in the form of a capsule containing pellets, beads or granules.

[00281] Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[00282] In other embodiments, the formulations described herein are delivered using a pulsatile dosage form. A pulsatile dosage form is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Exemplary pulsatile dosage forms and methods of their manufacture are disclosed in U.S. Pat. Nos. 5,011,692, 5,017,381, 5,229,135, 5,840,329 and 5,837,284. In one embodiment, the pulsatile dosage form includes at least two groups of particles, (i.e. multiparticulate) each containing the formulation described herein. The first group of particles provides a substantially immediate dose of the active compound upon ingestion by a mammal. The first group of particles can be either uncoated or include a coating and/or sealant. In one aspect, the second group of particles comprises coated particles. The coating on the second group of particles provides a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. Suitable coatings for pharmaceutical compositions are described herein or in the art.

[00283] In some embodiments, pharmaceutical formulations are provided that include particles of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, and at least one dispersing agent or suspending agent for oral administration to a subject. The formulations may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

[00284] In one aspect, liquid formulation dosage forms for oral administration are in the form of aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups. See, e.g., Singh *et al.*., Encyclopedia of Pharmaceutical Technology, 2nd Ed., pp. 754-757 (2002). In addition to the particles of the compound of Formula (I), the liquid dosage forms include additives, such as: (a) disintegrating agents; (b) dispersing agents; (c) wetting agents; (d) at least one preservative, (e) viscosity enhancing agents, (f) at least one sweetening agent, and (g) at least one flavoring agent. In some embodiments, the aqueous dispersions can further include a crystalline inhibitor.

[00285] Buccal formulations that include a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are administered using a variety of formulations known in the art. For example, such formulations include, but are not limited to, U.S. Pat. Nos. 4,229,447, 4,596,795, 4,755,386, and 5,739,136. In addition, the buccal dosage forms described herein can further include a bioerodible (hydrolysable) polymeric carrier that also serves to adhere the dosage form to the buccal mucosa. For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner.

[00286] In some embodiments, compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are prepared as transdermal dosage forms. In one embodiment, the transdermal formulations described herein include at least three components: (1) a formulation of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof; (2) a penetration enhancer; and (3) an aqueous adjuvant. In some embodiments the transdermal formulations include additional components such as, but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulation further includes a woven or non-woven backing material to enhance absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein can maintain a saturated or supersaturated state to promote diffusion into the skin.

[00287] In one aspect, formulations suitable for transdermal administration of compounds described herein employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In one aspect, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. Still further, transdermal delivery of the compounds described herein can be accomplished by means of iontophoretic patches and the like. In one aspect, transdermal patches provide controlled delivery of the active compound. In one aspect, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[00288] In one aspect, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is formulated into a pharmaceutical composition suitable for intramuscular, subcutaneous, or intravenous injection. In one aspect, formulations suitable for intramuscular, subcutaneous, or intravenous injection include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like), vegetable oils and organic esters, such as ethyl oleate. In some embodiments, formulations suitable for subcutaneous injection contain additives such as preserving, wetting, emulsifying, and dispensing agents. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[00289] For intravenous injections, compounds described herein are formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer.

[00290] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are known.

[00291] Parenteral injections may involve bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical composition described herein may be in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In one aspect, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[00292] In certain embodiments, delivery systems for pharmaceutical compounds may be employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein can also include an mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00293] In some embodiments, the compounds described herein may be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Methods of Dosing and Treatment Regimens

[00294] In one embodiment, the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from a reduction of estrogen receptor activity. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00295] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00296] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include admistering to a mammal, who previously experienced at least one symtom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00297] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00298] In certain embodiments wherein a patient's status does improve, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of

example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00299] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00300] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but can nevertheless be determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00301] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00302] In one embodiment, the daily dosages appropriate for the compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, described herein are from about 0.01 to about 10 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00303] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} and the ED_{50}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

Combination Treatments

[00304] In certain instances, it is appropriate to administer at least one compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in combination with one or more other therapeutic agents.

[00305] In one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant may have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00306] In one specific embodiment, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is co-administered with a second therapeutic agent, wherein the compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, and the second therapeutic agent modulate different aspects of the disease, disorder or condition being treated, thereby providing a greater overall benefit than administration of either therapeutic agent alone.

[00307] In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[00308] In certain embodiments, different therapeutically-effective dosages of the compounds disclosed herein will be utilized in formulating pharmaceutical composition and/or in treatment regimens when the compounds disclosed herein are administered in combination with one or more additional agent, such as an additional therapeutically effective drug, an adjuvant or the like. Therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens can be determined by means similar to those set forth hereinabove for the actives themselves. Furthermore, the methods of prevention/treatment described herein encompasses the use of metronomic dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects. In some embodiments, a combination treatment regimen encompasses treatment regimens in which administration of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is initiated prior to, during, or after treatment with a second agent described herein, and continues until any time during treatment with the second agent or after termination of treatment with the second agent. It also includes treatments in which a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, and the second agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[00309] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors (e.g. the disease, disorder or condition from which the subject suffers; the age, weight, sex, diet, and medical condition of the subject). Thus, in some instances, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

[00310] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In additional embodiments, when co-administered with one or more other therapeutic agents, the compound provided herein is administered either simultaneously with the one or more other therapeutic agents, or sequentially.

[00311] In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills).

[00312] The compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, as well as combination therapies, are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, in one embodiment, the compounds described herein are used as a prophylactic and are administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In another embodiment, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In specific embodiments, a compound described herein is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease. In some embodiments, the length required for treatment varies, and the treatment length is adjusted to suit the specific needs of each subject. For example, in specific embodiments, a compound described herein or a formulation containing the compound is administered for at least 2 weeks, about 1 month to about 5 years.

Exemplary Agent for use in Combination Therapy

[00313] In some embodiments, methods for treatment of estrogen receptor-dependent or estrogen receptor-mediated conditions or diseases, such as proliferative disorders, including cancer, comprises administration to a mammal a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent.

[00314] In some embodiments, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in combination with hormone blocking therapy, chemotherapy, radiation therapy, monoclonal antibodies, or combinations thereof.

[00315] Hormone blocking therapy includes the use of agents that block the production of estrogens or block the estrogen receptors. In some embodiments, hormone blocking therapy includes the use of estrogen receptor modulators and/ aromatase inhibitors. Estrogen receptor modulators include triphenylethylene derivatives (e.g. tamoxifen, toremifene, droloxifene, 3-hydroxytamoxifen, idoxifene, TAT-59 (a phosphorylated derivative of 4- hydroxytamoxifen) and GW5638 (a carboxylic acid derivative of tamoxifen)); non-steroidal estrogen receptor modulators (e.g. raloxifene, LY353381 (SERM3) and LY357489); steroidal estrogen receptor modulators (e.g. ICI-182,780). Aromatase inhibitors include steroidal aromatase inhibitors and non-steroidal aromatase inhibitors. Steroidal aromatase inhibitors include, but are not limited to, such exemestane. Non-steroidal aromatase inhibitors include, but are not limited to, as anastrozole, and letrozole.

[00316] Chemotherapy includes the use of anti-cancer agents.

[00317] Monoclonal antibodies include, but are not limited to, trastuzumab (Herceptin).

[00318] In some embodiments, the at least one additional therapeutic agent for use in combination with the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, include one or more of the following: abiraterone; abarelix; adriamycin; aactinomycin; acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; alemtuzumab; allopurinol; alitretinoin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; aminolevulinic acid; amifostine; amsacrine; anastrozole; anthramycin; aprepitant; arsenic trioxide; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; bendamustine hydrochloride; benzodepa; bevacizumab; bexarotene; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin; bleomycin sulfate; bortezomib; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; capecitabine; cedefingol; cetuximab; chlorambucil; cirolemycin; cisplatin; cladribine; clofarabine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dasatinib; daunorubicin hydrochloride; dactinomycin; darbepoetin alfa; decitabine; degarelix; denileukin diftitox; dexormaplatin; dexrazoxane hydrochloride; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; eltrombopag olamine; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; epoetin alfa; erbulozole; erlotinib hydrochloride; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; everolimus; exemestane; fadrozole hydrochloride; fazarabine; fenretinide; filgrastim; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; fulvestrant; gefitinib; gemcitabine; gemcitabine hydrochloride; gemcitabine –cisplatin; gemtuzumab ozogamicin; goserelin acetate; histrelin acetate; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; ibritumomab tiuxetan; idarubicin; ifosfamide; imatinib mesylate; imiquimod; interleukin Il (including recombinant interleukin II, or rlL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3;

interferon beta-l a; interferon gamma-l b; iproplatin; irinotecan hydrochloride; ixabepilone; lanreotide acetate; lapatinib; lenalidomide; letrozole; leuprolide acetate; leucovorin calcium; leuprolide acetate; levamisole; liposomal cytarabine; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; methoxsalen; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin C; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nandrolone phenpropionate; nelarabine; nilotinib; nocodazoie; nofetumomab; nogalamycin; ofatumumab; oprelvekin; ormaplatin; oxaliplatin;oxisuran; paclitaxel; palifermin; palonosetron hydrochloride; pamidronate; pegfilgrastim; pemetrexed disodium; pentostatin; panitumumab; pazopanib hydrochloride; pemetrexed disodium; plerixafor; pralatrexate; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; quinacrine; raloxifene hydrochloride; rasburicase; recombinant HPV bivalent vaccine; recombinant HPV quadrivalent vaccine; riboprine; rogletimide; rituximab; romidepsin; romiplostim; safingol; safingol hydrochloride; sargramostim; semustine; simtrazene; sipuleucel-T; sorafenib; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; sunitinib malate; talisomycin; tamoxifen citrate; tecogalan sodium; tegafur; teloxantrone hydrochloride; temozolomide; temoporfin; temsirolimus; teniposide; teroxirone; testolactone; thalidomide;thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; topotecan hydrochloride; toremifene; tositumomab and I 131 Iodine tositumomab; trastuzumab; trestolone acetate; tretinoin; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; valrubicin; vapreotide; verteporfin; vinblastine; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorinostat; vorozole; zeniplatin; zinostatin; zoledronic acid; or zorubicin hydrochloride.

[00319] In some embodiments, the at least one additional chemotherapeutic agent is selected from, by way of example only, alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

[00320] In one aspect, the compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is administered or formulated in combination with one or more anti-cancer agents. In some embodiments, one or more of the anti-cancer agents are proapoptotic agents. Examples of anti-cancer agents include, but are not limited to, any of the following: gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib, geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, or PD184352, paclitaxel, and analogs of paclitaxel. Compounds that have the basic taxane skeleton as a common structure feature, have also been shown to have the ability to arrest cells in the G2-M phases due to stabilized microtubules and may be useful for treating cancer in combination with the compounds described herein.

[00321] Further examples of anti-cancer agents for use in combination with the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, include inhibitors of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002; Syk inhibitors; mTOR inhibitors; and antibodies (e.g., rituxan).

[00322] Further examples of anti-cancer agents for use in combination with the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, include aromatase inhibitors. Aromatase inhibitors include steroidal aromatase inhibitors and non-steroidal aromatase inhibitors. Steroidal aromatase inhibitors include, but are not limited to, exemestane. Non-steroidal aromatase inhibitors include, but are not limited to, anastrozole, and letrozole.

[00323] Yet other anticancer agents for use in combination with the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, include alkylating agents, antimetabolites, natural products, or hormones, e.g., nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, etc.), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, ete.), or triazenes (decarbazine, etc.). Examples of antimetabolites include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin).

[00324] Examples of natural products for use in combination with the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, include but are not limited to vinca alkaloids (e.g., vinblastin, vincristine), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), or biological response modifiers (e.g., interferon alpha).

[00325] Examples of alkylating agents for use in combination with the compounds of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, include, but are not limited to,

nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan, etc.), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin, etc.), or triazenes (decarbazine, ete.).

[00326] In some embodiments, compounds of F Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, are used to treat cancer in combination with: a second antiestrogen (e.g., tamoxifen), an antiandrogen (e.g., bicalutamide, flutamide), a gonadotropin releasing hormone analog (e.g., leuprolide).

[00327] Other agents that can be used in the methods and compositions described herein for the treatment or prevention of cancer include platinum coordination complexes (e.g., cisplatin, carboblatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide).

[00328] Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules include without limitation the following marketed drugs and drugs in development: Erbulozole, Dolastatin 10, Mivobulin isethionate, Vincristine, NSC-639829, Discodermolide, ABT-751, Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride, Epothilones (such as Epothilone A, Epothilone B, Epothilone C, Epothilone D, Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B, 21-hydroxyepothilone D, 26-fluoroepothilone, Auristatin PE, Soblidotin, Vincristine sulfate, Cryptophycin 52, Vitilevuamide, Tubulysin A, Canadensol, Centaureidin, Oncocidin A1 Fijianolide B, Laulimalide, Narcosine, Nascapine, Hemiasterlin, Vanadocene acetylacetonate, Indanocine Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, Diazonamide A, Taccalonolide A, Diozostatin, (-)-Phenylahistin, Myoseverin B, Resverastatin phosphate sodium.

[00329] In one aspect, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is co-administered with thrombolytic agents (e.g., alteplase anistreplase, streptokinase, urokinase, or tissue plasminogen activator), heparin, tinzaparin, warfarin, dabigatran (e.g., dabigatran etexilate), factor Xa inhibitors (e.g., fondaparinux, draparinux, rivaroxaban, DX-9065a, otamixaban, LY517717, or YM150), ticlopidine, clopidogrel, CS-747 (prasugrel, LY640315), ximelagatran, or BIBR 1048.

[00330] In some embodiments, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is used in combination with anti-emetic agents to treat nausea or emesis, which may result from the use of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, anti-cancer agent(s) and/or radiation therapy.

[00331] Anti-emetic agents include, but are not limited to: neurokinin-1 receptor antagonists, 5HT3 receptor antagonists (such as ondansetron, granisetron, tropisetron, palonosetron, and zatisetron), $GABA_B$ receptor agonists (such as baclofen), corticosteroids (such as dexamethasone, prednisone, prednisolone, or others), dopamine antagonists (such as, but not limited to, domperidone, droperidol, haloperidol, chlorpromazine, promethazine, prochlorperazine, metoclopramide), antihistamines (H1 histamine receptor antagonists, such as but not limited to, cyclizine, diphenhydramine, dimenhydrinate, meclizine, promethazine, hydroxyzine), cannabinoids (such as but not limited to, cannabis, marinol, dronabinol), and others (such as, but not limited to, trimethobenzamide; ginger, emetrol, propofol).

[00332] In some embodiments, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is used in combination with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin-α).

[00333] In some embodiments, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is used in combination with an agent useful in the treatment of neutropenia. Examples of agents useful in the treatment of neutropenia include, but are not limited to, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

[00334] In some embodiments, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is adminsitered with corticosteroids. Corticosteroids, include, but are not limited to: betamethasone, prednisone, alclometasone, aldosterone, amcinonide, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, cortisone, cortivazol, deflazacort, deoxycorticosterone, desonide, desoximetasone, desoxycortone, dexamethasone, diflorasone, diflucortolone, difluprednate, fluclorolone, fludrocortisone, fludroxycortide, flumetasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin, fluocortolone, fluorometholone, fluperolone, fluprednidene, fluticasone, formocortal, halcinonide, halometasone, hydrocortisone/cortisol, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone butyrate, loteprednol, medrysone, meprednisone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, paramethasone, prednicarbate, prednisone/prednisolone, rimexolone, tixocortol, triamcinolone, and ulobetasol.

[00335] In one embodiment, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is administered to a mammal in combination with a non-steroidal anti-inflammatory drug (NSAID). NSAIDs include, but are not limited to: aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate,

meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, COX-2 specific inhibitors (such as, but not limited to, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, CS-502, JTE-522, L-745,337 and NS398).

[00336] In some embodiments, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is coadministered with an analgesic.

[00337] In some embodiments, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is used in combination with radiation therapy (or radiotherapy). Radiation therapy is the treatment of cancer and other diseases with ionizing radiation. Radiation therapy can be used to treat localized solid tumors, such as cancers of the skin, tongue, larynx, brain, breast, prostate, colon, uterus and/or cervix. It can also be used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively).

[00338] A technique for delivering radiation to cancer cells is to place radioactive implants directly in a tumor or body cavity. This is called internal radiotherapy (brachytherapy, interstitial irradiation, and intracavitary irradiation are types of internal radiotherapy.) Using internal radiotherapy, the radiation dose is concentrated in a small area, and the patient stays in the hospital for a few days. Internal radiotherapy is frequently used for cancers of the tongue, uterus, prostate, colon, and cervix.

[00339] The term "radiotherapy" or "ionizing radiation" include all forms of radiation, including but not limited to α, β, and γ radiation and ultraviolet light.

Kits/Articles of Manufacture

[00340] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from any acceptable material including, e.g., glass or plastic.

[00341] For example, the container(s) can comprise one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[00342] A kit will typically comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package,

container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

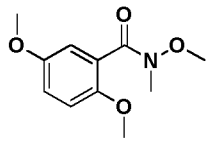
[00343] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

EXAMPLES

[00344] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Intermediate 1

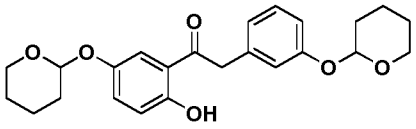
N,2,5-Trimethoxy-N-methylbenzamide



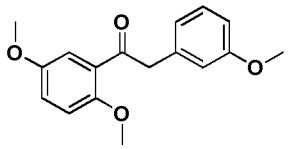
[00345] Oxalyl chloride (3.6 mL, 41.3 mmol) was added to a solution of 2,5-dimethoxybenzoic acid (6.00 g, 33.0 mmol) in DCM (100 mL) at room temperature. Then, DMF (0.2 mL) was added to the mixture. The resulting solution was stirred at room temperature for 2 h, and the solvent was removed on a rotary evaporator. The crude material was placed under vacuum for 30 minutes to remove the residual oxalyl chloride to give the crude acid chloride. Crude material was dissolved in DCM (100 mL) and cooled down to 0 °C. To this solution, *N,O*-dimethylhydroxylamine hydrochloride (4.03 g, 41.32 mmol) and triethylamine (6.8 mL, 48.78 mmol) were added respectively. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for additional 30 min. The reaction was diluted with DCM (50 mL), washed with H_2O (2x100 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude material was purified by silica gel chromatography to yield N,2,5-trimethoxy-N-methylbenzamide (7.32 g, 99%) as clear oil which solidified over time. ^{1}H NMR ($CDCl_3$): δ 7.90 (m, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.58 (br s, 3H), 3.32 (br s, 3H).

Intermediate 2

1-(2-Hydroxy-5-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)ethanone

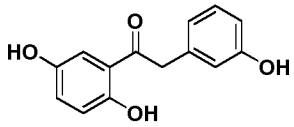


Step 1: 1-(2,5-Dimethoxyphenyl)-2-(3-methoxyphenyl)ethanone



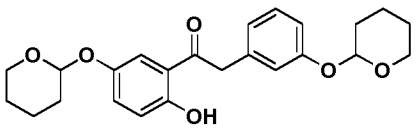
[00346] A 5 mL portion of 3-methoxybenzyl chloride (12.8 mL, 88.1 mmol) in THF (60 mL) was added to a mixture of magnesium (2.88 g, 118 mmol) and iodine (1 crystal) in THF (30 mL). The reaction mixture was stirred until the color disappeared and the remaining solution of 3-methoxybenzyl chloride was added dropwise over 45 min. The mixture was heated at 60 °C for 1 h and then cooled to 0 °C. A solution of **Intermediate 1** (6.65 g 29.6 mmol) in THF (70 mL) was added to this mixture over 30 min at 0 °C. The reaction was stirred for 30 min at 0 °C and quenched with brine (50 mL). The mixture was extracted with ethyl acetate (3x100 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator to give 1-(2,5-dimethoxyphenyl)-2-(3-methoxyphenyl)ethanone (7.99 g, 95%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.25 (m, 2H), 7.01 (dd, 1H), 6.92 (d, 1H), 6.83 (m, 3H), 4.30 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H).

Step 2: 1-(2,5-Dihydroxyphenyl)-2-(3-hydroxyphenyl)ethanone



[00347] To a solution of 1-(2,5-dimethoxyphenyl)-2-(3-methoxyphenyl)ethanone (3.35 g, 11.7 mmol) in DCM (50 mL) at -78 °C, boron tribromide (1M in DCM, 48.0 mL, 48.0 mmol) was added dropwise. The reaction mixture was warmed to 0 °C, stirred for 30 min, re-cooled to -78 °C, and then quenched with methanol (15 mL). The reaction mixture was warmed to room temperature, concentrated on a rotary evaporator and purified by silica gel chromatography to give 1-(2,5-dihydroxyphenyl)-2-(3-hydroxyphenyl)ethanone (1.78 g, 62%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 11.24 (s, 1H), 9.34 (s, 1H), 9.20 (s, 1H), 7.26 (m, 1H), 7.10 (t, 1H), 6.98 (dd, 1H), 6.83 (d, 1H), 6.70(m, 3H), 4.24 (s, 2H).

Step 3: 1-(2-Hydroxy-5-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)ethanone

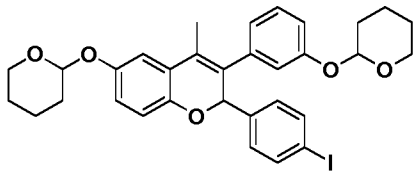


[00348] 3,4-Dihydro-2H-pyran (2.65 g, 30.8 mmol) in DCM (6 mL) was added to a mixture of 1-(2,5-dihydroxyphenyl)-2-(3-hydroxyphenyl)ethanone (1.50 g, 6.15 mmol) and pyridinium *p*-toluene sulfonate (320 mg, 1.27 mmol) in DCM (40 mL). The reaction mixture was stirred at room temperature

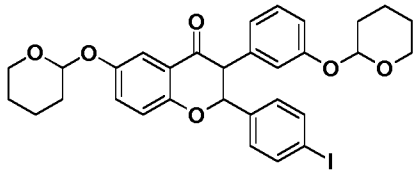
for 1 h and diluted with DCM (100 mL). The solution was washed with sat'd $NaHCO_3$ (2x50 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude material was purified by silica gel chromatography to give 1-(2-hydroxy-5-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)ethanone (2.42 g, 96%) as yellow oil which solidified over time. ^1H NMR ($CDCl_3$): δ 11.88 (s, 1H), 7.60 (m, 1H), 7.30 (m, 2H), 7.00 (m, 2H), 6.92 (m, 2H), 5.42 (m, 1H), 5.28 (m, 1H), 4.25 (s, 2H), 3.92 (m, 2H), 3.62 (m, 2H), 1.55-2.07 (m, 12H).

Intermediate 3

2-(4-Iodophenyl)-4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromene

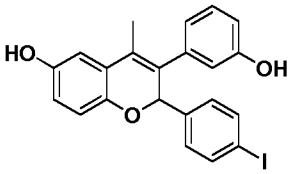


Step 1: 2-(4-Iodophenyl)-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)chroman-4-one



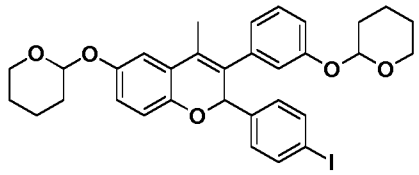
[00349] A solution of **Intermediate 2** (2.41 g, 5.84 mmol), 4-iodobenzaldehyde (1.37 g, 5.91 mmol), piperidine (166 mg, 1.95 mmol), and DBU (301 mg, 1.98 mmol) in *s*-butanol (10 mL) was heated at reflux. Using a Dean-Stark trap, half (5 mL) of the solvent was collected over 45 min, and the reaction was kept at reflux without further concentration for additional 45 min. The reaction mixture was cooled to 90 °C, *i*-propanol (10 mL) was added, and the reaction was allowed to cool to room temperature and stirred overnight. The resulting precipitate was collected by filtration to yield 2-(4-iodophenyl)-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)chroman-4-one (3.17 g, 87%) as a white solid. ^1H NMR (DMSO-d_6): δ 7.63 (d, 2H), 7.42 (m, 1H), 7.33 (m, 1H), 7.21 (d, 2H), 7.07 (m, 2H), 6.79 (m, 3H), 5.88 (m, 1H), 5.48 (m, 1H), 5.31 (m, 1H), 4.60 (d, 1H), 3.40-3.80 (m, 4H), 1.55-1.90 (m, 12H).

Step 2: 3-(3-Hydroxyphenyl)-2-(4-iodophenyl)-4-methyl-2H-chromen-6-ol



[00350] Methyl magnesium chloride (3M in THF, 4.0 mL, 12 mmol) was added dropwise to a solution of 2-(4-iodophenyl)-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)chroman-4-one (1.99 g, 3.18 mmol) in THF (40 mL) at 0 °C. The reaction was stirred at 0 °C for 15 min and allowed to warm to room temperature. After stirring for 2 h, the solution was cooled to 0 °C, quenched with sat'd ammonium chloride, and then allowed to warm to room temperature. Ethyl acetate (100 mL) and H_2O (50 mL) were added, and the layers were separated. The organic layer was dried over Na_2SO_4, concentrated on a rotary evaporator, and purified by silica gel chromatography to yield a white foam (1.75 g). This purified material was heated in 80% acetic acid/H_2O (50 mL) overnight at 90 °C. The solution was diluted with ethyl acetate (100 mL), washed with H_2O (50mL), washed with sat'd $NaHCO_3$ (50 mL), washed with brine (50 mL), and dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude material was purified by silica gel chromatography to give 3-(3-hydroxyphenyl)-2-(4-iodophenyl)-4-methyl-2H-chromen-6-ol (0.99 g, 68 %) as a beige solid. ^{1}H NMR (DMSO-d_6): δ 9.46 (s, 1H), 9.00 (s, 1H), 7.62 (d, 2H), 7.17 (t, 1H), 7.01 (d, 2H), 6.70 (m, 4H), 6.51 (s, 2H), 5.90 (s, 1H), 2.03 (s, 3H).

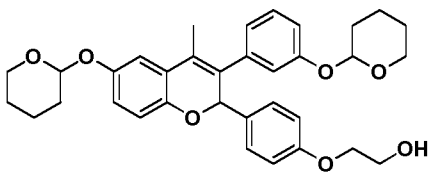
Step 3: 2-(4-Iodophenyl)-4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromene



[00351] 3,4-Dihydro-2H-pyran (1.1 mL, 12 mmol) was added to a solution of 3-(3-hydroxyphenyl)-2-(4-iodophenyl)-4-methyl-2H-chromen-6-ol (990 mg, 2.19 mmol) and pyridinium *p*-toluene sulfonate (115 mg, 0.458 mmol) in DCM (30 mL). The reaction was stirred at room temperature for 3 h, diluted with DCM (100 mL), washed with sat'd $NaHCO_3$ (100 mL), washed with H_2O (2x50 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude material was purified by silica gel chromatography to give 2-(4-iodophenyl)-4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromene (1.30 g, 95%) as a white foam. ^{1}H NMR (DMSO-d_6): δ7.62 (d, 2H), 7.27 (t, 1H), 7.10 (d, 2H), 6.92 (m, 4H), 6.81 (d, 1H), 6.63 (d, 1H), 6.04 (d, 1H), 5.43 (m, 1H), 5.36 (s, 1H), 3.75 (m, 2H), 3.55 (m, 2H), 2.05 (s, 3H), 1.50-1.99 (m, 12H).

Intermediate 4

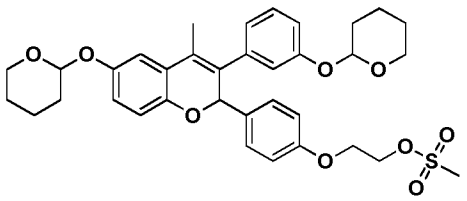
2-(4-(4-Methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethanol



[00352] A mixture of 2-(4-iodophenyl)-4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromene (**Intermediate 3**, 1.0 g, 1.6 mmol), ethane-1,2-diol (0.49 g, 8.0 mmol), copper iodide (0.03 g, 0.16 mmol), 1,10-phenanthroline (0.058 g, 0.32 mmol), potassium carbonate (0.44 g, 3.2 mmol) in butyronitrile (3.2 mL) was degassed three times via nitrogen/vacuum cycles. The reaction mixture was heated at 125 °C for 2 days, allowed to cool to room temperature, and diluted with ethyl acetate. This mixture was filtered through Celite. The organic phase was washed twice with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give 2-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethanol. ^{1}H NMR (DMSO-d_6): δ 7.27-7.13 (m, 3H), 6.98 (t, 1H), 6.93-6.84 (m, 3H), 6.80-6.76 (m, 3H), 6.59 (d, 1H), 5.97 (d, 1H), 5.43 (dt, 1H), 5.34 (br, 1H), 4.79 (t, 1H), 3.88 (t, 2H), 3.80-3.70 (m, 2H), 3.64 (q, 2H), 3.54-3.50 (m, 2H), 2.06 (s, 3H), 1.86-1.66 (m, 6H), 1.59-1.51 (m, 6H).

Intermediate 5

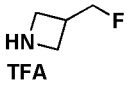
2-(4-(4-Methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethyl methanesulfonate



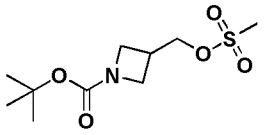
[00353] To a solution of 2-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethanol (**Intermediate 4**, 0.7 g, 1.25 mmol) in DCM (25 mL) at 0 °C, triethylamine (0.26 mL, 1.87 mmol) and methanesulfonyl chloride (0.146 mL, 1.87 mmol) were added respectively. The reaction mixture was stirred at 0 °C for 1 h, and then diluted with DCM. To this mixture, water (20 mL), and sat'd ammonium chloride (20 mL) were added. The layers were separated and the organic layer was washed with water, washed with saturated $NaHCO_3$, washed with brine, dried over Na_2SO_4, and concentrated to give 2-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethyl methanesulfonate (0.7 g). ^{1}H NMR (DMSO-d_6): δ 7.25 (d, 3H), 6.99-6.98 (m, 1H), 6.93-6.87 (m, 3H), 6.85-6.78 (m, 2H), 6.77-6.75 (dd, 1H), 6.61 (d, 1H), 5.98 (d, 1H), 5.43 (d, 1H), 5.34 (br, 1H), 4.47-4.45 (m, 2H), 4.16 (br, 2H), 3.83-3.70 (m, 2H), 3.56-3.47 (m, 2H), 3.18 (s, 3H), 2.05 (s, 3H), 1.92-1.65 (m, 6H), 1.60-1.40 (m, 6H).

Intermediate 6

3-(Fluoromethyl)azetidine 2,2,2-trifluoroacetate

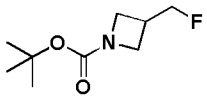


Step 1: tert-Butyl 3-(((methylsulfonyl)oxy)methyl)azetidine-1-carboxylate



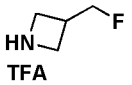
[00354] To a solution of tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (8.8 g, 47 mmol) in DCM (188 mL) at 0 °C, triethylamine (7.8 mL, 56 mmol) was added in one portion. Then, neat methanesulfonyl chloride (4.38 mL, 56 mmol) was added via an additional funnel over 30 minutes. The resulting mixture was stirred at 0 °C for 1.5 h. Upon completion of the reaction, water (100 mL) and sat'd aqueous ammonium chloride (100 mL) were added respectively. The organic phase was separated and washed twice with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford the crude tert-butyl 3-(((methylsulfonyl)oxy)methyl) azetidine-1-carboxylate as a pale yellow oil (12.5 g). This compound was used directly for the next step without further purification.

Step 2: tert-Butyl 3-(fluoromethyl)azetidine-1-carboxylate



[00355] A mixture of tert-butyl 3-(((methylsulfonyl)oxy)methyl)azetidine-1-carboxylate (12.5 g, 47 mmol) and 235 mL tetrabutylammonium fluoride (1M solution in THF, 5 equiv.) was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and excess THF was removed on a rotary evaporator. The residue was dissolved in ethyl acetate. The organic phase was washed with sat'd aqueous $NaHCO_3$, washed with water, washed with brine, dried over Na_2SO_4, filtered and concentrated on a rotary evaporator to give the crude product. This crude product was purified by silica gel chromatography to afford tert-butyl 3-(fluoromethyl)azetidine-1-carboxylate as clear oil (7.5 g). ^{1}H NMR (DMSO-d_6): δ 4.52 (dd, 2H), 3.89 (br, 2H), 3.61 (br, 2H), 2.92-2.77 (m, 1H), 1.36 (s, 9H).

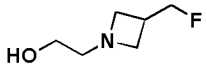
Step 3: 3-(Fluoromethyl)azetidine 2,2,2-trifluoroacetate



[00356] tert-Butyl 3-(fluoromethyl)azetidine-1-carboxylate (0.1 g, 0.53 mmol) and trifluoroacetic acid/DCM (1:1, 5.3 mL) was stir at room temperature for 30 min. Then the reaction mixture was concentrated on a rotary evaporator to afford 3-(fluoromethyl)azetidine 2,2,2-trifluoroacetate as clear oil. ^{1}H NMR (DMSO-d_6; TFA salt): δ 8.74 (br, 2H), 4.54 (dd, 2H), 4.08-3.98 (m, 2H), 3.84-3.76 (m, 2H), 3.20-3.06 (m, 1H).

Intermediate 7

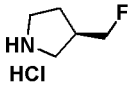
2-(3-(Fluoromethyl)azetidin-1-yl)ethanol



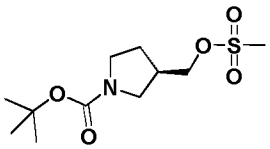
[00357] A mixture of 3-(fluoromethyl)azetidine 2,2,2-trifluoroacetate (**Intermediate 6**, 100 mg, 0.5 mmol), 2-bromoethanol (60 mg, 0.5 mmol), and potassium carbonate (0.2 g, 1.5 mmol) in acetonitrile (5 mL) was heated to 80 °C overnight. After cooling, solids were filtered off and washed with acetonitrile. The filtrate was concentrated on a rotary evaporator to give a residue that was purified by silica gel chromatography eluting with 10:7 ethyl acetate/hexanes to 10:7:2:1 ethyl acetate/hexane/methanol/triethylamine to afford 52 mg of 2-(3-(fluoromethyl)azetidin-1-yl)ethanol as a pale yellow oil. ^{1}H NMR (DMSO-d_6): δ 5.13 (t, 1H), 4.62 (d, 1H), 4.50 (d, 1H), 4.06 (t, 2H), 3.84 (dd, 2H), 3.54 (q, 2H), 3.11 (t, 2H), 3.06-3.03 (m, 1H).

Intermediate 8

(*R*)-3-(Fluoromethyl)pyrrolidine hydrochloride

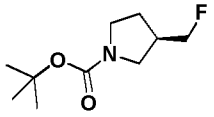


Step 1: (*R*)-tert-Butyl 3-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate



[00358] A mixture of (R)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (21.5 g, 107 mmol) and triethylamine (30 mL, 214 mmol) in dichloromethane (250 mL) was cooled to 0 °C. Methanesulfonyl chloride (12.5 mL, 160.5 mmol) was added dropwise via an addition funnel and the resulting mixture was stirred at 0 °C then gradually warmed to room temperature over 3 h. A 10% aqueous citric acid solution was added and the two layers were separated. The organic layer was washed with 10% aqueous citric acid, sat'd aqueous $NaHCO_3$, and brine. The organic layer was dried over sodium sulfate, filtered and the solvent removed on a rotary evaporator to afford 30 g of (*R*)-tert-butyl 3-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate as an orange oil that was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.17 (m, 2H), 3.33 (m, 2H), 3.20 (m, 1H), 3.18 (s, 3H), 3.00 (m, 1H), 2.55 (m, 1H), 2.01 (m, 1H), 1.53 (m, 1H), 1.40 (s, 9H).

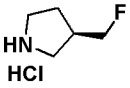
Step 2: (*R*)-tert-Butyl 3-(fluoromethyl)pyrrolidine-1-carboxylate



[00359] Tetrabutylammonium fluoride (1M solution in THF, 530 mL) was added to (*R*)-tert-butyl 3-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (30 g from previous step) and the resulting

mixture was refluxed overnight. After cooling, the solvent was removed and the residue was partitioned between 10% aqueous citric acid and dichloromethane. The organic layer was washed with water, dried over sodium sulfate, filtered and the solvent was removed on a rotary evaporator. The residue was purified by flash chromatography on a silica gel column (0 to 50% ethyl acetate/hexanes) to afford 14.3g of (*R*)-tert-butyl 3-(fluoromethyl)pyrrolidine-1-carboxylate as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.49-4.41 (m, 1H), 4.37-4.29 (m, 1H), 3.40-3.28 (m, 2H), 3.24-3.18 (m, 1H), 3.02-2.98 (m, 1H), 2.58-2.52 (m, 1H), 1.95-1.88 (m, 1H), 1.67-1.54 (m, 1H), 1.38 (s, 9H).

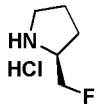
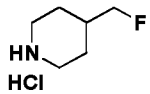
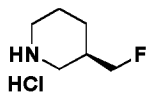
Step 3: (*R*)-3-(Fluoromethyl)pyrrolidine hydrochloride



[00360] (*R*)-tert-Butyl 3-(fluoromethyl)pyrrolidine-1-carboxylate (14.3 g, 70.4 mmol) in 1,4-dioxane (60 mL) was cooled in an ice bath. HCl (4M in 1,4-dioxane, 44 mL, 176 mmol) was then added and the resulting pink solution was stirred at room temperature overnight. The solvent was removed on a rotary evaporator and the residue was triturated with diethyl ether. Diethyl ether was removed under vacuum and the pink solid was dried to afford 9.5 g of (*R*)-3-(fluoromethyl)pyrrolidine hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6; HCl salt) δ 9.35 (bs, 2H), 4.57-4.47 (m, 1H), 4.44-4.33 (m, 1H), 3.33-3.10 (m, 3H), 2.95-2.87 (m, 1H), 2.69-2.57 (m, 1H), 2.005-1.97 (m, 1H), 1.70-1.61 (m, 1H).

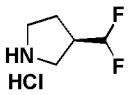
[00361] Intermediates in Table 2 were prepared from commercially available amines following the general procedures described for **Intermediate 8**.

Table 2

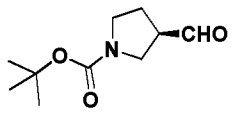
Intermediate	Structure	Name and ^{1}H NMR Data
9		**(S)-2-(fluoromethyl)pyrrolidine hydrochloride:** ^{1}H NMR (DMSO-d_6; HCl salt): δ 9.52 (br, 1H), 9.15 (br, 1H), 4.77-4.22 (m, 2H), 3.88-3.73 (m, 1H), 3.17 (t, 2H), 2.08-1.98 (m, 1H), 1.98-1.82 (m, 2H), 1.67-1.59 (m, 1H).
10		**4-(Fluoromethyl)piperidine hydrochloride :** ^{1}H NMR (DMSO-d_6; HCl salt): δ 9.22 (br, 1H), 8.90 (br, 1H), 4.30 (dd, 2H), 3.27-3.18 (m, 2H), 2.90-2.77 (m, 2H), 2.03-1.87 (m, 1H), 1.81-1.72 (m, 2H), 1.52-1.39 (m, 2H).
11		**(R)-3-(fluoromethyl)piperidine hydrochloride:** ^{1}H NMR (DMSO-d_6: HCl salt): δ 9.11 (br, 2H), 4.49-4.24 (m, 2H), 3.21(t, 2H), 2.80-2.62 (m, 2H), 2.22-2.07 (m, 1H), 1.82-1.63 (m, 3H), 1.32-1.21 (m, 1H).

Intermediate 12

(*R*)-3-(Difluoromethyl)pyrrolidine hydrochloride

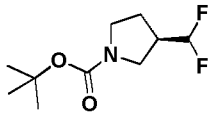


Step 1: (*R*)-tert-Butyl 3-formylpyrrolidine-1-carboxylate



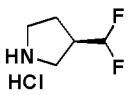
[00362] DMSO (1.4 mL, 19.69 mmol) in dichloromethane (2 mL) was added dropwise to a solution of oxalyl chloride (0.86 mL, 9.85 mmol) in dichloromethane (10 mL) at -78°C. After 10 min at -78 °C, (*R*)-tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (1.8 g, 8.95 mmol) in dichloromethane (6 mL) was added dropwise. After the resulting mixture was stirred at -78 °C for 30 min, triethylamine (6.2 mL, 44.75 mmol) was added and the mixture was stirred at -78 °C for 45 min then at room temperature for 30 min. Water was added to the reaction mixture and the two layers were separated. The organic layer was washed with water, dried over sodium sulfate, filtered and the solvent removed. The crude material was purified by flash chromatography on silica gel eluting with 0 to 50% ethyl acetate/hexanes to afford 0.6 g of (*R*)-tert-butyl 3-formylpyrrolidine-1-carboxylate as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 3.54 (dd, 1H), 3.32-3.21 (m, 2H), 3.12 (m, 2H), 2.04 (m, 2H), 1.39 (s, 9H).

Step 2: (*R*)-tert-Butyl 3-(difluoromethyl)pyrrolidine-1-carboxylate



[00363] (R)-tert-Butyl 3-formylpyrrolidine-1-carboxylate (0.6 g, 3.06 mmol) in dichloromethane (5 mL) was cooled to 0°C. **Diethylaminosulfur trifluoride** (DAST, 0.52 mL, 3.98 mmol) was added dropwise and the resulting mixture was stirred at room temperature overnight. Water was added to the reaction mixture and the two layers were separated. The organic layer was washed with sat'd aqueous $NaHCO_3$, dried over sodium sulfate, filtered and the filtrate was concentrated on a rotary evaporator. The crude material was purified by flash chromatography on silica gel eluting with 0 to 50% ethyl acetate/hexanes to afford 0.45 g of (*R*)-tert-butyl 3-(difluoromethyl)pyrrolidine-1-carboxylate as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.08 (td, 1H), 3.34 (m, 2H), 3.19 (m, 2H), 2.70 (m, 1H), 1.95 (m, 1H), 1.82 (m, 1H), 1.39 (s, 9H).

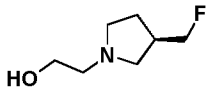
Step 3: (*R*)-3-(Difluoromethyl)pyrrolidine hydrochloride



[00364] (*R*)-tert-Butyl 3-(difluoromethyl)pyrrolidine-1-carboxylate (0.45 g, 2.03 mmol) in 1,4-dioxane (1 mL) was cooled to 15 °C in an ice bath. HCl (4M in 1,4-dioxane,1.5 mL, 6.11 mmol) was then added and the resulting solution was stirred at room temperature overnight. The solvent was removed on a rotary evaporator and the residue was triturated with diethyl ether. Diethyl ether was removed under vacuum and solid was dried to afford 0.31 g of (*R*)-3-(difluoromethyl)pyrrolidine hydrochloride as a grey solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (bs, 2H), 6.19 (td, 1H), 3.34 (m, 1H), 3.22-3.06 (m, 3H), 2.82 (m, 1H), 2.05 (m, 1H), 1.85 (m, 1H).

Intermediate 13

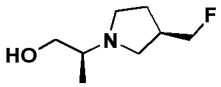
(*R*)-2-(3-(Fluoromethyl)pyrrolidin-1-yl)ethanol



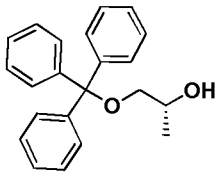
[00365] A mixture of (*R*)-3-(fluoromethyl)pyrrolidine hydrochloride (**Intermediate 8**, 4.26 g, 30.6 mmol), 2-bromoethanol (4.35 mL, 61.3 mmol), and potassium carbonate (12.7 g, 92 mmol) in acetonitrile (120 mL) was heated at 80 °C overnight. After cooling, solids were filtered off and washed with acetonitrile. The filtrate was concentrated on a rotary evaporator to give a residue that was purified by silica gel chromatography eluting with 10:7 ethyl acetate/hexanes to 10:7:2:1 ethyl acetate/hexane/methanol/triethylamine to afford 2.9 g of (*R*)-2-(3-(fluoromethyl)pyrrolidin-1-yl)ethanol as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.44 (t, 1H), 4.34 (dd, 1H), 4.22 (dd, 1H), 3.44 (q, 2H), 2.58-2.51 (m, 1H), 2.48-2.38 (m, 5H), 2.32-2.28 (m, 1H), 1.85-1.74 (m, 1H), 1.39-1.31 (m, 1H).

Intermediate 14

(*S*)-2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)propan-1-ol



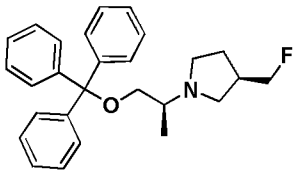
Step 1: (*R*)-1-(Trityloxy)propan-2-ol



[00366] Dimethylaminopyridine (165 mg, 1.35 mmol) was added to a solution of (*R*)-propane-1,2-diol (10.3 g, 135.4 mmol) and trityl chloride (38.1 g 136.7 mmol) in DCM (400 mL) at 0 °C. Triethylamine (47.2 mL, 338.4 mmol) was then added dropwise to this mixture. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with 1.0 N aq HCl (200 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography to give (*R*)-1-(trityloxy)propan-2-ol (36.4 g,

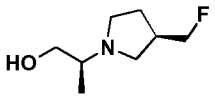
84%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43-7.39 (m, 6H) 7.34-7.31 (m, 6H) 7.26-7.22 (m, 3H), 4.70 (d, 1H), 3.82-3.76 (m, 1H), 2.95-2.92 (dd, 1H), 2.70-2.67 (dd, 1H), 1.06 (d, 3H).

Step 2: (*R*)-3-(Fluoromethyl)-1-((*S*)-1-(trityloxy)propan-2-yl)pyrrolidine



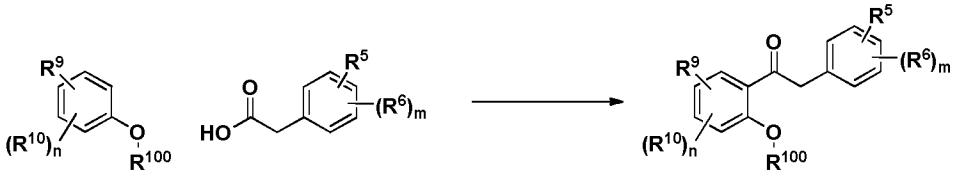
[00367] Triflic anhydride (1.0 M in DCM, 51.8 mL, 51.8 mmol) was added dropwise to a solution of (*R*)-1-(trityloxy)propan-2-ol (15.0 g, 47.1 mmol) and diisopropylethylamine (32.8 mL, 188.4 mmol) in DCM (190 mL) at -78 °C . The reaction mixture was allowed to stir at -78 °C for 1.5 h. (*R*)-3-(Fluoromethyl)pyrrolidine hydrochloride (**Intermediate 8**, 7.9 g, 56.5 mmol) in DCM (20 mL) was added dropwise to the reaction mixture at -78 °C. The mixture was allowed to warm to room temperature and stirred at this temperature overnight. Water (200 mL) and sat'd aqueous $NaHCO_3$ (200 mL) was added to the mixture. The mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was washed twice with DCM. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator to afford the crude material that was used directly for the next step without further purification.

Step 3: (*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propan-1-ol



[00368] A mixture of (*R*)-3-(fluoromethyl)-1-((*S*)-1-(trityloxy)propan-2-yl)pyrrolidine (19.0 g, 47.1 mmol) and formic acid/diethyl ether (4:1, 189 mL) was stirred at room temperature for 8 h. This reaction mixture was concentrated on a rotary evaporator. The residue was dissolved in DCM, washed with sat'd aqueous K_2CO_3, and washed with brine. Organic layer was dried over Na_2SO_4, filtered, and concentrated to give the crude product that was purified by silica gel chromatography (10:7 ethyl acetate/hexanes to 10:7:2:1 ethyl acetate/hexane/methanol/ triethylamine) to afford (*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propan-1-ol (3.9 g) as a dark orange oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.38-4.32 (m, 2H), 4.22-4.20 (m, 1H), 3.49-3.44 (m, 1H), 3.21-3.16 (m, 1H), 2.65-2.61 (m, 1H), 2.58-2.53 (m, 1H), 2.52-2.47 (m, 1H), 2.45-2.35 (m, 1H), 2.34-2.30 (m, 1H), 2.29-2.24 (m, 1H), 1.83-1.75 (m, 1H), 1.38-1.30 (m, 1H), 0.98 (d, 3H).

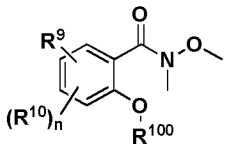
General Procedure A: Friedel-Crafts acylation



[00369] A mixture of 1.8 equivalents of a 1-methoxybenzene (for example 1,4-dimethoxybenzene), the appropriate phenylacetic acid (1.0 equiv) and polyphosphoric acid (1.3-1.5 M) was heated at 75 °C for 5-24 h and cooled to 50 °C. Water (1-2 fold of PPA v/v) was added, and the mixture was allowed to cool to room temperature. Additional water (1-2 fold PPA v/v) was added and the mixture was extracted with DCM (or ether). The organic phase was washed with H_2O, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding alkoxyaryl ketone.

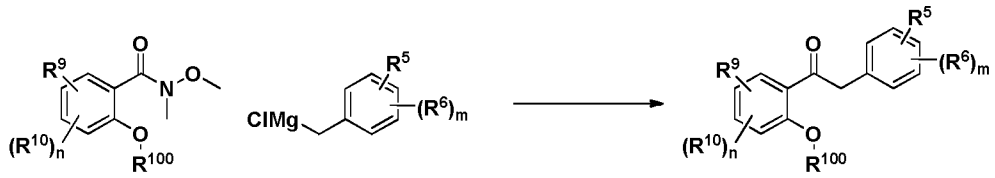
General Procedure B

Step 1: Synthesis of Weinreb amide



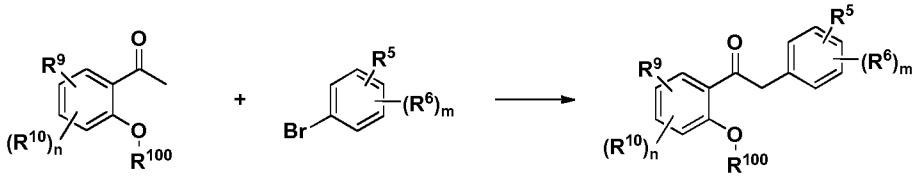
[00370] Oxalyl chloride (1.25 equiv) was added to a solution of a 1.0 equivalents of a 2-alkoxybenzoic acid (for example 2,5-dimethoxybenzoic acid) in DCM (0.33 M). Then DMF (5% v/v of oxalyl chloride) was added to the mixture. The solution was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. The crude material was placed under vacuum for 30 min to remove the residual oxalyl chloride. Triethylamine (1.2 equiv) was added dropwise to a solution of the residue and N,O-dimethylhydroxylamine hydrochloride (1.0 equiv) in DCM (0.33 M) at 0 °C. The solution was stirred at 0 °C for 30 min and then at room temperature for additional 30 min. The reaction was diluted with DCM, washed twice with water, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding Weinreb amide.

Step 2: Grignard addition to Weinreb amide



[00371] The appropriate benzylmagnesium chloride (1.9 equiv) was added *via* syringe to a solution of a Weinreb amide (1.0 equiv) in THF (0.5 M) at 0 °C over 30 min. The reaction was stirred at 0 °C for 30 min and then allowed to warm to room temperature over 1 h. The mixture was cooled to 0 °C and quenched with 1.0 M aqueous HCl solution. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers was washed with water, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding alkoxyaryl ketone.

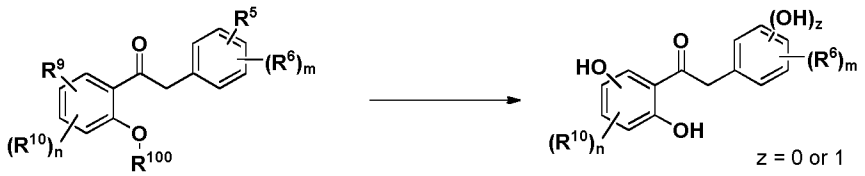
General Procedure C: Pd-mediated arylation of ketones



[00372] A mixture of Pd_2dba_3 (0.015 equiv), BINAP (0.035 equiv), and NaO^tBu (1.3 equiv) in a flask was placed under N_2 atmosphere by use of a vacuum and back-filling with N_2. THF (0.3 M) was added, followed by a solution of the corresponding arylbromide (1.0 equiv) and 1.2 equivalents of a 2-methoxyphenyl-ethanone (for example 1-(2,5-dimethoxyphenyl)ethanone) in THF (0.5 M). The resulting mixture was heated at 70 °C for 16 h. Water (100% v/v of THF) was added, and the mixture was extracted with ether (3 x). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by column chromatography on silica gel to give the corresponding alkoxyaryl ketone.

General Procedure D

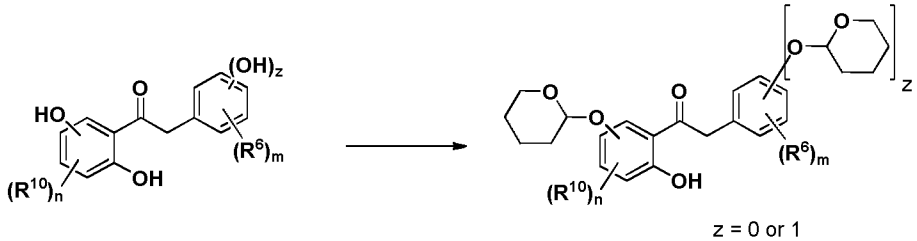
Step 1: Demethylation



[00373] Neat boron tribromide (3 equiv) was added dropwise to a solution of alkoxyaryl ketone (1.0 equiv) in DCM (0.25M) at -78 °C. The reaction mixture was allowed to warm to 0 °C, stirred for 30 min, re-cooled to -78 °C, and then carefully quenched with methanol (Note 1). The mixture was allowed to warm to room temperature, washed with water, washed twice with sat'd aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding phenol.

[00374] Note 1: In some instances, when the material crashes out of solution after quenching with methanol, ethyl acetate is added to dissolve material prior to work up.

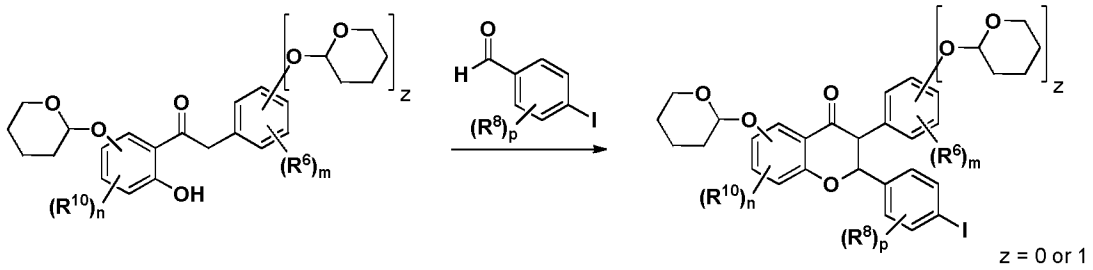
Step 2: Protection of phenol(s)



[00375] 3,4-Dihydro-2H-pyran (5.0 equiv) was added to a mixture of dihydroxyaryl ketone (1 equiv) and pyridinium *p*-toluene sulfonate (0.20 equiv) in DCM (0.25M) at room temperature. The resulting mixture was stirred at this temperature for 2-24h. The mixture was washed with water, washed with

sat'd aqueous $NaHCO_3$, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding THP-protected hydroxyarylketone.

Step 3: Cyclization to chromanone



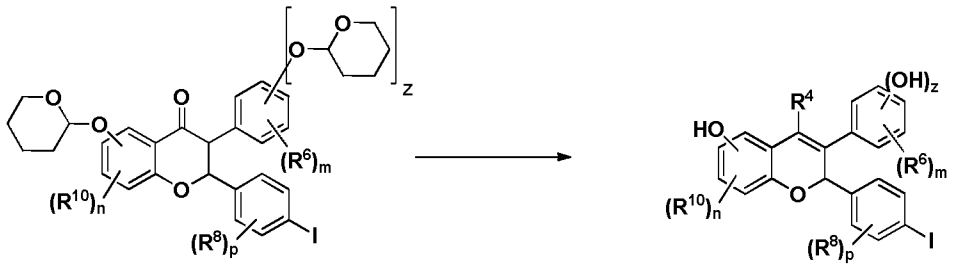
[00376] A solution of protected hydroxyarylketone (1.0 equiv), 4-iodoarylaldehyde (1.0 equiv), piperidine (0.35 equiv), and DBU (0.35 equiv) in *s*-butanol (1.0 M) was heated at reflux. Using a Dean-Stark trap, half of the solvent was removed over 30-40 min, and the reaction was kept at reflux without further concentration for an additional 4-8 h. The reaction mixture was cooled to 90 °C, *i*-propanol (0.7-1.0 fold of *s*-butanol v/v) was added, and the reaction was allowed to cool to room temperature. Any large pieces of material were broken down with a spatula, and the suspension was stirred overnight (Note 1 & 2). The precipitate was collected by filtration to give the corresponding chromanone.

[00377] Note 1: In some instances, the stirring time after cooling to room temperature may be longer (2-3 days).

[00378] Note 2: In some instances, a work up procedure is used when no solid precipitates out. The mixture is diluted with an organic solvent (DCM or EtOAc) and washed with water and washed with brine. The organic layer was dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography.

General Procedure E

[00379] Step 1: Grignard addition and elimination

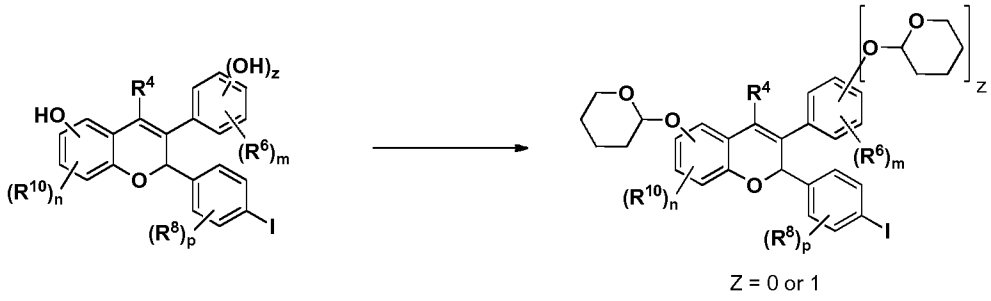


[00380] A solution of Grignard reagent (for example methyl magnesium chloride; 3.75 equiv, 3M in THF) was added dropwise to a solution of chromanone (1 equiv) in THF (0.25M) at 0 °C. The reaction was stirred at 0 °C for 15-30 min and allowed to warm to room temperature. After stirring for 2-2.5 h, the solution was cooled to 0 °C and quenched with sat'd aqueous ammonium chloride. The mixture

was allowed to warm to room temperature, diluted with ethyl acetate and water, and the layers were separated. The organic layer was washed with water, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to yield the corresponding tertiary alcohol. This crude material was suspended in 80% acetic acid/H_2O (0.1 M) and heated at 90 °C for 3-5 days. The reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate (Note 1). The organic phase was washed with water, washed twice with sat'd aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding chromene.

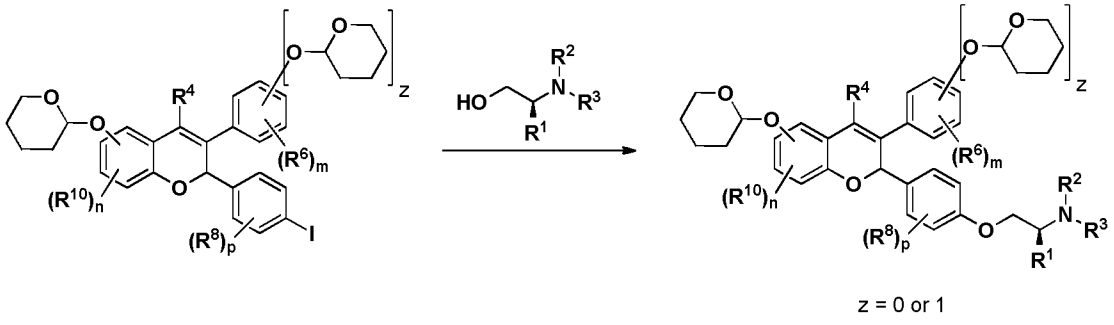
[00381] Note 1: In some instances, the reaction mixture was directly diluted with water and extracted three times with ethyl acetate. The organic layers combine and washed twice with a water/brine mixture, washed twice with saturated aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding chromene.

Step 2: Protection of the phenol(s)



[00382] 3,4-Dihydro-2H-pyran (1.5-5 equiv) was added to a solution of hydroxyaryl chromene (1.0 equiv) and pyridinium *p*-toluene sulfonate (0.20-0.25 equiv) in DCM (0.25 M) and stirred at room temperature for 4-5 h. The mixture was washed with sat'd aqueous $NaHCO_3$, washed with water, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding THP-protected chromene.

General Procedure F: Ullmann coupling



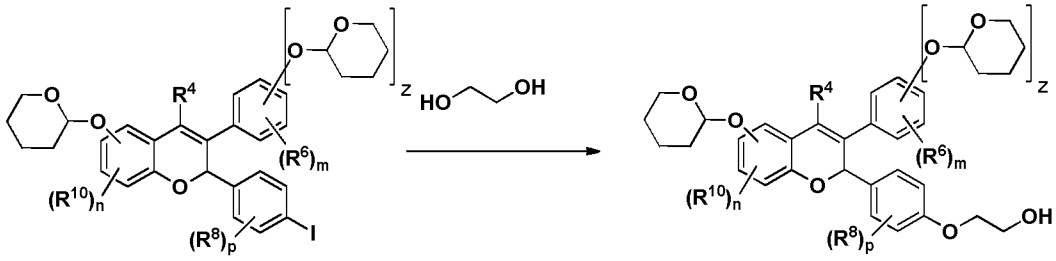
[00383] A mixture of THP-protected iodochromene (1.0 equiv), 1.5 – 2.0 equivalents of the corresponding amino-alcohol side-chain (for example **Intermediate 7, 13 or 14**), copper iodide (0.10

equiv), and potassium carbonate (2.0 equiv) in butyronitrile (0.5 M) was degassed by bubbling nitrogen through the mixture for 15 min. The reaction mixture was heated at 125 °C for 1-5 days, allowed to cool to room temperature, and diluted with ethyl acetate. The mixture was filtered through a pad of Celite and washed with ethyl acetate. The organic phase was washed twice with water, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding Ullmann coupled product.

[00384] Note: In some cases: i) the reaction time varied depending on the amino alcohol (overnight to 5 days; progress was monitored by LCMS), and ii) cesium carbonate was used instead of potassium carbonate.

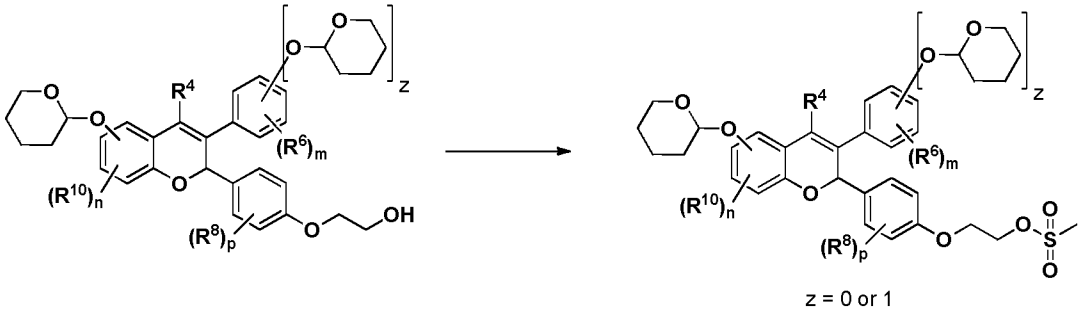
General Procedure G

Step 1: Ullmann coupling



[00385] A mixture of THP-protected iodochromene (1.0 equiv), diol (4.0 equiv), copper iodide (0.10 equiv), 1,10-phenanthroline (0.20 equiv), and potassium carbonate (2.0 equiv) in butyronitrile (0.5 M) was degassed. The reaction mixture was heated at 125 °C for 3 days, allowed to cool to room temperature, and diluted with ethyl acetate. The organic phase was washed twice with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding Ullmann product.

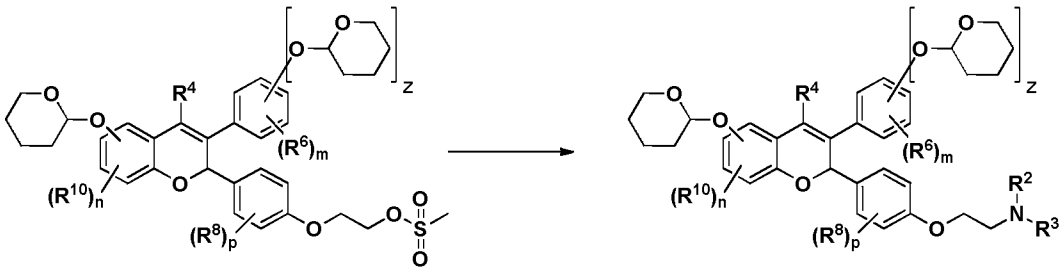
Step 2: Mesylation



[00386] Methanesulfonyl chloride (1.3 equiv) was added dropwise to a solution of alcohol (1.0 equiv) and triethylamine (1.5 equiv) in DCM (0.1 M) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, then diluted with DCM, and quenched with 1N aqueous HCl. The layers were separated and the

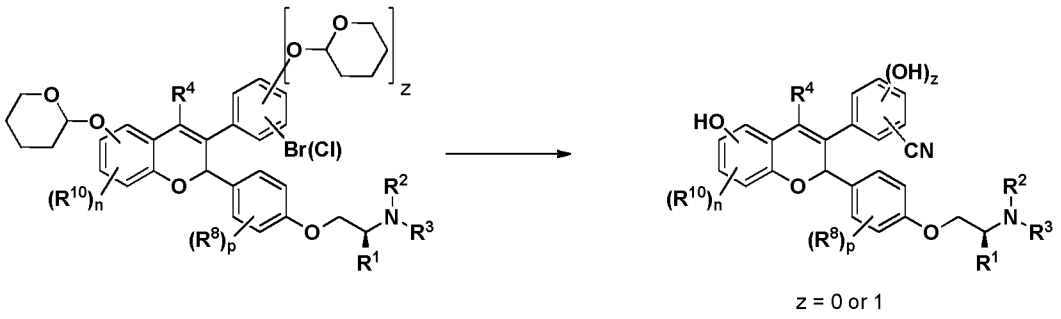
organic layer was washed with water, washed with sat'd aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4, and concentrated to give the desired mesylate.

Step 3: Alkylation



[00387] A suspension of mesylate (1.0 equiv), amine (2-3 equiv), and potassium carbonate (2.0 equiv) in acetonitrile (0.1 M) was heated at 80°C for 3-24 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and diluted with DCM (0.01M). The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. This crude product was then purified by silica gel chromatography to give the corresponding alkylation product.

General Procedure H: Cyanation of aryl halides and removal of THP group(s)

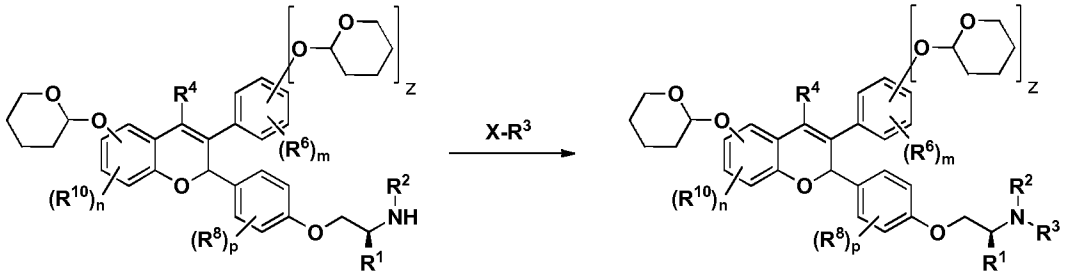


[00388] A mixture of arylbromide (1.0 equiv), 1-butylimidazole (20.0 equiv), copper iodide (1.0 equiv), potassium ferrocyanide trihydrate (2.0 equiv), and m-xylene (0.1 M) was degassed by 3 vacuum / nitrogen cycles. The reaction mixture was heated at 140 °C for 1-3 days. The mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was washed with water, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was then purified by silica gel chromatography to give the corresponding arylnitrile (Note 1). This purified material (1.0 equiv) was stirred in 80% acetic acid/H_2O (0.25 M) at room temperature for 3-24h. The solvent was removed under reduced pressure, and the residue was purified by reverse-phase HPLC (Note 2). The purified fractions were pooled, concentrated under reduced pressure down to approximately third of volume, and extracted with ethyl acetate. The organic layer was washed with sat'd aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated under reduced pressure. The resulting solid was dissolved in ethyl acetate (0.05 M) and treated with HCl (2N in diethyl ether, 2.0 equiv). The solvent was removed under reduced pressure to give the corresponding hydrochloride salt.

[00389] Note 1: An alternative procedure may also be used: A mixture of arylbromide (or arylchloride) (1.0 equiv), zinc powder (0.72 equiv), [1,1'-binaphthalen]-2-yldi-tert-butylphosphine (0.30 equiv), zinc cyanide (2.1 equiv), and dimethylacetamide (0.12-0.14 M) was degassed by 3 vacuum / nitrogen cycles. Palladium trifluoroacetate (0.13 equiv) was added and degassed again with 3 additional vacuum/ nitrogen cycles. The reaction mixture was heated at 95 °C for 3.5-5 h, allowed to cool to room temperature, and diluted with ethyl acetate. The organic phase was washed twice with water, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated to afford the crude product. This crude product was then purified by silica gel chromatography to give the corresponding arylnitrile.

[00390] Note 2: For some compounds, after purification by reverse-phase HPLC, the fractions were concentrated down under reduced pressure to give the corresponding trifluoroacetate salt without any further manipulation.

General Procedure I: N-Alkylation

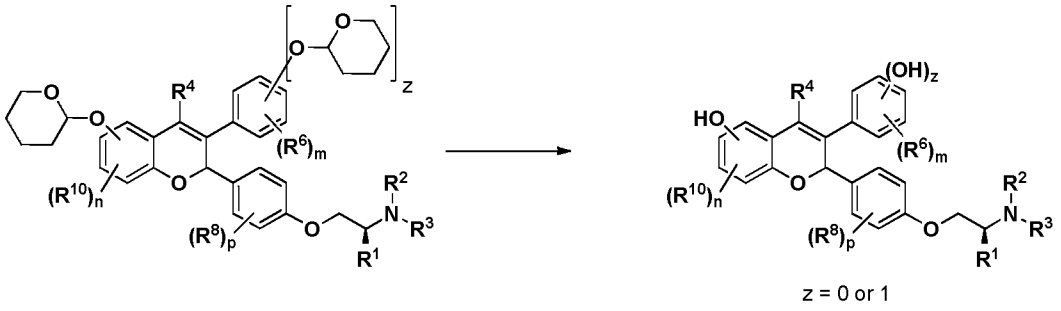


[00391] A mixture of amine (1.0 eq), alkyl iodide (1.5 eq) and sodium bicarbonate (2.0 eq) in DMA was heated at 50°C for 6 hrs, allowed to cool to RT and diluted with ethyl acetate. The organic extract was washed with water, washed with brine, dried over Na_2SO_4 (or MgSO4), filtered, concentrated, and purified by silica gel chromatography to give the corresponding alkylation product.

[00392] Note 1: In some instances, the reaction was heated at 80°C to shorten the reaction time.

[00393] Note 2: In some instances, additional alkyl iodide and sodium bicarbonate were added to drive the reaction to completion.

General Procedure J: Removal of THP protecting group(s)



[00394] The THP protected chromene (1.0 equiv) was stirred in 80% acetic acid/H_2O (0.25 M) at room temperature for 3-24h. The solvent was removed under reduced pressure, and the residue was purified

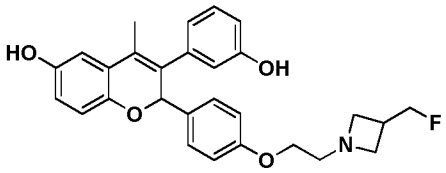
by reverse-phase HPLC (Note 1 & 2). The purified fractions were pooled, concentrated under reduced pressure down to approximately third of volume, and extracted with ethyl acetate. The organic layer was washed with sat'd aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated under reduced pressure. The resulting solid was dissolved in ethyl acetate (0.05 M) and treated with HCl (2N in diethyl ether, 2.0 equiv). The solvent was removed under reduced pressure to give the corresponding hydrochloride salt.

[00395] Note 1: For some compounds, after purification by reverse-phase HPLC, the fractions were concentrated down under reduced pressure to give the corresponding trifluoroacetate salt without any further manipulation.

[00396] Note 2: For some instances, the residue was dissolved in ethyl acetate and washed with sat'd aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4 (or $MgSO_4$), filtered, and concentrated under reduced pressure to give the crude product. This crude product was purified by silica gel chromatography.

Example 1

2-(4-(2-(3-(Fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

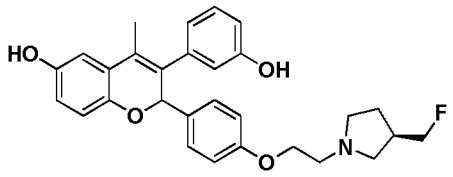


[00397] A mixture of **Intermediate 5** (0.11 g, 0.17 mmol), **Intermediate 6** (0.32 mg, 0.25 mmol), potassium carbonate (70 mg, 0.51mmol) in acetonitrile (1.7 mL) was heated at 80 °C for 6 h, allowed to cool to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water, with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator to afford the crude 3-(fluoromethyl)-1-(2-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethyl)azetidine. This crude material was stirred in 80% acetic acid/H_2O (5 mL) at room temperature for 3 h. The solvents were removed on a rotary evaporator, and the residue was dissolved in ethyl acetate. The organic layer was washed with sat'd aqueous aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. This crude material was then purified by reverse phase C18 chromatography (30-40% acetonitrile/water/0.1% TFA). Fractions were pooled, concentrated and dissolved in ethyl acetate. The organic layer was washed with sat'd aqueous $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol as pale yellow solid. ^1H NMR (DMSO-d_6): δ 9.40 (s, 1H), 8.94 (s, 1H), 7.18 (d, 2H),

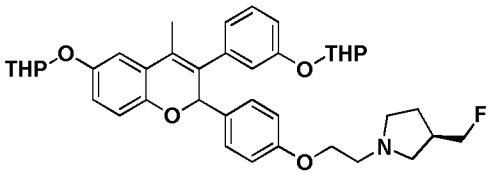
7.12 (t, 1H), 6.75 (d, 2H), 6.73 (m, 1H), 6.68-6.57 (m, 2H), 6.60 (s, br, 1H), 6.47 (m, 2H), 5.82 (s, 1H), 4.53 (d, 1H), 4.41 (d, 1H), 3.81 (t, 2H), 3.26 (dd, 2H), 2.94 (t, 2H), 2.76-2.64 (m, 1H), 2.63 (t, 2H), 2.02 (s, 3H). ; LCMS: 462 $(M+H)^+$.

Example 2

2-(4-(2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

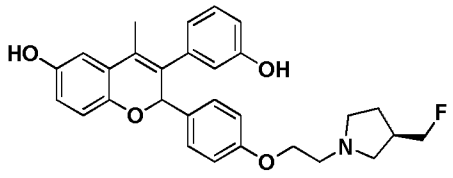


Step 1: (3*R*)-3-(Fluoromethyl)-1-(2-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethyl)pyrrolidine



[00398] A mixture of **Intermediate 3** (2.1 g, 3.35 mmol), **Intermediate 13** (738 mg, 5.02 mmol), copper iodide (127 mg, 0.67 mmol), and potassium carbonate (925 mg, 6.7 mmol) in butyronitrile (7 mL) was degassed three times and then heated to 125°C for 2 days. After cooling, ethyl acetate and water were added and the two layers were separated. The organic layer was washed with brine, dried over sodium sulfate, filtered and the solvent removed. The residue was purified by flash chromatography on silica gel (20 to 100% ethyl acetate/hexanes) to afford 1.87 g of (3*R*)-3-(fluoromethyl)-1-(2-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethyl)pyrrolidine as a yellow foam. LCMS: 644 $(M+H)^+$.

Step 2: (R)-2-(4-(2-(3-(Fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

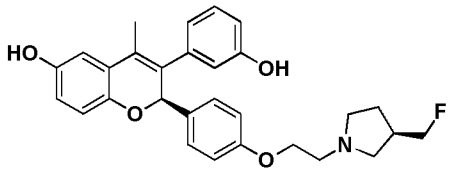


[00399] A mixture of (3*R*)-3-(fluoromethyl)-1-(2-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)ethyl)pyrrolidine (1.87 g, 2.9 mmol) in acetic acid (80% aq., 30 mL) was stirred at room temperature overnight. The acetic acid was removed and the residue was partitioned between ethyl acetate and sat'd aqueous $NaHCO_3$. The organic layer was washed with sat'd aqueous $NaHCO_3$, dried over sodium sulfate, filtered and the solvent removed. The residue was purified by flash chromatography on silica gel (0 to 5%

methanol/dichloromethane) to afford 1.1 g of (*R*)-2-(4-(2-(3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol as a pinkish foam. ^{1}H NMR (DMSO-d_6): δ 9.43 (s, 1H), 8.94 (s, 1H), 7.18 (d, 2H), 7.14 (t, 1H), 6.78 (d, 2H), 6.73 (s, 1H), 6.67-6.65 (m, 2H), 6.65 (s, 1H), 6.49-6.45 (m, 2H), 5.83 (s, 1H), 4.35-4.30 (m, 1H), 4.23-4.19 (m, 1H), 3.96 (t, 2H), 2.71 (t, 2H), 2.60 (t, 1H), 2.46-2.40 (m, 3H), 2.36-2.31 (m, 1H), 2.02 (s, 3H), 1.83-1.76 (m, 1H), 1.39-1.30 (m, 1H); LCMS: 476 $(M+H)^+$.

Example 2a

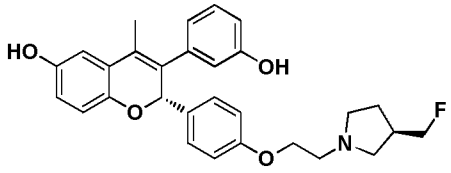
(*R*)-2-(4-(2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00400] The title compound was the 1st eluting diastereomer when **Example 2** was separated on a RegisCell (250 x 4.6 mm, 5 μm) column [hexanes/ethanol/diethylamine (75/25/0.1%)]. Diastereomeric ratio: >99:1. ^{1}H NMR (DMSO-d_6; HCl salt): δ 10.61 (br, 1H), 9.47 (s, 1H), 8.98 (s, 1H), 7.23 (d, 2H), 7.12 (t, 1H), 6.86 (d, 2H), 6.74 (br, 1H), 6.70-6.57 (m, 3H), 6.47-6.45 (m, 2H), 5.86 (s, 1H), 4.53-4.47 (m, 1H), 4.46-4.36 (m, 1H), 4.25 (br, 2H), 3.73-3.49 (m, 3H), 3.34-3.22 (m, 1H), 3.18-3.06 (m, 1H), 2.98-2.86 (m, 1H), 2.20-2.11 (m, 1H), 2.02 (s, 3H), 1.87-1.75 (m, 1H), 1.67-1.55 (m, 1H). LCMS: 476.1 $(M+H)^+$.

Example 2b

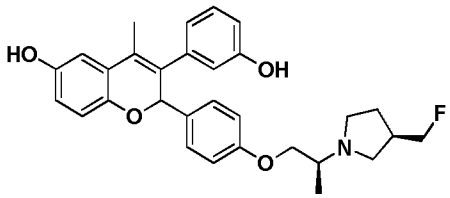
(*S*)-2-(4-(2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



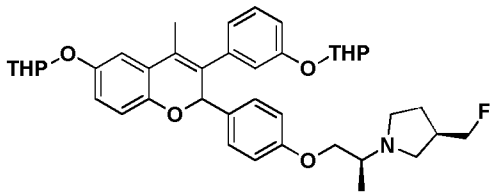
[00401] The title compound was the 2nd eluting diastereomer when **Example 2** was separated on a RegisCell (250 x 4.6 mm, 5 μm) column [hexanes/ethanol /diethylamine (75/25/0.1%)]. Diastereomeric ratio: > 99:1. ^{1}H NMR (DMSO-d_6; HCl salt): δ 10.61 (br, 1H), 9.48 (s, 1H), 8.98 (s, 1H), 7.24 (d, 2H), 7.12 (t, 1H), 6.86 (d, 2H), 6.75 (d, 1H), 6.70-6.57 (m, 3H), 6.48-6.45 (m, 2H), 5.86 (s, 1H), 4.57-4.47 (m, 1H), 4.45-4.35 (m, 1H), 4.30-4.22 (m, 2H), 3.75-3.50 (m, 3H), 3.33-3.21 (m, 1H), 3.18-3.08 (m, 1H), 2.97-2.86 (m, 1H), 2.20-2.09 (m, 1H), 2.03 (s, 3H), 1.86-1.74 (m, 1H), 1.66-1.58 (m, 1H). LCMS: 476.1 $(M+H)^+$.

Example 3

2-(4-((*S*)-2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

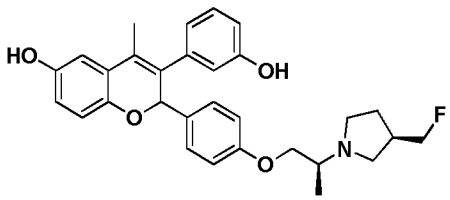


Step 1: (3*R*)-3-(fluoromethyl)-1-((2*S*)-1-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)propan-2-yl)pyrrolidine



[00402] A mixture of **Intermediate 3** (1.0 g, 1.6 mmol), **Intermediate 14** (388 mg, 2.4 mmol), copper iodide (61 mg, 0.32 mmol), and potassium carbonate (443 g, 3.2 mmol) in butyronitrile (3.2 mL) was degassed three times with vacuum/nitrogen cycles. The reaction mixture was heated at 125 °C for 2 days, allowed to cool to room temperature, and diluted with ethyl acetate. Insoluble material was filtered through Celite, and the Celite was washed with ethyl acetate. The filtrate was washed twice with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (0-100% EtOAc/hexane) to give (3*R*)-3-(fluoromethyl)-1-((2*S*)-1-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)propan-2-yl)pyrrolidine (785 mg, 74%) as a beige foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27-7.19 (m, 3H), 6.99 (t, 1H), 6.93-6.88 (m, 3H), 6.81-6.76 (m, 3H), 6.59 (d, 1H), 5.97 (d, 1H), 5.43-5.38(dt, 1H), 5.34 (m, 1H), 4.32-4.30 (m, 1H), 4.20-4.19 (m, 1H), 3.99-3.93 (m, 1H), 3.73-3.69 (m, 3H), 3.58-3.47 (m, 2H), 2.69-2.60 (m, 2H), 2.59-2.52 (m, 2H), 2.45-2.30 (m, 2H), 2.06 (s, 3H), 1.90-1.65 (m, 7H), 1.64-1.47 (m, 6H), 1.40-1.30 (m, 1H), 1.06 (d, 3H); LCMS: 658.3 $(M+H)^+$.

Step 2: 2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

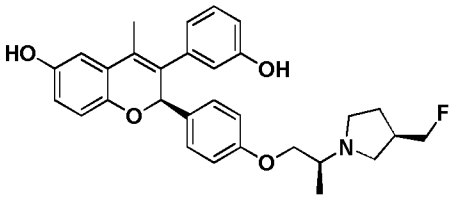


[00403] (3*R*)-3-(fluoromethyl)-1-((2*S*)-1-(4-(4-methyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-3-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-2H-chromen-2-yl)phenoxy)propan-2-yl)pyrrolidine (785 mg,

1.19 mmol) was stirred in 80% acetic acid/H_2O (6.0 mL) at room temperature for 2 days. The solvents were removed on a rotary evaporator, and the residue was dissolved in ethyl acetate. The organic layer was washed with sat'd aqueous $NaHCO_3$, washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This crude material was then purified by silica gel chromatography (0-4% MeOH/DCM) to afford 2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol (410 mg, 70%) as pale pink solid. ^{1}H NMR (DMSO-d_6): δ 9.43 (s, 1H), 8.94 (s, 1H), 7.18 (d, 2H), 7.12 (t, 1H), 6.79 (d, 2H), 6.73 (m, 1H), 6.68 (dt, 1H), 6.65 (m, 1H), 6.61 (m, 1H), 6.49-6.45 (m, 2H), 5.83 (s, 1H), 4.35-4.30 (m, 1H), 4.23-4.18 (m, 1H), 3.99-3.93 (m, 1H), 3.74-3.70 (m, 1H), 2.69-2.60 (m, 2H), 2.58-2.52 (m, 2H), 2.45-2.32 (m, 2H), 2.02 (s, 3H), 1.82-1.75 (m, 1H), 1.36-1.30 (m, 1H), 1.07 (d, 3H); LCMS: 490.2 $(M+H)^+$.

Example 3a

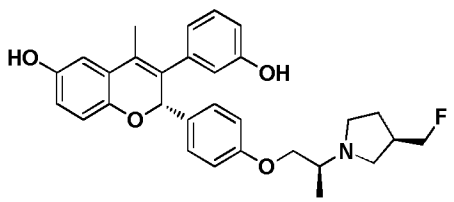
(*R*)-2-(4-((*S*)-2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00404] The title compound was the 1st eluting diastereomer when **Example 3** was separated on a RegisCell (250 x 4.6 mm, 5 μm) column [hexanes/ethanol/diethylamine (75/25/0.1%)]. Diastereomeric ratio: > 99:1. ^{1}H NMR (DMSO-d_6; HCl salt): δ 10.60 (br, 1H), 9.47 (s, 1H), 8.98 (s, 1H), 7.24 (d, 2H), 7.12 (t, 1H), 6.87 (d, 2H), 6.74 (d, 1H), 6.70-6.60 (m, 3H), 6.48-6.45 (m, 2H), 5.86 (s, 1H), 4.56-4.47 (m, 1H), 4.47-4.36 (m, 1H), 4.20-4.15 (m, 2H), 3.74-3.66 (m, 1H), 3.62-3.49 (m, 2H), 3.28-3.12 (m, 1H), 3.03-2.90 (m, 1H), 2.15-2.07 (m, 1H), 2.03 (s, 3H), 1.84-1.73 (m, 1H), 1.66-1.55 (m, 1H), 1.35 (d, 3H); LCMS: 490.1 $(M+H)^+$.

Example 3b

(*S*)-2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

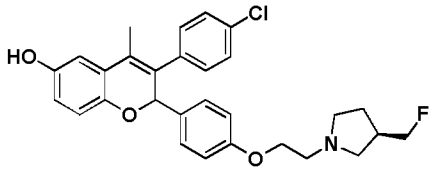


[00405] The title compound was the 2nd eluting diastereomer when **Example 3** was separated on a RegisCell (250 x 4.6 mm, 5 μm) column column [hexanes/ethanol /diethylamine (75/25/0.1%)]. Diastereomeric ratio: > 99:1. ^{1}H NMR (DMSO-d_6; HCl salt): δ 10.65-10.60 (br, 1H), 9.47 (s, 1H), 8.98

(s, 1H), 7.24 (d, 2H), 7.12 (t, 1H), 6.87 (d, 2H), 6.74 (d, 1H), 6.70-6.63 (m, 3H), 6.48-6.45 (m, 2H), 5.86 (s, 1H), 4.56-4.47 (m, 1H), 4.45-4.35 (m, 1H), 4.22-4.11 (m, 2H), 3.74-3.64 (m, 1H), 3.62-3.49 (m, 2H), 3.28-3.12 (m, 1H), 3.03-2.90 (m, 1H), 2.15-2.07 (m, 1H), 2.03 (s, 3H), 1.84-1.73 (m, 1H), 1.66-1.55 (m, 1H), 1.35 (d, 3H); LCMS: 490.1 $(M+H)^+$.

Example 4

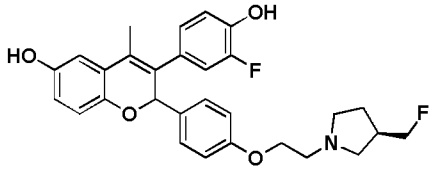
3-(4-Chlorophenyl)-2-(4-(2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol



[00406] The title compound was synthesized as described in general procedures A, D, E, G and J (z = 0) using 1,4-dimethoxybenzene and 2-(4-chlorophenyl)acetic acid in general procedure A, and **Intermediate 8** in general procedure G. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.40 (m, 2H), 7.31 (m, 2H), 7.19 (d, 2H), 6.78 (m, 2H), 6.75 (m, 1H), 6.52-6.47 (m, 2H), 5.91 (s, 1H), 4.33-4.30 (m, 1H), 4.21-4.18 (m,1H), 3.95 (t, 2H), 2.70 (t, 2H), 2.59 (t, 1H), 2.55-2.47 (m, 1H), 2.50-2.40 (m, 2H), 2.35-2.31 (m, 1H), 1.98 (s, 3H), 1.83-1.77 (m, 1H), 1.37-1.32 (m, 1H); LCMS: 494.1 $(M+H)^+$.

Example 5

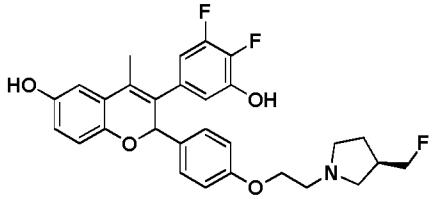
3-(3-Fluoro-4-hydroxyphenyl)-2-(4-(2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol



[00407] The title compound was synthesized as described in general procedures A, D, E, F and J (z = 1) using 1,4-dimethoxybenzene and 2-(3-fluoro-4-methoxyphenyl)acetic acid in general procedure A and **Intermediate 13** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.93 (s, 1H), 7.17 (d, 2H), 7.09 (m, 1H), 6.93-6.86 (m, 2H), 6.77 (m, 2H), 6.71 (m, 1H), 6.46 (m, 2H), 5.89 (s, 1H), 4.32-4.30 (m, 1H), 4.20-4.18 (m, 1H), 3.95 (t, 2H), 2.69 (t, 2H), 2.59 (t, 1H), 2.55-2.47 (m, 1H), 2.48-2.42 (m, 2H), 2.35-2.31 (m, 1H), 2.03 (s, 3H), 1.83-1.78 (m, 1H), 1.37-1.34 (m, 1H); LCMS: 494.1 $(M+H)^+$.

Example 6

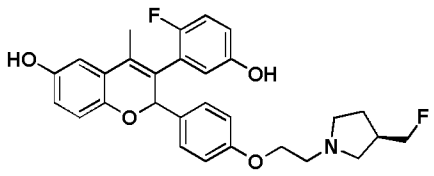
3-(3,4-Difluoro-5-hydroxyphenyl)-2-(4-(2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy) phenyl)-4-methyl-2H-chromen-6-ol



[00408] The title compound was synthesized as described in general procedures C, D, E, F and J (z = 1) using 1-(2,5-dimethoxyphenyl)ethanone and 5-bromo-1,2-difluoro-3-methoxybenzene in general procedure C and **Intermediate 13** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (br s, 1H), 8.97 (s, 1H), 7.17 (d, 2H), 6.81-6.74 (m, 4H), 6.61 (m, 1H), 6.51-6.46 (m, 2H), 5.83 (s, 1H), 4.33-4.28 (m, 1H), 4.23-4.16 (m, 1H), 3.96 (t, 2H), 2.70 (t, 2H), 2.61 (t, 1H), 2.55-2.47 (m, 2H), 2.48-2.42 (m, 1H), 2.36-2.32 (m, 1H), 2.02 (s, 3H), 1.85-1.76 (m, 1H), 1.39-1.31 (m, 1H); LCMS: 512.1 $(M+H)^+$.

Example 7

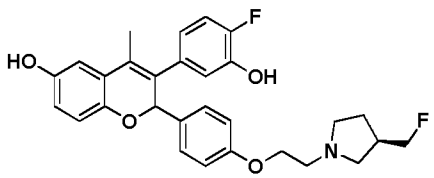
3-(2-Fluoro-5-hydroxyphenyl)-2-(4-(2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol



[00409] The title compound was synthesized as described in general procedures C, D, E, F and J (z = 1) using 1-(2,5-dimethoxyphenyl)ethanone and 2-bromo-1-fluoro-4-methoxybenzene in general procedure C and **Intermediate 13** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.98 (s, 1H), 7.19 (d, 2H), 6.99 (t, 1H), 6.79 (d, 2H), 6.74 (d, 1H), 6.68-6.64 (m, 1H), 6.54-6.47 (m, 3H), 5.77 (s, 1H), 4.33-4.30 (m, 1H), 4.21-4.18 (m, 1H), 3.96 (t, 2H), 2.70 (t, 2H), 2.60 (t, 1H), 2.55-2.47 (m, 1H), 2.48-2.42 (m, 2H), 2.34-2.32 (m, 1H), 1.92 (s, 3H), 1.83-1.78 (m, 1H), 1.38-1.33 (m, 1H); LCMS: 494.1 $(M+H)^+$

Example 8

3-(4-Fluoro-3-hydroxyphenyl)-2-(4-(2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol

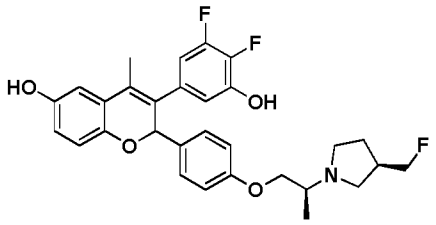


[00410] The title compound was synthesized as described in general procedures C, D, E, F and J (z = 1) using 1-(2,5-dimethoxyphenyl)ethanone and 4-bromo-1-fluoro-2-methoxybenzene in general procedure

C and **Intermediate 13** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.94 (s, 1H), 7.17 (d, 2H), 7.11-7.06 (m, 1H), 6.79 (m, 3H), 6.73 (m, 1H), 6.68-6.65 (m, 1H), 6.48-6.45 (m, 2H), 5.81 (s, 1H), 4.31-4.30 (m, 1H), 4.21-4.18 (m, 1H), 3.96 (t, 2H), 2.70 (t, 2H), 2.62 (t, 1H), 2.55-2.47 (m, 1H), 2.48-2.42 (m, 2H), 2.35-2.32 (m, 1H), 2.01 (s, 3H), 1.83-1.79 (m, 1H), 1.37-1.33 (m, 1H); LCMS: 494.1 $(M+H)^+$

Example 9

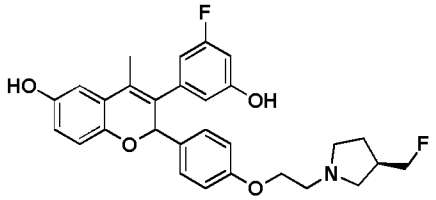
3-(3,4-Difluoro-5-hydroxyphenyl)-2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy) phenyl)-4-methyl-2H-chromen-6-ol



[00411] The title compound was synthesized as described in general procedures C, D, E, F and J (z = 1) using 1-(2,5-dimethoxyphenyl)ethanone and 5-bromo-1,2-difluoro-3-methoxybenzene in general procedure C and **Intermediate 14** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (br s, 1H), 8.97 (s, 1H), 7.17 (d, 2H), 6.81-6.74 (m, 4H), 6.61 (m, 1H), 6.51-6.46 (m, 2H), 5.83 (s, 1H), 4.33-4.30 (m, 1H), 4.21-4.19 (m, 1H), 3.99-3.94 (m, 1H), 3.73 (m, 1H), 2.69-2.53 (m, 4H), 2.41-2.32 (m, 2H), 2.02 (s, 3H), 1.82-1.77 (m, 1H), 1.36-1.32 (m, 1H), 1.07 (d, 3H); LCMS: 526.1 $(M+H)^+$.

Example 10

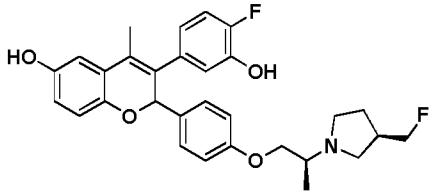
3-(3-Fluoro-5-hydroxyphenyl)-2-(4-(2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-4-methyl-2H-chromen-6-ol



[00412] The title compound was synthesized as described in general procedures C, D, E, F and J (z =1) using 1-(2,5-dimethoxyphenyl)ethanone and 1-bromo-3-fluoro-5-methoxybenzene in general procedure C and **Intermediate 13** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.96 (s, 1H), 7.18 (d, 2H), 6.81 (d, 2H), 6.74 (d, 1H), 6.55-6.52 (dt, 1H), 6.51-6.43 (m, 4H), 5.84 (s, 1H), 4.33-4.30 (m, 1H), 4.21-4.18 (m, 1H), 3.96 (t, 2H), 2.70 (t, 2H), 2.62 (t, 1H), 2.55-2.47 (m, 1H), 2.48-2.42 (m, 2H), 2.35-2.32 (m, 1H), 2.03 (s, 3H), 1.83-1.78 (m, 1H), 1.39-1.33 (m, 1H); LCMS: 494.1 $(M+H)^+$

Example 11

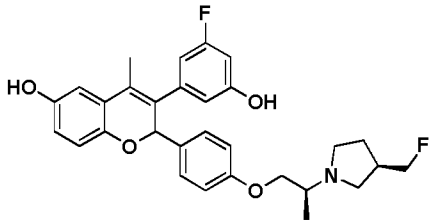
3-(4-Fluoro-3-hydroxyphenyl)-2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy) phenyl)-4-methyl-2H-chromen-6-ol



[00413] The title compound was synthesized as described in general procedures C, D, E, F and J (z = 1) using 1-(2,5-dimethoxyphenyl)ethanone and 4-bromo-1-fluoro-2-methoxybenzene in general procedure C and **Intermediate 14** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 8.95 (s, 1H), 7.17 (d, 2H), 7.11-7.06 (m, 1H), 6.79 (m, 3H), 6.73 (m, 1H), 6.69-6.65 (m, 1H), 6.50-6.45 (m, 2H), 5.81 (s, 1H), 4.33-4.30 (m, 1H), 4.21-4.18 (m, 1H), 3.97-3.93 (m, 1H), 3.73-3.71 (m, 1H), 2.69-2.60 (m, 2H), 2.58- 2.54 (m, 2H), 2.41-2.35 (m, 2H), 2.01 (s, 3H), 1.80-1.78 (m, 1H), 1.40-1.33 (m, 1H), 1.07 (d, 3H); LCMS: 508.1 $(M+H)^+$

Example 12

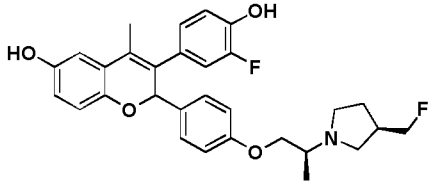
3-(3-Fluoro-5-hydroxyphenyl)-2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy) phenyl)-4-methyl-2H-chromen-6-ol



[00414] The title compound was synthesized as described in general procedures C, D, E, F and J (z = 1) using 1-(2,5-dimethoxyphenyl)ethanone and 1-bromo-3-fluoro-5-methoxybenzene in general procedure C and **Intermediate 14** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.96 (s, 1H), 7.18 (d, 2H), 6.80 (d, 2H), 6.74 (d, 1H), 6.55-6.52 (dt, 1H), 6.51-6.43 (m, 4H), 5.84 (s, 1H), 4.33-4.30 (m, 1H), 4.21-4.19 (m, 1H), 3.98-3.94 (m, 1H), 3.73-3.71 (m, 1H), 2.67-2.60 (m, 2H), 2.58- 2.54 (m, 2H), 2.38-2.35 (m, 2H), 2.03 (s, 3H), 1.85-1.74 (m, 1H), 1.40-1.33 (m, 1H), 1.07 (d, 3H); LCMS: 508.1 $(M+H)^+$

Example 13

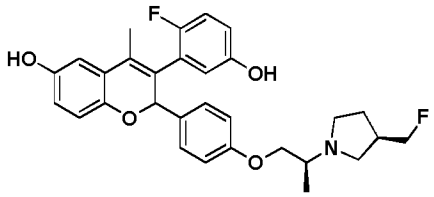
3-(3-Fluoro-4-hydroxyphenyl)-2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy) phenyl)-4-methyl-2H-chromen-6-ol



[00415] The title compound was synthesized as described in general procedures A, D, E, F and J (z =1) using 1,4-dimethoxybenzene and 2-(3-fluoro-4-methoxyphenyl)acetic acid in general procedure A and **Intermediate 14** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.93 (s, 1H), 7.17 (d, 2H), 7.10-7.07 (m, 1H), 6.93-6.86 (m, 2H), 6.78 (d, 2H), 6.71 (t, 1H), 6.46 (m, 2H), 5.89 (s, 1H), 4.32-4.30 (m, 1H), 4.20-4.18 (m, 1H), 3.96-3.92 (m, 1H), 3.74-3.70 (m, 1H), 2.66-2.60 (m, 2H), 2.58-2.52 (m, 2H), 2.38-2.35 (m, 2H), 2.03 (s, 3H), 1.80-1.78 (m, 1H), 1.35-1.33 (m, 1H), 1.06 (d, 3H); LCMS: 508.1 $(M+H)^+$.

Example 14

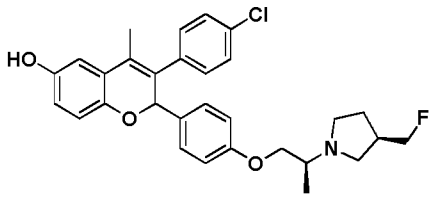
3-(2-Fluoro-5-hydroxyphenyl)-2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol



[00416] The title compound was synthesized as described in general procedures C, D, E, F and J (z = 1) using 1-(2,5-dimethoxyphenyl)ethanone and 2-bromo-1-fluoro-4-methoxybenzene in general procedure C and **Intermediate 14** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.98 (s, 1H), 7.19 (d, 2H), 6.99 (t, 1H), 6.79 (d, 2H), 6.74 (d, 1H), 6.68-6.64 (m, 1H), 6.52-6.46 (m, 3H), 5.76 (s, 1H), 4.32-4.30 (m, 1H), 4.20-4.19 (m, 1H), 3.96-3.93 (m, 1H), 3.93-3.71 (m, 1H), 2.67-2.60 (m, 2H), 2.58-2.52 (m, 2H), 2.48-2.35 (m, 2H), 1.91 (s, 3H), 1.87-1.73 (m, 1H), 1.38-1.33 (m, 1H), 1.07 (d, 3H); LCMS: 508.1 $(M+H)^+$

Example 15

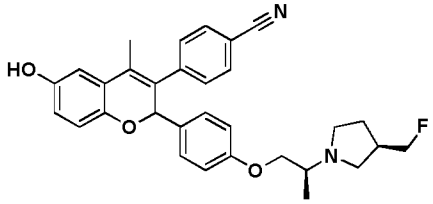
3-(4-Chlorophenyl)-2-(4-((*S*)-2-((*R*)-3-(fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-4-methyl-2H-chromen-6-ol



[00417] The title compound was synthesized as described in general procedures A, D, E, F and J (z = 0) using 1,4-dimethoxybenzene and 2-(4-chlorophenyl)acetic acid in general procedure A and **Intermediate 14** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.40 (m, 2H), 7.31 (m, 2H), 7.18 (d, 2H), 6.78 (m, 2H), 6.75 (m, 1H), 6.51-6.47 (m, 2H), 5.92 (s, 1H), 4.32-4.30 (m, 1H), 4.21-4.18 (m,1H), 3.96-3.92 (m, 1H), 3.74-3.69 (m, 1H), 2.68-2.60 (m, 2H), 2.59-2.52 (m, 2H), 2.48-2.35 (m, 2H), 2.02 (s, 3H), 1.81-1.76 (m, 1H), 1.36-1.31 (m, 1H), 1.06 (d, 3H); LCMS: 508.1 $(M+H)^+$.

Example 16

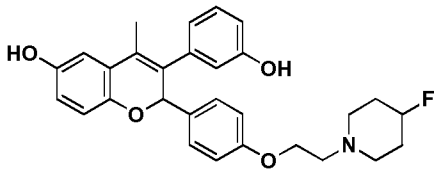
4-(2-(4-((*S*)-2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-6-hydroxy-4-methyl-2H-chromen-3-yl)benzonitrile



[00418] The title compound was synthesized as described in general procedures A, D, E, F and H (z = 0) using 1,4-dimethoxybenzene and 2-(4-chlorophenyl)acetic acid in general procedure A and **Intermediate 14** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.81 (d, 2H), 7.50 (d, 2H), 7.19 (d, 2H), 6.79 (d, 3H), 6.52-6.49 (m, 2H), 5.98 (s, 1H), 4.31-4.30 (m, 1H), 4.20-4.18 (m, 1H), 3.96-3.93 (m, 1H), 3.73-3.72 (m, 1H), 2.66-2.60 (m, 2H), 2.57-2.52 (m, 2H), 2.41-2.35 (m, 2H), 2.03 (s, 3H), 1.85-1.75 (m, 1H), 1.34-1.33 (m, 1H), 1.06 (d, 3H); LCMS: 499.1 $(M+H)^+$.

Example 17

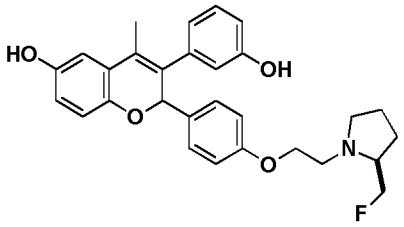
2-(4-(2-(4-Fluoropiperidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00419] The title compound was synthesized as described in general procedures G and J (z = 1) using 4-fluoropiperidine hydrochloride and **Intermediate 3.** ^{1}H NMR (DMSO-d_6): δ 9.43 (s, 1H), 8.94 (s, 1H), 7.18 (d, 2H), 7.13 (t, 1H), 6.79 (d, 2H), 6.73 (m, 1H), 6.78 (d, 1H), 6.65 (dd, 1H), 6.62 (m, 1H), 6.47 (m, 2H), 5.83 (s, 1H), 4.72-4.53 (m, 1H), 3.97 (t, 2H), 2.63 (t, 2H), 2.60-2.53(m, 2H), 2.38-2.28 (m, 2H), 2.03 (s, 3H), 1.88-1.73 (m, 2H), 1.71-1.58 (m, 2H); LCMS: 476.2 $(M+H)^+$.

Example 18

2-(4-(2-((*S*)-2-(Fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

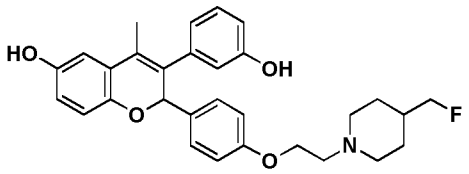


[00420] The title compound was synthesized as described in general procedures G and J (z = 1) using **Intermediate 3** and **Intermediate 9.** ^{1}H NMR (DMSO-d_6; TFA salt): δ 9.88 (s, 1H), 9.43 (br, 1H),

9.00 (br, 1H), 7.24 (d, 2H), 7.13 (t, 1H), 6.86 (d, 2H), 6.74 (m, 1H), 6.69 (d, 1H), 6.65 (dd, 1H), 6.62 (m, 1H), 6.46 (m, 2H), 5.88 (s, 1H), 4.88-4.59 (m, 2H), 4.24 (m, 2H), 4.00-3.84 (m, 1H), 3.73-3.44 (m, 3H), 3.26 (m, 1H), 2.20-2.08 (m, 1H), 2.03 (s, 3H), 2.05-1.95 (m, 1H), 1.90-1.79 (m, 1H), 1.78-1.67 (m, 1H); LCMS: 476.1 $(M+H)^+$.

Example 19

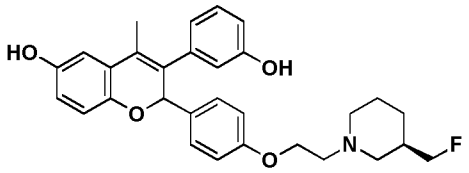
2-(4-(2-(4-(Fluoromethyl)piperidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00421] The title compound was synthesized as described in general procedures G and J (z = 1) using **Intermediate 3** and **Intermediate 10.** ^{1}H NMR (DMSO-d_6): δ 9.44 (s, 1H), 8.94 (s, 1H), 7.18 (d, 2H), 7.13 (t, 1H), 6.78 (d, 2H), 6.74 (m, 1H), 6.69 (m, 1H), 6.65 (m, 1H), 6.62 (m, 1H), 6.48 (m, 2H), 5.83 (s, 1H), 4.26 (dd, 2H), 3.95 (t, 2H), 2.93-2.87 (m, 1H), 2.61 (t, 2H), 2.03 (s, 3H), 2.00-1.92 (m, 2H), 1.62-1.53 (m, 3H), 1.22-1.13 (m, 3H); LCMS: 490.1 $(M+H)^+$.

Example 20

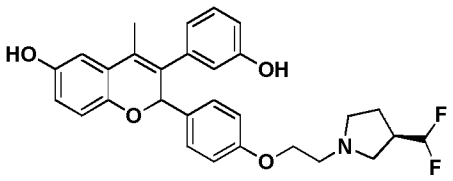
2-(4-(2-((*R*)-3-(Fluoromethyl)piperidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00422] The title compound was synthesized as described in general procedures G and J (z = 1) using **Intermediate 3** and **Intermediate 11.** ^{1}H NMR (DMSO-d_6): δ 9.43 (s, 1H), 8.94 (s, 1H), 7.21 (d, 2H), 7.13 (t, 1H), 6.79 (d, 2H), 6.73 (m, 1H), 6.68 (m, 1H), 6.65 (m, 1H), 6.61 (m, 1H), 6.47 (m, 2H), 5.83 (s, 1H), 4.38-4.17 (m, 2H), 3.97 (t, 2H), 2.87-2.82 (m, 1H), 2.78-2.72 (m, 1H), 2.62 (t, 2H), 2.03 (s, 3H), 2.02-1.93 (m, 1H), 1.90-1.80 (m, 2H), 1.64-1.54 (m, 2H), 1.48-1.37 (m, 1H), 1.02-0.92 (m, 1H); LCMS: 490.2 $(M+H)^+$.

Example 21

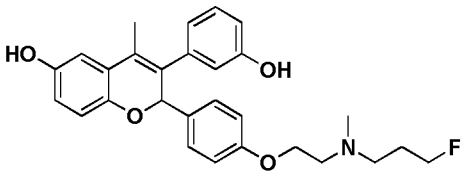
(*R*)-2-(4-(2-(3-(Difluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00423] The title compound was synthesized as described in general procedures G and J (z = 1) using **Intermediate 3** and **Intermediate 12.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.94 (s, 1H), 7.19 (d, 2H), 7.12 (t, 1H), 6.78 (d, 2H), 6.73 (s, 1H), 6.69-6.60 (m, 3H), 6.47 (m, 2H), 5.92 (td, 1H), 5.83 (s, 1H), 3.96 (t, 2H), 2.73-2.64 (m, 3H), 2.54-2.44 (m, 4H), 2.02 (s, 3H), 1.83 (m, 1H), 1.61 (m, 1H); LCMS: 494 $(M+H)^+$.

Example 22

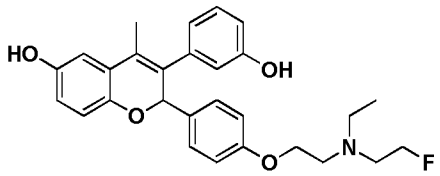
2-(4-(2-((3-Fluoropropyl)(methyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00424] The title compound was synthesized as described in general procedures F, I and J (z = 1) using **Intermediate 3** and 2-(methylamino)ethanol in general procedure F, and 1-fluoro-3-iodopropane in general procedure I. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.44 (s, 1H), 8.95 (s, 1H), 7.19 (d, 2H), 7.13 (t, 1H), 6.79 (d, 2H), 6.75-6.72 (m, 1H), 6.68 (d, 1H), 6.67-6.62 (m, 1H), 6.62-6.60 (m, 1H), 6.48 (s, 2H), 5.84 (s, 1H), 4.50 (t, 1H), 4.38 (t, 1H), 3.95 (t, 2H), 2.65 (t, 2H), 2.44 (t, 2H), 2.19 (s, 3H), 2.03 (s, 3H), 1.81-1.72 (m, 1H), 1.72-1.69 (m, 1H). LCMS: 464.2 $(M+H)^+$.

Example 23

2-(4-(2-(Ethyl(2-fluoroethyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol

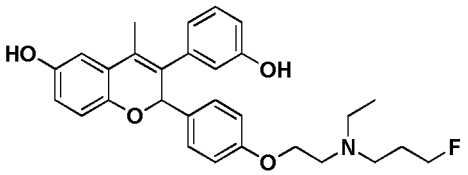


[00425] The title compound was synthesized as described in general procedures F, I and J (z = 1) using **Intermediate 3** and 2-(ethylamino)ethanol in general procedure F, and 1-fluoro-2-iodoethane in general procedure I. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.46 (s, 1H), 8.95 (s, 1H), 7.19 (d, 2H), 7.13 (t, 1H),

6.78 (d, 2H), 6.76-6.71 (m, 1H), 6.78 (d, 1H), 6.78-6.62 (m, 1H), 6.62-6.60 (m, 1H), 6.58 (s, 2H), 5.83 (s, 1H), 4.50 (t, 1H), 4.38 (t, 1H), 3.92 (t, 2H), 2.83-2.77 (m, 3H), 2.74 (t, 1H), 2.58 (q, 2H), 2.03 (s, 3H), 0.94 (t, 3H). LCMS: 464.1 $(M+H)^+$.

Example 24

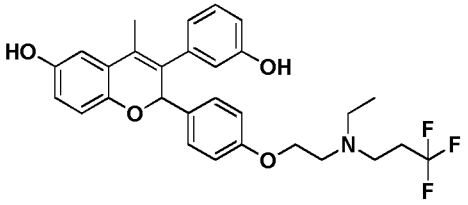
2-(4-(2-(Ethyl(3-fluoropropyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00426] The title compound was synthesized as described in general procedures F, I and J (z = 1) using **Intermediate 3** and 2-(ethylamino)ethanol in general procedure F, and 1-fluoro-3-iodopropane in general procedure I. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.94 (s, 1H), 7.19 (d, 2H), 7.13 (t, 1H), 6.78 (d, 2H), 6.76-6.72 (m, 1H), 6.68 (d, 1H), 6.67-6.62 (m, 1H), 6.62-6.60 (m, 1H), 6.48 (s, 2H), 5.84 (s, 1H), 4.50 (t, 1H), 4.39 (t, 1H), 3.91 (t, 2H), 2.72 (t, 2H), 2.58-2.45 (m, 4H), 2.03 (s, 3H), 1.80-1.71 (m, 1H), 1.71-1.65 (m, 1H), 0.93 (t, 3H). LCMS: 478.1 $(M+H)^+$.

Example 25

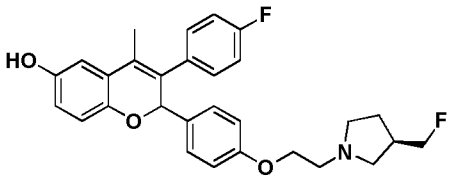
2-(4-(2-(Ethyl(3,3,3-trifluoropropyl)amino)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol



[00427] The title compound was synthesized as described in general procedures F, I and J (z =1) using **Intermediate 3** and 2-(ethylamino)ethanol in general procedure F, and 1,1,1-trifluoro-3-iodopropane in general procedure I. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.43 (s, 1H), 8.94 (s, 1H), 7.20 (d, 2H), 7.13 (t, 1H), 6.78 (d, 2H), 6.75-6.71 (m, 1H), 6.68 (d, 1H), 6.66-6.62 (m, 1H), 6.62-6.60 (m, 1H), 6.46 (s, 2H), 5.84 (s, 1H), 3.93 (t, 2H), 2.76 (t, 2H), 2.70 (t, 2H), 2.57-2.49 (m, 2H), 2.45-2.31 (m, 2H), 2.03 (s, 3H), 0.94 (t, 3H). LCMS: 514.1 $(M+H)^+$.

Example 26

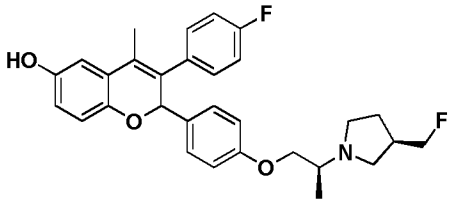
2-(4-(2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)ethoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol



[00428] The title compound was synthesized as described in general procedures A, D, E, F and J (z = 0) using 1,4-dimethoxybenzene and 2-(4-fluorophenyl)acetic acid in general procedure A, and **Intermediate 13** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.35-7.29 (m, 2H), 7.22-7.13 (m, 4H), 6.78 (d, 2H), 6.75 (s, 1H), 6.49 (s, 2H), 5.91 (s, 1H), 4.35-4.28 (m, 1H), 4.25-4.16 (m, 1H), 3.96 (t, 2H), 2.70 (t, 2H), 2.60 (t, 1H), 2.57-2.38 (m, 3H), 2.37-2.30 (m, 1H), 2.01 (s, 3H), 1.87-1.76 (m, 1H), 1.41-1.30 (m, 1H). LCMS: 478.1 $(M+H)^+$.

Example 27

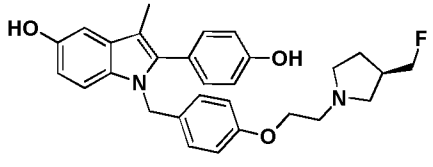
2-(4-((*S*)-2-((*R*)-3-(Fluoromethyl)pyrrolidin-1-yl)propoxy)phenyl)-3-(4-fluorophenyl)-4-methyl-2H-chromen-6-ol



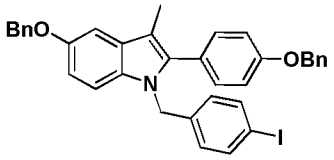
[00429] The title compound was synthesized as described in general procedures A, D, E, F, and J (z = 0) using 1,4-dimethoxybenzene and 2-(4-fluorophenyl)acetic acid in general procedure A, and **Intermediate 14** in general procedure F. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 7.35-7.29 (m, 2H), 7.22-7.14 (m, 4H), 6.79 (d, 2H), 6.76-6.73 (m, 1H), 6.52-6.46 (m, 2H), 5.91 (s, 1H), 4.36-4.28 (m, 1H), 4.24 (m, 1H), 3.99 (m, 1H), 3.76-3.69 (m, 1H), 2.70-2.51 (m, 4H), 2.43-2.31 (m, 2H), 2.02 (s, 3H), 1.88-1.75 (m, 1H), 1.40-1.30 (m, 1H), 1.07 (d, 3H). LCMS: 492.2 $(M+H)^+$.

Example 28

(*R*)-1-(4-(2-(3-(Fluoromethyl)pyrrolidin-1-yl)ethoxy)benzyl)-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol

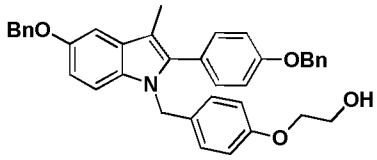


Step 1: 5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-1-(4-iodobenzyl)-3-methyl-1H-indole



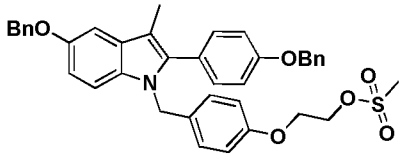
[00430] A solution of 5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-methyl-1H-indole (4.2 g, 10 mmol; see PCT/US98/21609 for synthesis) in DMF (40 mL) was cooled to 0 °C under nitrogen atmosphere. Sodium hydride (60% dispersion in mineral oil; 420 mg, 10.5 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 5 min, and then ice bath was removed and allowed to warm to room temperature. After 1 h, the reaction was cooled back to 0 °C and 4-iodobenzyl bromide (3.7 g, 12.5 mmol) was added slowly. After 5 minutes, the ice bath was removed and the reaction mixture was stirred at room temperature for 6 h. The reaction was diluted with water (200 mL), and ethyl acetate. The precipitate was sonicated, filtered off and dried to give 1.99 g of the desired product. The filtrate was extracted with ethyl acetate (50 mL), the organic layer was washed with water, washed with brine and dried ($MgSO_4$), filtered, concentrated and purified by silica gel chromatography (20%-70% DCM in hexanes) to afford 2.62 g. The reaction resulted in total 4.6 g of 5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-1-(4-iodobenzyl)-3-methyl-1H-indole as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (d, 2H), 7.51-7.46 (m, 4H), 7.44-7.38 (m, 4H), 7.38-7.32 (m, 2H), 7.29 (d, 2H), 7.16 (d, 1H), 7.16-7.10 (m, 3H), 6.82 (dd, 1H), 6.62 (d, 2H), 5.20 (s, 2H), 5.14 (d, 4H), 2.17 (s, 3H).

Step 2: 2-(4-((5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-3-methyl-1H-indol-1-yl)methyl)phenoxy)ethanol



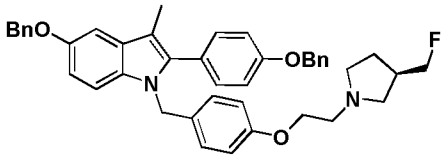
[00431] A mixture of 5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-1-(4-iodobenzyl)-3-methyl-1H-indole (1.01 g, 1.58 mmol), ethylene glycol (0.44 mL, 7.89 mmol), copper iodide (32 mg, 0.17 mmol), 1,10-phenanthroline (60 mg, 0.33 mmol), and potassium carbonate (436 mg, 3.15 mmol) in butyronitrile (3 mL) was degassed with three vacuum/N_2 cycles. The reaction was heated at 125 °C for 26 hrs and upon completion, allowed to cool to room temperature. It was then diluted with water. The aqueous layer was extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered, concentrated and purified by silica gel chromatography (0%-40% ethyl acetate in hexanes) to give 554 mg of 2-(4-((5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-methyl-1H-indol-1-yl)methyl)phenoxy)ethanol as a pale yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, 4H), 7.45-7.37 (m, 4H), 7.37-7.32 (m, 2H), 7.30 (d, 2H), 7.21 (d, 1H), 7.15-7.10 (m, 3H), 6.81 (dd, 1H), 6.74 (s, 4H), 5.20-5.10 (m, 6H), 4.81 (t, 1H), 3.87 (t, 2H), 3.64 (q, 2H), 2.16 (s, 3H). LCMS: 570.0 $(M+H)^+$.

Step 3: 2-(4-((5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-3-methyl-1H-indol-1-yl)methyl)phenoxy)ethyl methanesulfonate



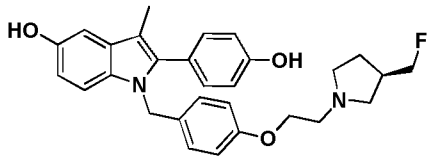
[00432] A solution of 2-(4-((5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-methyl-1H-indol-1-yl)methyl)phenoxy)ethanol (546 mg, 0.96 mmol) in DCM (10 mL) was cooled to 0 °C. Triethylamine (0.2 mL, 1.43 mmol) and methanesulfonyl chloride (0.1 mL, 1.29 mmol) were added and the reaction was stirred at 0 °C for 1 h. The reaction was diluted with DCM (30 mL) and then washed with 1M HCl (20 mL), washed with water (20 mL), dried ($MgSO_4$), filtered and concentrated under vacuum to give 597 mg of 2-(4-((5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-methyl-1H-indol-1-yl)methyl)phenoxy)ethyl methanesulfonate as a yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, 4H), 7.44-7.37 (m, 4H), 7.37-7.32 (m, 2H), 7.30 (d, 2H), 7.21 (d, 1H), 7.15-7.10 (m, 3H), 6.83-6.74 (m, 5H), 5.20-5.10 (m, 6H), 4.50-4.45 (m, 2H), 4.17-4.11 (m, 2H), 2.16 (s, 3H). LCMS: 648.1 $(M+H)^+$.

Step 4: (*R*)-5-(Benzyloxy)-2-(4-(benzyloxy)phenyl)-1-(4-(2-(3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)benzyl)-3-methyl-1H-indole



[00433] A mixture of 2-(4-((5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-methyl-1H-indol-1-yl)methyl)phenoxy)ethyl methanesulfonate, (*R*)-3-(fluoromethyl)pyrrolidine **(Intermediate 8)** and potassium carbonate in acetonitrile was degassed with three vacuum/N_2 cycles. The reaction was heated at 80 °C for 10 hrs, allowed to cool to room temperature and then diluted with water (40 mL). The aqueous layer was extracted with ethyl acetate (2x40 mL) and the combined ethyl acetate extracts were then washed with water (40 mL), washed with brine (40 mL), dried ($MgSO_4$), filtered, concentrated and purified by silica gel chromatography (0%-5% MeOH in DCM) to give 274 mg of (*R*)-5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-1-(4-(2-(3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)benzyl)-3-methyl-1H-indole. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, 4H), 7.44-7.37 (m, 4H), 7.37-7.32 (m, 2H), 7.30 (d, 2H), 7.21 (d, 1H), 7.15-7.10 (m, 3H), 6.81 (dd, 1H), 6.74 (s, 4H), 5.17-5.10 (m, 6H), 4.33-4.30 (m, 1H), 4.22-4.18 (m, 1H), 3.94 (t, 2H), 2.70 (t, 2H), 2.56-2.40 (m, 3H), 2.60 (t, 1H), 2.36-2.31 (m, 1H), 2.16 (s, 3H), 1.86-1.76 (m, 1H), 1.40-1.30 (m, 1H). LCMS: 655.3 $(M+H)^+$.

Step 5: (*R*)-1-(4-(2-(3-(Fluoromethyl)pyrrolidin-1-yl)ethoxy)benzyl)-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol



[00434] A solution of (*R*)-5-(benzyloxy)-2-(4-(benzyloxy)phenyl)-1-(4-(2-(3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)benzyl)-3-methyl-1H-indole (263 mg, 0.40 mmol) in ethyl acetate/ethanol (4:1, 6 mL) was degassed with three vacuum/N_2 cycles. To this solution was added 10% Pd on carbon (120 mg, 0.11 mmol) and then the needle of a H_2 balloon was placed into the reaction flask. The mixture was stirred at room temperature for 15 hrs then diluted with ethyl acetate, filtered through Celite and concentrated. The residue was dried further on high vacuum to give 171 mg of (*R*)-1-(4-(2-(3-(fluoromethyl)pyrrolidin-1-yl)ethoxy)benzyl)-2-(4-hydroxyphenyl)-3-methyl-1H-indol-5-ol as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.67 (s, 1H), 8.69 (s, 1H), 7.16 (d, 2H), 7.06 (d, 1H), 6.85 (d, 2H), 6.80 (d, 1H), 6.75 (s, 4H), 6.57 (dd, 1H), 5.10 (s, 2H), 4.35-4.30 (m, 1H), 4.23-4.18 (m, 1H), 3.94 (t, 2H), 2.70 (t, 2H), 2.62 (t, 1H), 2.56-2.40 (m, 3H), 2.38-2.31 (m, 1H), 2.10 (s, 3H), 1.87-1.76 (m, 1H), 1.40-1.31 (m, 1H). LCMS: 475.2 $(M+H)^+$.

Example 29: 3x ERE MCF-7 Reporter Assay

[00435] MCF7 cells were maintained in RPMI 1640 supplemented with 10% FCS. Transcriptional assays were performed by seeding 100 μL of cells at a density of 250,000 cells/mL into 96-well cell culture plates in RPMI 1640 supplemented with 10% charcoal stripped serum and allowed to attach overnight. Cells were transiently transfected using Lipofectin (Life Technologies) according to the manufacturer's protocol. Triplicate transfections were performed using 300 ng 3X ERE-TK-Luc (reporter vector), 50 ng CMVpRL (normalization vector), and 130 ng pCMX (filler DNA). Transfected cells were incubated overnight then treated with ligand. For ER agonist assays, the compounds were serially diluted and 50 μL of compound plus RPMI 1640 supplemented with charcoal stripped serum was added to the cells. For ER antagonist assays, the compounds were serially diluted and 50 μL of compound with RPMI plus 17β-estradiol supplemented with charcoal stripped serum were added to the cells. The final 17β-estradiol concentration used in the antagonist assays was 0.1 nM. Following 24 hour incubation the medium was removed and the cells were lysed in 40 μL of lysis buffer (25mM Tris Phosphate, 2mM CDTA, 10% Glycerol, 0.5% Triton X-100, 2 mM DTT). Firefly luciferase activity was measured immediately following the addition of 40 μL luciferase buffer (20mM tricine, 0.1 mM EDTA, 1.07 mM $(MgCO_3)_4$ $Mg(OH)_2$ • $5H_2O$, 2.67 mM $MgSO_4$, 33.3 mM DTT, 270 μM Coenzyme A, 470 μM luciferin, 530 μM ATP). Renilla luciferase was measured following the addition of 40 μL colelenterazine buffer (1.1 M NaCl, 2.2 mM Na_2EDTA, 0.22 M $KxPO_4$ (pH 5.1), 0.44 mg/mL BSA, 1.3 mM NaN_3, 1.43 μM coelenterazine, final pH adjusted to 5.0).

Example 30: Breast Cancer Cell Viability Assays

[00436] MCF-7 cells were adjusted to a concentration of 20,000 cells per mL in RPMI containining 10% FBS and 20 mM HEPES. 16 microliters of the cell suspension (320 cells) was added to each well of a 384 well plate, and the cells were incubated overnight to allow the cells to adhere. The following day an eleven point, serial semilog dilution of each compound was added to the cells in 16 μL at a final concentration ranging from 0.3-0.000003 μM. After 5 days' compound exposure, 16 μL of CellTiter-GLo (Promega, Madison WI) was added to the cells the the relative luminescence units (RLUs) of each well was determined. CellTiter-Glo added to 32 μL of medium without cells was used to obtain a background value. The Percent viability of each sample was determined as follows: (RLU sample-RLU background/RLU untreated cells-RLU background) x 100=%viability.

[00437] Viability effects in additional ER+ breast cancer cell lines, including BT474, CAMA1, MDA-MB-361, ZR-75-1, T47D, can be profiled in assays similar to Example 30.

[00438] Illustrative biological data for representative compounds disclosed herein is presented in the following table:

Table 3.

Example	MCF7 Viability Assay IC_{50}	MCF7 Viability Assay Max Response
1	A	++
2	A	++
2a	B	++
2b	A	++
3	A	++
3a	B	++
3b	A	++
4	B	++
5	A	++
6	A	++
7	A	++
8	B	++
9	A	++
10	A	++
11	A	++
12	A	++
13	A	++
14	A	++
15	B	++
16	B	++
17	A	++
18	B	++
19	A	++
20	A	+
21	A	++

Example	MCF7 Viability Assay IC_{50}	MCF7 Viability Assay Max Response
22	A	+
23	B	++
24	A	++
25	B	+
26	B	++
27	B	++
28	A	++

A = single $IC_{50} \leq 1$ nM; B = single $IC_{50} > 1$ nM;
+ = a single % value < 50%; ++ = a single % value ≥ 50%

Example 31: Breast Cancer Cell ER-α In Cell Western Assay (SP1)

[00439] MCF-7 cells were adjusted to a concentration of 200,000 cells per mL in RPMI containing 10% charcoal-stripped FBS and 20 mM HEPES. 16 microliters of the cell suspension (3200 cells) was added to each well of a poly-D-lysine 384 well plate, and the cells were incubated overnight to allow the cells to adhere. The following day an eleven point, serial semilog dilution of each compound was added to the cells in 16 µL at a final concentration ranging from 0.3-0.000003 µM. At 4 or 24 hr post compound addition, the cells were fixed (10% formalin in PBS) for 20 minutes. Cells were permeablized in PBS 0.1% Triton and blocked with LICOR blocking buffer (50 µl/well, 90'). The wells were then incubated overnight at 4 °C with SP1 rabbit monoclonal Ab (Thermo Scientific) diluted 1:1000 in LICOR blocking buffer/0.1% Tween-20. Wells which were treated with blocking buffer with Tween but no antibody were used as a background control. Wells were washed with 0.1% Tween-20/PBS and then incubated in goat anti-rabbit IRDye™ 800CW (LICOR Inc.;1:1000) and DRAQ5 DNA dye (1:2000 for 2 mM stock) diluted in LICOR blocking buffer containing 0.1% Tween-20 and 0.01% SDS for 60 minutes. Cells were washed (50 µl/well, 5' each) in 0.1%Tween-20/PBS. Plates were scanned on a LICOR Odyssey infrared imaging system. Integrated intensities in the 800 nm channel and 700 nm channel were measured to determine levels of ER and DNA respectively. Percent ER levels were determined as follows:

(Integrated intensity 800 nm sample/integrated intensity 700 nm sample)/ (Integrated intensity 800 nm untreated cells/integrated intensity 700 nm untreated cells) x 100=%ER levels.

[00440] Effects on steady state levels of ER-α in additional ER+ breast cancer cell lines, including BT474, CAMA1, MDA-MB-361, ZR-75-1, T47D, can be profiled in assays similar to Example 31.

[00441] Illustrative biological data for representative compounds disclosed herein is presented in the following table:

Table 4.

Example	ER In-Cell Western Assay (SP1); IC_{50}	ER In-Cell Western Assay (SP1); Max Response
1	A	+++
2	A	+++
2a	B	+++
2b	A	+++
3	A	+++
3a	B	+++
3b	A	+++
4	B	+++
5	A	+++
6	A	+++
7	A	+++
8	A	+++
9	A	+++
10	A	+++
11	A	+++
12	A	+++
13	A	+++
14	A	+++
15	B	+++
16	B	+++
17	A	++
18	A	++
19	A	++
20	A	+
21	A	+++
22	A	+
23	A	+
24	A	+
25	A	+
26	A	+++
27	A	+++
28	A	+++

A = single IC_{50} ≤1 nM; B = single IC_{50} >1 nM
+ = a single % value that is <60%; ++ = a single % value that is % ≥60% to <85%;
+++ = a single % value that is ≥85%.

Example 32: Ishikawa Uterine Cell Alkaline Phosphatase Assay

[00442] Subconfuent Ishikawa cells in a T225 are incubated 24 hours in an estrogen free basal medium (EFBM) consisting of DMEM:Ham's F-12 50:50 phenol red free basal medium containing 5% Charcoal Dextran treated FBS and 20 mM HEPES. Cells are plated the following day in EFBM in clear 384 well plates at a concentration of 2.5 x 105 cells per mL, 16 µL per well (4000 cells per well). A 12

point semilog dilution of each compound is carried out in DMSO and subsequently diluted in EFBM. An equal volume of compound in EFBM is added immediately after plating cells, and the cells are incubated for 3 days. The cells are fixed with 5% formalin, and rinsed with PBS. Alkaline Phosphatase substrate 4-Nitrophenyl phosphate disodium salt hexahydrate is added to a solution containing 2 mM $MgCl_2$, 1 M diethanolamine, and adjusted to pH 9.0. The substrate solution is added to the cell cultures (16 µL per well), and OD405 is measured in a multiwall plate spectrophotometer when the optical density at 405 nm wavelength of cells treated with 17β-estradiol in the concentration range of 1-30 nM reaches 1.0-1.2 absorbance units. Cells treated with DMSO alone serve as a background control. Percent activity in background subtracted samples is measured as follows: % activity=OD405 sample/OD405 max of 17β-estradiol treated cells x 100.

Example 33: Ovarian Cancer Cell Viability Assays

[00443] BG-1, cells were adjusted to a concentration of 20,000 cells per mL in RPMI containining 10% FBS and 20 mM HEPES. 16 microliters of the cell suspension (320 cells) was added to each well of a 384 well plate, and the cells were incubated overnight to allow the cells to adhere. The following day an eleven point, serial semilog dilution of each compound was added to the cells in 16 µL at a final concentration ranging from 0.3-0.000003 µM. After 5 days' compound exposure, 16 µL of CellTiter-GLo (Promega, Madison WI) was added to the cells the the relative luminescence units (RLUs) of each well was determined. CellTiter-Glo added to 32 µL of medium without cells was used to obtain a background value. The Percent viability of each sample was determined as follows: (RLU sample-RLU background/RLU untreated cells-RLU background) x 100=%viability.

[00444] Viability effects in additional ER+ ovarian cancer cell lines, including A1847, SKOV3, SW626, A2780, can be profiled in assays similar to Example 33.

Example 34: Ovarian Cancer Cell ER-α In Cell Western Assay

[00445] BG-1 cells were adjusted to a concentration of 200,000 cells per mL in RPMI containining 10% charcoal-stripped FBS and 20 mM HEPES. 16 microliters of the cell suspension (3200 cells) was added to each well of a poly-D-lysine 384 well plate, and the cells were incubated overnight to allow the cells to adhere. The following day an eleven point, serial semilog dilution of each compound was added to the cells in 16 µL at a final concentration ranging from 0.3-0.000003 µM. At 4 or 24 hr post compound addition, the cells were fixed (10% formalin in PBS) for 20 minutes. Cells were permeablized in PBS 0.1% Triton and blocked with LICOR blocking buffer (50 µl/well, 90'). The wells were then incubated overnight at 4 °C with ER1D5 (Santa Cruz Biotechnology) diluted 1:100 in LICOR blocking buffer/0.1% Tween-20. Wells which were treated with blocking buffer with Tween but no antibody were used as a background control. Wells were washed with 0.1% Tween-20/PBS and then incubated in goat anti-mouse IRDye™ 800CW (LICOR Inc.;1:1000) and DRAQ5 DNA dye (1:2000 for 2mM stock) diluted in LICOR blocking buffer containing 0.1% Tween-20 and 0.01% SDS for 60 minutes. Cells were washed (50 µl/well, 5' each) in 0.1%Tween-20/PBS. Plates were scanned on a LICOR Odyssey

infrared imaging system. Integrated intensities in the 800 nm channel and 700 nm channel were measured to determine levels of ER and DNA respectively. Percent ER levels were determined as follows:

(Integrated intensity 800 nm sample/integrated intensity 700 nm sample)/ (Integrated intensity 800 nm untreated cells/integrated intensity 700 nm untreated cells) x 100=%ER levels.

[00446] Effects on steady state levels of ER-α in additional ER+ ovarian cancer cell lines, including A1847, SKOV3, SW626, A2780, can be profiled in assays similar to Example 34.

[00447] Other cancer cell lines contemplated for testing compounds described herein include: ER-positive endometrial cell lines (Ishikawa, ECC1, HEC-1, EnCa-101) and ER-positive cervical cell lines (Caski, HeLa, SiHa).

Example 35: PEO Cell Viability Assays

[00448] PEO-1, PEO-4 and PEO-6 ovarian cancer cell lines were adjusted to a concentration of 20,000 cells per mL in RPMI containing 10% FBS. 16 microliters of the cell suspension (320 cells) was added to each well of a 384 well plate, and the cells were incubated overnight to allow the cells to adhere. The following day a 10 point, serial 1:5 dilution of each compound was added to the cells in 16 μL at a final concentration ranging from 1-0.0000005 μM. After 7 days' compound exposure, 16 μL of CellTiter-GLo (Promega, Madison WI) was added to the cells the the relative luminescence units (RLUs) of each well was determined. CellTiter-Glo added to 32 μL of medium without cells was used to obtain a background value. The Percent viability of each sample was determined as follows: (RLU sample-RLU background/RLU untreated cells-RLU background) x 100=%viability.

Example 36: PEO ER Western Analysis

[00449] Cells were plated in RPMI 5% CSS for 48 hours, then treated with compound for 4 or 24 hours. Cells were lysed in modified radioimmunoprecipitation buffer (mRIPA; 10 mM Tris, 150 mM NaCl, 1% (v/v) NP-40, 0.5% deoxycholate, 0.1% SDS, 5 mM EDTA, pH 7.4) containing Halt Protease & Phosphatase Single-Use Inhibitor Cocktail (Thermo Scientific, Cat. No. 78442). Total protein of the clarified lysates was quantitated by Lowry Assay (Biorad DC protein assay). NuPAGE® LDS Sample Buffer and Sample Reducing Agent were added to the lysates and heated to 70°C for 10 mins. 15 ug of total cell protein was separated electrophoretically in a NuPAGE 4-12% Bis Tris Gel in MOPS SDS running buffer, then transferred to a nitrocellulose membrane in transfer buffer using an XCell II blot module. Membranes were incubated in Blocking Buffer (LI-COR, Lincoln, NE) for 30 minutes at room temperature, followed by 60 minute incubations with a rabbit antibody against ER alpha (SP-1, Thermo Fisher Scientific, Cat. No. RM-9101), ER beta (Cell Signaling Technology, Cat. No. 5513), or mouse antibody against alpha tubulin (Sigma, Cat. No. T6199). Following incubation with an IRDye® Conjugated Goat Anti Mouse or Anti Rabbit IgG (LI-COR), protein bands were quantified using an Odyssey® Infrared Imaging System. Graphing of data to determine ER levels was performed using Graphpad PRISM® software. %ER levels were calculated as follows:

%ER= (fluorescence ER band of sample-bkgrd/fluorescence Tubulin band of sample-bkgrd)/
(fluorescence ER band of untreated cells-bkgrd/fluorescence Tubulin of untreated cells-bkgrd)

Example 37: Breast Cancer Model; Xenograft Assay (MCF-7)

[00450] Time release pellets containing 0.72 mg 17-β Estradiol were subcutaneously implanted into nu/nu mice. MCF-7 cells were grown in RPMI containing 10% FBS at 5% CO_2, 37 °C. Cells were spun down and re-suspended in 50% RPMI (serum free) and 50% Matrigel at $1X10^7$ cells/mL. MCF-7 cells were subcutaneously injected (100µL/animal) on the right flank 2-3 days post pellet implantation. Tumor volume (length x $width^2/2$) was monitored bi-weekly. When tumors reached an average volume of ~200 mm^3 animals were randomized and treatment was started. Animals were treated with Vehicle or Compound daily for 4 weeks. Tumor volume and body weight were monitored bi-weekly throughout the study. At the conclusion of the treatment period, plasma and tumor samples were taken for pharmacokinetic and pharmacodynamic analyses, respectively.

Example 38: Breast Cancer Model; Xenograft Assay (MCF-7 derivative)

[00451] Female nu/nu mice (with supplemental 17-β Estradiol pellets; 0.72mg; 60 day slow release) bearing MCF-7 tumors (mean tumor volume 200mm^3) were treated with Tamoxifen (citrate) by oral gavage. Tumor volume (length x $width^2/2$) and body weight were monitored twice weekly. Following a significant anti-tumor response in which tumor volume remained static, evident tumor growth was first observed at approximately 100 days of treatment. At 120 days of treatment, tamoxifen dose was increased. Rapidly growing tumors were deemed tamoxifen resistant and selected for in vivo passage into new host animals. Tumor Fragments (~100mm^3/animal) from the tamoxifen resistant tumors were subcutaneously implanted into the right flank of female nu/nu mice (with 17-β Estradiol pellets (0.72mg; 60 day slow release)). Passaged tumors were maintained under constant Tamoxifen selection, and Tumor volume (length x $width^2/2$) was monitored weekly. When tumor volume reached ~150-250 mm^3, animals were randomized into treatment groups (mean tumor volume 200 mm^3) and tamoxifen treatment was terminated (except for a tamoxifen control arm). Animals were treated with Vehicle or Compound daily for 4 weeks. Tumor volume and body weight were monitored twice weekly for the duration of the study. At the conclusion of the treatment period; plasma and tumor samples were taken for pharmacokinetic and pharmacodynamic analyses, respectively.

Example 39: Ovarian Cancer Model; Xenograft Assay (BG-1)

[00452] Time release pellets (0.72 mg 17-β Estradiol/60 days) were subcutaneously implanted into female nu/nu mice. BG-1 cells were grown in DMEM Ham's F-12 50/50 containing 10% FBS, 10 mM Sodium Pyruvate, 10 mM Non-Essential Amino Acids at 5% CO_2, 37 °C. Cells were spun down and re-suspended in 50% DMEM Ham's F-12 (serum free) and 50% Matrigel at $5X10^7$ cells/mL. BG-1 cells were subcutaneously injected (100µL/animal) on the right flank 2-3 days post pellet implantation. Tumor volume (length x $width^2/2$) was monitored bi-weekly. When tumors reached an average volume

of ~250 mm^3 animals were randomized and treatment was started. Animals were treated with Vehicle or Compound daily for 4 weeks. Tumor volume and body weight were monitored bi-weekly throughout the study. At the conclusion of the treatment period; plasma and tumor samples were taken for pharmacokinetic and pharmacodynamic analyses, respectively.

Example 40: Endometrial Cancer Model; Xenograft Assay (ECC-1)

[00453] ECC-1 cells were grown in DMEM (phenol red, 4.5g/L glucose and L-glutamine) containing 10% FBS, 1% Non-Essential Amino Acids and 100units Penicillin/Streptomycin at 10% CO_2, 37 °C. Cells were spun down and re-suspended in 50% DMEM (serum free) and 50% Matrigel (BD, high concentration) at $5X10^7$ cells/mL. Time release pellets (0.72 mg 17-β Estradiol/60 days) were subcutaneously implanted into female nu/nu mice. ECC-1 cells were subcutaneously injected (100μL/animal) on the right flank 2-3 days post pellet implantation. Tumor volume was monitored and when tumors reached a suitable size for transplant they were excised. Excised tumors were cut into small pieces (~$100mm^3$) and serially transplanted (10G trocar, right flank) into female nu/nu containing estradiol pellets (0.72mg 17-β Estradiol/60 days) for 2-3 days. Tumor volume (length x width x width/2) was monitored and when palpable tumors were observed, animals were randomized and treatment was started. Animals were treated with Vehicle or Compound daily for 4 weeks or until tumor volume reached $2000mm^3$ (whichever came first). Tumor volume and body weight were monitored bi-weekly throughout the study. At the conclusion of the treatment period; plasma and tumor samples were taken for pharmacokinetic and pharmacodynamic analyses, respectively.

Example 41: Immature Uterine Wet Weight-Antagonist Mode

[00454] Female immature CD-IGS rats (21 days old upon arrival) were treated for three days. Animals were dosed daily for three days. Vehicle or test compound was administered orally by gavage followed 15 minutes later by an oral dose of 0.1 mg/kg Ethynyl Estradiol. On the fourth day 24 hours after dose, plasma was collected for pharmacokinetic analysis. Immediately following plasma collection, the animals were euthanized and the uterus was removed and weighed.

Example 42: Immature Uterine Wet Weight-Agonist Mode

[00455] Female immature CD-IGS rats (21 days old upon arrival) were treated for three days. Animals were dosed daily for three days. Vehicle or test compound was administered orally by gavage followed 15 minutes later by a second oral dose of vehicle. On the fourth day 24 hours after dose, plasma was collected for pharmacokinetic analysis. Immediately following plasma collection, the animals were euthanized and the uterus was removed and weighed.

Example 43: Adult Uterine Wet Weight-10 Day

[00456] Female CD-IGS rats (69 days old, Charles River Laboratories) were purchased and split into groups. Group 1 was ovariectomized at the vendor (Charles River Laboratories) at 60 days of age and the study was started 2 weeks after surgery, while groups 2-8 were intact. Vehicle or test compound

was administered orally for 10 days. Two hours after the 10th and final dose, cardiac punctures were performed and serum was collected for pharmacokinetic and estradiol analyses. Immediately following serum collection, the animals were euthanized and the uterus and ovaries were removed and weighed. Uteri and ovaries from 2 animals per group were fixed in 10% neutral buffered formalin and sent out to be paraffin embedded, sectioned and stained for H&E (SDPath). Stained tissues were analyzed in house and then sent out to be read by a board certified pathologist. Uteri and ovaries from 4 animals per group were flash frozen in liquid N_2 for transcriptional analysis, examining a select set of genes modulated by the estrogen receptor.

Example 44: Breast Cancer Clinical Trial

[00457] Purpose: The purposes of this study are to assess the efficacy of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as first- or second-line treatment of estrogen receptor (ER) positive metastatic breast cancer, collect information on any side effects the compound may cause, and evaluate the pharmacokinetic properties of the compound.

[00458] Intervention: Patients are administered 1-50 mg/kg of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, per day or twice a day.

[00459] Outcome Measures: Primary Outcome Measures: tumor response and/or disease control.

[00460] Secondary Outcome Measures: (a) side-effects; (b) pharmacokinetic properties; (c) proportion of patients that have complete or partial response or stable disease at defined time points; (d) time to progression and overall survival; and (e) biomarkers predictive of clinical response.

[00461] Detailed Description: Patients will be given a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, orally once or twice a day. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed. Every 12 weeks the patient's cancer will be re-evaluated with either a CT scan or MRI to determine whether the treatment is working. Participation in this study will last until disease progression or unacceptable toxicity.

[00462] Eligibility: Female subjects that are 18 years and older.

[00463] Inclusion Criteria: Histologically or cytologically confirmed diagnosis of invasive breast cancer, stage IV disease; at least one measurable target lesion as defined by RECIST that has not been previously treated with local therapy; post-menopausal status; ER positive breast cancer; HER2-negative breast cancer; up to one prior hormonal therapy for advanced or metastatic disease; ECOG performance status 0-1; life expectancy > 12 weeks; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior radiation and recovered from treatment-related toxicity.

[00464] Exclusion Criteria: HER2-positive breast cancer; prior chemotherapy regimen for metastatic disease; history of, or presence of brain metastases; concurrent investigational drug treatment; prior bone marrow or stem cell transplant; history of other malignancy within the last 5 years, not including

curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; uncontrolled infection; active bleeding, or history of bleeding requiring transfusion; active cardiac disease; serious medical or psychiatric illness.

Example 45: Endometrial Carcinoma Clinical Trial

[00465] Purpose: The purposes of this study are to assess the efficacy of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in the treatment of advanced or metastatic endometrial carcinoma, collect information on any side effects the compound may cause, and evaluate the pharmacokinetic properties of the compound.

[00466] Intervention: Patients are administered 1-50 mg/kg of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, per day or twice a day.

[00467] Outcome Measures: Primary Outcome Measures: tumor response and/or disease control Secondary Outcome Measures: (a) side-effects; (b) pharmacokinetic properties; (c) proportion of patients that have complete or partial response or stable disease at defined time points; (d) time to progression and overall survival; and (e) biomarkers predictive of clinical response.

[00468] Detailed Description: Patients will be given a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, orally once or twice a day. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed. Every 12 weeks the patient's cancer will be re-evaluated with either a CT scan or MRI to determine whether the treatment is working. Participation in this study will last until disease progression or unacceptable toxicity.

[00469] Eligibility: Female subjects that are 18 years and older.

[00470] Inclusion Criteria: Histologically or cytologically confirmed diagnosis of advanced or metastatic endometrial carcinoma; at least one measurable target lesion as defined by RECIST that has not been previously treated with local therapy; hormone receptor positive endometrial carcinoma; ECOG performance status 0-1; life expectancy > 12 weeks; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior radiation and recovered from prior surgery or treatment-related toxicity.

[00471] Exclusion Criteria: History of, or presence of brain metastases; concurrent investigational drug treatment; prior bone marrow or stem cell transplant; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; uncontrolled infection; active bleeding, or history of bleeding requiring transfusion; active cardiac disease; serious medical or psychiatric illness.

Example 46: Ovarian Cancer Clinical Trial

[00472] Purpose: The purposes of this study are to assess the efficacy of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, in the treatment of advanced

ovarian cancer, collect information on any side effects the compound may cause, and evaluate the pharmacokinetic properties of the compound.

[00473] Intervention: Patients are administered 1-50 mg/kg of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, per day or twice a day.

[00474] Outcome Measures: Primary Outcome Measures: tumor response and/or disease control

[00475] Secondary Outcome Measures: (a) side-effects; (b) pharmacokinetic properties; (c) proportion of patients that have complete or partial response or stable disease at defined time points; (d) time to progression and overall survival; and (e) biomarkers predictive of clinical response.

[00476] Detailed Description: Patients will be given a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, orally once or twice a day. Prior to each dosing cycle, a physical exam, blood work (including tumor markers, e.g., CA-125) and assessment of any side effects will be performed. Every 12 weeks the patient's cancer will be re-evaluated with either a CT scan or MRI to determine whether the treatment is working. Participation in this study will last until disease progression or unacceptable toxicity.

[00477] Eligibility: Female subjects that are 18 years and older.

[00478] Inclusion Criteria: Histologically or cytologically confirmed diagnosis of advanced ovarian cancer; at least one measurable target lesion as defined by RECIST that has not been previously treated with local therapy; ER positive ovarian cancer; ECOG performance status 0-1; life expectancy > 12 weeks; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior radiation and recovered from prior surgery or treatment-related toxicity.

[00479] Exclusion Criteria: History of, or presence of brain metastases; concurrent investigational drug treatment; prior bone marrow or stem cell transplant; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; uncontrolled infection; active bleeding, or history of bleeding requiring transfusion; active cardiac disease; serious medical or psychiatric illness.

Example 47: ER-Positive NSCLC Clinical Trial

[00480] Purpose: The purposes of this study are to assess the efficacy of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, as single agent or in combination in the treatment of advanced or metastatic estrogen receptor (ER) positive non-small cell lung cancer (NSCLC), collect information on any side effects the compound may cause as single agent or in combination, and evaluate the pharmacokinetic properties of the compound as single agent or in combination.

[00481] Intervention: Patients are administered 1-50 mg/kg of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, per day or twice a day as single agent or in combination.

[00482] Outcome Measures: Primary Outcome Measures: tumor response and/or disease control. Secondary Outcome Measures: (a) side-effects; (b) pharmacokinetic properties; (c) proportion of patients that have complete or partial response or stable disease at defined time points; (d) time to progression and overall survival; and (e) biomarkers predictive of clinical response.

[00483] Detailed Description: Patients will be given a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, orally once or twice a day as single agent or in combination. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed. Every 12 weeks the patient's cancer will be re-evaluated with either a CT scan or MRI to determine whether the treatment is working. Participation in this study will last until disease progression or unacceptable toxicity.

[00484] Eligibility: Male and female subjects that are 18 years and older.

[00485] Inclusion Criteria: Histologically or cytologically confirmed diagnosis of advanced or metastatic ER-positive NSCLC; at least one measurable target lesion as defined by RECIST that has not been previously treated with local therapy; ECOG performance status 0-1; life expectancy > 12 weeks; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior radiation and recovered from prior surgery or treatment-related toxicity.

[00486] Exclusion Criteria: History of, or presence of brain metastases; concurrent investigational drug treatment; prior bone marrow or stem cell transplant; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; uncontrolled infection; active bleeding, or history of bleeding requiring transfusion; active cardiac disease; serious medical or psychiatric illness.

Example 48: Endometriosis Clinical Trial

[00487] Purpose: The purposes of this study are to assess the efficacy of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, as single agent or in combination in the treatment of patients with symptomatic/severe endometriosis, collect information on any side effects the compound may cause as single agent or in combination, and evaluate the pharmacokinetic properties of the compound as single agent or in combination.

[00488] Intervention: Patients are administered 1-50 mg/kg of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, per day or twice a day as single agent or in combination.

[00489] Outcome Measures: The outcome measures of this study are symptoms improvement and/or pain relief and shrinkage of endometrial tissue.

[00490] Detailed Description: Patients will be given a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, orally once or twice a day as single agent or in

combination. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed.

[00491] Eligibility: Female subjects that are 18 years and older.

[00492] Inclusion Criteria: Diagnosis of symptomatic endometriosis; pre- or peri-menopausal status; ECOG performance status 0-1; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior surgery or treatment-related toxicity.

[00493] Exclusion Criteria: Pregnancy or lactating; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; concurrent investigational drug treatment; uncontrolled infection; active cardiac disease; aerious medical or psychiatric illness.

Example 49: Uterine Leiomyoma Clinical Trial

[00494] Purpose: The purposes of this study are to assess the efficacy of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, as single agent or in combination in the treatment of patients with symptomatic uterine leiomyoma, collect information on any side effects the compound may cause as single agent or in combination, and evaluate the pharmacokinetic properties of the compound as single agent or in combination.

[00495] Intervention: Patients are administered 1-50 mg/kg of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, per day or twice a day as single agent or in combination.

[00496] Outcome Measures: The outcome measures of this study are symptoms improvement and/or pain relief and shrinkage of leiomyomas.

[00497] Detailed Description: Patients will be given a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, orally once or twice a day as single agent or in combination. Prior to each dosing cycle, a physical exam, blood work and assessment of any side effects will be performed.

[00498] Eligibility: Female subjects that are 18 years and older.

[00499] Inclusion Criteria: Diagnosis of symptomatic uterine leiomyoma; pre- or peri-menopausal status; ECOG performance status 0-1; adequate liver and bone marrow function: AST < 2.5 x ULN; Bilirubin < 1.5 x ULN; ANC > 1,500/ul; platelet count > 100,000/ul; normal PT and PTT; at least 2 weeks since prior surgery or treatment-related toxicity.

[00500] Exclusion Criteria: Pregnancy or lactating; history of other malignancy within the last 5 years, not including curatively-treated carcinoma in situ of the cervix or non-melanoma skin cancer; concurrent investigational drug treatment; uncontrolled infection; active cardiac disease; serious medical or psychiatric illness.

Example 50: Parenteral Pharmaceutical Composition

[00501] To prepare a parenteral pharmaceutical composition suitable for administration by injection (subcutaneous, intravenous), 100 mg of a water-soluble compound of Formula (I), (II), (III), (IV), (V), or (VI), or pharmaceutically acceptable salt thereof, is dissolved in sterile water and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection

[00502] In another embodiment, the following ingredients are mixed to form an injectable formulation: 1.2 g of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, 2.0 mL of sodium acetate buffer solution (0.4 M), HCl (1 N) or NaOH (1 M) (q.s. to suitable pH), water (distilled, sterile) (q.s.to 20 mL). All of the above ingredients, except water, are combined and stirred and if necessary, with slight heating if necessary. A sufficient quantity of water is then added.

Example 51: Oral Solution

[00503] To prepare a pharmaceutical composition for oral delivery, an aqueous 20% propylene glycol solution is prepared. To this is added a sufficient amount of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, to provide a 20 mg/mL solution.

Example 52: Oral Capsule

[00504] To prepare a pharmaceutical composition for oral delivery, 100-500 mg of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is mixed with starch. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

[00505] In another embodiment, 100-500 mg of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is placed into Size 4 capsule, or size 1 capsule (hypromellose or hard gelatin) and the capsule is closed.

Example 53: Oral Tablet

[00506] A tablet is prepared by mixing 48% by weigh of a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, 45% by weight of microcrystalline cellulose, 5% by weight of low-substituted hydroxypropyl cellulose, and 2% by weight of magnesium stearate. Tablets are prepared by direct compression. The total weight of the compressed tablets is maintained at 250 -500 mg.

Example 54: Topical Gel Composition

[00507] To prepare a pharmaceutical topical gel composition, a compound of Formula (I), (II), (III), (IV), (V), or (VI), or a pharmaceutically acceptable salt thereof, is mixed with hydroxypropyl celluose, propylene glycol, isopropyl myristate and purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

[00508] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

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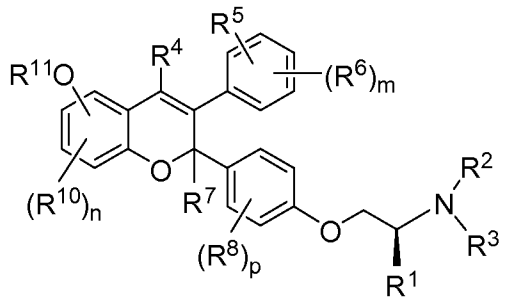
WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

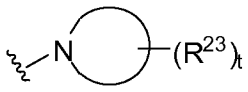
wherein,

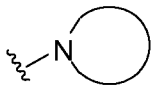
R^1 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form

 ;

 is a monocyclic C_2-C_{10} heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

t is 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl or C_3-C_6cycloalkyl;

R^5 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

R^7 is H or C_1-C_4alkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

each R^{10} is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{11} is independently selected from H, -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-

C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

m is 0, 1, 2, 3 or 4;

n is 0, 1, or 2;

p is 0, 1, or 2;

provided that the compound is not 2-(4-((S)-2-((R)-3-fluoropyrrolidin-1-yl)propoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol.

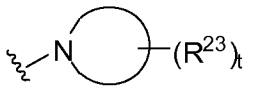
2. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is H or C_1-C_6alkyl;

R^2 is H, C_1-C_6alkyl, or C_1-C_6fluoroalkyl;

R^3 is C_1-C_6fluoroalkyl;

or R^2 and R^3 are taken together with the N atom to which they are attached to form



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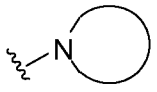


is a 4-, 5-, 6- or 7-membered monocyclic C_2-C_6heterocycloalkyl;

each R^{23} is independently F or C_1-C_6fluoroalkyl;

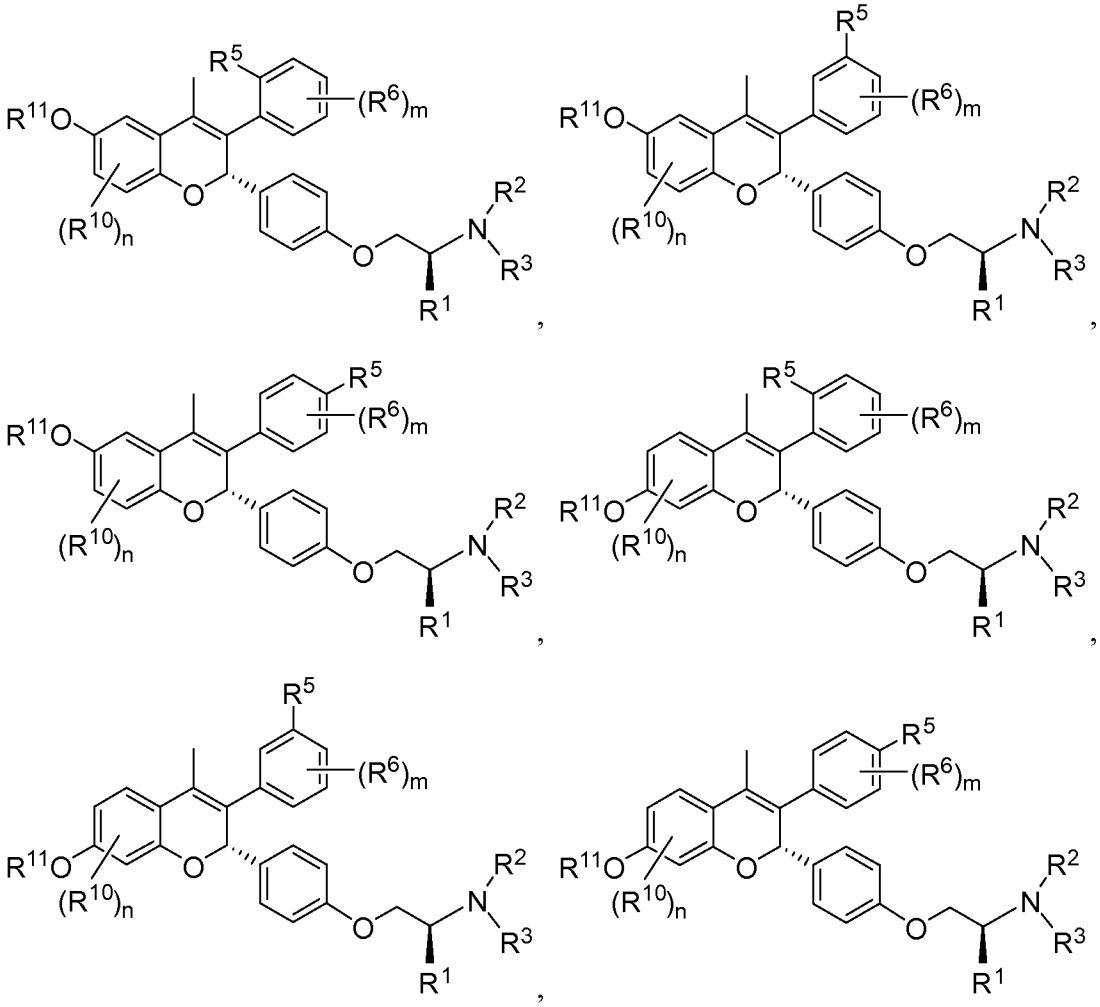
t is 1 or 2;

R^4 is -CH_3;

R^7 is H;

p is 0 or 1.

3. The compound of claim 1 or claim 2, wherein the compound has one of the following structures:



or is a pharmaceutically acceptable salt, or solvate thereof.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^5 is -OH;

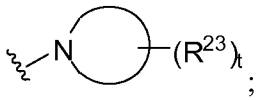
each R^{10} is independently selected from H, halogen, -CN, -OH, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

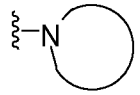
R^{11} is H.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is H, or $-CH_3$;

R^2 and R^3 are taken together with the N atom to form

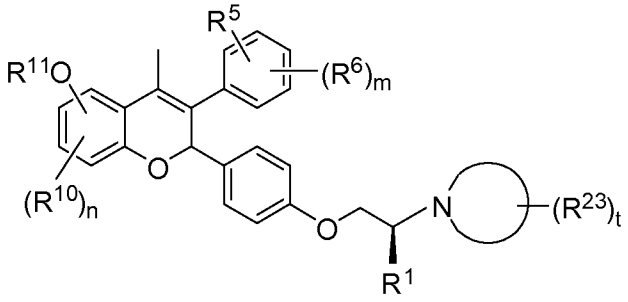
 ;



is azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, morpholinyl, or piperazinyl;

each R^{23} is independently F, -CH_2F, -CHF_2, -CF_3, -$CHFCH_3$, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -$CH_2CH_2CF_3$, -$CH_2CH_2CH_2CF_3$, -$CHCH_3CF_3$, -$CH(CF_3)_2$, or –$CF(CH_3)_2$.

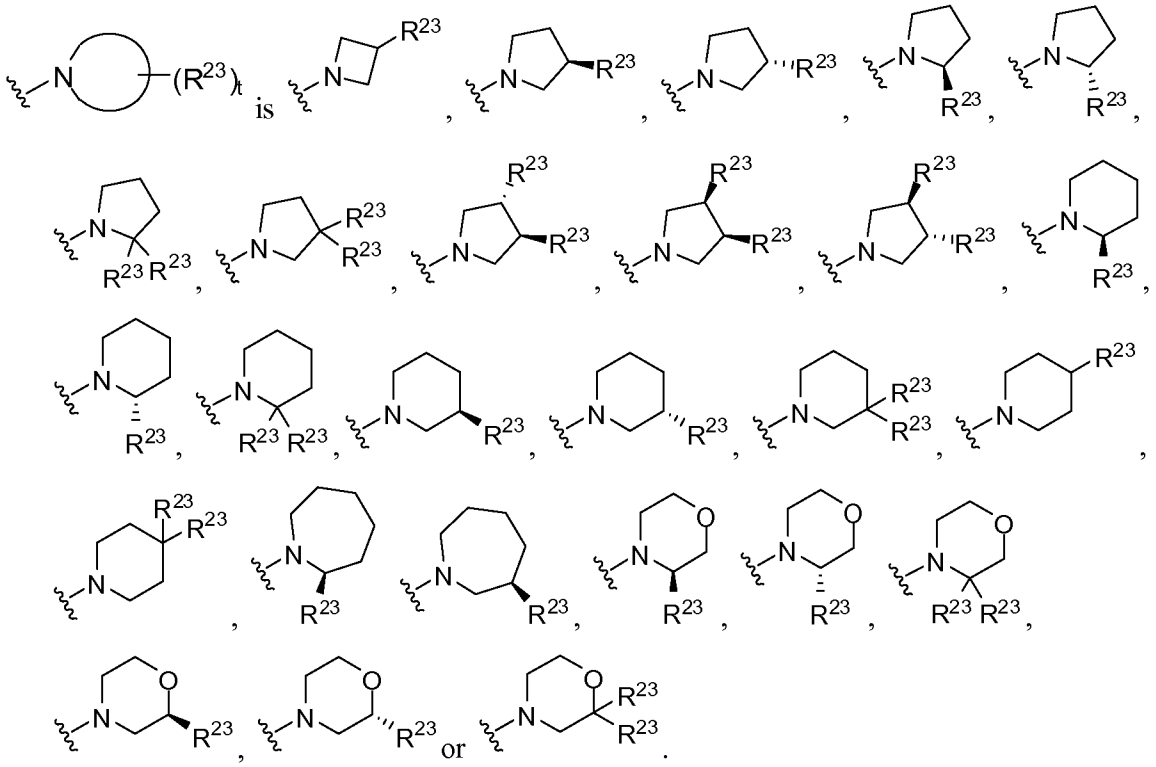
6. The compound of claim 1 or claim 2, wherein the compound of Formula (I) has the structure of Formula (II):



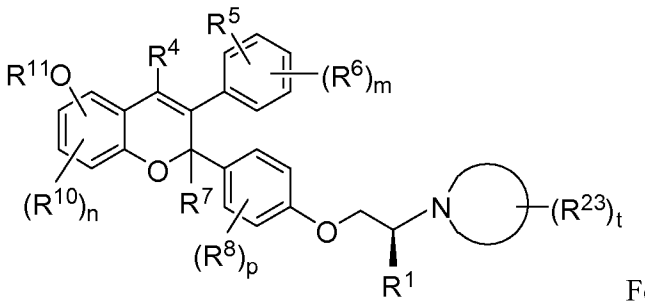
Formula (II)

or is a pharmaceutically acceptable salt, or solvate thereof.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



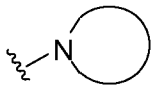
8. A compound of Formula (III), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (III)

wherein,

R^1 is C_1-C_6fluoroalkyl;

 is a monocyclic C_2-C_{10}heterocycloalkyl;

each R^{23} is independently F, C_1-C_6alkyl or C_1-C_6fluoroalkyl;

t is 0, 1, 2, 3, or 4;

R^4 is H, halogen, -CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl or C_3-C_6cycloalkyl;

R^5 is H, halogen, -CN, -OH, -OR^{11}, -NHR^{11}, -$NR^{11}R^{12}$, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, or C_1-C_6heteroalkyl;

each R^6 is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^8 is independently selected from H, halogen, -CN, -OH, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, and C_1-C_6alkoxy;

each R^{10} is independently selected from H, halogen, -CN, -OH, -OR^{11}, -SR^{11}, -S(=O)R^{12}, -$S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

each R^{11} is independently selected from H, -C(=O)R^{12}, -C(=O)OR^{12}, -C(=O)NHR^{12}, C_1-C_6alkyl, C_1-C_6heteroalkyl, C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

each R^{12} is independently selected from substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_2alkylene-(substituted or unsubstituted C_3-C_{10}cycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted C_2-C_{10}heterocycloalkyl), -C_1-C_2alkylene-(substituted or unsubstituted aryl), and -C_1-C_2alkylene-(substituted or unsubstituted heteroaryl);

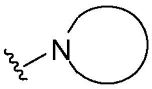
m is 0, 1, 2, 3 or 4;

n is 0, 1, or 2;

p is 0, 1, or 2.

9. The compound of claim 8, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

R^1 is -CH_2F, -CHF_2, or -CF_3;

 is an azetidinyl, pyrrolidinyl, piperidinyl, or azepanyl;

each R^{23} is independently F, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CHFCH_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CHCH_3CF_3$, $-CH(CF_3)_2$, or $-CF(CH_3)_2$;

t is 0, 1 or 2;

R^4 is $-CH_3$;

R^7 is H;

p is 0 or 1.

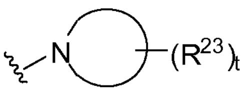
10. The compound of claim 8 or claim 9, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

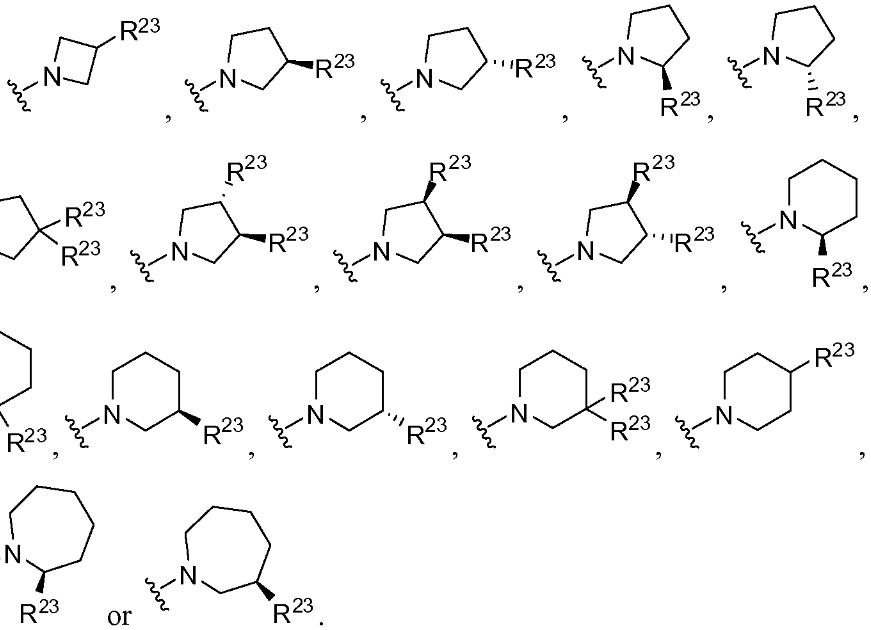
R^5 is -OH;

each R^{10} is independently selected from H, halogen, -CN, -OH, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6fluoroalkoxy, C_1-C_6alkoxy, and C_1-C_6heteroalkyl;

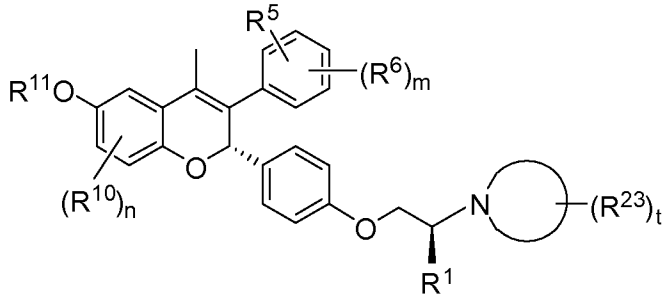
R^{11} is H.

11. The compound of any one of claims 8-10, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

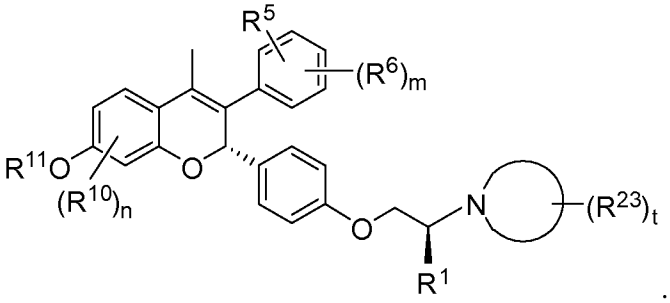
 is



12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has one of the following structures:



or



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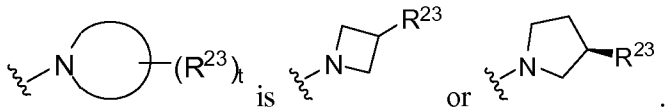
13. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



.

14. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof.

15. The pharmaceutical composition of claim 14, wherein the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, or topical administration.

16. The pharmaceutical composition of claim 14, wherein the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, a suspension, a gel, a dispersion, a solution, an emulsion, an ointment, or a lotion.

17. A compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof, for use in the treatment of an estrogen receptor dependent or estrogen receptor mediated disease or condition in mammal, wherein the estrogen receptor dependent or estrogen receptor mediated disease or condition is selected from cancer, uterine disease, central nervous system (CNS) defects, cardiovascular system defects, hematological system defects, immune and inflammation diseases, susceptibility to infection, metabolic defects, neurological defects, psychiatric defects and reproductive defects

18. A compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof, for use in the treatment of bone cancer, breast cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian cancer, uterine cancer, cervical cancer, lung cancer, leiomyoma,

uterine leiomyoma, migraine, cardiovascular disease, hypertension, Graves' Disease, arthritis, multiple sclerosis, cirrhosis, hepatitis B, chronic liver disease, bone density, cholestasis, hypospadias, obesity, osteoarthritis, osteopenia, osteoporosis, Alzheimer's disease, Parkinson's disease, dementia, major depressive disorder, psychosis, age of menarche, endometrial hyperplasia, or endometriosis in a mammal.

19. A compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt, or solvate thereof, for use in medicine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/069933

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 15, 16
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

claims 15, 16 are referring to the multiple dependent claims which do not comply with PCT rule 6.4(a). As a result, these claims are too unclear to make meaningful search possible.

3. ☒ Claims Nos.: 4, 5, 7, 11-14, 17-19
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/069933

A. CLASSIFICATION OF SUBJECT MATTER

C07D 405/12(2006.01)i, C07D 405/14(2006.01)i, A61K 31/397(2006.01)i, A61K 31/4025(2006.01)i, A61P 35/00(2006.01)i, A61P 25/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 405/12; A61K 31/445; C07D 405/10; A61K 31/452; A61K 31/40; C07D 493/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords : "estrogen modulator"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 05407947A A (BRYANT, H. U. et al.) 18 April 1995 See abstract and claim 1.	1-3,6,8-10
A	US 6262270 B1 (DRAPER, R. W. et al.) 17 July 2001 See abstract and claims 7-10.	1-3,6,8-10
A	US 2004-0259915 A1 (KANOJIA, R. M. et al.) 23 December 2004 See abstract and claims 1-2.	1-3,6,8-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 2013 (15.04.2013)	**16 April 2013 (16.04.2013)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

NA, Young Min

Telephone No. 82-42-481-8466

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/069933

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 05407947A A	18.04.1995	EP 0652007 A1	10.05.1995
		JP 07-188008 A	25.07.1995
US 6262270 B1	17.07.2001	None	
US 2004-0259915 A1	23.12.2004	AU 2003-295822 A1	23.06.2004
		CA 2505857 A1	17.06.2004
		CN 101450950 A	10.06.2009
		CN 1745085 A	08.03.2006
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		EP 1569939 A1	07.09.2005
		JP 2006-514941 A	18.05.2006
		US 2003-0216463 A1	20.11.2003
		US 7105679 B2	12.09.2006
		US 7329654 B2	12.02.2008
		WO 2004-050660 A1	17.06.2004

(19)中华人民共和国国家知识产权局

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(87)PCT国际申请的公布数据
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(74)专利代理机构 北京安信方达知识产权代理有限公司 11262
代理人 王思琪 郑霞
(51)Int.Cl.
C07D 405/12(2006.01)
C07D 405/14(2006.01)
A61K 31/397(2006.01)
A61K 31/4025(2006.01)
A61P 35/00(2006.01)
A61P 25/00(2006.01)

权利要求书7页 说明书147页

(54)发明名称

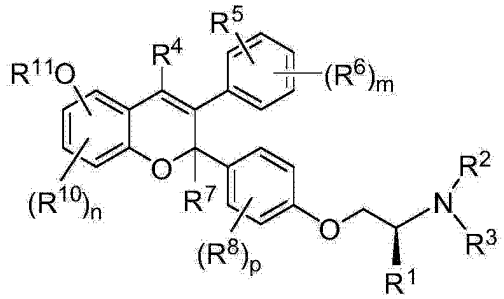
氟化雌激素受体调节剂及其用途

(57)摘要

本文描述了作为雌激素受体调节剂的化合物。还描述了包含本文所述的化合物的药物组合物和药物，以及单独地和与其它化合物联合地使用此类雌激素受体调节剂来治疗雌激素受体介导或依赖的疾病或状况的方法。

CN 104114551 A

1. 式 (I) 的化合物或其药学上可接受的盐或溶剂化物：



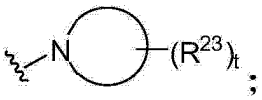
式(I)

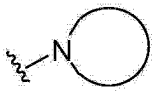
其中：

R^1 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^3 是 C_1-C_6 氟烷基；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是单环 C_2-C_{10} 杂环烷基；

各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；

t 是 1、2、3 或 4；

R^4 是 H、卤素、-CN、C_1-C_4 烷基、C_1-C_4 氟烷基或 C_3-C_6 环烷基；

R^5 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基或 C_1-C_6 杂烷基；

各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

R^7 是 H 或 C_1-C_4 烷基；

各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；

各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、C_1-C_6 烷基、C_1-C_6 杂烷基、C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、-C_1-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的芳基）和 -C_1-C_2 亚烷基 -（取代或未取代的杂芳基）；

各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、-C_1-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、-C_1-C_2 亚烷基 -（取代或未取代

的芳基）和 -C_1-C_2 亚烷基 -（取代或未取代的杂芳基）；

m 是 0、1、2、3 或 4；

n 是 0、1 或 2；

p 是 0、1 或 2；

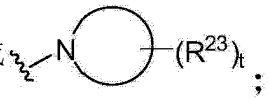
条件是所述化合物不是 2-(4-((S)-2-((R)-3- 氟吡咯烷 -1- 基）丙氧基）苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇。

2. 根据权利要求 1 所述的化合物，或其药学上可接受的盐或溶剂化物，其中：

R^1 是 H 或 C_1-C_6 烷基；

R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^3 是 C_1-C_6 氟烷基；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是 4 元、5 元、6 元或 7 元单环 C_2-C_6 杂环烷基；

各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；

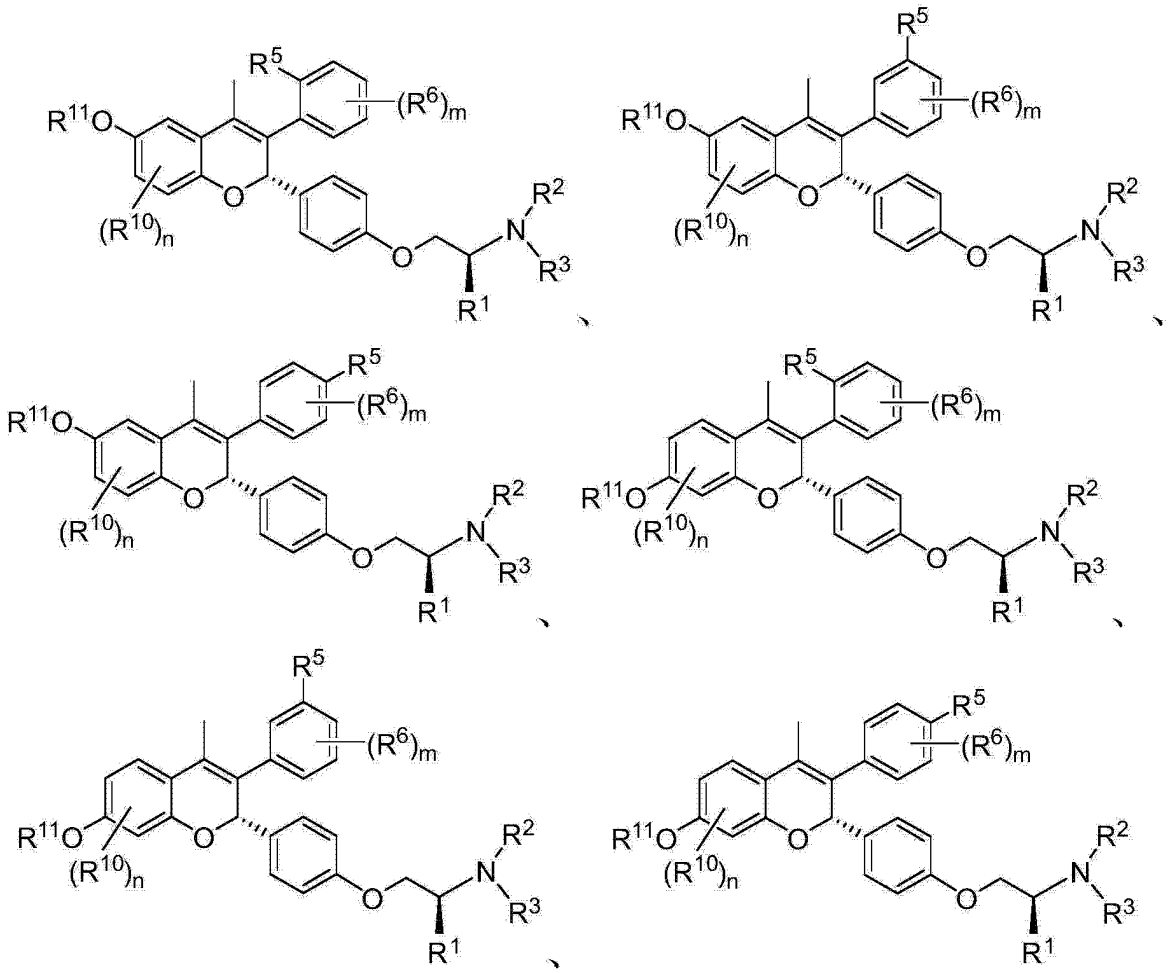
t 是 1 或 2；

R^4 是 -CH_3；

R^7 是 H；

p 是 0 或 1。

3. 根据权利要求 1 或 2 所述的化合物，其中所述化合物具有下列结构之一：



或是其药学上可接受的盐或溶剂化物。

4. 根据权利要求 1-3 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其中：

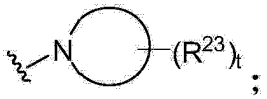
R^5 是 -OH；

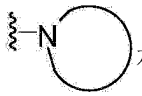
各个 R^{10} 独立地选自 H、卤素、-CN、-OH、-S(=O)R^{12}、-S(=O)$_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

R^{11} 是 H。

5. 根据权利要求 1-4 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其中：

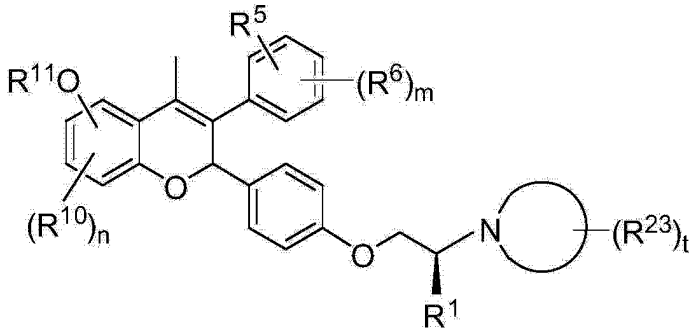
R^1 是 H 或 $-CH_3$；

R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是氮杂环丁基、吡咯烷基、哌啶基、氮杂环庚基、吗啉基或哌嗪基；

各个 R^{23} 独立地是 F、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。

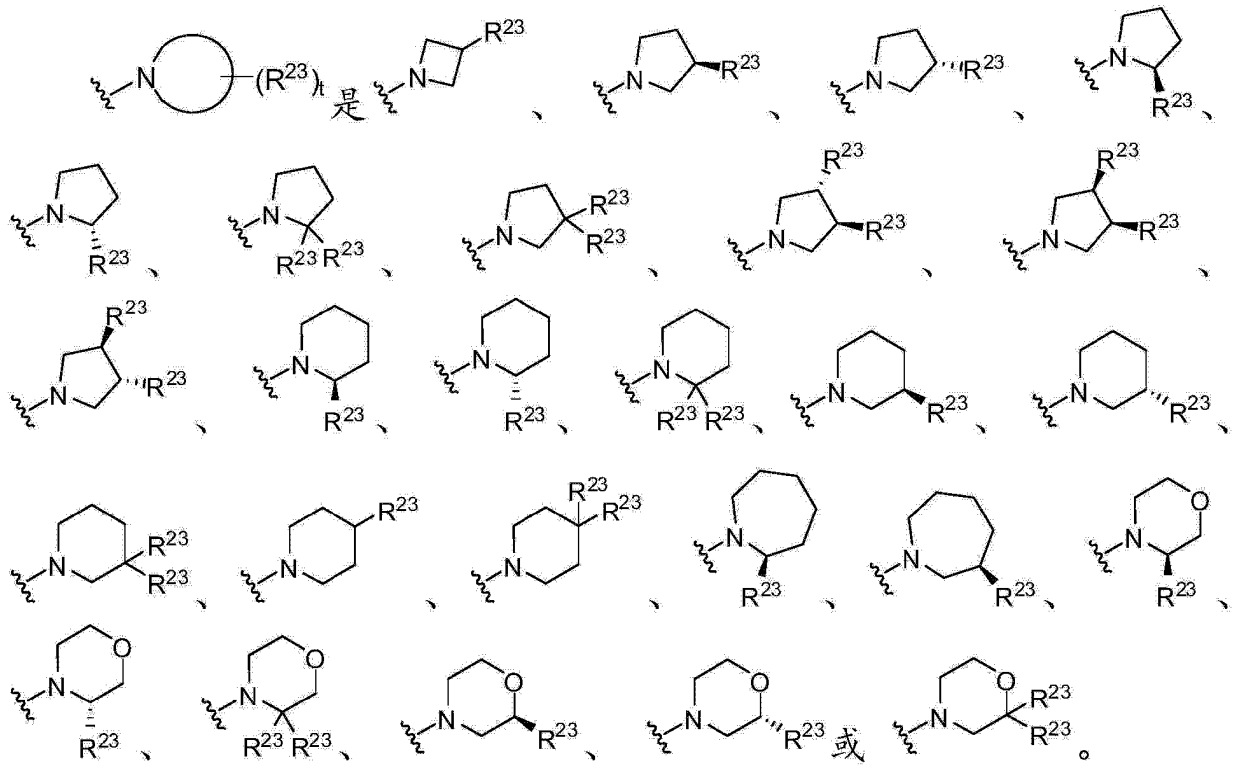
6. 根据权利要求 1 或 2 所述的化合物，其中式 (I) 的化合物具有式 (II) 的结构：



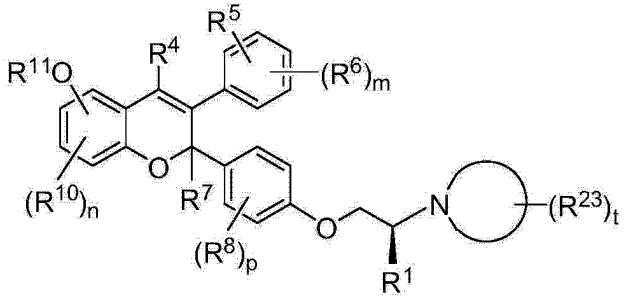
式(II)

或是其药学上可接受的盐或溶剂化物。

7. 根据权利要求 1-6 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其中：



8. 式 (III) 的化合物或其药学上可接受的盐或溶剂化物：



式(III)

其中，

R^1 是 C_1-C_6 氟烷基；

 是单环 C_2-C_{10} 杂环烷基；

各个 R^{23} 独立地是 F、C_1-C_6 烷基或 C_1-C_6 氟烷基；

t 是 0、1、2、3 或 4；

R^4 是 H、卤素、-CN、C_1-C_4 烷基、C_1-C_4 氟烷基或 C_3-C_6 环烷基；

R^5 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基或 C_1-C_6 杂烷基；

各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；

各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、C_1-C_6 烷基、C_1-C_6 杂烷基、C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基 -（取代或未取代的杂芳基）；

各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基 -（取代或未取代的杂芳基）；

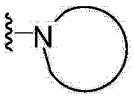
m 是 0、1、2、3 或 4；

n 是 0、1 或 2；

p 是 0、1 或 2。

9. 根据权利要求 8 所述的化合物，或其药学上可接受的盐或溶剂化物，其中：

R^1 是 $-CH_2F$、$-CHF_2$ 或 $-CF_3$；

 是氮杂环丁基、吡咯烷基、哌啶基或氮杂环庚基；

各个 R^{23} 独立地是 F、$-CH_3$、$-CH_2CH_3$、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$；

t 是 0、1 或 2；

R^4 是 $-CH_3$；

R^7 是 H；

p 是 0 或 1。

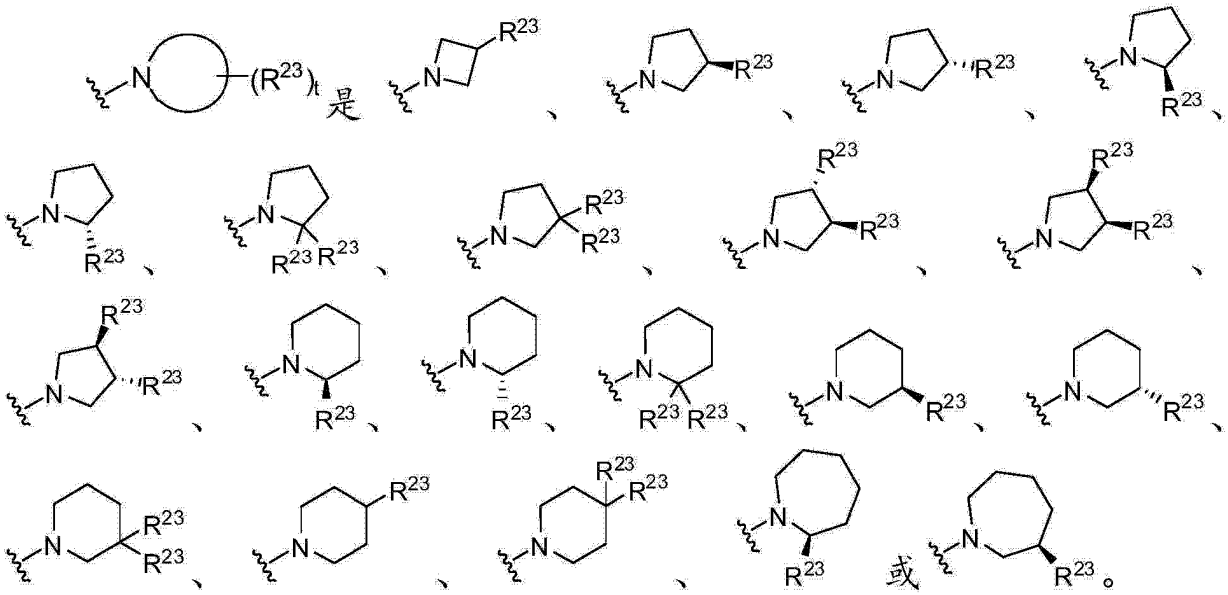
10. 根据权利要求 8 或 9 所述的化合物，或其药学上可接受的盐或溶剂化物，其中：

R^5 是 -OH；

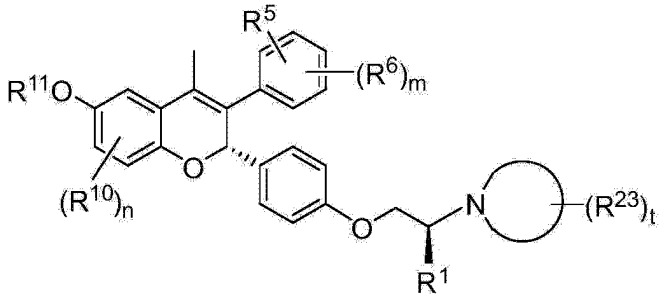
各个 R^{10} 独立地选自 H、卤素、-CN、-OH、-S(= O)R^{12}、-S(= O)$_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

R^{11} 是 H。

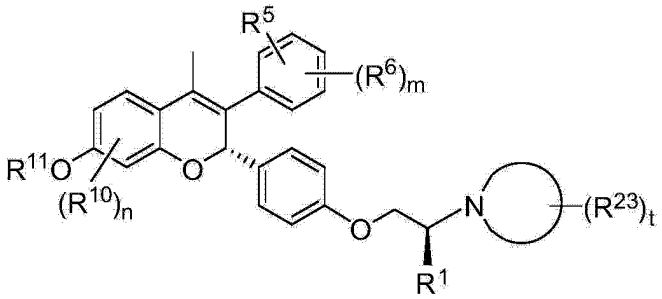
11. 根据权利要求 8-10 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其中：



12. 根据权利要求 1-11 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其中所述化合物具有下列结构之一：

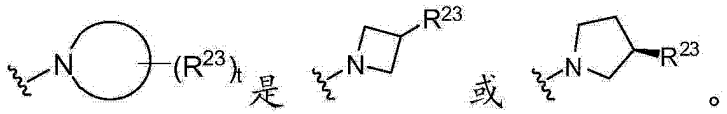


或



。

13. 根据权利要求 1-13 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其中：



。

14. 一种药物组合物，其包含权利要求 1-13 中任一项所述的化合物或其药学上可接受的盐或溶剂化物。

15. 根据权利要求 14 所述的药物组合物，其中所述药物组合物配制为用于静脉内注射、皮下注射、口服给药或局部给药。

16. 根据权利要求 14 所述的药物组合物，其中所述药物组合物是片剂、丸剂、胶囊、液体、悬浮液、凝胶、分散体、溶液、乳剂、软膏或洗剂。

17. 根据权利要求 1-13 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其用于治疗哺乳动物的雌激素受体依赖的或雌激素受体介导的疾病或状况，其中所述雌激素受体依赖的或雌激素受体介导的疾病或状况选自癌症、子宫疾病、中枢神经系统 (CNS) 缺陷、心血管系统缺陷、血液系统缺陷、免疫及炎症疾病、感染易感性、代谢缺陷、神经缺陷、精神缺陷和生殖缺陷。

18. 根据权利要求 1-13 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其用于治疗哺乳动物的骨癌、乳腺癌、结直肠癌、子宫内膜癌、前列腺癌、卵巢癌、子宫癌、宫颈癌、肺癌、平滑肌瘤、子宫平滑肌瘤、偏头痛、心血管疾病、高血压、格雷夫斯病、关节炎、多发性硬化、硬化、乙型肝炎、慢性肝病、骨密度、胆汁淤积、尿道下裂、肥胖症、骨关节炎、骨质减少、骨质疏松症、阿尔茨海默病、帕金森病、痴呆、严重抑郁障碍、精神病、月经初潮年龄、子宫内膜增生或子宫内膜异位症。

19. 根据权利要求 1-13 中任一项所述的化合物，或其药学上可接受的盐或溶剂化物，其用于医学。

氟化雌激素受体调节剂及其用途

相关申请

[0001] 本申请要求 2011 年 12 月 14 日提交的、名称为“雌激素受体调节剂及其用途 (ESTROGEN RECEPTOR MODULATORS AND USES THEREOF)”的美国临时专利申请号 61/570,756 的权益，该临时专利申请通过引用全文并入本文。

技术领域

[0002] 本文描述了化合物，包括其药学上可接受的盐、溶剂化物、代谢物、前药，制备此类化合物的方法，包含此类化合物的药物组合物，以及使用此类化合物治疗、预防或诊断雌激素敏感的、雌激素受体依赖的或雌激素受体介导的疾病或状况的方法。

背景技术

[0003] 雌激素受体（“ER”）是配体激活的转录调节蛋白，它通过与内源性雌激素的相互作用介导多种生物效应的诱导。内源性雌激素包括 17β- 雌二醇和雌酮。已发现 ER 具有两种同种型 :ER-α 和 ER-β 。

[0004] 雌激素和雌激素受体与众多的疾病或状况有关，例如乳腺癌、肺癌、卵巢癌、结肠癌、前列腺癌、子宫内膜癌、子宫癌以及其它疾病或状况。

发明内容

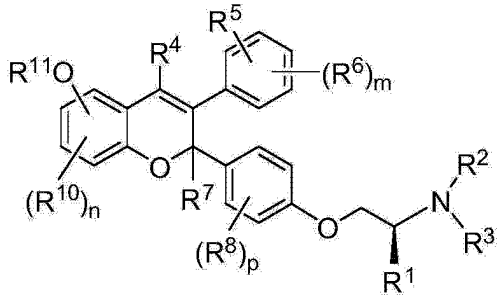
[0005] 在一个方面，本文提出了式 (I)、(II)、(III)、(IV)、(V) 和 (VI) 的化合物，该化合物削弱雌激素与雌激素受体的效应和 / 或降低雌激素受体的浓度，因此可作为药剂用于治疗或预防这样的疾病或状况 :其中雌激素和 / 或雌激素受体的作用与该疾病或状况的病因学或病理学有关，或者导致该疾病或状况的至少一种症状，并且其中雌激素和 / 或雌激素受体的这样的作用是不期望的。在一些实施方案中，本文公开的化合物是雌激素受体降解剂化合物。

[0006] 在一个方面，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物可用于治疗 ER- 相关的疾病或状况，包括但不限于 :与癌症（骨癌、乳腺癌、肺癌、结直肠癌、子宫内膜癌、前列腺癌、卵巢癌和子宫癌）相关的 ER-α 功能障碍、中枢神经系统 (CNS) 缺陷（酒精中毒、偏头痛）、心血管系统缺陷（主动脉瘤、心肌梗死易感性、主动脉瓣硬化、心血管疾病、冠状动脉疾病、高血压）、血液系统缺陷（深静脉血栓形成）、免疫及炎症疾病（格雷夫斯病、关节炎、多发性硬化、硬化）、感染易感性（乙型肝炎、慢性肝病）、代谢缺陷（骨密度、胆汁淤积、尿道下裂、肥胖症、骨关节炎、骨质减少、骨质疏松症）、神经缺陷（阿尔茨海默病、帕金森病、偏头痛、眩晕）、精神缺陷（神经性厌食、注意力缺陷多动障碍 (ADHD)、痴呆、严重抑郁障碍、精神病）、子宫疾病（如平滑肌瘤、子宫平滑肌瘤、子宫内膜增生、子宫内膜异位症）和生殖缺陷（月经初潮年龄、子宫内膜异位症、不育症）。

[0007] 在一个方面，本文描述了式 (I)、(II)、(III)、(IV)、(V) 和 (VI) 的化合物，其药学上可接受的盐、溶剂化物、代谢物和前药。本文所述的化合物是雌激素受体调节剂。在一些

实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物是雌激素受体拮抗剂。在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物是雌激素受体降解剂。在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物是雌激素受体拮抗剂以及雌激素受体降解剂。在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物不表现或表现出最低的雌激素受体激动剂活性。在一些实施方案中，在癌症治疗方面，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物可以提供改善的治疗活性，其特征为完全的或较持久的肿瘤消退、较低的治疗抗性发生率或发展速度和 / 或肿瘤侵袭性的降低。

[0008] 在一个方面，本文描述了式 (I) 的化合物或其药学上可接受的盐或溶剂化物：



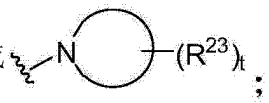
式(I)

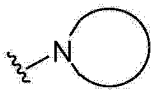
其中：

R^1 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^3 是 C_1-C_6 氟烷基；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是单环 C_2-C_{10} 杂环烷基；

各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；

t 是 1、2、3 或 4；

R^4 是 H、卤素、-CN、C_1-C_4 烷基、C_1-C_4 氟烷基或 C_3-C_6 环烷基；

R^5 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基或 C_1-C_6 杂烷基；

各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

R^7 是 H 或 C_1-C_4 烷基；

各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；

各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、C_1-C_6 烷基、C_1-C_6 杂烷基、C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取

代或未取代的芳基、取代或未取代的杂芳基、-C_1-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的芳基）和 -C_1-C_2 亚烷基 -（取代或未取代的杂芳基）；

各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、-C_1-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的芳基）和 -C_1-C_2 亚烷基 -（取代或未取代的杂芳基）；

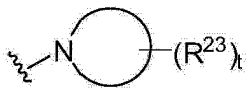
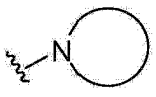
m 是 0、1、2、3 或 4；

n 是 0、1 或 2；

p 是 0、1 或 2；

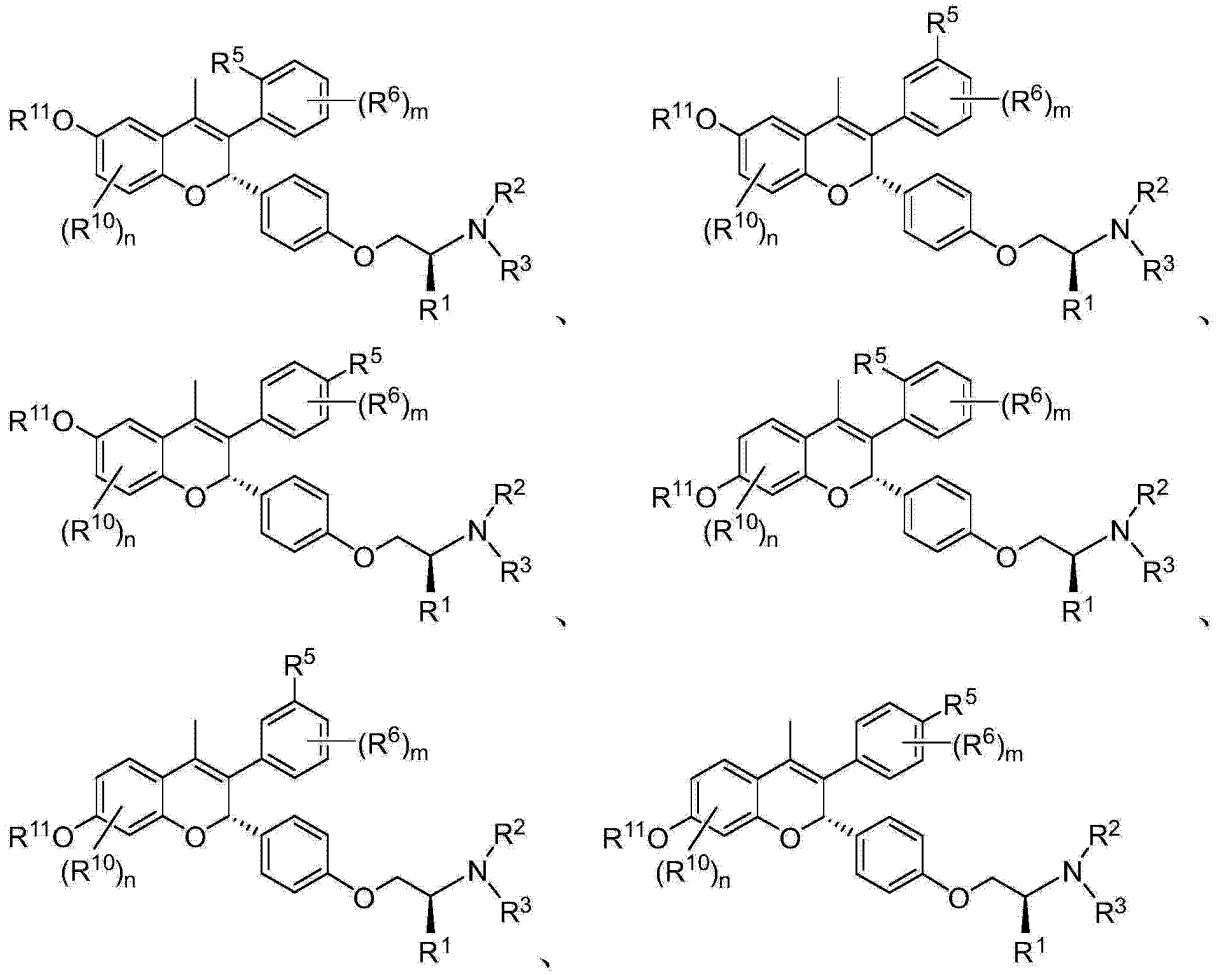
条件是所述化合物不是 2-(4-((S)-2-((R)-3- 氟吡咯烷 -1- 基）丙氧基）苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇。

[0009] 对于本文所述的任何及全部实施方案，取代基选自所列出的备选物的子集。例如，在一些实施方案中，R^7 是 H 或 -CH_3。在其它实施方案中，R^7 是 H。

[0010] 在一些实施方案中，R^1 是 H 或 C_1-C_6 烷基；R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；R^3 是 C_1-C_6 氟烷基；或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ； 

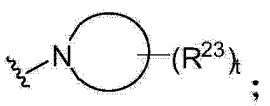
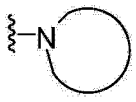
是 4 元、5 元、6 元或 7 元单环 C_2-C_6 杂环烷基；各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；t 是 1 或 2；R^4 是 -CH_3；R^7 是 H；p 是 0 或 1。

[0011] 在一些实施方案中，所述化合物具有下列结构之一：

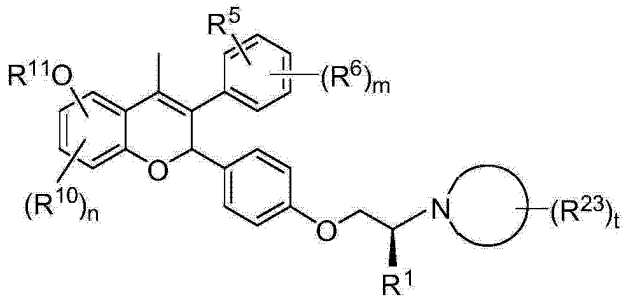


或是其药学上可接受的盐或溶剂化物。

[0012] 在一些实施方案中，R^5 是 -OH；各个 R^{10} 独立地选自 H、卤素、-CN、-OH、-S(=O)R^{12}、-S(=O)$_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；R^{11} 是 H。

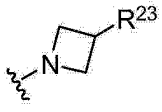
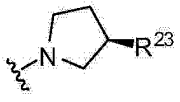
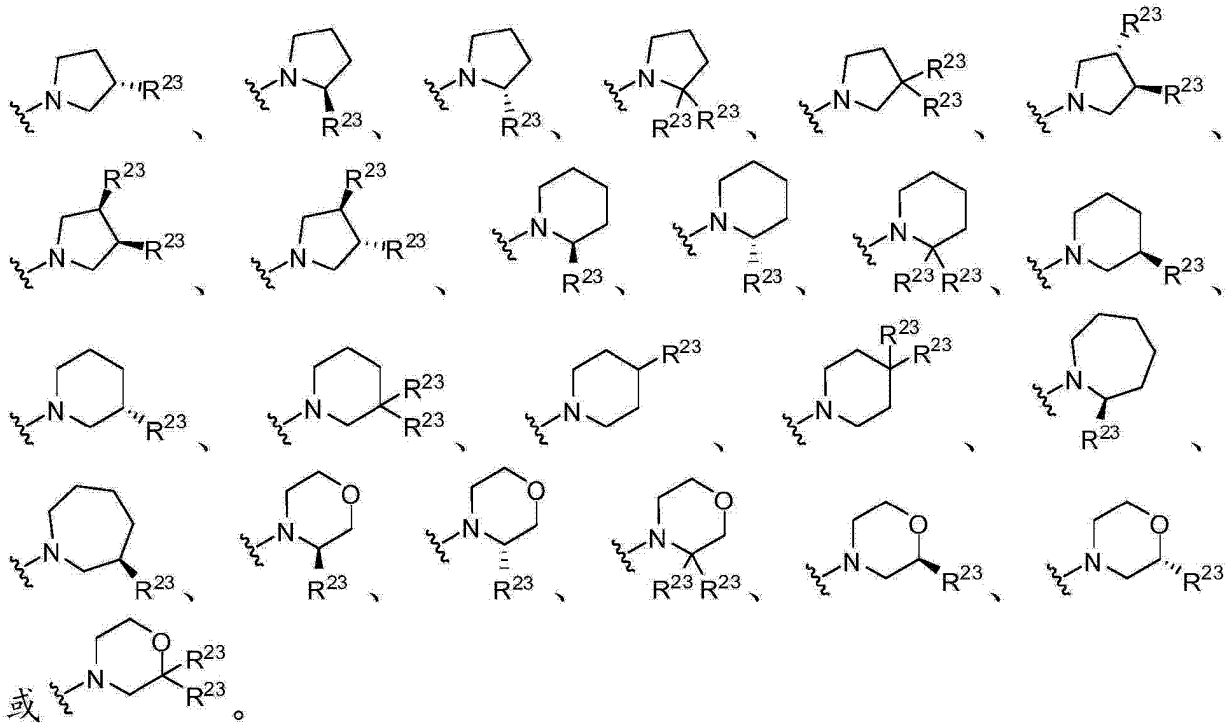
[0013] 在一些实施方案中，R^1 是 H 或 $-CH_3$；R^2 和 R^3 与它们所连接的 N 原子一起形成  ；  是氮杂环丁基、吡咯烷基、哌啶基、氮杂环庚基、吗啉基或哌嗪基；各个 R^{23} 独立地是 F、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。

[0014] 在一些实施方案中，式 (I) 的化合物具有式 (II) 的结构：

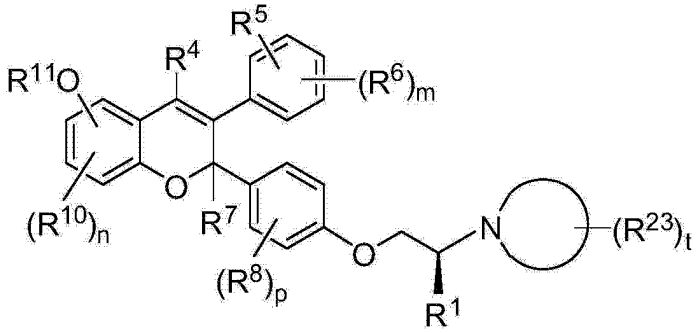


式(II)

或是其药学上可接受的盐或溶剂化物。

[0015] 在一些实施方案中，  是  、  、  或。

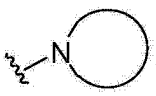
[0016] 在另一方面，本文所描述的是式（III）的化合物，或其药学上可接受的盐或溶剂化物：



式(III)

其中，

R^1 是 C_1-C_6 氟烷基；

 是单环 C_2-C_{10} 杂环烷基；

各个 R^{23} 独立地是 F、C_1-C_6 烷基或 C_1-C_6 氟烷基；

t 是 0、1、2、3 或 4；

R^4 是 H、卤素、-CN、C_1-C_4 烷基、C_1-C_4 氟烷基或 C_3-C_6 环烷基；

R^5 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6

烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基或 C_1-C_6 杂烷基；

各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；

各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

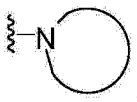
各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、C_1-C_6 烷基、C_1-C_6 杂烷基、C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基 -（取代或未取代的杂芳基）；

各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基 -（取代或未取代的杂芳基）；

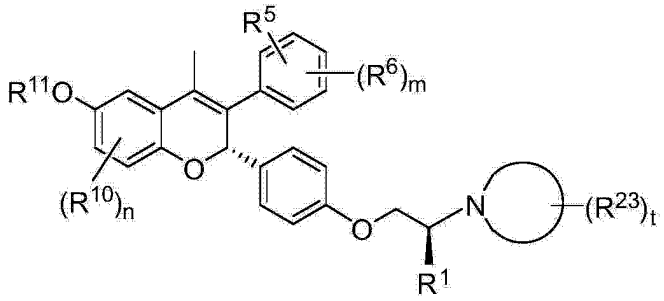
m 是 0、1、2、3 或 4；

n 是 0、1 或 2；

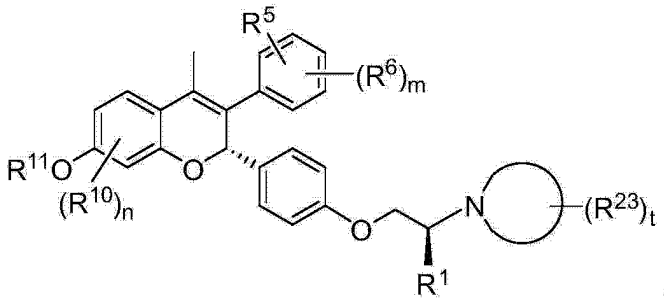
p 是 0、1 或 2。

[0017] 在一些实施方案中，R^1 是 $-CH_2F$、$-CHF_2$ 或 $-CF_3$；  是氮杂环丁基、吡咯烷基、哌啶基或氮杂环庚基；各个 R^{23} 独立地是 F、$-CH_3$、$-CH_2CH_3$、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$；t 是 0、1 或 2；R^4 是 $-CH_3$；R^7 是 H；P 是 0 或 1。

[0018] 在一些实施方案中，所述化合物具有下列结构之一：

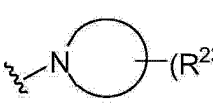
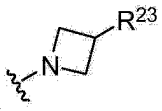
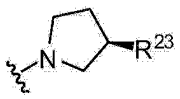
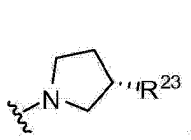
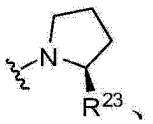
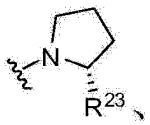
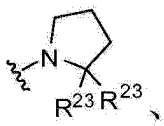
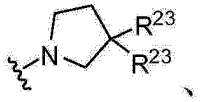
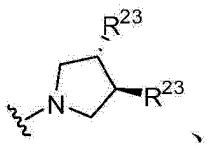
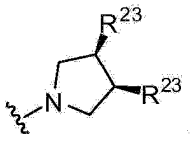
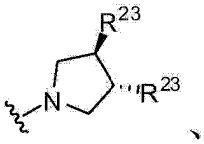
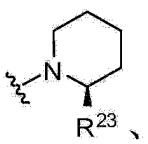
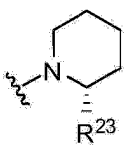
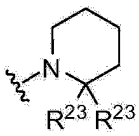
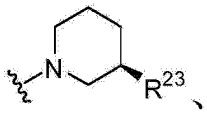
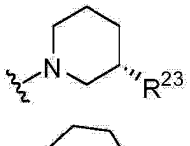
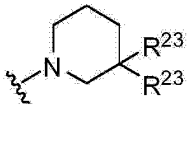
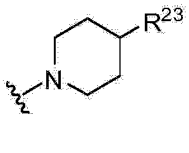
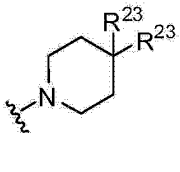
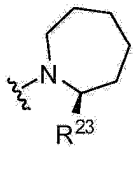
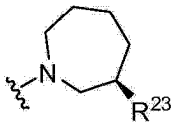


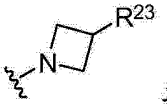
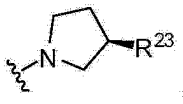
或

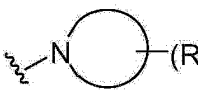
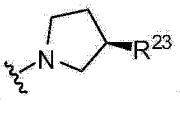


。

[0019] 在一些实施方案中，R^5 是 -OH；各个 R^{10} 独立地选自 H、卤素、-CN、-OH、-S(=O)R^{12}、-S(=O)$_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；R^{11} 是 H。

[0020] 在一些实施方案中，  是  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  、  或  。

[0021] 在一些实施方案中，  是  或  。

[0022] 在一些实施方案中，  是  。

[0023] 在一些实施方案中，各个 R^{23} 独立地是 F、$-CH_3$、$-CH_2CH_3$、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。在一些实施方案中，各个 R^{23} 独立地是 F、$-CH_3$、$-CH_2F$、$-CHF_2$ 或 $-CF_3$。在一些实施方案中，各个 R^{23} 独立地是 F、$-CH_2F$、$-CHF_2$ 或 $-CF_3$。在一些实施方案中，各个 R^{23} 独立地是 $-CH_2F$、$-CHF_2$ 或 $-CF_3$。在一些实施方案中，各个 R^{23} 独立地是 $-CH_3$、$-CH_2F$、$-CHF_2$ 或 $-CF_3$。在一些实施方案中，各个 R^{23} 独立地是 $-CH_3$。

[0024] 在一些实施方案中，R^2 和 R^3 与它们所连接的 N 原子一起形成取代或未取代的吡咯烷基。

[0025] 在一些实施方案中，R^1 是 $-CH_3$。在一些实施方案中，R^1 是 $-CH_3$；R^4 是 $-CH_3$。

[0026] 本文公开的化合物是雌激素受体调节剂。在一些实施方案中，本文公开的化合物对雌激素受体具有高度特异性，并且具有期望的、组织选择性的药理学活性。期望的、组织选择性的药理学活性包括但不限于在乳腺细胞中具有 ER 拮抗剂活性而在子宫细胞中无 ER 激动剂活性。在一些实施方案中，本文公开的化合物是雌激素受体降解剂，其表现出完全的雌激素受体拮抗剂活性，而具有可忽略的或最低的雌激素受体激动剂活性。

[0027] 在一些实施方案中，本文公开的化合物是雌激素受体降解剂。在一些实施方案中，本文公开的化合物是雌激素受体拮抗剂。在一些实施方案中，本文公开的化合物具有最低的或可忽略的雌激素受体激动剂活性。

[0028] 在一些实施方案中，本文提出了选自式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物的活性代谢物、互变异构体、药学上可接受的溶剂化物、药学上可接受的盐或前药的化合物。

[0029] 还描述了包含治疗有效量的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的药物组合物。在一些实施方案中，该药物组合物还包含至少一种药学上可接受的非活性成分。在一些实施方案中，该药物组合物被配制为用于静脉内注射、皮下注射、口服给药或局部给药。在一些实施方案中，该药物组合物是片剂、丸剂、胶囊、液体、悬浮液、凝胶、分散体、悬浮液、溶液、乳剂、软膏或洗剂。

[0030] 在一些实施方案中，该药物组合物进一步包含一种或多种另外的治疗活性剂，该治疗活性剂选自：皮质类固醇、止吐剂、止痛剂、抗癌剂、抗炎剂、激酶抑制剂、抗体、HSP90 抑制剂、组蛋白脱乙酰酶 (HDAC) 抑制剂、聚 ADP- 核糖聚合酶 (PARP) 抑制剂和芳香酶抑制剂。

[0031] 在一些实施方案中，本文提供了一种方法，其包括向患有雌激素敏感的、雌激素受体介导的或雌激素受体依赖的疾病或状况的人施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐。在一些实施方案中，该人已施用了除式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐以外的一种或多种另外的治疗活性剂。在一些实施方案中，该方法进一步包括施用除式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐以外的一种或多种另外的治疗活性剂。

[0032] 在一些实施方案中，除式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐以外的一种或多种另外的治疗活性剂选自：皮质类固醇、止吐剂、止痛剂、抗癌剂、抗炎剂、激酶抑制剂、抗体、HSP90 抑制剂、组蛋白脱乙酰酶 (HDAC) 抑制剂和芳香酶抑制剂。

[0033] 本文所述的药物制剂以多种方式向哺乳动物施用，包括但不限于口服、肠胃外（例如静脉内、皮下、肌肉内）、口腔、局部或透皮给药途径。本文描述的药物制剂包括但不限于水性液体分散体、自乳化分散体、固溶体、脂质体分散体、固体剂型、粉末、立即释放制剂、控制释放制剂、速溶制剂、片剂、胶囊、丸剂、延迟释放制剂、延长释放制剂、脉冲释放制剂、多颗粒制剂，和混合的立即释放和控制释放制剂。

[0034] 在一些实施方案中，口服施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐。

[0035] 在一些实施方案中，全身施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐。

[0036] 在一些实施方案中，静脉内施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物。

[0037] 在一些实施方案中，皮下施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐。

[0038] 在一些实施方案中，局部施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐。在这样的实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐被配制为多种可局部施用的组合物，例如溶液、悬浮液、洗剂、凝胶、糊剂、香波、擦洗剂、揉搓剂、涂布剂、药棒、含药绷带、香膏、乳膏或软膏。在一些实施方案中，向哺乳动物的皮肤局部施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐。

[0039] 在另一方面，是式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐在制备药物中的应用，该药物用于治疗其中雌激素受体的活性造成疾病或状况的病理和 / 或症状的疾病、病症或状况。在一个方面，该疾病或状况是任意本文列举的疾病或状况。

[0040] 在任一上述方面，是进一步的实施方案，其中，将有效量的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐 (a) 全身施用于哺乳动物；和 / 或 (b) 口服施用于哺乳动物；和 / 或 (c) 静脉内施用于哺乳动物；和 / 或 (d) 通过注射施用于哺乳动物；和 / 或 (e) 局部施用于哺乳动物；和 / 或 (f) 非全身地或局部地施用于哺乳动物。

[0041] 在任一上述方面，是包括单一施用有效量的化合物的进一步的实施方案，包括以下进一步的实施方案，其中 (i) 施用一次该化合物；(ii) 在一日内多次向哺乳动物施用该化合物；(iii) 频繁地施用；或 (iv) 连续地施用。

[0042] 在任一上述方面，是包括多次施用有效量的化合物的进一步的实施方案，包括以下进一步的实施方案，其中 (i) 连续或间歇地施用该化合物，如在单剂量中；(ii) 多次施用之间的时间是每隔 6 小时；(iii) 每隔 8 小时向哺乳动物施用该化合物；(iv) 每隔 12 小时向哺乳动物施用该化合物；(v) 每隔 24 小时向哺乳动物施用该化合物。在进一步的或可替代的实施方案中，该方法包括休药期，其中暂时中止化合物的施用或暂时减少施用的化合物的剂量；在休药期结束时，恢复化合物的施用。在一个实施方案中，休药期的长度从 2 天到 1 年不等。

[0043] 还提供了减少哺乳动物中的 ER 激活的方法，包括向哺乳动物施用至少一种具有式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的结构的化合物或其药学上可接受的盐。在一些实施方案中，该方法包括减少哺乳动物的乳腺细胞、肺细胞、卵巢细胞、结肠细胞、前列腺细

胞、子宫内膜细胞或子宫细胞中的 ER 激活。在一些实施方案中，该方法包括减少哺乳动物的乳腺细胞、卵巢细胞、结肠细胞、前列腺细胞、子宫内膜细胞或子宫细胞中的 ER 激活。在一些实施方案中，减少哺乳动物中的 ER 激活的方法包括降低哺乳动物中的雌激素与雌激素受体的结合。在一些实施方案中，减少哺乳动物中的 ER 激活的方法包括降低哺乳动物中的 ER 浓度。

[0044] 在一个方面，是式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐在治疗或预防哺乳动物的子宫的疾病或状况中的应用。在一些实施方案中，所述子宫的疾病或状况是平滑肌瘤、子宫平滑肌瘤、子宫内膜增生或子宫内膜异位症。在一些实施方案中，所述子宫的疾病或状况是子宫的癌性疾病或状况。在一些其它实施方案中，所述子宫的疾病或状况是子宫的非癌性疾病或状况。

[0045] 在一个方面，是式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐在制备用于治疗雌激素敏感的、雌激素受体依赖的或雌激素受体介导的疾病或状况的药物中的用途。在一些实施方案中，该疾病或状况是乳腺癌、肺癌、卵巢癌、结肠癌、前列腺癌、子宫内膜癌或子宫癌。在一些实施方案中，该疾病或状况在本文中描述。

[0046] 在一些情况下，本文公开了式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐在治疗或预防雌激素敏感的、雌激素受体依赖的或雌激素受体介导的疾病或状况中的用途。在一些实施方案中，该疾病或状况在本文中描述。

[0047] 在任何本文公开的实施方案中，所述哺乳动物是人。

[0048] 在一些实施方案中，本文提供的化合物用来削弱、降低或消除雌激素受体的活性。

[0049] 提供了制品，其包括 ：包装材料 ；包装材料内的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐、活性代谢物、前药或药学上可接受的溶剂化物或其组合物 ；和标签，该标签指示出所述化合物或其药学上可接受的盐、活性代谢物、前药或药学上可接受的溶剂化物或其组合物，或其组合物，用于降低、削弱或消除雌激素受体的效应，或者用于治疗、预防或改善将受益于雌激素受体活性降低或消除的疾病或状况的一种或多种症状。

[0050] 通过以下详细描述，本文所述的化合物、方法和组合物的其它目的、特征和优点将变得显而易见。但是，应当理解，尽管说明了具体实施方案，但详细描述和具体实施例仅作为说明给出，因为通过该详细描述，本公开内容的精神和范围内的各种变化和修改对本领域技术人员来说将变得显而易见。

发明详述

[0051] 雌激素受体 α (ER-α ；NR3A1) 和雌激素受体 β (ER-β ；NR3A2) 是类固醇激素受体，它们是大核受体超家族的成员。核受体具有相同的模块结构，该结构至少包括 DNA 结合域 (DBD) 和配体结合域 (LBD)。类固醇激素受体是可溶性的细胞内蛋白质，其作为配体调节的转录因子起作用。脊椎动物含有 5 种密切相关的类固醇激素受体 (雌激素受体、雄激素受体、孕酮受体、糖皮质激素受体、盐皮质激素受体)，它们调节大范围的生殖、代谢和发育活性。通过包括 17β - 雌二醇和雌酮在内的内源性雌激素的结合来控制 ER 的活性。

[0052] ER-α 基因位于 6q25.1 上并且编码 595 个氨基酸的蛋白质。ER-β 基因位于染色体 14q23.3 上并且产生 530 个氨基酸的蛋白质。然而，由于可变剪接和翻译起始位点，这些基因中的每一个可产生多个同种型。除了 DNA 结合域 (称为 C 域) 和配体结合域 (E 域)

以外，这些受体还含有 N- 末端 (A/B) 域、连接 C 域和 E 域的铰链 (D) 域以及 C- 末端延伸 (F 域)(Gronemeyer 和 Laudet ;Protein Profile 2:1173-1308, 1995)。ER-α 和 ER-β 的 C 域和 E 域非常保守 (分别具有 95％和 55％的氨基酸同一性)，而 A/B、D 域和 F 域的保守性较差 (低于 30％的氨基酸同一性)。两种受体都参与女性生殖道的调节和发育，但是也在中枢神经系统、心血管系统和骨代谢中发挥不同的作用。

[0053] 类固醇激素受体的配体结合袋深埋在配体结合域内。在结合后，配体变成该域的疏水核心的一部分。因此大部分类固醇激素受体在不存在激素的情况下不稳定，并且为了保持激素结合能力需要陪伴分子如 Hsp90 的帮助。与 Hsp90 的相互作用也控制这些受体的核转位。配体结合稳定了受体，并且启动连续的构象变化，该构象变化释放陪伴分子，改变各个受体结构域之间的相互作用并重建允许这些受体转位到核内的蛋白质相互作用表面，结合 DNA 并参与同染色质重建复合物的相互作用和转录机制。尽管 ER 能够与 Hsp90 相互作用，但是激素结合不需要这种相互作用，并且取决于细胞环境，apo-ER 既可以是细胞质的，也可以是细胞核的。生物物理学研究表明，是 DNA 结合而不是配体结合对受体的稳定性作出贡献 (Greenfield 等人 , Biochemistry 40:6646-6652, 2001)。

[0054] ER 能够通过结合到被称为雌激素应答元件 (ERE) 的特定 DNA 基序而直接地与 DNA 相互作用 (经典途径)，也可以通过蛋白质 - 蛋白质相互作用而间接地与 DNA 相互作用 (非经典途径)(Welboren 等人 , Endocrine-Related Cancer 16:1073-1089, 2009)。在非经典途径中，已证明 ER 栓系到包括 SP-1、AP-1 和 NF-κB 在内的其它转录因子上。这些相互作用似乎在 ER 调节细胞增殖和分化的能力中起关键作用。

[0055] 两种类型的 ER DNA 相互作用都可以导致基因激活或抑制，这取决于由各自的 ER-ERE 复合物募集的转录共调节剂 (Klinge, Steroid 65:227-251, 2000)。共调节剂的募集主要由两种蛋白质相互作用表面即 AF2 和 AF1 来介导。AF2 位于 ER E- 域中，其构象由配体直接调节 (Brzozowski 等人 , Nature 389:753-758, 1997)。完全激动剂似乎促进共激活剂的募集，而弱激动剂和拮抗剂则促进协阻遏物的结合。关于 AF1 对蛋白质的调节知之甚少，但是它可以通过丝氨酸磷酸化来控制 (Ward 和 Weigel, Biofactors 35:528-536, 2009)。一个有关的磷酸化位点 (S118) 似乎在拮抗剂如他莫昔芬的存在下控制 ER 的转录活性，它在乳腺癌的治疗中起重要作用。完全激动剂似乎将 ER 阻滞于某些构象，而弱激动剂倾向于使 ER 在不同构象之间保持平衡，从而允许共调节剂所有组成成分中依赖于细胞的差别以依赖于细胞的方式调节 ER 的活性 (Tamrazi 等人 , Mol. Endocrinol. 17:2593-2602, 2003)。ER 与 DNA 的相互作用是动态的，包括但不限于蛋白酶体对 ER 的降解 (Reid 等人 , Mol Cell 11:695-707, 2003)。配体对 ER 的降解提供了一种具有吸引力的、针对雌激素敏感的和 / 或对可用的抗激素治疗具有抗性的疾病或状况的治疗策略。

[0056] ER 信号传导对于包括乳房、排卵和子宫内膜增厚在内的女性生殖器官的发育和保持至关重要。ER 信号传导还在骨量、脂类代谢、癌症等中具有作用。大约 70％的乳腺癌表达 ER-α (ER-α 阳性)，并且其生长和存活依赖于雌激素。其它癌症的生长和存活也被认为依赖于 ER-α 信号传导，例如卵巢癌和子宫内膜癌。ER-α 拮抗剂他莫昔芬已经用于治疗绝经前和绝经后妇女中的早期和晚期 ER-α 阳性乳腺癌。氟维司群 (Faslodex™)，一种基于类固醇的 ER 拮抗剂，用于治疗尽管用他莫昔芬治疗但仍然进展的妇女中的乳腺癌。甾类和非甾

类芳香酶抑制剂也用于治疗人类的癌症。在一些实施方案中，甾类和非甾类芳香酶抑制剂阻断绝经后妇女中由雄烯二酮和睾酮生成雌激素，从而阻断了癌症中的ER依赖性生长。除了这些抗激素剂以外，在有些情况下还用多种其它化疗剂，例如，蒽环类、铂类、紫杉烷类，来治疗进行性的ER阳性乳腺癌。在一些情况下，用单克隆抗体曲妥珠单抗(Herceptin™)或小分子全-ERB-B抑制剂拉帕替尼治疗具有ERB-B/HER2酪氨酸激酶受体的基团扩增的ER阳性乳腺癌。尽管进行了这一系列抗激素、化学治疗及基于小分子和抗体的靶向治疗，但是许多ER-α阳性乳腺癌妇女仍发展为进行性转移性疾病，因而需要新的疗法。重要的是，对于大多数在现有的抗激素以及其它治疗下仍然进展的ER阳性肿瘤，认为其生长和存活仍然依赖于ER-α。因此，需要在转移性疾病和获得抗性的情况下具有活性的新的ER-α靶向剂。在一个方面，本文描述了作为选择性雌激素受体调节剂(SERM)的化合物。在特定实施方案中，本文描述的SERM是选择性雌激素受体降解剂(SERD)。在一些实施方案中，在基于细胞的试验中，本文所述的化合物导致稳态ER-α水平的降低(即ER降解)，并且可用于治疗雌激素敏感的疾病或状况和/或已发展了针对抗激素治疗的抗性的疾病或状况。

[0057] 鉴于ER-α在乳腺癌发展和进展中的核心作用，本文公开的化合物可以单独地或与其它能够调节乳腺癌中其它关键途径的药剂联合地用于乳腺癌的治疗，该其它药剂包括但不限于靶向IGF1R、EGFR、erB-B2和3、PI3K/AKT/mTOR轴、HSP90、PARP或组蛋白脱乙酰酶的药剂。

[0058] 鉴于ER-α在乳腺癌发展和进展中的核心作用，本文公开的化合物可以单独地或与其它用来治疗乳腺癌的药剂联合地用于乳腺癌的治疗，该其它药剂包括但不限于芳香酶抑制剂、蒽环类、铂类、氮芥烷化剂、紫杉烷类。用来治疗乳腺癌的示例性药剂包括但不限于紫杉醇、阿那曲唑、依西美坦、环磷酰胺、表柔比星、氟维司群、来曲唑、吉西他滨、曲妥珠单抗、培非司亭、非格司亭、他莫昔芬、多西他赛、托瑞米芬、长春瑞滨、卡培他滨、伊沙匹隆以及本文所述的其它药剂。

[0059] ER-相关疾病或状况包括与癌症(骨癌、乳腺癌、肺癌、结直肠癌、子宫内膜癌、前列腺癌、卵巢癌和子宫癌)相关的ER-α功能障碍、中枢神经系统(CNS)缺陷(酒精中毒、偏头痛)、心血管系统缺陷(主动脉瘤、心肌梗死易感性、主动脉瓣硬化、心血管疾病、冠状动脉疾病、高血压)、血液系统缺陷(深静脉血栓形成)、免疫及炎症疾病(格雷夫斯病、关节炎、多发性硬化、硬化)、感染易感性(乙型肝炎、慢性肝病)、代谢缺陷(骨密度、胆汁淤积、尿道下裂、肥胖症、骨关节炎、骨质减少、骨质疏松症)、神经缺陷(阿尔茨海默病、帕金森病、偏头痛、眩晕)、精神缺陷(神经性厌食、注意力缺陷多动障碍(ADHD)、痴呆、严重抑郁障碍、精神病)和生殖缺陷(月经初潮年龄、子宫内膜异位症、不育症)。

[0060] 在一些实施方案中，本文公开的化合物用于治疗哺乳动物中的雌激素受体依赖的或雌激素受体介导的疾病或状况。

[0061] 在一些实施方案中，雌激素受体依赖的或雌激素受体介导的疾病或状况选自癌症、中枢神经系统(CNS)缺陷、心血管系统缺陷、血液系统缺陷、免疫及炎症疾病、感染易感性、代谢缺陷、神经缺陷、精神缺陷和生殖缺陷。

[0062] 在一些实施方案中，雌激素受体依赖的或雌激素受体介导的疾病或状况选自骨癌、乳腺癌、肺癌、结直肠癌、子宫内膜癌、前列腺癌、卵巢癌、子宫癌、酒精中毒、偏头痛、主动脉瘤、心肌梗死易感性、主动脉瓣硬化、心血管疾病、冠状动脉疾病、高血压、深静脉血栓

形成、格雷夫斯病、关节炎、多发性硬化、硬化、乙型肝炎、慢性肝病、骨密度、胆汁淤积、尿道下裂、肥胖症、骨关节炎、骨质减少、骨质疏松症、阿尔茨海默病、帕金森病、偏头痛、眩晕、神经性厌食、注意力缺陷多动障碍 (ADHD)、痴呆、严重抑郁障碍、精神病、月经初潮年龄、子宫内膜异位症和不育症。

[0063] 在一些实施方案中，本文公开的化合物用来治疗哺乳动物中的癌症。在一些实施方案中，该癌症是乳腺癌、卵巢癌、子宫内膜癌、前列腺癌或子宫癌。在一些实施方案中，该癌症是乳腺癌、肺癌、卵巢癌、子宫内膜癌、前列腺癌或子宫癌。在一些实施方案中，该癌症是乳腺癌。在一些实施方案中，该癌症是激素依赖性癌症。在一些实施方案中，该癌症是雌激素受体依赖性癌症。在一些实施方案中，该癌症是雌激素敏感的癌症。在一些实施方案中，该癌症对于抗激素治疗具有抗性。在一些实施方案中，该癌症是对于抗激素治疗具有抗性的雌激素敏感的癌症或雌激素受体依赖的癌症。在一些实施方案中，该癌症是对于抗激素治疗具有抗性的激素敏感的癌症或激素受体依赖的癌症。在一些实施方案中，抗激素治疗包括使用至少一种选自他莫昔芬、氟维司群、甾类芳香酶抑制剂和非甾类芳香酶抑制剂的药剂进行的治疗。

[0064] 在一些实施方案中，本文公开的化合物用来治疗在抗雌激素治疗后疾病进展的绝经后妇女中的激素受体阳性转移性乳腺癌。

[0065] 在一些实施方案中，本文公开的化合物用来治疗哺乳动物中乳房或生殖道的激素依赖性良性或恶性疾病。在一些实施方案中，该良性或恶性疾病是乳腺癌。

[0066] 在一些实施方案中，本文所述的任一种方法中使用的化合物是雌激素受体降解剂；是雌激素受体拮抗剂；具有最低的或可忽略的雌激素受体激动剂活性；或是其组合。

[0067] 在一些实施方案中，用本文所述的化合物进行治疗的方法包括包含向哺乳动物施用放射疗法的治疗方案。

[0068] 在一些实施方案中，用本文所述的化合物进行治疗的方法包括在手术之前或之后施用该化合物。

[0069] 在一些实施方案中，用本文所述的化合物进行治疗的方法包括向哺乳动物施用至少一种另外的抗癌剂。

[0070] 在一些实施方案中，本文公开的化合物用来治疗哺乳动物中的癌症，其中该哺乳动物是未经化疗的。

[0071] 在一些实施方案中，本文公开的化合物用于哺乳动物中癌症的治疗。在一些实施方案中，本文公开的化合物用来治疗哺乳动物中的癌症，其中所述哺乳动物正在用至少一种抗癌剂治疗癌症。在一个实施方案中，该癌症是激素难治性癌症。

[0072] 在一些实施方案中，本文公开的化合物用于治疗或预防哺乳动物中子宫的疾病或状况。在一些实施方案中，所述子宫的疾病或状况是平滑肌瘤、子宫平滑肌瘤、子宫内膜增生或子宫内膜异位症。在一些实施方案中，所述子宫的疾病或状况是子宫的癌性疾病或状况。在一些其它实施方案中，所述子宫的疾病或状况是子宫的非癌性疾病或状况。

[0073] 在一些实施方案中，本文公开的化合物用于哺乳动物中的子宫内膜异位症的治疗。

[0074] 在一些实施方案中，本文公开的化合物用于哺乳动物中的平滑肌瘤的治疗。在一些实施方案中，所述平滑肌瘤是子宫平滑肌瘤、食管平滑肌瘤、皮肤平滑肌瘤或小肠平滑肌

瘤。在一些实施方案中，本文公开的化合物用于哺乳动物中纤维瘤的治疗。在一些实施方案中，本文公开的化合物用于哺乳动物中的子宫纤维瘤的治疗。

化合物

[0075] 式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物，包括其药学上可接受的盐、前药、活性代谢物和药学上可接受的溶剂化物，是雌激素受体调节剂。在特定实施方案中，本文所述的化合物是雌激素受体降解剂。在特定实施方案中，本文所述的化合物是雌激素受体拮抗剂。在特定实施方案中，本文所述的化合物是没有或具有最低的雌激素受体激动剂活性的雌激素受体降解剂和雌激素受体拮抗剂。

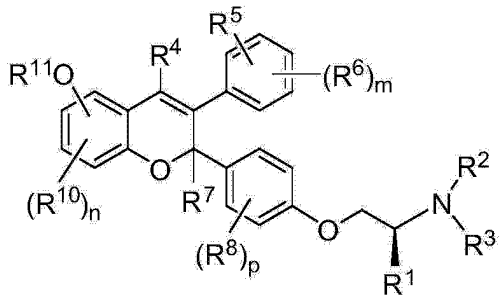
[0076] 在一些实施方案中，本文公开的化合物是雌激素受体降解剂和雌激素受体拮抗剂，它们表现出：无雌激素受体激动；和 / 或对乳腺癌、卵巢癌、子宫内膜癌、宫颈癌细胞系的抗增殖活性；和 / 或在体外对乳腺癌、卵巢癌、子宫内膜癌、宫颈细胞系的最大抗增殖效力；和 / 或在人类子宫内膜 (Ishikawa) 细胞系中的最低激动；和 / 或在人类子宫内膜 (Ishikawa) 细胞系中无激动；和 / 或在未成熟大鼠子宫试验中在体内无激动；和 / 或在未成熟大鼠子宫试验中在体内逆转的激动；和 / 或在体内异种移植试验中或在这些癌症的其它啮齿动物模型中在乳腺癌、卵巢癌、子宫内膜癌、宫颈癌细胞系中的抗肿瘤活性。

[0077] 在一些实施方案中，本文所述的化合物与 hERG(人类 Ether-à-go-go- 相关基因) 通道具有减少的或最小的相互作用，和 / 或显示出降低的 QT 延长的可能性和 / 或降低的室性快速型心律失常比如尖端扭转性室速的风险。

[0078] 在一些实施方案中，本文所述的化合物具有降低的或最小的进入下丘脑的可能性，和 / 或具有降低的或最小的调节下丘脑 - 垂体 - 卵巢 (HPO) 轴的可能性，和 / 或显示降低的引起卵巢的超刺激的可能性，和 / 或显示降低的卵巢毒性的可能性。

[0079] 在一些实施方案中，用于治疗绝经前妇女的疾病或状况的本文所描述的化合物具有降低的或最小的进入下丘脑的可能性，和 / 或具有降低的或最小的调节下丘脑 - 垂体 - 卵巢 (HPO) 轴的可能性，和 / 或显示降低的引起卵巢的超刺激的可能性，和 / 或显示降低的卵巢毒性的可能性。在一些实施方案中，所述绝经前妇女的疾病或状况是子宫内膜异位症。在一些实施方案中，所述绝经前妇女的疾病或状况是子宫疾病或状况。

[0080] 在一方面，本文所描述的是式 (I) 的化合物，或其药学上可接受的盐或溶剂化物：



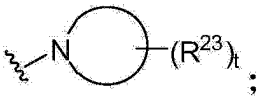
式(I)

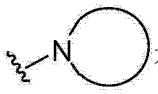
其中：

R^1 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^3 是 C_1-C_6 氟烷基；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是单环 C_2-C_{10} 杂环烷基；

各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；

t 是 1、2、3 或 4；

R^4 是 H、卤素、-CN、C_1-C_4 烷基、C_1-C_4 氟烷基或 C_3-C_6 环烷基；

R^5 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基或 C_1-C_6 杂烷基；

各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

R^7 是 H 或 C_1-C_4 烷基；

各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；

各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、C_1-C_6 烷基、C_1-C_6 杂烷基、C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基 -（取代或未取代的杂芳基）；

各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基 -（取代或未取代的杂芳基）；

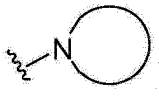
m 是 0、1、2、3 或 4；

n 是 0、1 或 2；

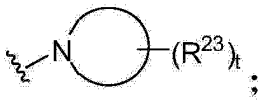
p 是 0、1 或 2；

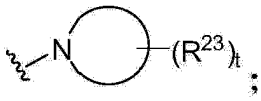
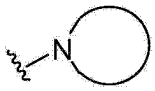
条件是所述化合物不是 2-(4-((S)-2-((R)-3- 氟吡咯烷 -1- 基）丙氧基）苯基）-3-(3- 羟基苯基）-4- 甲基 -2H- 苯并吡喃 -6- 醇。

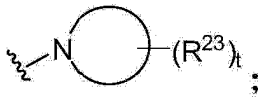
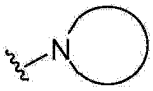
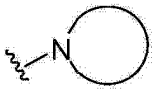
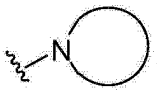
[0081] 对于本文所述的任何及全部实施方案，取代基选自所列出的备选物的子集。例如，在一些实施方案中，R^7 是 H 或 $-CH_3$。在其它实施方案中，R^7 是 H。

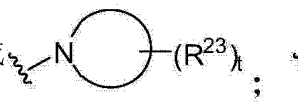
[0082] 在一些实施方案中，  是单环 C_2-C_{10} 杂环烷基；各个 R^{23} 独立地是 C_1-C_6 氟烷基；t 是 1、2、3 或 4。

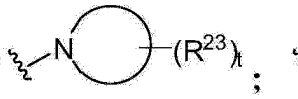
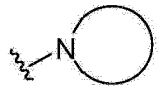
[0083] 在一些实施方案中，R^2 和 R^3 与它们所连接的 N 原子一起形成

 ；  是单环 C_2-C_{10} 杂环烷基。

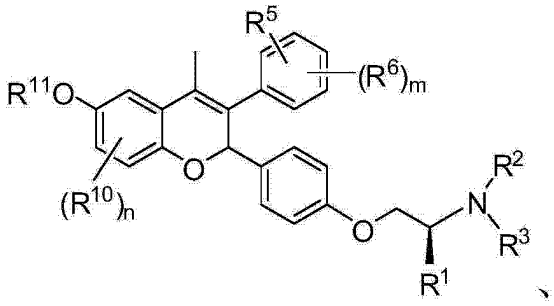
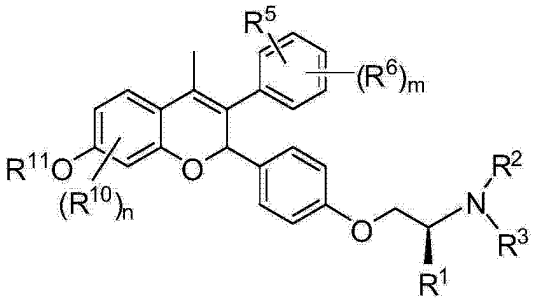
[0084] 在一些实施方案中，R^2 和 R^3 与它们所连接的 N 原子一起形成  ；  是单环 C_2-C_6 杂环烷基。

[0085] 在一些实施方案中，R^2 和 R^3 与它们所连接的 N 原子一起形成  ；  是 4 元、5 元、6 元或 7 元单环 C_2-C_6 杂环烷基。在一些实施方案中，  是氮杂环丁基、吡咯烷基、哌啶基或氮杂环庚基。在一些实施方案中，  是吡咯烷基。

[0086] 在一些实施方案中，R^1 是 H 或 C_1-C_6 烷基；R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；R^3 是 C_1-C_6 氟烷基；或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；  是 4 元、5 元、6 元或 7 元单环 C_2-C_6 杂环烷基；各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；t 是 1 或 2；R^4 是 $-CH_3$；R^7 是 H；p 是 0 或 1。

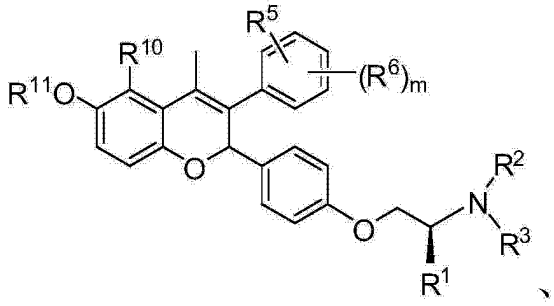
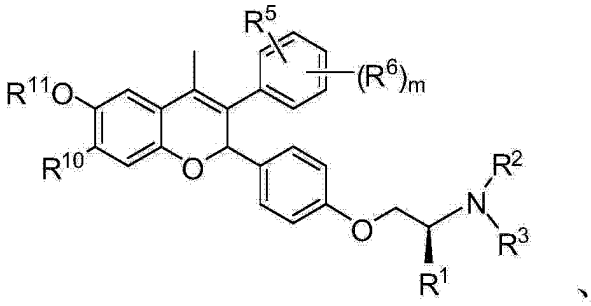
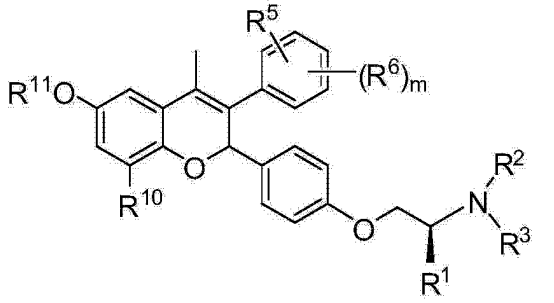
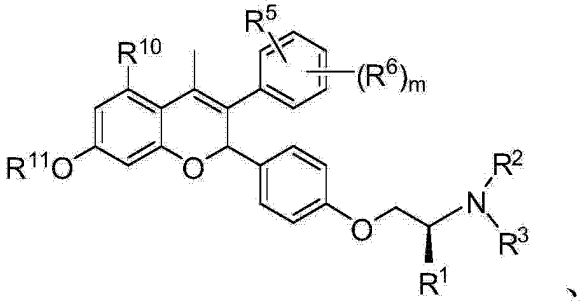
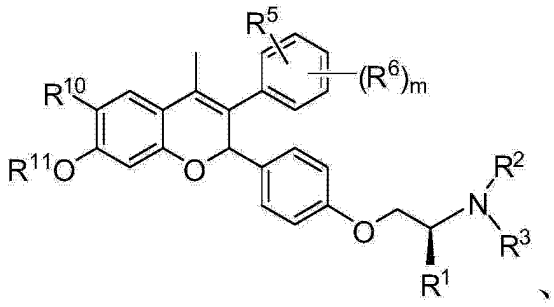
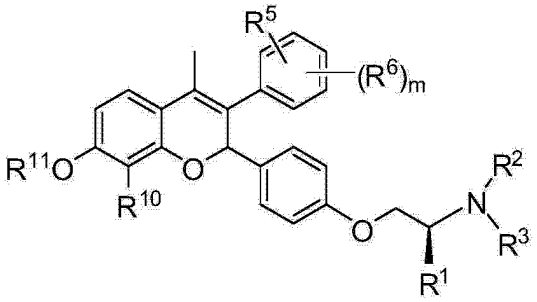
[0087] 在一些实施方案中，R^1 是 H 或 C_1-C_6 烷基；R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；R^3 是 C_1-C_6 氟烷基；或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；  是 4 元、5 元、6 元或 7 元单环 C_2-C_6 杂环烷基；各个 R^{23} 独立地是 C_1-C_6 氟烷基；t 是 1 或 2；R^4 是 $-CH_3$；R^7 是 H；p 是 0 或 1。

[0088] 在一些实施方案中，所述化合物具有下列结构之一：

 、 

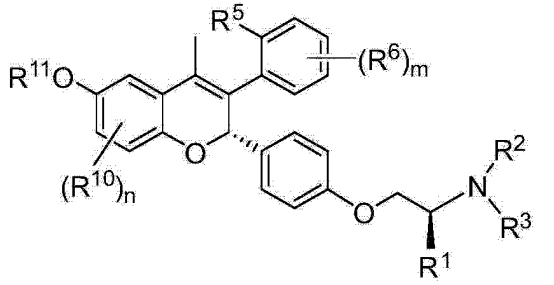
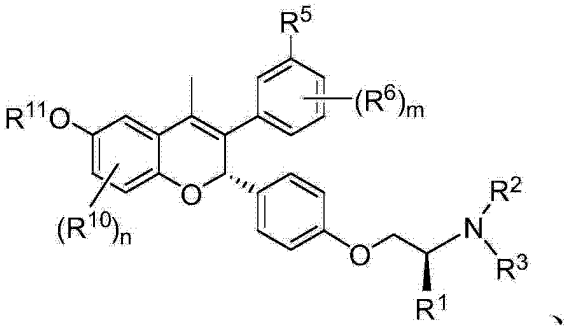
或是其药学上可接受的盐或溶剂化物。

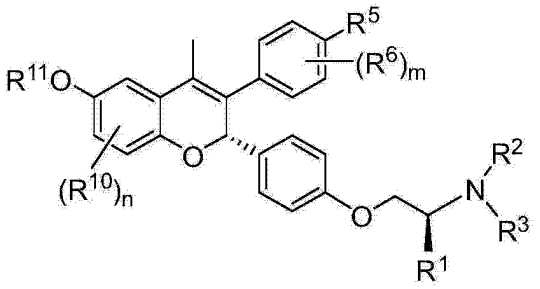
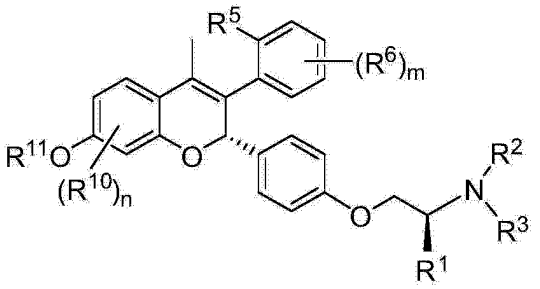
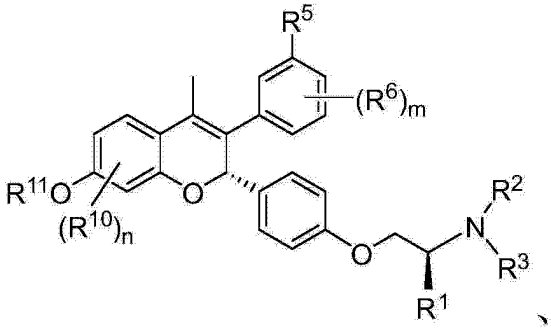
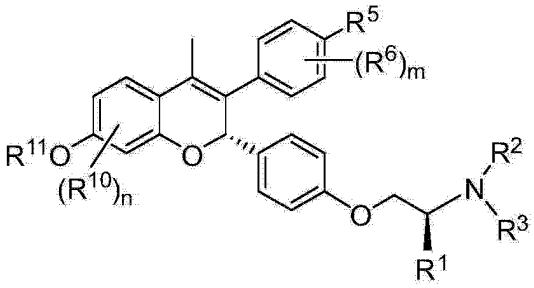
[0089] 在一些实施方案中，所述化合物具有下列结构之一：


、

、

、

、

、


或是其药学上可接受的盐或溶剂化物。

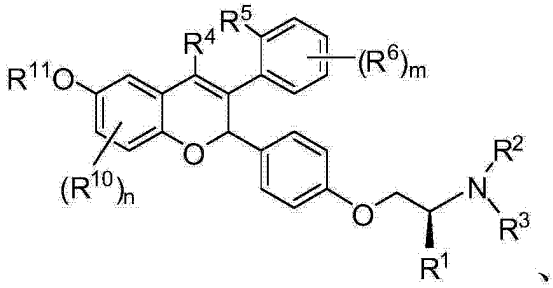
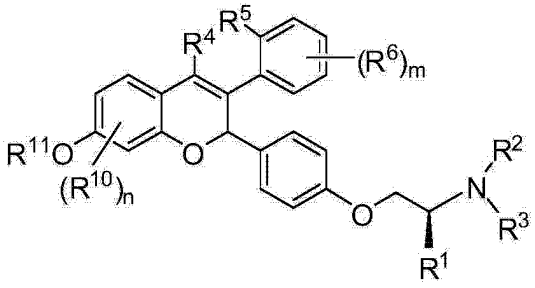
[0090] 在一些实施方案中，所述化合物具有下列结构之一：


、

、

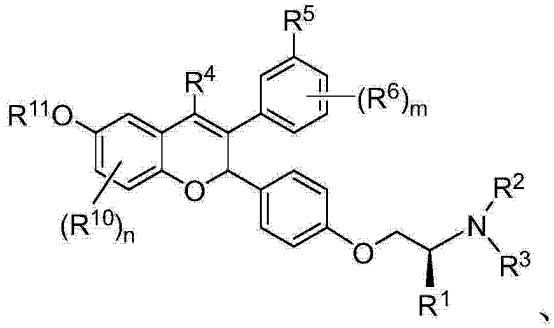
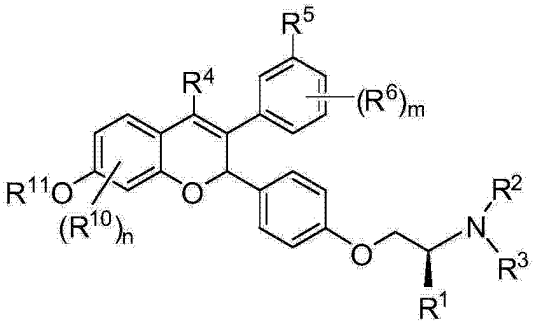
或是其药学上可接受的盐或溶剂化物。

[0091] 在一些实施方案中，所述化合物具有下列结构之一：

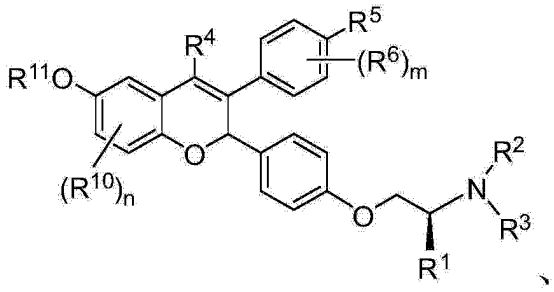
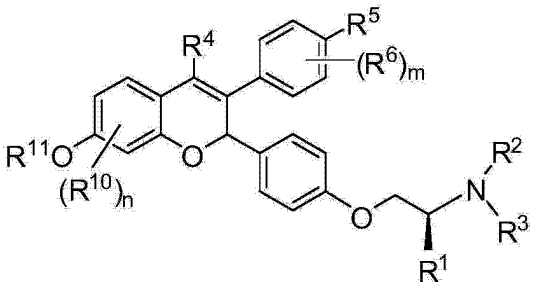
或是其药学上可接受的盐或溶剂化物。

[0092] 在一些实施方案中，所述化合物具有下列结构之一：

或是其药学上可接受的盐或溶剂化物。

[0093] 在一些实施方案中，所述化合物具有下列结构之一：

或是其药学上可接受的盐或溶剂化物。

[0094] 在一些实施方案中，各个 R^{10} 独立地选自 -CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基。在一些实施方案中，各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基。在一些实施方案中，各个 R^{10} 独立地选自 H、F、Cl、-CN、$-CH_3$ 和 $-CF_3$。在一些实施方案中，各个 R^{10} 独立地选自 H 和 F。

[0095] 在一些实施方案中，n 是 0 或 1。在一些实施方案中，n 是 0。

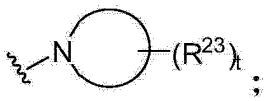
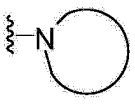
[0096] 在一些实施方案中，R^5 是 $-OR^{11}$。在一些实施方案中，R^{11} 是 H。在一些实施方案中，R^5 是 -OH；R^{11} 是 H。

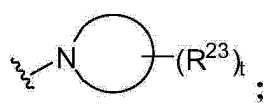
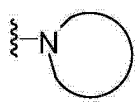
[0097] 在一些实施方案中，R^5 是 -OH；各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；R^{11} 是 H。

[0098] 在一些实施方案中，各个 R^6 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基。在一些实施方案中，各个 R^6 独立地选自 H、卤素和 -CN。在一些实施方案中，各个 R^6 是 H、F、Cl、-CN、$-CH_3$ 和 $-CF_3$。在一些实施方案中，m 是 0 或 1。在一些实施方案中，m 是 0。

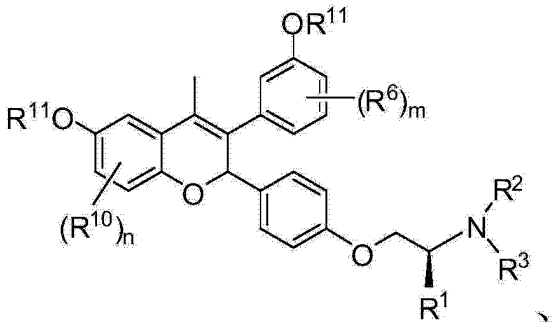
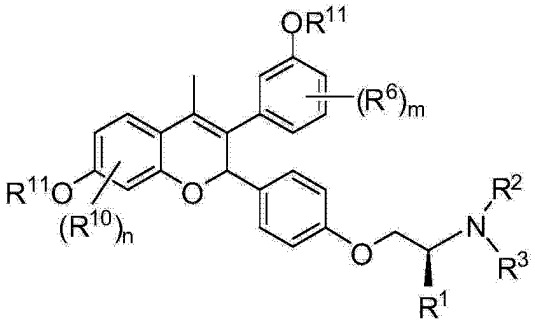
[0099] 在一些实施方案中，R^4 是 $-CH_3$。

[0100] 在一些实施方案中，R^1 是 H 或 $-CH_3$。在一些实施方案中，R^1 是 $-CH_3$。

[0101] 在一些实施方案中，R^1 是 H 或 $-CH_3$；R^2 和 R^3 与它们所连接的 N 原子一起形成  ；  是氮杂环丁基、吡咯烷基、哌啶基、氮杂环庚基、吗啉基或哌嗪基；各个 R^{23} 独立地是 F、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。

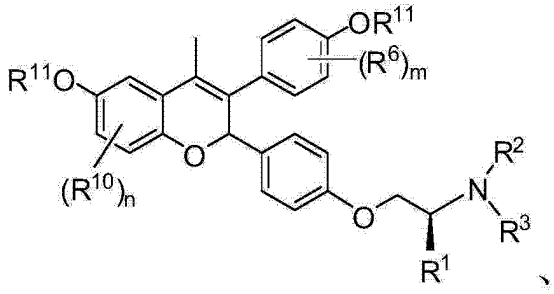
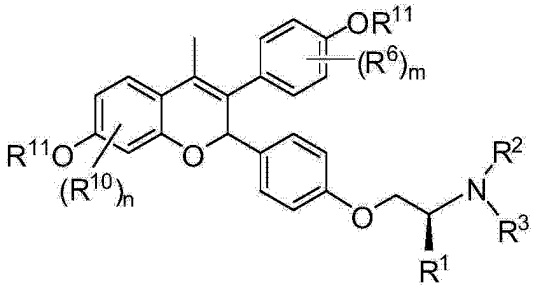
[0102] 在一些实施方案中，R^1 是 H 或 $-CH_3$；R^2 和 R^3 与它们所连接的 N 原子一起形成  ；  是氮杂环丁基、吡咯烷基、哌啶基、氮杂环庚基、吗啉基或哌嗪基；各个 R^{23} 独立地是 $-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。

[0103] 在一些实施方案中，所述化合物具有下列结构之一：

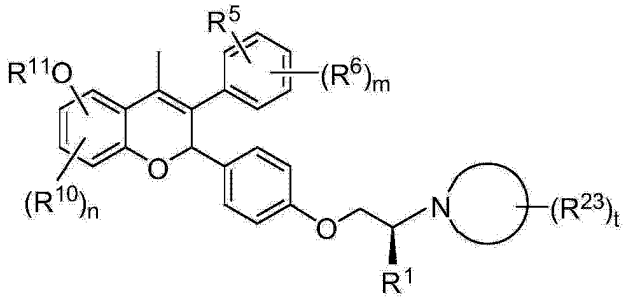
或是其药学上可接受的盐或溶剂化物。

[0104] 在一些实施方案中，所述化合物具有下列结构之一：

或是其药学上可接受的盐或溶剂化物。

[0105] 在一些实施方案中，式（I）的化合物具有式（II）的结构：

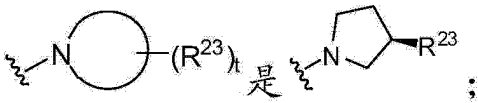


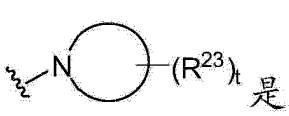
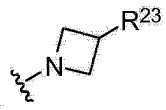
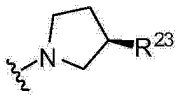
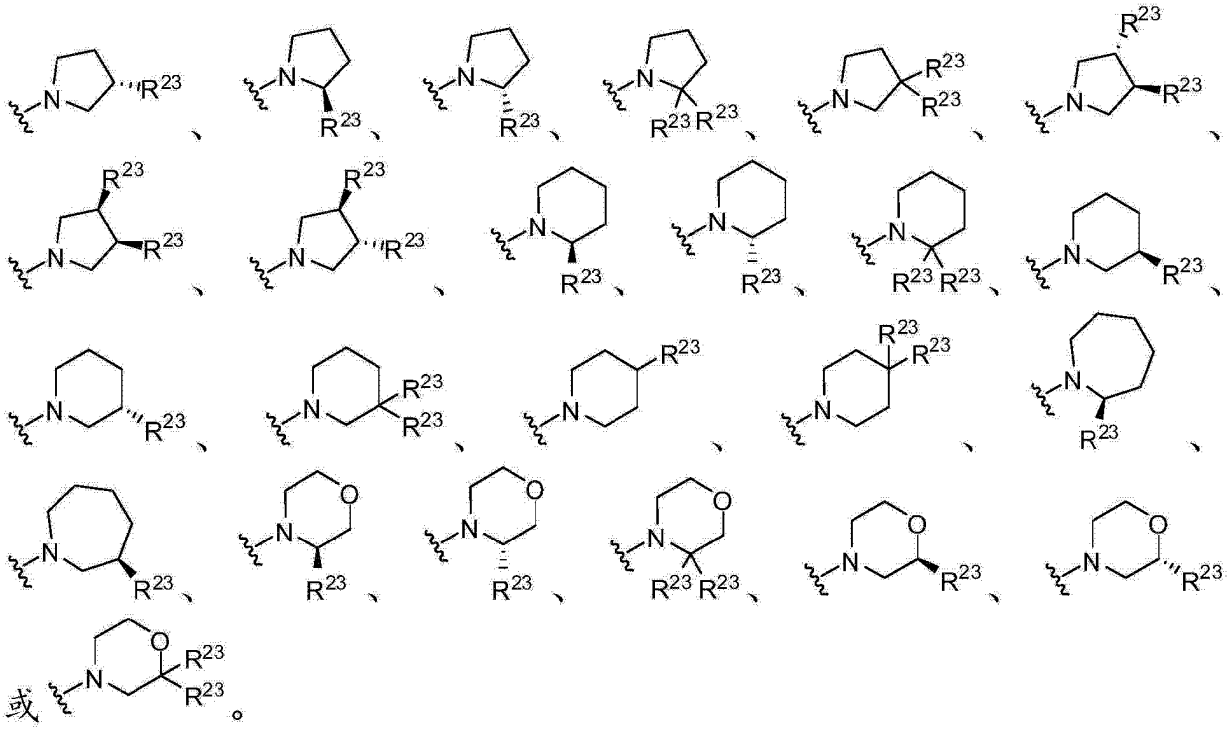
式(II)

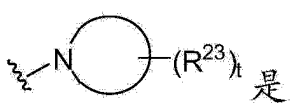
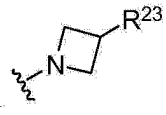
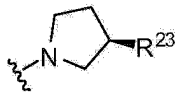
或是其药学上可接受的盐或溶剂化物。

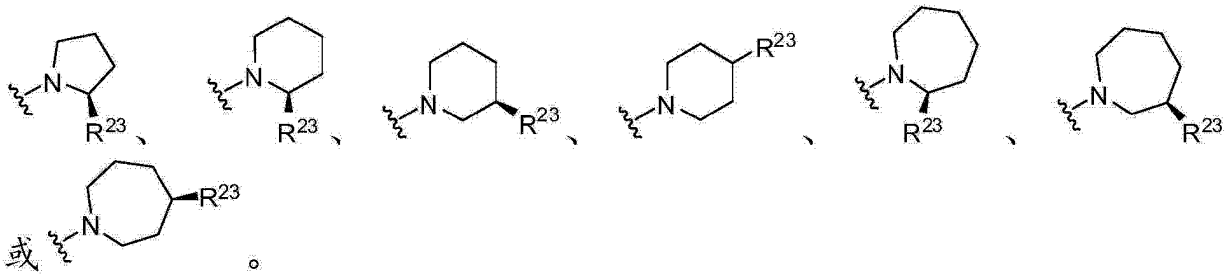
[0106] 在式（II）的化合物的一些实施方案中，R^1 是 H 或 $-CH_3$；  是单环 C_2-C_6 杂环烷基；各个 R^{23} 独立地是 C_1-C_6 氟烷基；t 是 1 或 2；R^5 是 $-OR^{11}$；各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、C_1-C_6 烷基、C_1-C_6 杂烷基、C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基-（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基-（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基-（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基-（取代或未取代的杂芳基）；各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代

的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、-C_1-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的芳基）和 -C_1-C_2 亚烷基 -（取代或未取代的杂芳基）；m 是 0 或 1；n 是 0 或 1。在一些实施方案中，m 是 0。在一些实施方案中，n 是 0。在一些实施方案中，各个 R^{11} 是 H。

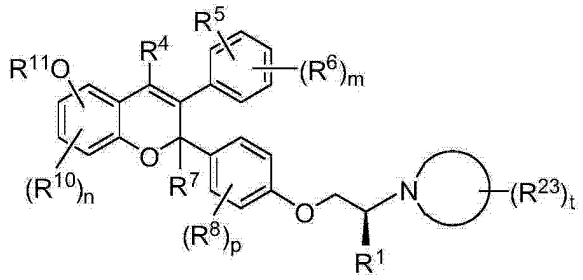
[0107] 在式（II）的化合物的一些其它实施方案中，R^1 是 H 或 $-CH_3$；  是；R^{23} 是 C_1-C_4 氟烷基；R^5 是 $-OR^{11}$；各个 R^6 独立地选自 H、卤素和 -CN；各个 R^{10} 独立地选自 H、卤素和 -CN；各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$ 和 C_1-C_6 烷基；各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、-C_1-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的芳基）和 -C_1-C_2 亚烷基 -（取代或未取代的杂芳基）；m 是 0 或 1；n 是 0 或 1。在一些实施方案中，各个 R^{11} 是 H。在一些实施方案中，m 是 0。在一些实施方案中，n 是 0。

[0108] 在一些实施方案中，  是  、  、  或。

[0109] 在一些实施方案中，  是  、  、



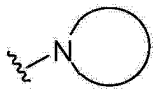
[0110] 在另一方面，本文描述的是式（III）的化合物，或其药学上可接受的盐或溶剂化物：



式(III)

其中，

R^1 是 C_1-C_6 氟烷基；

 是单环 C_2-C_{10} 杂环烷基；

各个 R^{23} 独立地是 F、C_1-C_6 烷基或 C_1-C_6 氟烷基；

t 是 0、1、2、3 或 4；

R^4 是 H、卤素、-CN、C_1-C_4 烷基、C_1-C_4 氟烷基或 C_3-C_6 环烷基；

R^5 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基或 C_1-C_6 杂烷基；

各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；

各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；

各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、C_1-C_6 烷基、C_1-C_6 杂烷基、C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、-C_1-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的芳基）和 -C_1-C_2 亚烷基 -（取代或未取代的杂芳基）；

各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、-C_1-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷

基）、-C_1-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、-C_1-C_2 亚烷基 -（取代或未取代的芳基）和 -C_1-C_2 亚烷基 -（取代或未取代的杂芳基）；

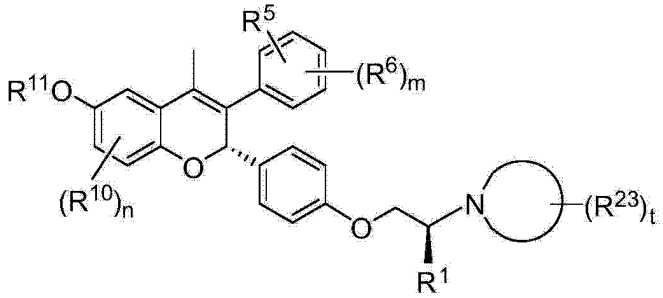
m 是 0、1、2、3 或 4；

n 是 0、1 或 2；

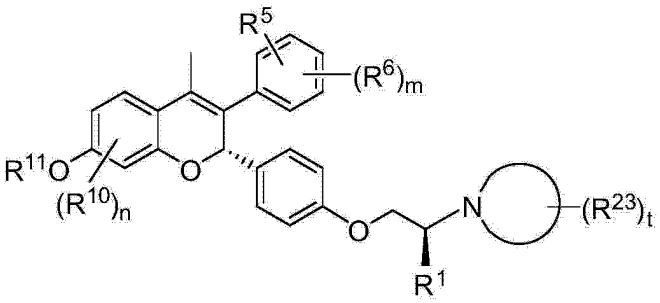
p 是 0、1 或 2。

[0111] 在一些实施方案中，R^1 是 -CH_2F、-CHF_2 或 -CF_3；  是氮杂环丁基、吡咯烷基、哌啶基或氮杂环庚基；各个 R^{23} 独立地是 F、-CH_3、-CH_2CH_3、-CH_2F、-CHF_2、-CF_3、-$CHFCH_3$、-CH_2CH_2F、-CH_2CHF_2、-CH_2CF_3、-$CH_2CH_2CF_3$、-$CH_2CH_2CH_2CF_3$、-$CHCH_3CF_3$、-$CH(CF_3)_2$ 或 -$CF(CH_3)_2$；t 是 0、1 或 2；R^4 是 -CH_3；R^7 是 H；p 是 0 或 1。

[0112] 在一些实施方案中，式 (I)、(II) 或 (III) 的化合物具有下列结构之一：

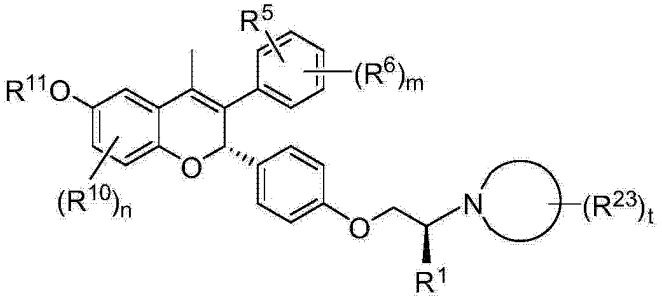


或



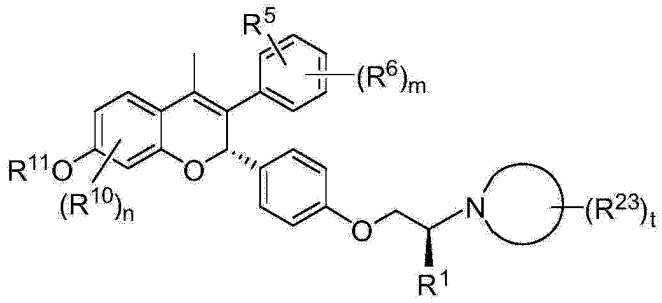
。

[0113] 在一些实施方案中，式 (I)、(II) 或 (III) 的化合物具有下列结构：



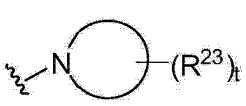
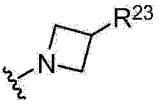
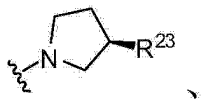
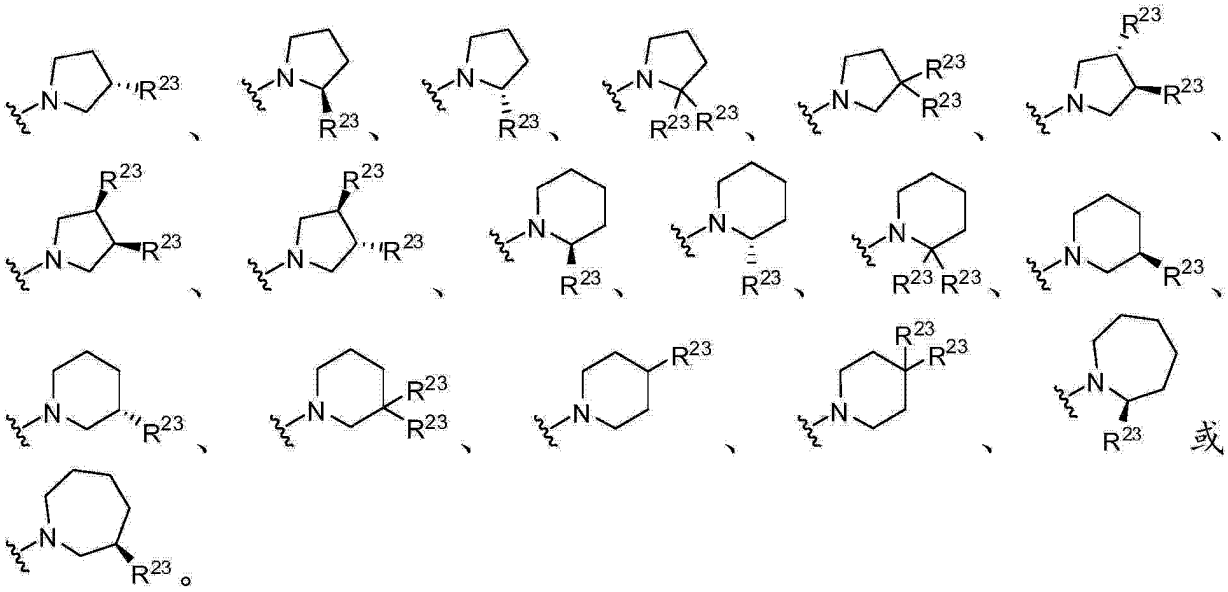
。

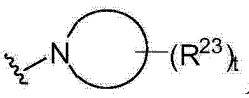
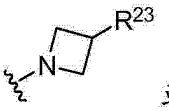
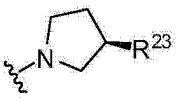
[0114] 在一些实施方案中，式 (I)、(II) 或 (III) 的化合物具有下列结构：

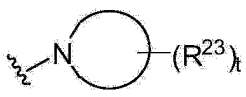
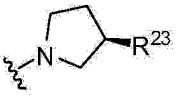


。

[0115] 在一些实施方案中，R^5 是 -OH；各个 R^{10} 独立地选自 H、卤素、-CN、-OH、-S(=O)R^{12}、-S(=O)$_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；R^{11} 是 H。在一些实施方案中，R^5 是 -OH；各个 R^6 独立地选自 H 和卤素；各个 R^{10} 独立地选自 H 和卤素；R^{11} 是 H。

[0116] 在一些实施方案中，  是  、  、  或。

[0117] 在一些实施方案中，  是  或  。

[0118] 在一些实施方案中，  是  。

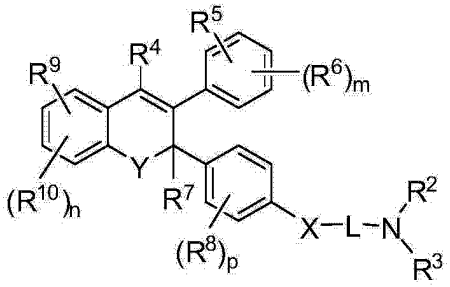
[0119] 在一些实施方案中，各个 R^{23} 独立地是 F、-CH_3、-CH_2CH_3、-CH_2F、-CHF_2、-CF_3、-$CHFCH_3$、-CH_2CH_2F、-CH_2CHF_2、-CH_2CF_3、-$CH_2CH_2CF_3$、-$CH_2CH_2CH_2CF_3$、-$CHCH_3CF_3$、-$CH(CF_3)_2$ 或 -$CF(CH_3)_2$。在一些实施方案中，各个 R^{23} 独立地是 F、-CH_3、-CH_2F、-CHF_2 或 -CF_3。在一些实施方案中，R^{23} 独立地是 F、-CH_2F、-CHF_2 或 -CF_3。在一些实施方案中，各个 R^{23} 独立地是 -CH_2F、-CHF_2 或 -CF_3。在一些实施方案中，各个 R^{23} 独立地是 -CH_2F。在一些实施方案中，各个 R^{23} 独立地是 -CH_3、-CH_2F、-CHF_2 或 -CF_3。在一些实施方案中，各个 R^{23} 独立地是 -CH_3。

[0120] 在一些实施方案中，R^2 和 R^3 与它们所连接的 N 原子一起形成取代或未取代的吡咯

烷基。

[0121] 在一些实施方案中，R^1 是 $-CH_3$。在一些实施方案中，R^1 是 $-CH_3$；R^4 是 $-CH_3$。

[0122] 在一些实施方案中，本文所描述的是式（IV）的化合物，或其药学上可接受的盐或溶剂化物：



式(IV)

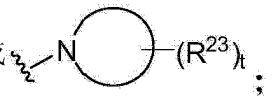
其中，

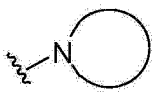
L 是取代或未取代的 C_1-C_6 的氟亚烷基，其中如果 L 被取代，则 L 被 1 或 2 个 R^1 取代。

R^1 是 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_6 环烷基、C_3-C_6 氟环烷基或 C_1-C_6 杂烷基；

R^2 是 H 或 R^{12}；

R^3 是 $-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、$-S(=O)_2R^{12}$ 或 R^{12}；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是单环杂环烷基或双环杂环烷基；

各个 R^{23} 独立地选自 F、Cl、$-CN$、$-OH$、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、$-C(=O)R^{12}$、取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_1-C_6 氟烷氧基、取代或未取代的 C_1-C_6 烷氧基和取代或未取代的 C_1-C_6 杂烷基；

或在同一碳原子上的两个 R^{23} 与它们所连接的碳原子一起形成 $-C(=O)-$；

或在相邻的碳原子上的两个 R^{23} 与它们所连接的碳原子一起形成 C_3-C_6 环烷基；

或 1 个 R^{23} 与 R^1 以及将 R^{23} 连接至 R^1 的中间原子一起形成 5-7 元环；

t 是 0、1、2、3 或 4；

R^4 是 H、卤素、$-CN$、C_1-C_4 烷基、C_1-C_4 氟烷基、C_1-C_4 烷氧基、C_1-C_4 氟烷氧基、C_3-C_6 环烷基、C_3-C_6 氟环烷基、C_3-C_6 杂环烷基、C_1-C_6 杂烷基、$-C_1$-C_4 亚烷基 $-C_3$-C_6 环烷基、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、$-C(=O)R^{12}$、$-C(=O)NHR^{12}$ 或 $-C(=O)N(R^{12})_2$；

R^5 是 H、卤素、$-CN$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、$-C(=O)R^{12}$、$-C(=O)OH$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、$-C(=O)N(R^{12})_2$、取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_1-C_6 氟烷氧基、取代或未取代的 C_1-C_6 烷氧基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基或取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基；取代或未取代的芳基或取代或未取代的杂芳基；

各个 R^6 独立地选自 H、卤素、$-CN$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、$-C(=O)R^{12}$、$-C(=O)OH$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、$-C(=O)N(R^{12})_2$、取代或未取代的 C_1-C_6 烷基、取代或未

取代的 C_1-C_6 氟烷基、取代或未取代的 C_1-C_6 氟烷氧基、取代或未取代的 C_1-C_6 烷氧基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基；

R^7 是 H 或 C_1-C_4 烷基；

各个 R^8 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_1-C_6 氟烷氧基、取代或未取代的 C_1-C_6 烷氧基和取代或未取代的 C_1-C_6 杂烷基；

R^9 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_1-C_6 氟烷氧基、取代或未取代的 C_1-C_6 烷氧基和取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基或取代或未取代的杂芳基；

各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_1-C_6 氟烷氧基、取代或未取代的 C_1-C_6 烷氧基和取代或未取代的 C_1-C_6 杂烷基；

各个 R^{11} 独立地选自 H、$-C(=O)R^{12}$、$-C(=O)OR^{12}$、$-C(=O)NHR^{12}$、取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基 -（取代或未取代的杂芳基）；

各个 R^{12} 独立地选自取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_{10} 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基、取代或未取代的杂芳基、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_3-C_{10} 环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的 C_2-C_{10} 杂环烷基）、$-C_1$-C_2 亚烷基 -（取代或未取代的芳基）和 $-C_1$-C_2 亚烷基 -（取代或未取代的杂芳基）；

Y 是 -O-、-S-、$-S(=O)-$、$-S(=O)_2-$ 或 $-NR^{13}-$；R^{13} 是 H、$-C(=O)R^{12}$、取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 氟烷基、取代或未取代的 C_3-C_7 环烷基或取代或未取代的 C_1-C_6 杂烷基；

X 是 -O-、-S-、$-S(=O)-$、$-S(=O)_2-$、$-CH_2-$、-NH- 或 $-N(C_1$-C_6 烷基$)-$；

m 是 0、1、2、3 或 4；

n 是 0、1 或 2；

p 是 0、1 或 2。

[0123] 在一些实施方案中，p 是 0、1 或 2。在一些实施方案中，p 是 0 或 1。在一些实施方案中，p 是 1。在一些实施方案中，p 是 0。

[0124] 在一些实施方案中，n 是 0、1 或 2。在一些实施方案中，n 是 0 或 1。在一些实施方案中，n 是 0。在一些实施方案中，n 是 1。在一些实施方案中，n 是 1 或 2。

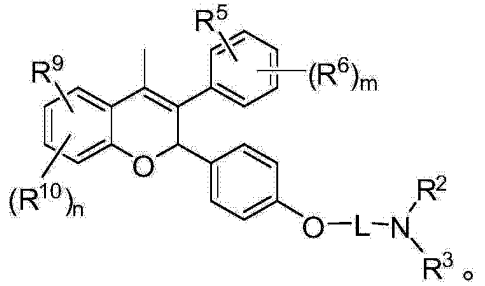
[0125] 在一些实施方案中，m 是 0、1、2、3 或 4。在一些实施方案中，m 是 1、2、3 或 4。在一些实施方案中，m 是 0、1、2 或 3。在一些实施方案中，m 是 0、1 或 2。在一些实施方案中，m 是 0 或 1。在一些实施方案中，m 是 1、2 或 3。在一些实施方案中，m 是 1 或 2。在一些实施方案中，m 是 1。在一些实施方案中，m 是 0 或 1。在一些实施方案中，m 是 0。

[0126] 在一些实施方案中，Y 是 -O-。在一些实施方案中，X 是 -O-。

[0127] 在一些实施方案中，L 是取代或未取代的氟乙烯，其中如果 L 被取代，则 L 被 1 或 2 个 R^1 取代；R^4 是 C_1-C_4 烷基；R^5 是卤素、-CN、-NHR^{11}、-$NR^{11}R^{12}$、-SR^{11}、-S(=O)R^{12}、-S(=O)$_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基、C_1-C_6 杂烷基、取代或未取代的 C_3-C_6 环烷基、取代或未取代的 C_2-C_6 杂环烷基；取代或未取代的苯基或取代或未取代的单环杂芳基；各个 R^6 独立地选自 H、卤素、-CN、-SR^{11}、-S(=O)R^{12}、-S(=O)$_2R^{12}$、-C(=O)R^{12}、-C(=O)OH、-C(=O)OR^{12}、-C(=O)NHR^{12}、-C(=O)N$(R^{12})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基、C_1-C_6 杂烷基、C_1-C_6 氟烷基；R^7 是 H；R^9 是 H、卤素、-CN、-OH、-OR^{11}、-NHR^{11}、-$NR^{11}R^{12}$、-SR^{11}、-S(=O)R^{12}、-S(=O)$_2R^{12}$、-C(=O)R^{12}、-C(=O)OH、-C(=O)OR^{12}、-C(=O)NHR^{12}、-C(=O)N$(R^{12})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基、C_1-C_6 杂烷基、C_1-C_6 氟烷基或取代或未取代的 C_3-C_6 环烷基、取代或未取代的 C_2-C_6 杂环烷基、取代或未取代的苯基或取代或未取代的单环杂芳基；各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；各个 R^{10} 独立地选自 H、卤素、-CN、-SR^{11}、-S(=O)R^{12}、-S(=O)$_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；Y 是 -O-；X 是 -O-；p 是 0 或 1。

[0128] 在一些实施方案中，R^5 是 -OH 或 -OR^{11}；R^9 是 -OH 或 -OR^{11}；p 是 0 或 1。

[0129] 在一些实施方案中，式 (IV) 的化合物具有以下结构：



。

[0130] 在一些实施方案中，R^2 是 H、取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_1-C_6 杂烷基或取代或未取代的 C_1-C_6 氟烷基；R^3 是 -C(=O)R^{12}、-C(=O)OR^{12}、-C(=O)NHR^{12}、-S(=O)$_2R^{12}$ 或 R^{12}；R^4 是 C_1-C_4 烷基；R^7 是 H；Y 是 -O-；X 是 -O-。

[0131] 在一些实施方案中，R^4 是 C_1-C_4 烷基。在一些实施方案中，R^4 是 C_1-C_4 氟烷基。在一些实施方案中，R^4 是 H、卤素、-CN、C_1-C_4 氟烷基、C_1-C_4 烷氧基、C_1-C_4 氟烷氧基、C_3-C_6 环烷基、C_3-C_6 氟环烷基、C_3-C_6 杂环烷基、C_1-C_6 杂烷基、-C_1-C_4 亚烷基 -C_3-C_6 环烷基、-SR^{11}、-S(=O)R^{12}、-S(=O)$_2R^{12}$、-C(=O)R^{12}、-C(=O)NHR^{12} 或 -C(=O)N$(R^{12})_2$。在一些实施方案中，R^4 是卤素、-CN、C_1-C_4 烷氧基、C_1-C_4 氟烷氧基、C_3-C_6 环烷基、C_3-C_6 氟环烷基、C_3-C_6 杂环烷基、C_1-C_6 杂烷基、-C_1-C_4 亚烷基 -C_3-C_6 环烷基、-SR^{11}、-S(=O)R^{12}、-S(=O)$_2R^{12}$、-C(=O)R^{12}、-C(=O)NHR^{12} 或 -C(=O)N$(R^{12})_2$。

[0132] 在一些实施方案中，R^9 是 -OH 或 -OR^{11}。在一些实施方案中，R^9 是 -OH。在一些实施方案中，R^9 是 -OH 或 -OR^{11}；p 是 0 或 1。

[0133] 在一些实施方案中，R^5 是 -OH。在一些实施方案中，R^5 是 -OH 或 -OR^{11}；p 是 0 或 1。

[0134] 在一些实施方案中，R^9 是 -OR^{11}。在一些实施方案中，R^9 是 -OH。在一些实施方案中，R^5 是 -OR^{11}。在一些实施方案中，R^5 是 -OH。在一些实施方案中，R^9 是 -OR^{11}；且 R^5

是 $-OR^{11}$。在一些实施方案中，R^{11} 是 H。在一些实施方案中，R^9 是 -OH；且 R^5 是 -OH。

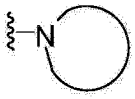
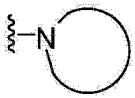
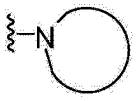
[0135] 在一些实施方案中，R^4 是 C_1-C_4 烷基；各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；R^7 是 H；各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；Y 是 -O-；X 是 -O-；p 是 0 或 1。

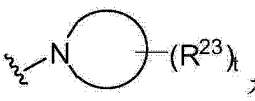
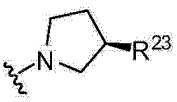
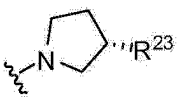
[0136] 在一些实施方案中，R^9 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基、C_1-C_6 杂烷基、取代或未取代的 C_3-C_6 环烷基、取代或未取代的 C_2-C_6 杂环烷基、取代或未取代的苯基或取代或未取代的单环杂芳基；各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基。

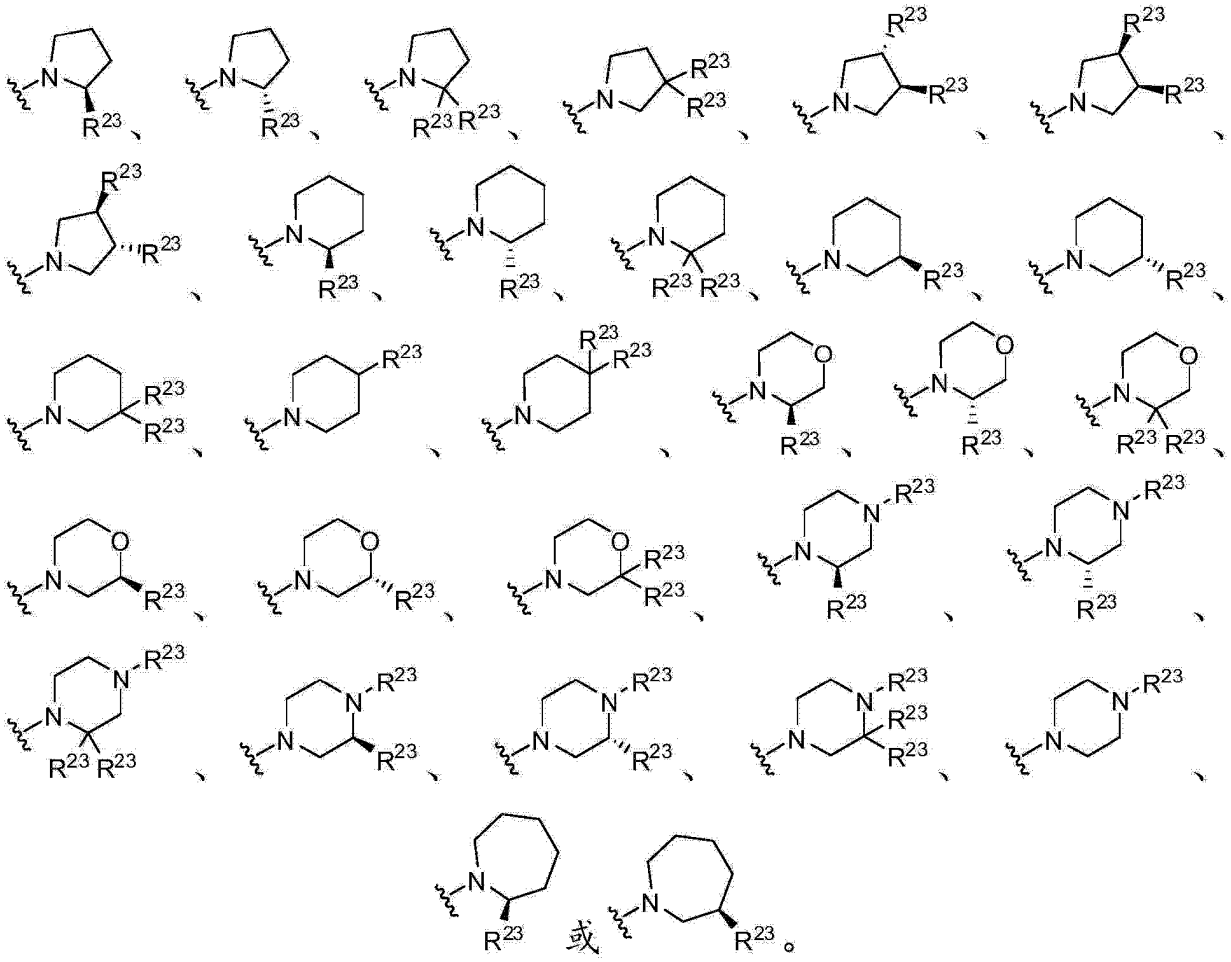
[0137] 在一些实施方案中，R^4 是 C_1-C_4 烷基；R^5 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基或 C_1-C_6 杂烷基；各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；R^7 是 H；Y 是 -O-；X 是 -O-。

[0138] 在一些实施方案中，R^4 是 C_1-C_4 烷基；各个 R^6 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基；R^7 是 H；各个 R^8 独立地选自 H、卤素、-CN、-OH、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基和 C_1-C_6 烷氧基；Y 是 -O-；X 是 -O-；p 是 0 或 1。

[0139] 在一些实施方案中，R^9 是 H、卤素、-CN、-OH、$-OR^{11}$、$-NHR^{11}$、$-NR^{11}R^{12}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基、C_1-C_6 杂烷基、取代或未取代的 C_3-C_6 环烷基、取代或未取代的 C_2-C_6 杂环烷基、取代或未取代的苯基或取代或未取代的单环杂芳基；各个 R^{10} 独立地选自 H、卤素、-CN、-OH、$-OR^{11}$、$-SR^{11}$、$-S(=O)R^{12}$、$-S(=O)_2R^{12}$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 氟烷氧基、C_1-C_6 烷氧基和 C_1-C_6 杂烷基。

[0140] 在一些实施方案中，  是氮杂环丁基、吡咯烷基、哌啶基、氮杂环庚基、吗啉基、哌嗪基、3-氮杂双环[3.1.0]己烷-3-基、3-氮杂双环[3.2.0]庚烷-3-基或八氢环戊[c]吡咯基。在一些实施方案中，  是氮杂环丁基、吡咯烷基、哌啶基或氮杂环庚基。在一些实施方案中，  是吡咯烷基。

[0141] 在一些实施方案中，  是  、  、

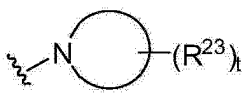
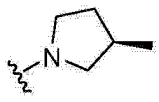
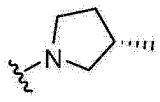
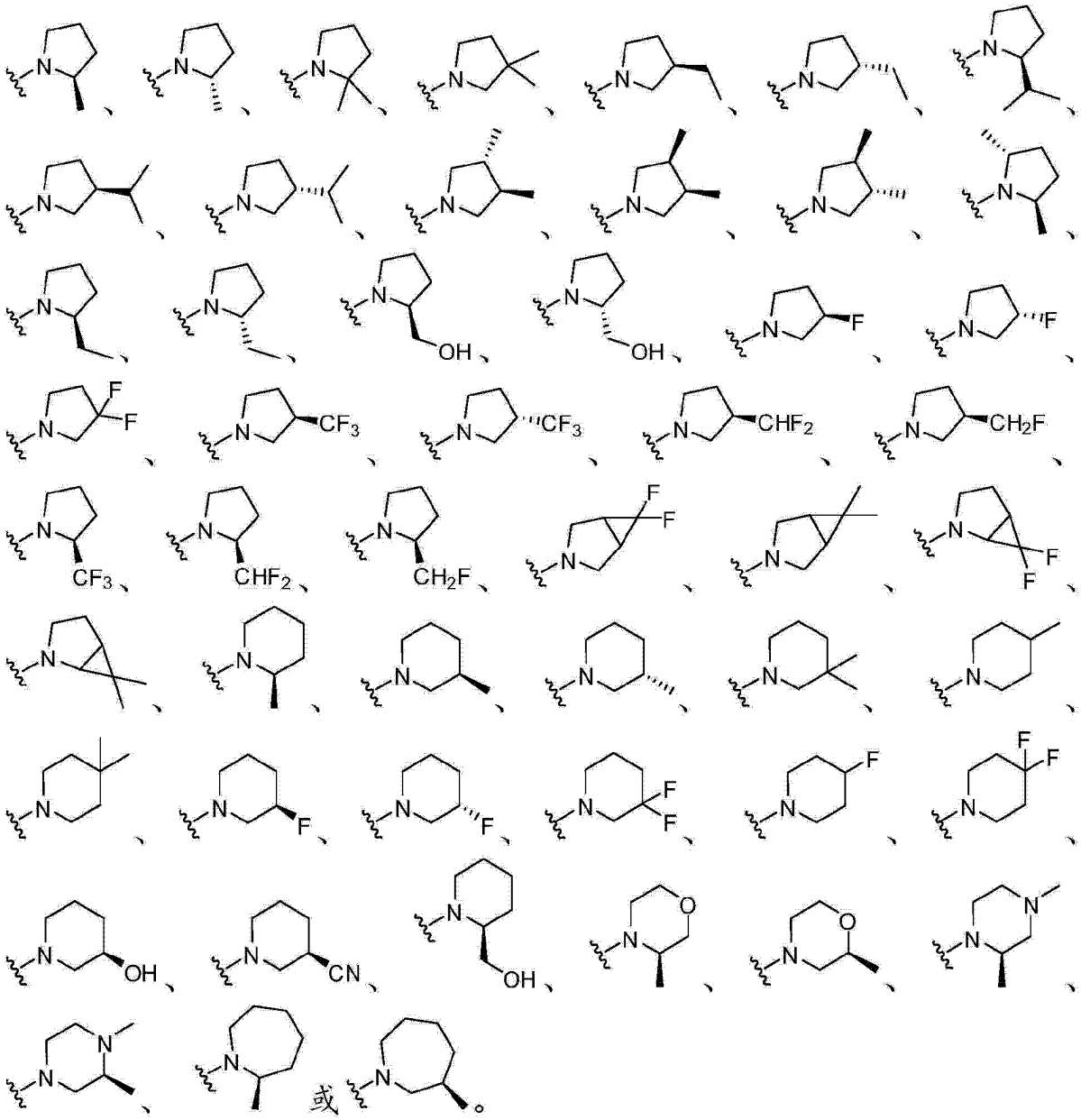


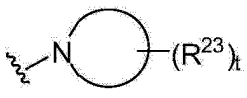
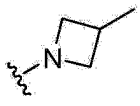
[0142] 在一些实施方案中，各个 R^{23} 独立地选自 F、Cl、-CN、-OH、$-CH_3$、$-CH_2CH_3$、$-CH(CH_3)_2$、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$、$-CF(CH_3)_2$、$-OCF_3$、$-OCH_2CF_3$、$-OCH_3$、$-OCH_2CH_3$、$-CH_2OCH_3$、$-CH_2OCH_2CH_3$ 和 $-CH_2OH$。在一些实施方案中，各个 R^{23} 独立地选自 F、Cl、-CN、-OH、$-CH_3$、$-CH_2CH_3$、$-CH(CH_3)_2$、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$、$-CF(CH_3)_2$、$-OCF_3$、$-OCH_2CF_3$、$-OCH_3$、$-OCH_2CH_3$、$-CH_2OCH_3$、$-CH_2OCH_2CH_3$ 和 $-CH_2OH$，条件是至少一个 R^{23} 是 F 或氟烷基。

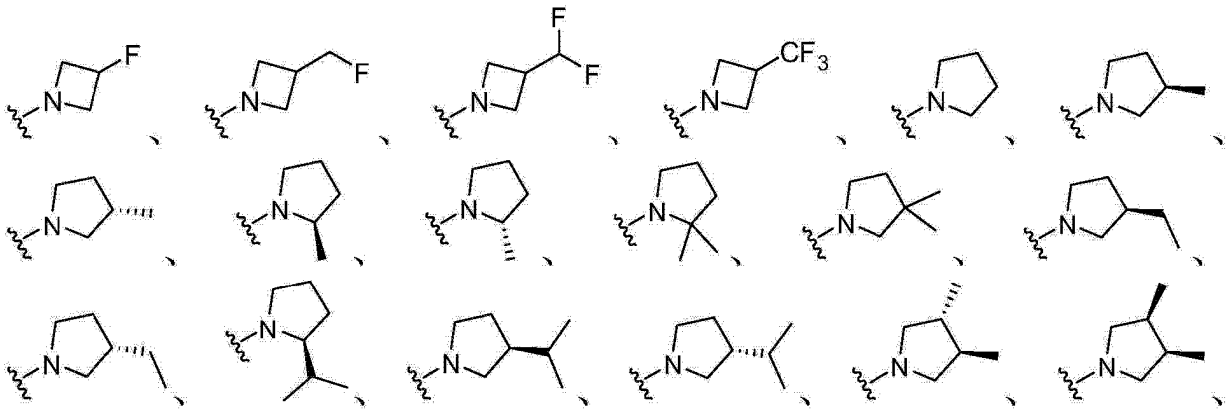
[0143] 在一些实施方案中，各个 R^{23} 独立地选自 F、Cl、-CN、-OH、$-CH_3$、$-CH_2CH_3$、$-CH(CH_3)_2$、$-CF_3$、$-CH_2CF_3$、$-OCF_3$、$-OCH_2CF_3$、$-OCH_3$、$-OCH_2CH_3$、$-CH_2OCH_3$、$-CH_2OCH_2CH_3$ 和 $-CH_2OH$。

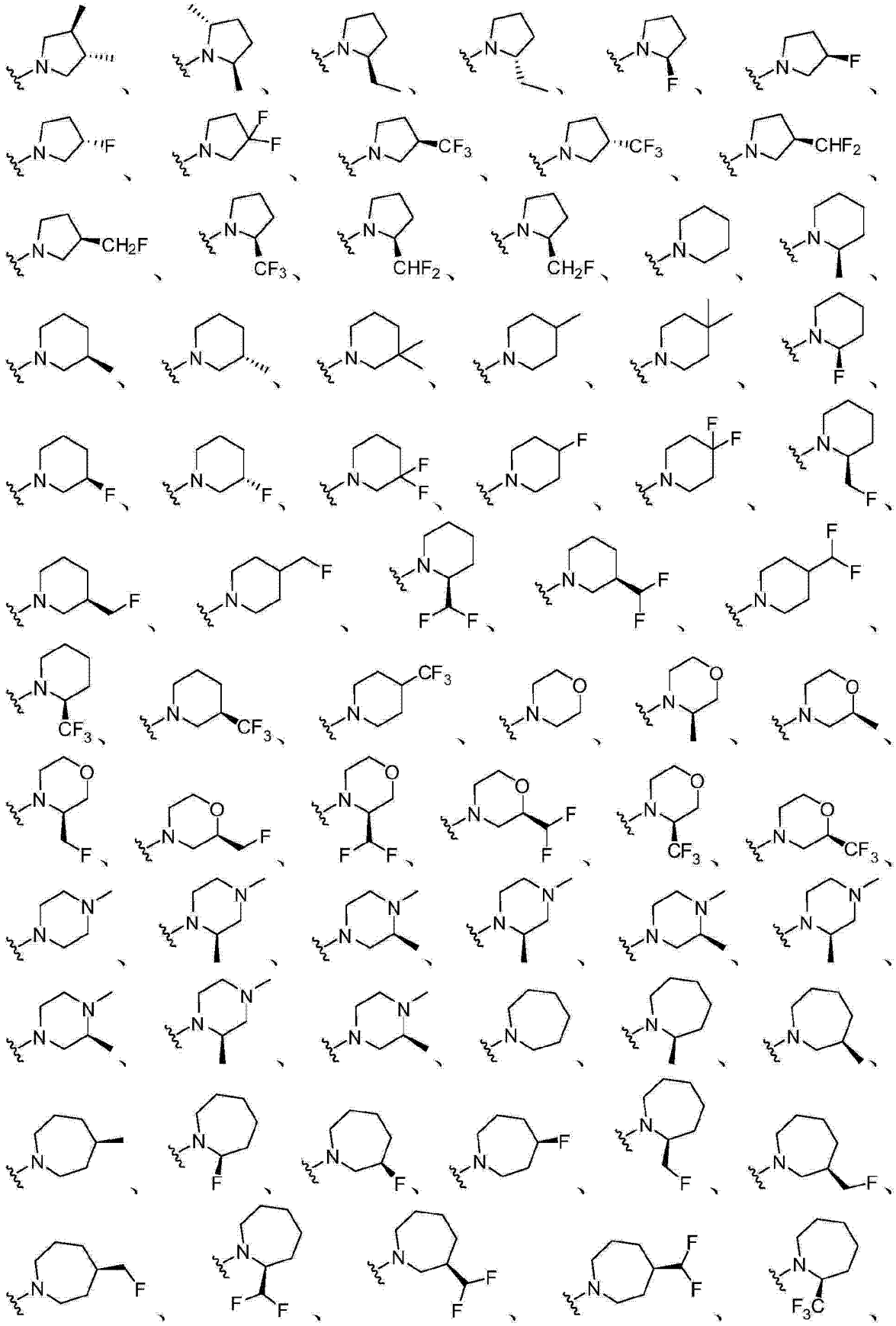
[0144] 在一些实施方案中，各个 R^{23} 独立地选自 F、$-CH_3$、$-CH_2CH_3$、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。在一些实施方案中，各个 R^{23} 独立地选自 $-CH_3$、$-CH_2CH_3$、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。

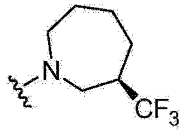
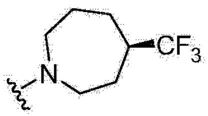
[0145] 在一些实施方案中，各个 R^{23} 独立地选自 F、$-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。在一些实施方案中，各个 R^{23} 独立地选自 $-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。在一些实施方案中，各个 R^{23} 独立地选自 $-CH_2F$。

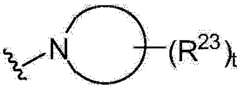
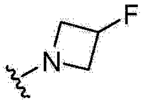
[0146] 在一些实施方案中，  是  、  、  。

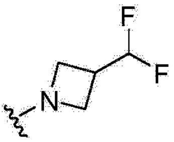
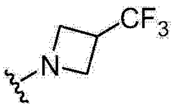
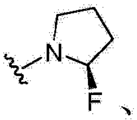
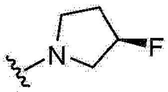
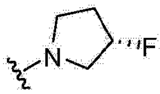
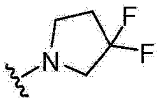
[0147] 在一些实施方案中，  是  、  、

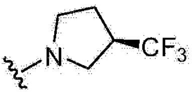
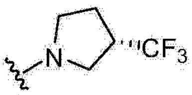
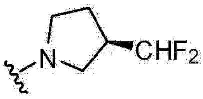
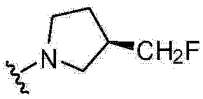
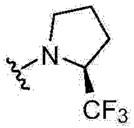


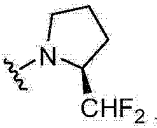
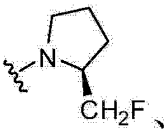
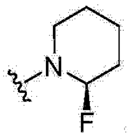
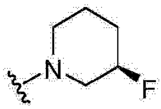
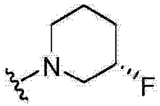
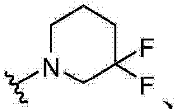


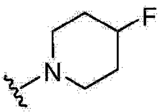
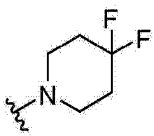
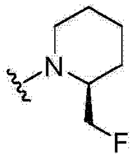
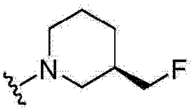
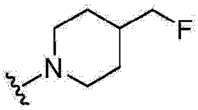
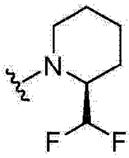
 或  。

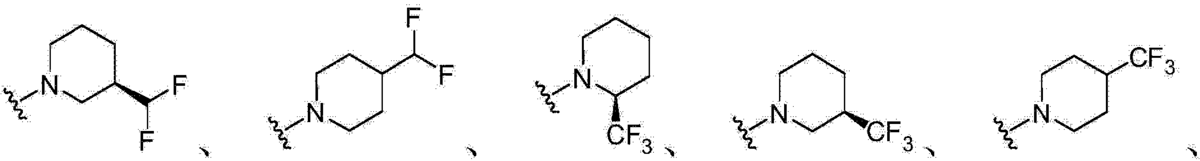
[0148] 在一些实施方案中，  是  、  、

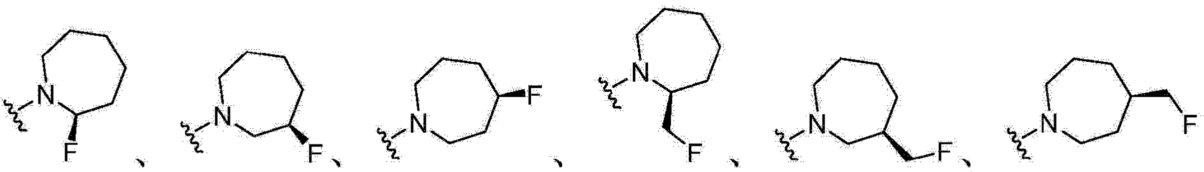
 、  、  、  、  、  、

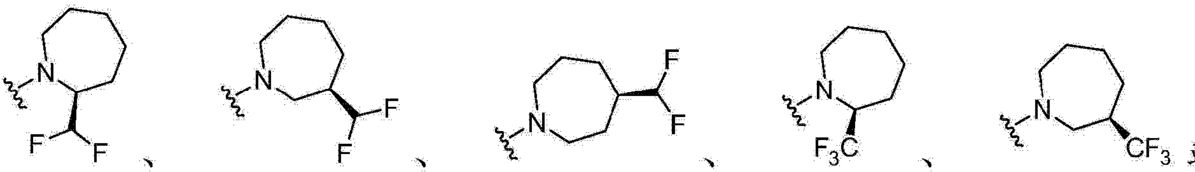
 、  、  、  、  、

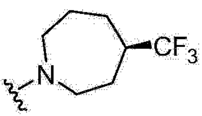
 、  、  、  、  、  、

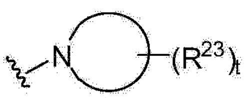
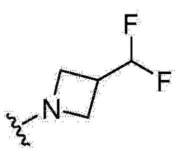
 、  、  、  、  、  、

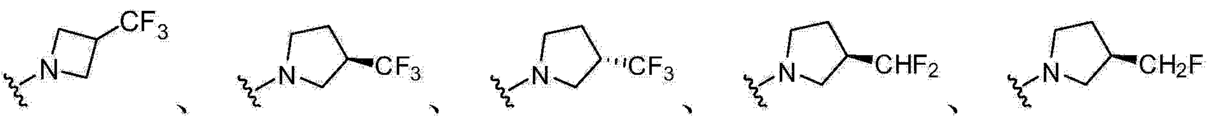
 、

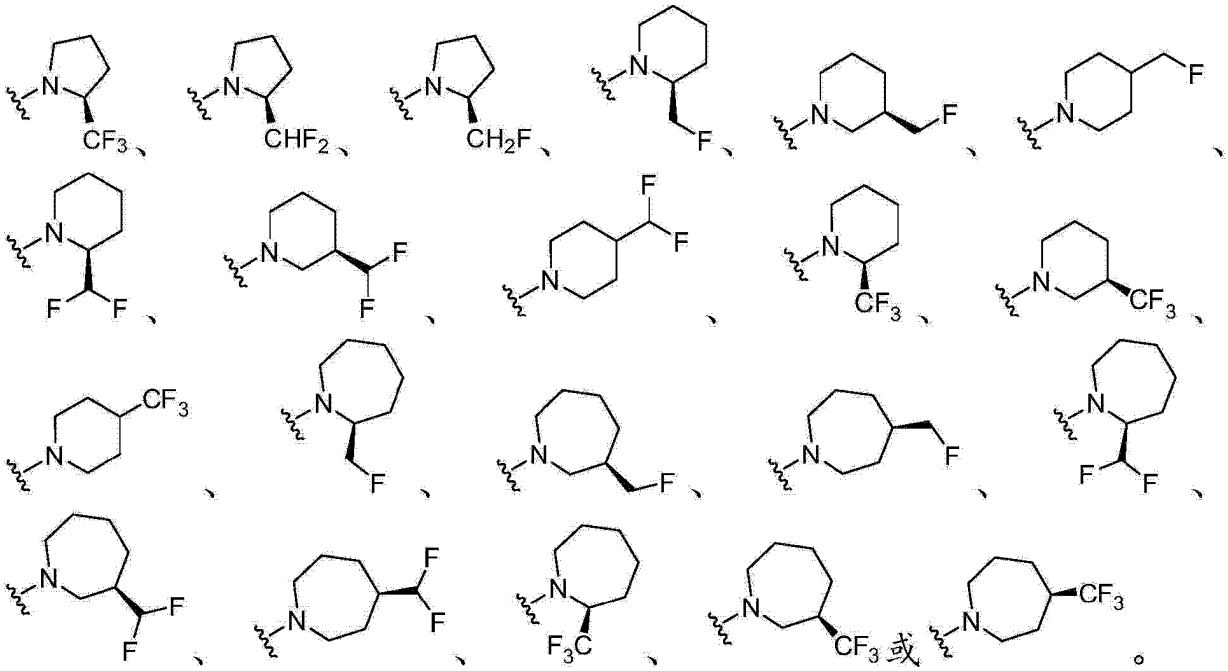
 、

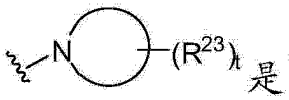
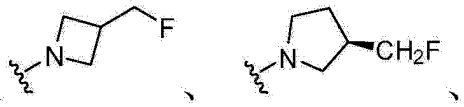
 或

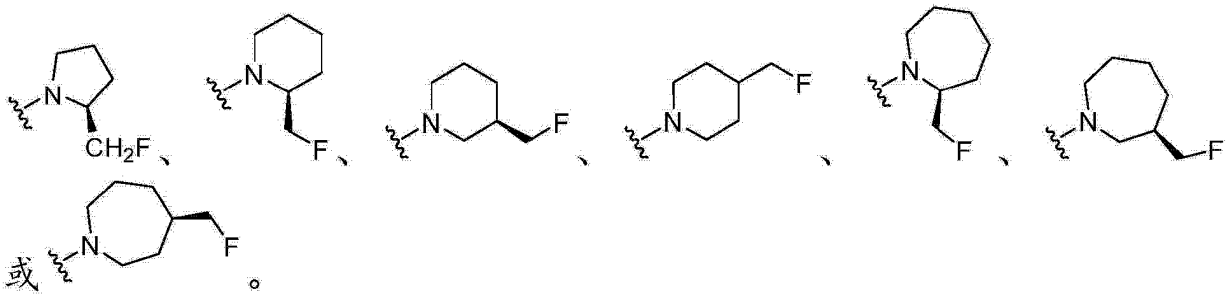
 。

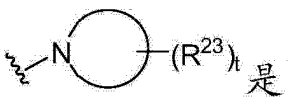
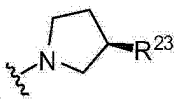
[0149] 在一些实施方案中，  是  、  、

 、



[0150] 在一些实施方案中，  是  。



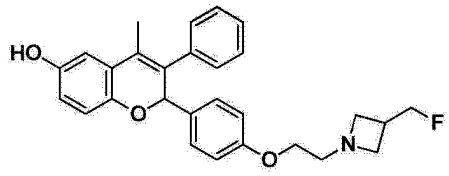
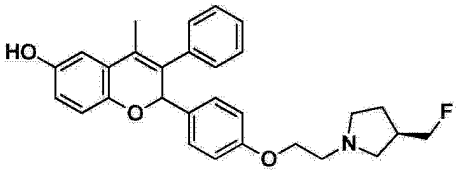
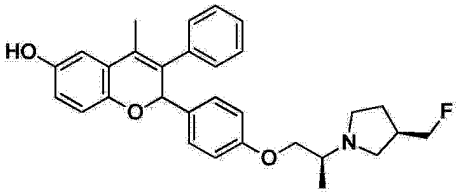
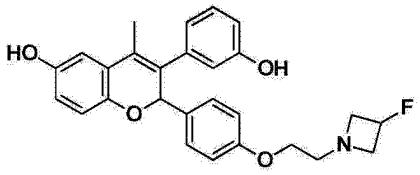
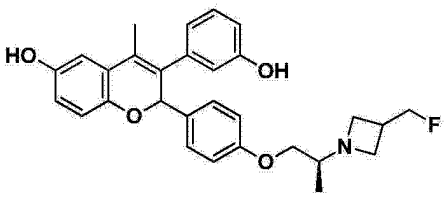
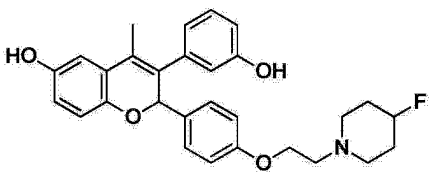
[0151] 在一些实施方案中，  是  。在一些实施方案中，R^{23} 是 $-CH_3$。在一些实施方案中，R^{23} 是 $-CH_2F$。

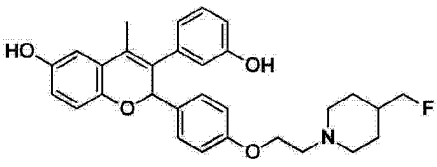
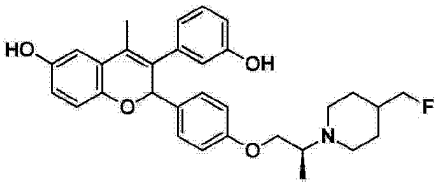
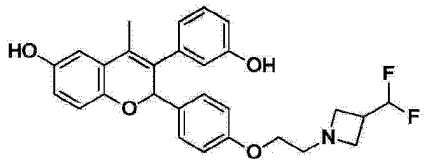
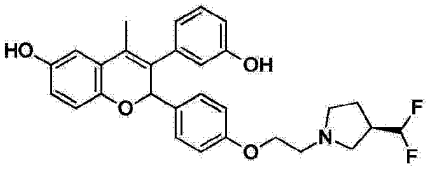
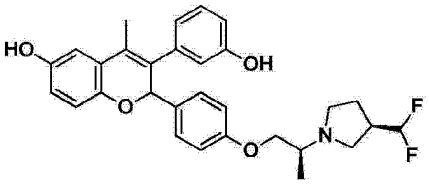
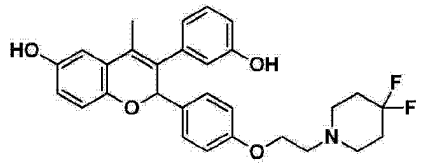
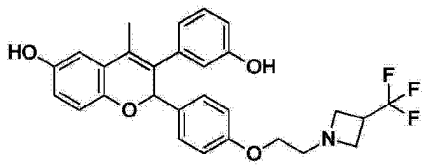
[0152] 在一些实施方案中，R^2 和 R^3 与它们所连接的 N 原子一起形成取代或未取代的吡咯烷基。

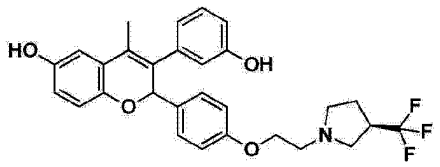
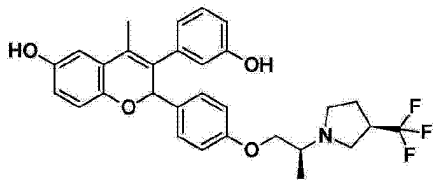
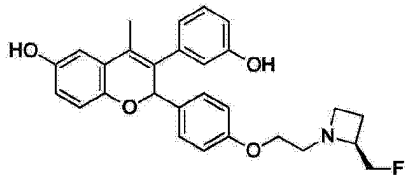
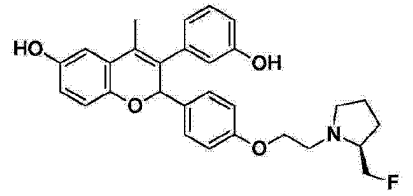
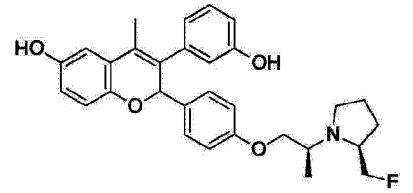
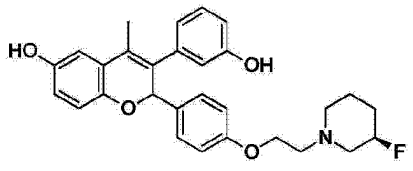
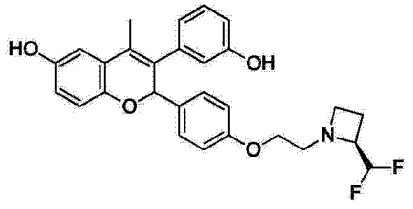
[0153] 在一些实施方案中，R^1 是 H 或 $-CH_3$；R^4 是 $-CH_3$。在一些实施方案中，R^1 是 $-CH_3$；R^4 是 $-CH_3$。

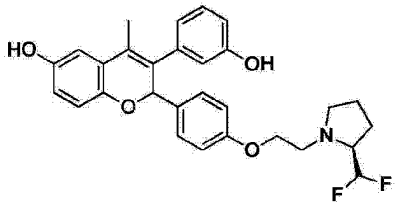
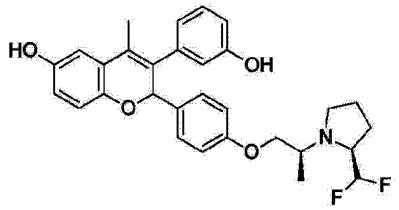
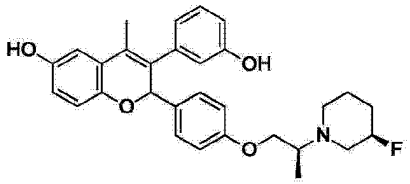
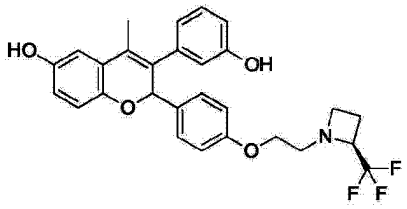
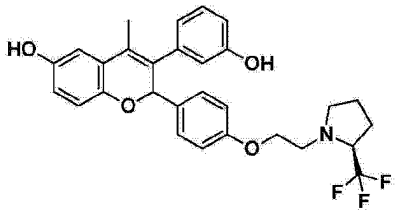
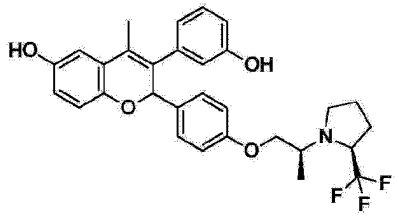
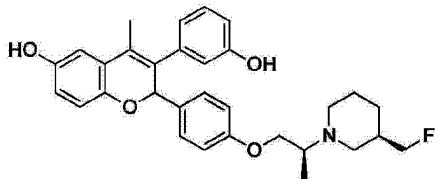
[0154] 式 (I)、(II)、(III) 或 (IV) 的化合物包括但不限于下表中的化合物。

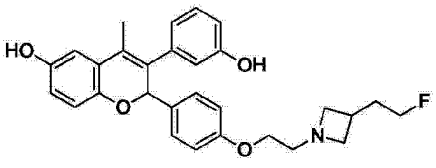
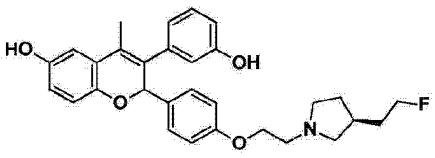
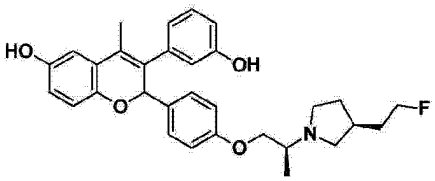
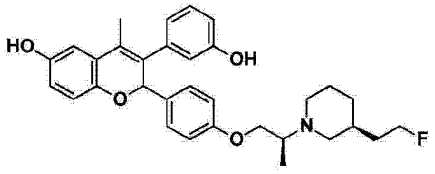
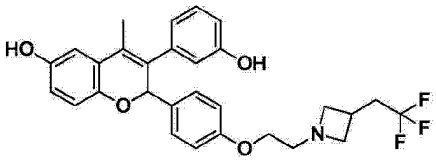
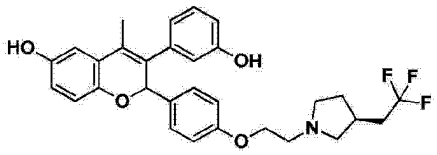
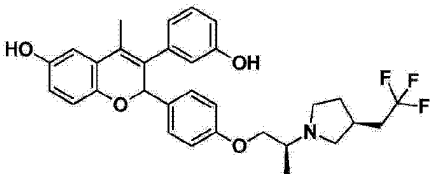
表 1

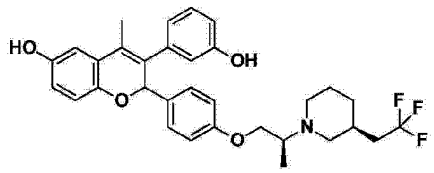
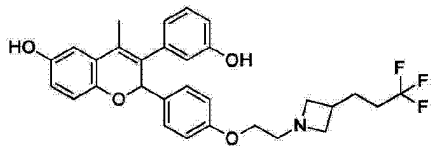
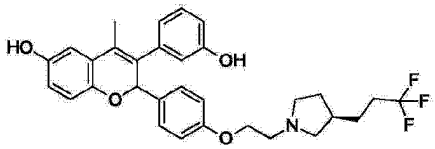
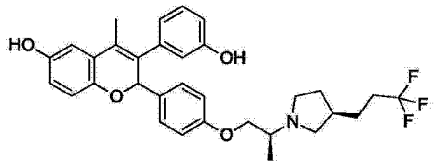
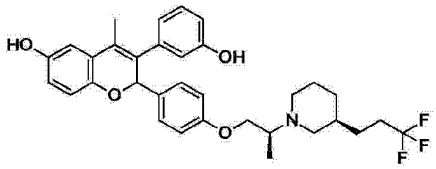
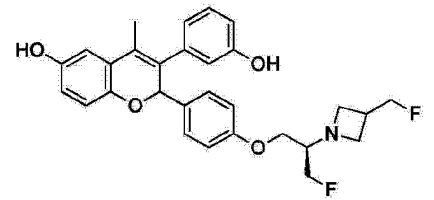
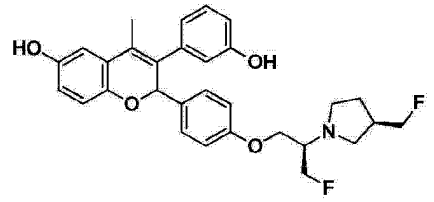
结构	名称
	2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-3-苯基-2H-苯并吡喃-6-醇
	2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-3-苯基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-3-苯基-2H-苯并吡喃-6-醇
	2-(4-(2-(3-氟氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-(3-(氟甲基)氮杂环丁-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(4-氟哌啶-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	2-(4-(2-(4-(氟甲基)哌啶-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-(4-(氟甲基)哌啶-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(3-(二氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((R)-3-(二氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(二氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(4,4-二氟哌啶-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-(2-(3-(三氟甲基)氮杂环丁-1-基)乙氧基)苯基)-2H-苯并吡喃-6-醇

结构	名称
	3-(3-羟基苯基)-4-甲基-2-(4-(2-((R)-3-(三氟甲基)吡咯烷-1-基)乙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-((S)-2-((R)-3-(三氟甲基)吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	2-(4-(2-((S)-2-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((S)-2-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((S)-2-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((R)-3-氟哌啶-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((S)-2-(二氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	2-(4-(2-((S)-2-(二氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((S)-2-(二氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-氟哌啶-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-(2-((S)-2-(三氟甲基)氮杂环丁-1-基)乙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-(2-((S)-2-(三氟甲基)吡咯烷-1-基)乙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-((S)-2-((S)-2-(三氟甲基)吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(氟甲基)哌啶-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	2-(4-(2-(3-(2-氟乙基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((S)-3-(2-氟乙基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((S)-3-(2-氟乙基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((S)-3-(2-氟乙基)哌啶-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-(2-(3-(2,2,2-三氟乙基)氮杂环丁-1-基)乙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-(2-((S)-3-(2,2,2-三氟乙基)吡咯烷-1-基)乙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-((S)-2-((S)-3-(2,2,2-三氟乙基)吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇

结构	名称
	3-(3-羟基苯基)-4-甲基-2-(4-((S)-2-((S)-3-(2,2,2-三氟乙基)哌啶-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-(2-(3-(3,3,3-三氟丙基)氮杂环丁-1-基)乙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-(2-((R)-3-(3,3,3-三氟丙基)吡咯烷-1-基)乙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-((S)-2-((R)-3-(3,3,3-三氟丙基)吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-((S)-2-((S)-3-(3,3,3-三氟丙基)哌啶-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	2-(4-((R)-3-氟-2-(3-(氟甲基)氮杂环丁-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((R)-3-氟-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

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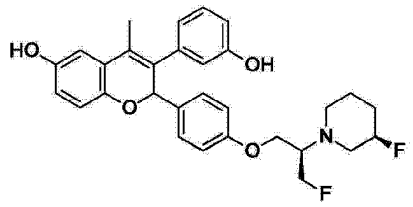
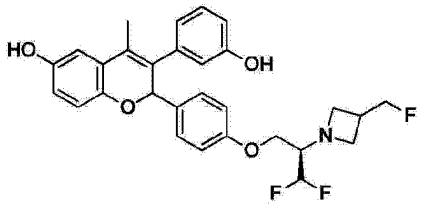
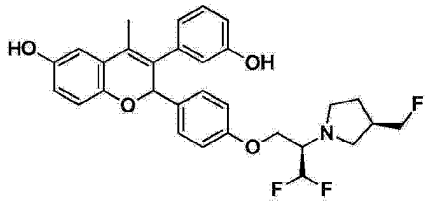
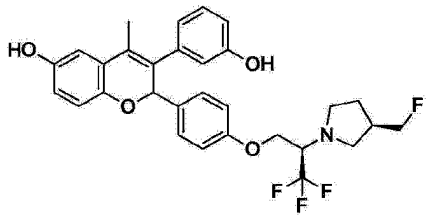
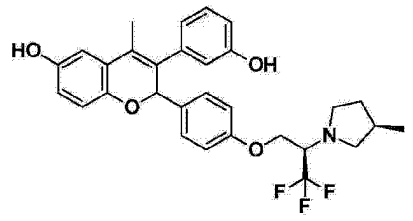
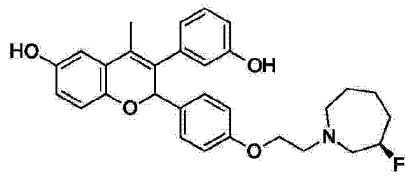
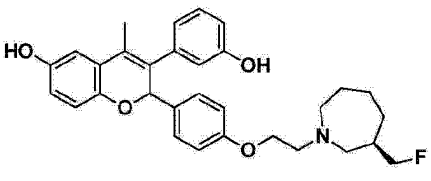
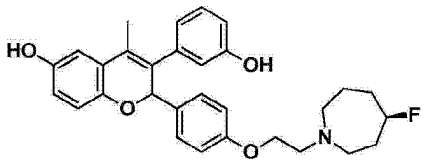
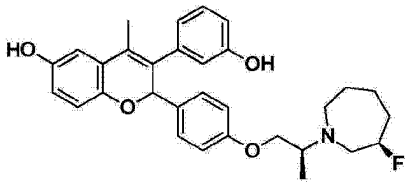
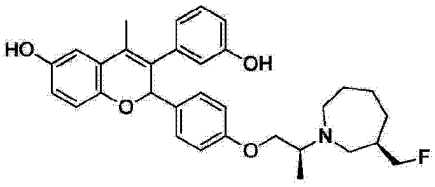
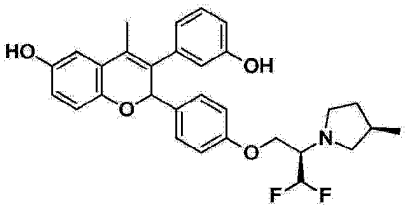
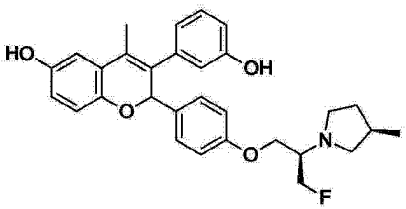
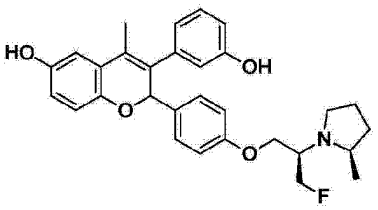
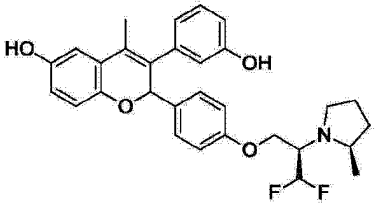
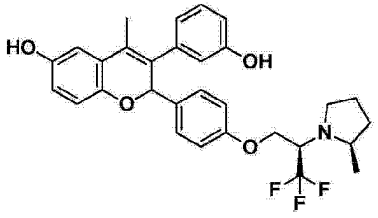
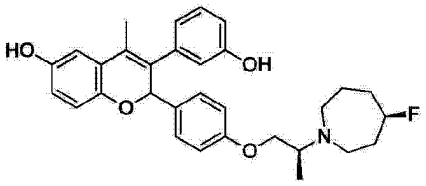
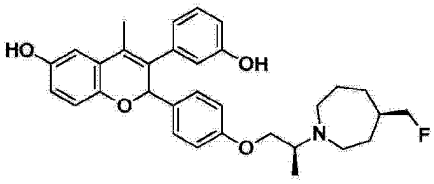
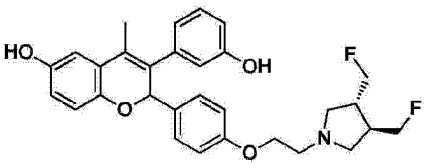
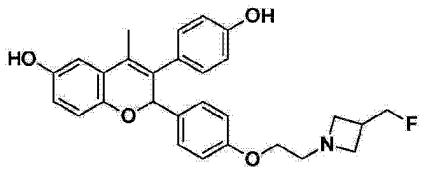
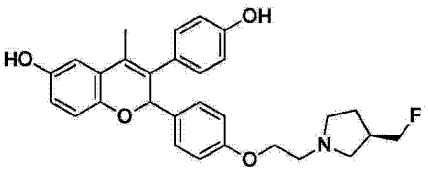
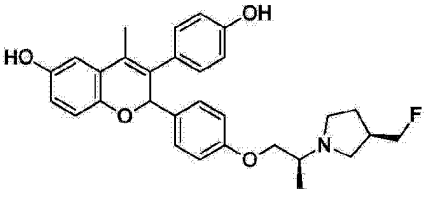
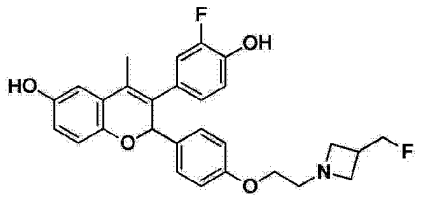
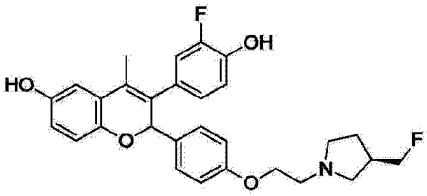
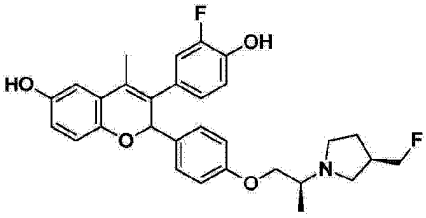
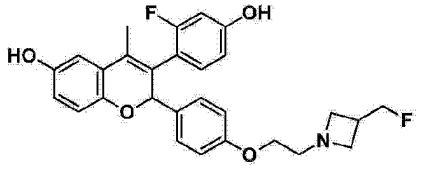
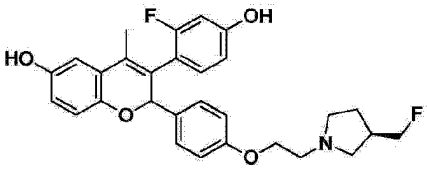
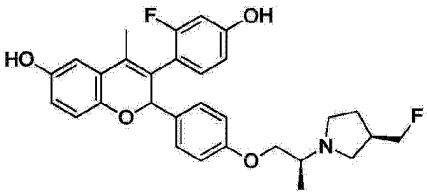
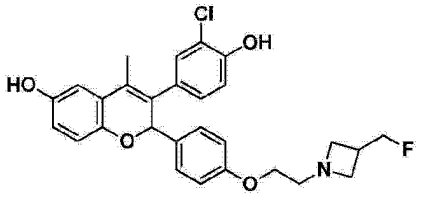
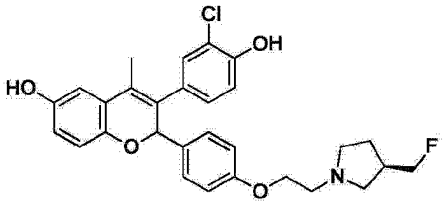
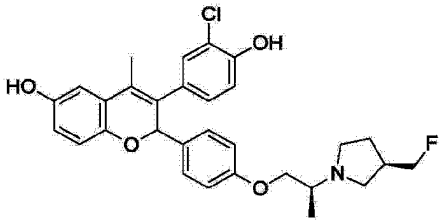
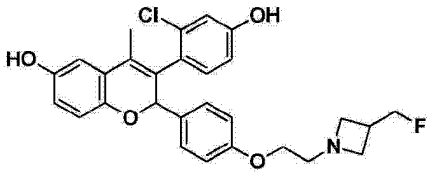
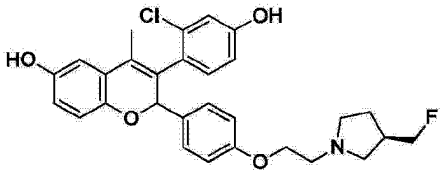
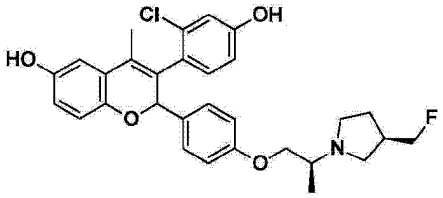
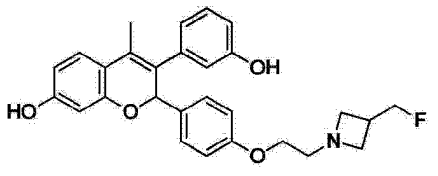
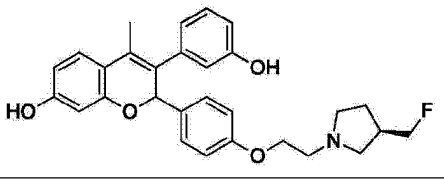
	2-(4-((R)-3-氟-2-((R)-3-氟哌啶-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((R)-3,3-二氟-2-(3-(氟甲基)氮杂环丁-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((R)-3,3-二氟-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-((R)-3,3,3-三氟-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-((R)-3,3,3-三氟-2-((R)-3-甲基吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	2-(4-(2-((R)-3-氟氮杂环庚-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((R)-3-(氟甲基)氮杂环庚-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	2-(4-(2-((R)-4-氟氮杂环庚-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-氟氮杂环庚-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(氟甲基)氮杂环庚-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((R)-3,3-二氟-2-((R)-3-甲基吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((R)-3-氟-2-((R)-3-甲基吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((R)-3-氟-2-((R)-2-甲基吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((R)-3,3-二氟-2-((R)-2-甲基吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	3-(3-羟基苯基)-4-甲基-2-(4-((R)-3,3,3-三氟-2-((R)-2-甲基吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-4-氟氮杂环庚-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-4-(氟甲基)氮杂环庚-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((3R,4R)-3,4-双(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(4-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(4-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(4-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	3-(3-氟-4-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氟-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氟-4-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氟-4-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氟-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氟-4-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯-4-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	3-(3-氯-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯-4-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氯-4-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氯-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氯-4-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-7-醇
	2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-7-醇

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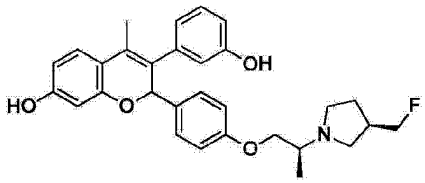
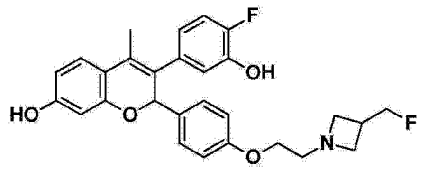
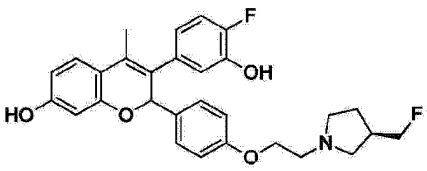
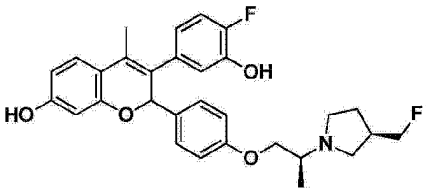
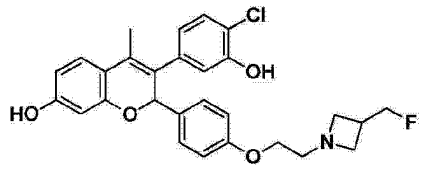
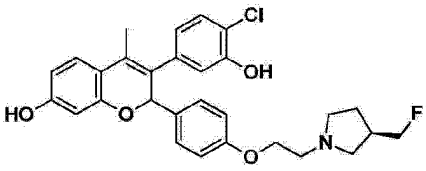
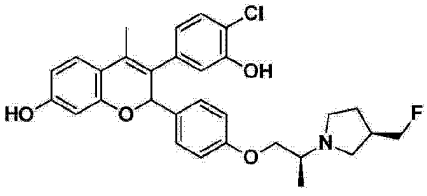
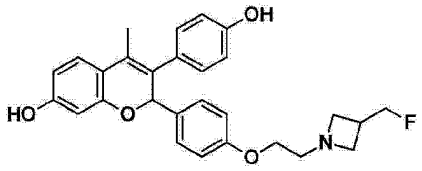
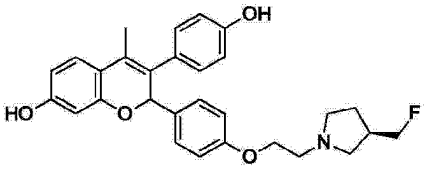
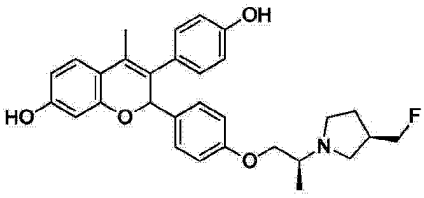
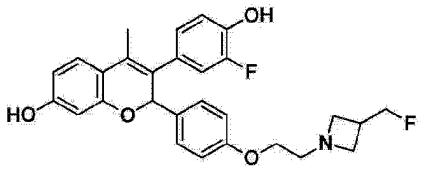
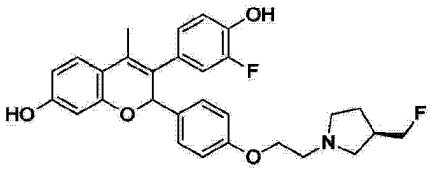
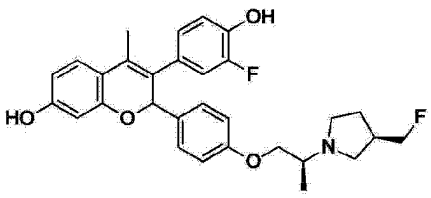
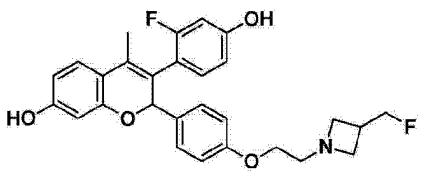
	2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(4-氟-3-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(4-氟-3-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(4-氟-3-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(4-氯-3-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(4-氯-3-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(4-氯-3-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇

结构	名称
	2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(4-羟基苯基)-4-甲基-2H-苯并吡喃-7-醇
	2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(4-羟基苯基)-4-甲基-2H-苯并吡喃-7-醇
	2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(4-羟基苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(3-氟-4-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(3-氟-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(3-氟-4-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(2-氟-4-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇

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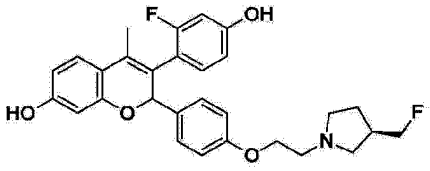
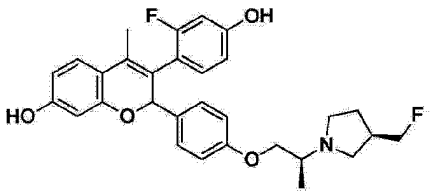
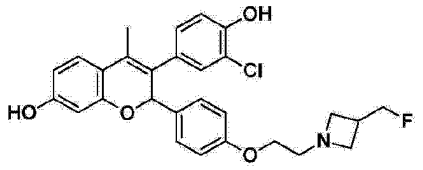
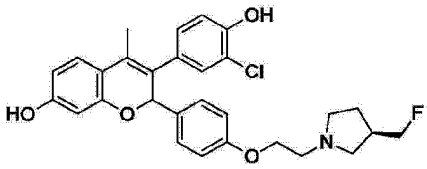
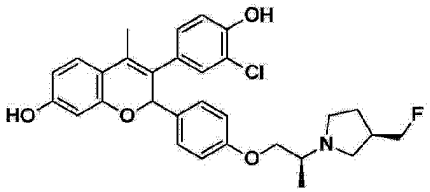
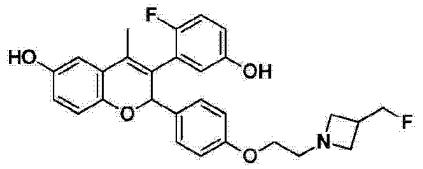
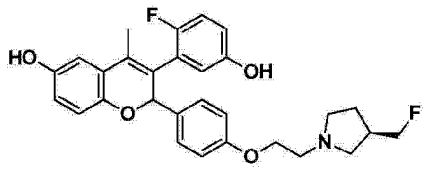
	3-(2-氟-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(2-氟-4-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(3-氯-4-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(3-氯-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(3-氯-4-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-7-醇
	3-(2-氟-5-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氟-5-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇

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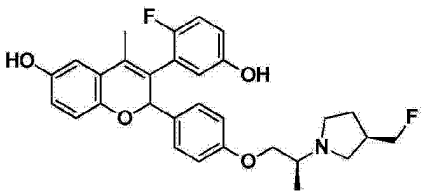
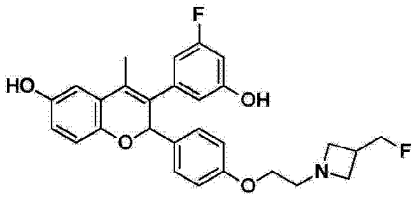
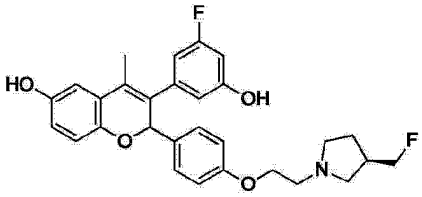
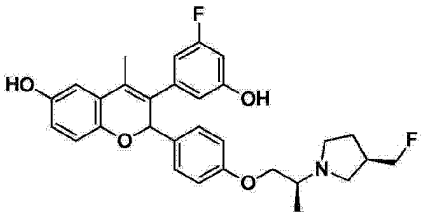
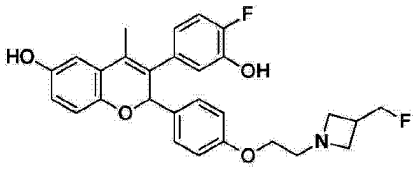
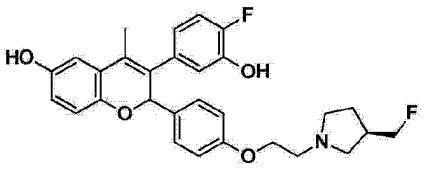
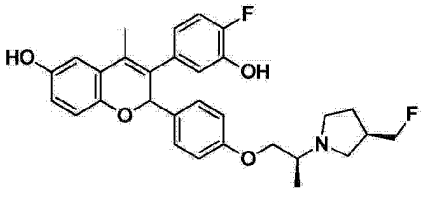
	3-(2-氟-5-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氟-5-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氟-5-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氟-5-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(4-氟-3-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(4-氟-3-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(4-氟-3-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇

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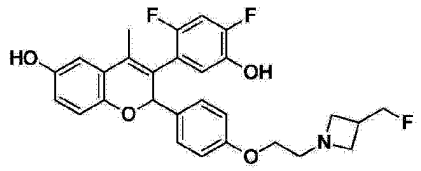
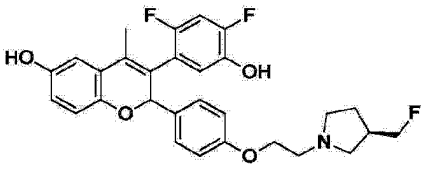
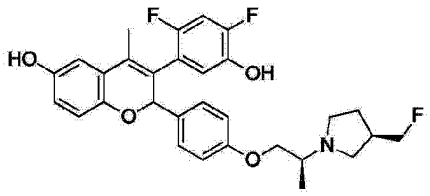
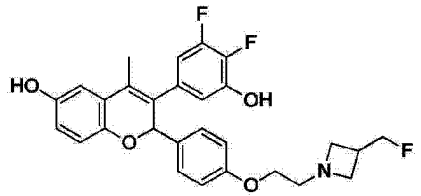
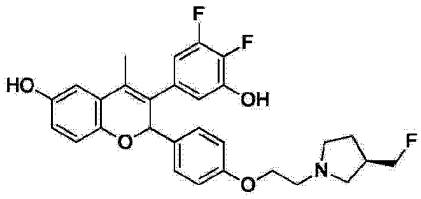
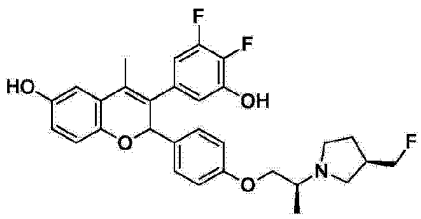
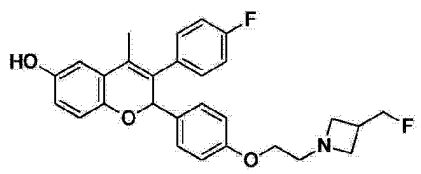
	3-(2,4-二氟-5-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2,4-二氟-5-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2,4-二氟-5-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3,4-二氟-5-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3,4-二氟-5-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3,4-二氟-5-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(4-氟苯基)-4-甲基-2H-苯并吡喃-6-醇

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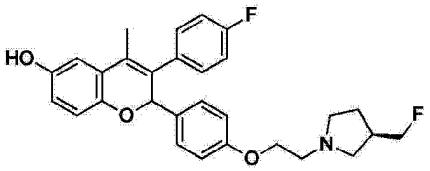
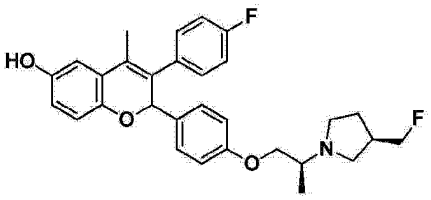
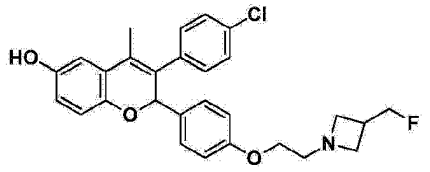
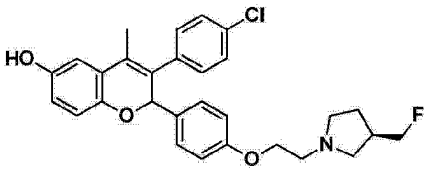
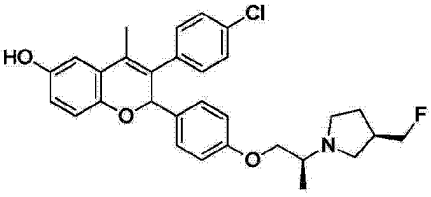
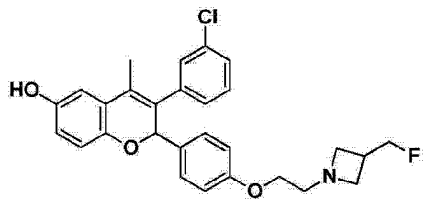
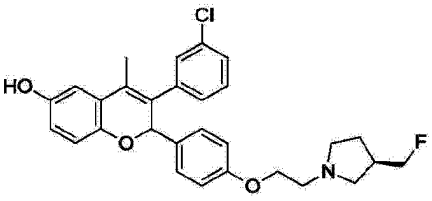
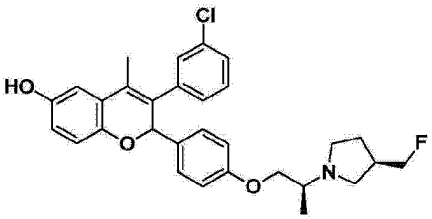
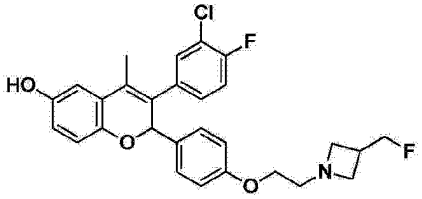
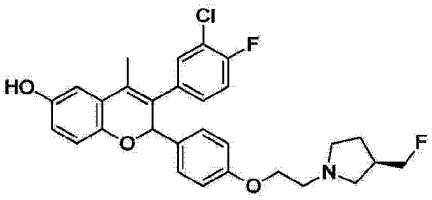
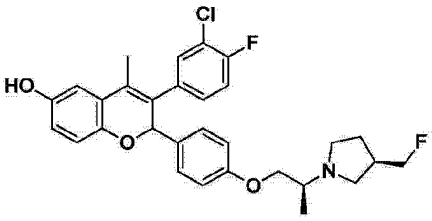
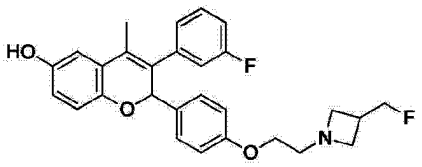
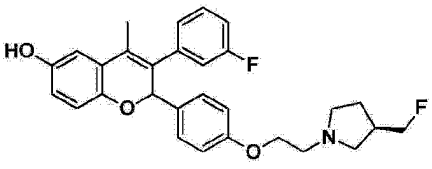
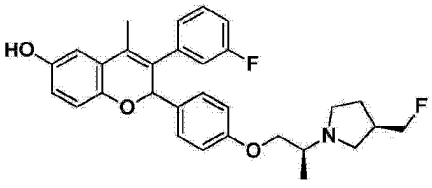
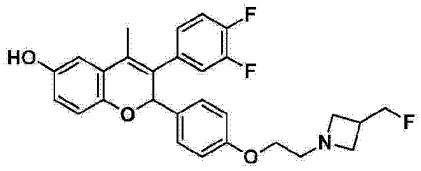
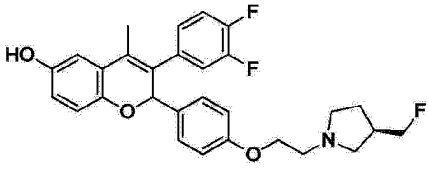
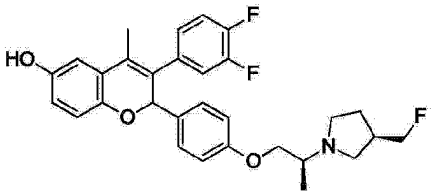
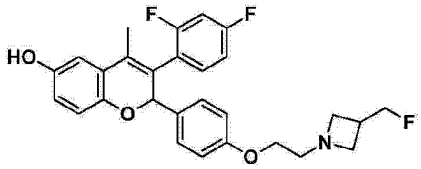
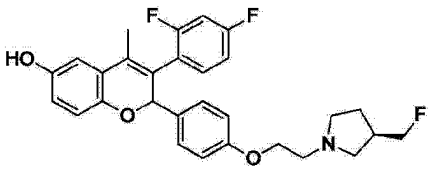
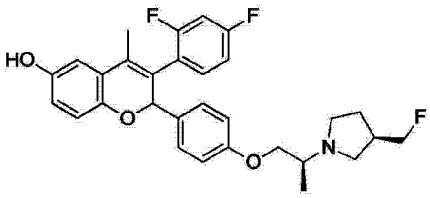
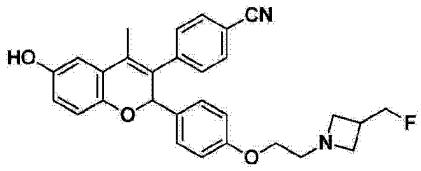
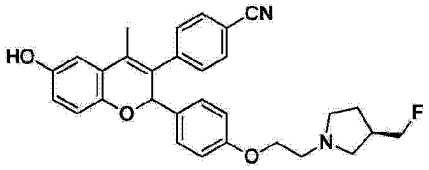
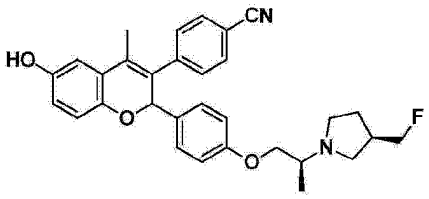
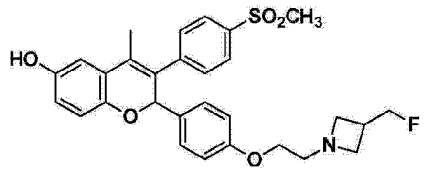
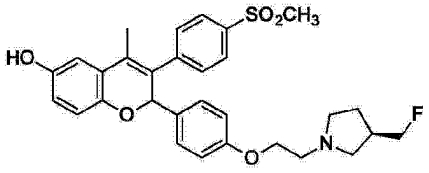
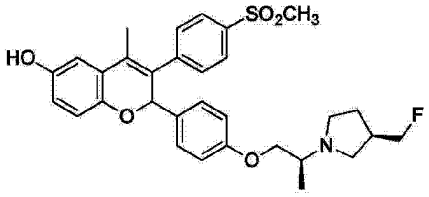
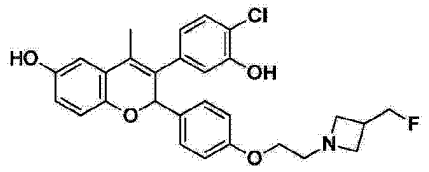
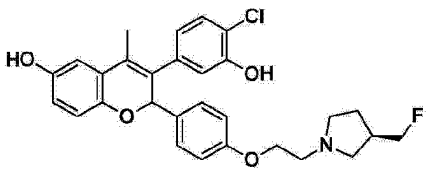
	2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(4-氟苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(4-氟苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(4-氯苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(4-氯苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(4-氯苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	3-(3-氯苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯-4-氟苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯-4-氟苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯-4-氟苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-氟苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-氟苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-氟苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	3-(3,4-二氟苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3,4-二氟苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3,4-二氟苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2,4-二氟苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2,4-二氟苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2,4-二氟苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	4-(2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-6-羟基-4-甲基-2H-苯并吡喃-3-基)苄腈

结构	名称
	4-(2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-6-羟基-4-甲基-2H-苯并吡喃-3-基)苄腈
	4-(2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-6-羟基-4-甲基-2H-苯并吡喃-3-基)苄腈
	2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-3-(4-(甲基磺酰基)苯基)-2H-苯并吡喃-6-醇
	2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-3-(4-(甲基磺酰基)苯基)-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-3-(4-(甲基磺酰基)苯基)-2H-苯并吡喃-6-醇
	3-(4-氯-3-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(4-氯-3-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇

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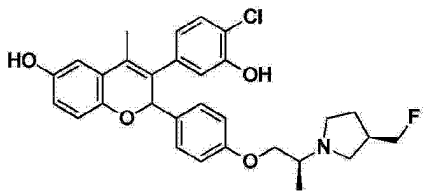
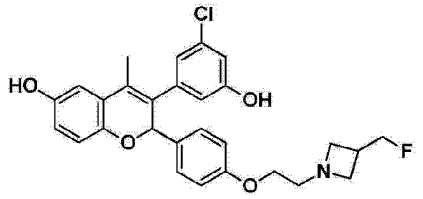
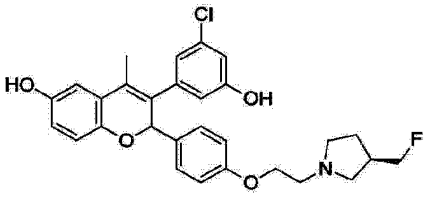
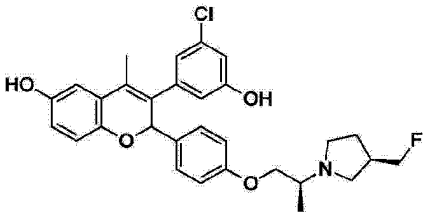
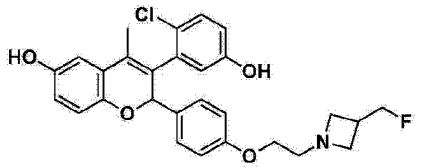
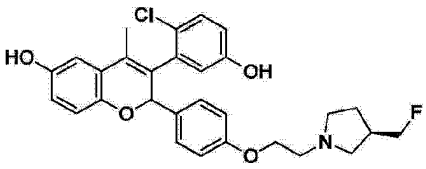
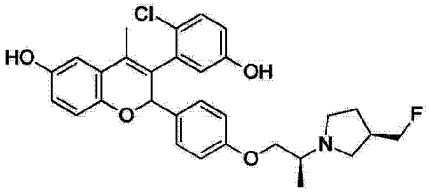
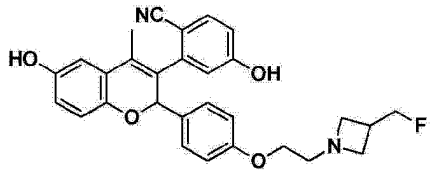
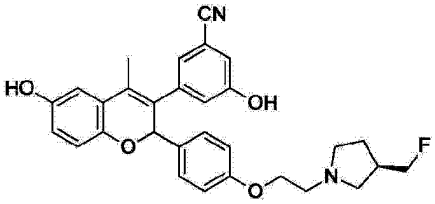
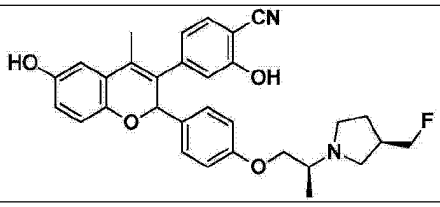
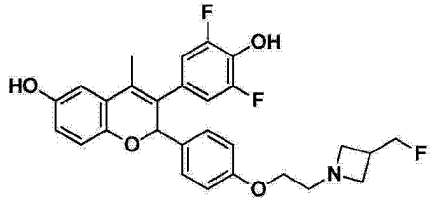
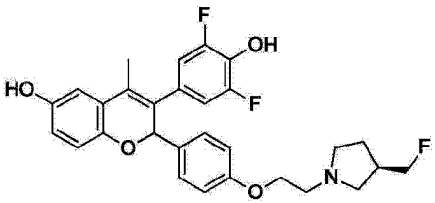
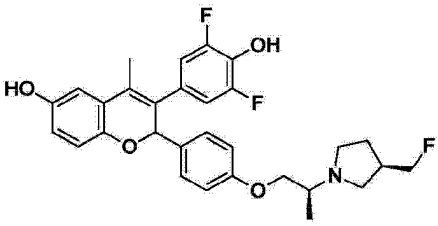
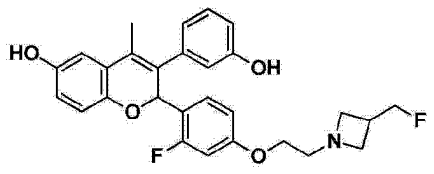
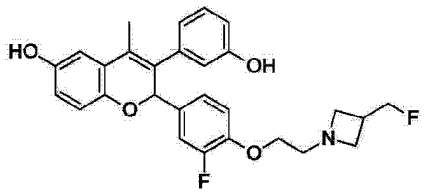
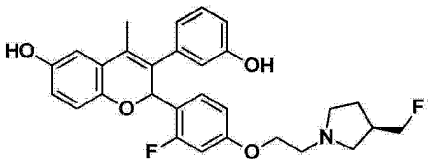
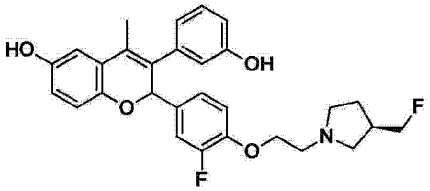
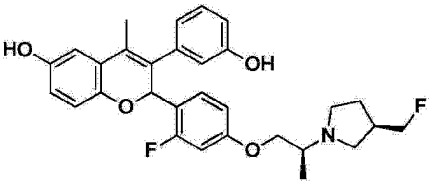
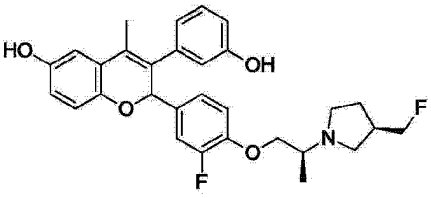
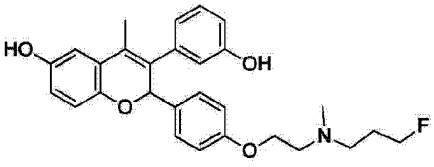
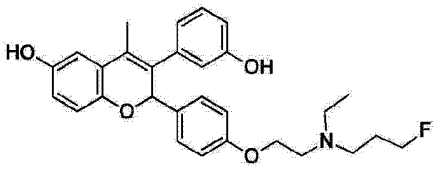
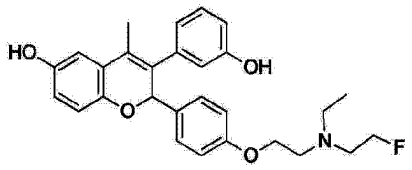
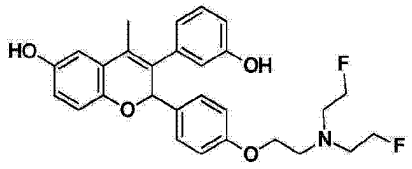
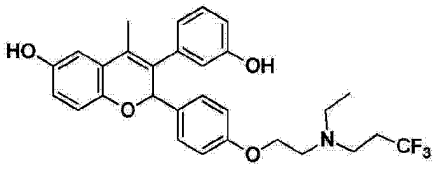
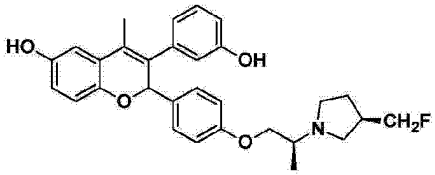
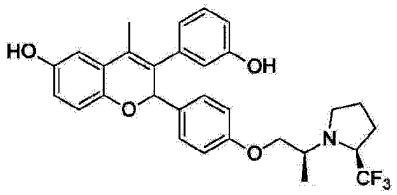
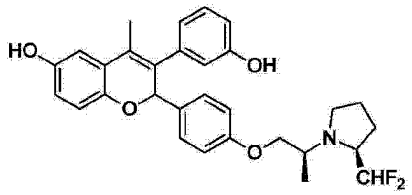
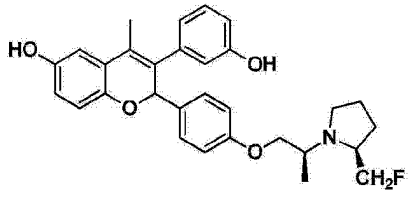
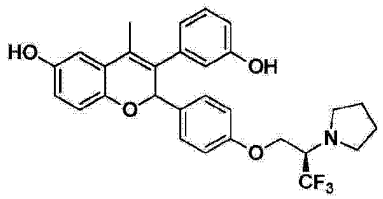
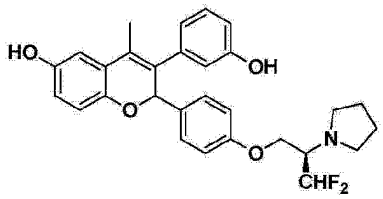
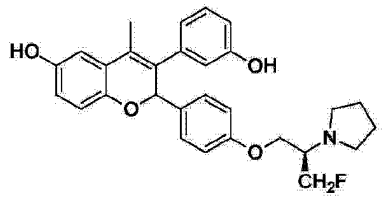
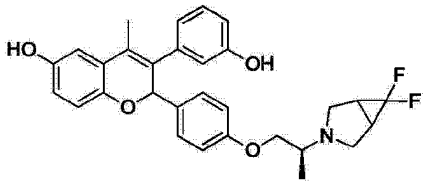
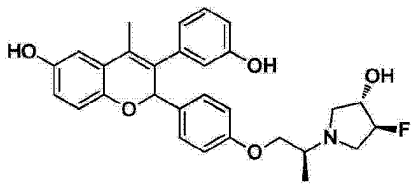
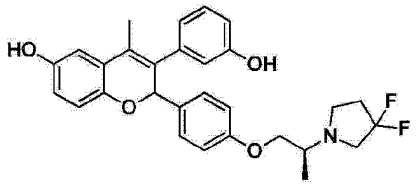
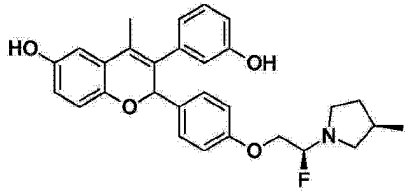
	3-(4-氯-3-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯-5-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯-5-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氯-5-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氯-5-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氯-5-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氯-5-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	2-(2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-6-羟基-4-甲基-2H-苯并吡喃-3-基)-4-羟基苄腈
	3-(2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-6-羟基-4-甲基-2H-苯并吡喃-3-基)-5-羟基苄腈
	4-(2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-6-羟基-4-甲基-2H-苯并吡喃-3-基)-2-羟基苄腈
	3-(3,5-二氟-4-羟基苯基)-2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3,5-二氟-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3,5-二氟-4-羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(2-氟-4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	2-(3-氟-4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(2-氟-4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(3-氟-4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(2-氟-4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(3-氟-4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-((3-氟丙基)(甲基)氨基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(乙基(3-氟丙基)氨基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	2-(4-(2-(乙基(2-氟乙基)氨基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(双(2-氟乙基)氨基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(2-(乙基(3,3,3-三氟丙基)氨基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-羟基苯基)-4-甲基-2-(4-((S)-2-((S)-2-(三氟甲基)吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((S)-2-(二氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-((S)-2-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

结构	名称
	3-(3-羟基苯基)-4-甲基-2-(4-((R)-3,3,3-三氟-2-(吡咯烷-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇
	2-(4-((R)-3,3-二氟-2-(吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((R)-3-氟-2-(吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((2S)-2-(6,6-二氟-3-氮杂双环[3.1.0]己烷-3-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	(3S,4S)-4-氟-1-((2S)-1-(4-(6-羟基-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-2-基)苯氧基)丙烷-2-基)吡咯烷-3-醇
	2-(4-((S)-2-(3,3-二氟吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-氟-2-((R)-3-甲基吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

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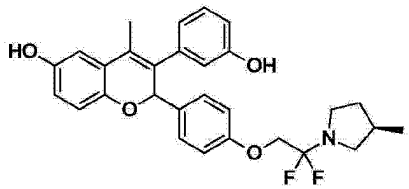
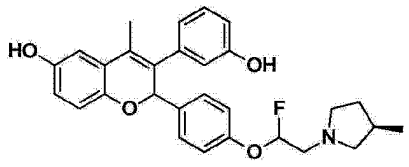
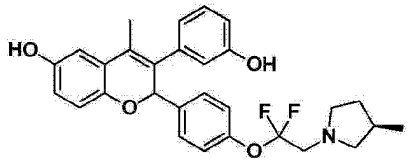
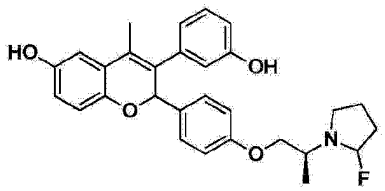
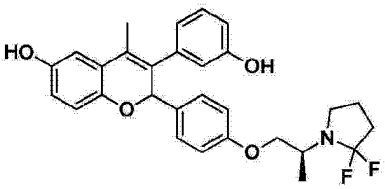
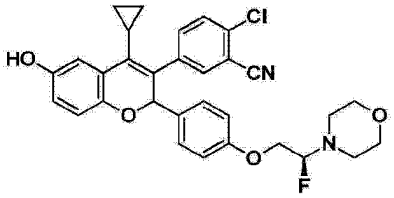
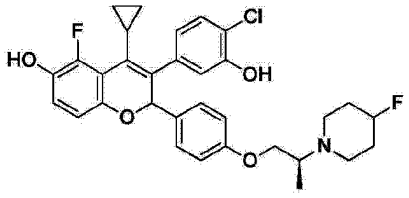
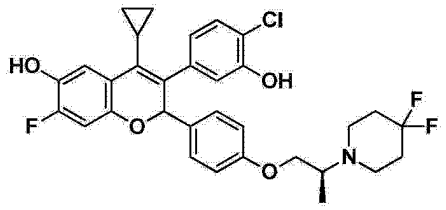
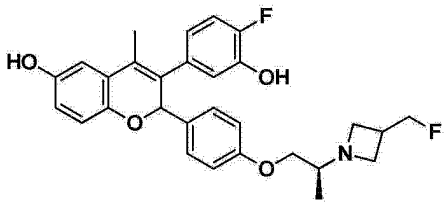
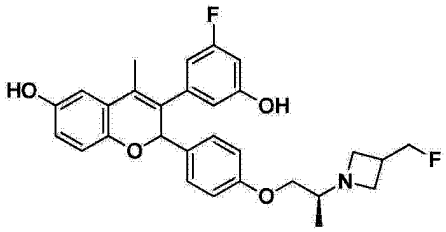
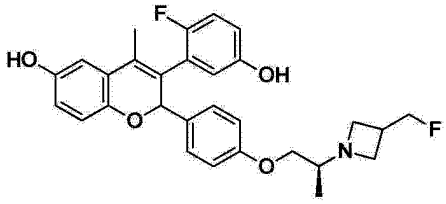
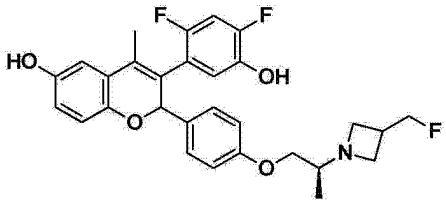
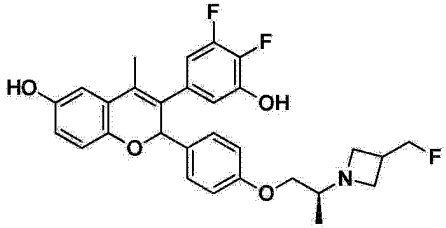
	2-(4-(2,2-二氟-2-((R)-3-甲基吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(1-氟-2-((R)-3-甲基吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-(1,1-二氟-2-((R)-3-甲基吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((2S)-2-(2-氟吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-(4-((S)-2-(2,2-二氟吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇
	2-氯-5-(4-环丙基-2-(4-((S)-2-氟-2-吗啉基乙氧基)苯基)-6-羟基-2H-苯并吡喃-3-基)苄腈
	3-(4-氯-3-羟基苯基)-4-环丙基-5-氟-2-(4-((S)-2-(4-氟哌啶-1-基)丙氧基)苯基)-2H-苯并吡喃-6-醇

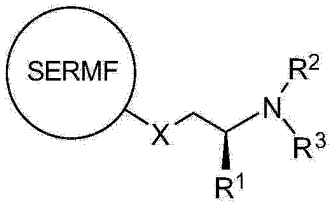
结构	名称
	3-(4-氯-3-羟基苯基)-4-环丙基-2-(4-((S)-2-(4,4-二氟哌啶-1-基)丙氧基)苯基)-7-氟-2H-苯并吡喃-6-醇
	3-(4-氟-3-羟基苯基)-2-(4-((S)-2-(3-(氟甲基)氮杂环丁-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3-氟-5-羟基苯基)-2-(4-((S)-2-(3-(氟甲基)氮杂环丁-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2-氟-5-羟基苯基)-2-(4-((S)-2-(3-(氟甲基)氮杂环丁-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(2,4-二氟-5-羟基苯基)-2-(4-((S)-2-(3-(氟甲基)氮杂环丁-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇
	3-(3,4-二氟-5-羟基苯基)-2-(4-((S)-2-(3-(氟甲基)氮杂环丁-1-基)丙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇

[0155] 在一些实施方案中，相对于 2H- 苯并吡喃化合物的 2 位上的立体化学，本文所述的任意一种 2H- 苯并吡喃化合物作为外消旋混合物存在。在其它实施方案中，相对于 2H- 苯并吡喃化合物的 2 位上的立体化学，本文所述的任意一种 2H- 苯并吡喃化合物作为单个立体异构体存在。在一些实施方案中，相对于 2H- 苯并吡喃化合物的 2 位上的立体化学，本文所述的任意一种 2H- 苯并吡喃化合物作为 (S)- 异构体存在。在一些其它实施方案中，相对

于 2H- 苯并吡喃化合物的 2 位上的立体化学，本文所述的任意一种 2H- 苯并吡喃化合物作为 (R)- 异构体存在。

[0156] 在一些实施方案中，式 (I)、(II)、(III) 或 (IV) 的化合物的药学上可接受的盐包括在前述化合物表格中的任意一种化合物的药学上可接受的盐。

[0157] 在另一方面，本文所描述的是具有式 (V) 结构的化合物或其药学上可接受的盐：



式(V)

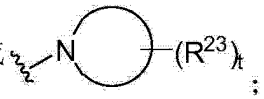
其中：

SEMF 是选择性雌激素受体调节剂片段；

R^1 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^3 是 C_1-C_6 氟烷基；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成 

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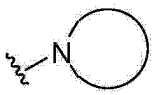


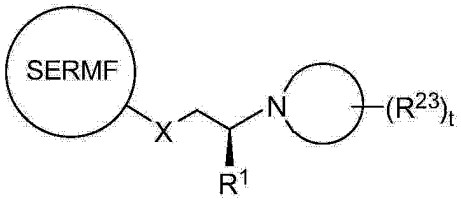
是单环 C_2-C_6 杂环烷基；

各个 R^{23} 独立地是 C_1-C_6 氟烷基或 F；

t 是 1、2、3 或 4；

X 是不存在的、-O-、-S-、-S(=O)-、-S(=O)$_2$-、-C(=O)-、-CH_2-、-NH- 或 -N(C_1-C_6 烷基)-。

[0158] 在另一方面，本文所述的是具有下述式 (VI) 结构的化合物或其药学上可接受的盐：

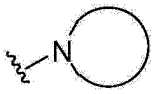


式(VI)

其中：

SEMF 是选择性雌激素受体调节剂片段；

R^1 是 C_1-C_6 氟烷基；



是单环 C_2-C_{10} 杂环烷基；

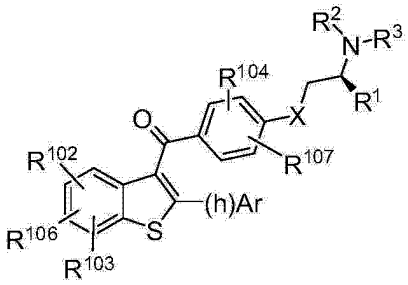
各个 R^{23} 独立地是 F、C_1-C_6 烷基或 C_1-C_6 氟烷基；

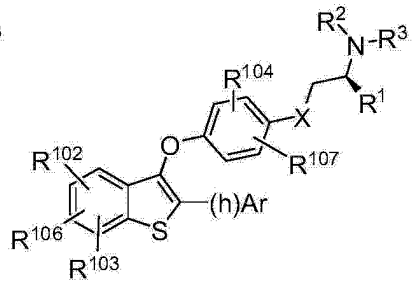
t 是 0、1、2、3 或 4；

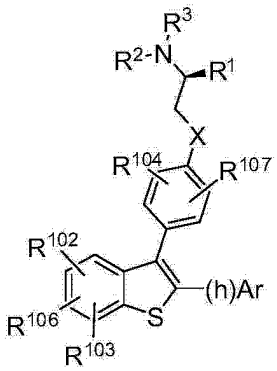
X 是不存在的、-O-、-S-、-S(=O)-、-S(=O)$_2$-、-C(=O)-、-CH_2-、-NH- 或 -N(C_1-C_6 烷基)-。

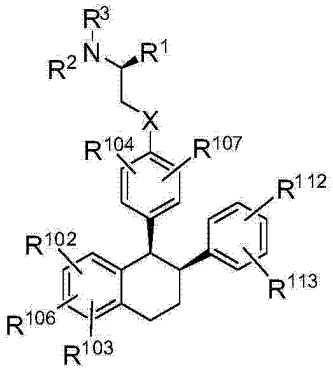
[0159] 在一些实施方案中，X 是不存在的、O、S、-CH_2-、-C(=O)-、-NH- 或 -N(C_1-C_4 烷基)-。在一些其它实施方案中，X 是 O。

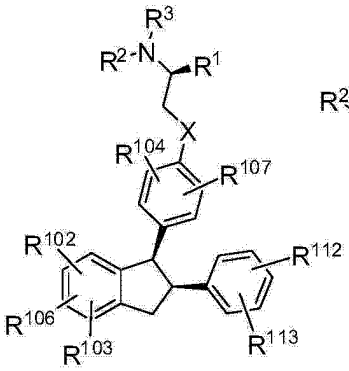
[0160] 在一些实施方案中，式 (V) 的化合物具有下列结构之一或其药学上可接受的盐：

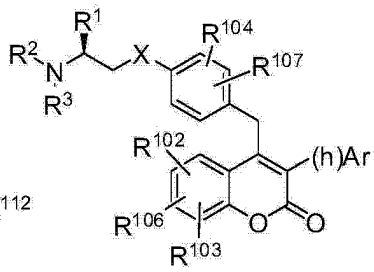


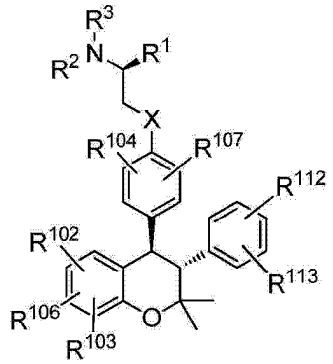


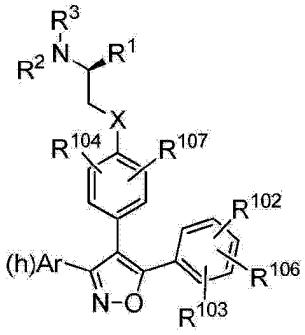


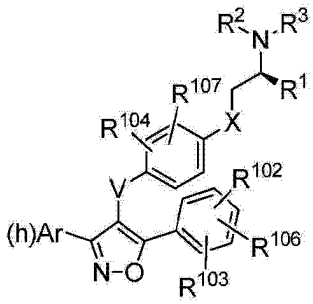


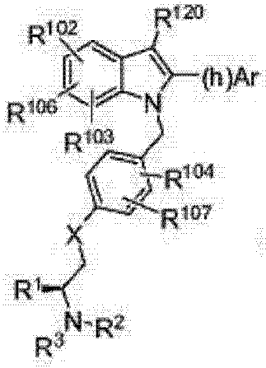


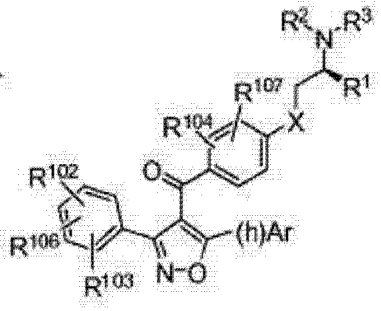


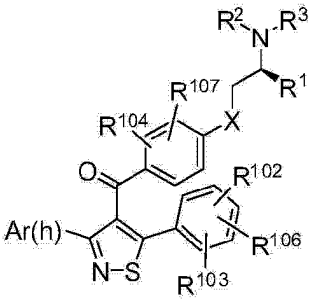


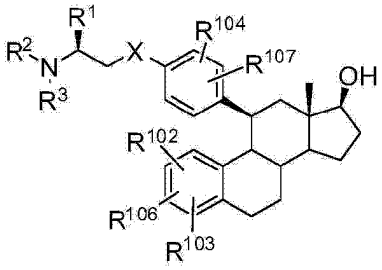


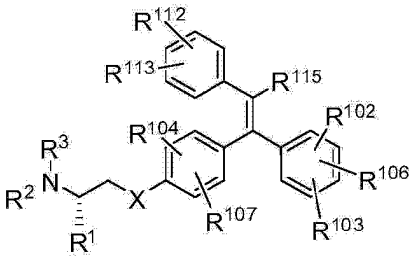


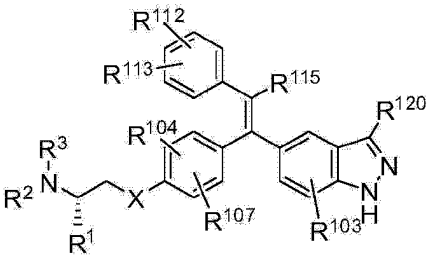


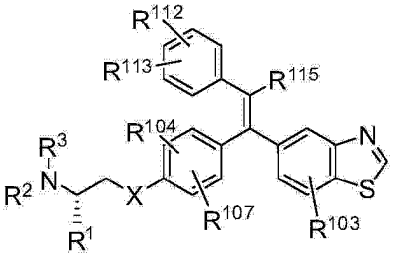


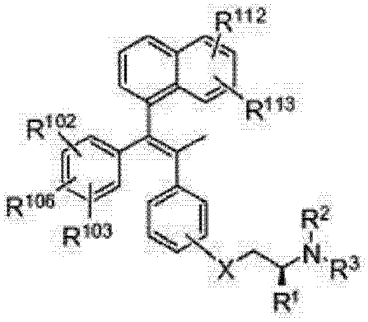


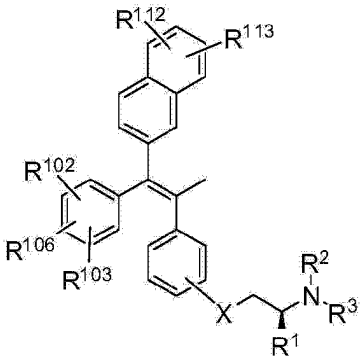


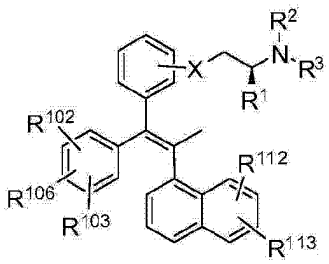


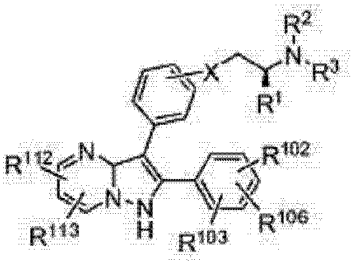


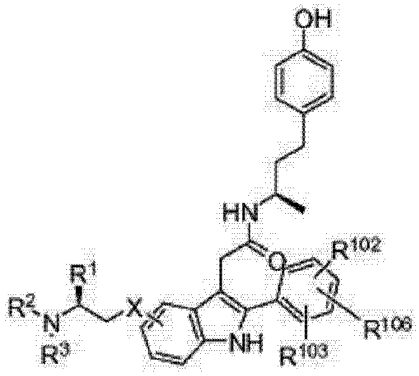


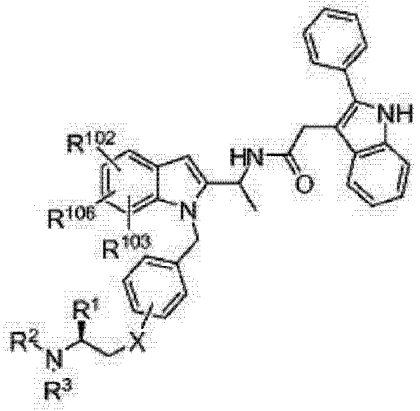


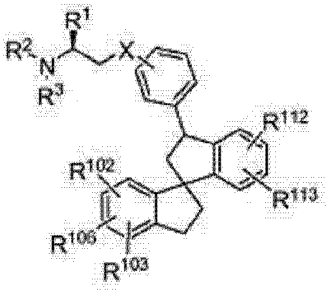


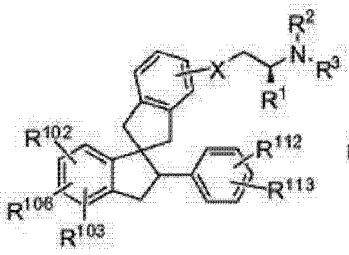


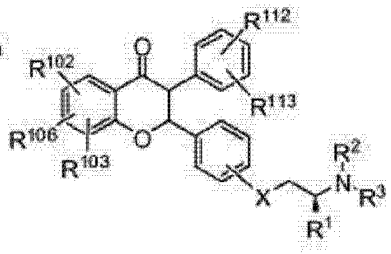


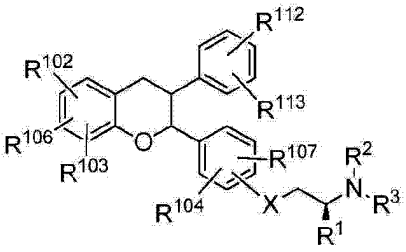


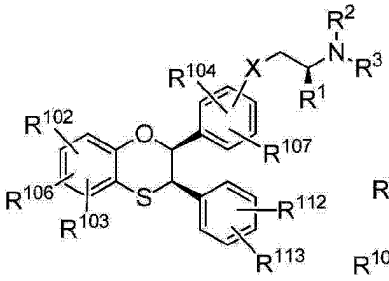


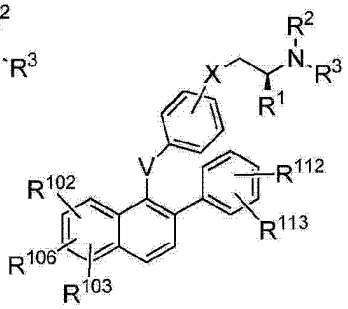


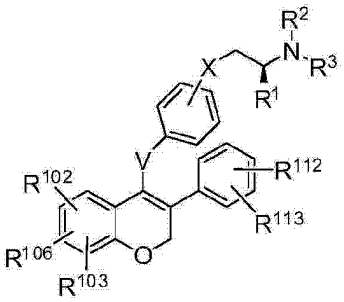


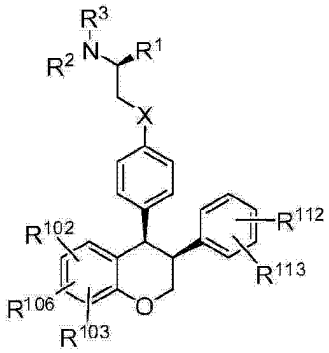


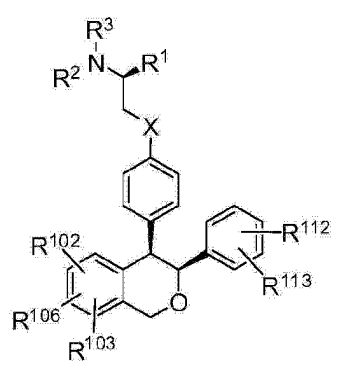


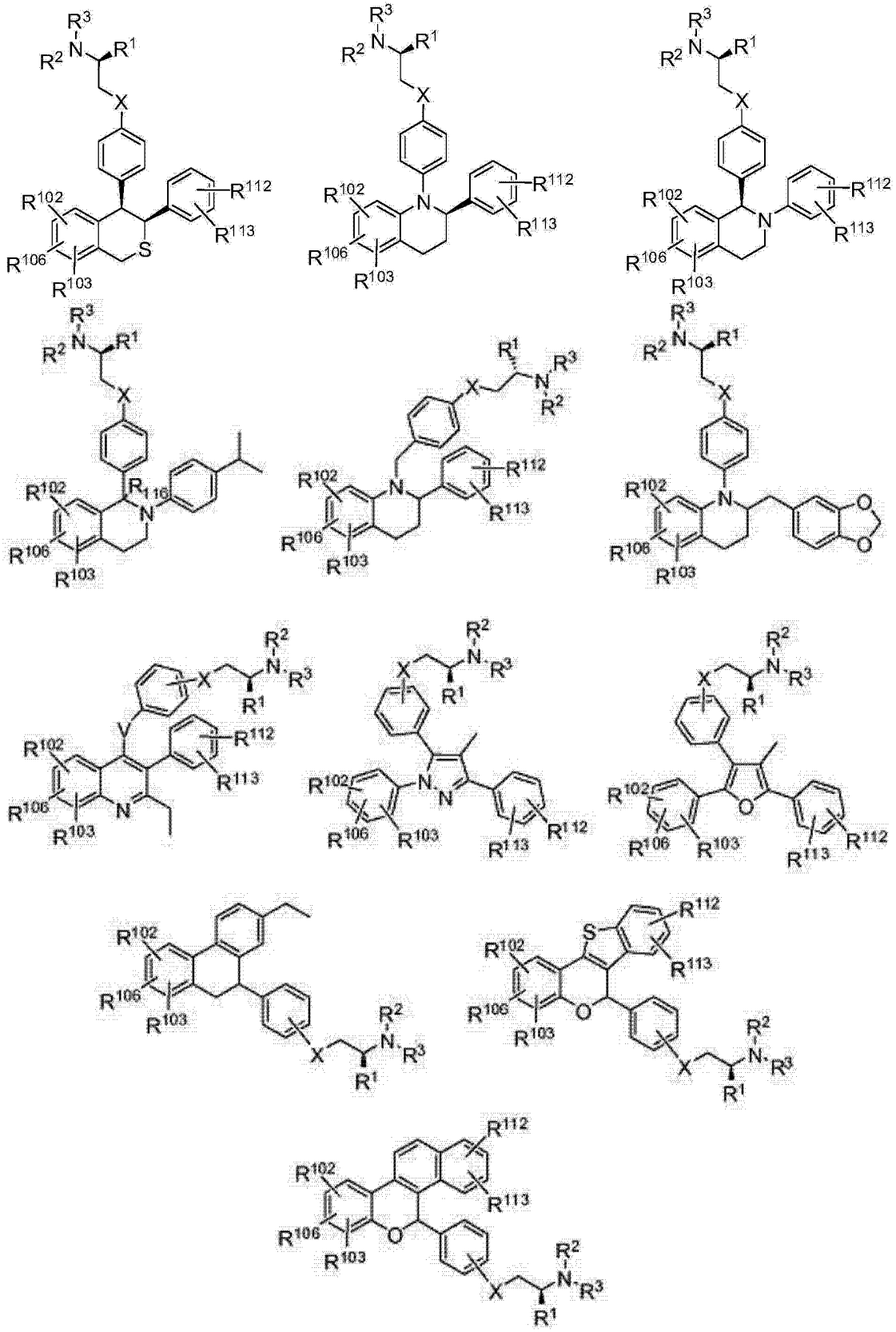


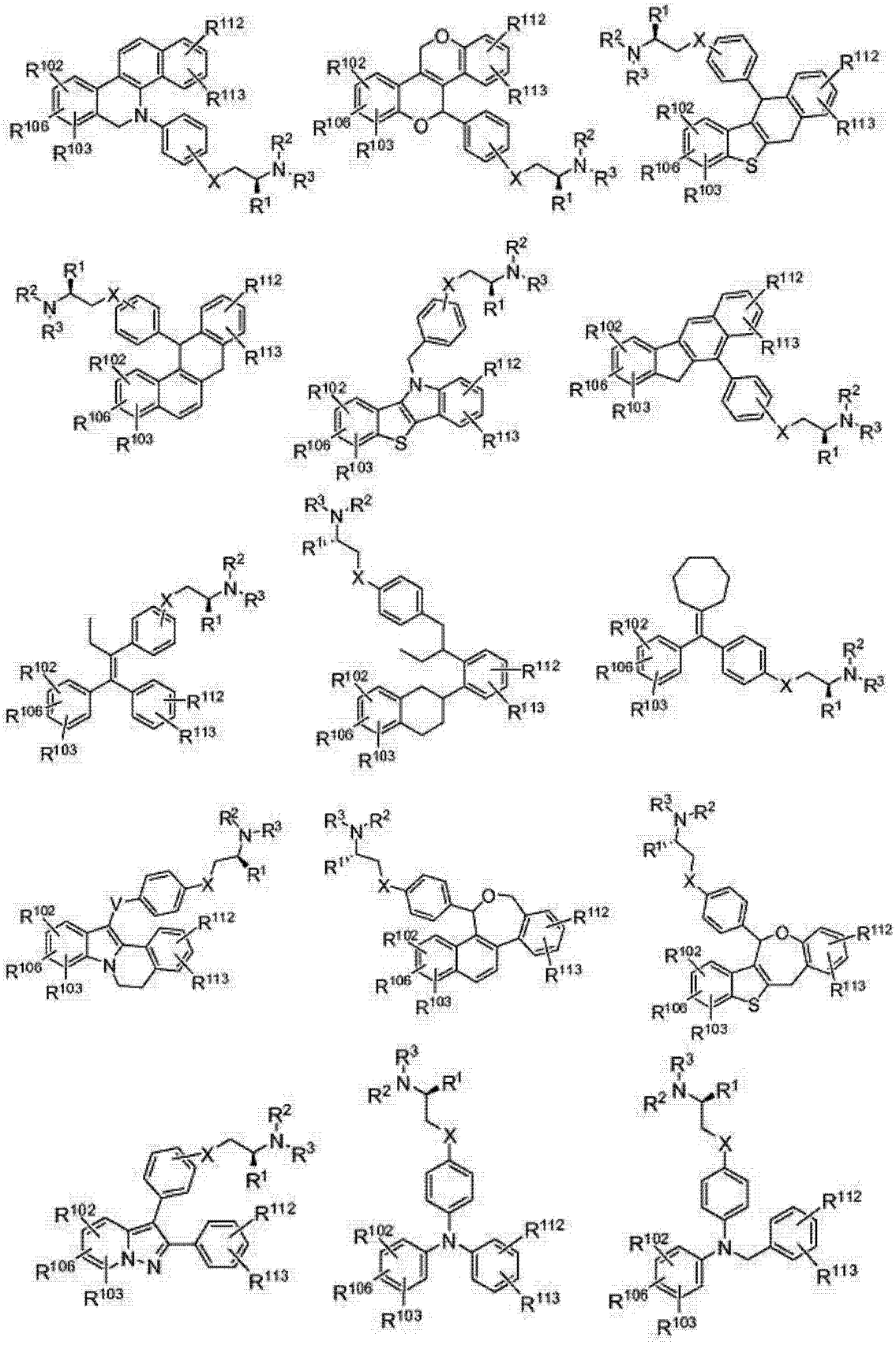


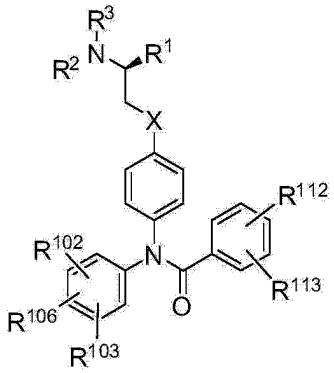












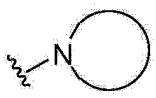
其中：

R^1 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^3 是 C_1-C_6 氟烷基；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是单环 C_2-C_6 杂环烷基；

各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；

t 是 1、2、3 或 4；

X 是不存在的、O、S、$-CH_2-$、-C(=O)-、-NH- 或 -N(C_1-C_4 烷基)-。

(h)Ar 是（杂）芳环，任选地被 R^{112} 和 R^{113} 取代；

R^{102} 和 R^{103} 独立地选自 H、F、Cl、C_1-C_3 烷基、C_1-C_3 烷氧基、C_1-C_3 烷硫基 (alkylthio)、$-CF_3$ 或 -CN；

R^{104} 和 R^{107} 独立地选自 H、氟、氯、C_1-C_2 烷基、$-CF_3$ 或 -CN；

R^{112} 是 H、氟、氯、C_1-C_2 烷基、C_1-C_2 烷氧基、-CN 或羟基；

R^{113} 是 H、氟、氯、C_1-C_3 烷基、C_1-C_3 烷氧基、C_1-C_3 烷硫基、$-CF_3$ 或 -CN；

R^{106} 是 H、羟基、胺或 C_1-C_6 烷氧基；

R^{106} 和 R^{102} 可连接形成任选地被氟、氯或 C_1-C_3 烷基取代的（杂）芳环；

R^{105} 是 H、C_1-C_3 烷基，任选地被一个或多个氟取代；

V 是 -O-、-S-、$-CH_2-$、-CH(OH)-、-CH(C_1-C_3 烷氧基)-、-C=CH_2、羰基、-N-R^{116}；

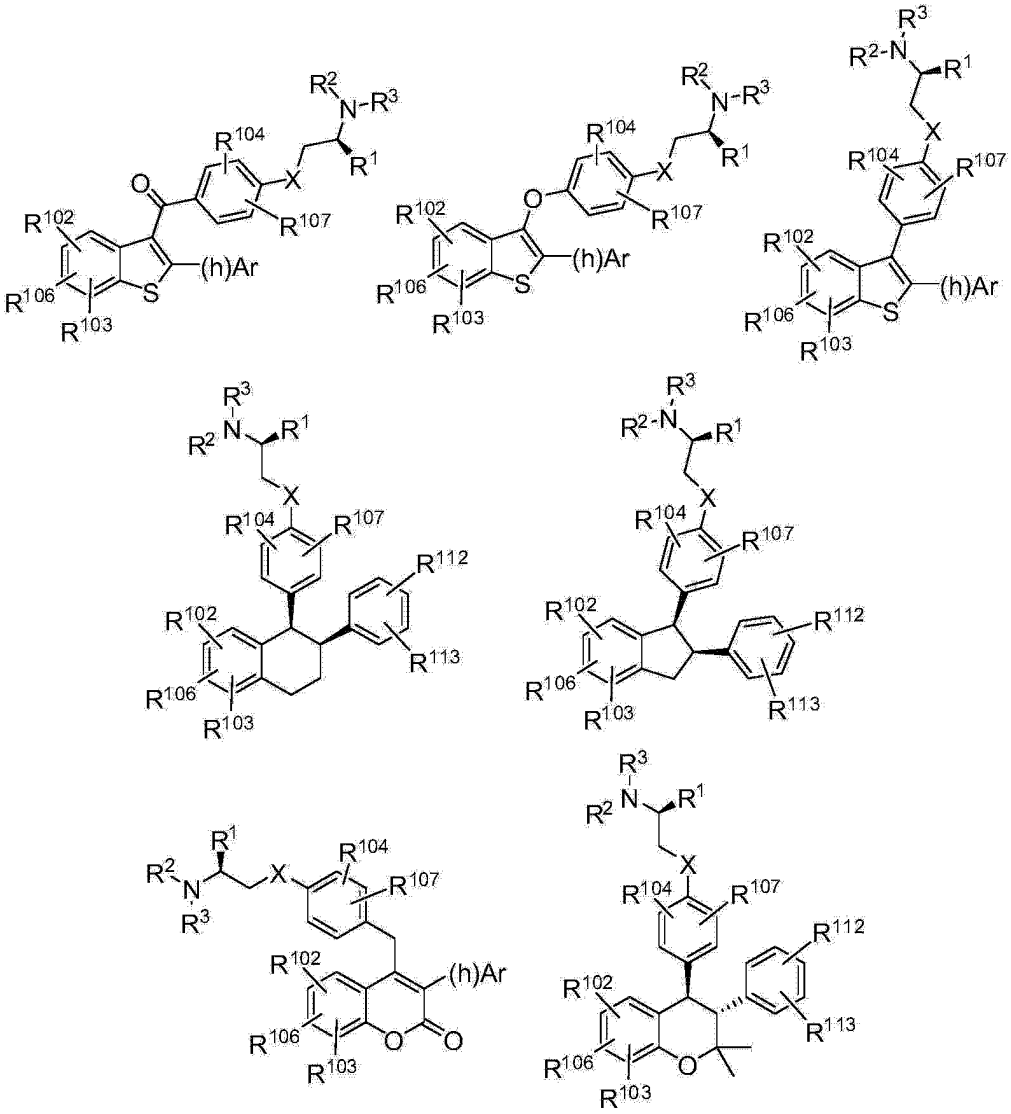
R^{115} 是 H、卤素、硝基、腈或 C_1-C_6 烷基、C_1-C_6 环烷基，任选地被一个或多个卤素取代；

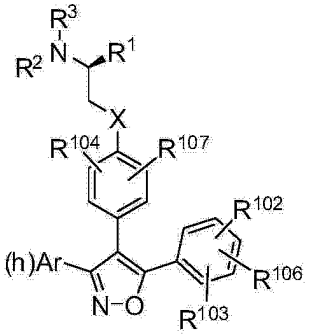
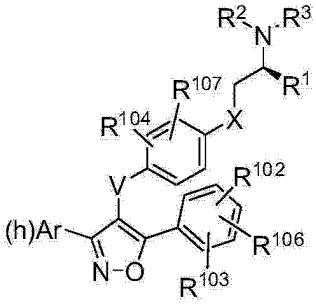
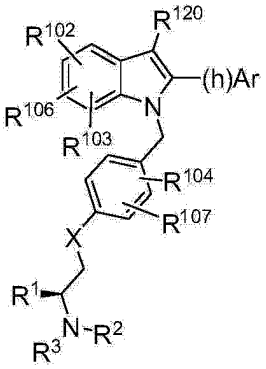
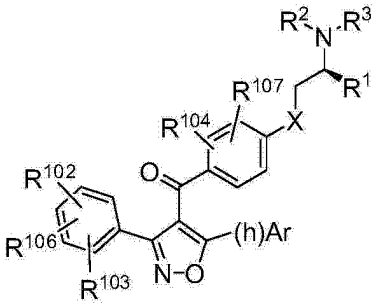
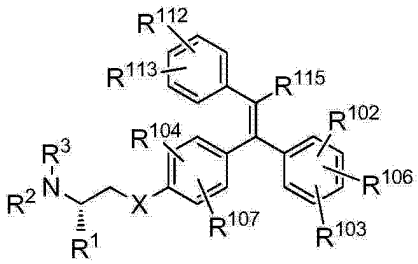
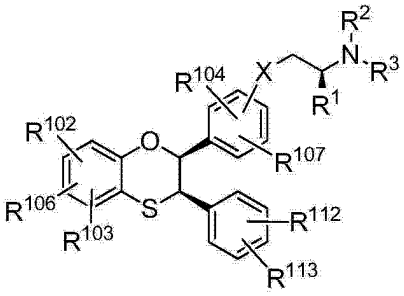
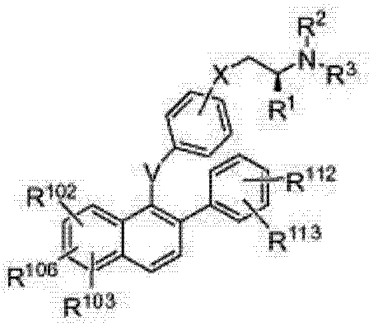
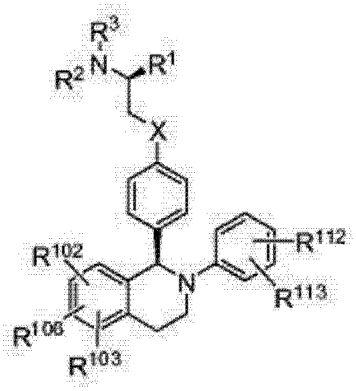
R^{116} 是 H、C_1-C_4 烷基、C_1-C_4 烯基，任选地被一个或多个卤素取代；

R^{120} 是 C_1-C_3 烷基，任选地被一个或多个氟取代。

[0161] 术语 (h)Ar 或（杂）芳环是指芳族或杂芳族环系，其芳族骨架含有 5-10 个原子，其中 0-4 个非碳的原子选自氧、氮或硫。实例是苯基、萘基、吡啶基、噻吩基、呋喃基、噻唑基、噁唑基、吡咯基、噻二唑基、四唑基、苯并吡咯基和苯并吡唑基。

[0162] 在另一实施方案中，式 (V) 的化合物具有下列结构之一或其药学上可接受的盐：



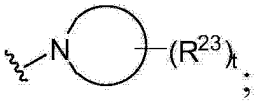









其中：

R^1 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^3 是 C_1-C_6 氟烷基；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是单环 C_2-C_6 杂环烷基；

各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；

t 是 1、2、3 或 4；

X 是不存在的、O、S、$-CH_2-$、-C(=O)-、-NH- 或 -N(C_1-C_4 烷基)-；

(h)Ar 是（杂）芳环，任选地被 R^{112} 和 R^{113} 取代；

R^{102} 和 R^{103} 独立地选自 H、F、Cl、C_1-C_3 烷基、C_1-C_3 烷氧基、C_1-C_3 烷硫基、$-CF_3$ 或 -CN；

R^{104} 和 R^{107} 独立地选自 H、氟、氯、C_1-C_2 烷基、$-CF_3$ 或 -CN；

R^{112} 是 H、氟、氯、C_1-C_2 烷基、C_1-C_2 烷氧基、-CN 或羟基；

R^{113} 是 H、氟、氯、C_1-C_3 烷基、C_1-C_3 烷氧基、C_1-C_3 烷硫基、$-CF_3$ 或 -CN；

R^{106} 是 H、羟基、胺或 C_1-C_6 烷氧基；

R^{106} 和 R^{102} 可连接形成任选地被氟、氯或 C_1-C_3 烷基取代的（杂）芳环；

R^{105} 是 H、C_1-C_3 烷基，任选地被一个或多个氟取代；

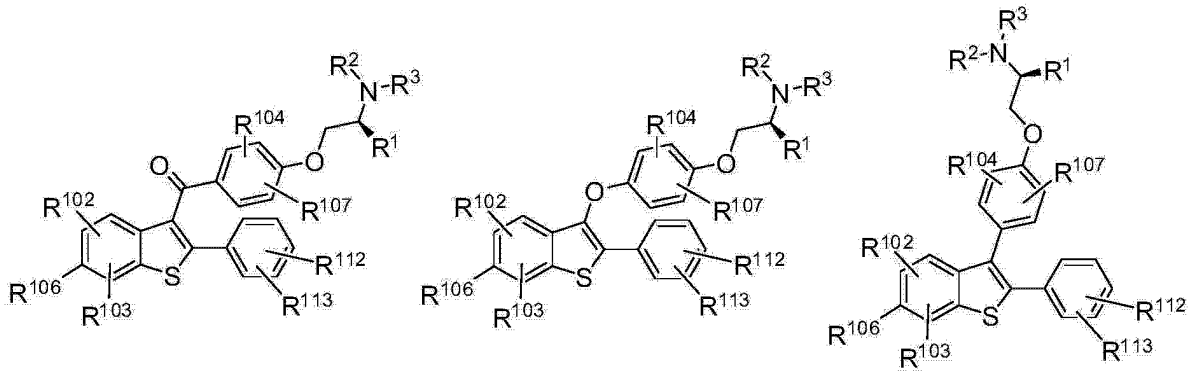
V 是 -O-、-S-、$-CH_2-$、-CH(OH)-、-CH(C_1-C_3 烷氧基)-、-C=CH_2、羰基、-N-R^{116}；

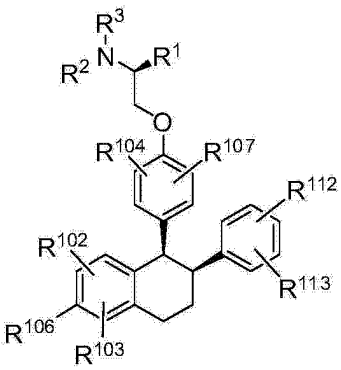
R^{115} 是 H、卤素、硝基、腈或 C_1-C_6 烷基、C_1-C_6 环烷基，任选地被一个或多个卤素取代；

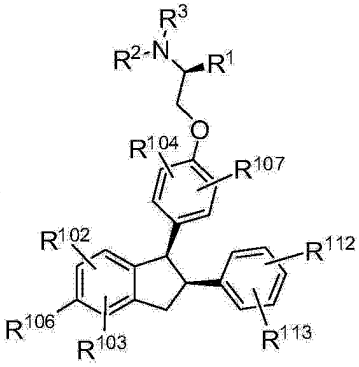
R^{116} 是 H、C_1-C_4 烷基、C_1-C_4 烯基，任选地被一个或多个卤素取代；

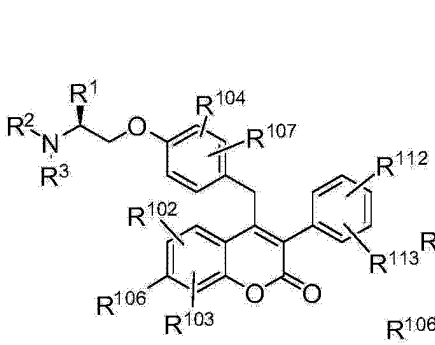
R^{120} 是 C_1-C_3 烷基，任选地被一个或多个氟取代。

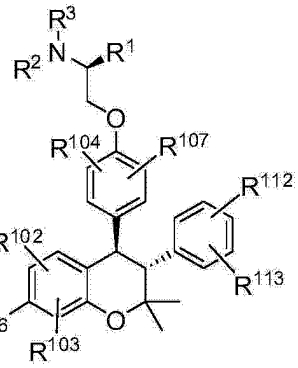
[0163] 在另一实施方案中，式 (V) 的化合物具有下列结构之一或其药学上可接受的盐：

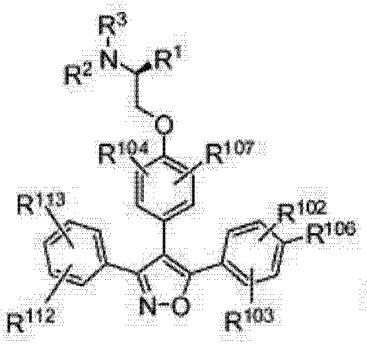


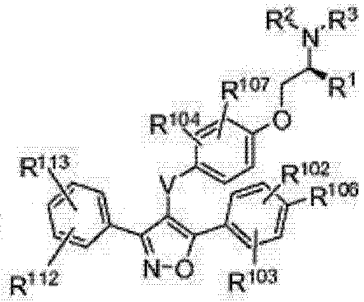


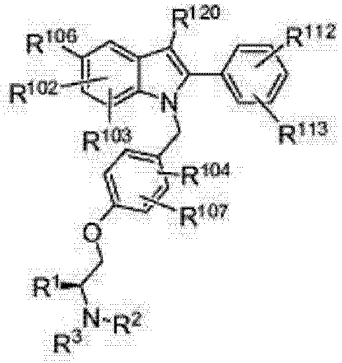


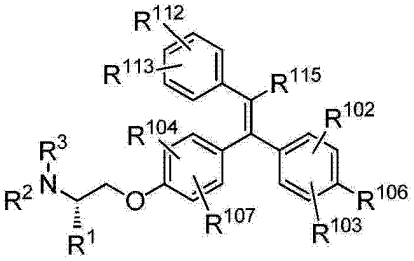


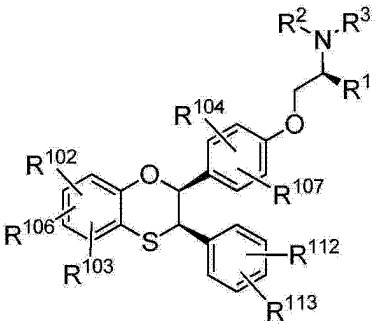


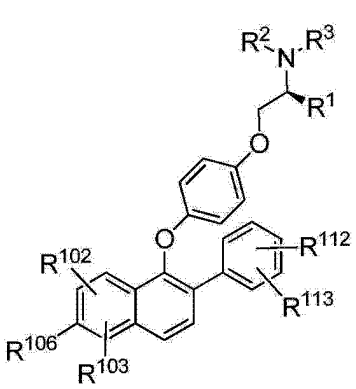
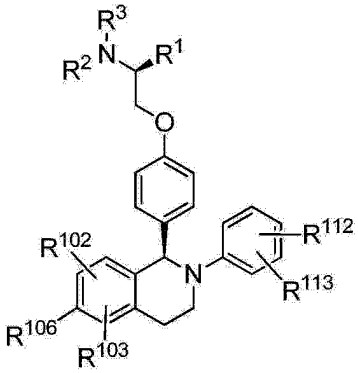










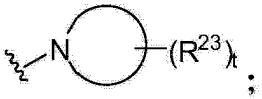



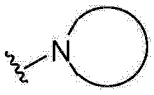
其中：

R^1 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^2 是 H、C_1-C_6 烷基或 C_1-C_6 氟烷基；

R^3 是 C_1-C_6 氟烷基；

或 R^2 和 R^3 与它们所连接的 N 原子一起形成  ；

 是单环 C_2-C_6 杂环烷基；

各个 R^{23} 独立地是 F 或 C_1-C_6 氟烷基；

t 是 1、2、3 或 4；

X 是不存在的、-O-、-S-、$-CH_2-$、-C(=O)-、-NH- 或 -N(C_1-C_4 烷基)-；

R^{102} 和 R^{103} 独立地选自 H、F、Cl、C_1-C_3 烷基、C_1-C_3 烷氧基、C_1-C_3 烷硫基、$-CF_3$ 或 -CN；

R^{104} 和 R^{107} 独立地选自 H、氟、氯、C_1-C_2 烷基、$-CF_3$ 或 -CN；

R^{112} 是 H、氟、氯、C_1-C_2 烷基、C_1-C_2 烷氧基、-CN 或羟基；

R^{113} 是 H、氟、氯、C_1-C_3 烷基、C_1-C_3 烷氧基、C_1-C_3 烷硫基、$-CF_3$ 或 -CN；

R^{106} 是 H、羟基、胺或 C_1-C_6 烷氧基；

R^{106} 和 R^{102} 可连接形成任选地被氟、氯或 C_1-C_3 烷基取代的（杂）芳环；

R^{105} 是 H、C_1-C_3 烷基，任选地被一个或多个氟取代；

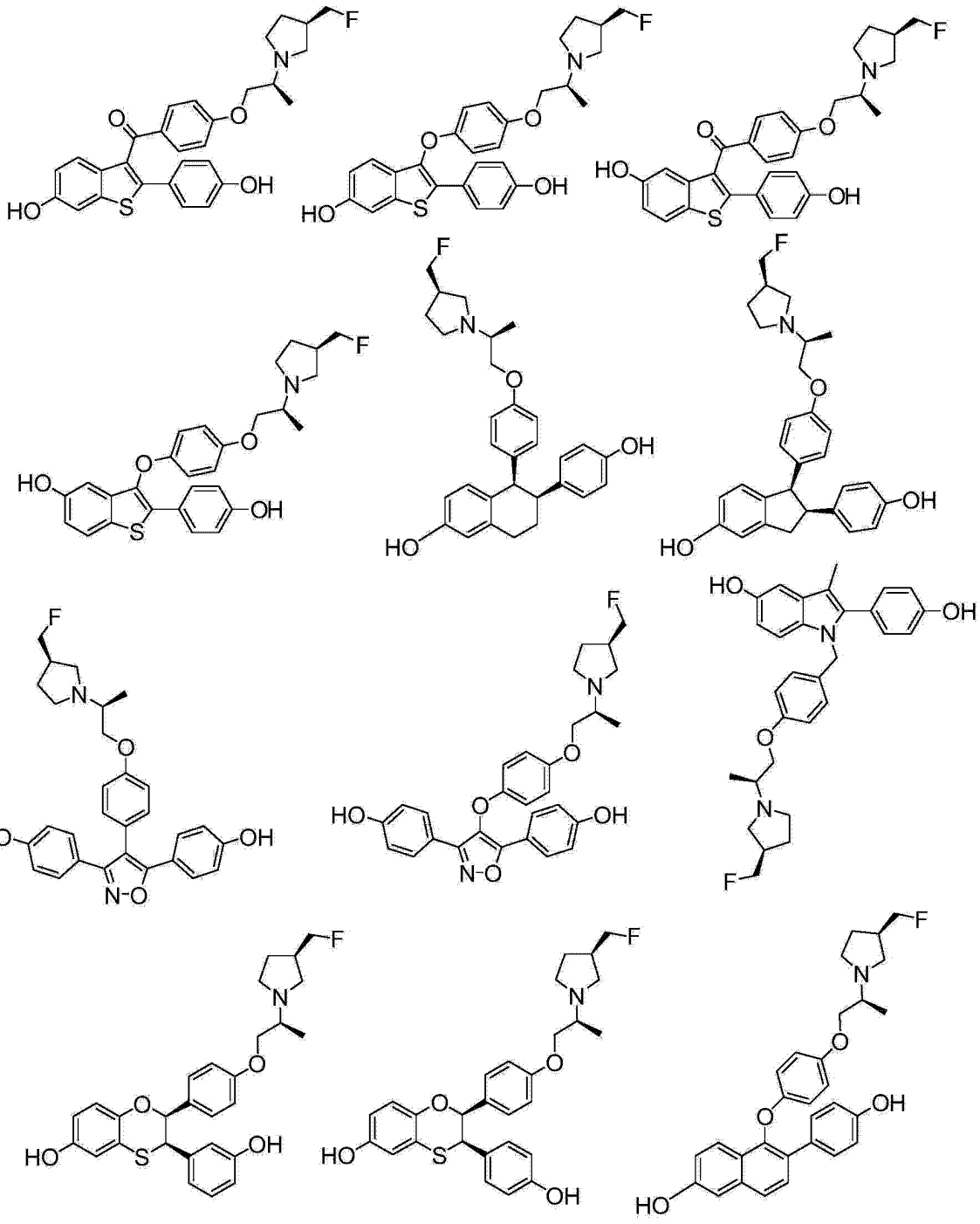
V 是 -O-、-S-、$-CH_2-$、-CH(OH)-、-CH(C_1-C_3 烷氧基)-、-C＝CH_2、羰基、-N-R^{116}；

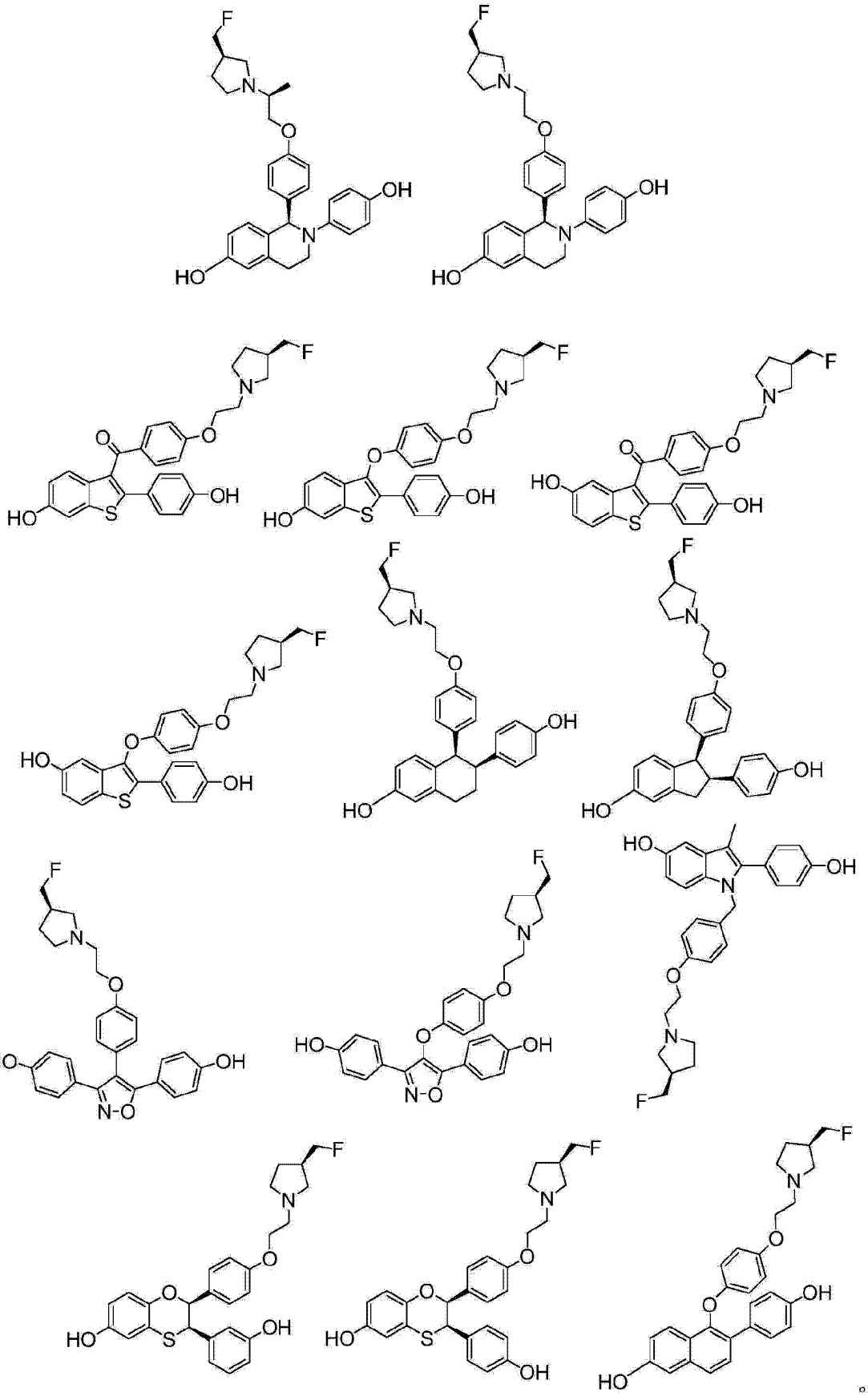
R^{115} 是 H、卤素、硝基、腈或 C_1-C_6 烷基、C_1-C_6 环烷基，任选地被一个或多个卤素取代；

R^{116} 是 H、C_1-C_4 烷基、C_1-C_4 烯基，任选地被一个或多个卤素取代；

R^{120} 是 C_1-C_3 烷基，任选地被一个或多个氟取代。

[0164] 在一些实施方案中，式 (V) 的化合物具有下列结构之一，或是其药学上可接受的盐或溶剂化物或前药：





化合物的合成

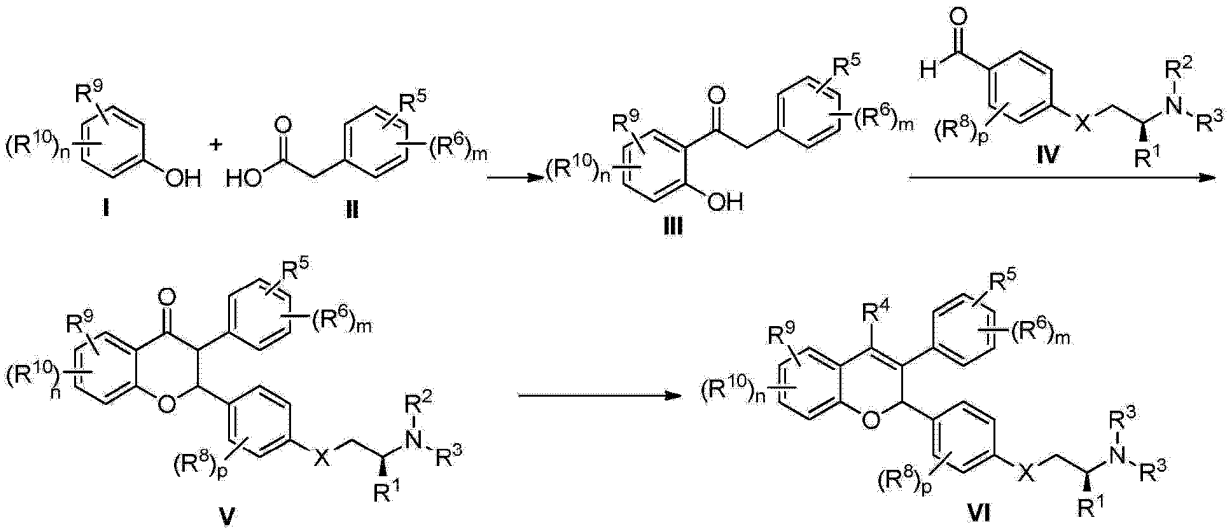
[0165] 本文所述的化合物使用标准合成技术或使用本领域已知的方法结合本文描述的

方法进行合成。另外，本文所述的溶剂、温度和其它反应条件可以变化。

[0166] 用于合成本文所述的化合物的起始材料是合成的或者从例如但不限于 Sigma-Aldrich、Fluka、Acros Organics、Alfa Aesar 等商业来源获得的。本文所述的化合物和具有不同取代基的其它相关化合物使用本文描述的或另外已知的技术和材料合成，包括在 March, ADVANCED ORGANIC CHEMISTRY 第 4 版，(Wiley 1992)；Carey 和 Sundberg, ADVANCED ORGANIC CHEMISTRY 第 4 版.，A 卷和 B 卷 (Plenum 2000, 2001) 以及 Green 和 Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 第 3 版，(Wiley 1999) 中记载的那些。制备化合物的一般方法可以利用适当的试剂和条件进行修改，以便引入在本文提供的通式中所见的各种部分。

[0167] 在一些实施方案中，如以下流程所述制备本文所述的化合物。

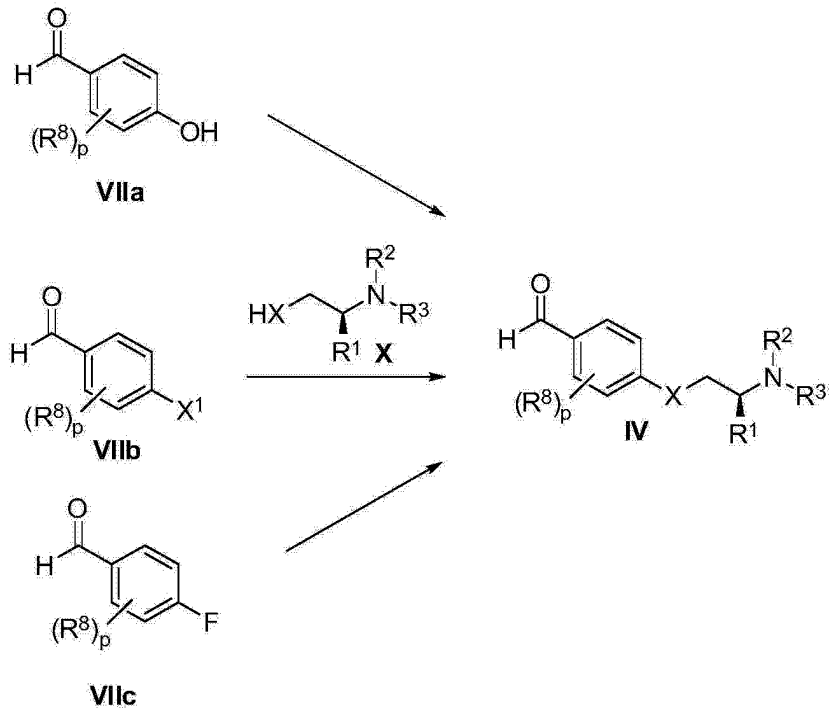
流程 1：



[0168] 在合适的路易斯酸的存在下用结构 II 的苯基乙酸处理结构 I 的酚生成结构 III 的酮。在一些实施方案中，合适的路易斯酸是 BF_3-Et_2O。在一些实施方案中，合适的溶剂是甲苯。在一些实施方案中，对该反应加热。在一些实施方案中，将该反应加热至 90℃ 2 小时。结构 III 的酮与结构 IV 的苯甲醛在合适的碱和合适的溶剂的存在下反应，生成结构 V 的化合物。在一些实施方案中，合适的碱是哌啶和 1,8- 二氮杂双环 [5.4.0] 十一碳 -7- 烯 (DBU)。在一些实施方案中，合适的溶剂是仲丁醇和 / 或异丙醇。在一些实施方案中，结构 III 的酮与结构 IV 的苯甲醛在回流下在哌啶、DBU 的存在下在仲丁醇中反应 3 小时，然后加入异丙醇，并在室温下搅拌反应液 1-3 天。用合适的有机金属试剂处理结构 V 的化合物以得到叔醇，然后将其脱水以生成结构 VI 的苯并吡喃。在一些实施方案中，合适的有机金属试剂是 R^4-Li 或 R^4-MgCl。在一些实施方案中，合适的有机金属试剂是甲基锂、甲基氯化镁或甲基溴化镁。在一些实施方案中，结构 V 的化合物溶解于四氢呋喃中，并用甲基锂在 -78℃ 至室温下处理 1 小时或用甲基氯化镁在 0℃ 至室温下处理 2 小时。然后用乙酸 / 水处理生成的叔醇从而得到苯并吡喃。

[0169] 在一些实施方案中，如流程 2 所述制备结构 IV 的苯甲醛。

流程 2：

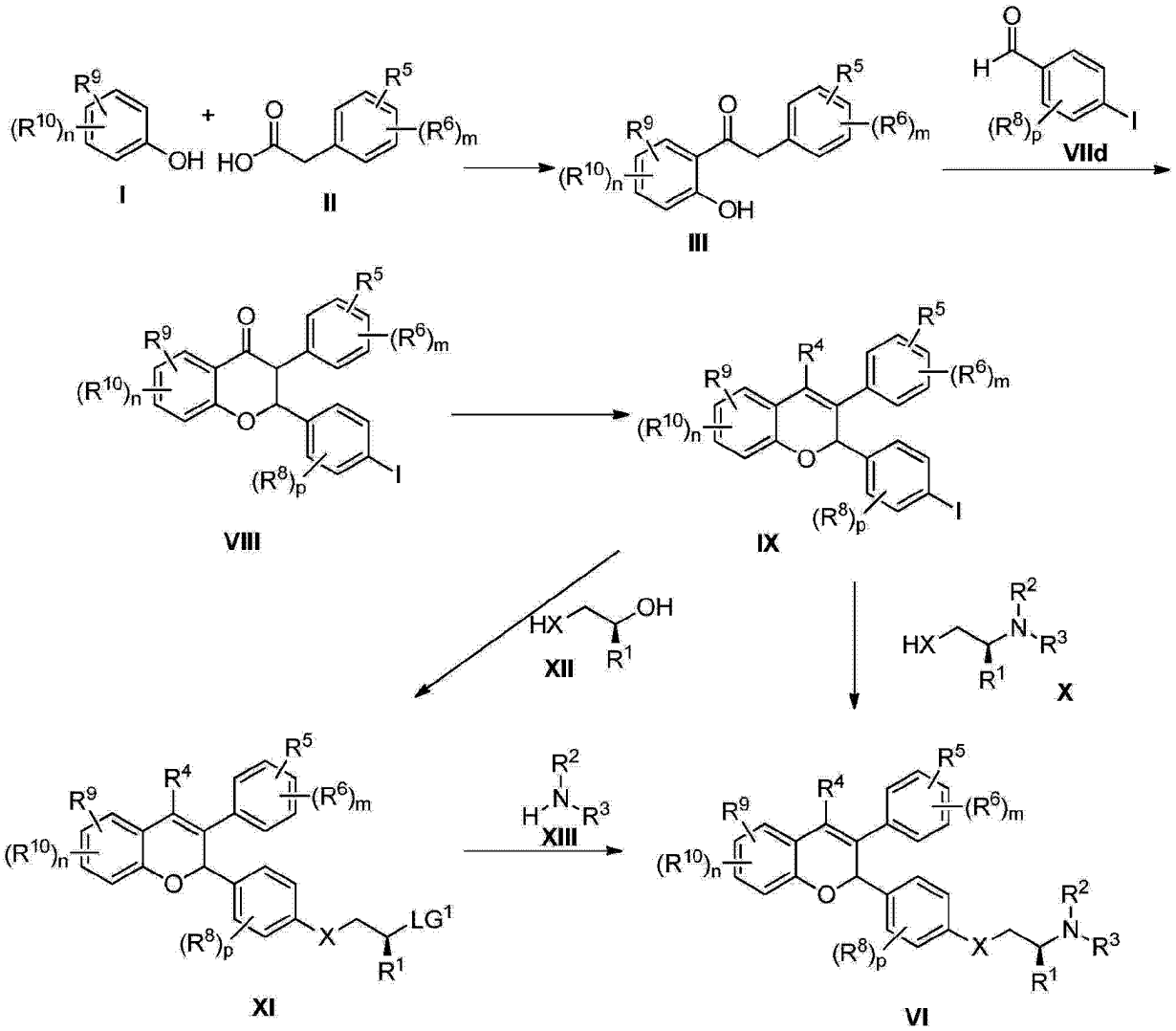


[0170] 在一些实施方案中，在合适的偶合条件下，结构 VIIa 的 4- 羟基苯甲醛与结构 X 的氨基化合物偶合。在一些实施方案中，合适的偶合条件包括使用三苯基膦、偶氮二甲酸二异丙酯和四氢呋喃。在一些实施方案中，所述偶合在室温下进行。

[0171] 在一些实施方案中，在合适的偶合条件下，结构 VIIb 的 4- 卤代苯甲醛（例如，其中 X1 是 Br 或 I）或结构 VIIc 的 4- 氟苯甲醛与结构 X 的氨基化合物偶合。在一些实施方案中，当 X^1 是 I 且 X 是 O 时，则合适的反应条件包括使用 CuI、碳酸钾、丁腈且加热至大约 125℃。在可替代的实施方案中，当 X^1 是 I 且 X 是 O 时，则合适的反应条件包括使用 CuI、碳酸铯、间二甲苯且加热至大约 125℃。在一些实施方案中，在这些铜介导的偶合反应条件中使用菲咯啉。在一些实施方案中，当 X^1 是 Br 且 X 是 N 时，则合适的反应条件包括使用 $Pd_2(dba)_3$、BINAP、碳酸铯和甲苯且加热至约 100℃。在一些实施方案中，当 X^1 是 Br 且 X 是 S 时，则合适的反应条件包括使用氢化钠和二甲基甲酰胺或碳酸铯和 N- 甲基吡咯烷酮且加热。在一些实施方案中，使用氢化钠和二甲基甲酰胺或在二甲基甲酰胺中采用叔丁醇钾，使结构 VIIc 的 4- 氟苯甲醛与结构 X 的氨基化合物（其中 X 是 O）偶合。在一些实施方案中，使用碳酸钾和二甲基甲酰胺加热至回流或在乙醇中采用碳酸钾加热至回流，使结构 VIIc 的 4- 氟苯甲醛与结构 X 的氨基化合物（其中 X 是 N）偶合，或者所述反应在热源加热下进行。在一些实施方案中，在室温下使用氢化钠和二甲基甲酰胺，使结构 VIIc 的 4- 氟苯甲醛与结构 X 的氨基化合物（其中 X 是 S）偶合。

[0172] 在一些实施方案中，如流程 3 所述制备化合物。

流程 3：



[0173] 在一些实施方案中，如流程 1 所述制备结构 III 的酮，然后结构 III 的酮与结构 VIId 的 4- 卤代苯甲醛在合适的碱和合适的溶剂的存在下进行反应得到结构 VIII 的化合物。在一些实施方案中，合适的碱是哌啶和 1,8- 二氮杂双环 [5.4.0] 十一碳 -7- 烯 (DBU)。在一些实施方案中，合适的溶剂是仲丁醇和异丙醇。然后用合适的有机金属试剂处理结构 VIII 的化合物，随后进行叔醇脱水得到结构 IX 的苯并吡喃。在一些实施方案中，合适的有机金属试剂是 R^4-Li 或 MgCl-R^4。在一些实施方案中，在室温下在合适的溶剂中，结构 VIII 的化合物与 CsF 和 CF_3TMS 发生反应，随后使 TMS 保护基脱保护，然后得到的叔醇脱水生成结构 IX 的苯并吡喃 (其中 R^4 是 $-CF_3$)。然后在乌尔曼 (Ullmann) 反应条件下，结构 IX 的苯并吡喃与结构 X 的氨基化合物反应，得到结构 VI 的苯并吡喃。乌尔曼反应条件包括使用铜盐。在一些实施方案中，乌尔曼反应条件包括使用 CuI、Cs_2CO_3 和丁腈，并加热至大约 125℃。在一些实施方案中，乌尔曼反应条件包括使用 CuI、联吡啶和 K_2CO_3，并加热至大约 140℃。在一些其它的实施方案中，乌尔曼反应条件包括使用 CuI、碳酸钾和丁腈，并加热至大约 125℃约 5 天。

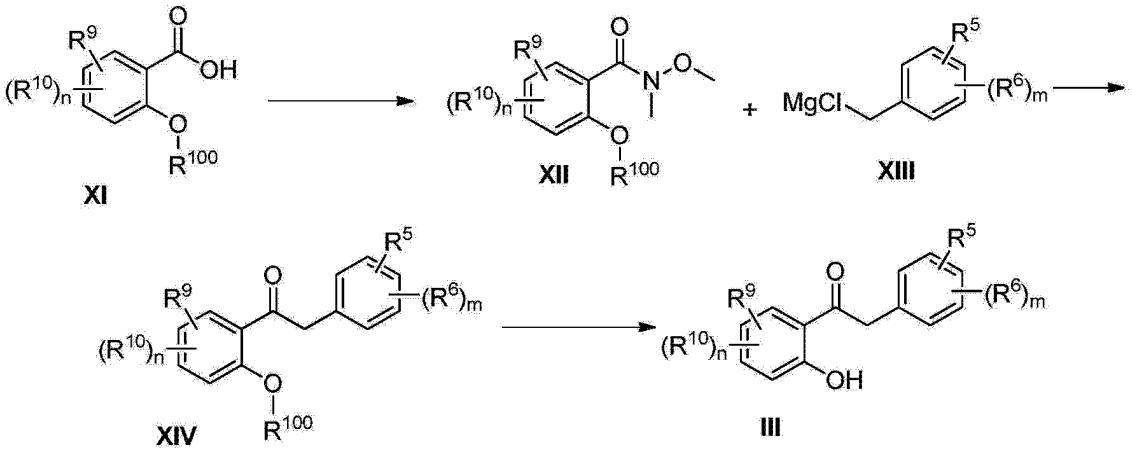
[0174] 在可替代的实施方案中，在乌尔曼反应条件下，结构 IX 的苯并吡喃与结构 XII 的化合物反应，随后将 -OH 转化成适合的离去基团 (LG^1) 以得到结构 XI 的苯并吡喃。在一些实施方案中，在结构 XII 的化合物中 X 是 O 且所述乌尔曼反应条件包括使用 CuI、碳酸钾

和丁腈并加热至大约 125℃。适合的离去基团 (LG1) 的实例包括 -Cl、-Br、-I、-OTf、-OMs 和 -OTs。在一些实施方案中，通过在大约 0℃下在二氯甲烷中用 MsCl 和三乙胺处理 -OH，使 -OH 转化成 -OMs。在一些实施方案中，通过在大约 -78℃下在二氯甲烷中用 Tf_2O 和三乙胺处理 -OH 并升温至室温，使 -OH 转化成 -OTf。

[0175] 然后在合适的反应条件下用结构 XIII 的胺处理结构 XI 的苯并吡喃得到结构 VI 的苯并吡喃。在一些实施方案中，当 LG^1 是 -OMs 时，则合适的反应条件包括使用碳酸钾、乙腈且加热至大约 80℃。在一些实施方案中，当 LG^1 是 -OTf 时，则合适的反应条件包括使用在大约 -78℃下的二异丙基乙胺、二氯甲烷并升温至室温。

[0176] 在一些实施方案中，如流程 4 所述制备结构 III 的酮。

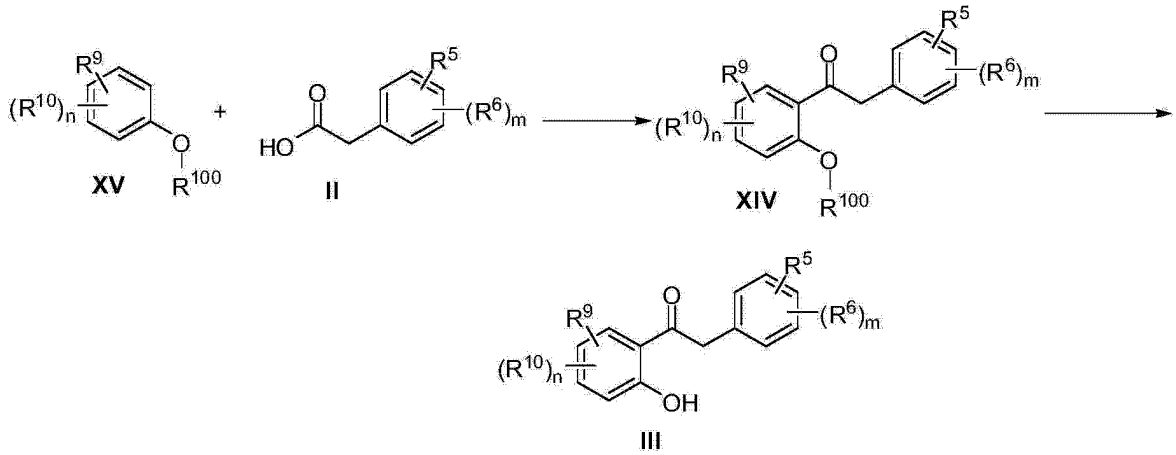
流程 4：



[0177] 结构 XI 的苯甲酸化合物转化为结构 XII 的 Weinreb 酰胺。在一些实施方案中，在室温下用草酰氯、二甲基甲酰胺 (DMF)、二氯甲烷 (DCM) 处理结构 XI 的苯甲酸化合物 2 小时，随后用三乙胺 (Et_3N)、N,O- 二甲基羟胺 -HCl、DCM 在 0℃至室温下处理 1 小时，从而得到结构 XII 的 Weinreb 酰胺。然后用合适的结构 XIII 的有机金属试剂处理结构 XII 的 Weinreb 酰胺，得到结构 XIV 的酮。在一些实施方案中，R^{100} 是酚保护基。在一些实施方案中，R^{100} 是甲基。在一些实施方案中，当 R^{100} 是甲基时，用 BBr_3、DCM 在 -78℃至 0℃下处理结构 XIV 的酮大约 30 分钟，得到结构 III 的酮。

[0178] 在一些实施方案中，如流程 5 所述制备结构 III 的酮：

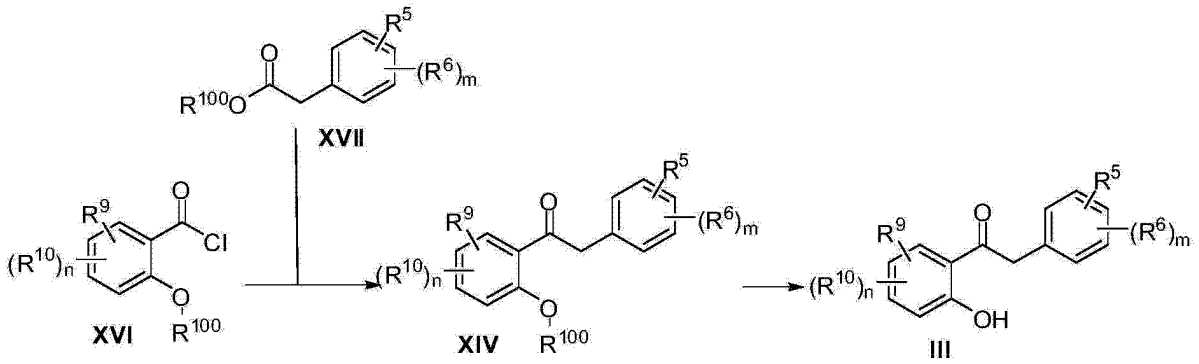
流程 5：



[0179] 在一些实施方案中，用聚磷酸和结构 II 的苯基乙酸处理结构 XV 的被适当保护的酚，从而得到结构 XIV 的酮。在一些实施方案中，R^{100} 是酚保护基。在一些实施方案中，R^{100} 是甲基。然后如流程 4 所述，结构 XIV 的酮转化为结构 III 的酮。

[0180] 在一些实施方案中，如流程 6 所述制备结构 III 的酮：

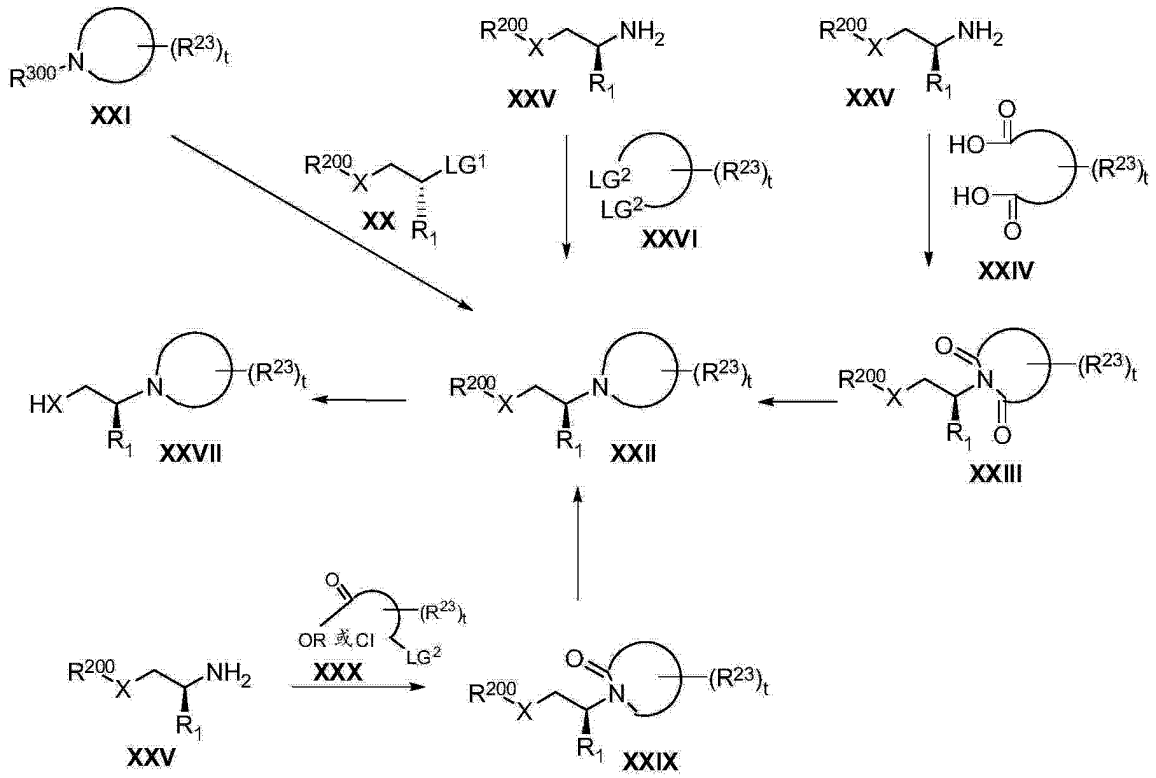
流程 6：



[0181] 将苯基乙酸的烷基酯，如结构 XVII 的化合物，用合适的碱处理，然后与结构 XVI 的酰基氯反应，从而得到酮 - 酯，该酮 - 酯脱羧得到结构 XIV 的酮。在一些实施方案中，R^{100} 是烷基。在一些实施方案中，R^{100} 是甲基。在一些实施方案中，合适的碱是双（三甲基甲硅烷基）酰胺锂 (LiHMDS)。在一些实施方案中，结构 XVII 的化合物在 -78℃下用 LiHMDS 在四氢呋喃中处理大约 15 分钟，然后在 -78℃下与结构 XVI 的酰基氯反应约 1 小时。在一些实施方案中，使用 Krapcho 脱羧条件完成酮 - 酯的脱羧。在一些实施方案中，Krapcho 脱羧条件包括二甲亚砜、盐水，加热至大约 150℃大约 5 小时。其它脱羧条件包括在 130℃下在乙醇中使用浓盐酸大约 3 小时。然后如流程 4 所述从结构 XIV 的酮中除去 R^{100}，从而得到结构 III 的酮。

[0182] 在一些实施方案中，当 R^2 和 R^3 与它们所连接的 N 原子一起形成取代或未取代的杂环时，如流程 7 所述制备该取代或未取代的杂环。

流程 7：



[0183] 在一些实施方案中，首先将结构 XXI 的取代或未取代的杂环（其中 R300 是保护基，如 t-BOC 或 Cbz）脱保护，然后与结构 XX 的化合物（其中 LG^1 是离去基团）在合适的反应条件下反应生成结构 XXII 的化合物。在一些实施方案中，当 R300 是 t-BOC 时，则在室温下使用盐酸在二氧杂环己烷中进行脱保护。在一些实施方案中，当 LG^1 是 -OMs 时，则合适的反应条件包括使用碳酸钾（或碳酸铯）、乙腈（或甲醇、乙醇、异丙醇或四氢呋喃）并任选地加热。在一些实施方案中，当 LG^1 是 -OMs 时，则合适的反应条件包括纯净地（例如胺作为溶剂）进行反应且加热。在一些实施方案中，当 LG^1 是 -OTf 时，合适的反应条件包括使用二异丙基乙胺、二氯甲烷，在初始时在 -78℃下进行反应然后再升温至室温。在一些实施方案中，R^{200} 是 X 的合适的保护基。在一些实施方案中，X 是氧。在一些实施方案中，R^{200} 是三苯甲基或苯甲基。在一些实施方案中，将 R^{200} 从结构 XXII 的化合物中去除以得到结构 XXVII 的化合物。在一些实施方案中，合适的脱保护条件包括在二氧杂环己烷（或四氢呋喃）中使用盐酸；或在二乙醚中使用甲酸；或使用醋酸醚（当 R^{200} 是三苯甲基时）。

[0184] 或者，结构 XXV 的胺与结构 XXVI 的活化烷烃（其中 LG^2 是合适的离去基团）在合适的反应条件下的反应得到结构 XXII 的化合物。合适的离去基团包括氯、溴、碘、甲苯磺酸酯、甲磺酸酯和三氟甲磺酸酯。在一些实施方案中，合适的反应条件包括碳酸钾、乙腈或纯净的，在室温下进行。

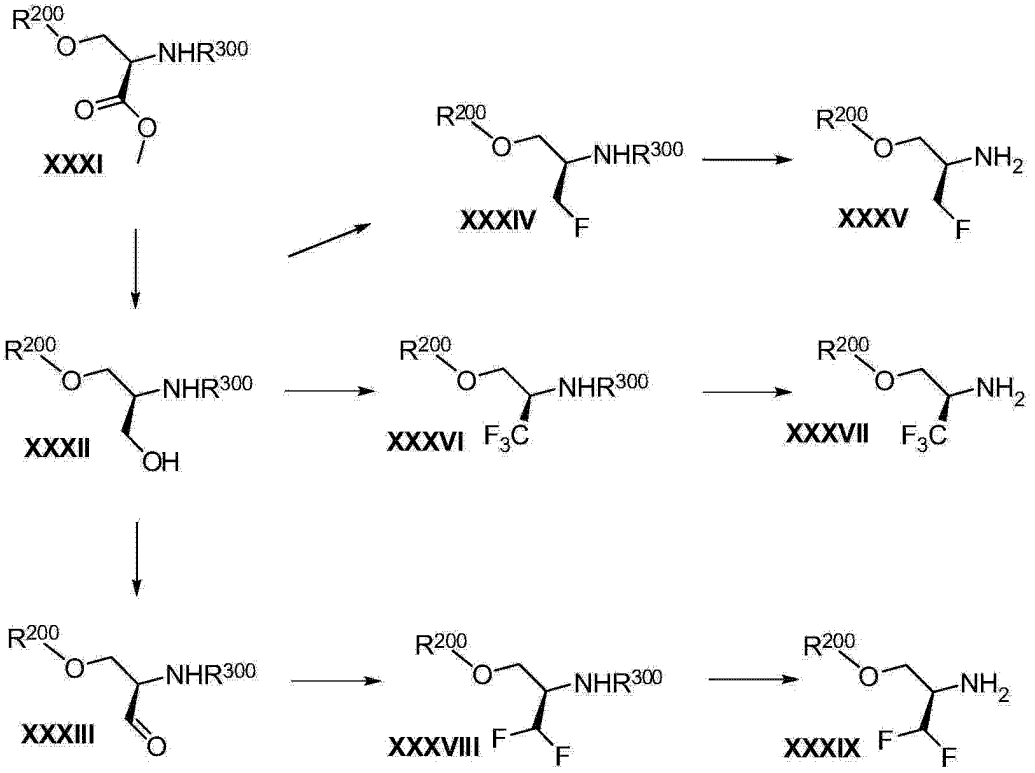
[0185] 可替代地，结构 XXIV 的二酸与乙酸酐在约 85℃下反应大约 30 分钟生成酸酐，然后使用结构 XXV 的胺对其进行处理，随后用乙酸酐处理，得到结构 XXIII 的酰胺。然后还原结构 XXIII 的酰胺得到结构 XXII 的胺。在一些实施方案中，所述还原反应采用在四氢呋喃中的氢化铝锂（$LiAlH_4$、THF）或 DIBAL、THF 进行。

[0186] 在一些实施方案中，结构 XXV 的胺与结构 XXX 的化合物在合适的反应条件下反应生成结构 XXIX 的化合物。在一些实施方案中，合适的反应条件包括在四氢呋喃或二甲基甲

酰胺中使用碳酸钾。在一些实施方案中，随后如上文所述还原结构 XXIX 的酰胺以生成结构 XXII 的胺。

[0187] 在一些实施方案中，如流程 8 所述引入氟化的 R^1 基团。

流程 8.



[0188] R^{200} 是氧原子的合适的保护基。在一些实施方案中，R^{200} 是三苯甲基。R^{300} 是氮原子的合适的保护基。在一些实施方案中，R^{300} 是甲磺酰基、甲苯磺酰基或 Cbz。在一些实施方案中，R^{200} 和 R^{300} 与它们所连接的氧原子和氮原子一起形成环状保护基。在一些情况下，所保护的氨基醇是噁唑烷，例如在 Garner 醛中的氨基醇。

[0189] 在一些实施方案中，在合适的反应条件下还原结构 XXXI 的酯得到结构 XXXII 的醇。在一些实施方案中，合适的还原反应条件包括在四氢呋喃中使用硼氢化钠或在四氢呋喃中使用 DIBAL-H。在合适的氧化条件下对醇的氧化得到结构 XXXIII 的醛。示例性的氧化条件包括戴斯马丁氧化剂 (Dess-Martin periodinane)、斯文氧化 (Swern oxidation) 或 PDC。

[0190] 使用合适的氟化剂处理结构 XXXII 的醇得到结构 XXXIV 的单氟化合物。在一些实施方案中，此类合适的氟化条件包括在约 -78℃下在二氯甲烷中使用二乙基氨基三氟化硫 (DAST)，并升温至室温。可替代地，合适的氟化反应条件包括在约 -78℃下在二氯甲烷中使用双 (2- 甲氧基乙基) 氨基三氟化硫 (Deoxo-fluor)，并升温至室温。在又一个可替代的实施方案中，合适的氟化反应条件包括使用 SF_4、HF。在又一个实施方案中，合适的氟化反应条件包括在约 0℃的二氯甲烷中使用甲磺酰氯、三乙胺，随后使用四丁基氟化铵。

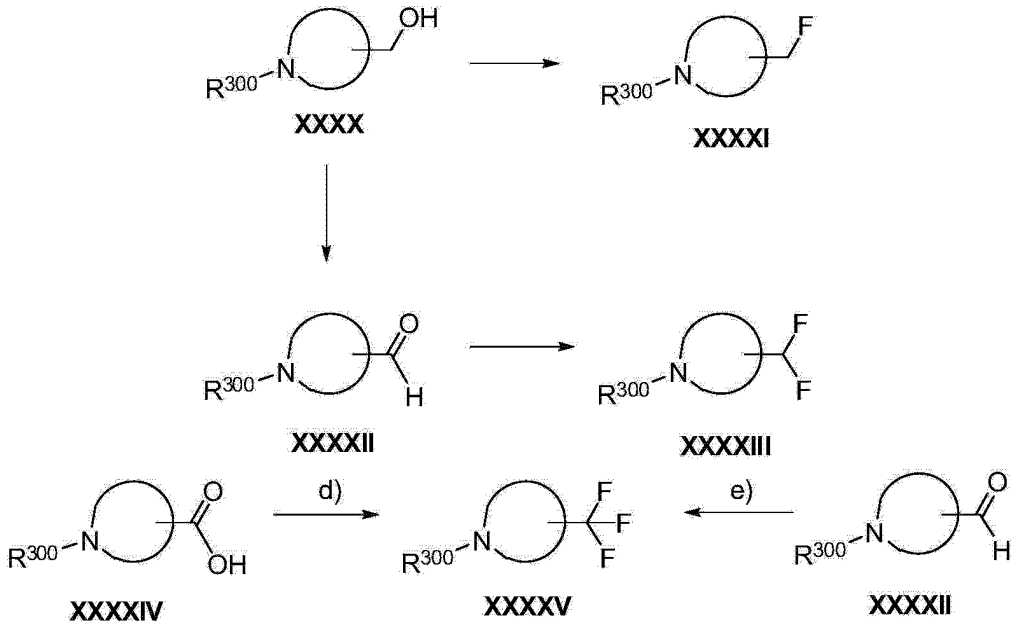
[0191] 在一些实施方案中，使用结构 XXXII 的醇制备结构 XXXVI 的三氟化合物。在一些实施方案中，将结构 XXXII 的醇用 PDC 或高锰酸钾氧化，然后使用 SF_4、HF 进行处理，得到结构 XXXVI 的三氟化合物。

[0192] 在一些实施方案中，使用结构 XXXIII 的醛制备结构 XXXVIII 的二氟化合物。在一些实施方案中，在约 -78℃在二氯甲烷中采用二乙基氨基三氟化硫 (DAST) 处理结构 XXXIII 的醛并升温至室温。在一些其它实施方案中，在约 -78℃在二氯甲烷中采用双 (2- 甲氧基乙基) 氨基三氟化硫 (Deoxo-fluor) 处理结构 XXXIII 的醛并升温至室温。

[0193] 在合适的脱保护反应条件下除去 R^{300}。在一些实施方案中，当 R^{300} 是 Ms 或 Ts 时，则合适的脱保护反应条件包括使用氢氧化钠和水且加热。在一些实施方案中，当 R^{300} 是 Cbz 时，则合适的脱保护反应条件包括使用氢气和碳载钯。

[0194] 在一些实施方案中，如流程 9 所述引入氟化的 R^{23} 基团。

流程 9 ：



[0195] 在合适的反应条件下使用合适的氟化剂处理结构 XXXX 的醇得到结构 XXXXI 的单氟化合物。在一些实施方案中，合适的氟化剂是二乙基氨基三氟化硫 (DAST) 且合适的反应条件包括在约 -78℃下使用二氯乙烷且升温至室温。在一些其它实施方案中，合适的氟化剂是 SF_4、HF。在可替代的实施方案中，在约 0℃下在二氯甲烷中使用甲磺酰氯和三乙胺处理结构 XXXX 的醇，随后用四丁基氟化铵进行处理，得到结构 XXXXI 的单氟化合物。

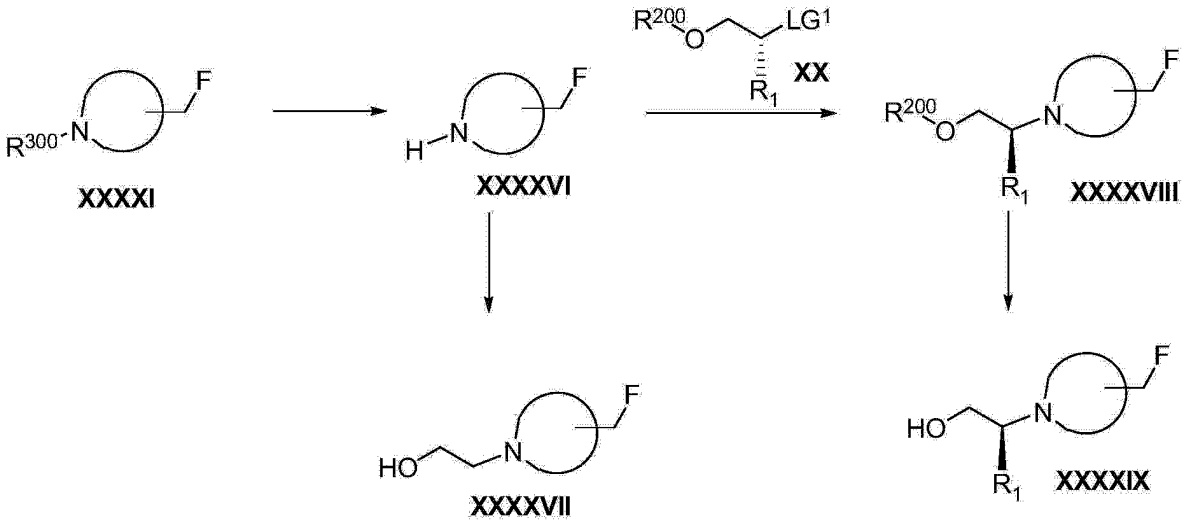
[0196] 结构 XXXX 的醇的氧化得到结构 XXXXII 的醛，然后在约 -78℃在二氯甲烷中使用二乙基氨基三氟化硫 (DAST) 进行处理并升温至室温，得到结构 XXXXIII 的二氟化物。在一些其它实施方案中，在约 -78℃在二氯甲烷中使用双 (2- 甲氧基乙基) 氨基三氟化硫 (Deoxo-fluor) 处理结构 XXXXII 的醛并升温至室温，得到结构 XXXXIII 的二氟化物。

[0197] 由结构 XXXXIV 的酸或结构 XXXXII 的醛制备结构 XXXXV 的三氟化合物。在一些实施方案中，在约 -78℃在二氯甲烷中使用二乙基氨基三氟化硫 (DAST) 处理结构 XXXXIV 的酸并升温至室温，得到结构 XXXXV 的三氟化合物。在一些其它实施方案中，在约 -78℃在二氯甲烷中使用双 (2- 甲氧基乙基) 氨基三氟化硫 (Deoxo-fluor) 处理结构 XXXXIV 的酸并升温至室温，得到结构 XXXXV 的三氟化合物。在一些实施方案中，在二氯甲烷中使用 1,3- 丙二硫醇、BF_3-OEt_2 处理结构 XXXXII 的醛，随后在 0℃二氯甲烷中使用吡啶、氢氟化物 (1:9)、二溴二甲基海因进行处理，得到结构 XXXXV 的三氟化合物。

[0198] 在一些实施方案中，如流程 10 所示将结构 XXXXI 的单氟化合物合成为结构

XXXXVII 或 XXXXIX 的化合物。虽然显示了单氟化合物，但应理解，相同的转化也可用于其它的氟化化合物。

流程 10：



[0199] 在一些实施方案中，当 R^{300} 是 t-Boc 时，则在室温下在二氧杂环己烷中使用盐酸处理结构 XXXXI 的单氟化合物，得到结构 XXXXVI 的胺。然后将结构 XXXXVI 的胺与结构 XX 的化合物偶合，且如流程 7 所述除去 R^{200} 保护基。在一些实施方案中，在乙腈中使用溴乙醇和碳酸钾处理结构 XXXXVI 的胺且加热至约 80℃。在其它实施方案中，在乙醇中使用溴乙醇和碳酸钾处理结构 XXXXVI 的胺且加热至约 80℃。

[0200] 在一个方面，如实施例中所述合成本文所述的化合物。

[0201] 在整个说明书中，基团及其取代基由本领域技术人员选择，以提供稳定的部分和化合物。

[0202] 关于保护基的创建及其去除的适用技术的详细描述在 Greene 和 Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley&Sons, New York, NY, 1999 以及 Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994 中描述，它们并入本文以参考这些公开内容。

化合物的其它形式

[0203] 在一个方面，本文所述的化合物具有一个或多个立构中心，并且各个立构中心独立地以 R 或 S 构型存在。本文所述的化合物包括所有非对映异构、对映异构和差向异构形式，及其适当的混合物。本文提供的化合物和方法包括所有顺、反、顺式 (syn)、反式 (anti)、entgegen(E) 和 zusammen(Z) 异构体及其适当的混合物。在某些实施方案中，通过使化合物的外消旋混合物与旋光性拆分剂反应形成一对非对映异构化合物 / 盐，分离非对映异构体，并回收光学纯的对映异构体，将本文所述的化合物制备为其单独的立体异构体。在一些实施方案中，使用本文所述的化合物的共价非对映异构衍生物进行对映异构体的拆分。在另一个实施方案中，通过基于溶解度差异的分离 / 拆分技术分离非对映异构体。在其它实施方案中，通过色谱法，或者通过形成非对映异构的盐并通过再结晶或色谱法或其任意组合来分离，进行立体异构体的分离。Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981。在一些实施方案中，通过立体选择性合成获得立体异构体。

[0204] 本文所述的方法和组合物包括无定形形式和晶体形式（也称作多晶型物）的使用。一方面，本文所述的化合物为药学上可接受的盐的形式。同样地，这些化合物的具有同类型活性的活性代谢物也包括在本公开内容的范围中。另外，本文所述的化合物可以以非溶剂化物的形式存在，也可以以与药学上可接受的溶剂例如水、乙醇等形成溶剂化物的形式存在。本文所述的化合物的溶剂化物形式也被认为在本文中公开。

[0205] 在一些实施方案中，本文所述的化合物制备为前药。“前药”是指在体内转化成母体药物的药剂。前药通常是有用的，因为在一些情况下它们可能比母体药物更容易施用。它们通过口服施用可能是例如可生物利用的，而母体则不是。前药也可能在药物组合物中具有比母体药物改善的溶解性。在一些实施方案中，前药的设计提高了有效的水溶性。前药的一个非限制性的实例是本文所述的化合物，其作为酯（“前药”）施用，但是随后经代谢水解而提供活性实体。在一些实施方案中，该活性实体是如本文所述的酚类化合物。前药的一个进一步的实例可以是结合在酸性基团上的短肽（聚氨基酸），该肽在此基团处代谢从而暴露出活性部分。在某些实施方案中，在体内施用后，前药以化学方式转化成该化合物的生物学、药学或治疗活性形式。在某些实施方案中，通过一个或多个步骤或过程，前药以酶学方式代谢成该化合物的生物学、药学或治疗活性形式。

[0206] 本文所述的化合物的前药包括但不限于酯、醚、碳酸酯、硫代碳酸酯、N- 酰基衍生物、N- 酰氧基烷基衍生物、叔胺的季胺衍生物、N- 曼尼希碱、席夫碱、氨基酸偶联物、磷酸酯和磺酸酯。参见，例如，Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 和 Method in Enzymology, Widder, K. 等人, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. “Design and Application of Prodrugs”, A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; 和 Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, 其中每一个均通过引用并入本文。在一些实施方案中，利用本文公开的化合物中的羟基形成前药，其中该羟基并入酰氧基烷基酯、烷氧基羰氧基烷基酯、烷基酯、芳基酯、磷酸酯、糖酯、醚等之中。

[0207] 权利要求的范围内包括本文所述的化合物的前药形式，其中前药在体内代谢生成如本文所述的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物。在一些情况下，一些本文所述的化合物可以是另一种衍生物或活性化合物的前药。

[0208] 在一些实施方案中，本文所述的化合物的芳环部分上的位点对各种代谢反应敏感。在芳环结构上引入适当的取代基将降低、最小化或消除该代谢途径。在特定实施方案中，仅作为举例，降低或消除芳环对代谢反应的敏感性的合适的取代基是卤素、氘或烷基。

[0209] 在另一个实施方案中，本文所述的化合物是同位素（例如放射性同位素）标记的或通过另一种其它手段标记的，包括但不限于使用发色团或荧光部分、生物发光标记或化学发光标记。

[0210] 本文所述的化合物包括同位素标记的化合物，除了以下事实以外，它们与本文提供的各种通式和结构中所述的那些化合物是相同的：一个或多个原子被替换成具有的原子质量或质量数与自然界中通常发现的原子质量或质量数不同的原子。可以引入本发明化合物中的同位素的实例包括氢、碳、氮、氧、氟和氯的同位素，例如 ^{2}H、^{3}H、^{13}C、^{14}C、^{15}N、^{18}O、^{17}O、^{35}S、^{18}F、^{36}Cl。在一个方面，同位素标记的本文所述的化合物，例如引入了放射性同位素例如 ^{3}H 和 ^{14}C 的化合物，在药物和 / 或底物组织分布试验中是有用的。在一个方面，用同位素例如

氘替换提供了由更高的代谢稳定性所带来的一定的治疗优势，例如体内半衰期的延长或剂量需求的减少。在一些实施方案中，存在于本文所述化合物中的一个或多个氢原子被一个或多个氘原子所替代。

[0211] 在另外的或进一步的实施方案中，本文所述的化合物在向需要的生物施用后代谢，产生代谢物，该代谢物然后用来产生所需的效果，包括所需的治疗效果。

[0212] 本文使用的“药学上可接受的”是指不消除化合物的生物活性或特性并且相对无毒的材料，例如载体或稀释剂，即，该材料可以向个体施用，而不会引起不希望的生物效应或以有害的方式与含有它的组合物中的任何成分相互作用。

[0213] 术语“药学上可接受的盐”是指对所施用的生物不引起显著刺激，并且不消除化合物的生物活性和性质的化合物的制剂。在一些实施方案中，通过将本文所述的化合物与酸反应而获得药学上可接受的盐。也可以通过将本文所述的化合物与碱反应形成盐而获得药学上可接受的盐。

[0214] 本文所述的化合物可以作为药学上可接受的盐形成和 / 或使用。药学上可接受的盐的类型包括但不限于 :(1) 酸加成盐，它是通过将化合物的游离碱形式与药学上可接受的酸反应而形成的，所述酸包括 :无机酸，用以形成盐，例如盐酸盐、氢溴酸盐、硫酸盐、磷酸盐、偏磷酸盐等 ;或有机酸，用以形成盐，例如乙酸盐、丙酸盐、己酸盐、环戊烷丙酸盐、羟基乙酸盐、丙酮酸盐、乳酸盐、丙二酸盐、琥珀酸盐、苹果酸盐、马来酸盐、富马酸盐、三氟乙酸盐、酒石酸盐、柠檬酸盐、苯甲酸盐、3-(4- 羟基苯甲酰基) 苯甲酸盐、肉桂酸盐、扁桃酸盐、甲磺酸盐、乙磺酸盐、1,2- 乙二磺酸盐、2- 羟基乙磺酸盐、苯磺酸盐、甲苯磺酸盐、2- 萘磺酸盐、4- 甲基双环 -[2.2.2] 辛 -2- 烯 -1- 羧酸盐、葡庚糖酸盐、4,4’- 亚甲基双 -(3- 羟基 -2- 烯 -1- 羧酸) 盐、3- 苯基丙酸盐、三甲基乙酸盐、叔丁基乙酸盐、十二烷基硫酸盐、葡糖酸盐、谷氨酸盐、羟基萘甲酸盐、水杨酸盐、硬脂酸盐、粘康酸盐、丁酸盐、苯乙酸盐、苯丁酸盐、丙戊酸盐等 ;(2) 当母体化合物中存在的酸性质子被置换成金属离子例如碱金属离子（例如锂盐、钠盐或钾盐）、碱土金属离子（例如镁盐或钙盐）或铝离子（例如铝盐）时形成的盐。在一些情况下，本文所述的化合物可以与有机碱配位以形成盐，例如但不限于乙醇胺盐、二乙醇胺盐、三乙醇胺盐、氨丁三醇盐、N- 甲基葡糖胺盐、二环己胺盐或三（羟甲基）甲胺盐。在其它情况下，本文所述的化合物可以与氨基酸形成盐，例如但不限于精氨酸盐、赖氨酸盐等。用来与包含酸性质子的化合物形成盐的可接受的无机碱包括但不限于氢氧化铝、氢氧化钙、氢氧化钾、碳酸钠、氢氧化钠等。

[0215] 应当理解，得到的药学上可接受的盐包括其溶剂加成形式。溶剂化物包含化学计量或非化学计量的量的溶剂，并且可以在与药学上可接受的溶剂例如水、乙醇等结晶的过程中形成。当溶剂是水时，形成水合物，或者，当溶剂是醇时，形成醇化物。本文所述的化合物的溶剂化物在本文所述的过程中可以方便地制备或形成。另外，本文提供的化合物可以以非溶剂化物和溶剂化物的形式存在。

某些术语

[0216] 除非另有说明，在本申请（包括说明书和权利要求书）中使用的以下术语具有下面给出的定义。必须指出，除非上下文另外明确指示，本说明书和所附的权利要求书中使用的单数形式“一个”、“一种”和“该”包括复数的指示物。除非另外指出，使用质谱法、NMR、HPLC、蛋白质化学、生物化学、重组 DNA 技术和药理学等常规方法。在本申请中，除非另外说

明，使用“或”或“和”意味着“和 / 或”。此外，术语“包括”以及其它形式的使用，例如“包含”、“含有”和“具有”，不是限制性的。本文使用的章节标题仅仅是为了组织的目的，而不应解释为对所描述的主题的限制。

[0217] “烷基”基团是指脂肪族烃基。烷基是饱和或不饱和的。烷基部分，不管是饱和的还是不饱和的，可以是支链的或直链的。“烷基”可以具有 1-6 个碳原子（每当在本文中出现时，数值范围例如“1-6”是指给定范围中的每个整数；例如，“1-6 个碳原子”表示烷基可以由 1 个碳原子、2 个碳原子、3 个碳原子……直到且包括 6 个碳原子组成，虽然本定义也涵盖未指定数值范围的术语“烷基”的存在）。在一个方面，烷基选自甲基、乙基、丙基、异丙基、正丁基、异丁基、仲丁基和叔丁基。典型的烷基包括但绝不限于甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基、叔丁基、戊基、新戊基、己基、烯丙基、乙烯基、乙炔、丁 -2- 烯基、丁 -3- 烯基等。在一些实施方案中，烷基的一个或多个氢原子被一个或多个氘原子所替代。

[0218] 术语“亚烷基”是指二价的烷基。任何上述的单价烷基通过从烷基抽取第二个氢原子可以成为亚烷基。典型的亚烷基包括但不限于 $-CH_2-$、$-CH(CH_3)-$、$-C(CH_3)_2-$、$-CH_2CH_2-$、$-CH_2CH_2CH_2-$ 等。

[0219] “烷氧基”基团是指（烷基）O- 基团，其中烷基如本文所定义。

[0220] 术语“烷基氨基”是指 -N（烷基）xHy 基团，其中 x 和 y 选自 x = 1、y = 1 和 x = 2、y = 0。

[0221] 术语“芳香族”是指具有包含 4n+2 个 π 电子的非定域 π 电子体系的平面环，其中 n 是整数。芳香族化合物任选地被取代。术语“芳香族”包括碳环芳基（“芳基”，例如苯基）和杂环芳基（或者“杂芳基”或“芳杂环”）基团（例如吡啶）。该术语包括单环或稠环多环（即共用相邻碳原子对的环）基团。

[0222] 术语“碳环的”或“碳环”是指其中构成环骨架的原子全部是碳原子的环或环系。该术语因此区分开碳环和杂环，杂环中的环骨架含有至少一个不同于碳的原子。

[0223] 本文使用的术语“芳基”是指其中构成环的每个原子都是碳原子的芳环。芳基任选地被取代。在一个方面，芳基是苯基或萘基。在一个方面，芳基是苯基。在一个方面，芳基是 C_6-C_{10} 芳基。取决于结构，芳基可以是单价基团或双价基团（即亚芳基）。在一些实施方案中，芳基的一个或多个氢原子被一个或多个氘原子所替代。

[0224] 术语“环烷基”是指单环或多环脂肪族非芳香族基团，其中构成环的每个原子（即骨架原子）是碳原子。环烷基可以是饱和或部分不饱和的。环烷基可以与芳环稠合，并且连接点处于不是芳环碳原子的碳上。环烷基包括具有 3-10 个环原子的基团。在一些实施方案中，环烷基选自环丙基、环丁基、环戊基、环戊烯基、环己基、环己烯基、环庚基和环辛基。环烷基可以是取代或未取代的。取决于结构，环烷基可以是单价基团或双价基团（即亚环烷基，例如但不限于环丙 -1,1- 二基、环丁 -1,1- 二基、环戊 -1,1- 二基、环己 -1,1- 二基、环己 -1,4- 二基、环庚 -1,1- 二基等）。在一个方面，环烷基是 C_3-C_6 环烷基。

[0225] 术语“卤代”或者“卤素”或“卤化物”是指氟 (F)、氯 (Cl)、溴 (Br) 或碘 (I)。在一些实施方案中，卤素是 F 或 Cl。在一些实施方案中，卤素是 F。

[0226] 术语“氟烷基”是指其中的一个或多个氢原子被替换成氟原子的烷基。在一个方面，氟烷基是 C_1-C_6 氟烷基。在一些实施方案中，氟烷基是单氟烷基，其中烷基的一个氢原子被氟原子所替代。在一些实施方案中，氟烷基是二氟烷基，其中烷基的两个氢原子被氟原子

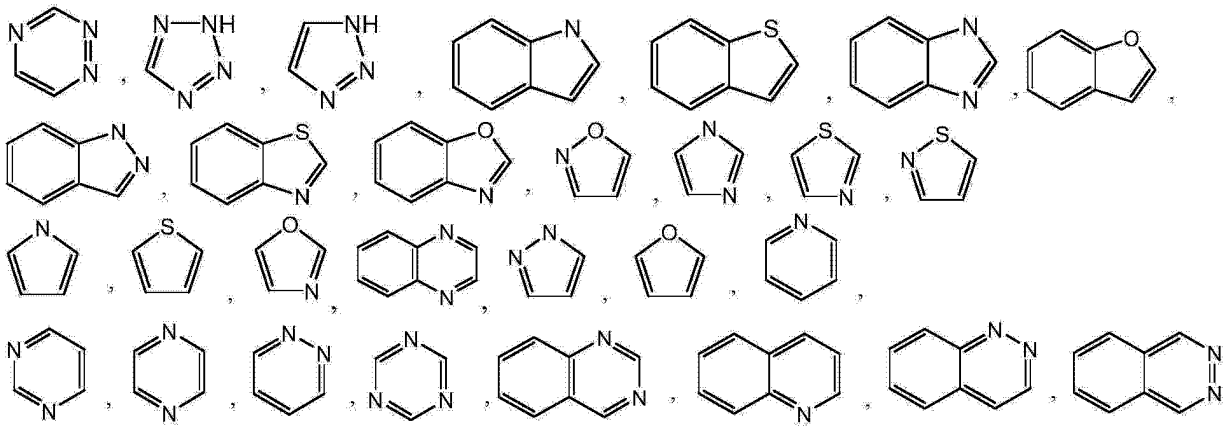
所替代。在一些实施方案中，氟烷基是三氟烷基，其中烷基的三个氢原子被氟原子所替代。在一些实施方案中，氟烷基是单氟烷基、二氟烷基或三氟烷基。在一些实施方案中，单氟烷基是 $-CH_2F$、$-CHF_2$、$-CF_3$、$-CHFCH_3$、$-CH_2CH_2F$、$-CH_2CHF_2$、$-CH_2CF_3$、$-CH_2CH_2CF_3$、$-CH_2CH_2CH_2CF_3$、$-CHCH_3CF_3$、$-CH(CF_3)_2$ 或 $-CF(CH_3)_2$。

[0227] 术语“氟亚烷基”是指二价氟烷基。任何上述的一价氟烷基可通过从氟烷基上夺取第二个氢原子而成为氟亚烷基。典型的亚烷基包括但不限于 $-CF_2-$、$CHF-$、$-CH(CF_3)-$、$-C(CF_3)_2-$、$-CHFCH_2-$、$-CH_2CHF-$、$-CF_2CH_2-$、$-CH_2CF_2-$、$-CH_2CH(CF_3)-$、$-CH_2CH(CHF_2)-$、$-CH_2CH(CFH_2)-$ 等。

[0228] 术语“杂烷基”是指这样的烷基，其中烷基的一个或多个骨架原子选自碳以外的原子，例如氧、氮（例如 $-NH-$、$-N($烷基$)-$）、硫或其组合。在一个方面，杂烷基是 C_1-C_6 杂烷基。在一些实施方案中，杂烷基是 C_1-C_4 杂烷基。在一些实施方案中，杂烷基是这样的烷基，其中该烷基的一个或多个骨架原子是氧原子（例如：羟基烷基或烷氧基烷基）。

[0229] 术语“杂环”或“杂环的”是指环中含有 1-4 个杂原子的芳香杂环（也称作杂芳基）和杂环烷基环（也称作杂脂环基团），其中环中的各个杂原子选自 O、S 和 N，其中各个杂环基团在其环系中含有 4-10 个原子，并且条件是任何环不含有两个相邻的 O 或 S 原子。非芳香族杂环基团（也称作杂环烷基）包括在其环系中仅含有 3 个原子的基团，而芳香族杂环基团在其环系中必须含有至少 5 个原子。杂环基团包括苯并稠合的环系。3 元杂环基团的一个例子是吖丙啶基。4 元杂环基团的一个例子是吖丁啶基。5 元杂环基团的一个例子是噻唑基。6 元杂环基团的一个例子是吡啶基，而 10 元杂环基团的一个例子是喹啉基。非芳香族杂环基团的例子有吡咯烷基、四氢呋喃基、二氢呋喃基、四氢噻吩基、噁唑烷酮基、四氢吡喃基、二氢吡喃基、四氢噻喃基、哌啶基、吗啉基、硫代吗啉基、噻噁烷基、哌嗪基、吖丙啶基、吖丁啶基、氧杂环丁烷基、硫杂环丁烷基、高哌啶基、氧杂环庚烷基、硫杂环庚烷基、氧氮杂䓬基、二氮杂䓬基、硫氮杂䓬基、1,2,3,6- 四氢吡啶基、二氢吡咯 -2- 基、二氢吡咯 -3- 基、吲哚啉基、2H- 吡喃基、4H- 吡喃基、二噁烷基、1,3- 二氧戊环基、吡唑啉基、二噻烷基、二硫戊环基、二氢吡喃基、二氢噻吩基、二氢呋喃基、吡唑烷基、咪唑啉基、咪唑烷基、3- 氮杂双环 [3.1.0] 己烷基、3- 氮杂双环 [4.1.0] 庚烷基、3H- 吲哚基和喹嗪基。芳香族杂环基团的例子有吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、萘啶基和呋喃并吡啶基。只要可能的话，前述基团可以是 C 连接的（或 C- 联结的）或 N- 连接的。例如，由吡咯衍生的基团可以是吡咯 -1- 基（N- 连接的）或吡咯 -3- 基（C 连接的）。此外，由咪唑衍生的基团可以是咪唑 -1- 基或咪唑 -3- 基（均为 N- 连接的）或咪唑 -2- 基、咪唑 -4- 基或咪唑 -5- 基（均为 C- 连接的）。杂环基团包括苯并稠合的环系。非芳香族杂环可以被一个或两个氧代（＝ O）部分取代，例如吡咯烷 -2- 酮。

[0230] 术语“杂芳基”或者“杂芳香族的”是指包含一个或多个选自氮、氧和硫的环杂原子的芳基。杂芳基的说明性例子包括以下部分：



等。单环杂芳基包括吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、哒嗪基、三嗪基、噁二唑基、噻二唑基和呋咱基。在一些实施方案中，杂芳基在环中含有 0-3 个 N 原子。在一些实施方案中，杂芳基在环中含有 1-3 个 N 原子。在一些实施方案中，杂芳基在环中含有 0-3 个 N 原子、0-1 个 O 原子和 0-1 个 S 原子。在一些实施方案中，杂芳基是单环或双环杂芳基。在一些实施方案中，杂芳基是 C_1-C_9 杂芳基。在一些实施方案中，单环杂芳基是 C_1-C_5 杂芳基。在一些实施方案中，单环杂芳基是 5 元或 6 元杂芳基。在一些实施方案中，双环杂芳基是 C_6-C_9 杂芳基。取决于结构，杂芳基可以是单价基团或双价基团（即亚杂芳基）。

[0231] “杂环烷基”或“杂脂环”基团是指这样的环烷基基团，其中该环烷基的至少一个碳原子被氮（取代或未取代的，例如 -NH-、-NR^{23}-）、氧（-O-）或硫（例如，-S-、-S(=O)- 或 -S(=O)$_2$-）所替代。该基团可以与芳基或杂芳基稠合。在一些实施方案中，杂环烷基选自噁唑烷酮基、吡咯烷基、四氢呋喃基、四氢噻吩基、四氢吡喃基、四氢噻喃基、哌啶基、吗啉基、硫代吗啉基、哌嗪基和吲哚啉基。术语杂脂环还包括所有环形式的碳水化合物，包括但不限于单糖、二糖和寡糖。在一个方面，杂环烷基是 C_2-C_{10} 杂环烷基。在另一方面，杂环烷基是 C_4-C_{10} 杂环烷基。在一些实施方案中，杂环烷基在环中含有 0-2 个 N 原子。在一些实施方案中，杂环烷基在环中含有 0-2 个 N 原子、0-2 个 O 原子和 0-1 个 S 原子。

[0232] 术语“键”或“单键”是指两个原子之间的化学键，或当由键连接的原子被视作更大的亚结构的一部分时，指两个部分之间的化学键。一方面，当本文所述的基团是一个键时，提及的基团不存在，从而允许在剩下的所述基团之间形成一个键。

[0233] 术语“部分”是指分子的特定片段或官能团。化学部分通常被认为是嵌入分子中或附加在分子上的化学实体。

[0234] 术语“任选取代的”或“取代的”是指所提及的基团可以被一个或多个另外的基团取代，这些另外的基团分别且独立地选自烷基、环烷基、芳基、杂芳基、杂脂环基、羟基、烷氧基、芳氧基、烷硫基、芳硫基、烷基亚砜、芳基亚砜、烷基砜、芳基砜、氰基、卤代、硝基、卤代烷基、氟烷基、氟烷氧基和氨基（包括单取代的和二取代的氨基），及其受保护的衍生物。在一些实施方案中，任选的取代基独立地选自卤素、-CN、-NH_2、-NH(CH_3)、-N(CH_3)$_2$、-OH、-CO_2H、-CO_2 烷基、-C(=O)NH_2、-C(=O)NH(烷基)、-C(=O)N(烷基)$_2$、-S(=O)$_2NH_2$、-S(=O)$_2$NH(烷基)、-S(=O)$_2$N(烷基)$_2$、烷基、环烷基、氟烷基、杂烷基、烷氧基、氟烷氧基、杂环烷基、芳基、杂芳基、芳氧基、烷硫基、芳硫基、烷基亚砜、芳基亚砜、烷基砜和芳基砜。在一些实施方案中，任选的取代基独立地选自卤素、-CN、-NH_2、-OH、-NH(CH_3)、-N(CH_3)$_2$、-CH_3、-CH_2C

H_3、$-CF_3$、$-OCH_3$ 和 $-OCF_3$。在一些实施方案中，取代基被一或二个前述基团取代。在一些实施方案中，脂肪族碳原子（非环或环的，饱和或不饱和的碳原子，不包括芳香族碳原子）上的任选的取代基包括氧代（＝O）。

[0235] 在某些实施方案中，本文提出的化合物具有一个或多个立构中心，并且各个中心独立地以 R 或 S 构型存在。本文所述的化合物包括所有非对映异构、对映异构和差向异构形式，及其适当的混合物。如果需要的话，通过例如立体选择性合成和／或经手性色谱柱分离立体异构体等方法获得立体异构体。

[0236] 本文所述的方法和制剂包括使用具有式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 结构的化合物的 N- 氧化物（如果合适的话）、晶体形式（也称作多晶型物）或药学上可接受的盐，以及这些化合物的具有相同类型活性的活性代谢物。在一些情况下，化合物可作为互变异构体存在。所有互变异构体都包括在本文所述的化合物的范围内。在特定实施方案中，本文所述的化合物以与药学上可接受的溶剂例如水、乙醇等形成溶剂化物的形式存在。在其它实施方案中，本文所述的化合物以非溶剂化物的形式存在。

[0237] 本文对于制剂、组合物或成分使用的术语“可接受的”是指对被治疗的受试者的一般健康状况没有持续的不利影响。

[0238] 本文使用的术语“调节”是指与靶标直接或间接地相互作用，以便改变靶标的活性，仅作为举例，包括增强靶标的活性，抑制靶标的活性，限制靶标的活性，或扩展靶标的活性。

[0239] 本文使用的术语“调节剂”是指与靶标直接或间接地相互作用的分子。相互作用包括但不限于激动剂、部分激动剂、反向激动剂、拮抗剂、降解剂或其组合的相互作用。在一些实施方案中，调节剂是拮抗剂。在一些实施方案中，调节剂是降解剂。

[0240] 本文使用的“选择性雌激素受体调节剂”或“SERM”是指有差别地调节不同组织中的雌激素受体活性的分子。例如，在一些实施方案中，SERM 在某些组织中显示 ER 拮抗剂活性而在其它组织中显示 ER 激动剂活性。在一些实施方案中，SERM 在某些组织中显示 ER 拮抗剂活性而在其它组织中不显示或显示最低的 ER 激动剂活性。在一些实施方案中，SERM 在乳腺组织、卵巢组织、子宫内膜组织和／或宫颈组织中显示 ER 拮抗剂活性而在子宫组织中不显示或显示最低的 ER 激动剂活性。

[0241] 本文使用的术语“拮抗剂”是指这样的小分子药剂，它与核激素受体结合并随后降低核激素受体的激动剂诱导的转录活性。

[0242] 本文使用的术语“激动剂”是指这样的小分子药剂，它与核激素受体结合并随后在不存在已知激动剂时提高核激素受体的转录活性。

[0243] 本文使用的术语“反向激动剂”是指这样的小分子药剂，它与核激素受体结合并随后降低在不存在已知激动剂时存在的核激素受体转录活性的基础水平。

[0244] 本文使用的术语“降解剂”是指与核激素受体结合并随后降低所述受体的稳态蛋白质水平的小分子药剂。在一些实施方案中，本文所述的降解剂使稳态雌激素受体水平降低至少 10％、至少 20％、至少 30％、至少 40％、至少 50％、至少 60％、至少 65％、至少 70％、至少 75％、至少 80％、至少 85％、至少 90％或至少 95％。在一些实施方案中，本文所述的降解剂使稳态雌激素受体水平降低至少 65％。在一些实施方案中，本文所述的降解剂使稳态雌激素受体水平降低至少 85％。

[0245] 本文使用的术语“选择性雌激素受体降解剂”或“SERD”是指与其它受体相比优先结合雌激素受体并且随后降低稳态雌激素受体水平的小分子药剂。

[0246] 本文使用的术语“ER 依赖的”是指在不存在雌激素受体的情况下将不会发生或者将不会相同程度地发生的疾病或状况。

[0247] 本文使用的术语“ER 介导的”是指在不存在雌激素受体的情况下将不会发生但在雌激素受体的存在下能够发生的疾病或状况。

[0248] 本文使用的术语“ER 敏感的”是指在不存在雌激素的情况下将不会发生或者将不会相同程度地发生的疾病或状况。

[0249] 本文使用的术语“癌症”是指倾向于以不受控的方式增殖而且在一些情况下转移（扩散）的细胞的异常生长。癌症的类型包括但不限于处于疾病的任何阶段、发生或未发生转移的实体瘤（如膀胱、肠、脑、乳腺、子宫内膜、心、肾、肺、子宫、淋巴组织（淋巴瘤）、卵巢、胰腺或其它内分泌器官（甲状腺）、前列腺、皮肤（黑色素瘤或基底细胞癌）的肿瘤或血液肿瘤（如白血病和淋巴瘤）。

[0250] 癌症的其它非限制性例子包括：急性淋巴细胞白血病、急性髓样白血病、肾上腺皮质癌、肛门癌、阑尾癌、星形细胞瘤、非典型畸胎瘤 / 杆状瘤、基底细胞癌、胆管癌、膀胱癌、骨癌（骨肉瘤和恶性纤维组织细胞瘤）、脑干胶质瘤、脑瘤、脑和脊髓肿瘤、乳腺癌、支气管肿瘤、伯基特淋巴瘤、宫颈癌、慢性淋巴细胞白血病、慢性髓性白血病、结肠癌、结直肠癌、颅咽管瘤、皮肤 T 细胞淋巴瘤、胚胎瘤、子宫内膜癌、室管膜母细胞瘤、室管膜瘤、食道癌、尤因肉瘤家族肿瘤、眼癌、视网膜母细胞瘤、胆囊癌、胃癌、胃肠道类癌瘤、胃肠道间质瘤 (GIST)、胃肠道基质细胞瘤、胚细胞瘤、神经胶质瘤、毛细胞白血病、头颈癌、肝细胞（肝）癌、何杰金淋巴瘤、下咽癌、眼内黑色素瘤、胰岛细胞瘤（内分泌胰腺）、卡波西肉瘤、肾癌、朗格罕细胞增生症、喉癌、白血病、急性淋巴细胞白血病、急性髓样白血病、慢性淋巴细胞白血病、慢性髓性白血病、毛细胞白血病、肝癌、肺癌、非小细胞肺癌、小细胞肺癌、伯基特淋巴瘤、皮肤 T 细胞淋巴瘤、何杰金淋巴瘤、非何杰金淋巴瘤、淋巴瘤、瓦尔登斯特伦巨球蛋白血症、髓母细胞瘤、髓上皮瘤、黑色素瘤、间皮瘤、口腔癌、慢性髓性白血病、髓样白血病、多发性骨髓瘤、鼻咽癌、神经母细胞瘤、非何杰金淋巴瘤、非小细胞肺癌、口癌、口咽癌、骨肉瘤、骨恶性纤维组织细胞瘤、卵巢癌、卵巢上皮癌、卵巢生殖细胞肿瘤、卵巢低度潜在恶性肿瘤、胰腺癌、乳头状瘤、甲状旁腺癌、阴茎癌、咽癌、中度分化的松果体实质瘤、松果体母细胞瘤和幕上原始神经外胚瘤、垂体瘤、浆细胞瘤 / 多发性骨髓瘤、胸膜肺母细胞瘤、主要中枢神经系统淋巴瘤、前列腺癌、直肠癌、肾细胞（肾）癌、视网膜母细胞瘤、横纹肌肉瘤、唾液腺癌、肉瘤、尤因肉瘤家族肿瘤、肉瘤、卡波西、Sézary 综合征、皮肤癌、小细胞肺癌、小肠癌、软组织肉瘤、鳞状细胞癌、胃癌、幕上原始神经外胚瘤、T- 细胞淋巴瘤、睾丸癌、喉癌、胸腺瘤和胸腺癌、甲状腺癌、尿道癌、子宫癌、子宫肉瘤、阴道癌、外阴癌、瓦尔登斯特伦巨球蛋白血症、肾母细胞瘤。

[0251] 本文使用的术语“共施用”或类似用语意在包括对一名患者施用多种选定的治疗剂，并且旨在包括通过相同或不同的施用途径或者在相同或不同的时间施用多种药剂的治疗方案。

[0252] 本文使用的术语“有效量”或“治疗有效量”是指足以在一定程度上缓解所治疗的疾病或状况的一种或多种症状的药剂或化合物的给药量。结果可以是疾病的体征、症状或

起因的减少和 / 或缓解，或者生物系统的任何其它希望的变化。例如，用于治疗应用的“有效量”是包含本文公开的化合物的组合物的量，该量是提供疾病症状的临床显著下降所需要的。在任意单独的情况下，可以使用例如剂量递增研究等技术来确定适当的“有效”量。

[0253] 本文使用的术语“增强”是指所需效果的效能或持续时间的提高或延长。因此，关于增强治疗剂的效果，术语“增强”是指在效能或持续时间上提高或延长其它治疗剂对系统的效果的能力。本文使用的“增强有效量”是指足以增强另一种治疗剂在所需系统中的效果的量。

[0254] 本文使用的术语“药物组合”是指通过混合或组合超过一种活性成分而得到的产品，并且包括活性成分的固定和非固定组合。术语“固定组合”是指活性成分例如式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐和联合药剂以单一实体或剂量的形式同时向患者施用。术语“非固定组合”是指活性成分例如式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐和联合药剂作为单独的实体同时、并行或相继地向患者施用，没有具体的间隔时间限制，其中这样的施用在患者体内提供这两种化合物的有效水平。后者也应用于鸡尾酒疗法，例如三种或更多种活性成分的施用。

[0255] 术语“试剂盒”和“制品”作为同义词使用。

[0256] 本文公开的化合物的“代谢物”是化合物代谢时形成的该化合物的衍生物。术语“活性代谢物”是指化合物代谢时形成的该化合物的生物活性衍生物。本文使用的术语“代谢”是指特定物质被生物体改变的过程（包括但不限于水解反应和酶催化的反应）的总和。因此，酶可以对化合物产生特定的结构改变。例如，细胞色素 P450 催化多种氧化和还原反应，而尿苷二磷酸葡糖醛酸基转移酶催化活化的葡糖醛酸分子向芳香醇、脂肪醇、羧酸、胺和游离巯基的转移。任选地通过对宿主施用化合物并分析来自宿主的组织样品，或通过化合物与肝细胞一起在体外孵育并分析得到的化合物，来鉴定本文公开的化合物的代谢物。

[0257] 术语“受试者”或“患者”包括哺乳动物。哺乳动物的例子包括但不限于哺乳纲的任意成员：人，非人灵长类动物，例如黑猩猩以及其它猿和猴物种；农畜，例如牛、马、绵羊、山羊、猪；家畜，例如兔、狗和猫；实验动物，包括啮齿动物，例如大鼠、小鼠和豚鼠，等等。在一个方面，哺乳动物是人。

[0258] 本文使用的术语“治疗”包括预防性地和 / 或治疗性地缓解、消除或改善疾病或状况的至少一种症状，预防另外的症状，抑制疾病或状况，例如阻止疾病或状况的发展、缓解疾病或状况、使疾病或状况消退、缓解疾病或状况引起的状况，或者停止疾病或状况的症状。

给药途径

[0259] 合适的给药途径包括但不限于口服、静脉内、直肠、喷雾、肠胃外、眼、肺、经粘膜、透皮、阴道、耳、鼻和局部给药。另外，仅作为举例，肠胃外递送包括肌肉内、皮下、静脉内、髓内注射以及鞘内、直接心室内、腹膜内、淋巴管内和鼻内注射。

[0260] 在某些实施方案中，如本文所述的化合物以局部而不是系统方式给药，例如，通过将化合物直接注射到器官中，通常在迟效制剂或持续释放制剂中。在特定实施方案中，通过植入（例如皮下或肌肉内）或通过肌肉内注射施用长效制剂。此外，在其它实施方案中，在定向药物递送系统中，例如，在包被了器官特异性抗体的脂质体中递送药物。在这样的实施方案中，脂质体靶向至器官并且被器官选择性吸收。在另外的实施方案中，以快速释放制剂

形式、以延长释放制剂形式或以立即释放制剂形式提供本文所述的化合物。在另外的实施方案中，局部施用本文所述的化合物。

药物组合物 / 制剂

[0261] 在一些实施方案中，将本文所述的化合物配制为药物组合物。药物组合物以常规方式使用一种或多种药学上可接受的非活性成分来配制，该非活性成分有利于将活性化合物加工成可以药学使用的制剂。合适的制剂取决于选择的给药途径。本文所述的药物组合物的概述可见，例如 Remington:The Science and Practice of Pharmacy, 第十九版 (Easton, Pa.:Mack Publishing Company, 1995) ;Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975 ; Liberman, H.A. 和 Lachman, L. 编 , Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980 ;以及 Pharmaceutical Dosage Forms and Drug Delivery Systems, 第七版 (Lippincott Williams&Wilkins1999), 它们并入本文以参考这些公开内容。

[0262] 本文提供了包含式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐和至少一种药学上可接受的非活性成分的药物组合物。在一些实施方案中，本文所述的化合物作为药物组合物施用，在该药物组合物中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与其它活性成分混合，如同在联合治疗中一样。在其它实施方案中，药物组合物包含其它医学或药学上的制剂、载体、佐剂、防腐剂、稳定剂、湿润剂或乳化剂、溶解促进剂、用于调节渗透压的盐和 / 或缓冲剂。在另外的实施方案中，药物组合物包含其它有治疗价值的物质。

[0263] 本文使用的药物组合物是指式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与其它化学成分 (即药学上可接受的非活性成分) 例如载体、赋形剂、粘合剂、填充剂、悬浮剂、调味剂、甜味剂、崩解剂、分散剂、表面活性剂、润滑剂、着色剂、稀释剂、增溶剂、润湿剂、增塑剂、稳定剂、渗透促进剂、湿润剂、抗泡沫剂、抗氧化剂、防腐剂或其一种或多种组合的混合物。药物组合物有利于向哺乳动物施用该化合物。

[0264] 取决于疾病的严重程度、受试者的年龄和相对健康、使用的化合物的效能和其它因素，治疗有效量可能差异很大。化合物可以单独使用，或者作为混合物的成分与一种或多种治疗剂联合使用。

[0265] 本文所述的药物制剂通过适当的给药途径施用于受试者，包括但不限于口服、肠胃外 (例如静脉内、皮下、肌肉内)、鼻内、口腔、局部、直肠或透皮给药途径。本文所述的药物制剂包括但不限于水性液体分散体、自乳化分散体、固溶体、脂质体分散体、气雾剂、固体剂型、粉末、立即释放制剂、控制释放制剂、速溶制剂、片剂、胶囊、丸剂、延迟释放制剂、延长释放制剂、脉冲释放制剂、多颗粒制剂，和混合的立即释放和控制释放制剂。

[0266] 包含式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的药物组合物以常规方式制备，例如，仅作为举例，利用常规的混合、溶解、制粒、制锭、研磨、乳化、包封、包埋或压制工艺制备。

[0267] 药物组合物将包含游离酸或游离碱形式或药学上可接受的盐形式的至少一种式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物作为活性成分。另外，本文所述的方法和药物组合物包括使用这些化合物的具有相同类型活性的 N- 氧化物 (如果合适的话)、晶体形式、无定形相以及活性代谢物。在一些实施方案中，本文所述的化合物以非溶剂化物的形式

存在，或者以与药学上可接受的溶剂例如水、乙醇等形成溶剂化物的形式存在。本文所述的化合物的溶剂化物形式也被认为在本文中公开。

[0268] 包含式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的本文所述的药物组合物被配制为任意合适的剂型，包括但不限于水性口服分散体、液体、凝胶、糖浆、酏剂、浆剂、悬浮液、固体口服剂型、控制释放制剂、速溶制剂、泡腾制剂、冻干制剂、片剂、粉末、丸剂、糖锭剂、胶囊、延迟释放制剂、延长释放制剂、脉冲释放制剂、多颗粒制剂，和混合的立即释放和控制释放制剂。

[0269] 口服施用的药物制剂包括由明胶制成的推入配合式胶囊以及由明胶和增塑剂例如甘油或山梨糖醇制成的密封软胶囊。推入配合式胶囊包含与填充剂例如乳糖、粘合剂例如淀粉和 / 或润滑剂例如滑石或硬脂酸镁以及任选的稳定剂混合的活性成分。在一些实施方案中，推入配合式胶囊除胶囊壳和活性成分以外不包含任何其它成分。在软胶囊中，活性化合物溶解或悬浮在合适的液体例如脂肪油、液体石蜡或液体聚乙二醇中。在一些实施方案中，加入稳定剂。

[0270] 所有用于口服施用的制剂都处于适合该施用的剂量。

[0271] 在一个方面，通过混合式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐和一种或多种以下成分来制备固体口服剂型 :抗氧化剂、调味剂和载体材料，例如粘合剂、悬浮剂、崩解剂、填充剂、表面活性剂、增溶剂、稳定剂、润滑剂、湿润剂和稀释剂。

[0272] 在一些实施方案中，本文公开的固体剂型为片剂 (包括混悬片剂、速熔片剂、咀嚼崩解片剂、快速崩解片剂、泡腾片剂或囊片)、丸剂、粉末、胶囊、固体分散体、固溶体、可生物蚀解剂型、控制释放制剂、脉冲释放剂型、多颗粒剂型、珠子、微丸、颗粒的形式。在其它实施方案中，药物制剂为粉末形式。在另外的实施方案中，药物制剂为片剂形式。在其它实施方案中，药物制剂为胶囊形式。

[0273] 在一些实施方案中，通过混合式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的颗粒和一种或多种药物赋形剂形成掺混组合物来制备固体剂型，例如片剂、泡腾片剂和胶囊。该掺混物容易细分成等效的单位剂型，例如片剂、丸剂和胶囊。在一些实施方案中，个体单位剂量包含薄膜包衣。这些制剂通过常规配制技术制备。

[0274] 常规配制技术包括例如下列方法之一或其组合 :(1) 干混，(2) 直接压制，(3) 碾磨，(4) 干法或非水法制粒，(5) 湿法制粒，或 (6) 融合。其它方法包括例如喷雾干燥、锅包衣、熔融制粒、制粒、流化床喷雾干燥或包衣 (例如沃斯特 (wurster) 包衣法)、切向包衣、顶部喷雾、制片、挤出等。

[0275] 在一些实施方案中，片剂将包含围绕最终的压制片剂的薄膜。在一些实施方案中，薄膜包衣可以提供式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐从制剂中的延迟释放。在其它实施方案中，薄膜包衣有助于患者的依从性 (例如 Opadry® 包衣或糖包衣)。薄膜包衣包括 Opadry®，一般为片重的约 1％到约 3％。

[0276] 例如，通过将上述化合物的制剂的掺混物放置到胶囊内部，可以制备胶囊。在一些实施方案中，将制剂 (非水性悬浮液和溶液) 放置在明胶软胶囊中。在其它实施方案中，将制剂放置在标准明胶胶囊或非明胶胶囊例如包含 HPMC 的胶囊中。在其它实施方案中，将制剂放置在撒布胶囊中，其中整个吞下该胶囊或者在食用前打开该胶囊并将内容物撒布到食

物上。

[0277] 在各个实施方案中，将式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的颗粒与一种或多种赋形剂干混并压制成块，例如片剂，其具有的硬度足以提供在口服施用后不到约 30 分钟、不到约 35 分钟、不到约 40 分钟、不到约 45 分钟、不到约 50 分钟、不到约 55 分钟或不到约 60 分钟内基本崩解从而将制剂释放到胃肠液中的药物组合物。

[0278] 在另外的实施方案中，还制备了泡腾粉末。已使用泡腾盐来将药物分散在水中以供口服施用。

[0279] 在一些实施方案中，药物固体口服剂型被配制为提供活性化合物的控制释放。控制释放是指活性化合物依照期望的特征在延长的时间段内从其所掺入的剂型中释放。控制释放特征包括，例如持续释放、延长释放、脉冲释放和延迟释放特征。不同于立即释放组合物，控制释放组合物允许依照预定的特征在延长的时间段内向受试者递送药剂。这样的释放速率可以在延长的时间段内提供治疗有效水平的药剂，从而与常规的快速释放剂型相比，在提供更长的药理反应时期的同时使副作用最小化。这样的更长的反应时间提供了相应的短效立即释放制剂无法达到的许多固有益处。

[0280] 在一些实施方案中，本文所述的固体剂型被配制为肠溶衣延迟释放口服剂型，即，如本文所述的药物组合物的口服剂型，其利用肠溶衣影响在小肠或大肠中的释放。在一个方面，肠溶衣剂型是压制或模制或挤出的片剂 / 制模 (包衣或未包衣的)，包含活性成分和 / 或其它组合物成分的颗粒、粉末、微丸、珠子或颗粒，它们自身包衣或未包衣。在一个方面，肠溶衣口服剂型为包含微丸、珠子或颗粒的胶囊的形式。

[0281] 使用常规包衣技术例如喷雾或锅包衣来施加包衣。包衣厚度必须足以确保口服剂型在到达肠道中的所需局部递送部位前保持完整。

[0282] 在其它实施方案中，使用脉冲剂型递送本文所述的制剂。脉冲剂型能够在控制的延迟时间后的预定时间点或在特定部位提供一个或多个立即释放脉冲。示例性的脉冲剂型及其制备方法在美国专利号 5,011,692、5,017,381、5,229,135、5,840,329 和 5,837,284 中公开。在一个实施方案中，脉冲剂型包括至少两组颗粒 (即多颗粒)，每组颗粒包含本文所述的制剂。当被哺乳动物摄入时，第一组颗粒提供基本立即剂量的活性化合物。第一组颗粒可以未包衣，或者包含包衣和 / 或密封剂。在一个方面，第二组颗粒包含包衣颗粒。第二组颗粒上的包衣在摄入后在第二剂量释放前提供约 2 小时到约 7 小时的延迟。用于药物组合物的合适的包衣在本文中或在本领域中已有描述。

[0283] 在一些实施方案中，提供了包含式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的颗粒和至少一种分散剂或悬浮剂的药物制剂，用于向受试者口服施用。该制剂可以是用于悬浮的粉末和 / 或颗粒，并且当与水混合时获得基本均匀的悬浮液。

[0284] 在一个方面，用于口服施用的液体制剂剂型为水性悬浮液的形式，其选自包括但不限于药学上可接受的水性口服分散体、乳剂、溶液、酏剂、凝胶和糖浆的组。参见，例如 Singh 等，Encyclopedia of Pharmaceutical Technology, 第二版，754-757 页 (2002))。除了式 (I) 的化合物的颗粒以外，液体剂型还包含添加剂，例如：(a) 崩解剂；(b) 分散剂；(c) 湿润剂；(d) 至少一种防腐剂；(e) 增稠剂；(f) 至少一种甜味剂；和 (g) 至少一种调味

剂。在一些实施方案中，水性分散体可以进一步包含结晶抑制剂。

[0285] 包含式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的口腔制剂使用多种本领域已知的制剂来施用。例如，这样的制剂包括但不限于美国专利号 4,229,447、4,596,795、4,755,386 和 5,739,136。另外，本文所述的口腔剂型可以进一步包含生物可蚀解（可水解）的聚合物载体，该载体也用于将剂型粘附于口腔粘膜。对于口腔或舌下施用，组合物可以采取以常规方式配制的片剂、锭剂或凝胶的形式。

[0286] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐被制备为透皮剂型。在一个实施方案中，本文所述的透皮制剂包含至少三种成分：(1) 式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的制剂；(2) 渗透促进剂；和 (3) 水性佐剂。在一些实施方案中，透皮制剂包含另外的成分，例如但不限于胶凝剂、乳膏和软膏基质等。在一些实施方案中，透皮制剂进一步包含织造或非织造的背衬材料，以增强吸收并防止透皮制剂从皮肤上移除。在其它实施方案中，本文所述的透皮制剂可以保持饱和或过饱和状态，以促进向皮肤内的扩散。

[0287] 在一个方面，适合透皮施用本文所述的化合物的制剂采用透皮递送装置和透皮递送贴片，并且可以是溶解和 / 或分散在聚合物或粘合剂中的亲脂性乳剂或缓冲的水溶液。在一个方面，构造这样的贴片以连续、脉冲或按需递送药剂。更进一步地，本文所述的化合物的透皮递送可以通过离子电渗贴片等手段完成。在一个方面，透皮贴片提供了活性化合物的控制递送。在一个方面，透皮装置为绷带的形式，其包含背衬部分；储层，其包含化合物，任选地包含载体；任选的速率控制屏障，以在延长的时间段内以受控的和预定的速率向宿主的皮肤递送化合物；以及将该装置固定在皮肤上的工具。

[0288] 在一个方面，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐被配制为适合肌肉内、皮下或静脉内注射的药物组合物。在一个方面，适合肌肉内、皮下或静脉内注射的制剂包括生理学上可接受的无菌水性或非水性溶液、分散体、悬浮液或乳剂，以及用于重配成无菌可注射溶液或分散体的无菌粉末。合适的水性和非水性载体、稀释剂、溶剂或赋形剂的例子包括水、乙醇、多元醇（丙二醇、聚乙二醇、甘油、克列莫佛等）、植物油和有机酯例如油酸乙酯。在一些实施方案中，适合皮下注射的制剂含有添加剂，例如防腐剂、湿润剂、乳化剂和分散剂。可以通过使用吸收延迟剂例如单硬脂酸铝和明胶来引起可注射的药物形式的延长吸收。

[0289] 对于静脉内注射，本文所述的化合物被配制到水溶液中，优选生理学相容的缓冲液例如汉克斯液、林格液或生理盐水缓冲液中。

[0290] 对于经粘膜施用，在制剂中使用适合将要渗透的屏障的渗透剂。这样的渗透剂是本领域公知的。对于其它肠胃外注射，合适的制剂包括水性或非水性溶液，优选地包含生理学上相容的缓冲剂或赋形剂。这样的赋形剂是已知的。

[0291] 肠胃外注射可以包括快速浓注或连续输注。用于注射的制剂可以呈现于单位剂型中，例如在安瓿中或多剂量容器中，其中添加有防腐剂。本文所述的药物组合物可以为适合肠胃外注射的形式，如在油性或水性载体中的无菌悬浮液、溶液或乳剂，并且可以含有配制用剂，例如悬浮剂、稳定剂和 / 或分散剂。在一个方面，活性成分为粉末的形式，用于在使用前用合适的载体例如无菌无热原的水重配。

[0292] 在某些实施方案中，可以使用用于药物化合物的递送系统，例如脂质体和乳剂。在

某些实施方案中，本文提供的组合物还可以包含选自例如羧甲基纤维素、卡波姆（丙烯酸聚合物）、聚（甲基丙烯酸甲酯）、聚丙烯酰胺、聚卡波非、丙烯酸/丙烯酸丁酯共聚物、藻酸钠和葡聚糖的粘膜粘附聚合物。

[0293] 在一些实施方案中，本文所述的化合物可以局部施用，并且可以配制为多种可局部施用的组合物，例如溶液、悬浮液、洗剂、凝胶、糊剂、药棒、香膏、乳膏或软膏。这样的药物化合物可以包含增溶剂、稳定剂、张力增强剂、缓冲剂和防腐剂。

给药方法和治疗方案

[0294] 在一个实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐用于制备治疗哺乳动物中将受益于雌激素受体活性降低的疾病或状况的药物。在需要这种治疗的哺乳动物中治疗任何本文所述的疾病或状况的方法包括向所述哺乳动物施用治疗有效量的药物组合物，该药物组合物包含至少一种式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，或其药学上可接受的盐、活性代谢物、前药或药学上可接受的溶剂化物。

[0295] 在某些实施方案中，为了预防性和/或治疗性处理，施用包含本文所述的化合物的组合物。在某些治疗性应用中，以足以治愈或至少部分阻止疾病或状况的至少一种症状的量，向已患有该疾病或状况的患者施用该组合物。对于该应用有效的量取决于疾病或状况的严重程度和进程，先前的治疗，患者的健康状况、体重和对药物的响应，以及治疗医生的判断。任选地通过包括但不限于剂量递增临床试验的方法确定治疗有效量。

[0296] 在预防性应用中，向易患特定疾病、病症或状况或处于患病风险中的患者施用包含本文所述的化合物的组合物。这样的量被定义为“预防有效量或剂量”。在这种应用中，精确的量也取决于患者的健康状态、体重等。当在患者中使用时，针对该应用的有效量将取决于疾病、病症或状况的严重程度和进程，先前的治疗，患者的健康状况和对药物的响应，以及治疗医生的判断。在一个方面，预防性处理包括向先前经历了所治疗的疾病的至少一种症状而目前处于缓解期的哺乳动物施用包含式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的药物组合物，以预防该疾病或状况的症状的复发。

[0297] 在患者的状况没有得到改善的某些实施方案中，根据医生的判断，长期进行化合物的给药，即持续延长的一段时间，包括患者生命的整个持续时间，以便改善或者以其它方式控制或限制患者的疾病或状况的症状。

[0298] 在患者的状态得到改善的某些实施方案中，所施用的药物的剂量可以暂时减少或暂时中止某个时间长度（即“休药期”）。在特定实施方案中，休药期的长度为 2 天至 1 年，仅作为举例，包括 2 天、3 天、4 天、5 天、6 天、7 天、10 天、12 天、15 天、20 天、28 天或 28 天以上。仅作为举例，休药期期间的剂量减少是 10％ -100％，仅作为举例，包括 10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％和 100％。

[0299] 一旦患者状况已发生改善，如果必要的话，施用维持剂量。随后，在特定实施方案中，施用剂量或频率或此二者根据症状减少到疾病、病症或状况保持改善的水平。但是，在某些实施方案中，当症状有任何复发时，患者需要长期的间歇治疗。

[0300] 对应于该量的给定药剂的量根据例如具体化合物、疾病状况及其严重程度、需要治疗的受试者或宿主的特性（例如体重、性别）等因素而不同，但是仍然可以根据病例的具

体情况进行确定，包括例如所施用的具体药剂、给药途径、所治疗的病症和所治疗的受试者或宿主。

[0301] 但是，通常，成人治疗所用的剂量一般在每天 0.01mg-5000mg 的范围内。在一个方面，成人治疗所用的剂量是每天约 1mg 到约 1000mg。在一个实施方案中，所需剂量方便地以单一剂量或分份剂量呈现，该分份剂量同时施用或以适当间隔施用，例如每天二次、三次、四次或更多次亚剂量。

[0302] 在一个实施方案中，适合于本文所述的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的日剂量是约 0.01 到约 10mg/kg 体重。在一些实施方案中，基于单个治疗方案相关的许多变量，日剂量或剂型中活性成分的量低于或高于本文所述的范围。在各种实施方案中，日剂量和单位剂量根据许多变量而改变，包括但不限于所使用的化合物的活性、所治疗的疾病或状况、给药模式、受试个体的需求、所治疗的疾病或状况的严重程度和从业医生的判断。

[0303] 此类治疗方案的毒性和治疗效果在细胞培养或实验动物中通过标准药学程序来确定，包括但不限于 LD_{50} 和 ED_{50} 的测定。毒性作用和治疗效果之间的剂量比是治疗指数，并且其表示成 LD_{50} 与 ED_{50} 之比。在某些实施方案中，从细胞培养试验和动物研究中获得的数据用于制定在包括人的哺乳动物中使用的治疗有效日剂量范围和 / 或治疗有效的单位剂量。在一些实施方案中，本文所述的化合物的日剂量处于具有最小毒性的、包括 ED_{50} 的循环浓度范围内。在某些实施方案中，取决于所使用的剂型和所采用的给药途径，日剂量范围和 / 或单位剂量在该范围内变化。

联合治疗

[0304] 在某些情况下，至少一种式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与一种或多种其它治疗剂联合给药是合适的。

[0305] 在一个实施方案中，辅助剂的给药增强了一种本文所述的化合物的治疗有效性 (即，辅助剂本身可能具有极小的治疗益处，但当与另一种治疗剂联合时，对患者的总体治疗益处增强)。或者，在一些实施方案中，通过施用一种本文所述的化合物和另一种也具有治疗益处的治疗剂 (也包括治疗方案)，患者获得的益处增加。

[0306] 在一个具体的实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与第二治疗剂共同给药，其中式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐和第二治疗剂调节所治疗的疾病、病症或状况的不同方面，从而比任一治疗剂的单独给药提供更大的总体益处。

[0307] 在任何情况下，不管所治疗的疾病、病症或状况如何，患者获得的总体益处可以仅仅是两种治疗剂的累加，或者，患者可以获得协同益处。

[0308] 在某些实施方案中，当本文公开的化合物与一种或多种另外的药剂例如另外的治疗有效药物、辅助剂等联合给药时，在配制药物组合物中和 / 或在治疗方案中将使用不同治疗有效剂量的本文公开的化合物。联合治疗方案中使用的药物和其它药剂的治疗有效剂量可以通过与上文对于活性剂本身阐述的手段类似的那些手段来确定。此外，本文所述的预防 / 治疗方法包括采用节律给药，即提供更频繁的、更低的剂量，以使毒副作用最小化。在一些实施方案中，联合治疗方案包括这样的治疗方案 :其中式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐的给药在用本文所述的第二药剂治疗之前、期

间或之后开始，并且持续到用第二药剂治疗期间的任意时间或用第二药剂治疗结束后。也包括这样的治疗：其中式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐和联合使用的第二药剂在治疗期期间同时或在不同时间和 / 或以减少或增加的间隔给药。联合治疗进一步包括周期性治疗，其在不同的时间开始和停止，以帮助患者的临床处理。

[0309] 应当理解，可根据多种因素（例如受试者患有的疾病、病症或状况；受试者的年龄、体重、性别、饮食和医疗状况）来修改用于治疗、预防或改善所寻求缓解的病症的剂量方案。因此，在一些情况下，实际使用的剂量方案有所变化，并且在一些实施方案中偏离本文所述的剂量方案。

[0310] 对于本文所述的联合治疗，共同施用的化合物的剂量根据所用的联合药物的类型、所用的具体药物、所治疗的疾病或状况等而变化。在另外的实施方案中，当与一种或多种其它治疗剂共同施用时，本文提供的化合物与一种或多种其它治疗剂同时或相继施用。

[0311] 在联合治疗中，多种治疗剂（其中之一是一种本文所述的化合物）以任意次序施用或甚至同时施用。如果同时施用，仅作为举例，多种治疗剂以单一的统一形式提供，或者以多种形式提供（例如，作为单一丸剂或作为两种分开的丸剂）。

[0312] 在疾病或状况发生之前、期间或之后施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐以及联合治疗，并且施用含有化合物的组合物的时机各异。因此，在一个实施方案中，本文所述的化合物用作预防剂，并且对具有发展成状况或疾病的倾向的受试者连续施用，以预防该疾病或状况的发生。在另一个实施方案中，在症状发作期间或在症状发作后尽可能快地对受试者施用化合物和组合物。在特定实施方案中，在检测到或怀疑疾病或状况发作后，在可行的最短时间内施用本文所述的化合物，并且持续治疗疾病所需的一段时间。在一些实施方案中，治疗需要的时间长短各异，并且调整治疗时间长度以适应各受试者的具体需求。例如，在特定实施方案中，本文所述的化合物或含有该化合物的制剂施用至少 2 周、约 1 个月到约 5 年。

在联合治疗中使用的示例性药剂

[0313] 在一些实施方案中，治疗雌激素受体依赖的或雌激素受体介导的状况或疾病例如增殖性病症（包括癌症）的方法包括向哺乳动物联合施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与至少一种另外的治疗剂。

[0314] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与激素阻断疗法、化学疗法、放射疗法、单克隆抗体或其组合相联合。

[0315] 激素阻断疗法包括使用阻断雌激素的产生或阻断雌激素受体的药剂。在一些实施方案中，激素阻断疗法包括使用雌激素受体调节剂和 / 或芳香酶抑制剂。雌激素受体调节剂包括三苯乙烯衍生物（例如他莫昔芬、托瑞米芬、屈洛昔芬、3- 羟基他莫昔芬、艾多昔芬、TAT-59(4- 羟基他莫昔芬的磷酸化衍生物）和 GW5638（他莫昔芬的羧酸衍生物））；非甾类雌激素受体调节剂（例如雷洛昔芬、LY353381(SERM3) 和 LY357489）；甾类雌激素受体调节剂（例如 ICI-182,780）。芳香酶抑制剂包括甾类芳香酶抑制剂和非甾类芳香酶抑制剂。甾类芳香酶抑制剂包括但不限于，如依西美坦。非甾类芳香酶抑制剂包括但不限于，如阿那曲唑和来曲唑。

[0316] 化学疗法包括抗癌剂的使用。

[0317] 单克隆抗体包括但不限于曲妥珠单抗（赫塞汀 (Herceptin)）。

[0318] 在一些实施方案中，与式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐联合使用的至少一种另外的治疗剂包括以下一种或多种：阿比特龙；阿巴瑞克；阿霉素；放线菌素 D；阿西维辛；阿柔比星；盐酸阿考达唑；阿克罗宁；阿多来新；阿地白介素；阿仑珠单抗；别嘌呤醇；阿利维 A 酸；六甲蜜胺；安波霉素；醋酸阿美蒽醌；氨鲁米特；氨基酮戊酸；氨磷汀；安吖啶；阿那曲唑；安曲霉素；阿瑞匹坦；三氧化二砷；天冬酰胺酶；曲林菌素；阿扎胞苷；阿扎替派；阿佐霉素；巴马司他；盐酸苯达莫司汀；苯佐替派；贝伐珠单抗；贝沙罗汀；比卡鲁胺；盐酸比生群；二甲磺酸双奈法德；比折来新；博来霉素；硫酸博来霉素；硼替佐米；布喹那钠；溴匹立明；白消安；放线菌素 C；卡普睾酮；卡醋胺；卡贝替姆；卡铂；卡莫司汀；盐酸卡柔比星；卡折来新；卡培他滨；西地芬戈；西妥昔单抗；苯丁酸氮芥；西罗霉素；顺铂；克拉屈滨；氯法拉滨；甲磺酸克立那托；环磷酰胺；阿糖胞苷；达卡巴嗪；达沙替尼；盐酸柔红霉素；更生霉素；达促红素 α；地西他滨；地加瑞克；地尼白介素 2；右奥马铂；盐酸右丙亚胺；地扎胍宁；甲磺酸地扎胍宁；地吖醌；多西他赛；多柔比星；盐酸多柔比星；屈洛昔芬；柠檬酸屈洛昔芬；丙酸屈他雄酮；达佐霉素；依达曲沙；盐酸依氟鸟氨酸；依沙芦星；艾曲泊帕乙醇胺；恩洛铂；恩普氨酯；依匹哌啶；盐酸表柔比星；促红素 α；厄布洛唑；盐酸厄洛替尼；盐酸依索比星；雌莫司汀；雌莫司汀磷酸钠；依他硝唑；依托泊苷；磷酸依托泊苷；氯苯乙嘧胺；依维莫司；依西美坦；盐酸法倔唑；法扎拉滨；芬维 A 胺；非格司亭；氟尿苷；磷酸氟达拉滨；氟尿嘧啶；氟西他滨；磷喹酮；福司曲星钠；氟维司群；吉非替尼；吉西他滨；盐酸吉西他滨；吉西他滨 - 顺铂；吉妥珠单抗奥佐米星；醋酸戈舍瑞林；醋酸组氨瑞林；羟基脲；盐酸伊达比星；异环磷酰胺；伊莫福新；替伊莫单抗；伊达比星；异环磷酰胺；甲磺酸伊马替尼；咪喹莫德；白细胞介素 I1（包括重组白细胞介素 II 或 r1L2）、干扰素 α-2a；干扰素 α-2b；干扰素 α-n1；干扰素 α-n3；干扰素 β-1a；干扰素 γ-1b；异丙铂；盐酸伊立替康；伊沙匹隆；醋酸兰瑞肽；拉帕替尼；来那度胺；来曲唑；醋酸亮丙瑞林；亚叶酸钙；醋酸亮丙瑞林；左旋咪唑；脂质体阿糖胞苷；盐酸利阿唑；洛美曲索钠；洛莫司汀；盐酸洛索蒽醌；马索罗酚；美登素；二氯甲基二乙胺盐酸盐；醋酸甲地孕酮；醋酸美仑孕酮；美法仑；美诺立尔；巯基嘌呤；甲氨蝶呤；甲氨蝶呤钠；甲氧沙林；氯苯氨啶；美妥替哌；米丁度胺；米托克星；丝裂红素；米托洁林；米托马星；丝裂霉素 C；丝裂帕菌素；米托坦；盐酸米托蒽醌；麦考酚酸；苯丙酸南诺龙；奈拉滨；尼洛替尼；诺考达唑；诺非单抗；诺拉霉素；奥法木单抗；奥普瑞白介素；奥马铂；奥沙利铂；奥昔舒仑；紫杉醇；帕利夫明；盐酸帕洛诺司琼；帕米膦酸二钠；培非司亭；培美曲塞二钠；喷司他丁；帕木单抗；盐酸帕唑帕尼；培美曲塞二钠；普乐沙福；普拉曲沙；培门冬酶；培利霉素；戊氮芥；硫酸培洛霉素；培磷酰胺；哌泊溴烷；哌泊舒凡；盐酸吡罗蒽醌；普卡霉素；普洛美坦；卟吩姆钠；泊非霉素；泼尼莫司汀；盐酸丙卡巴肼；嘌呤霉素；盐酸嘌呤霉素；吡唑呋喃菌素；奎纳克林；盐酸雷洛昔芬；拉布立酶；重组 HPV 二价疫苗；重组 HPV 四价疫苗；利波腺苷；罗谷亚胺；利妥昔单抗；罗米地新；罗米司亭；沙芬戈；盐酸沙芬戈；沙格司亭；司莫司汀；辛曲秦；sipuleucel-T；索拉非尼；磷乙酰天冬氨酸钠；司帕霉素；盐酸锗螺胺；螺莫司汀；螺铂；链黑菌素；链佐星；磺氯苯脲；苹果酸舒尼替尼；他利霉素；柠檬酸他莫昔芬；替可加兰钠；替加氟；盐酸替洛蒽醌；替莫唑胺；替莫泊芬；坦罗莫司；替尼泊苷；替罗昔隆；睾内酯；沙立度胺；硫咪嘌呤；硫鸟嘌呤；噻替派；噻唑羧胺核苷；替拉扎明；盐酸拓扑替康；托瑞米芬；

托西莫单抗和 I131 碘托西莫单抗；曲妥珠单抗；醋酸曲托龙；维甲酸；磷酸曲西立滨；三甲曲沙；三甲曲沙葡糖醛酸酯；曲普瑞林；盐酸妥布氯唑；乌拉莫司汀；乌瑞替哌；戊柔比星；伐普肽；维替泊芬；长春碱；硫酸长春碱；硫酸长春新碱；长春地辛；硫酸长春地辛；硫酸长春匹定；硫酸长春甘酯；硫酸长春罗新；酒石酸长春瑞滨；硫酸长春罗定；硫酸长春利定；伏林司他；伏氯唑；折尼铂；净司他丁；唑来膦酸；或盐酸佐柔比星。

[0319] 在一些实施方案中，仅作为举例，至少一种另外的化疗剂选自阿仑珠单抗、三氧化二砷、天冬酰胺酶（聚乙二醇化的或非聚乙二醇化的）、贝伐珠单抗、西妥昔单抗、铂基化合物例如顺铂、克拉屈滨、柔红霉素 / 多柔比星 / 伊达比星、伊立替康、氟达拉滨、5- 氟尿嘧啶、吉妥珠单抗、甲氨蝶呤、泰素、替莫唑胺、硫鸟嘌呤，或包括激素的药物类型（抗雌激素、抗雄激素或促性腺激素释放激素类似物）、干扰素例如 α 干扰素、氮芥例如白消安或美法仑或二氯甲基二乙胺、类维生素 A 例如维甲酸、拓扑异构酶抑制剂例如伊立替康或拓扑替康、酪氨酸激酶抑制剂例如吉非替尼或伊马替尼，或治疗由此类治疗诱发的体征或症状的药剂，包括别嘌呤醇、非格司亭、格拉司琼 / 昂丹司琼 / 帕洛诺司琼、屈大麻酚。

[0320] 在一个方面，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与一种或多种抗癌剂联合给药或配制。在一些实施方案中，一种或多种抗癌剂是促凋亡剂。抗癌剂的实例包括但不限于以下任一种：棉酚、根纳三思 (genasense)、多酚 E、Chlorofusin、全反式维甲酸 (ATRA)、苔藓虫素、肿瘤坏死因子相关的凋亡诱导配体 (TRAIL)、5- 氮杂 -2'- 脱氧胞苷、全反式维甲酸、多柔比星、长春新碱、依托泊苷、吉西他滨、伊马替尼、格尔德霉素、17-N- 烯丙基氨基 -17- 去甲氧基格尔德霉素 (17AAG)、夫拉平度、LY294002、硼替佐米、曲妥珠单抗、BAY11-7082、PKC412 或 PD184352、紫杉醇以及紫杉醇类似物。也已证明具有基本紫杉烷骨架作为共同结构特征的化合物由于稳定化的微管而具有将细胞阻滞在 G2-M 期的能力，并且可用于与本文所述的化合物联合治疗癌症。

[0321] 与式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐联合使用的抗癌剂的其它实例包括有丝分裂原激活的蛋白激酶信号传导的抑制剂，例如 U0126、PD98059、PD184352、PD0325901、ARRY-142886、SB239063、SP600125、BAY 43-9006、渥曼青霉素或 LY294002；Syk 抑制剂；mTOR 抑制剂；和抗体（例如利妥昔单抗 (rituxan)）。

[0322] 与式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐联合使用的抗癌剂的其它实例包括芳香酶抑制剂。芳香酶抑制剂包括甾类芳香酶抑制剂和非甾类芳香酶抑制剂。甾类芳香酶抑制剂包括但不限于依西美坦。非甾类芳香酶抑制剂包括但不限于阿那曲唑和来曲唑。

[0323] 与式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐联合使用的另外一些抗癌剂包括烷化剂、抗代谢物、天然产物或激素，例如氮芥（例如二氯甲基二乙胺、环磷酰胺、苯丁酸氮芥等）、烷基磺酸酯（例如白消安）、亚硝基脲（例如卡莫司汀、洛莫司汀等）或三氮烯（氨烯咪胺等）。抗代谢物的实例包括但不限于叶酸类似物（例如甲氨蝶呤）或嘧啶类似物（例如阿糖胞苷）、嘌呤类似物（例如巯基嘌呤、硫鸟嘌呤、喷司他丁）。

[0324] 与式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐联合使用的天然产物的实例包括但不限于长春花生物碱（例如长春碱、长春新碱）、表鬼臼毒素（例如依托泊苷）、抗生素（例如柔红霉素、多柔比星、博来霉素）、酶（例如 L- 天冬酰胺酶）

或生物反应调节剂（例如干扰素 α）。

[0325] 与式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐联合使用的烷化剂的实例包括但不限于氮芥（例如二氯甲基二乙胺、环磷酰胺、苯丁酸氮芥、美法仑等）、乙烯亚胺和甲基三聚氰胺（例如六甲基三聚氰胺、噻替派）、烷基磺酸酯（例如白消安）、亚硝基脲（例如卡莫司汀、洛莫司汀、司莫司汀、链佐星等）或三氮烯（氨烯咪胺等）。

[0326] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐用来与以下药剂联合治疗癌症：第二抗雌激素（例如三苯氧胺）、抗雄激素（例如比卡鲁胺、氟他胺）、促性腺激素释放激素类似物（例如亮丙瑞林）。

[0327] 可以在本文所述的方法和组合物中用于治疗或预防癌症的其它药剂包括铂配位络合物（例如顺铂、卡铂）、蒽醌（例如米托蒽醌）、取代的脲（例如羟基脲）、甲基肼衍生物（例如丙卡巴肼）、肾上腺皮质抑制剂（例如米托坦、氨鲁米特）。

[0328] 对于通过由于稳定化的微管而将细胞阻滞在 G2-M 期来起作用的抗癌剂，其实例包括但不限于以下市售药物和开发中的药物：厄布洛唑、多拉司他汀 10、羟乙磺酸米伏布林、长春新碱、NSC-639829、圆皮海绵内酯 (Discodermolide)、ABT-751、Altorhyrtin（例如 Altorhyrtin A 和 Altorhyrtin C）、海绵抑制素（例如海绵抑制素 1、海绵抑制素 2、海绵抑制素 3、海绵抑制素 4、海绵抑制素 5、海绵抑制素 6、海绵抑制素 7、海绵抑制素 8 和海绵抑制素 9）、盐酸西马多丁、埃博霉素（例如埃博霉素 A、埃博霉素 B、埃博霉素 C、埃博霉素 D、埃博霉素 E、埃博霉素 F、埃博霉素 B N- 氧化物、埃博霉素 A N- 氧化物、16- 氨杂 - 埃博霉素 B、21- 氨基埃博霉素 B、21- 羟基埃博霉素 D、26- 氟埃博霉素、Auristatin PE、Soblidotin、硫酸长春新碱、Cryptophycin 52、Vitilevuamide、Tubulysin A、Canadensol、矢车菊黄素、Oncocidin A1 Fijianolide B、Laulimalide、诺司卡品 (Narcosine)、Nascapine、哈米特林、乙酰丙酮二茂钒、Indanocine Eleutherobin（例如 Desmethyleleutherobin、Desaetyleleutherobin、lsoeleutherobin A 和 Z-Eleutherobin）、Caribaeoside、Caribaeolin、大田软海绵素 B(Halichondrin B)、Diazonamide A、根薯酮内酯 A、Diozostatin、(-)-Phenylahistin、Myoseverin B、Resverastatin 磷酸钠。

[0329] 在一个方面，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与血栓溶解剂（例如阿替普酶、阿尼普酶、链激酶、尿激酶或组织纤溶酶原激活物）、肝素、亭扎肝素、华法林、达比加群（例如达比加群酯）、因子 Xa 抑制剂（例如磺达肝素、draparinux、利伐沙班、DX-9065a、奥米沙班、LY517717 或 YM150）、噻氯匹定、氯吡格雷、CS-747（普拉格雷、LY640315）、希美加群或 BIBR 1048 联合给药。

[0330] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与止吐剂联合使用，以治疗可能由使用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐、抗癌剂和 / 或放射疗法而引起的恶心或呕吐。

[0331] 止吐剂包括但不限于：神经激肽 -1 受体拮抗剂、5HT3 受体拮抗剂（例如昂丹司琼、格拉司琼、托烷司琼、帕洛诺司琼和扎托司琼）、$GABA_B$ 受体激动剂（例如巴氯芬）、皮质类固醇（例如地塞米松、泼尼松、泼尼松龙等）、多巴胺拮抗剂（例如但不限于多潘立酮、氟哌利多、氟哌啶醇、氯丙嗪、异丙嗪、丙氯拉嗪、胃复安）、抗组胺剂 (H1 组胺受体拮抗剂，例如但不限于苯甲嗪、苯海拉明、茶苯海明、氯苯甲嗪、异丙嗪、羟嗪）、大麻素（例如但不限于大麻、四氢大麻酚、屈大麻酚）及其它（例如但不限于曲美苄胺；姜、愈吐宁 (emetrol)、异

丙酚）。

[0332] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与用于治疗贫血的药剂联合使用。该贫血治疗剂是，例如连续红细胞生成受体激活剂（例如红细胞生成素 -α）。

[0333] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与用于治疗嗜中性粒细胞减少症的药剂联合使用。用于治疗嗜中性粒细胞减少症的药剂的实例包括但不限于调节中性粒细胞的产生和功能的造血生长因子，例如人粒细胞集落刺激因子 (G-CSF)。G-CSF 的实例包括非格司亭。

[0334] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与皮质类固醇一起施用。皮质类固醇包括但不限于：倍他米松、泼尼松、阿氯米松、醛固酮、安西奈德、倍氯米松、倍他米松、布地奈德、环索奈德、氯倍他索、氯倍他松、氯可托龙、氯泼尼醇、可的松、可的伐唑、地夫可特、脱氧皮质酮、地索奈德、去羟米松、去氧皮质酮、地塞米松、双氟拉松、双氟可龙、二氟泼尼酯、氟氯奈德、氟氢可的松、氟氢缩松、氟米松、氟尼缩松、氟轻松醋酸酯、醋酸氟轻松、氟可丁、氟可龙、氟米龙、氟培龙、氟泼尼定、氟替卡松、福莫可他、哈西奈德、卤米松、氢化可的松 / 皮质醇、醋丙氢化可的松、丙丁酸氢化可的松、丁酸氢化可的松、氯替泼诺、甲羟松、甲泼尼松、甲泼尼龙、醋丙甲泼尼龙、糠酸莫米松、帕拉米松、泼尼卡酯、泼尼松 / 泼尼松龙、利美索龙、替可的松、曲安西龙和乌倍他索。

[0335] 在一个实施方案中，向哺乳动物联合施用式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与非甾类抗炎药 (NSAID)。NSAID 包括但不限于：阿司匹林、水杨酸、龙胆酸、水杨酸镁胆碱、水杨酸胆碱、水杨酸镁胆碱、水杨酸胆碱、水杨酸镁、水杨酸钠、二氟尼柳、卡洛芬、非诺洛芬、非诺洛芬钙、氟比洛芬、布洛芬、酮洛芬、萘丁美酮、酮咯酸、酮咯酸氨丁三醇、萘普生、奥沙普秦、双氯芬酸、依托度酸、吲哚美辛、舒林酸、托美丁、甲氯灭酸、甲氯灭酸钠、甲芬那酸、吡罗昔康、美洛昔康、COX-2 特异性抑制剂（例如但不限于塞来昔布、罗非昔布、伐地昔布、帕瑞昔布、依托昔布、罗美昔布、CS-502、JTE-522、L-745,337 和 NS398）。

[0336] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与止痛剂共同施用。

[0337] 在一些实施方案中，式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与放射疗法（或放疗）联合使用。放射疗法是用电离辐射治疗癌症和其它疾病。放射疗法可以用来治疗局部的实体瘤，例如皮肤、舌、喉、脑、乳房、前列腺、结肠、子宫和 / 或子宫颈的癌症。它也可以用来治疗白血病和淋巴瘤（分别是造血细胞和淋巴系统的癌症）。

[0338] 向癌细胞递送辐射的一种技术是直接在肿瘤或体腔中放置放射性植入物。这叫做内放射疗法（短距离放射疗法、间质内照射和腔内照射是内放射疗法的类型）。使用内放射疗法，辐射剂量集中在小的区域，并且患者只住院几天。内放射疗法常常用于舌、子宫、前列腺、结肠和子宫颈的癌症。

[0339] 术语“放射疗法”或“电离辐射”包括所有形式的辐射，包括但不限于 α、β、γ 辐射和紫外线。

试剂盒 / 制品

[0340] 为了在本文所述的治疗性应用中使用，本文还描述了试剂盒和制品。此类试剂盒可以包括载体、包装或容器，该容器被区室化以接纳一个或多个容器，例如小瓶、试管等，各个容器包含在本文所述的方法中使用的单独元件中的一种。合适的容器包括例如瓶子、小瓶、注射器和试管。容器由任意可接受的材料形成，包括例如玻璃或塑料。

[0341] 例如，容器可以包含一种或多种本文所述的化合物，任选地在组合物中或与另一种如本文所公开的药剂联合。容器任选地具有无菌入口（例如容器可以是静脉内溶液袋或带有可被皮下注射针头刺穿的塞子的小瓶）。此类试剂盒任选地包含化合物，以及辨识性说明或标签，或关于其在本文所述的方法中的用法的说明书。

[0342] 试剂盒一般包含一个或多个另外的容器，各容器含有从商业和使用者的角度来看期望用于本文所述的化合物的一种或多种不同材料（例如试剂，任选地为浓缩形式，和/或装置）。此类材料的非限制性实例包括但不限于缓冲液、稀释剂、过滤器、针头、注射器；托架、包装、容器、小瓶和/或试管标签——该标签列出了内容物和/或使用说明，以及带有使用说明的包装插入物。一般也包括一套说明书。

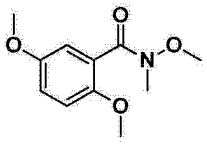
[0343] 标签可以位于容器上或与容器相关联。当构成标签的字母、数字或其它字符附着、模塑或铭刻于容器本身上时，标签可以位于容器上；当它存在于也支撑容器的托座或托架内时，标签可以与容器相关联，例如作为包装插入物。标签可以用来指明内容物将用于特定的治疗性应用。标签还可以指出内容物的使用说明，例如在本文所述的方法中的使用说明。

实施例

[0344] 这些实施例仅为了说明性目的而提供，而不是限制本文提供的权利要求书的范围。

中间体 1

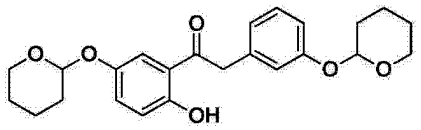
N,2,5- 三甲氧基 -N- 甲基苯甲酰胺



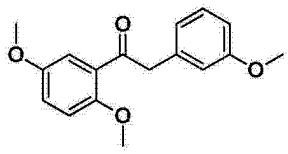
[0345] 在室温下向 2,5- 二甲氧基苯甲酸 (6.00g,33.0mmol) 的 DCM(100mL) 溶液中添加草酰氯 (3.6mL,41.3mmol)。然后向混合液中添加 DMF(0.2mL)。将得到的溶液在室温下搅拌 2 小时，并在旋转蒸发器上除去溶剂。将粗物质置于真空下 30 分钟以除去残余的草酰氯从而得到粗酰基氯。将粗物质溶解于 DCM(100ml) 中且冷却至 0℃。向该溶液中分别加入 N,O- 二甲基羟基胺盐酸盐 (4.03g,41.32mmol) 和三乙胺 (6.8mL,48.78mmol)。将得到的混合物在 0℃下搅拌 30 分钟，然后在室温下再搅拌 30 分钟。将反应液用 DCM(50mL) 稀释，用 H_2O 洗涤 (2x100mL)，用盐水 (100ml) 洗涤，经 Na_2SO_4 干燥，过滤，并在旋转蒸发器上浓缩。通过硅胶层析纯化该粗物质，得到呈澄清的油的 N,2,5- 三甲氧基 -N- 甲基苯甲酰胺 (7.32g，99％)，其随时间推移而凝固。^1H NMR($CDCl_3$)：δ 7.90(m,3H),3.82(s,3H),3.79(s,3H),3.58(br s,3H),3.32(br s,3H).

中间体 2

1-(2- 羟基 -5-((四氢 -2H- 吡喃 -2- 基）氧基）苯基）-2-(3-((四氢 -2H- 吡喃 -2- 基）氧基）苯基）乙酮

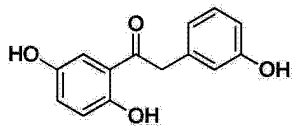


第 1 步 :1-(2,5- 二甲氧基苯基)-2-(3- 甲氧基苯基) 乙酮



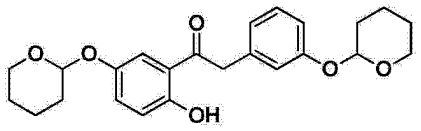
[0346] 向镁 (2.88g,118mmol) 和碘 (1 个晶体) 在 THF(30mL) 中的混合物中添加一份 5mL 的 3- 甲氧基苄基氯 (12.8mL,88.1mmol) 的 THF(60mL) 溶液。搅拌反应混合物直到颜色消失,并在 45 分钟里逐滴加入剩余的 3- 甲氧基苄基氯溶液。在 60℃加热该混合物 1 小时,然后冷却至 0℃。在 0℃下于 30 分钟里向该混合物中加入中间体 1(6.65g 29.6mmol) 在 THF(70mL) 中的溶液。于 0℃搅拌反应液 30 分钟并用盐水 (50mL) 猝灭。用乙酸乙酯萃取 (3x100mL) 该混合物。将合并的有机萃取物用盐水 (50ml) 洗涤,经 Na_2SO_4 干燥,过滤,并在旋转蒸发器上浓缩,得到呈白色固体的 1-(2,5- 二甲氧基苯基)-2-(3- 甲氧基苯基) 乙酮 (7.99g,95%)。^1H NMR($CDCl_3$):δ 7.25(m,2H),7.01(dd,1H),6.92(d,1H),6.83(m,3H),4.30(s,2H),3.90(s,3H),3.82(s,3H),3.79(s,3H).

第 2 步 :1-(2,5- 二羟基苯基)-2-(3- 羟基苯基) 乙酮



[0347] 向 -78℃的 1-(2,5- 二甲氧基苯基)-2-(3- 甲氧基苯基) 乙酮 (3.35g,11.7mmol) 的 DCM(50mL) 溶液中逐滴加入三溴化硼 (1M,在 DCM 中,48.0mL,48.0mmol)。使反应混合物升温至 0℃,搅拌 30 分钟,再次冷却至 -78℃,然后用甲醇 (15mL) 猝灭。使反应混合物升温至室温,在旋转蒸发器上浓缩,并通过硅胶层析纯化,得到呈黄色固体的 1-(2,5- 二羟基苯基)-2-(3- 羟基苯基) 乙酮 (1.78g,62%)。^1H NMR(DMSO-d_6):δ 11.24(s,1H),9.34(s,1H),9.20(s,1H),7.26(m,1H),7.10(t,1H),6.98(dd,1H),6.83(d,1H),6.70(m,3H),4.24(s,2H).

第 3 步 :1-(2- 羟基 -5-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基) 乙酮

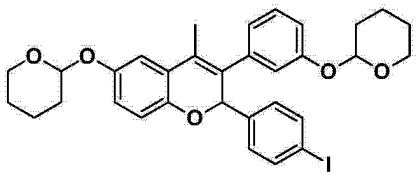


[0348] 将在 DCM(6mL) 中的 3,4- 二氢 -2H- 吡喃 (2.65g,30.8mmol) 添加至 1-(2,5- 二羟基苯基)-2-(3- 羟基苯基) 乙酮 (1.50g,6.15mmol) 和对甲苯磺酸吡啶 (320mg,1.27mmol) 在 DCM(40mL) 中的混合物中。在室温下搅拌反应混合物 1 小时,并用 DCM(100mL) 稀释。将溶液用饱和 $NaHCO_3$ 洗涤 (2x50mL),用盐水 (50mL) 洗涤,经 Na_2SO_4 干燥,过滤,并在旋转蒸发器上浓缩。通过硅胶层析纯化粗物质,得到呈黄色油的 1-(2- 羟基 -5-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基) 乙酮 (2.42g,96%),

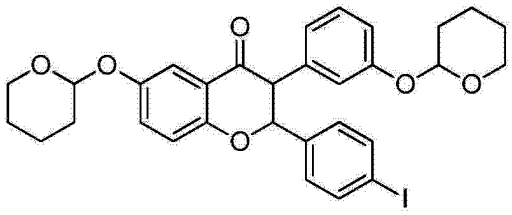
其随时间推移而凝固。^{1}H NMR($CDCl_3$)：δ 11.88(s,1H),7.60(m,1H),7.30(m,2H),7.00(m,2H),6.92(m,2H),5.42(m,1H),5.28(m,1H),4.25(s,2H),3.92(m,2H),3.62(m,2H),1.55-2.07(m,12H).

中间体 3

2-(4- 碘苯基)-4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2H- 苯并吡喃

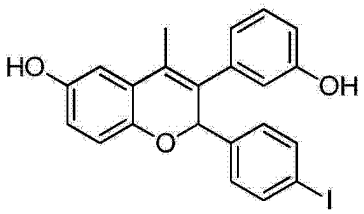


第 1 步 :2-(4- 碘苯基)-6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基) 苯并二氢吡喃 -4- 酮



[0349] 在回流下加热中间体 2(2.41g,5.84mmol)、4- 碘苯甲醛 (1.37g,5.91mmol)、哌啶 (166mg,1.95mmol) 和 DBU(301mg,1.98mmol) 在仲丁醇 (10mL) 中的溶液。使用 Dean-Stark 阱,经 45 分钟收集一半 (5mL) 溶剂,无需进一步浓缩使反应液保持在回流再过 45 分钟。将反应混合物冷却至 90℃,添加异丙醇 (10mL),使反应冷却至室温并搅拌过夜。通过过滤收集得到的沉淀物,得到呈白色固体的 2-(4- 碘苯基)-6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基) 苯并二氢吡喃 -4- 酮 (3.17g,87％)。^{1}H NMR(DMSO-d_6)：δ 7.63(d,2H),7.42(m,1H),7.33(m,1H),7.21(d,2H),7.07(m,2H),6.79(m,3H),5.88(m,1H),5.48(m,1H),5.31(m,1H),4.60(d,1H),3.40-3.80(m,4H),1.55-1.90(m,12H).

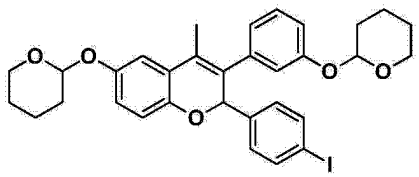
第 2 步 :3-(3- 羟基苯基)-2-(4- 碘苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0350] 在 0℃下将甲基氯化镁 (3M,在 THF 中,4.0ml,12mmol) 逐滴加入至 2-(4- 碘苯基)-6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基) 苯并二氢吡喃 -4- 酮 (1.99g,3.18mmol) 在 THF(40mL) 中的溶液中。于 0℃搅拌反应液 15 分钟,并使之升温至室温。搅拌 2 小时后,将该溶液冷却至 0℃,用饱和氯化铵猝灭,然后使之升温至室温。加入乙酸乙酯 (100mL) 和 H_2O(50mL),并分离各层。有机层经 Na_2SO_4 干燥,在旋转蒸发器上浓缩,并经硅胶层析纯化,得到白色泡沫 (1.75g)。该纯化的物质在 80％乙酸 /H_2O(50mL) 中于 90℃加热过夜。将该溶液用乙酸乙酯 (100mL) 稀释,用 H_2O(50ml) 洗涤,用

饱和 $NaHCO_3$(50ml) 洗涤，用盐水 (50ml) 洗涤，并经 Na_2SO_4 干燥，过滤，并在旋转蒸发器上浓缩。通过硅胶层析纯化粗物质，得到呈米色固体的 3-(3- 羟基苯基)-2-(4- 碘苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇 (0.99g,68％)。^1H NMR(DMSO-d_6)：δ 9.46(s,1H),9.00(s,1H),7.62(d,2H),7.17(t,1H),7.01(d,2H),6.70(m,4H),6.51(s,2H),5.90(s,1H),2.03(s,3H).

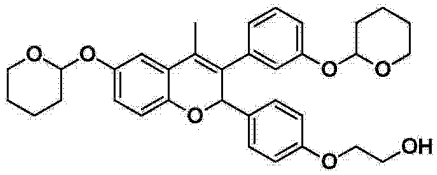
第 3 步 :2-(4- 碘苯基)-4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2H- 苯并吡喃



[0351] 将 3,4- 二氢 -2H- 吡喃 (1.1mL,12mmol) 添加至 3-(3- 羟基苯基)-2-(4- 碘苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇 (990mg,2.19mmol) 和对甲苯磺酸吡啶 (115mg,0.458mmol) 在 DCM(30mL) 中的溶液中。将反应液在室温下搅拌 3 小时，用 DCM(100mL) 稀释，用饱和 $NaHCO_3$(100mL) 洗涤，用 H_2O 洗涤 (2x50mL)，用盐水 (50mL) 洗涤，经 Na_2SO_4 干燥，过滤，并在旋转蒸发器上浓缩。通过硅胶层析纯化粗物质，得到呈白色泡沫的 2-(4- 碘苯基)-4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2H- 苯并吡喃 (1.30g,95％)。^1H NMR(DMSO-d_6)：δ 7.62(d,2H),7.27(t,1H),7.10(d,2H),6.92(m,4H),6.81(d,1H),6.63(d,1H),6.04(d,1H),5.43(m,1H),5.36(s,1H),3.75(m,2H),3.55(m,2H),2.05(s,3H),1.50-1.99(m,12H).

中间体 4

2-(4-(4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2H- 苯并吡喃 -2- 基) 苯氧基) 乙醇

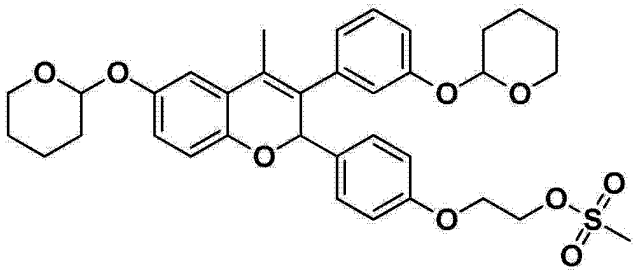


[0352] 将 2-(4- 碘苯基)-4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2H- 苯并吡喃 (中间体 3,1.0g,1.6mmol)、1,2- 乙二醇 (0.49g,8.0mmol)、碘化亚铜 (0.03g,0.16mmol)、1,10- 菲咯啉 (0.058g,0.32mmol)、碳酸钾 (0.44g,3.2mmol) 在丁腈中的混合物通过氮气 / 真空循环脱气三次。将反应混合物在 125℃ 加热 2 天，使其冷却至室温，并用乙酸乙酯稀释。通过 Celite 过滤该混合物。将有机相用水洗涤两次，用盐水洗涤，经 Na_2SO_4 干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化粗产物得到 2-(4-(4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2H- 苯并吡喃 -2- 基) 苯氧基) 乙醇。^1H NMR(DMSO-d_6)：δ 7.27-7.13(m,3H),6.98(t,1H),6.93-6.84(m,3H),6.80-6.76(m,3H),6.59(d,1H),5.97(d,1H),5.43(dt,1H),5.34(br,1H),4.79(t,1H),3.88(t,2H),3.80-3.70(m,2H),3.64(q,2H),3.54-3.50(m,2H),2.06(s,3H),1.86-1.66(m,6H),1.59-1.51(m,6H).

中间体 5

2-(4-(4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基)

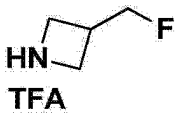
氧基）苯基）-2H- 苯并吡喃 -2- 基）苯氧基）乙基甲磺酸酯



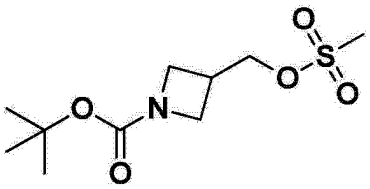
[0353] 向 0℃的 2-(4-(4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基）氧基）-3-(3-((四氢 -2H- 吡喃 -2- 基）氧基）苯基）-2H- 苯并吡喃 -2- 基）苯氧基）乙醇（中间体 4，0.7g，1.25mmol）的 DCM(25ml) 溶液中分别加入三乙胺 (0.26ml，1.87mmol) 和甲磺酰氯 (0.146ml，1.87mmol)。在 0℃搅拌反应混合物 1h，然后用 DCM 稀释。向该混合物中加入水 (20ml) 和饱和氯化铵 (20ml)。分离各层，且将有机层用水洗涤，用饱和 $NaHCO_3$ 洗涤，用盐水洗涤，经 Na_2SO_4 干燥，并浓缩得到 2-(4-(4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基）氧基）-3-(3-((四氢 -2H- 吡喃 -2- 基）氧基）苯基）-2H- 苯并吡喃 -2- 基）苯氧基）乙基甲磺酸酯。^{1}HNMR(DMSO-d_6)：δ 7.25(d,3H),6.99-6.98(m,1H),6.93-6.87(m,3H),6.85-6.78(m,2H),6.77-6.75(dd,1H),6.61(d,1H),5.98(d,1H),5.43(d,1H),5.34(br,1H),4.47-4.45(m,2H),4.16(br,2H),3.83-3.70(m,2H),3.56-3.47(m,2H),3.18(s,3H),2.05(s,3H),1.92-1.65(m,6H),1.60-1.40(m,6H).

中间体 6

3-（氟甲基）氮杂环丁烷 2,2,2- 三氟乙酸盐

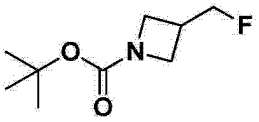


第 1 步 :3-(((甲磺酰基）氧基）甲基）氮杂环丁烷 -1- 甲酸叔丁酯



[0354] 向 0℃的 3-（羟甲基）氮杂环丁烷 -1- 甲酸叔丁酯 (8.8g，47mmol) 的 DCM(188ml) 溶液中一次性加入三乙胺 (7.8mL，56mmol)。然后，在 30 分钟内通过加料漏斗加入纯甲磺酰氯 (4.38ml，56mmol)。将得到的混合物在 0℃搅拌 1.5 小时。反应完成后，分别加入水 (100ml) 和饱和氯化铵水溶液 (100ml)。分离有机相，并将有机相用水洗涤两次，用盐水洗涤，经 Na_2SO_4 干燥，过滤，并浓缩得到呈浅黄色油的 3-(((甲磺酰基）氧基）甲基）氮杂环丁烷 -1- 甲酸叔丁酯 (12.5g)。该化合物无需进一步纯化而直接用于下一步骤。

第 2 步 :3-（氟甲基）氮杂环丁烷 -1- 甲酸叔丁酯



[0355] 将 3-(((甲磺酰基）氧基）甲基）氮杂环丁烷 -1- 甲酸叔丁酯 (12.5g，47mmol) 和

235ml 四丁基氟化铵（在 THF 中的 1M 溶液，5 当量）的混合物在回流下加热 18 小时。将反应混合物冷却至室温并在旋转蒸发器上除去过量的 THF。将残余物溶解在乙酸乙酯中。将有机相用饱和 $NaHCO_3$ 水溶液洗涤，用水洗涤，用盐水洗涤，经 Na_2SO_4 干燥，过滤，并在旋转蒸发器上浓缩得到粗产物。通过硅胶层析纯化粗产物得到呈澄清的油的 3-（氟甲基）氮杂环丁烷 -1- 甲酸叔丁酯 (7.5g)。^1H NMR(DMSO-d_6)：δ 4.52(dd,2H),3.89(br,2H),3.61(br,2H),2.92-2.77(m,1H),1.36(s,9H).

第 3 步 :3-（氟甲基）氮杂环丁烷 2,2,2- 三氟乙酸盐

[0356] 在室温下将 3-（氟甲基）氮杂环丁烷 -1- 甲酸叔丁酯 (0.1g,0.53mmol) 和三氟乙酸 /DCM(1:1,5.3ml) 搅拌 30 分钟。然后在旋转蒸发器上浓缩反应混合物得到呈澄清的油的 3-（氟甲基）氮杂环丁烷 2,2,2- 三氟乙酸盐。^1H NMR(DMSO-d_6 ;TFA 盐）：δ 8.74(br,2H),4.54(dd,2H),4.08-3.98(m,2H),3.84-3.76(m,2H),3.20-3.06(m,1H).

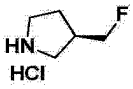
中间体 7

2-(3-（氟甲基）氮杂环丁 -1- 基）乙醇

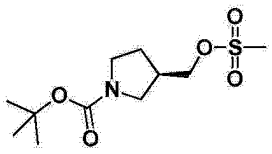
[0357] 将 3-（氟甲基）氮杂环丁烷 2,2,2- 三氟乙酸盐（中间体 6,100mg,0.5mmol）、2- 溴乙醇 (60mg,0.5mmol) 和碳酸钾 (0.2g,1.5mmol) 在乙腈 (5ml) 中的混合物加热至 80℃过夜。冷却后，将固体滤出并用乙腈洗涤。将滤液在旋转蒸发器上浓缩得到残余物，该残余物通过硅胶层析（用 10:7 乙酸乙酯 / 己烷至 10:7:2:1 乙酸乙酯 / 己烷 / 甲醇 / 三乙胺洗脱）纯化得到 52mg 呈浅黄色油的 2-(3-（氟甲基）氮杂环丁 -1- 基）乙醇。^1H NMR(DMSO-d_6)：δ 5.13(t,1H),4.62(d,1H),4.50(d,1H),4.06(t,2H),3.84(dd,2H),3.54(q,2H),3.11(t,2H),3.06-3.03(m,1H).

中间体 8

(R)-3-（氟甲基）吡咯烷盐酸盐



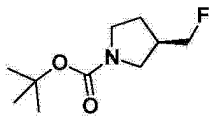
第 1 步 :(R)-(((甲磺酰基）氧基）甲基）吡咯烷 -1- 甲酸叔丁酯



[0358] 将 (R)-（羟甲基）吡咯烷 -1- 甲酸叔丁酯 (21.5g,107mmol) 和三乙胺 (30mL,214mmol) 在二氯甲烷 (250mL) 中的混合物冷却至 0℃。通过加料漏斗滴加甲磺酰氯 (12.5ml,160.5mmol)，并将所得混合物在 0℃下搅拌，然后经 3 小时逐渐升温至室温。加入 10％柠檬酸水溶液并将两层分离。将有机层用 10％柠檬酸水溶液、饱和 $NaHCO_3$ 水溶液和盐水洗涤。将有机层经硫酸钠干燥，过滤，并在旋转蒸发器上除去溶剂得到 30g 呈橙色的油的

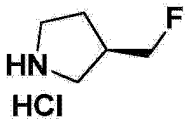
(R)-3-(((甲磺酰基)氧基)甲基)吡咯烷-1-甲酸叔丁酯,其无需进一步纯化而使用。^{1}H NMR(400MHz,DMSO-d_6) δ 4.17(m,2H),3.33(m,2H),3.20(m,1H),3.18(s,3H),3.00(m,1H),2.55(m,1H),2.01(m,1H),1.53(m,1H),1.40(s,9H).

第2步:(R)-3-(氟甲基)吡咯烷-1-甲酸叔丁酯



[0359] 将四丁基氟化铵(在THF中的1M溶液,530ml)加入至(R)-3-(((甲磺酰基)氧基)甲基)吡咯烷-1-甲酸叔丁酯(30g,来自前一步骤),并将得到的混合物回流过夜。冷却后,除去溶剂并将残余物在10%柠檬酸水溶液和二氯甲烷之间分配。将有机层用水洗涤,经硫酸钠干燥,过滤,并在旋转蒸发器上除去溶剂。通过在硅胶柱上的急骤层析(0至50%乙酸乙酯/己烷)纯化该残余物,得到14.3g呈黄色的油的(R)-3-(氟甲基)吡咯烷-1-甲酸叔丁酯。^{1}H NMR(400MHz,DMSO-d_6) δ 4.49-4.41(m,1H),4.37-4.29(m,1H),3.40-3.28(m,2H),3.24-3.18(m,1H),3.02-2.98(m,1H),2.58-2.52(m,1H),1.95-1.88(m,1H),1.67-1.54(m,1H),1.38(s,9H).

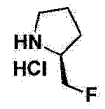
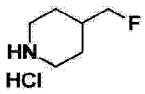
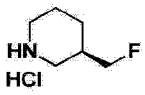
第三步:(R)-3-(氟甲基)吡咯烷盐酸盐



[0360] 将在1,4-二氧杂环己烷(60mL)中的(R)-3-(氟甲基)吡咯烷-1-甲酸叔丁酯(14.3g,70.4mmol)在冰浴中冷却。然后加入HCl(4M,在1,4-二氧杂环己烷中,44mL,176mmol),并将所得到的粉色溶液在室温下搅拌过夜。在旋转蒸发器上除去溶剂并用乙醚磨碎残余物。在真空下除去乙醚并干燥粉色固体得到9.5g(R)-3-(氟甲基)吡咯烷盐酸盐。^{1}H NMR(400MHz,DMSO-d_6;HCl盐) δ 9.35(bs,2H),4.57-4.47(m,1H),4.44-4.33(m,1H),3.33-3.10(m,3H),2.95-2.87(m,1H),2.69-2.57(m,1H),2.005-1.97(m,1H),1.70-1.61(m,1H).

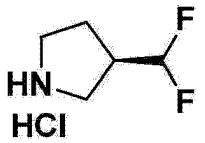
[0361] 根据针对中间体8所述的一般程序,由市售获得的胺制备表2中的中间体。

表2

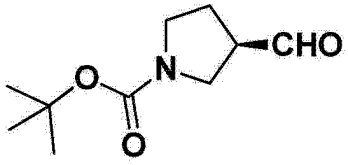
中间体	结构	名称和 ^{1}H NMR 数据
9		**(S)-2-(氟甲基)吡咯烷盐酸盐:** ^{1}H NMR (DMSO-d_6; HCl 盐): δ 9.52 (br, 1H), 9.15 (br, 1H), 4.77-4.22 (m, 2H), 3.88-3.73 (m, 1H), 3.17 (t, 2H), 2.08-1.98 (m, 1H), 1.98-1.82 (m, 2H), 1.67-1.59 (m, 1H).
10		**4-(氟甲基)哌啶盐酸盐:** ^{1}H NMR (DMSO-d_6; HCl 盐): δ 9.22 (br, 1H), 8.90 (br, 1H), 4.30 (dd, 2H), 3.27-3.18 (m, 2H), 2.90-2.77 (m, 2H), 2.03-1.87 (m, 1H), 1.81-1.72 (m, 2H), 1.52-1.39 (m, 2H).
11		**(R)-3-(氟甲基)哌啶盐酸盐:** ^{1}H NMR (DMSO-d_6: HCl 盐): δ 9.11 (br, 2H), 4.49-4.24 (m, 2H), 3.21(t, 2H), 2.80-2.62 (m, 2H), 2.22-2.07 (m, 1H), 1.82-1.63 (m, 3H), 1.32-1.21 (m, 1H).

中间体 12

(R)-3-(二氟甲基)吡咯烷盐酸盐



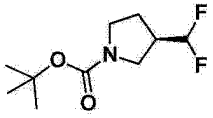
第 1 步:(R)-3- 甲酰吡咯烷 -1- 甲酸叔丁酯



[0362] 将在二氯甲烷 (2mL) 中的 DMSO(1.4mL,19.69mmol) 逐滴加入至 -78℃的草酰氯 (0.86mL,9.85mmol) 的二氯甲烷 (10mL) 溶液中。10 分钟后,在 -78℃下,逐滴加入在二氯甲烷 (6mL) 中的 (R)-3-(羟甲基)吡咯烷 -1- 甲酸叔丁酯 (1.8g,8.95mmol)。将得到的混合物在 -78℃下搅拌 30 分钟后,加入三乙胺 (6.2mL,44.75mmol),并将混合物在 -78℃下搅拌 45 分钟,随后在室温下搅拌 30 分钟。将水加入至该反应混合物并将两层分离。将有机层用水洗涤,经硫酸钠干燥,过滤,并除去溶剂。通过在硅胶上的急骤层析(用 0 至 50% 乙酸乙酯 / 己烷洗脱)纯化该粗物质得到 0.6g 呈澄清的油的 (R)-3- 甲酰吡咯烷 -1- 甲酸叔丁酯。^{1}H NMR(400MHz,DMSO-d_6) δ 9.60(s,1H),3.54(dd,1H),3.32-3.21(m,2H),3.12(m,2H

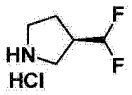
),2.04(m,2H),1.39(s,9H).

第 2 步 :(R)-3-(二氟甲基) 吡咯烷 -1- 甲酸叔丁酯



[0363] 将在二氯甲烷 (5mL) 中的 (R)-3- 甲酰吡咯烷 -1- 甲酸叔丁酯 (0.6g,3.06mmol) 冷却至 0℃。逐滴加入二乙基氨基三氟化硫 (DAST,0.52mL,3.98mmol),并将所得混合物在室温下搅拌过夜。将水加入至该反应混合物中并将两层分离。将有机层用饱和 $NaHCO_3$ 水溶液洗涤,经硫酸钠干燥,过滤,并将滤液在旋转蒸发器上浓缩。通过在硅胶上的急骤层析 (用 0 至 50% 乙酸乙酯 / 己烷洗脱) 纯化粗物质,得到 0.45g 呈澄清的油的 (R)-3-(二氟甲基) 吡咯烷 -1- 甲酸叔丁酯。^1H NMR(400MHz,DMSO-d_6) δ 6.08(td,1H),3.34(m,2H),3.19(m,2H),2.70(m,1H),1.95(m,1H),1.82(m,1H),1.39(s,9H).

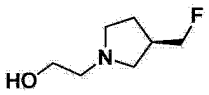
第 3 步 :(R)-3-(二氟甲基) 吡咯烷盐酸盐



[0364] 将在 1,4- 二氧杂环己烷 (1mL) 中的 (R)-3-(二氟甲基) 吡咯烷 -1- 甲酸叔丁酯 (0.45g,2.03mmol) 在冰浴中冷却至 15℃。然后加入 HCl(4M,在 1,4- 二氧杂环己烷中,1.5mL,6.11mmol),并将得到的溶液在室温下搅拌过夜。在旋转蒸发器上除去溶剂并用乙醚磨碎残余物。在真空下除去乙醚并干燥固体得到 0.31g 灰色固体 (R)-3-(二氟甲基) 吡咯烷盐酸盐。^1H NMR(400MHz,DMSO-d_6) δ 9.57(bs,2H),6.19(td,1H),3.34(m,1H),3.22-3.06(m,3H),2.82(m,1H),2.05(m,1H),1.85(m,1H).

中间体 13

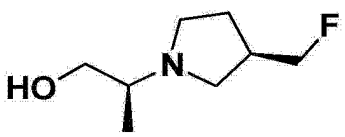
(R)-2-(3-(氟甲基) 吡咯烷 -1- 基) 乙醇



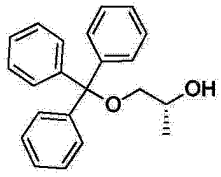
[0365] 在 80℃加热 (R)-3-(氟甲基) 吡咯烷盐酸盐 (中间体 8,4.26g,30.6mmol)、2- 溴乙醇 (4.35mL,61.3mmol) 和碳酸钾 (12.7g,92mmol) 在乙腈 (120mL) 中的混合物过夜。冷却后,将固体滤出并用乙腈洗涤。在旋转蒸发器上浓缩滤液得到残余物,通过硅胶层析 (用 10:7 乙酸乙酯 / 己烷至 10:7:2:1 乙酸乙酯 / 己烷 / 甲醇 / 三乙胺洗脱) 纯化该残余物得到 2.9g 呈澄清的油的 (R)-2-(3-(氟甲基) 吡咯烷 -1- 基) 乙醇。^1H NMR(400MHz,DMSO-d_6) δ 4.44(t,1H),4.34(dd,1H),4.22(dd,1H),3.44(q,2H),2.58-2.51(m,1H),2.48-2.38(m,5H),2.32-2.28(m,1H),1.85-1.74(m,1H),1.39-1.31(m,1H).

中间体 14

(S)-2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 丙烷 -1- 醇

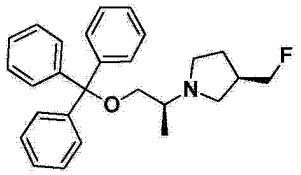


第 1 步 :(R)-1-(三苯甲基氧基) 丙烷 -2- 醇



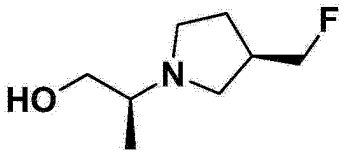
[0366] 将二甲基氨基吡啶 (165mg,1.35mmol) 加入至0℃的 (R)-丙烷-1,2-二醇 (10.3g,135.4mmol) 和三苯甲基氯 (38.1g 136.7mmol) 在 DCM(400mL) 中的溶液中。然后将三乙胺 (47.2mL,338.4mmol) 逐滴加入至该混合物中。将该溶液升温至室温并搅拌过夜。将反应混合物用 1.0N 的 HCl 水溶液 (200mL) 洗涤,用盐水洗涤,经 Na_2SO_4 干燥,过滤,并减压浓缩。通过硅胶层析纯化粗物质得到呈白色固体的 (R)-1-(三苯甲基氧基)丙烷-2-醇 (36.4g,84%)。^1H NMR(400MHz,DMSO-d_6):δ 7.43-7.39(m,6H)7.34-7.31(m,6H)7.26-7.22(m,3H),4.70(d,1H),3.82-3.76(m,1H),2.95-2.92(dd,1H),2.70-2.67(dd,1H),1.06(d,3H).

第 2 步 :(R)-3-(氟甲基)-1-((S)-1-(三苯甲基氧基)丙烷-2-基)吡咯烷



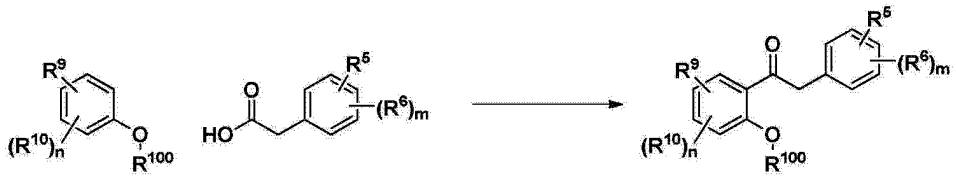
[0367] 将三氟甲磺酸酐 (1.0M 在 DCM 中,51.8mL,51.8mmol) 逐滴加入至 -78℃的 (R)-1-(三苯甲基氧基)丙烷-2-醇 (15.0g,47.1mmol) 和二异丙基乙胺 (32.8mL,188.4mmol) 在 DCM(190mL) 中的溶液中。将反应混合物在 -78℃搅拌 1.5 小时。将在 DCM(20mL) 中的 (R)-3-(氟甲基)吡咯烷盐酸盐 (中间体 8,7.9g,56.5mmol) 逐滴加入至 -78℃的反应混合物中。将该混合物升温至室温并在室温下搅拌过夜。将水 (200ml) 和饱和 $NaHCO_3$ 水溶液 (200ml) 加入至该混合物中。将该混合物倒入分液漏斗中并分离各层。用 DCM 洗涤水层两次。将有机层合并,经 Na_2SO_4 干燥,过滤,并在旋转蒸发器上浓缩得到粗物质,该粗物质无需进一步纯化而直接用于下一步。

第 3 步 :(S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙烷-1-醇



[0368] 在室温下,搅拌 (R)-3-(氟甲基)-1-((S)-1-(三苯甲基氧基)丙烷-2-基)吡咯烷 (19.0g,47.1mmol) 和甲酸/乙醚 (4:1,189mL) 的混合物 8 小时。在旋转蒸发器上浓缩该反应混合物。将残余物溶解于 DCM 中,用饱和 K_2CO_3 水溶液洗涤,并用盐水洗涤。将有机层经 Na_2SO_4 干燥,过滤,并浓缩得到粗产物,通过硅胶层析 (10:7 乙酸乙酯/己烷至 10:7:2:1 乙酸乙酯/己烷/甲醇/三乙胺) 纯化该粗产物得到呈深橙色的油的 (S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙烷-1-醇 (3.9g)。^1H NMR(400MHz,DMSO-d_6) δ 4.38-4.32(m,2H),4.22-4.20(m,1H),3.49-3.44(m,1H),3.21-3.16(m,1H),2.65-2.61(m,1H),2.58-2.53(m,1H),2.52-2.47(m,1H),2.45-2.35(m,1H),2.34-2.30(m,1H),2.29-2.24(m,1H),1.83-1.75(m,1H),1.38-1.30(m,1H),0.98(d,3H).

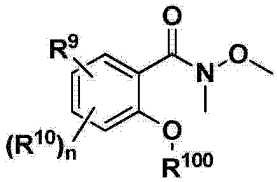
一般程序 A :Friedel-Crafts 酰化反应



[0369] 在75℃下加热1.8当量的1-甲氧基苯（例如1,4-二甲氧基苯）、适量的苯乙酸（1.0当量）和聚磷酸（1.3-1.5M）的混合物5-24小时，并冷却至50℃。加入水（PPA的1-2倍，v/v），并使该混合物冷却至室温。加入额外的水（PPA的1-2倍，v/v）并用DCM（或醚）萃取该混合物。将有机相用H_2O洗涤，用盐水洗涤，经Na_2SO_4（或$MgSO_4$）干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的烷氧基芳基酮。

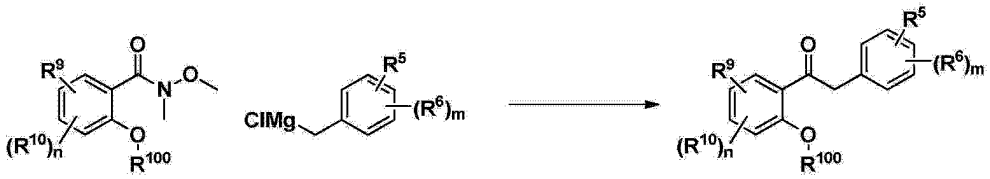
一般程序B

第1步：Weinreb酰胺的合成



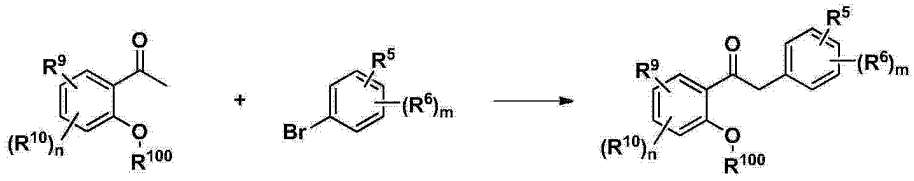
[0370] 将草酰氯（1.25当量）加入至1.0当量的2-烷氧基苯甲酸（例如2,5-二甲氧基苯甲酸）在DCM(0.33M)中的溶液中。然后将DMF(5％ v/v的草酰氯）加入至混合物中。在室温下搅拌该溶液2小时，并减压除去溶剂。将粗物质在真空下放置30分钟以除去残余的草酰氯。将三乙胺（1.2当量）逐滴加入至0℃的残余物和N,O-二甲基羟胺盐酸盐（1.0当量）在DCM(0.33M)中的溶液中。在0℃搅拌该溶液30分钟，然后在室温下再搅拌30分钟。将反应液用DCM稀释，用水洗涤两次，用盐水洗涤，经Na_2SO_4（或$MgSO_4$）干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的Weinreb酰胺。

第2步：向Weinreb酰胺上的格氏（Grignard）加成



[0371] 经30分钟将适量的苄基氯化镁（1.9当量）通过注射器加入至0℃的Weinreb酰胺（1.0当量）的THF(0.5M)溶液中。在0℃下搅拌该反应液30分钟，然后使之经1小时升温至室温。将该混合物冷却至0℃并用1.0M的HCl水溶液猝灭。分离各层，并用醚萃取水层。将合并的有机层用水洗涤，用盐水洗涤，经Na_2SO_4（或$MgSO_4$）干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的烷氧基芳基酮。

一般程序C:Pd-介导的酮的芳基化

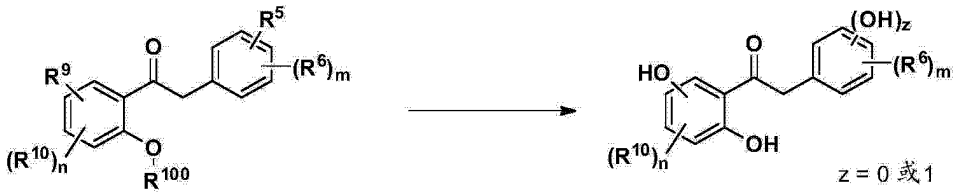


[0372] 通过使用真空和氮气回填，将在烧瓶中的Pd_2dba_3(0.015当量）、BINAP(0.035当量）和NaO^tBu(1.3当量）的混合物放置于N_2气氛下。加入THF(0.3M)，随后加入相应的芳

基溴化物（1.0 当量）和 1.2 当量的 2- 甲氧基苯基 - 乙酮（例如 1-(2,5- 二甲氧基苯基）乙酮）在 THF(0.5M) 中的溶液。将得到的混合物在 70℃加热 16 小时。加入水（THF 的 100％ v/v）并将混合物用醚萃取（3x）。将合并的有机层经无水 Na_2SO_4 干燥，过滤，并浓缩得到粗产物，通过在硅胶上的柱层析纯化该粗产物得到相应的烷氧基芳基酮。

一般程序 D

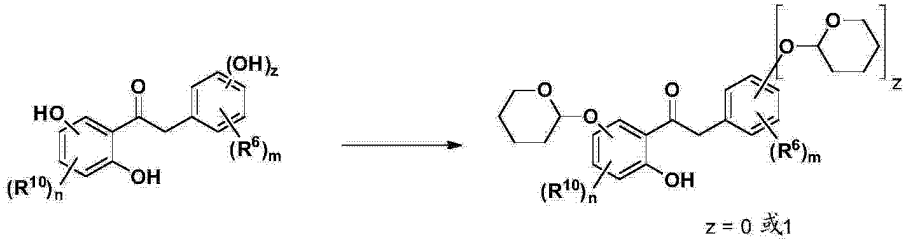
第 1 步 :脱甲基化



[0373] 将纯三溴化硼（3 当量）逐滴加入至 -78℃的烷氧基芳基酮（1.0 当量）的 DCM(0.25M) 溶液中。将该反应混合物升温至 0℃，搅拌 30 分钟，再冷却至 -78℃，然后用甲醇小心地猝灭（注释 1）。将该混合物升温至室温，用水洗涤，用饱和 $NaHCO_3$ 水溶液洗涤两次，用盐水洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的苯酚。

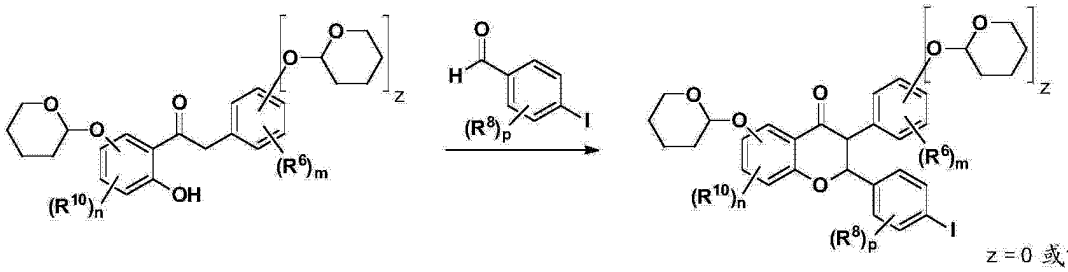
[0374] 注释 1 :在一些情况下，当用甲醇猝灭后物质从溶液中析出时，在进一步反应之前加入乙酸乙酯溶解该物质。

第 2 步 :苯酚的保护



[0375] 在室温下，将 3,4- 二氢 -2H- 吡喃（5.0 当量）加入至二羟基芳基酮（1 当量）和吡啶对甲苯磺酸盐（0.20 当量）在 DCM(0.25M) 中的混合物中。在该温度下将得到的混合物搅拌 2-24 小时。将该混合物用水洗涤，用饱和 $NaHCO_3$ 水溶液洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的 THP- 保护的羟基芳基酮。

第 3 步 :环化为苯并二氢吡喃酮



[0376] 将保护的羟基芳基酮（1.0 当量）、4- 碘代芳基醛（1.0 当量）、哌啶（0.35 当量）和 DBU(0.35 当量）在仲丁醇（1.0M）中的溶液在回流下加热。使用 Dean-Stark 阱，经 30-40 分钟除去一半溶剂，并在无进一步浓缩的情况下保持该反应液再回流 4-8h。将该反应混合

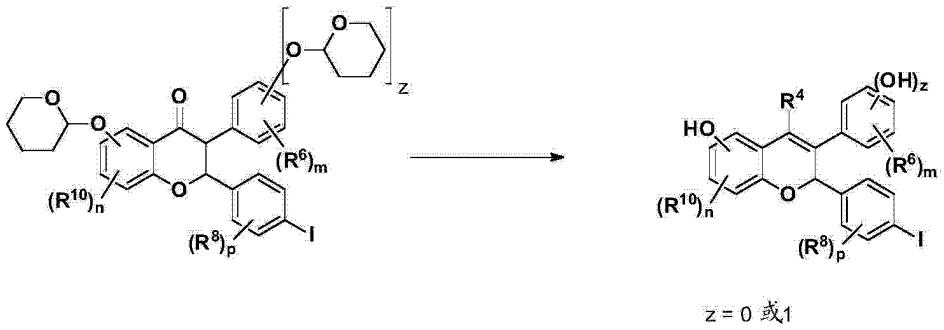
物冷却至 90℃，加入异丙醇（仲丁醇的 0.7-1.0 倍，v/v）并将该反应液冷却至室温。使用刮勺将任何大块的材料破碎，并搅拌该悬浮液过夜（注释 1 和 2）。通过过滤收集沉淀得到相应的苯并二氢吡喃酮。

[0377] 注释 1：在一些情况下，冷却至室温后的搅拌时间可更长（2-3 天）。

[0378] 注释 2：在一些情况下，当没有固体物沉淀析出时，使用激发（work up）程序。该混合物用有机溶剂（DCM 或 EtOAc）稀释并用水洗涤，用盐水洗涤。将该有机层经 Na_2SO_4（或 $MgSO_4$）干燥，过滤，并浓缩得到粗产物，然后通过硅胶层析纯化该粗产物。

一般程序 E

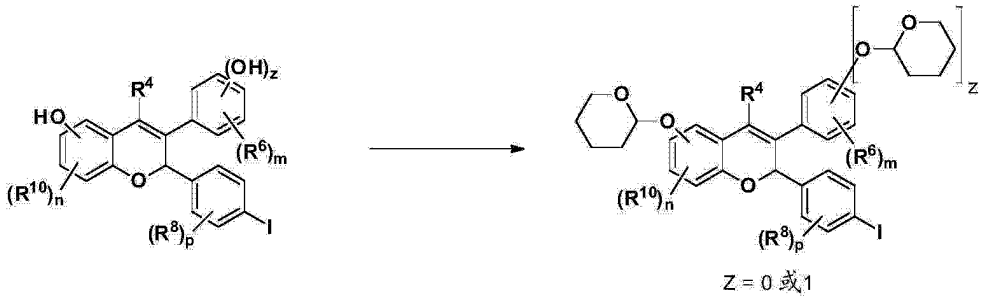
[0379] 第 1 步：格氏加成和消除



[0380] 将格氏试剂（例如甲基氯化镁；3.75 当量，3M，在 THF 中）的溶液逐滴加入至 0℃的苯并二氢吡喃酮（1 当量）的 THF(0.25M) 溶液中。在 0℃下搅拌该反应液 15-30 分钟并使之升温至室温。搅拌 2-2.5 小时后，将该溶液冷却至 0℃并使用饱和氯化铵水溶液猝灭。将该混合物升温至室温，用乙酸乙酯和水稀释并分离各层。将有机层用水洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，过滤，并浓缩得到相应的叔醇。该粗物质悬浮于 80％乙酸 / 水 (0.1M) 中并在 90℃加热 3-5 天。将反应混合物减压浓缩并用乙酸乙酯稀释（注释 1）。将有机相用水洗涤，用饱和 $NaHCO_3$ 水溶液洗涤两次，用盐水洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的苯并吡喃。

[0381] 注释 1：在一些情况下，将反应混合物直接用水稀释并用乙酸乙酯萃取三次。将有机层合并并用水 / 盐水混合物洗涤两次，用饱和 $NaHCO_3$ 水溶液洗涤两次，用盐水洗涤，经 Na_2SO_4 干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的苯并吡喃。

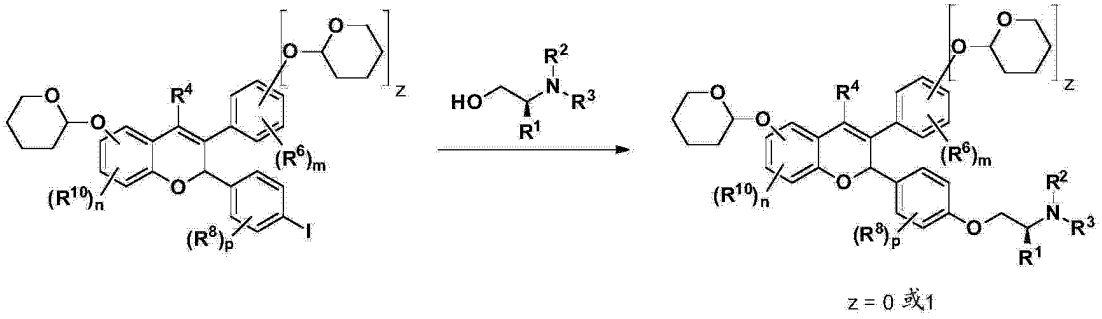
第 2 步：苯酚的保护



[0382] 将 3,4- 二氢 -2H- 吡喃（1.5-5 当量）加入至羟基芳基苯并吡喃（1.0 当量）和吡啶对甲苯磺酸盐（0.20-0.25 当量）在 DCM(0.25M) 中的溶液中并在室温下搅拌 4-5 小时。将该混合物用饱和 $NaHCO_3$ 水溶液洗涤，用水洗涤，用盐水洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，

过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的 THP- 保护的苯并吡喃。

一般程序 F: 乌尔曼偶合



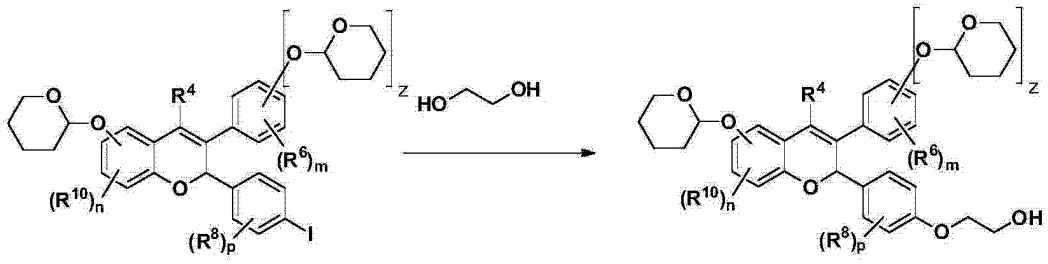
z = 0 或 1

[0383] 将 THP- 保护的碘代苯并吡喃 (1.0 当量）、1.5-2.0 当量的相应的氨基醇侧链（例如中间体 7、13 或 14)、碘化亚铜 (0.10 当量）和碳酸钾 (2.0 当量）在丁腈 (0.5M) 中的混合物通过经该混合物氮气鼓泡 15 分钟来进行脱气。将该反应混合物在 125℃加热 1-5 天，使之冷却至室温，并用乙酸乙酯稀释。将该混合物通过一层 Celite 过滤并用乙酸乙酯洗涤。将有机相用水洗涤两次，用盐水洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的乌尔曼偶合产物。

[0384] 注释 :在一些情况下 :i) 反应时间根据氨基醇而不同（过夜至 5 天 ;通过 LCMS 监测进度）;和 ii) 用碳酸铯代替碳酸钾。

一般程序 G

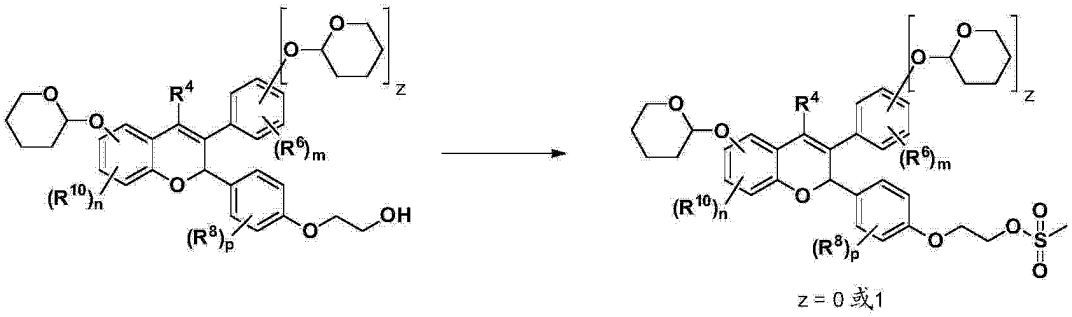
第 1 步：乌尔曼偶合



z = 0 或 1

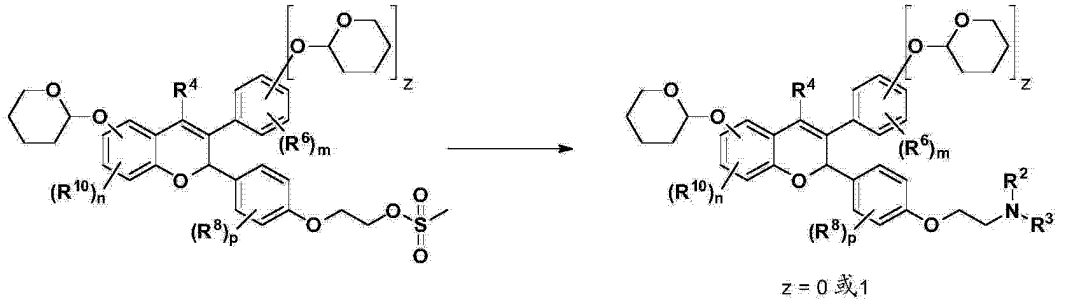
[0385] 将 THP- 保护的碘代苯并吡喃 (1.0 当量）、二醇 (4.0 当量）、碘化亚铜 (0.10 当量）、1,10- 菲咯啉 (0.20 当量）和碳酸钾 (2.0 当量）在丁腈 (0.5M) 中的混合物进行脱气。将该反应混合物在 125℃下加热 3 天，使之冷却至室温，并用乙酸乙酯稀释。将有机相用水洗涤两次，用盐水洗涤，经 Na_2SO_4 干燥，过滤，并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的乌尔曼产物。

第 2 步 :甲磺酰化



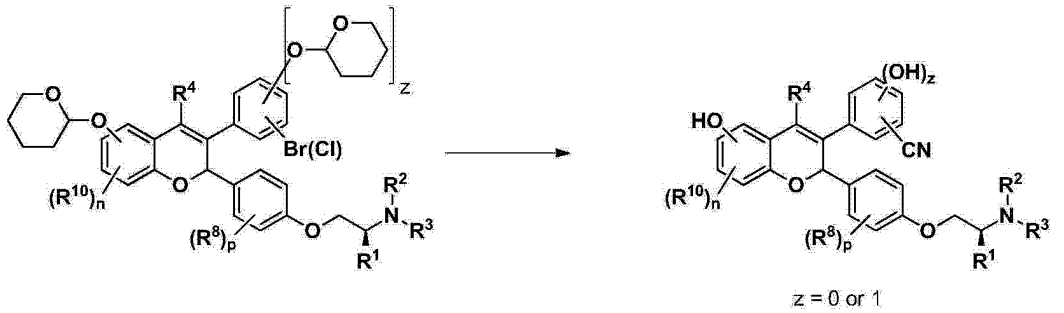
[0386] 将甲磺酰氯（1.3 当量）逐滴加入至 0℃的醇（1.0 当量）和三乙胺（1.5 当量）在 DCM(0.1M) 中的溶液中。将反应混合物在 0℃下搅拌 1 小时，然后用 DCM 稀释，并用 1N 的 HCl 水溶液猝灭。分离各层，并将有机层用水洗涤，用饱和 $NaHCO_3$ 水溶液洗涤，用盐水洗涤，经 Na_2SO_4 干燥，并浓缩得到期望的甲磺酸酯。

第 3 步 :烷基化



[0387] 在 80℃下加热甲磺酸酯（1.0 当量）、胺（2-3 当量）和碳酸钾（2.0 当量）在乙腈 (0.1M) 中的悬浮液 3-24 小时。将该反应混合物冷却至室温，减压浓缩，并用 DCM(0.01M) 稀释。将得到的沉淀滤出且减压浓缩滤液。然后通过硅胶层析纯化该粗产物得到相应的烷基化产物。

一般程序 H :芳基卤的氰化和 THP 基团的去除



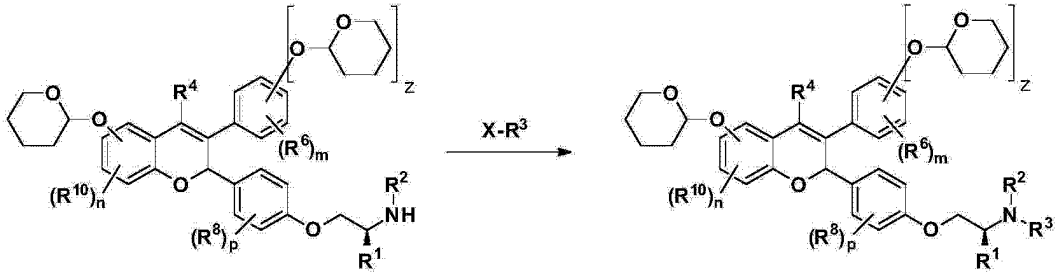
[0388] 将芳基溴化物（1.0 当量）、1 丁基咪唑（20.0 当量）、碘化亚铜（1.0 当量）、亚铁氰化钾三水合物（2.0 当量）和间二甲苯 (0.1M) 的混合物通过 3 次真空 / 氮气循环进行脱气。在 140℃下加热该反应混合物 1-3 天。将该混合物通过一层 Celite 过滤并用乙酸乙酯洗涤。将该滤液用水洗涤，用盐水洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，过滤，并减压浓缩。然后通过硅胶层析纯化该粗物质得到相应的芳基腈（注释 1）。在室温下，在 80％乙酸 /H_2O(0.25M) 中搅拌该纯化的物质（1.0 当量）3-24 小时。减压除去溶剂，并通过反相 HPLC 纯化该残余物（注释 2）。合并纯化的级分，减压浓缩至大约三分之一的体积，并用乙酸乙酯萃取。将有机层用饱和 $NaHCO_3$ 水溶液洗涤，用盐水洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，过滤，并减压浓缩。

将得到的固体溶解于乙酸乙酯 (0.05M) 中并用 HCl(2N,在乙醚中,2.0 当量) 处理。减压除去溶剂得到相应的盐酸盐。

[0389] 注释 1 :也可使用可替代的程序 :将芳基溴化物 (或芳基氯化物)(1.0 当量)、锌粉 (0.72 当量)、[1,1'- 联萘]-2- 基二叔丁基膦 (0.30 当量)、氰化锌 (2.1 当量) 和二甲基乙酰胺 (0.12-0.14M) 的混合物通过 3 次真空 / 氮气循环进行脱气。加入三氟乙酸钯 (0.13 当量) 并再经 3 次另外的真空 / 氮气循环脱气。将该反应混合物在 95℃下加热 3.5-5 小时,使之冷却至室温,并用乙酸乙酯稀释。将有机相用水洗涤两次,经 Na_2SO_4(或 $MgSO_4$) 干燥,过滤,并浓缩得到粗产物。然后通过硅胶层析纯化该粗产物得到相应的芳基腈。

[0390] 注释 2 :对于一些化合物,通过反相 HPLC 纯化后,将级分减压浓缩,得到相应的三氟乙酸盐,而无需任何进一步的操作。

一般程序 I :N- 烷基化

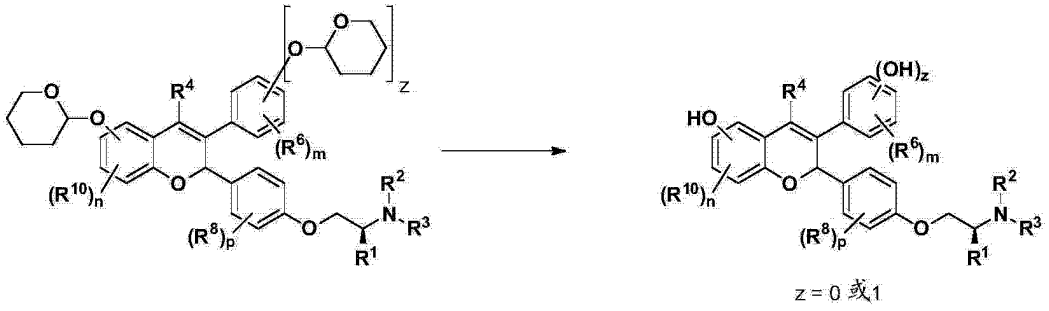


[0391] 将胺 (1.0 当量)、烷基碘化物 (1.5 当量) 和碳酸氢钠 (2.0 当量) 在 DMA 中的混合物在 50℃加热 6 小时,使之冷却至室温并用乙酸乙酯稀释。将有机萃取物用水洗涤,用盐水洗涤,经 Na_2SO_4(或 $MgSO_4$) 干燥,过滤,浓缩,并通过硅胶层析纯化,从而得到相应的烷基化产物。

[0392] 注释 1 :在一些情况下,在 80℃加热反应液以缩短反应时间。

[0393] 注释 2 :在一些情况下,加入额外的烷基碘化物和碳酸氢钠以促进反应完成。

一般程序 J :THP 保护基的去除



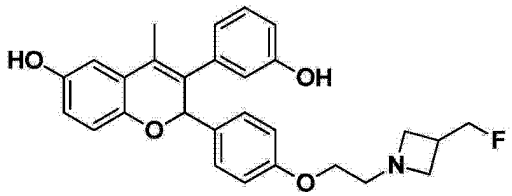
[0394] 在室温下,将 THP 保护的苯并吡喃 (1.0 当量) 在 80％乙酸 /H_2O(0.25M) 中搅拌 3-24 小时。减压除去溶剂,并通过反相 HPLC 纯化残余物 (注释 1 和 2)。合并纯化的级分,减压浓缩至大约三分之一的体积,并用乙酸乙酯萃取。将有机层用饱和 $NaHCO_3$ 水溶液洗涤,用盐水洗涤,经 Na_2SO_4(或 $MgSO_4$) 干燥,过滤,并减压浓缩。将得到的固体溶解于乙酸乙酯 (0.05M) 中并用 HCl(2N,在乙醚中,2.0 当量) 进行处理。减压除去溶剂得到相应的盐酸盐。

[0395] 注释 1 :对于一些化合物,通过反相 HPLC 纯化后,将级分减压浓缩,从而得到相应的三氟乙酸盐,而无需任何进一步的操作。

[0396] 注释 2：在一些情况下，将残余物溶解于乙酸乙酯中并用饱和 $NaHCO_3$ 水溶液洗涤，用盐水洗涤，经 Na_2SO_4（或 $MgSO_4$）干燥，过滤，并减压浓缩，从而得到粗产物。通过硅胶层析纯化该粗产物。

实施例 1

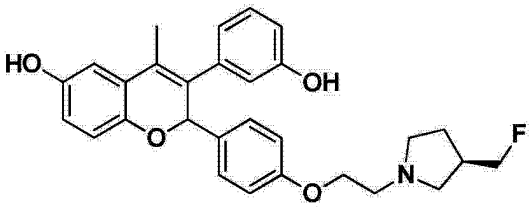
2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇



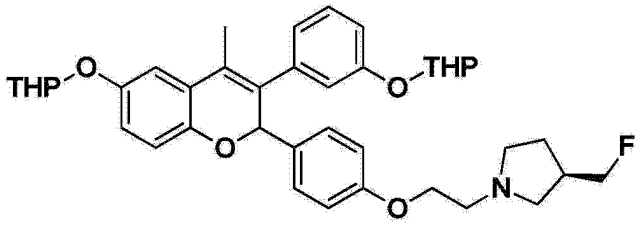
[0397] 将中间体 5(0.11g,0.17mmol)、中间体 6(0.32mg,0.25mmol)、碳酸钾 (70mg,0.51mmol) 在乙腈 (1.7mL) 中的混合物在 80℃下加热 6 小时，使之冷却至室温，用水 (10mL) 稀释并用乙酸乙酯萃取 (3x 10ml)。将合并的有机层用水洗涤，用盐水洗涤，经 Na_2SO_4 干燥，在旋转蒸发器上浓缩得到粗 3-(氟甲基)-1-(2-(4-(4-甲基-6-((四氢-2H-吡喃-2-基)氧基)-3-(3-((四氢-2H-吡喃-2-基)氧基)苯基)-2H-苯并吡喃-2-基)苯氧基)乙基)氮杂环丁烷。在室温下，将该粗物质在 80％乙酸 /H_2O(5mL) 中搅拌 3 小时。在旋转蒸发器上除去溶剂，将残余物溶解于乙酸乙酯中。将有机层用饱和 $NaHCO_3$ 水溶液洗涤，用盐水洗涤，经 Na_2SO_4 干燥，过滤，并减压浓缩得到粗产物。然后通过反相 C18 层析 (30-40％乙腈 / 水 /0.1％ TFA) 纯化该粗物质。合并级分，将其浓缩并溶解于乙酸乙酯中。将有机层用饱和 $NaHCO_3$ 水溶液洗涤，用盐水洗涤，经 Na_2SO_4 干燥，过滤，并减压浓缩得到呈浅黄色固体的 2-(4-(2-(3-(氟甲基)氮杂环丁-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇。^1H NMR(DMSO-d_6)：δ 9.40(s,1H),8.94(s,1H),7.18(d,2H),7.12(t,1H),6.75(d,2H),6.73(m,1H),6.68-6.57(m,2H),6.60(s,br,1H),6.47(m,2H),5.82(s,1H),4.53(d,1H),4.41(d,1H),3.81(t,2H),3.26(dd,2H),2.94(t,2H),2.76-2.64(m,1H),2.63(t,2H),2.02(s,3H)．；LCMS:462$(M+H)^+$.

实施例 2

2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

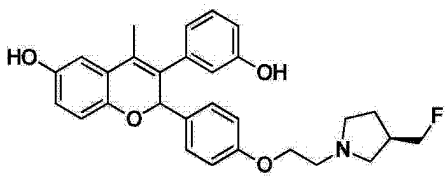


第 1 步：(3R)-3-(氟甲基)-1-(2-(4-(4-甲基-6-((四氢-2H-吡喃-2-基)氧基)-3-(3-((四氢-2H-吡喃-2-基)氧基)苯基)-2H-苯并吡喃-2-基)苯氧基)乙基)吡咯烷



[0398] 将中间体 3(2.1g,3.35mmol)、中间体 13(738mg,5.02mmol)、碘化亚铜 (127mg,0.67mmol) 和碳酸钾 (925mg,6.7mmol) 在丁腈 (7mL) 中的混合物脱气三次,然后加热至 125℃ 2 天。冷却后,加入乙酸乙酯和水并将两层分离。将有机层用盐水洗涤,经硫酸钠干燥,过滤,并除去溶剂。通过在硅胶上的急骤层析 (20 至 100%乙酸乙酯 / 己烷) 纯化该残余物得到 1.87g 呈黄色泡沫的 (3R)-3-(氟甲基)-1-(2-(4-(4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2H- 苯并吡喃 -2- 基) 苯氧基) 乙基) 吡咯烷。LCMS :644(M+H)$^+$.

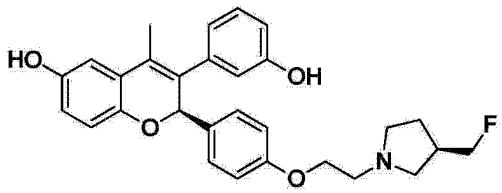
第 2 步 :(R)-2-(4-(2-(3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0399] 将 (3R)-3-(氟甲基)-1-(2-(4-(4- 甲基 -6-((四氢 -2H- 吡喃 -2- 基) 氧基)-3-(3-((四氢 -2H- 吡喃 -2- 基) 氧基) 苯基)-2H- 苯并吡喃 -2- 基) 苯氧基) 乙基) 吡咯烷 (1.87g,2.9mmol) 在乙酸 (80%水溶液,30mL) 中的混合物在室温下搅拌过夜。除去乙酸并将残余物在乙酸乙酯和饱和 $NaHCO_3$ 水溶液之间分配。将有机层用饱和 $NaHCO_3$ 水溶液洗涤,经硫酸钠干燥,过滤,并除去溶剂。通过在硅胶上的急骤层析 (0-5%甲醇 / 二氯甲烷) 纯化该残余物得到 1.1g 呈浅桃色泡沫的 (R)-2-(4-(2-(3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇。^{1}H NMR(DMSO-d_6) : δ 9.43(s,1H),8.94(s,1H),7.18(d,2H),7.14(t,1H),6.78(d,2H),6.73(s,1H),6.67-6.65(m,2H),6.65(s,1H),6.49-6.45(m,2H),5.83(s,1H),4.35-4.30(m,1H),4.23-4.19(m,1H),3.96(t,2H),2.71(t,2H),2.60(t,1H),2.46-2.40(m,3H),2.36-2.31(m,1H),2.02(s,3H),1.83-1.76(m,1H),1.39-1.30(m,1H) ;LCMS:476(M+H)$^+$.

实施例 2a

(R)-2-(4-(2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇

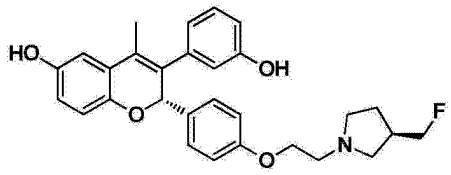


[0400] 当在 RegisCell(250x 4.6mm,5μm) 柱 [己烷 / 乙醇 / 二乙胺 (75/25/0.1%)] 上分离实施例 2 时,标题化合物为第一次洗脱的非对映异构体。非对应异构比率 :>99:1。^{1}H

NMR(DMSO-d_6;HCl 盐):δ 10.61(br,1H),9.47(s,1H),8.98(s,1H),7.23(d,2H),7.12(t,1H),6.86(d,2H),6.74(br,1H),6.70-6.57(m,3H),6.47-6.45(m,2H),5.86(s,1H),4.53-4.47(m,1H),4.46-4.36(m,1H),4.25(br,2H),3.73-3.49(m,3H),3.34-3.22(m,1H),3.18-3.06(m,1H),2.98-2.86(m,1H),2.20-2.11(m,1H),2.02(s,3H),1.87-1.75(m,1H),1.67-1.55(m,1H).LCMS:476.1$(M+H)^+$.

实施例 2b

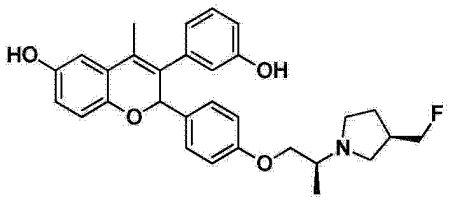
(S)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇



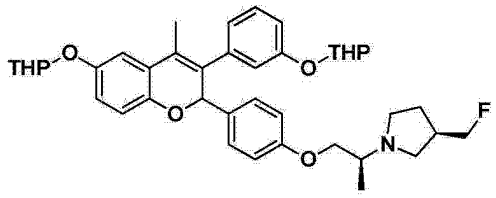
[0401] 当在 RegisCell(250x 4.6mm,5μm)柱[己烷/乙醇/二乙胺(75/25/0.1%)]上分离实施例 2 时,标题化合物为第二次洗脱的非对映异构体。非对应异构比率:>99:1。^{1}H NMR(DMSO-d_6;HCl 盐):δ 10.61(br,1H),9.48(s,1H),8.98(s,1H),7.24(d,2H),7.12(t,1H),6.86(d,2H),6.75(d,1H),6.70-6.57(m,3H),6.48-6.45(m,2H),5.86(s,1H),4.57-4.47(m,1H),4.45-4.35(m,1H),4.30-4.22(m,2H),3.75-3.50(m,3H),3.33-3.21(m,1H),3.18-3.08(m,1H),2.97-2.86(m,1H),2.20-2.09(m,1H),2.03(s,3H),1.86-1.74(m,1H),1.66-1.58(m,1H).LCMS:476.1$(M+H)^+$.

实施例 3

2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇



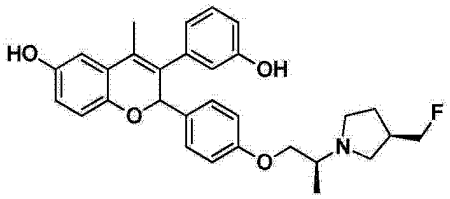
第 1 步:(3R)-3-(氟甲基)-1-((2S)-1-(4-(4-甲基-6-((四氢-2H-吡喃-2-基)氧基)-3-(3-((四氢-2H-吡喃-2-基)氧基)苯基)-2H-苯并吡喃-2-基)苯氧基)丙烷-2-基)吡咯烷



[0402] 采用真空/氮气循环将中间体 3(1.0g,1.6mmol)、中间体 14(388mg,2.4mmol)、碘化亚铜(61mg,0.32mmol)和碳酸钾(443g,3.2mmol)在丁腈(3.2mL)中的混合物脱气 3 次。将反应混合物在 125℃下加热 2 天,使之冷却至室温,并用乙酸乙酯稀释。通过 Celite 过滤不可溶物质并用乙酸乙酯洗涤该 Celite。将滤液用水洗涤两次,用盐水洗涤,经 Na_2SO_4 干燥,过滤,并减压浓缩。通过硅胶层析(0-100% EtOAc/己烷)纯化该粗物质得到呈米

色泡沫的 (3R)-3-(氟甲基)-1-((2S)-1-(4-(4-甲基-6-((四氢-2H-吡喃-2-基)氧基)-3-(3-((四氢-2H-吡喃-2-基)氧基)苯基)-2H-苯并吡喃-2-基)苯氧基)丙烷-2-基)吡咯烷 (785mg,74%)。^{1}H NMR(400MHz,DMSO-d_6):δ 7.27-7.19(m,3H),6.99(t,1H),6.93-6.88(m,3H),6.81-6.76(m,3H),6.59(d,1H),5.97(d,1H),5.43-5.38(dt,1H),5.34(m,1H),4.32-4.30(m,1H),4.20-4.19(m,1H),3.99-3.93(m,1H),3.73-3.69(m,3H),3.58-3.47(m,2H),2.69-2.60(m,2H),2.59-2.52(m,2H),2.45-2.30(m,2H),2.06(s,3H),1.90-1.65(m,7H),1.64-1.47(m,6H),1.40-1.30(m,1H),1.06(d,3H) ;LCMS:658.3(M+H)$^+$.

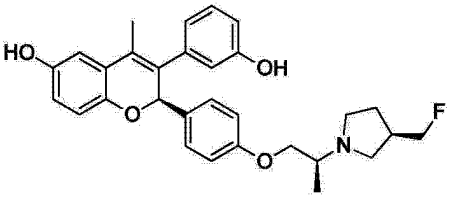
第 2 步 :2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇



[0403] 在室温下,将 (3R)-3-(氟甲基)-1-((2S)-1-(4-(4-甲基-6-((四氢-2H-吡喃-2-基)氧基)-3-(3-((四氢-2H-吡喃-2-基)氧基)苯基)-2H-苯并吡喃-2-基)苯氧基)丙烷-2-基)吡咯烷 (785mg,1.19mmol) 在 80%乙酸 /H_2O(6.0mL) 中搅拌 2 天。在旋转蒸发器上除去溶剂并将残余物溶解于乙酸乙酯中。将有机层用饱和 $NaHCO_3$ 水溶液洗涤,用水洗涤,用盐水洗涤,经 Na_2SO_4 干燥,过滤,并减压浓缩。然后通过硅胶层析 (0-4% MeOH/DCM) 纯化该粗物质得到呈浅粉色固体的 2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇 (410mg,70%)。^{1}HNMR(DMSO-d_6):δ 9.43(s,1H),8.94(s,1H),7.18(d,2H),7.12(t,1H),6.79(d,2H),6.73(m,1H),6.68(dt,1H),6.65(m,1H),6.61(m,1H),6.49-6.45(m,2H),5.83(s,1H),4.35-4.30(m,1H),4.23-4.18(m,1H),3.99-3.93(m,1H),3.74-3.70(m,1H),2.69-2.60(m,2H),2.58-2.52(m,2H),2.45-2.32(m,2H),2.02(s,3H),1.82-1.75(m,1H),1.36-1.30(m,1H),1.07(d,3H) ;LCMS:490.2(M+H)$^+$.

实施例 3a

(R)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

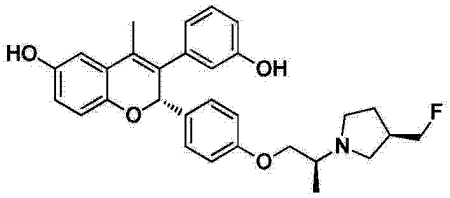


[0404] 当在 RegisCell(250x 4.6mm,5μm) 柱 [己烷 / 乙醇 / 二乙胺 (75/25/0.1%)] 上分离实施例 3 时,标题化合物为第一次洗脱的非对映异构体。非对应异构比率 :>99:1。^{1}H NMR(DMSO-d_6 ;HCl 盐):δ 10.60(br,1H),9.47(s,1H),8.98(s,1H),7.24(d,2H),7.12(t,1H),6.87(d,2H),6.74(d,1H),6.70-6.60(m,3H),6.48-6.45(m,2H),5.86(s,1H),4.56-4.47(m,1H),4.47-4.36(m,1H),4.20-4.15(m,2H),3.74-3.66(m,1H),3.62-3.49(m,2H),3.28-3.12(m,1H),3.03-2.90(m,1H),2.15-2.07(m,1H),2.03(s,3H),1.84-1.73(m,1H),1.66-1.55(m

,1H),1.35(d,3H) ;LCMS:490.1(M+H)$^+$.

实施例 3b

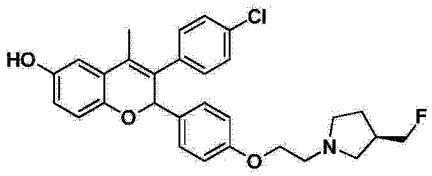
(S)-2-(4-((S)-2-((R)-3-(氟甲基)吡咯烷-1-基)丙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇



[0405] 当在 RegisCell(250x 4.6mm,5μm) 柱[己烷/乙醇/二乙胺 (75/25/0.1%)]上分离实施例 3 时,标题化合物为第二次洗脱的非对映异构体。非对应异构比率 :>99:1。^{1}H NMR(DMSO-d_6 ;HCl 盐): δ 10.65-10.60(br,1H),9.47(s,1H),8.98(s,1H),7.24(d,2H),7.12(t,1H),6.87(d,2H),6.74(d,1H),6.70-6.63(m,3H),6.48-6.45(m,2H),5.86(s,1H),4.56-4.47(m,1H),4.45-4.35(m,1H),4.22-4.11(m,2H),3.74-3.64(m,1H),3.62-3.49(m,2H),3.28-3.12(m,1H),3.03-2.90(m,1H),2.15-2.07(m,1H),2.03(s,3H),1.84-1.73(m,1H),1.66-1.55(m,1H),1.35(d,3H) ;LCMS:490.1(M+H)$^+$.

实施例 4

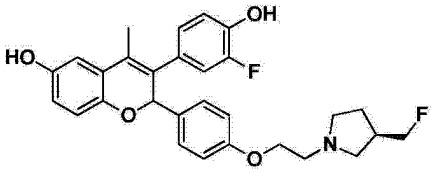
3-(4-氯苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇



[0406] 如一般程序 A、D、E、G 和 J(z = 0) 中所述,使用一般程序 A 中的 1,4-二甲氧基苯和 2-(4-氯苯基)乙酸与一般程序 G 中的中间体 8 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) δ 8.97(s,1H),7.40(m,2H),7.31(m,2H),7.19(d,2H),6.78(m,2H),6.75(m,1H),6.52-6.47(m,2H),5.91(s,1H),4.33-4.30(m,1H),4.21-4.18(m,1H),3.95(t,2H),2.70(t,2H),2.59(t,1H),2.55-2.47(m,1H),2.50-2.40(m,2H),2.35-2.31(m,1H),1.98(s,3H),1.83-1.77(m,1H),1.37-1.32(m,1H) ;LCMS:494.1(M+H)$^+$.

实施例 5

3-(3-氟-4-羟基苯基)-2-(4-(2-((R)-3-(氟甲基)吡咯烷-1-基)乙氧基)苯基)-4-甲基-2H-苯并吡喃-6-醇

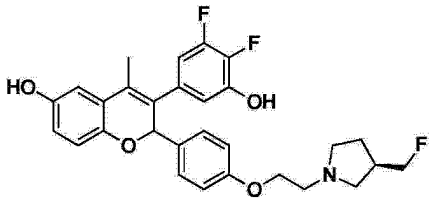


[0407] 如一般程序 A、D、E、F 和 J(z = 1) 中所述,使用一般程序 A 中的 1,4-二甲氧基苯和 2-(3-氟-4-甲氧基苯基)乙酸与一般程序 F 中的中间体 13 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) δ 9.95(s,1H),8.93(s,1H),7.17(d,2H),7.09(m,1H),6.93-6.86(m,

2H), 6.77(m, 2H), 6.71(m, 1H), 6.46(m, 2H), 5.89(s, 1H), 4.32-4.30(m, 1H), 4.20-4.18(m, 1H), 3.95(t, 2H), 2.69(t, 2H), 2.59(t, 1H), 2.55-2.47(m, 1H), 2.48-2.42(m, 2H), 2.35-2.31(m, 1H), 2.03(s, 3H), 1.83-1.78(m, 1H), 1.37-1.34(m, 1H) ;LCMS:494.1(M+H)$^+$.

实施例 6

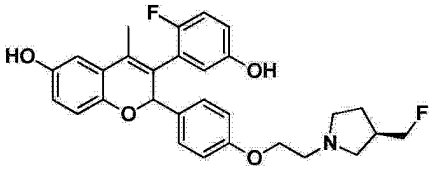
3-(3,4- 二氟 -5- 羟基苯基)-2-(4-(2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0408] 如一般程序 C、D、E、F 和 J(z = 1) 中所述,使用一般程序 C 中的 1-(2,5- 二甲氧基苯基) 乙酮和 5- 溴 -1,2- 二氟 -3- 甲氧基苯与一般程序 F 中的中间体 13 合成标题化合物。^{1}H NMR(400MHz, DMSO-d_6) δ 10.45(br s, 1H), 8.97(s, 1H), 7.17(d, 2H), 6.81-6.74(m, 4H), 6.61(m, 1H), 6.51-6.46(m, 2H), 5.83(s, 1H), 4.33-4.28(m, 1H), 4.23-4.16(m, 1H), 3.96(t, 2H), 2.70(t, 2H), 2.61(t, 1H), 2.55-2.47(m, 2H), 2.48-2.42(m, 1H), 2.36-2.32(m, 1H), 2.02(s, 3H), 1.85-1.76(m, 1H), 1.39-1.31(m, 1H) ;LCMS:512.1(M+H)$^+$.

实施例 7

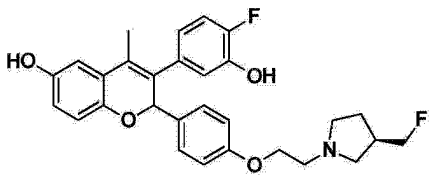
3-(2- 氟 -5- 羟基苯基)-2-(4-(2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0409] 如一般程序 C、D、E、F 和 J(z = 1) 中所述,使用一般程序 C 中的 1-(2,5- 二甲氧基苯基) 乙酮和 2- 溴 -1- 氟 -4- 甲氧基苯与一般程序 F 中的中间体 13 合成标题化合物。^{1}H NMR(400MHz, DMSO-d_6) δ 9.41(s, 1H), 8.98(s, 1H), 7.19(d, 2H), 6.99(t, 1H), 6.79(d, 2H), 6.74(d, 1H), 6.68-6.64(m, 1H), 6.54-6.47(m, 3H), 5.77(s, 1H), 4.33-4.30(m, 1H), 4.21-4.18(m, 1H), 3.96(t, 2H), 2.70(t, 2H), 2.60(t, 1H), 2.55-2.47(m, 1H), 2.48-2.42(m, 2H), 2.34-2.32(m, 1H), 1.92(s, 3H), 1.83-1.78(m, 1H), 1.38-1.33(m, 1H) ;LCMS:494.1(M+H)$^+$.

实施例 8

3-(4- 氟 -3- 羟基苯基)-2-(4-(2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇

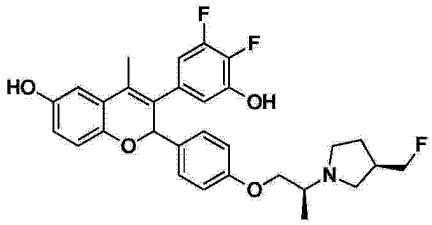


[0410] 如一般程序 C、D、E、F 和 J(z = 1) 中所述,使用一般程序 C 中的 1-(2,5- 二甲氧基苯基) 乙酮和 4- 溴 -1- 氟 -2- 甲氧基苯与一般程序 F 中的中间体 13 合成标题化合物。^{1}H

NMR(400MHz,DMSO-d_6) δ 9.87(s,1H),8.94(s,1H),7.17(d,2H),7.11-7.06(m,1H),6.79(m,3H),6.73(m,1H),6.68-6.65(m,1H),6.48-6.45(m,2H),5.81(s,1H),4.31-4.30(m,1H),4.21-4.18(m,1H),3.96(t,2H),2.70(t,2H),2.62(t,1H),2.55-2.47(m,1H),2.48-2.42(m,2H),2.35-2.32(m,1H),2.01(s,3H),1.83-1.79(m,1H),1.37-1.33(m,1H) ;LCMS:494.1(M+H)$^+$

实施例 9

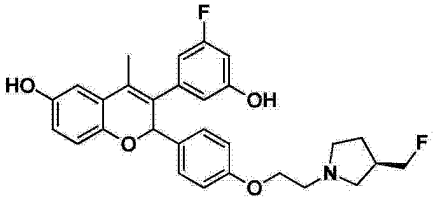
3-(3,4- 二氟 -5- 羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 丙氧基) 苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0411] 如一般程序 C、D、E、F 和 J(z = 1) 中所述,使用一般程序 C 中的 1-(2,5- 二甲氧基苯基) 乙酮和 5- 溴 -1,2- 二氟 -3- 甲氧基苯与一般程序 F 中的中间体 14 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) δ 10.45(br s,1H),8.97(s,1H),7.17(d,2H),6.81-6.74(m,4H),6.61(m,1H),6.51-6.46(m,2H),5.83(s,1H),4.33-4.30(m,1H),4.21-4.19(m,1H),3.99-3.94(m,1H),3.73(m,1H),2.69-2.53(m,4H),2.41-2.32(m,2H),2.02(s,3H),1.82-1.77(m,1H),1.36-1.32(m,1H),1.07(d,3H) ;LCMS:526.1(M+H)$^+$.

实施例 10

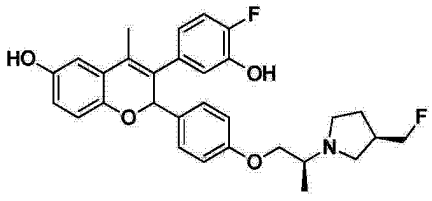
3-(3- 氟 -5- 羟基苯基)-2-(4-(2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0412] 如一般程序 C、D、E、F 和 J(z = 1) 中所述,使用一般程序 C 中的 1-(2,5- 二甲氧基苯基) 乙酮和 1- 溴 -3- 氟 -5- 甲氧基苯与一般程序 F 中的中间体 13 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) δ 9.95(s,1H),8.96(s,1H),7.18(d,2H),6.81(d,2H),6.74(d,1H),6.55-6.52(dt,1H),6.51-6.43(m,4H),5.84(s,1H),4.33-4.30(m,1H),4.21-4.18(m,1H),3.96(t,2H),2.70(t,2H),2.62(t,1H),2.55-2.47(m,1H),2.48-2.42(m,2H),2.35-2.32(m,1H),2.03(s,3H),1.83-1.78(m,1H),1.39-1.33(m,1H) ;LCMS:494.1(M+H)$^+$

实施例 11

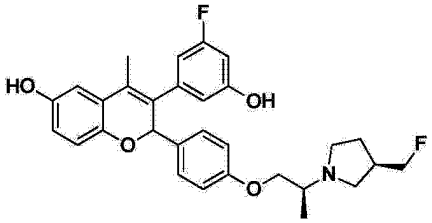
3-(4- 氟 -3- 羟基苯基)-2-(4-((S)-2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 丙氧基) 苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0413] 如一般程序 C、D、E、F 和 J(z = 1) 中所述，使用一般程序 C 中的 1-(2,5- 二甲氧基苯基）乙酮和 4- 溴 -1- 氟 -2- 甲氧基苯与一般程序 F 中的中间体 14 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) δ 9.87(s,1H),8.95(s,1H),7.17(d,2H),7.11-7.06(m,1H),6.79(m,3H),6.73(m,1H),6.69-6.65(m,1H),6.50-6.45(m,2H),5.81(s,1H),4.33-4.30(m,1H),4.21-4.18(m,1H),3.97-3.93(m,1H),3.73-3.71(m,1H),2.69-2.60(m,2H),2.58-2.54(m,2H),2.41-2.35(m,2H),2.01(s,3H),1.80-1.78(m,1H),1.40-1.33(m,1H),1.07(d,3H) ;LCMS:508.1(M+H)$^+$.

实施例 12

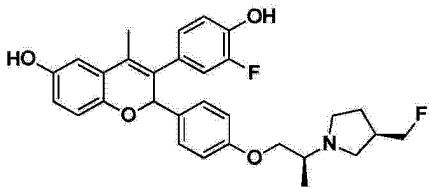
3-(3- 氟 -5- 羟基苯基）-2-(4-((S)-2-((R)-3-(氟甲基）吡咯烷 -1- 基）丙氧基）苯基）-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0414] 如一般程序 C、D、E、F 和 J(z = 1) 中所述，使用一般程序 C 中的 1-(2,5- 二甲氧基苯基）乙酮和 1- 溴 -3- 氟 -5- 甲氧基苯与一般程序 F 中的中间体 14 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) δ 9.95(s,1H),8.96(s,1H),7.18(d,2H),6.80(d,2H),6.74(d,1H),6.55-6.52(dt,1H),6.51-6.43(m,4H),5.84(s,1H),4.33-4.30(m,1H),4.21-4.19(m,1H),3.98-3.94(m,1H),3.73-3.71(m,1H),2.67-2.60(m,2H),2.58-2.54(m,2H),2.38-2.35(m,2H),2.03(s,3H),1.85-1.74(m,1H),1.40-1.33(m,1H),1.07(d,3H) ;LCMS:508.1(M+H)$^+$

实施例 13

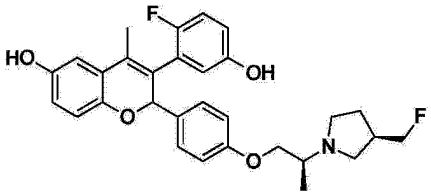
3-(3- 氟 -4- 羟基苯基）-2-(4-((S)-2-((R)-3-(氟甲基）吡咯烷 -1- 基）丙氧基）苯基）-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0415] 如一般程序 A、D、E、F 和 J(z = 1) 中所述，使用一般程序 A 中的 1,4- 二甲氧基苯和 2-(3- 氟 -4- 甲氧基苯基）乙酸与一般程序 F 中的中间体 14 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) δ 9.95(s,1H),8.93(s,1H),7.17(d,2H),7.10-7.07(m,1H),6.93-6.86(m,2H),6.78(d,2H),6.71(t,1H),6.46(m,2H),5.89(s,1H),4.32-4.30(m,1H),4.20-4.18(m,1H),3.96-3.92(m,1H),3.74-3.70(m,1H),2.66-2.60(m,2H),2.58-2.52(m,2H),2.38-2.35(m,2H),2.03(s,3H),1.80-1.78(m,1H),1.35-1.33(m,1H),1.06(d,3H) ;LCMS:508.1(M+H)$^+$.

实施例 14

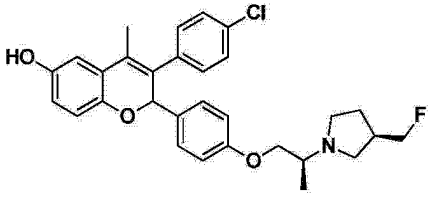
3-(2- 氟 -5- 羟基苯基）-2-(4-((S)-2-((R)-3-(氟甲基）吡咯烷 -1- 基）丙氧基）苯基）-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0416] 如一般程序 C、D、E、F 和 J(z = 1) 中所述，使用一般程序 C 中的 1-(2,5- 二甲氧基苯基) 乙酮和 2- 溴 -1- 氟 -4- 甲氧基苯与一般程序 F 中的中间体 14 合成标题化合物。^{1}H NMR(400MHz, DMSO-d_6) δ 9.41(s, 1H), 8.98(s, 1H), 7.19(d, 2H), 6.99(t, 1H), 6.79(d, 2H), 6.74(d, 1H), 6.68-6.64(m, 1H), 6.52-6.46(m, 3H), 5.76(s, 1H), 4.32-4.30(m, 1H), 4.20-4.19(m, 1H), 3.96-3.93(m, 1H), 3.93-3.71(m, 1H), 2.67-2.60(m, 2H), 2.58-2.52(m, 2H), 2.48-2.35(m, 2H), 1.91(s, 3H), 1.87-1.73(m, 1H), 1.38-1.33(m, 1H), 1.07(d, 3H) ; LCMS:508.1(M+H)$^+$

实施例 15

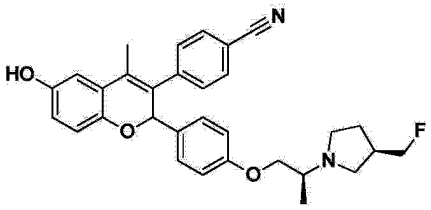
3-(4- 氯苯基)-2-(4-((S)-2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 丙氧基) 苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0417] 如一般程序 A、D、E、F 和 J(z = 0) 中所述，使用一般程序 A 中的 1,4- 二甲氧基苯和 2-(4- 氯苯基) 乙酸与一般程序 F 中的中间体 14 合成标题化合物。^{1}H NMR(400MHz, DMSO-d_6) δ 8.97(s, 1H), 7.40(m, 2H), 7.31(m, 2H), 7.18(d, 2H), 6.78(m, 2H), 6.75(m, 1H), 6.51-6.47(m, 2H), 5.92(s, 1H), 4.32-4.30(m, 1H), 4.21-4.18(m, 1H), 3.96-3.92(m, 1H), 3.74-3.69(m, 1H), 2.68-2.60(m, 2H), 2.59-2.52(m, 2H), 2.48-2.35(m, 2H), 2.02(s, 3H), 1.81-1.76(m, 1H), 1.36-1.31(m, 1H), 1.06(d, 3H) ;LCMS:508.1(M+H)$^+$.

实施例 16

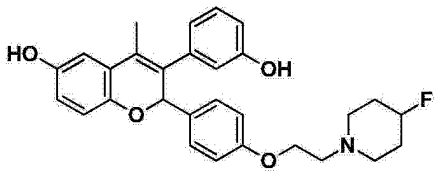
4-(2-(4-((S)-2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 丙氧基) 苯基)-6- 羟基 -4- 甲基 -2H- 苯并吡喃 -3- 基) 苄腈



[0418] 如一般程序 A、D、E、F 和 H(z = 0) 中所述，使用一般程序 A 中的 1,4- 二甲氧基苯和 2-(4- 氯苯基) 乙酸与一般程序 F 中的中间体 14 合成标题化合物。^{1}H NMR(400MHz, DMSO-d_6) δ 9.01(s, 1H), 7.81(d, 2H), 7.50(d, 2H), 7.19(d, 2H), 6.79(d, 3H), 6.52-6.49(m, 2H), 5.98(s, 1H), 4.31-4.30(m, 1H), 4.20-4.18(m, 1H), 3.96-3.93(m, 1H), 3.73-3.72(m, 1H), 2.66-2.60(m, 2H), 2.57-2.52(m, 2H), 2.41-2.35(m, 2H), 2.03(s, 3H), 1.85-1.75(m, 1H), 1.34-1.33(m, 1H), 1.06(d, 3H) ;LCMS:499.1(M+H)$^+$.

实施例 17

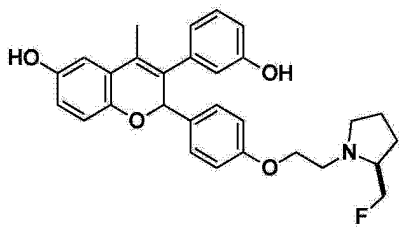
2-(4-(2-(4- 氟哌啶 -1- 基) 乙氧基) 苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0419] 如一般程序 G 和 J(z = 1) 中所述，使用 4- 氟哌啶盐酸盐和中间体 3 合成标题化合物。^{1}H NMR(DMSO-d_6)：δ 9.43(s,1H),8.94(s,1H),7.18(d,2H),7.13(t,1H),6.79(d,2H),6.73(m,1H),6.78(d,1H),6.65(dd,1H),6.62(m,1H),6.47(m,2H),5.83(s,1H),4.72-4.53(m,1H),3.97(t,2H),2.63(t,2H),2.60-2.53(m,2H),2.38-2.28(m,2H),2.03(s,3H),1.88-1.73(m,2H),1.71-1.58(m,2H) ;LCMS:476.2(M+H)$^+$.

实施例 18

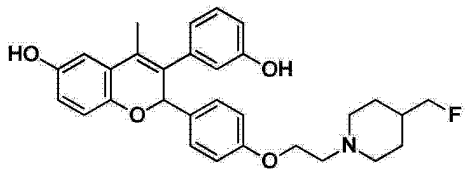
2-(4-(2-((S)-2-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0420] 如一般程序 G 和 J(z = 1) 中所述，使用中间体 3 和中间体 9 合成标题化合物。^{1}H NMR(DMSO-d_6 ;TFA 盐)：δ 9.88(s,1H),9.43(br,1H),9.00(br,1H),7.24(d,2H),7.13(t,1H),6.86(d,2H),6.74(m,1H),6.69(d,1H),6.65(dd,1H),6.62(m,1H),6.46(m,2H),5.88(s,1H),4.88-4.59(m,2H),4.24(m,2H),4.00-3.84(m,1H),3.73-3.44(m,3H),3.26(m,1H),2.20-2.08(m,1H),2.03(s,3H),2.05-1.95(m,1H),1.90-1.79(m,1H),1.78-1.67(m,1H) ;LCMS:476.1(M+H)$^+$.

实施例 19

2-(4-(2-(4-(氟甲基) 哌啶 -1- 基) 乙氧基) 苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0421] 如一般程序 G 和 J(z = 1) 中所述，使用中间体 3 和中间体 10 合成标题化合物。^{1}H NMR(DMSO-d_6)：δ 9.44(s,1H),8.94(s,1H),7.18(d,2H),7.13(t,1H),6.78(d,2H),6.74(m,1H),6.69(m,1H),6.65(m,1H),6.62(m,1H),6.48(m,2H),5.83(s,1H),4.26(dd,2H),3.95(t,2H),2.93-2.87(m,1H),2.61(t,2H),2.03(s,3H),2.00-1.92(m,2H),1.62-1.53(m,3H),1.22-1.13(m,3H) ;LCMS:490.1(M+H)$^+$.

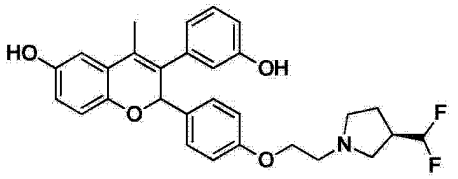
实施例 20

2-(4-(2-((R)-3-(氟甲基)哌啶-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇

[0422] 如一般程序G和J(z = 1)中所述,使用中间体3和中间体11合成标题化合物。^{1}H NMR(DMSO-d_6):δ9.43(s,1H),8.94(s,1H),7.21(d,2H),7.13(t,1H),6.79(d,2H),6.73(m,1H),6.68(m,1H),6.65(m,1H),6.61(m,1H),6.47(m,2H),5.83(s,1H),4.38-4.17(m,2H),3.97(t,2H),2.87-2.82(m,1H),2.78-2.72(m,1H),2.62(t,2H),2.03(s,3H),2.02-1.93(m,1H),1.90-1.80(m,2H),1.64-1.54(m,2H),1.48-1.37(m,1H),1.02-0.92(m,1H);LCMS:490.2$(M+H)^+$.

实施例21

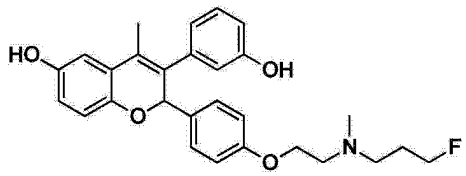
(R)-2-(4-(2-(3-(二氟甲基)吡咯烷-1-基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇



[0423] 如一般程序G和J(z = 1)中所述,使用中间体3和中间体12合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6)δ9.43(s,1H),8.94(s,1H),7.19(d,2H),7.12(t,1H),6.78(d,2H),6.73(s,1H),6.69-6.60(m,3H),6.47(m,2H),5.92(td,1H),5.83(s,1H),3.96(t,2H),2.73-2.64(m,3H),2.54-2.44(m,4H),2.02(s,3H),1.83(m,1H),1.61(m,1H);LCMS:494$(M+H)^+$.

实施例22

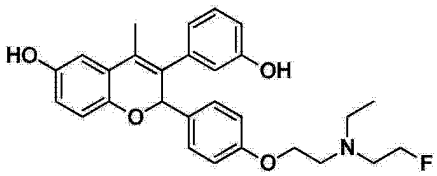
2-(4-(2-((3-氟丙基)(甲基)氨基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇



[0424] 如一般程序F、I和J(z = 1)中所述,使用一般程序F中的中间体3和2-(甲基氨基)乙醇和一般程序I中的1-氟-3-碘丙烷合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6):δ9.44(s,1H),8.95(s,1H),7.19(d,2H),7.13(t,1H),6.79(d,2H),6.75-6.72(m,1H),6.68(d,1H),6.67-6.62(m,1H),6.62-6.60(m,1H),6.48(s,2H),5.84(s,1H),4.50(t,1H),4.38(t,1H),3.95(t,2H),2.65(t,2H),2.44(t,2H),2.19(s,3H),2.03(s,3H),1.81-1.72(m,1H),1.72-1.69(m,1H).LCMS:464.2$(M+H)^+$.

实施例23

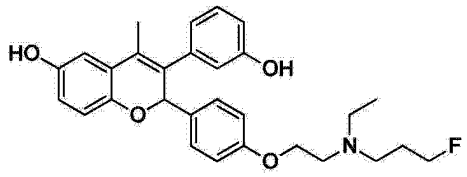
2-(4-(2-(乙基(2-氟乙基)氨基)乙氧基)苯基)-3-(3-羟基苯基)-4-甲基-2H-苯并吡喃-6-醇



[0425] 如一般程序 F、I 和 J(z = 1) 中所述，使用一般程序 F 中的中间体 3 和 2-(乙基氨基) 乙醇与一般程序 I 中的 1- 氟 -2- 碘乙烷合成标题化合物。^{1}H NMR(400MHz, DMSO-d_6): δ 9.46(s, 1H), 8.95(s, 1H), 7.19(d, 2H), 7.13(t, 1H), 6.78(d, 2H), 6.76-6.71(m, 1H), 6.78(d, 1H), 6.78-6.62(m, 1H), 6.62-6.60(m, 1H), 6.58(s, 2H), 5.83(s, 1H), 4.50(t, 1H), 4.38(t, 1H), 3.92(t, 2H), 2.83-2.77(m, 3H), 2.74(t, 1H), 2.58(q, 2H), 2.03(s, 3H), 0.94(t, 3H). LCMS:464.1(M+H)$^+$.

实施例 24

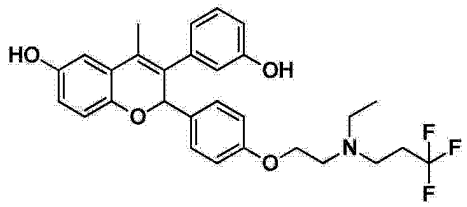
2-(4-(2-(乙基 (3- 氟丙基) 氨基) 乙氧基) 苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



[0426] 如一般程序 F、I 和 J(z = 1) 中所述，使用一般程序 F 中的中间体 3 和 2-(乙基氨基) 乙醇与一般程序 I 中的 1- 氟 -3- 碘丙烷合成标题化合物。^{1}H NMR(400MHz, DMSO-d_6): δ 9.43(s, 1H), 8.94(s, 1H), 7.19(d, 2H), 7.13(t, 1H), 6.78(d, 2H), 6.76-6.72(m, 1H), 6.68(d, 1H), 6.67-6.62(m, 1H), 6.62-6.60(m, 1H), 6.48(s, 2H), 5.84(s, 1H), 4.50(t, 1H), 4.39(t, 1H), 3.91(t, 2H), 2.72(t, 2H), 2.58-2.45(m, 4H), 2.03(s, 3H), 1.80-1.71(m, 1H), 1.71-1.65(m, 1H), 0.93(t, 3H). LCMS:478.1(M+H)$^+$.

实施例 25

2-(4-(2-(乙基 (3,3,3- 三氟丙基) 氨基) 乙氧基) 苯基)-3-(3- 羟基苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇

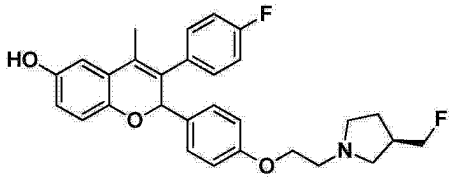


[0427] 如一般程序 F、I 和 J(z = 1) 中所述，使用一般程序 F 中的中间体 3 和 2-(乙基氨基) 乙醇与一般程序 I 中的 1,1,1- 三氟 -3- 碘丙烷合成标题化合物。^{1}H NMR(400MHz, DMSO-d_6): δ 9.43(s, 1H), 8.94(s, 1H), 7.20(d, 2H), 7.13(t, 1H), 6.78(d, 2H), 6.75-6.71(m, 1H), 6.68(d, 1H), 6.66-6.62(m, 1H), 6.62-6.60(m, 1H), 6.46(s, 2H), 5.84(s, 1H), 3.93(t, 2H), 2.76(t, 2H), 2.70(t, 2H), 2.57-2.49(m, 2H), 2.45-2.31(m, 2H), 2.03(s, 3H), 0.94(t, 3H). LCMS:514.1(M+H)$^+$.

实施例 26

2-(4-(2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苯基)-3-(4- 氟苯基)-4- 甲

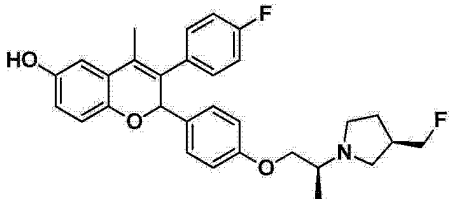
基 -2H- 苯并吡喃 -6- 醇



[0428] 如一般程序 A、D、E、F 和 J(z = 0) 中所述，使用一般程序 A 中的 1,4- 二甲氧基苯和 2-(4- 氟苯基) 乙酸与一般程序 F 中的中间体 13 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) : δ 8.96(s,1H),7.35-7.29(m,2H),7.22-7.13(m,4H),6.78(d,2H),6.75(s,1H),6.49(s,2H),5.91(s,1H),4.35-4.28(m,1H),4.25-4.16(m,1H),3.96(t,2H),2.70(t,2H),2.60(t,1H),2.57-2.38(m,3H),2.37-2.30(m,1H),2.01(s,3H),1.87-1.76(m,1H),1.41-1.30(m,1H). LCMS:478.1(M+H)$^+$.

实施例 27

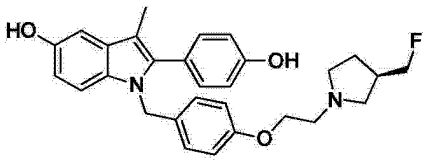
2-(4-((S)-2-((R)-3-(氟甲基) 吡咯烷 -1- 基) 丙氧基) 苯基)-3-(4- 氟苯基)-4- 甲基 -2H- 苯并吡喃 -6- 醇



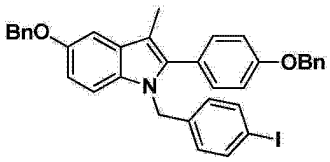
[0429] 如一般程序 A、D、E、F 和 J(z = 0) 中所述，使用一般程序 A 中的 1,4- 二甲氧基苯和 2-(4- 氟苯基) 乙酸和一般程序 F 中的中间体 14 合成标题化合物。^{1}H NMR(400MHz,DMSO-d_6) : δ 8.96(s,1H),7.35-7.29(m,2H),7.22-7.14(m,4H),6.79(d,2H),6.76-6.73(m,1H),6.52-6.46(m,2H),5.91(s,1H),4.36-4.28(m,1H),4.24(m,1H),3.99(m,1H),3.76-3.69(m,1H),2.70-2.51(m,4H),2.43-2.31(m,2H),2.02(s,3H),1.88-1.75(m,1H),1.40-1.30(m,1H),1.07(d,3H). LCMS:492.2(M+H)$^+$.

实施例 28

(R)-1-(4-(2-(3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苄基)-2-(4- 羟基苯基)-3- 甲基 -1H- 吲哚 -5- 醇

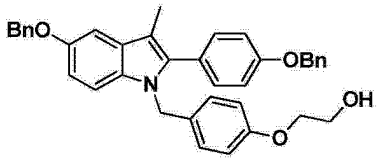


第 1 步 :5-(苄氧基)-2-(4-(苄氧基) 苯基)-1-(4- 碘苄基)-3- 甲基 -1H- 吲哚



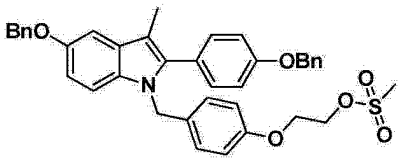
[0430] 在氮气气氛下，将 5-(苄氧基)-2-(4-(苄氧基) 苯基)-3- 甲基 -1H- 吲哚 (4.2g,10mmol ; 合成方法参见 PCT/US98/21609) 的 DMF(40mL) 溶液冷却至 0℃。一次性加入氢化钠 (在矿物油中的 60％分散体 ;420mg,10.5mmol)。将反应混合物在 0℃搅拌 5 分钟，

然后除去冰浴并使之升温至室温。1 小时后，将反应液冷却至 0℃并缓慢加入 4- 碘苄基溴 (3.7g，12.5mmol)。5 分钟后，除去冰浴并将反应混合物在室温下搅拌 6 小时。用水 (200mL) 和乙酸乙酯稀释该反应液。将沉淀物进行超声处理，滤出并干燥得到 1.99g 的期望的产物。用乙酸乙酯 (50ml) 萃取滤液，将有机层用水洗涤，用盐水洗涤并干燥 ($MgSO_4$)，过滤，浓缩并通过硅胶层析 (20％ -70％ DCM，在己烷中）纯化得到 2.62g。该反应总共得到 4.6g 呈白色固体的 5-(苄氧基)-2-(4-(苄氧基) 苯基)-1-(4- 碘苄基)-3- 甲基 -1H- 吲哚。^1H NMR(400MHz，DMSO-d_6)：δ 7.56(d，2H)，7.51-7.46(m，4H)，7.44-7.38(m，4H)，7.38-7.32(m，2H)，7.29(d，2H)，7.16(d，1H)，7.16-7.10(m，3H)，6.82(dd，1H)，6.62(d，2H)，5.20(s，2H)，5.14(d，4H)，2.17(s，3H)．第 2 步 :2-(4-((5-(苄氧基)-2-(4-(苄氧基) 苯基)-3- 甲基 -1H- 吲哚 -1- 基) 甲基) 苯氧基) 乙醇



[0431] 将 5-(苄氧基)-2-(4-(苄氧基) 苯基)-1-(4- 碘苄基)-3- 甲基 -1H- 吲哚 (1.01g，1.58mmol)、乙二醇 (0.44mL，7.89mmol)、碘化亚铜 (32mg，0.17mmol)、1，10- 菲咯啉 (60mg，0.33mmol) 和碳酸钾 (436mg，3.15mmol) 在丁腈 (3mL) 中的混合物通过 3 次真空 / 氮气循环进行脱气。将反应液在 125℃下加热 26 小时，并在反应完成后冷却至室温。然后用水稀释。用乙酸乙酯萃取水层 3 次。将合并的乙酸乙酯萃取物用水 (40mL) 和盐水 (40mL) 洗涤，干燥 ($MgSO_4$)，过滤，浓缩并通过硅胶层析 (0％ -40％乙酸乙酯，在己烷中）纯化得到 554mg 呈淡黄色泡沫的 2-(4-((5-(苄氧基)-2-(4-(苄氧基) 苯基)-3- 甲基 -1H- 吲哚 -1- 基) 甲基) 苯氧基) 乙醇。^1H NMR(400MHz，DMSO-d_6)：δ 7.48(d，4H)，7.45-7.37(m，4H)，7.37-7.32(m，2H)，7.30(d，2H)，7.21(d，1H)，7.15-7.10(m，3H)，6.81(dd，1H)，6.74(s，4H)，5.20-5.10(m，6H)，4.81(t，1H)，3.87(t，2H)，3.64(q，2H)，2.16(s，3H)．LCMS:570.0(M+H)$^+$.

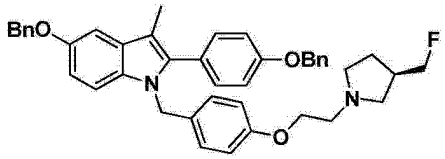
第 3 步 :2-(4-((5-(苄氧基)-2-(4-(苄氧基) 苯基)-3- 甲基 -1H- 吲哚 -1- 基) 甲基) 苯氧基) 乙基甲磺酸酯



[0432] 将 2-(4-((5-(苄氧基)-2-(4-(苄氧基) 苯基)-3- 甲基 -1H- 吲哚 -1- 基) 甲基) 苯氧基) 乙醇 (546mg，0.96mmol) 的 DCM(10mL) 溶液冷却至 0℃。加入三乙胺 (0.2mL，1.43mmol) 和甲磺酰氯 (0.1mL，1.29mmol)，并将反应液在 0℃搅拌 1 小时。将反应液用 DCM(30mL) 稀释，然后用 1M HCl(20mL) 洗涤，用水 (20mL) 洗涤，干燥 ($MgSO_4$)，过滤并在真空下浓缩得到 597mg 呈黄色泡沫的 2-(4-((5-(苄氧基)-2-(4-(苄氧基) 苯基)-3- 甲基 -1H- 吲哚 -1- 基) 甲基) 苯氧基) 乙基甲磺酸酯。^1H NMR(400MHz，DMSO-d_6)：δ 7.48(d，4H)，7.44-7.37(m，4H)，7.37-7.32(m，2H)，7.30(d，2H)，7.21(d，1H)，7.15-7.10(m，3H)，6.83-6.74(m，5H)，5.20-5.10(m，6H)，4.50-4.45(m，2H)，4.17-4.11(m，2H)，2.16(s，3H)．LCMS:648.1(M+H)$^+$.

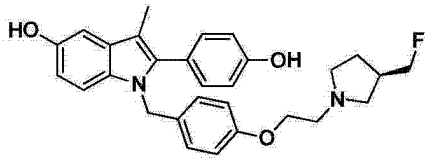
第 4 步 :(R)-5-(苄氧基)-2-(4-(苄氧基) 苯基)-1-(4-(2-(3-(氟甲基) 吡咯

烷 -1- 基) 乙氧基) 苄基)-3- 甲基 -1H- 吲哚



[0433] 将 2-(4-((5-(苄氧基)-2-(4-(苄氧基) 苯基)-3- 甲基 -1H- 吲哚 -1- 基) 甲基) 苯氧基) 乙基甲磺酸酯、(R)-3-(氟甲基) 吡咯烷 (中间体 8) 和碳酸钾在乙腈中的混合物经 3 次真空 / 氮气循环进行脱气。将反应液在 80℃下加热 10 小时,冷却至室温,然后用水 (40mL) 稀释。用乙酸乙酯萃取 (2x40mL) 水层,并将合并的乙酸乙酯萃取物用水 (40mL) 洗涤,用盐水 (40mL) 洗涤,干燥 ($MgSO_4$),过滤,浓缩并通过硅胶层析 (0% -5% MeOH,在 DCM 中) 纯化得到 274mg 的 (R)-5-(苄氧基)-2-(4-(苄氧基) 苯基)-1-(4-(2-(3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苄基)-3- 甲基 -1H- 吲哚。^1H NMR(400MHz,DMSO-d_6): δ 7.48(d,4H),7.44-7.37(m,4H),7.37-7.32(m,2H),7.30(d,2H),7.21(d,1H),7.15-7.10(m,3H),6.81(dd,1H),6.74(s,4H),5.17-5.10(m,6H),4.33-4.30(m,1H),4.22-4.18(m,1H),3.94(t,2H),2.70(t,2H),2.56-2.40(m,3H),2.60(t,1H),2.36-2.31(m,1H),2.16(s,3H),1.86-1.76(m,1H),1.40-1.30(m,1H). LCMS:655.3(M+H)$^+$.

第 5 步 :(R)-1-(4-(2-(3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苄基)-2-(4- 羟基苯基)-3- 甲基 -1H- 吲哚 -5- 醇



[0434] 将 (R)-5-(苄氧基)-2-(4-(苄氧基) 苯基)-1-(4-(2-(3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苄基)-3- 甲基 -1H- 吲哚 (263mg,0.40mmol) 在乙酸乙酯 / 乙醇 (4:1,6mL) 中的溶液通过 3 次真空 / 氮气循环进行脱气。向该溶液中加入 10% 碳载钯 (120mg,0.11mmol),然后将氢气球的阀针放置在反应烧瓶中。将混合物在室温下搅拌 15 小时,然后用乙酸乙酯稀释,经 Celite 过滤并浓缩。在高真空下进一步干燥该残余物,得到 171mg 呈米色固体的 (R)-1-(4-(2-(3-(氟甲基) 吡咯烷 -1- 基) 乙氧基) 苄基)-2-(4- 羟基苯基)-3- 甲基 -1H- 吲哚 -5- 醇。^1H NMR(400MHz,DMSO-d_6): δ 9.67(s,1H),8.69(s,1H),7.16(d,2H),7.06(d,1H),6.85(d,2H),6.80(d,1H),6.75(s,4H),6.57(dd,1H),5.10(s,2H),4.35-4.30(m,1H),4.23-4.18(m,1H),3.94(t,2H),2.70(t,2H),2.62(t,1H),2.56-2.40(m,3H),2.38-2.31(m,1H),2.10(s,3H),1.87-1.76(m,1H),1.40-1.31(m,1H). LCMS:475.2(M+H)$^+$.

实施例 29 :3x ERE MCF-7 报道分子试验

[0435] MCF7 细胞保持在补充有 10% FCS 的 RPMI 1640 中。转录试验如下进行 :将 100μL 细胞以 250,000 个细胞 /mL 的密度接种到 96 孔细胞培养板中,于补充有 10% 经炭吸附的血清的 RPMI 1640 中,并使其附着过夜。使用 Lipofectin(Life Technologies),按照制造商的方案瞬时转染细胞。使用 300ng 3X ERE-TK-Luc(报道载体)、50ng CMVpRL(标准化载体) 和 130ng pCMX(填充 DNA) 一式三份进行转染。将转染的细胞培养过夜,然后用配体处理。对于 ER 激动剂试验,连续稀释化合物,并向细胞添加 50μL 化合物 + 补充有经炭吸附的血清的 RPMI 1640。对于 ER 拮抗剂试验,连续稀释化合物,并向细胞添加 50μL 化合物以及补

充有经炭吸附的血清的 RPMI+17β-雌二醇。拮抗剂试验中使用的 17β-雌二醇终浓度为 0.1nM。培养 24 小时后，移除培养基，在 40μL 裂解缓冲液 (25mM Tris 磷酸盐，2mM CDTA，10％甘油，0.5％ Triton X-100，2mMDTT) 中裂解细胞。添加 40μL 萤光素酶缓冲液 (20mM 三 (羟甲基) 甲基甘氨酸，0.1mM EDTA，1.07mM$(MgCO_3)_4Mg(OH)_2 \cdot 5H_2O$，2.67mM$MgSO_4$，33.3mM DTT，270μM 辅酶 A，470μM 萤光素，530μM ATP) 后，立即测定萤火虫萤光素酶活性。添加 40μL 腔肠素 (colelenterazine) 缓冲液 (1.1M NaCl，2.2mM Na_2EDTA，0.22M $KxPO_4$(pH 5.1)，0.44mg/mL BSA，1.3mM NaN_3，1.43μM 腔肠素，终 pH 调节至 5.0) 后，测定海肾萤光素酶。

实施例 30：乳腺癌细胞活力试验

[0436] 将 MCF-7 细胞在含有 10％ FBS 和 20mM HEPES 的 RPMI 中调节至 20,000 个细胞 /mL 的浓度。向 384 孔板的各孔中添加 16 微升细胞悬浮液 (320 个细胞)，并培养细胞过夜，以使细胞附着。次日，将各化合物的十一点连续半对数稀释液以 0.3-0.000003μM 的终浓度以 16μL 加至细胞中。5 天的化合物暴露后，向细胞添加 16μL CellTiter-GLo(Promega，Madison WI)，并确定各孔的相对发光单位 (RLU)。利用加至 32μL 不含细胞的培养基的 CellTiter-Glo 获得背景值。如下确定每种样品的活力百分比：(样品 RLU- 背景 RLU/ 未处理细胞的 RLU- 背景 RLU)x 100 ＝％活力。

[0437] 在包括 BT474、CAMA1、MDA-MB-361、ZR-75-1、T47D 在内的其它 ER+ 乳腺癌细胞系中的活力效应可以在类似于实施例 30 的试验中进行概况分析。

[0438] 本文公开的代表性化合物的说明性生物学数据在下表中给出：

表 3

实施例	MCF7 活力试验 IC_{50}	MCF7 活力试验 最大响应
1	A	++
2	A	++
2a	B	++
2b	A	++
3	A	++
3a	B	++
3b	A	++
4	B	++
5	A	++
6	A	++
7	A	++
8	B	++
9	A	++
10	A	++
11	A	++
12	A	++
13	A	++
14	A	++
15	B	++

实施例	MCF7 活力试验 IC_{50}	MCF7 活力试验 最大响应
16	B	++
17	A	++
18	B	++
19	A	++
20	A	+
21	A	++
22	A	+
23	B	++
24	A	++
25	B	+
26	B	++
27	B	++
28	A	++

A ＝单 $IC_{50} \leqslant 1nM$;B ＝单 $IC_{50} > 1nM$;

+ ＝单%值 <50% ;++ ＝单%值≥ 50%

实施例 31: 乳腺癌细胞 ER-α 细胞内 Western 试验 (SP1)

[0439] 将MCF-7细胞在含有10%经炭吸附的FBS和20mM HEPES的RPMI中调节至200,000个细胞/mL的浓度。向聚-D-赖氨酸384孔板的各孔中添加16微升细胞悬浮液(3200个细胞),并培养细胞过夜,以使细胞附着。次日,将各化合物的十一点连续半对数稀释液以0.3-0.000003μM的终浓度以16μL加至细胞中。在添加化合物后4或24小时,将细胞固定(含10%福尔马林的PBS)20分钟。在PBS 0.1% Triton中透化细胞,并用LICOR封闭缓冲液(50μl/孔,90')封闭。然后各孔在4℃下与在LICOR封闭缓冲液/0.1%吐温-20中1:1000稀释的SP1兔单克隆抗体(Thermo Scientific)孵育过夜。用含吐温而不含抗体的封闭缓冲液处理的孔用作背景对照。用0.1%吐温-20/PBS洗涤各孔,然后在用含有0.1%吐温-20和0.01% SDS的LICOR封闭缓冲液中稀释的山羊抗兔IRDye™800CW(LICOR Inc.;1:1000)和DRAQ5 DNA染料(1:2000,对于2mM储备液)中孵育60分钟。在0.1%吐温-20/PBS中洗涤(50μl/孔,各5')细胞。在LICOR Odyssey红外成像系统上对板进行扫描。测量在800nm波道和700nm波道的累积强度,从而分别确定ER和DNA的水平。如下确定ER百分比水平:

(800nm样品累积强度/700nm样品累积强度)/(800nm未处理细胞的累积强度/700nm未处理细胞的累积强度)x 100 ＝% ER水平。

[0440] 对包括 BT474、CAMA1、MDA-MB-361、ZR-75-1、T47D 在内的其它 ER+ 乳腺癌细胞系中的 ER-α 稳态水平的影响可以在类似于实施例 31 的试验中进行概况分析。

[0441] 本文公开的代表性化合物的说明性生物学数据在下表中给出：

表 4

实施例	ER 细胞内 Western 试验 (SP1); IC_{50}	ER 细胞内 Western 试验 (SP1); 最大响应
1	A	+++
2	A	+++
2a	B	+++
2b	A	+++
3	A	+++
3a	B	+++
3b	A	+++
4	B	+++
5	A	+++
6	A	+++
7	A	+++
8	A	+++
9	A	+++
10	A	+++

实施例	ER 细胞内 Western 试验 (SP1); IC_{50}	ER 细胞内 Western 试验 (SP1); 最大响应
11	A	+++
12	A	+++
13	A	+++
14	A	+++
15	B	+++
16	B	+++
17	A	++
18	A	++
19	A	++
20	A	+
21	A	+++
22	A	+
23	A	+
24	A	+
25	A	+
26	A	+++
27	A	+++
28	A	+++

A ＝单 IC_{50} ≤ 1nM ;B ＝单 IC_{50}>1nM

+ ＝单%值 <60% ;++ ＝单%值， %≥ 60%至 <85% ;+++ ＝单%值≥ 85%。

实施例 32 :Ishikawa 子宫细胞碱性磷酸酶试验

[0442] 在 T225 中亚汇合的 Ishikawa 细胞在不含雌激素的基础培养基 (EFBM) 中培养 24 小时，该EFBM由含有5%经炭葡聚糖处理的FBS和20mM HEPES的DMEM:Ham's F-1250:50无酚红基础培养基组成。次日，将细胞以 2.5x 10^5 个细胞 /mL、16μL/ 孔 (4000 个细胞 / 孔) 的浓度接种到透明 384 孔板的 EFBM 中。在 DMSO 中进行各化合物的 12 点半对数稀释，随后在 EFBM 中稀释。细胞接种后立即加入等体积的在 EFBM 中的化合物，并培养细胞 3 天。用5%福尔马林固定细胞，并用PBS漂洗。将碱性磷酸酶底物4-硝基苯基磷酸二钠盐六水合物加至含有2mMMgCl_2、1M二乙醇胺的溶液中，并调节至pH 9.0。将底物溶液加至细胞培养物中 (16μL/孔)，当用1-30nM浓度范围的17β-雌二醇处理的细胞在405nm波长处的光密度达

到 1.0-1.2 个吸光度单位时，在多孔板分光光度计中测量 OD405。仅用 DMSO 处理的细胞作为背景对照。如下测量减除背景的样品中的活性百分比：%活性＝样品的 OD405/17β-雌二醇处理的细胞的 OD405 最大值 x100。

实施例 33: 卵巢癌细胞活力试验

[0443] 将 BG-1 细胞在含有 10％ FBS 和 20mM HEPES 的 RPMI 中调节至 20,000 个细胞 /mL 的浓度。向 384 孔板的各孔中添加 16 微升细胞悬浮液 (320 个细胞)，将培养细胞过夜，以使细胞附着。次日，将各化合物的十一点连续半对数稀释液以 0.3-0.000003μM的终浓度以 16μL加至细胞中。在5天的化合物暴露后，向细胞添加16μL CellTiter-GLo(Promega,Madison WI)，并确定各孔的相对发光单位 (RLU)。利用加至 32μL 不含细胞的培养基的 CellTiter-Glo 获得背景值。如下确定各样品的活力百分比：(样品 RLU- 背景 RLU/ 未处理细胞的 RLU- 背景 RLU)x 100 ＝％活力。

[0444] 在包括 A1847、SKOV3、SW626、A2780 在内的其它 ER+ 乳腺癌细胞系中的活力效应可以在类似于实施例 33 的试验中进行概况分析。

实施例 34：卵巢癌细胞 ER-α 细胞内 Western 试验

[0445] 将 BG-1 细胞在含有 10％经炭吸附的 FBS 和 20mM HEPES 的 RPMI 中调节至 200,000 个细胞 /mL 的浓度。向聚 -D- 赖氨酸 384 孔板的各孔中添加 16 微升细胞悬浮液 (3200 个细胞)，并将细胞培养过夜，以使细胞附着。次日，将各化合物的十一点连续半对数稀释液以 0.3-0.000003μM 的终浓度以 16μL 加至细胞中。在添加化合物后 4 或 24 小时，将细胞固定 (含 10％福尔马林的 PBS)20 分钟。在 PBS 0.1％ Triton 中透化细胞，并用 LICOR 封闭缓冲液 (50μl/ 孔，90') 封闭。然后各孔在 4℃下与在 LICOR 封闭缓冲液 /0.1％吐温 -20 中 1:100 稀释的 ER1D5(Santa Cruz Biotechnology) 孵育过夜。用含吐温而不含抗体的封闭缓冲液处理的孔用作背景对照。用 0.1％吐温 -20/PBS 洗涤各孔，然后在用含有 0.1％吐温 -20 和 0.01％ SDS 的 LICOR 封闭缓冲液中稀释的山羊抗小鼠 IRDye™800CW(LICOR Inc. ; 1:1000) 和 DRAQ5 DNA 染料 (1:2000，对于 2mM 储备液) 中孵育 60 分钟。在 0.1％吐温 -20/PBS 中洗涤 (50μl/ 孔，各 5') 细胞。在 LICOR Odyssey 红外成像系统上对板进行扫描。测量在 800nm 波道和 700nm 波道的累积强度，以分别确定 ER 和 DNA 的水平。如下确定 ER 百分比水平：

(800nm 样品累积强度 /700nm 样品累积强度)/(800nm 未处理细胞的累积强度 /700nm 未处理细胞的累积强度)x 100 ＝％ ER 水平。

[0446] 对包括 A1847、SKOV3、SW626、A2780 在内的其它 ER+ 卵巢癌细胞系中 ER-α 稳态水平的影响可以在类似于实施例 34 的试验中进行概况分析。

[0447] 计划用于测试本文所述的化合物的其它癌细胞系包括：ER- 阳性子宫内膜细胞系 (Ishikawa、ECC1、HEC-1、EnCa-101) 和 ER- 阳性宫颈细胞系 (Caski、HeLa、SiHa)。

实施例 35:PEO 细胞活力试验

[0448] 将 PEO-1、PEO-4 和 PEO-6 卵巢癌细胞系在含有 10％ FBS 的 RPMI 中调节至 20,000 个细胞 /mL 的浓度。向 384 孔板的各孔中添加 16 微升细胞悬浮液 (320 个细胞)，将细胞培养过夜，以使细胞附着。次日，将各化合物的 10 点连续 1:5 稀释液以 1-0.0000005μM的终浓度以 16μL加至细胞中。在7天的化合物暴露后，向细胞添加16μL CellTiter-GLo(Promega,Madison WI)，并确定各孔的相对发光单位 (RLU)。利用加至 32μL

不含细胞的培养基的 CellTiter-Glo 获得背景值。如下确定各样品的活力百分比 :(样品 RLU- 背景 RLU/ 未处理细胞的 RLU- 背景 RLU)x100 = % 活力。

实施例 36 :PEO ER Western 分析

[0449] 将细胞接种至 RPMI 5% CSS 中 48 小时,随后用化合物处理 4 或 24 小时。在改良的放射免疫沉淀缓冲液 (mRIPA ;10mM Tris,150mMNaCl,1% (v/v)NP-40,0.5% 脱氧胆酸盐,0.1% SDS,5mM EDTA, pH7.4) 中裂解细胞,该缓冲液含有停止蛋白酶和磷酸酶单次使用抑制剂混合物 (Halt Protease&Phosphatase Single-Use Inhibitor Cocktail)(Thermo Scientific,目录号 78442)。使用 Lowry 试验 (Biorad DC 蛋白质试验) 定量澄清的裂解液的蛋白质总量。将 NuPAGE® LDS 样品缓冲液和样品还原剂加入至该裂解液中并加热至 70℃ 10 分钟。在处于 MOPS SDS 电泳缓冲液中的 NuPAGE 4-12% Bis Tris 凝胶中电泳分离 15ug 的总细胞蛋白质,然后使用 XCell II 印迹模块将其转移至在转移缓冲液内的硝酸纤维素膜。室温下,将膜在封闭缓冲液 (LI-COR, Lincoln, NE) 中孵育 30 分钟,随后与抗 ERα (SP-1, Thermo Fisher Scientific,目录号 RM-9101)、ERβ (Cell Signaling Technology,目录号 5513) 的兔抗体或抗 α 微管蛋白的鼠抗体 (Sigma,目录号 T6199) 孵育 60 分钟。与 IRDye® 偶联的山羊抗小鼠或抗兔 IgG(LI-COR) 孵育后,用 Odyssey® 红外成像系统对蛋白质带进行定量。用 Graphpad PRISM® 软件对数据进行图形绘制以确定 ER 水平。如下计算 % ER 水平 :

% ER = (样品的荧光 ER 带 - 背景 / 样品的荧光微管蛋白带 - 背景)/(未处理细胞的荧光 ER 带 - 背景 / 未处理细胞的荧光微管蛋白 - 背景)

实施例 37 :乳腺癌模型 :异种移植试验 (MCF-7)

[0450] 将含有 0.72mg 17-β 雌二醇的延时释放微丸皮下植入到 nu/nu 小鼠中。MCF-7 细胞在含有 10% FBS 的 RPMI 中于 5% CO_2、37℃下生长。离心细胞,并以 $1X10^7$ 个细胞 /mL 重悬浮于 50% RPMI(不含血清) 和 50% Matrigel 中。在微丸植入后 2-3 天,将 MCF-7 细胞皮下注射 (100μL/ 动物) 到右胁。每两周监测一次肿瘤体积 (长度 x 宽度 ^{2}/2)。当肿瘤达到约 $200mm^3$ 的平均体积时,将动物随机分组并开始治疗。每天用载体或化合物治疗动物,持续 4 周。在整个研究中每两周监测一次肿瘤体积和体重。在治疗期结束时,采集血浆和肿瘤样品分别进行药代动力学和药效学分析。

实施例 38 :乳腺癌模型 :异种移植试验 (MCF-7 衍生物)

[0451] 通过经口管饲用他莫昔芬 (柠檬酸盐) 治疗荷有 MCF-7 肿瘤 (平均肿瘤体积为 $200mm^3$) 的雌性 nu/nu 小鼠 (带有补充的 17-β 雌二醇微丸 ;0.72mg ;60 天缓释)。每周监测两次肿瘤体积 (长度 x 宽度 ^{2}/2) 和体重。在肿瘤体积保持不变的显著的抗肿瘤反应后,在治疗的大约第 100 天第一次观察到明显的肿瘤生长。在治疗的第 120 天,提高他莫昔芬剂量。快速生长的肿瘤被认为是他莫昔芬抗性的,并且选择它用于体内传代至新的宿主动物。将来自他莫昔芬抗性肿瘤的肿瘤片段 (约 $100mm^3$/ 动物) 皮下植入到雌性 nu/nu 小鼠 (具有 17-β 雌二醇微丸 (0.72mg ;60 天缓释)) 的右胁。传代的肿瘤在恒定他莫昔芬选择下保持,并每周监测一次肿瘤体积 (长度 x 宽度 ^{2}/2)。当肿瘤体积达到约 150-250mm^3 时,将动物随机分入治疗组 (平均肿瘤体积为 $200mm^3$),并终止他莫昔芬治疗 (除了他莫昔芬对照组以外)。每天用载体或化合物治疗动物,持续 4 周。在整个研究中每周监测两次肿瘤体

积和体重。在治疗期结束时，采集血浆和肿瘤样品分别进行药代动力学和药效学分析。

实施例 39 ：卵巢癌模型 ：异种移植试验 (BG-1)

[0452] 将延时释放微丸 (0.72mg 17-β 雌二醇 /60 天）皮下植入雌性 nu/nu 小鼠中。BG-1 细胞在含有 10％ FBS、10mM 丙酮酸钠、10mM 非必需氨基酸的 DMEM Ham’s F-1250/50 中于 5％ CO_2、37℃生长。离心细胞，并以 $5X10^7$ 个细胞 /mL 重悬浮于 50％ DMEM Ham’s F-12（不含血清）和 50％ Matrigel 中。在微丸植入后 2-3 天，将 BG-1 细胞皮下注射 (100μL/ 动物）到右胁。每两周监测一次肿瘤体积 (长度 x 宽度 ^{2}/2)。当肿瘤达到约 250mm^3 的平均体积时，将动物随机分组并开始治疗。每天用载体或化合物治疗动物，持续 4 周。在整个研究中每两周监测一次肿瘤体积和体重。在治疗期结束时，采集血浆和肿瘤样品分别进行药代动力学和药效学分析。

实施例 40 ：子宫内膜癌模型 ：异种移植试验 (ECC-1)

[0453] 使 ECC-1 细胞在 10％ CO_2、37℃下在含有 10％ FBS、1％非必需氨基酸和 100 单位的青霉素 / 链霉素的 DMEM（酚红、4.5g/L 葡萄糖和 L- 谷氨酰胺）中生长。离心细胞，并以 $5X10^7$ 个细胞 /mL 重悬浮于 50％ DMEM（无血清）和 50％ Matrigel(BD，高浓度）中。将延时释放微丸 (0.72mg 17-β 雌二醇 /60 天）经皮下植入至雌性 nu/nu 小鼠中。在微丸植入后 2-3 天，将 ECC-1 细胞经皮下注射 (100μL/ 动物）到右胁。监测肿瘤体积，并当肿瘤达到适合移植的大小时，将它们切除。将切除的肿瘤切成小片 (约 100mm^3) 并连续地植入 (10G 套管针，右胁）至含有雌二醇微丸 (0.72mg17-β 雌二醇 /60 天）的雌性 nu/nu 2-3 天。监测肿瘤体积 (长 x 宽 x 宽 /2)，并当观察到明显的肿瘤时，将动物随机分组并开始治疗。每天用载体或化合物治疗动物，持续 4 周或直到肿瘤体积达到 2000mm^3（以先到者为准）。在整个研究中每两周监测一次肿瘤体积和体重。在治疗期结束时，采集血浆和肿瘤样品分别进行药代动力学和药效学分析。

实施例 41 ：未成熟的子宫湿重 - 拮抗剂模式

[0454] 治疗雌性未成熟 CD-IGS 大鼠 (到达时年龄为 21 天）三天。动物每天给药，持续三天。通过管饲经口施用载体或测试化合物，15 分钟后口服 0.1mg/kg 乙炔雌二醇。第四天，给药后 24 小时，采集血浆进行药代动力学分析。血浆采集后立即处死动物，取出子宫并称重。

实施例 42 ：未成熟的子宫湿重 - 激动剂模式

[0455] 治疗雌性未成熟 CD-IGS 大鼠 (到达时年龄为 21 天）三天。动物每天给药，持续三天。通过管饲经口施用载体或测试化合物，15 分钟后给予第二口服剂量的载体。第四天，给药后 24 小时，采集血浆进行药代动力学分析。血浆采集后立即处死动物，取出子宫并称重。

实施例 43 ：成年子宫湿重 -10 天

[0456] 购买雌性 CD-IGS 大鼠 (年龄为 69 天，Charles River Laboratories) 并分组。在年龄为 60 天时，在供应商 (Charles River Laboratories) 处切除第 1 组的卵巢，并在手术后 2 周开始进行研究，而第 2-8 组保持完整。口服载体或测试化合物 10 天。在第 10 个和最终剂量后 2 小时，进行心脏穿刺，收集血清进行药代动力学和药效学分析。血清收集后立即对动物施行安乐死，取出子宫和卵巢并称重。将每组两只动物的子宫和卵巢在 10％中性缓冲的福尔马林中固定，并送出进行石蜡包埋、切片和 H&E 染色 (SDPath)。将染色的组织在

实验室内进行分析，然后发送给委员会认证的病理学家进行读取。将每组 4 只动物的子宫和卵巢快速冷冻于液氮中用于转录分析，研究由雌激素受体调节的选定的一组基因。

实施例 44：乳腺癌临床试验

[0457] 目的：本研究的目的是评估式 (I) 化合物或其药学上可接受的盐作为雌激素受体 (ER) 阳性转移性乳腺癌的一线或二线治疗的疗效，收集关于该化合物可能引起的任何副作用的信息，并评价该化合物的药代动力学性质。

[0458] 干预：向患者施用 1-50mg/kg 的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，每天一次或一天两次。

[0459] 结果测量指标：主要结果测量指标：肿瘤反应和 / 或疾病控制。

[0460] 次要结果测量指标：(a) 副作用；(b) 药代动力学性质；(c) 在定义的时间点具有完全或部分反应或病情稳定的患者的比例；(d) 进展时间和总生存期；和 (e) 预示临床反应的生物标记物。

[0461] 详细描述：给予患者式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，一天一次或一天两次口服。在每个给药周期之前，进行身体检查、血液检查和任何副作用的评估。每 12 周用 CT 扫描或 MRI 重新评估患者的癌症以确定该治疗是否起作用。将会持续参与这项研究直到出现病情恶化或不可接受的毒性。

[0462] 资格：18 岁及年龄更大的女性受试者。

[0463] 入选标准：组织学或细胞学上确诊的浸润性乳腺癌，IV 期疾病；先前未采用局部疗法治疗的由 RECIST 定义的至少一个可测量的靶病变；绝经后状态；ER 阳性乳腺癌；HER2- 阴性乳腺癌；针对晚期或转移性疾病的多达一个先前的激素疗法；ECOG 体力状态 0-1；预期寿命 >12 周；充分的肝脏和骨髓功能：AST<2.5xULN；胆红素 <1.5xULN；ANC>1,500/ul；血小板计数 >100,000/ul；正常的 PT 和 PTT；自先前的辐射起至少 2 周并从治疗相关毒性中恢复。

[0464] 排除标准：HER2- 阳性乳腺癌；先前的针对转移性疾病的化疗方案；脑转移的病史或出现；并行的试验药物治疗；先前的骨髓或干细胞移植；在过去 5 年内有其它恶性肿瘤病史，不包括宫颈或非黑色素瘤皮肤癌的治愈性治疗的原位癌；不受控制的感染；活动性出血，或需要输血的出血史；活动性心脏疾病；严重的医学或精神疾病。

实施例 45：子宫内膜癌临床试验

[0465] 目的：本研究的目的是评估式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐在晚期或转移性子宫内膜癌治疗中的疗效，收集关于该化合物可能引起的任何副作用的信息，并评价该化合物的药代动力学性质。

[0466] 干预：向患者施用 1-50mg/kg 的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，每天一次或一天两次。

[0467] 结果测量指标：主要结果测量指标：肿瘤反应和 / 或疾病控制。次要结果测量指标：(a) 副作用；(b) 药代动力学性质；(c) 在定义的时间点具有完全或部分反应或病情稳定的患者的比例；(d) 进展时间和总生存期；和 (e) 预示临床反应的生物标记物。

[0468] 详细描述：给予患者式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，一天一次或一天两次口服。在每个给药周期之前，进行身体检查、血液检查和任何副作用的评估。每 12 周用 CT 扫描或 MRI 重新评估患者的癌症以确定该治疗是否起作

用。将会持续参与这项研究直到出现病情恶化或不可接受的毒性。

[0469] 资格：18 岁及年龄更大的女性受试者。

[0470] 入选标准：组织学或细胞学上确诊的晚期或转移性子宫内膜癌；先前未采用局部疗法治疗的由 RECIST 定义的至少一个可测量的靶病变；激素受体阳性子宫内膜癌；ECOG 体力状态 0-1；预期寿命 >12 周；充分的肝脏和骨髓功能：AST<2.5xULN；胆红素 <1.5xULN；ANC>1,500/ul；血小板计数 >100,000/ul；正常的 PT 和 PTT；自先前的辐射起至少 2 周并从先前的手术或治疗相关的毒性中恢复。

[0471] 排除标准：脑转移的病史或出现；并行的试验药物治疗；先前的骨髓或干细胞移植；在过去 5 年内有其它恶性肿瘤病史，不包括宫颈或非黑色素瘤皮肤癌的治愈性治疗的原位癌；不受控制的感染；活动性出血，或需要输血的出血史；活动性心脏疾病；严重的医学或精神疾病。

实施例 46：卵巢癌临床试验

[0472] 目的：本研究的目的是评估式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐在晚期卵巢癌治疗中的疗效，收集关于该化合物可能引起的任何副作用的信息，并评价该化合物的药代动力学性质。

[0473] 干预：向患者施用 1-50mg/kg 的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，每天一次或一天两次。

[0474] 结果测量指标：主要结果测量指标：肿瘤反应和 / 或疾病控制。

[0475] 次要结果测量指标：(a) 副作用；(b) 药代动力学性质；(c) 在定义的时间点具有完全或部分反应或病情稳定的患者的比例；(d) 进展时间和总生存期；和 (e) 预示临床反应的生物标记物。

[0476] 详细描述：给予患者式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，一天一次或一天两次口服。在每个给药周期之前，进行身体检查、血液检查 (包括肿瘤标志物，例如，CA-125) 和任何副作用的评估。每 12 周用 CT 扫描或 MRI 重新评估患者的癌症以确定该治疗是否起作用。将会持续参与这项研究直到出现病情恶化或不可接受的毒性。

[0477] 资格：18 岁及年龄更大的女性受试者。

[0478] 入选标准：组织学或细胞学上确诊的晚期卵巢癌；先前未采用局部疗法治疗的由 RECIST 定义的至少一个可测量的靶病变；ER 阳性卵巢癌；ECOG 体力状态 0-1；预期寿命 >12 周；充分的肝脏和骨髓功能：AST<2.5xULN；胆红素 <1.5xULN；ANC>1,500/ul；血小板计数 >100,000/ul；正常的 PT 和 PTT；自先前的辐射起至少 2 周和从先前的手术或治疗相关的毒性中恢复。

[0479] 排除标准：脑转移的病史或出现；并行的试验药物治疗；先前的骨髓或干细胞移植；在过去 5 年内有其它恶性肿瘤病史，不包括宫颈或非黑色素瘤皮肤癌的治愈性治疗的原位癌；不受控制的感染；活动性出血，或需要输血的出血史；活动性心脏疾病；严重的医学或精神疾病。

实施例 47：ER- 阳性 NSCLC 临床试验

[0480] 目的：本研究的目的是评估式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐作为单一药剂或组合用于治疗晚期或转移性雌激素受体 (ER) 阳性非小

细胞肺癌 (NSCLC) 的疗效，收集关于该化合物作为单一药剂或组合可能引起的任何副作用的信息，并评价该化合物作为单一药剂或组合的药代动力学性质。

[0481] 干预：向患者施用 1-50mg/kg 的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，作为单一药剂或组合每天一次或一天两次施用。

[0482] 结果测量指标：主要结果测量指标：肿瘤反应和 / 或疾病控制。次要结果测量指标：(a) 副作用；(b) 药代动力学性质；(c) 在定义的时间点具有完全或部分反应或病情稳定的患者的比例；(d) 进展时间和总生存期；和 (e) 预示临床反应的生物标记物。

[0483] 详细描述：给予患者式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，作为单一药剂或组合一天一次或两次口服。在每个给药周期之前，进行身体检查、血液检查和任何副作用的评估。每 12 周用 CT 扫描或 MRI 重新评估患者的癌症以确定该治疗是否起作用。将会持续参与这项研究直到出现病情恶化或不可接受的毒性。

[0484] 资格：18 岁及年龄更大的男性和女性受试者。

[0485] 入选标准：组织学或细胞学上确诊的晚期或转移性 ER- 阳性 NSCLC；先前未采用局部疗法治疗的由 RECIST 定义的至少一个可测量的靶病变；ECOG 体力状态 0-1；预期寿命 >12 周；充分的肝脏和骨髓功能：AST<2.5xULN；胆红素 <1.5xULN；ANC>1,500/ul；血小板计数 >100,000/ul；正常的 PT 和 PTT；自先前的辐射起至少 2 周并从先前的手术或治疗相关的毒性中恢复。

[0486] 排除标准：脑转移的病史或出现；并行的试验药物治疗；先前的骨髓或干细胞移植；在过去 5 年内有其它恶性肿瘤病史，不包括宫颈或非黑色素瘤皮肤癌的治愈性治疗的原位癌；不受控制的感染；活动性出血，或需要输血的出血史；活动性心脏疾病；严重的医学或精神疾病。

实施例 48：子宫内膜异位症临床试验

[0487] 目的：本研究的目的是评估式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐作为单一药剂或组合用于治疗患有症状性 / 重度子宫内膜异位症的患者的疗效，收集关于该化合物作为单一药剂或组合可能引起的任何副作用的信息，并评价该化合物作为单一药剂或组合的药代动力学性质。

[0488] 干预：向患者施用 1-50mg/kg 的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，作为单一药剂或组合每天一次或一天两次施用。

[0489] 结果测量指标：本研究的结果测量指标是症状改善和 / 或疼痛缓解和子宫内膜组织收缩。

[0490] 详细描述：给予患者式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，作为单一药剂或组合一天一次或两次口服。在每个给药周期之前，进行身体检查、血液检查和任何副作用的评估。

[0491] 资格：18 岁及年龄更大的女性受试者。

[0492] 入选标准：诊断有症状性子宫内膜异位症；绝经前或围绝经期状态；ECOG 体力状态 0-1；充分的肝脏和骨髓功能：AST<2.5xULN；胆红素 <1.5xULN；ANC>1,500/ul；血小板计数 >100,000/ul；正常的 PT 和 PTT；自先前的手术或治疗相关的毒性起至少 2 周。

[0493] 排除标准：妊娠或哺乳；在过去 5 年内有其它恶性肿瘤病史，不包括宫颈或非黑色素瘤皮肤癌的治愈性治疗的原位癌；并行的试验药物治疗；不受控制的感染；活动性心脏

疾病；严重的医学或精神疾病。

实施例 49：子宫平滑肌瘤临床试验

[0494] 目的：本研究的目的是评估式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐作为单一药剂或组合用于治疗患有症状性子宫平滑肌瘤的患者的疗效，收集关于该化合物作为单一药剂或组合可能引起的任何副作用的信息，并评价该化合物作为单一药剂或组合的药代动力学性质。

[0495] 干预：向患者施用 1-50mg/kg 的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，作为单一药剂或组合每天一次或一天两次施用。

[0496] 结果测量指标：本研究的结果测量指标是症状改善和 / 或疼痛缓解和平滑肌瘤收缩。

[0497] 详细描述：给予患者式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，作为单一药剂或组合一天一次或两次口服。在每个给药周期之前，进行身体检查、血液检查和任何副作用的评估。

[0498] 资格：18 岁及年龄更大的女性受试者。

[0499] 入选标准：诊断有症状性子宫平滑肌瘤；绝经前或围绝经期状态；ECOG 体力状态 0-1；充分的肝脏和骨髓功能：AST<2.5xULN；胆红素 <1.5xULN；ANC>1,500/ul；血小板计数 >100,000/ul；正常的 PT 和 PTT；自先前的手术或治疗相关的毒性起至少 2 周。

[0500] 排除标准：妊娠或哺乳；在过去 5 年内有其它恶性肿瘤病史，不包括宫颈或非黑色素瘤皮肤癌的治愈性治疗的原位癌；并行的试验药物治疗；不受控制的感染；活动性心脏疾病；严重的医学或精神疾病。

实施例 50：肠胃外药物组合物

[0501] 为了制备适合通过注射（皮下、静脉内）施用的肠胃外药物组合物，将 100mg 式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的水溶性化合物或其药学上可接受的盐溶解在无菌水中，然后与 10mL 0.9％无菌盐水混合。将该混合物引入到适合通过注射施用的剂量单位形式中。

[0502] 在另一个实施方案中，混合以下成分以形成可注射的制剂：1.2g 式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，2.0mL 乙酸钠缓冲溶液 (0.4M)，HCl(1N) 或 NaOH(1M)（适量，加至合适的 pH），水（蒸馏水，无菌的）（适量，加到 20mL）。混合除了水以外的所有以上成分，搅拌，必要时稍微加热。然后加入足量的水。

实施例 51：口服溶液

[0503] 为了制备经口递送的药物组合物，制备 20％丙二醇水溶液。向其中加入足量的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐，以提供 20mg/mL 溶液。

实施例 52：口服胶囊

[0504] 为了制备经口递送的药物组合物，将 100-500mg 式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与淀粉混合。将该混合物引入适合经口施用的口服剂量单位如明胶硬胶囊中。

[0505] 在另一个实施方案中，将 100-500mg 式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐置于 4 号胶囊或 1 号胶囊（羟丙甲纤维素或硬明胶）中，并封

闭胶囊。

实施例 53 :口服片剂

[0506] 如下制备片剂 :混合 48 重量%的式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐,45 重量%的微晶纤维素,5 重量%的低取代的羟丙基纤维素,和 2 重量%的硬脂酸镁。通过直接压制制备片剂。所压制的片剂的总重量保持在 250-500mg。

实施例 54 :局部凝胶组合物

[0507] 为了制备药物局部凝胶组合物,将式 (I)、(II)、(III)、(IV)、(V) 或 (VI) 的化合物或其药学上可接受的盐与羟丙基纤维素、丙二醇、肉豆蔻酸异丙酯和纯化的醇 USP 混合。然后将得到的凝胶混合物引入适合局部施用的容器如管中。

[0508] 本文所述的实施例和实施方案仅用于说明目的,并且本领域技术人员想到的各种修改或改变将包括在本申请的精神和范围内以及所附权利要求书的范围内。

Abstract

Described herein are compounds that are estrogen receptor modulators. Also described are pharmaceutical compositions and medicaments that include the compounds described herein, as well as methods of using such estrogen receptor modulators, alone and in combination with other compounds, for treating diseases or conditions that are mediated or dependent upon estrogen receptors.