

S1P₁ RECEPTOR AGONISTS AND USES THEREOF

FIELD OF THE INVENTION

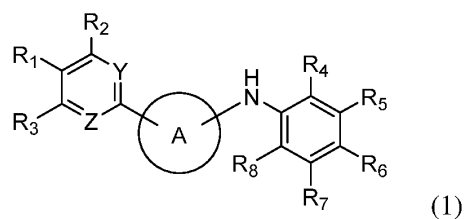
[0001] The present disclosure relates to compounds of formula (1a). The present disclosure further relates to pharmaceutical compositions comprising compounds of formula (1a) and to methods of treatment of autoimmune diseases, diseases of the central nervous system, and white blood cell disorders. The present disclosure further relates to processes for the preparation of compounds of formula (1a).

BACKGROUND OF THE INVENTION

[0002] The sphingosine-1-phosphate receptor 1 (“S1P₁ receptor”) is widely expressed in the animal body (*e.g.*, in endothelial cells, proximal tubular epithelial cells, and immune cells), and it helps regulate growth, survival, differentiation, motility, angiogenesis, calcium mobilization, lymphocyte trafficking, immune function, and cytoskeleton rearrangements. Chemical compounds that modulate the S1P₁ receptor are useful in the treatment of various diseases, such as multiple sclerosis (MS), relapsing-remitting multiple sclerosis (RRMS), amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease), psoriasis, systemic lupus erythematosus (SLE), ulcerative colitis, and Crohn’s disease. *See* M. Guerrero et al., Expert Opinion on Therapeutic Patents (2016), 26(4), 455-70; A. Marciniak et al., Bioorg. Med. Chem Lett. (2018), 28(23-24), 3585-91; each of which is incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

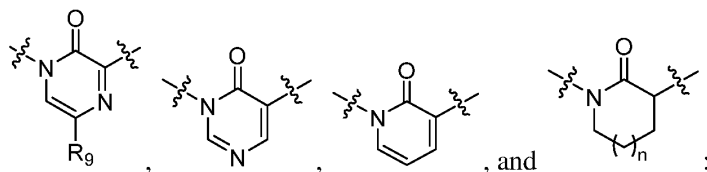
[0003] The present disclosure relates to a compound of formula (1):



wherein



is selected from the group consisting of:



R_1 is $-Q-(CR_gR_f)_m-U$;

R_2 and R_3 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, and CN;

R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, CN, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

Y is CR_a or N;

Z is CR_b or N;

Q is O, S, NH, or $-(CR_hR_d)_p-$;

U is $-COOR_e$, $-COSR_e$, $-CON(R_e)_2$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or $B(OH)_2$;

n is 0, 1, or 2;

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

p is 0, 1, or 2;

R_a and R_b are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, and CN;

R_c is H, unsubstituted C_1 - C_6 straight or branched alkyl, or substituted C_1 - C_6 straight or branched alkyl;

R_d is H, D, F, Cl, Br, I, or unsubstituted C_1 - C_6 straight or branched alkyl;

R_e is H or unsubstituted C_1 - C_6 straight or branched alkyl;

R_f is H, D, F, Cl, Br, I, or unsubstituted C_1 - C_6 straight or branched alkyl;

R_g is H, D, F, Cl, Br, I, or unsubstituted C_1 - C_6 straight or branched alkyl;

R_h is H, D, F, Cl, Br, I, or unsubstituted C_1 - C_6 straight or branched alkyl;

wherein R_1 and R_2 , R_1 and R_3 , R_2 and R_a , or R_3 and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted C_1 - C_6 straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr,

O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, COOH, COSH, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, COOH, COSH, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, COOH, COSH, and CONH₂;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, COOH, COSH, and CONH₂; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, COOH, COSH, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0004] The present disclosure further relates to pharmaceutical compositions comprising compounds of formula (1) or an enantiomer, racemate, or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

[0005] The present disclosure further relates to methods of treating autoimmune diseases, diseases of the central nervous system, and white blood cell disorders comprising administering to an individual in need thereof a pharmaceutical composition comprising a compound of formula (1) or an enantiomer, racemate, or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

[0006] The present disclosure further relates to processes for the preparation of compounds of formula (1) or an enantiomer, racemate, or pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] In order that the present disclosure may be well understood, there will now be described various forms thereof, given by way of example, reference being made to the accompanying drawings. The components in the figures are not necessarily to scale.

[0008] FIG. 1 illustrates a plot of % dextromethorphan remaining over time with NADPH in human liver microsome samples;

[0009] FIG. 2 illustrates a plot of % 1-(4-(2-(1*H*-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one (“Compound 3” in Table 29 below) remaining over time with NADPH in human liver microsome samples;

[0010] FIG. 3 illustrates a plot of % dextromethorphan remaining over time with NADPH in rat liver micorosome samples;

[0011] FIG. 4 illustrates a plot of % Compound 3 remaining over time with NADPH in rat liver microsome samples;

[0012] FIG. 5 illustrates a plot of enzyme inhibition for 1A2 CYP isoform by Compound 3 at various concentrations of Compound 3;

[0013] FIG. 6 illustrates a plot of enzyme inhibition for 2C9 CYP isoform by Compound 3 at various concentrations of Compound 3;

[0014] FIG. 7 illustrates a plot of enzyme inhibition for 2C19 CYP isoform by Compound 3 at various concentrations of Compound 3;

[0015] FIG. 8 illustrates a plot of enzyme inhibition for 2D6 CYP isoform by Compound 3 at various concentrations of Compound 3;

[0016] FIG. 9 illustrates a plot of enzyme inhibition for 3A4/5 CYP isoform by Compound 3 at various concentrations of Compound 3;

[0017] FIG. 10 illustrates a plot of enzyme inhibition for 2B6 CYP isoform by Compound 3 at various concentrations of Compound 3;

[0018] FIG. 11 illustrates a plot of enzyme inhibition for 2C8 CYP isoform by Compound 3 at various concentrations of Compound 3;

[0019] FIG. 12 illustrates a plot of enzyme inhibition for 1A2 CYP isoform by a positive control at various concentrations of the positive control;

[0020] FIG. 13 illustrates a plot of enzyme inhibition for 2C9 CYP isoform by a positive control at various concentrations of the positive control;

[0021] FIG. 14 illustrates a plot of enzyme inhibition for 2C19 CYP isoform by a positive control at various concentrations of the positive control;

[0022] FIG. 15 illustrates a plot of enzyme inhibition for 2D6 CYP isoform by a positive control at various concentrations of the positive control;

[0023] FIG. 16 illustrates a plot of enzyme inhibition for 3A4/5 CYP isoform by a positive control at various concentrations of the positive control;

[0024] FIG. 17 illustrates a plot of enzyme inhibition for 2B6 CYP isoform by a positive control at various concentrations of the positive control;

[0025] FIG. 18 illustrates a plot of enzyme inhibition for 2C8 CYP isoform by a positive control at various concentrations of the positive control;

[0026] FIG. 19 illustrates a plot of % remaining over time of phenacetin in human hepatocyte samples;

[0027] FIG. 20 illustrates a plot of % remaining over time of diclofenac in human hepatocyte samples;

[0028] FIG. 21 illustrates a plot of % remaining over time of dextromethorphan in human hepatocyte samples;

[0029] FIG. 22 illustrates a plot of % remaining over time of omeprazole in human hepatocyte samples;

[0030] FIG. 23 illustrates a plot of % remaining over time of midazolam in human hepatocyte samples;

[0031] FIG. 24 illustrates a plot of % remaining over time of 7-ethoxycoumarin in human hepatocyte samples;

[0032] FIG. 25 illustrates a plot of % remaining over time of Compound 3 in human hepatocyte samples;

[0033] FIG. 26 illustrates a plot of % remaining over time of phenacetin in rat hepatocyte samples;

[0034] FIG. 27 illustrates a plot of % remaining over time of diclofenac in rat hepatocyte samples;

[0035] FIG. 28 illustrates a plot of % remaining over time of dextromethorphan in rat hepatocyte samples;

[0036] FIG. 29 illustrates a plot of % remaining over time of omeprazole in rat hepatocyte samples;

[0037] FIG. 30 illustrates a plot of % remaining over time of midazolam in rat hepatocyte samples;

[0038] FIG. 31 illustrates a plot of % remaining over time of 7-ethoxycoumarin in rat hepatocyte samples;

[0039] FIG. 32 illustrates a plot of % remaining over time of Compound 3 in rat hepatocyte samples;

[0040] FIG. 33 illustrates a line plot of temporary lymphopenia with full recovery by

measure of circulating lymphocyte over time by administration of vehicle, or each of 8 mg/kg, 60 mg/kg, and 100 mg/kg Compound 3;

[0041] FIG. 34 illustrates a bar-graph plot of temporary lymphopenia with full recovery by measure of circulating lymphocyte over time by administration of vehicle, or each of 8 mg/kg, 60 mg/kg, and 100 mg/kg Compound 3;

[0042] FIG. 35 illustrates the circulating lymphocyte number for administration of vehicle over time;

[0043] FIG. 36 illustrates the circulating lymphocyte number for administration of 8 mg/kg Compound 3 over time;

[0044] FIG. 37 illustrates the circulating lymphocyte number of administration of 60 mg/kg Compound 3 over time;

[0045] FIG. 38 illustrates the circulating lymphocyte number of administration of 100 mg/kg Compound 3 over time;

[0046] FIG. 39 illustrates β -arrestin recruitment for a first experimental trial of administration of each of Compound 3, 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid ("Compound A"), sphingosine-1-phosphate ("S1P"), Ponesimod, and Siponimod;

[0047] FIG. 40 illustrates β -arrestin recruitment for a second experimental trial of administration of each of Compound 3, Compound A, S1P, Ponesimod, and Siponimod;

[0048] FIG. 41 illustrates $G_{\alpha i}$ -protein activation response curves for a first experimental trial of administration of each of Compound 3, Compound A, S1P, Ponesimod, and Siponimod;

[0049] FIG. 42 illustrates $G_{\alpha i}$ -protein activation response curves for a second experimental trial of administration of each of Compound 3, Compound A, S1P, Ponesimod, and Siponimod;

[0050] FIG. 43 illustrates mean $\pm$ standard deviation of rat plasma concentration of Compound 3 administered orally and intravenously;

[0051] FIG. 44 illustrates individual rat plasma concentrations over time of Compound 3 administered intravenously; and

[0052] FIG. 45 illustrates individual rat plasma concentrations over time of Compound 3 administered orally.

[0053] The drawings described herein are for illustration purposes only and are not intended to limit the scope of the present disclosure in any way.

DETAILED DESCRIPTION OF THE INVENTION

[0054] The following description is merely exemplary in nature and is not intended to limit the present disclosure, application, or uses.

[0055] The uses of the terms “a” and “an” and “the” and similar referents in the context of the describing the present disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term “plurality of” is defined by the Applicant in the broadest sense, superseding any other implied definitions or limitations hereinbefore or hereinafter unless expressly asserted by Applicant to the contrary, to mean a quantity of more than one. Recitations of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein may be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

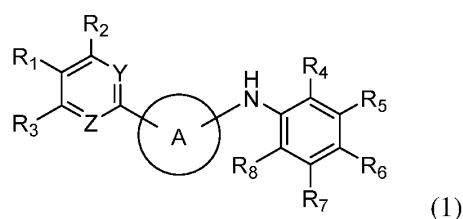
[0056] As used herein the terms “comprise(s),” “include(s),” “having,” “has,” “can,” “contain(s),” and variants thereof, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The present description also contemplates other examples “comprising,” “consisting,” and “consisting essentially of,” the examples or elements presented herein, whether explicitly set forth or not.

[0057] In describing elements of the present disclosure, the terms 1st, 2nd, first, second, A, B, (a), (b), and the like may be used herein. These terms are only used to distinguish one element from another element, but do not limit the corresponding elements irrespective of the nature or order of the corresponding elements.

[0058] Unless otherwise defined, all terms used herein, including technical or scientific terms, have the same meanings as those generally understood by those skilled in the art to which the present disclosure pertains. Such terms as those defined in a generally used dictionary are to be interpreted as having meanings equal to the contextual meanings in the relevant field of art.

[0059] As used herein, the term “about,” when used in the context of a numerical value or range set forth means a variation of $\pm 15\%$, or less, of the numerical value. For example, a value differing by $\pm 15\%$, $\pm 14\%$, $\pm 10\%$, or $\pm 5\%$, among others, would satisfy the definition of “about,” unless more narrowly defined in particular instances.

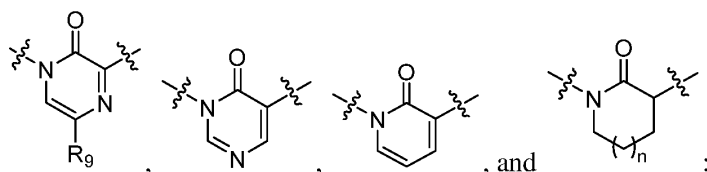
[0060] The present disclosure relates to a compound of formula (1):



wherein



is selected from the group consisting of:



R_1 is $-Q-(CR_gR_f)_m-U$;

R_2 and R_3 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, and CN;

R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, substituted or unsubstituted cycloalkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, CN, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

Y is CR_a or N;

Z is CR_b or N;

Q is O, S, NH, or $-(CR_hR_d)_p-$;

U is $-COOR_e$, $-COS(O)_pR_e$, $-CONHS(O)_pR_e$, $-CONHR_e$, $-CON(R_e)_2$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or $B(OH)_2$;

n is 0, 1, or 2;

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

p is 0, 1, or 2;

R_a and R_b are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, and CN;

R_c is H, unsubstituted C₁-C₆ straight or branched alkyl, or substituted C₁-C₆ straight or branched alkyl;

R_d is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_e is H, unsubstituted C₁-C₆ straight or branched alkyl, or C₁-C₆ straight or branched alkyl substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OR_c, SR_c, N(R_c)₂, and CN;

R_f is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_g is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_h is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight

or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0061] The term “alkyl,” by itself or as part of another substituent, means, unless otherwise stated, a straight, branched, or cyclic chain hydrocarbon (“cycloalkyl”) having the number of carbon atoms designated (i.e., “C₁-C₂₀” means one to twenty carbons, including C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁, C₁₂, C₁₃, C₁₄, C₁₅, C₁₆, C₁₇, C₁₈, C₁₉). In a particular example, C₁-C₂₀ may not include C₁alkyl, and/or may not include C₂alkyl, and/or may not include C₃alkyl, and/or may not include C₄alkyl, and/or may not include C₅alkyl, and/or may not include C₆alkyl, and/or may not include C₇alkyl, and/or may not include C₈alkyl, and/or may not include C₉alkyl, and/or may not include C₁₀alkyl, and/or may not include C₁₁alkyl, and/or may not include C₁₂alkyl, and/or may not include C₁₃alkyl, and/or may not include C₁₄alkyl, and/or may not include C₁₅alkyl, and/or may not include C₁₆alkyl, and/or may not include C₁₇alkyl, and/or may not include C₁₈alkyl, and/or may not include C₁₉alkyl, and/or may not include C₂₀alkyl. Examples may include methyl, ethyl, propyl, isopropyl, cyclopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, cyclobutyl, methylcyclopropyl, cyclopropylmethyl, pentyl, neopentyl, hexyl, and cyclohexyl.

[0062] Examples of cycloalkyl groups that may be used as R₄, R₅, R₆, R₇, R₈, R₉, U, or that any of R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form may include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

[0063] Each of the terms “alkene” and “olefin,” by itself or as part of another substituent, refers, unless otherwise stated, to a stable mono-unsaturated or di-unsaturated or poly-unsaturated straight chain, branched chain, or cyclic hydrocarbon (“cycloalkene”), “unsaturated” meaning a carbon-carbon double bond (–CH=CH–). The term “alkenyl,” by itself or as part of another substituent, refers to a stable mono-unsaturated or di-unsaturated or poly-unsaturated straight chain, branched chain, or cyclic hydrocarbon monovalent radical having the number of carbon atoms designated. Examples may include vinyl, propenyl, cyclopropenyl, allyl, crotyl, isopentenyl, butadienyl, cyclobutenyl, 1,3-pentadienyl, 1,4-pentadienyl, cyclopentenyl, cyclopentadienyl, 3-hydroxy-2-methyl-1-oxo-cyclopent-2-enyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cyclooctenyl, cyclooctadienyl, cyclooctatrienyl, and the higher homologs and isomers.

[0064] The term “aromatic” generally refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (i.e., having (4n+2) delocalized π (pi) electrons where n is an integer). The term “aryl,” by itself or in combination with

another substituent, means, unless otherwise stated, a carbocyclic aromatic system containing one or more rings (typically one, two, or three rings) wherein such rings may be attached together in a pendant manner, such as biphenyl, or may be fused, such as naphthalene.

[0065] The terms “heterocycle” or “heterocyclyl” or “heterocyclic,” by themselves or as part of other substituents, mean, unless otherwise stated, an unsubstituted or substituted, stable, mono- or multi-cyclic heterocyclic ring system that consists of carbon atoms and at least one heteroatom independently selected from the group consisting of N, O, and S, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen atom may be optionally quaternized. The heterocyclic system may be attached, unless otherwise stated, at any heteroatom or carbon atom that affords a stable structure.

[0066] Examples of heterocyclic groups that may be used as R₄, R₅, R₆, R₇, R₈, R₉, U, or that any of R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form may include, for example, azetidiny, pyrrolidiny, pyrroliny, pyrazolidiny, imidazolidiny, imidazolidiny, pyrazolidiny, piperidiny, piperaziny, oxetany, tetrahydrofurany, dihydrofurany, tetrahydropyrany, dihydropyrany, tetrahydrothiophene, dihydrothiophene, tetrahydrothiopyrany, 3,5-dioxoisoxazolidiny, and dihydrothiopyrany.

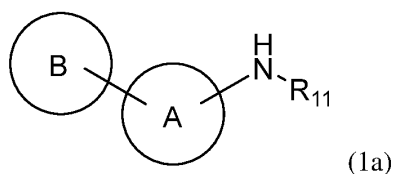
[0067] Examples of aryl groups that may be used as R₄, R₅, R₆, R₇, R₈, R₉, U, or that any of R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form may include, for example, phenyl, naphthalenyl, cyclobutadienyl, cyclopentadienyl, indenyl, anthracenyl, phenanthrenyl, terphenylenyl, fluorenyl, and pyrenyl.

[0068] The terms “heteroaryl” and “heteroaromatic,” by themselves or in combination with another substituent, refer, unless otherwise stated, to a heterocyclic having aromatic character. Examples of heteroaryl groups that may be used as R₄, R₅, R₆, R₇, R₈, R₉, U, or that any of R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form may include, for example, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, 5(4*H*)-oxo-1,2,4-thiadiazolyl, oxazolyl, 5(4*H*)-oxo-1,2,4-oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridiny, pyridaziny, pyrimidiny, pyraziny, tetrazolyl, 1*H*-indolyl, 3*H*-indolyl, 2*H*-isoindolyl, indoliziny, quinoliny, isoquinoliny, quinoxaliny, cinnoliny, quinazolinyl, phthalaziny, puriny, indazolyl, benzimidazolyl, benzo[*d*]oxazole, benzo[*d*]thiazole, benzo[*c*]isoxazole, benzo[*d*]isoxazole, benzo[*c*]isothiazole, benzo[*d*]isothiazole, quinolin-2(1*H*)-one, isoquinoline-1(2*H*)-one, indolin-2-one, isoindolin-1-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-thione, furany, carbazolyl, benzofurany, isobenzofurany, dibenzofurany, benzofuran-2(3*H*)-one, isobenzofuran-1(3*H*)-one, thiophenyl, benzo[*b*]thiophenyl, benzo[*c*]thiophenyl, benzo[*b*]thiophen-2(3*H*)-one, and benzo[*c*]thiophen-1(3*H*)-one.

[0069] Cycloalkyl groups, heterocyclic groups, aryl groups, and heteroaryl groups in compounds of formula (1) or (1a) may be substituted with one or more substituents selected from the group consisting of unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

[0070] C₁-C₆ straight or branched alkyl groups may be substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

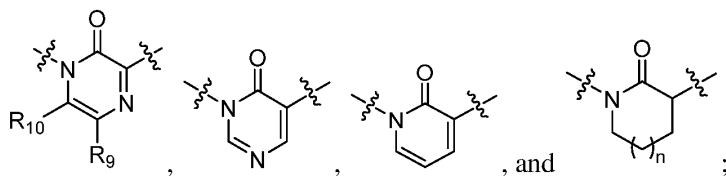
[0071] Another embodiment of the invention is a compound of formula (1a):



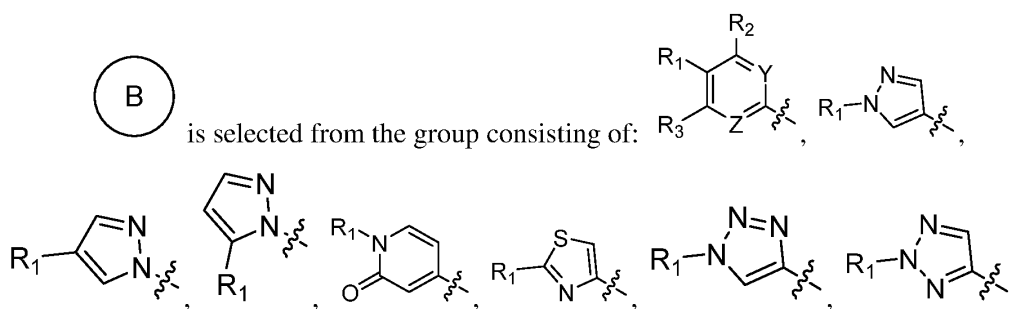
wherein

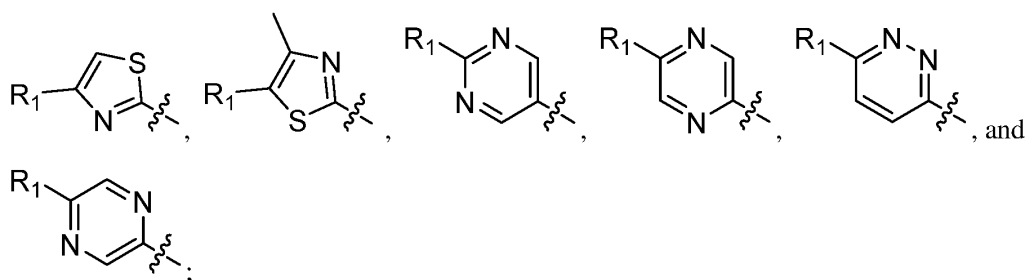


is selected from the group consisting of:



is selected from the group consisting of:

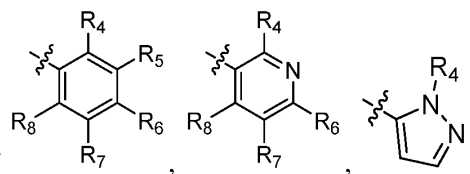




R_1 is $(T)_w-(CR_gR_f)_m-Q-(CR_gR_f)_m-U$;

R_2 and R_3 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, and CN;

R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} , are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $S(O)_2R_i$, $S(O)_2N(R_c)_2$, $N(R_c)_2$, CN, $C(O)R_i$, $N(R_c)C(O)R_i$, $C(O)N(R_c)_2$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkenyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;



R_{11} is selected from the group consisting of H, $OCH_2C(O)_2R_c$, an unsubstituted C_1 - C_6 straight or branched alkyl, a substituted C_1 - C_6 straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

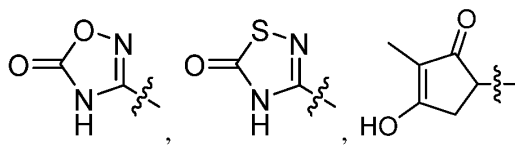
Y is CR_a or N;

Z is CR_b or N;

Q is O, S, NR_i , or $-(CR_hR_d)_p-$;

T is O, S, NR_i , or $-(CR_hR_d)_p-$;

U is $-COOR_e$, $-COS(O)_pR_e$, $-C(O)NHS(O)_pR_e$, $-CONHR_e$, $-CON(R_e)_2$, vinyl, a substituted C_1 - C_6 straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a



substituted or unsubstituted heteroaryl group,

or B(OH)₂;

n is 0, 1, or 2;

each m is independently 0, 1, 2, 3, 4, or 5;

p is 0, 1, or 2;

w is 0, 1, or 2;

R_a and R_b are independently selected from the group consisting of H, unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OR_c, SR_c, N(R_c)₂, and CN;

R_c is H, unsubstituted C₁-C₆ straight or branched alkyl, or unsubstituted C₁-C₆ straight or branched alkyl;

R_d is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_e is H, unsubstituted C₁-C₆ straight or branched alkyl, or C₁-C₆ straight or branched alkyl substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OR_c, SR_c, N(R_c)₂, and CN;

R_f is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_g is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_h is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_i is H, D, F, Cl, Br, I, unsubstituted C₁-C₆ straight or branched alkyl, or unsubstituted cycloalkyl;

R_j is a substituted or unsubstituted C₁-C₆ straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaryl group;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, R₄ and R₅, R₆ and R₇, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OC₄alkyl, OC₅alkyl, OC₆alkyl, unsubstituted cycloalkyl, substituted heterocyclyl, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂,

NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, CONMe₂, CONHMe, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, an unsubstituted heterocyclyl group, an unsubstituted heteroaryl group, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

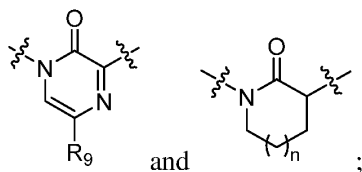
wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, CONH₂, and CONHPh; and

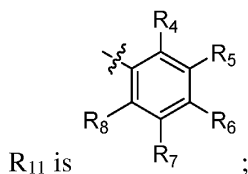
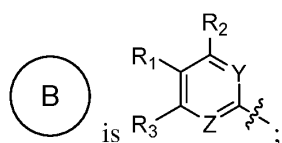
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0072] Another embodiment of the disclosure is a compound of formula (1) or (1a) wherein:

 is selected from the group consisting of:





R_1 is $-Q-(CHR_f)_m-U$;

R_2 and R_3 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, and OR_c ;

R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, substituted or unsubstituted cycloalkyl, F, Cl, Br, I, OR_c , a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

Y is CR_a or N;

Z is CR_b or N;

Q is O, S, or $-(CHR_d)_p-$;

U is $-COOR_e$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or $B(OH)_2$;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, and OR_c ;

R_c is H, unsubstituted C_1 - C_6 straight or branched alkyl, or substituted C_1 - C_6 straight or branched alkyl;

R_d is H, F, Cl, Br, I, or unsubstituted C_1 - C_6 straight or branched alkyl;

R_e is H or unsubstituted C_1 - C_6 straight or branched alkyl;

R_f is H, F, Cl, Br, I, or unsubstituted C_1 - C_6 straight or branched alkyl;

wherein R_1 and R_2 , R_1 and R_3 , R_2 and R_a , or R_3 and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a

substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

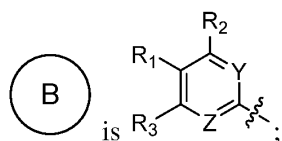
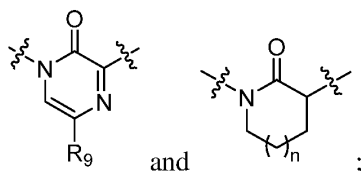
wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂; and

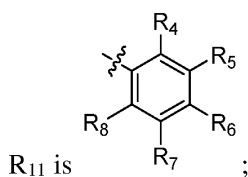
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0073] Another embodiment of the disclosure is a compound of formula (1) or (1a) wherein:

(A) is selected from the group consisting of:





R₁ is $-Q-(CHR_t)_m-U$;

R₂ and R₃ are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, F, Cl, Br, I, OR_c, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

Y is CR_a or N;

Z is CR_b or N;

Q is O or $-(CHR_d)_p-$;

U is $-COOR_e$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, and OR_c;

R_c is H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, or substituted isopropyl;

R_d is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

R_e is H, methyl, ethyl, *n*-propyl, or isopropyl;

R_f is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted methyl, ethyl, *n*-propyl, or isopropyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr,

O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂;

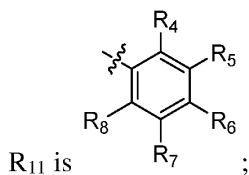
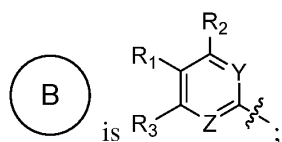
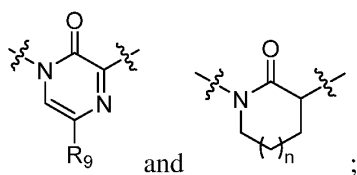
wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0074] Another embodiment of the disclosure is a compound of formula (1) or (1a) wherein:

(A) is selected from the group consisting of:



R_1 is $-Q-(CHR_f)_m-U$;

R_2 and R_3 are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c ;

R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, F, Cl, Br, I, OR_c , phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl;

Y is CR_a or N;

Z is CR_b or N;

Q is O or $-(CHR_d)_p-$;

U is $-COOR_e$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or $B(OH)_2$;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c ;

R_c is H, methyl, CH_2F , CHF_2 , CF_3 , ethyl, *n*-propyl, or isopropyl;

R_d is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

R_e is H, methyl, ethyl, *n*-propyl, or isopropyl;

R_f is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

wherein R_1 and R_2 , R_1 and R_3 , R_2 and R_a , or R_3 and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted methyl, ethyl, *n*-propyl, or isopropyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, NH_2 , carbonyl, and COOH;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH_2F , $OCHF_2$, OCF_3 , NH_2 , NMe_2 , NEt_2 , $N(nPr)_2$, $N(iPr)_2$, CH_2COOH , carbonyl, and COOH;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl,

Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, and COOH;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, and COOH; and

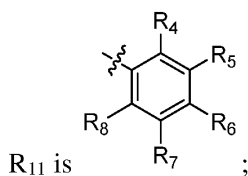
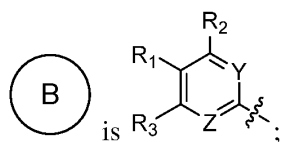
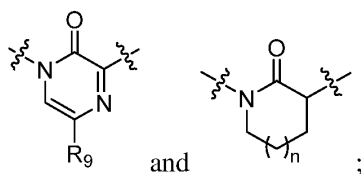
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, and COOH; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0075] Another embodiment of the disclosure is a compound of formula (1) or (1a) wherein:



is selected from the group consisting of:



R₁ is -Q-(CHR_f)_m-U;

R₂ and R₃ are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, CF₃, ethyl, *n*-propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, F, Cl, Br, I, OR_c, phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl;

Y is CR_a or N;

Z is CR_b or N;

Q is O or $-(\text{CHR}_d)_p-$;

U is $-\text{COOH}$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or $\text{B}(\text{OH})_2$;

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

R_a is H or methyl;

R_b is H or methyl;

R_c is H, methyl, or CF_3 ;

R_d is H, F, Cl, Br, or methyl;

R_f is H, F, Cl, Br, or methyl;

wherein R_1 and R_2 or R_1 and R_3 together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ; and

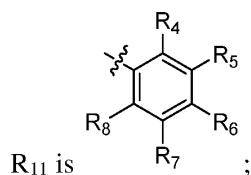
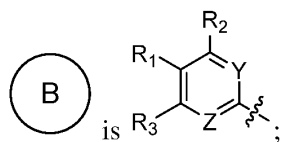
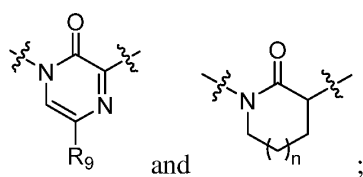
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0076] Another embodiment of the disclosure is a compound of formula (1) or (1a) wherein:



is selected from the group consisting of:



R₁ is $-Q-(CHR_f)_m-U$;

R₂ and R₃ are independently H or methyl;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, CF₃, F, Cl, Br, OMe, and OCF₃;

Y is CH or N;

Z is CH or N;

Q is O or $-(CHR_d)_p-$;

U is $-COOH$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

R_d is H, F, or methyl;

R_f is H, F, or methyl;

wherein R₁ and R₂ or R₁ and R₃ together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH;

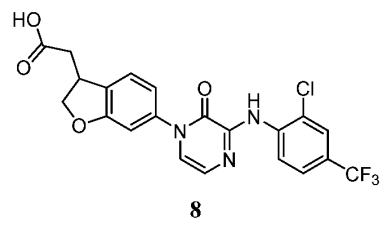
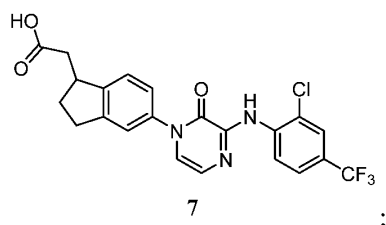
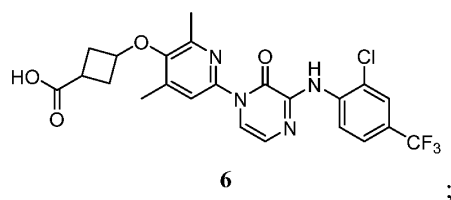
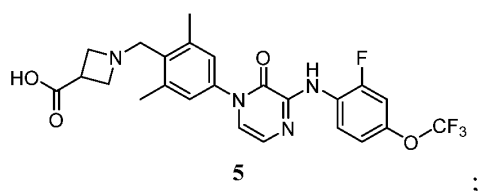
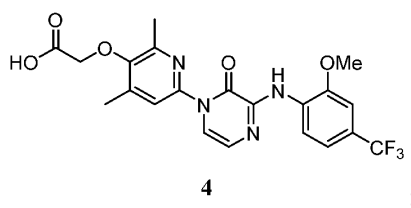
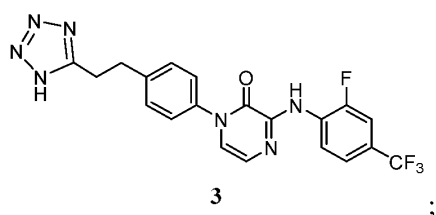
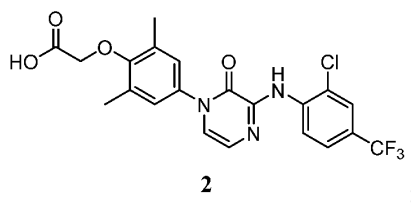
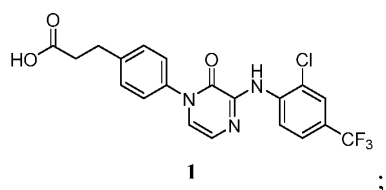
wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH;

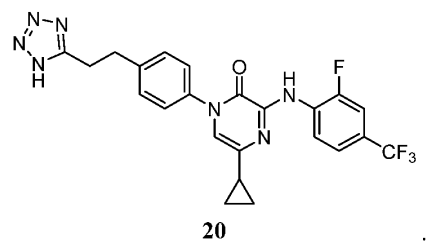
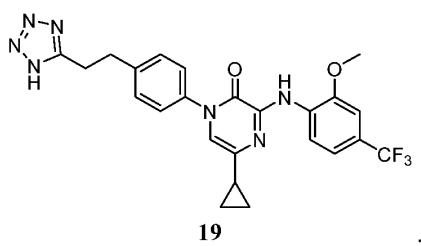
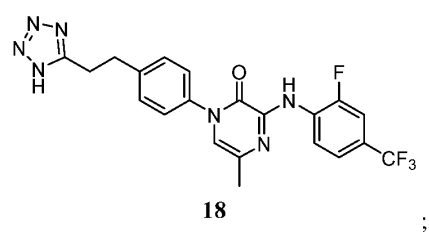
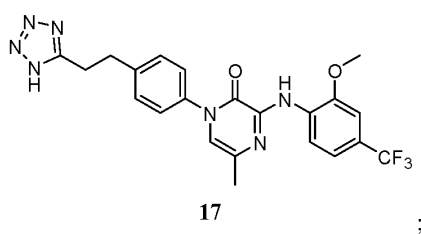
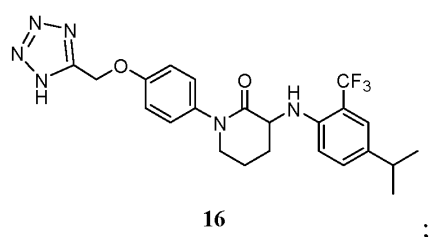
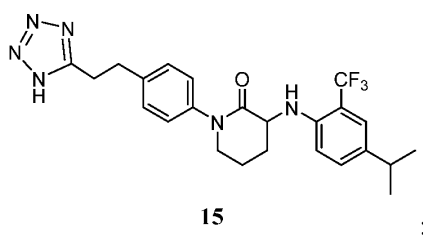
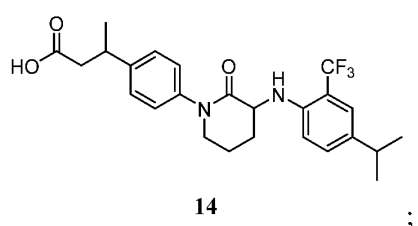
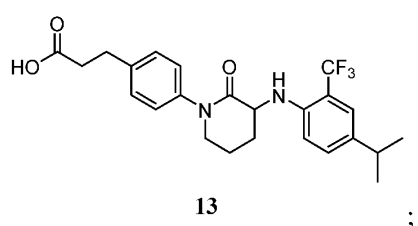
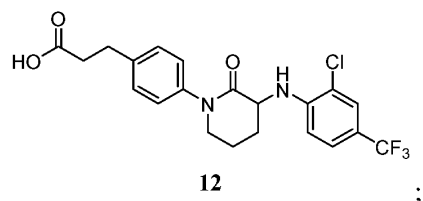
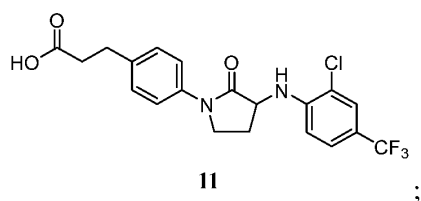
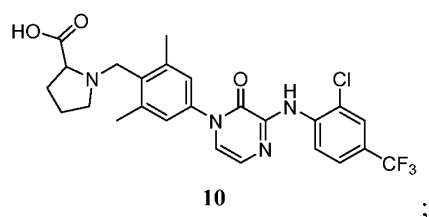
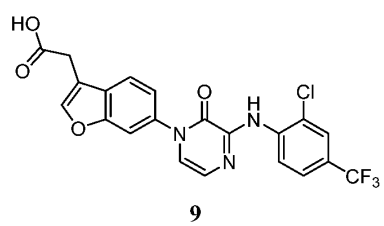
wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH; and

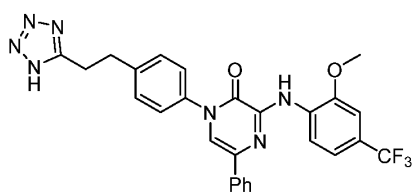
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0077] In some embodiments, the compound of formula (1) or (1a) is selected from the group consisting of:

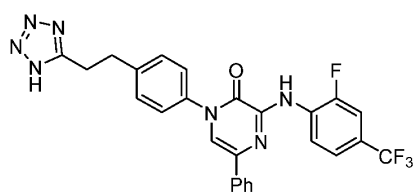






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; and



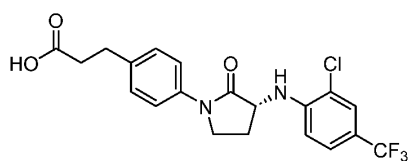
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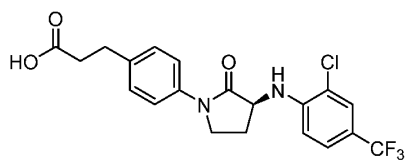
or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

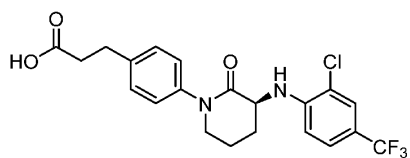
[0078] In some embodiments, the compound of formula (1) or (1a) is selected from the group consisting of:

11-(*R*)

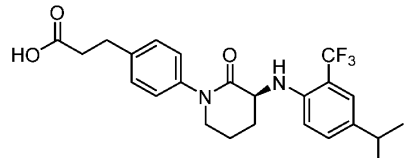
;

11-(*S*)

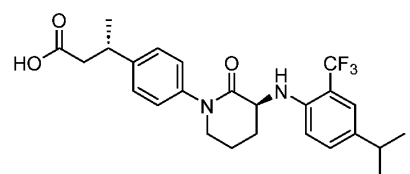
;

12-(*S*)

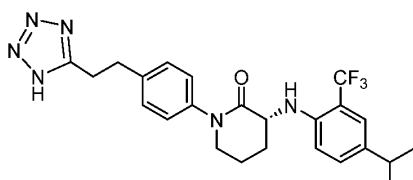
;

13-(*S*)

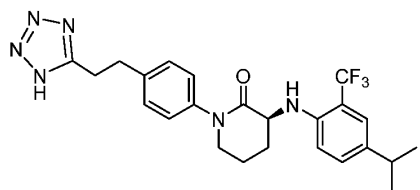
;

14-(*S,S*)

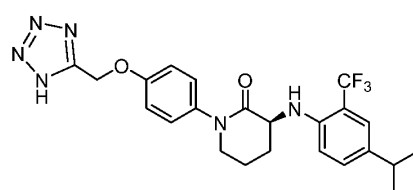
;

15-(*R*)

;

15-(*S*)

; and

16-(*S*)

or a pharmaceutically acceptable salt thereof.

[0079] Pharmaceutically acceptable salts of the compounds of formula (1) or (1a) may be prepared from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, metaphosphoric acid, nitric acid, and sulfuric acid, and of organic acids such as, for example, formic acid, acetic acid, trifluoroacetic acid,

benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, lactic acid, maleic acid, malic acid, methanesulfonic acid, succinic acid, *p*-toluenesulfonic acid, and tartaric acid by methods known in the art.

Pharmaceutical Compositions

[0080] The present disclosure further relates to pharmaceutical compositions comprising compounds of formula (1) or (1a) or an enantiomer, racemate, or pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0081] Suitable excipients for use in the pharmaceutical compositions of the present disclosure may be selected from the group consisting of diluents, such as lactose, sucrose, dextrose, dextrans, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, cellulose, microcrystalline cellulose, microcellulose, and talc; binders, such as copovidone, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, alginic acid, and carboxymethylcellulose sodium; disintegrating agents, such as natural starch, pregelatinized starch, sodium starch, clay, gum, sodium alginate, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch (*e.g.*, sodium starch glycolate), cross-linked polymer (*e.g.*, crospovidone), and cross-linked polyvinylpyrrolidone; lubricants, such as stearic acid, stearic acid salts (*e.g.*, magnesium stearate, calcium stearate, and zinc stearate), palmitic acid, palmitic acid salts (*e.g.*, magnesium palmitate, calcium palmitate, and zinc palmitate), myristic acid, myristic acid salts (*e.g.*, magnesium myristate, calcium myristate, and zinc myristate), fatty acid esters (*e.g.*, glyceryl monostearate, sorbitan monostearate, and sucrose monopalmitate), and sodium stearyl fumarate; surfactants, such as fatty acids (*e.g.*, oleic acid, palmitic acid, and stearic acid), fatty acid salts (*e.g.*, sodium oleate, triethanolamine oleate; sodium palmitate, triethanolamine palmitate, sodium stearate, and triethanolamine stearate), glyceryl fatty acid esters (*e.g.*, glyceryl monooleate, glyceryl monopalmitate, glyceryl monostearate), sorbitan esters (*e.g.*, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, and sorbitan tristearate), polyoxyethylene sorbitan esters (*e.g.*, polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80), sulfate surfactants (*e.g.*, sodium lauryl sulfate and sodium laureth sulfate), lecithin, quaternary ammonium compounds (*e.g.*, benzalkonium chloride, benzethonium chloride, and cetylpyridinium chloride), laurylaminopropionic acid, sodium laurylaminopropionate, alkyl polyglucosides (*e.g.*, octyl glucoside, decyl glucoside, and

lauryl glucoside), polyoxyethylene alkylphenyl ethers (*e.g.*, nonoxynol 9, nonoxynol 10, and octoxynol 9), poloxamers (*e.g.*, polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene alkyl ethers (*e.g.*, polyoxyethylene (20) cetostearyl ether), polyoxyethylene fatty acid esters (*e.g.*, polyoxyethylene (40) stearate), polyoxyethylene fatty acid glycerides and oils (*e.g.*, polyoxyethylene (35) castor oil, and polyoxyethylene (40) hydrogenated castor oil), propylene glycol fatty acid esters (*e.g.*, propylene glycol laureate); buffering agents, such as phosphate buffers, carbonate buffers, and citrate buffers; antioxidants, such as sulfites (*e.g.*, sodium sulfite), ascorbic acid, ascorbates (*e.g.*, sodium ascorbate, calcium ascorbate, and potassium ascorbate), ethylene diamine tetraacetic acid (EDTA), ethylene glycol-bis(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT), ascorbyl palmitate, fumaric acid, tocopherol, and vitamin E; preservatives, such as quaternary ammonium compounds (*e.g.*, benzalkonium chloride, benzethonium chloride, and cetylpyridinium chloride), benzoic acid, benzoic acid salts (*e.g.*, sodium benzoate), sorbic acid, and sorbic acid salts (*e.g.*, sodium sorbate); stabilizers, such as povidone, hydroxypropyl cellulose, and hydroxypropyl methylcellulose; salts, such as alkali metal salts (*e.g.*, sodium chloride); fillers, such as mannitol, sorbitol, maltodextrin, maltose, and dextrin; flavor enhancers, such as sweeteners; colorants, such as synthetic organic food additives (*e.g.*, food dyes, such as food red dye Nos. 3 and 40; food yellow dye Nos. 4, 5, and 6; green food dye No. 3; and food blue dye Nos. 1, 2, and 3), water-insoluble lake dyes (*e.g.*, aluminum salts of water-soluble synthetic organic food additives), and natural pigments (*e.g.*, beta-carotene, chlorophyll, betanin, ferric oxide); and mixtures thereof

[0082] The pharmaceutical compositions disclosed herein may be administered by inhalation (*i.e.*, intranasally as an aerosol or inhalation solution or suspension); topically (*i.e.*, in the form of an ointment, cream or lotion); orally (*i.e.*, in solid or liquid form as a tablet, capsule, gel cap, time release capsule, powder, solution, or suspension in aqueous or non-aqueous liquid); intravenously as an infusion or injection (*i.e.*, as a solution, suspension or emulsion in a pharmaceutically acceptable carrier); intramuscularly, intracutaneously, or subcutaneously as an infusion or injection (*i.e.*, as a solution, suspension or emulsion in a pharmaceutically acceptable carrier) or as a depot formulation; transdermally (*e.g.*, via a transdermal patch), rectally (*e.g.*, as a suppository), or intraperitoneally.

[0083] There is no limitation in the route of administration or dosage form, and the composition may be administered in accordance with specific form of the preparation, age, sex and the other conditions of a patient, severity of disease, etc. For example, in the case of tablet, pill, solution, suspension, emulsion, granule and capsule, the composition is orally administered. In the case of injection, the composition is intravenously administered alone or

in a mixture with conventional replacement fluid such as glucose and amino acids, and if necessary, and the preparation alone may be also administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally.

[0084] The dose of the pharmaceutical compositions of the invention is appropriately selected in accordance with dosage regimen, age, sex, and other conditions of a patient. The amount to be administered depends on the lipophilicity of the specific compound selected, since it is expected that this property of the compound will cause it to partition into fat deposits of the subject. The precise amount to be administered may be determined by the skilled practitioner in view of desired dosages, side effects, medical history of the patient, and the like. The amount is sufficient to treat or prevent the condition or disease state intended to be treated. In other words, the amount is sufficient to treat or prevent autoimmune diseases, including ulcerative colitis, Crohn's disease, psoriasis, and systemic lupus erythematosus (SLE); diseases of the central nervous system, including multiple sclerosis (MS), relapsing-remitting multiple sclerosis (RRMS), and amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease); and white blood cell disorders, including lymphopenia. The dosage may range from approximately 0.001 mg to 5,000 mg per dose. In some embodiments, the dosage ranges from approximately 0.010 mg to 1000 mg per dose. In some embodiments, the dosage ranges from approximately 0.100 mg to 500 mg per dose. In some embodiments, the dosage ranges from approximately 1 mg to 250 mg per dose. In certain examples, the dosage may range from approximately 0.001 mg, or from 0.010 mg, or from 0.020 mg, or from 0.030 mg, or from 0.040 mg, or from 0.050 mg, or from 0.060 mg, or from 0.070 mg, or from 0.080 mg, or from 0.090 mg, or from 0.100 mg, or from 0.110 mg, or from 0.120 mg, or from 0.130 mg, or from 0.140 mg, or from 0.150 mg, or from 0.160 mg, or from 0.170 mg, or from 0.180 mg, or from 0.190 mg, or from 0.200 mg, or from 0.210 mg, or from 0.220 mg, or from 0.230 mg, or from 0.240 mg, or from 0.250 mg, or from 0.260 mg, or from 0.270 mg, or from 0.280 mg, or from 0.290 mg, or from 0.300 mg, or from 0.310 mg, or from 0.320 mg, or from 0.330 mg, or from 0.340 mg, or from 0.350 mg, or from 0.360 mg, or from 0.370 mg, or from 0.380 mg, or from 0.390 mg, or from 0.400 mg, or from 0.410 mg, or from 0.420 mg, or from 0.430 mg, or from 0.440 mg, or from 0.450 mg, or from 0.460 mg, or from 0.470 mg, or from 0.480 mg, or from 0.490 mg, or from 0.500 mg, or from 0.510 mg, or from 0.520 mg, or from 0.530 mg, or from 0.540 mg, or from 0.550 mg, or from 0.560 mg, or from 0.570 mg, or from 0.580 mg, or from 0.590 mg, or from 0.600 mg, or from 0.610 mg, or from 0.620 mg, or from 0.630 mg, or from 0.640 mg, or from 0.650 mg, or from 0.660 mg, or from 0.670 mg, or from 0.680 mg, or from 0.690 mg, or from 0.700 mg, or from 0.710 mg, or from 0.720 mg, or from 0.730 mg, or from 0.740 mg, or from 0.750 mg, or from 0.760 mg, or from 0.770 mg, or from 0.780 mg, or from 0.790 mg, or from 0.800

mg, or from 0.810 mg, or from 0.820 mg, or from 0.830 mg, or from 0.840 mg, or from 0.850 mg, or from 0.860 mg, or from 0.870 mg, or from 0.880 mg, or from 0.890 mg, or from 0.900 mg, or from 0.910 mg, or from 0.920 mg, or from 0.930 mg, or from 0.940 mg, or from 0.950 mg, or from 0.960 mg, or from 0.970 mg, or from 0.980 mg, or from 0.990 mg, or from 1 mg, or from 5 mg, or from 10 mg, or from 15 mg, or from 20 mg, or from 25 mg, or from 30 mg, or from 35 mg, or from 40 mg, or from 45 mg, or from 50 mg, or from 55 mg, or from 60 mg, or from 65 mg, or from 70 mg, or from 75 mg, or from 80 mg, or from 85 mg, or from 90 mg, or from 95 mg, or from 100 mg, or from 105 mg, or from 110 mg, or from 115 mg, or from 120 mg, or from 125 mg, or from 130 mg, or from 135 mg, or from 140 mg, or from 145 mg, or from 150 mg, or from 155 mg, or from 160 mg, or from 165 mg, or from 170 mg, or from 175 mg, or from 180 mg, or from 185 mg, or from 190 mg, or from 195 mg, or from 200 mg, or from 205 mg, or from 210 mg, or from 220 mg, or from 225 mg, or from 230 mg, or from 235 mg, or from 240 mg, or from 245 mg, or from 250 mg, or from 255 mg, or from 260 mg, or from 265 mg, or from 270 mg, or from 275 mg, or from 280 mg, or from 285 mg, or from 290 mg, or from 295 mg, or from 300 mg, or from 305 mg, or from 310 mg, or from 315 mg, or from 320 mg, or from 325 mg, or from 330 mg, or from 335 mg, or from 340 mg, or from 345 mg, or from 350 mg, or from 355 mg, or from 360 mg, or from 365 mg, or from 370 mg, or from 375 mg, or from 380 mg, or from 385 mg, or from 390 mg, or from 395 mg, or from 400 mg, or from 405 mg, or from 410 mg, or from 415 mg, or from 420 mg, or from 425 mg, or from 430 mg, or from 435 mg, or from 440 mg, or from 445 mg, or from 450 mg, or from 455 mg, or from 460 mg, or from 465 mg, or from 470 mg, or from 475 mg, or from 480 mg, or from 485 mg, or from 490 mg, or from 495 mg, or from 500 mg, or from 510 mg, or from 520 mg, or from 530 mg, or from 540 mg, or from 550 mg, or from 560 mg, or from 570 mg, or from 580 mg, or from 590 mg, or from 600 mg, or from 610 mg, or from 620 mg, or from 630 mg, or from 640 mg, or from 650 mg, or from 660 mg, or from 670 mg, or from 680 mg, or from 690 mg, or from 700 mg, or from 710 mg, or from 720 mg, or from 730 mg, or from 740 mg, or from 750 mg, or from 760 mg, or from 770 mg, or from 780 mg, or from 790 mg, or from 800 mg, or from 810 mg, or from 820 mg, or from 830 mg, or from 840 mg, or from 850 mg, or from 860 mg, or from 870 mg, or from 880 mg, or from 890 mg, or from 900 mg, or from 910 mg, or from 920 mg, or from 930 mg, or from 940 mg, or from 950 mg, or from 960 mg, or from 970 mg, or from 980 mg, or from 990 mg, or from 1000 mg, or from 1050 mg, or from 1100 mg, or from 1150 mg, or from 1200 mg, or from 1250 mg, or from 1300 mg, or from 1350 mg, or from 1400 mg, or from 1450 mg, or from 1500 mg, or from 1550 mg, or from 1600 mg, or from 1650 mg, or from 1700 mg, or from 1750 mg, or from 1800 mg, or from 1850 mg, or from 1900 mg, or from 1950 mg, or from 2000 mg, or from 2050 mg, or

from 2100 mg, or from 2150 mg, or from 2200 mg, or from 2250 mg, or from 2300 mg, or from 2350 mg, or from 2400 mg, or from 2450 mg, or from 2500 mg, or from 2550 mg, or from 2600 mg, or from 2650 mg, or from 2700 mg, or from 2750 mg, or from 2800 mg, or from 2850 mg, or from 2900 mg, or from 2950 mg, or from 3000 mg, or from 3050 mg, or from 3100 mg, or from 3150 mg, or from 3200 mg, or from 3250 mg, or from 3300 mg, or from 3350 mg, or from 3400 mg, or from 3450 mg, or from 3500 mg, or from 3550 mg, or from 3600 mg, or from 3650 mg, or from 3700 mg, or from 3750 mg, or from 3800 mg, or from 3850 mg, or from 3900 mg, or from 3950 mg, or from 4000 mg, or from 4050 mg, or from 4100 mg, or from 4150 mg, or from 4200 mg, or from 4250 mg, or from 4300 mg, or from 4350 mg, or from 4400 mg, or from 4450 mg, or from 4500 mg, or from 4550 mg, or from 4600 mg, or from 4650 mg, or from 4700 mg, or from 4750 mg, or from 4800 mg, or from 4850 mg, or from 4900 mg, or from 4950 mg to 5000 mg; or from 0.001 mg to 0.010 mg, or to 0.020 mg, or to 0.030 mg, or to 0.040 mg, or to 0.050 mg, or to 0.060 mg, or to 0.070 mg, or to 0.080 mg, or to 0.090 mg, or to 0.100 mg, or to 0.110 mg, or to 0.120 mg, or to 0.130 mg, or to 0.140 mg, or to 0.150 mg, or to 0.160 mg, or to 0.170 mg, or to 0.180 mg, or to 0.190 mg, or to 0.200 mg, or to 0.210 mg, or to 0.220 mg, or to 0.230 mg, or to 0.240 mg, or to 0.250 mg, or to 0.260 mg, or to 0.270 mg, or to 0.280 mg, or to 0.290 mg, or to 0.300 mg, or to 0.310 mg, or to 0.320 mg, or to 0.330 mg, or to 0.340 mg, or to 0.350 mg, or to 0.360 mg, or to 0.370 mg, or to 0.380 mg, or to 0.390 mg, or to 0.400 mg, or to 0.410 mg, or to 0.420 mg, or to 0.430 mg, or to 0.440 mg, or to 0.450 mg, or to 0.460 mg, or to 0.470 mg, or to 0.480 mg, or to 0.490 mg, or to 0.500 mg, or to 0.510 mg, or to 0.520 mg, or to 0.530 mg, or to 0.540 mg, or to 0.550 mg, or to 0.560 mg, or to 0.570 mg, or to 0.580 mg, or to 0.590 mg, or to 0.600 mg, or to 0.610 mg, or to 0.620 mg, or to 0.630 mg, or to 0.640 mg, or to 0.650 mg, or to 0.660 mg, or to 0.670 mg, or to 0.680 mg, or to 0.690 mg, or to 0.700 mg, or to 0.710 mg, or to 0.720 mg, or to 0.730 mg, or to 0.740 mg, or to 0.750 mg, or to 0.760 mg, or to 0.770 mg, or to 0.780 mg, or to 0.790 mg, or to 0.800 mg, or to 0.810 mg, or to 0.820 mg, or to 0.830 mg, or to 0.840 mg, or to 0.850 mg, or to 0.860 mg, or to 0.870 mg, or to 0.880 mg, or to 0.890 mg, or to 0.900 mg, or to 0.910 mg, or to 0.920 mg, or to 0.930 mg, or to 0.940 mg, or to 0.950 mg, or to 0.960 mg, or to 0.970 mg, or to 0.980 mg, or to 0.990 mg, or to 1 mg, or to 5 mg, or to 10 mg, or to 15 mg, or to 20 mg, or to 25 mg, or to 30 mg, or to 35 mg, or to 40 mg, or to 45 mg, or to 50 mg, or to 55 mg, or to 60 mg, or to 65 mg, or to 70 mg, or to 75 mg, or to 80 mg, or to 85 mg, or to 90 mg, or to 95 mg, or to 100 mg, or to 105 mg, or to 110 mg, or to 115 mg, or to 120 mg, or to 125 mg, or to 130 mg, or to 135 mg, or to 140 mg, or to 145 mg, or to 150 mg, or to 155 mg, or to 160 mg, or to 165 mg, or to 170 mg, or to 175 mg, or to 180 mg, or to 185 mg, or to 190 mg, or to 195 mg, or to 200 mg, or to 205 mg, or to 210 mg, or to 215 mg, or to 220 mg, or to 225 mg, or to

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Treatment of Autoimmune Diseases, Diseases of the Central Nervous System, and White Blood Cell Disorders

[0085] The present disclosure further relates to methods of treating autoimmune diseases, diseases of the central nervous system, and white blood cell disorders comprising

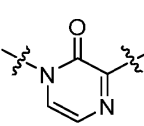
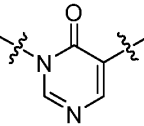
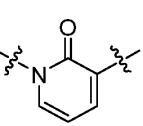
administering to an individual in need thereof a pharmaceutical composition comprising a compound of formula (1) or (1a) or an enantiomer, racemate, or pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

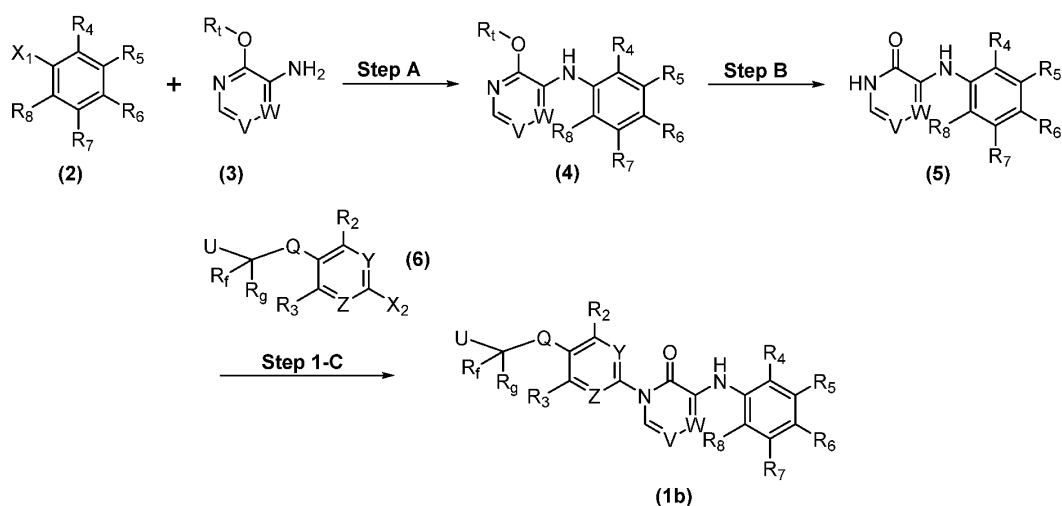
[0086] Chemical compounds that modulate the S1P₁ receptor are useful in the treatment of various diseases, such as multiple sclerosis (MS), relapsing-remitting multiple sclerosis (RRMS), amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), psoriasis, systemic lupus erythematosus (SLE), ulcerative colitis, and Crohn's disease. *See* M. Guerrero et al., *Expert Opinion on Therapeutic Patents* (2016), 26(4), 455-70; A. Marciniak et al., *Bioorg. Med. Chem. Lett.* (2018), 28(23-24), 3585-91.

[0087] The compounds of formula (1) or (1a) modulate the S1P₁ receptor. Without wishing to be bound by theory, it is believed that the compounds of formula (1) or (1a) modulate the S1P₁ receptor by acting as agonists of the S1P₁ receptor. Thus, the compounds of formula (1) or (1a) are useful in the treatment of autoimmune diseases, including ulcerative colitis, Crohn's disease, psoriasis, and systemic lupus erythematosus (SLE); diseases of the central nervous system, including multiple sclerosis (MS), relapsing-remitting multiple sclerosis (RRMS), and amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease); and white blood cell disorders, including lymphopenia.

Processes for Preparing Compounds of Formula (1) or (1a)

[0088] The present invention further relates to processes for the preparation of compounds of formula (1) or (1a) or an enantiomer, racemate, or pharmaceutically acceptable salt thereof. Overall process steps to make compounds of formula (1) or (1a) are shown in Schemes 1-6 below.

[0089] Compounds of formula (1) or (1a), wherein  is selected from the group consisting of , , , or an enantiomer, racemate, or pharmaceutically acceptable salt thereof, are prepared using the process shown in Scheme 1.



Scheme 1

wherein:

$R_2, R_3, R_4, R_5, R_6, R_7, R_8, Q, U, Y, Z, R_f$, and R_g are as defined above;

X_1 is F, Cl, Br, or I;

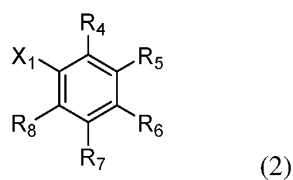
X_2 is F, Cl, Br, or I;

V is N or CH;

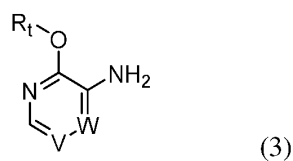
W is N or CH; and

R_t is H or unsubstituted C_1 - C_6 straight or branched alkyl.

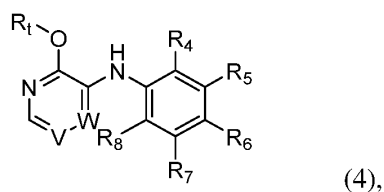
[0090] Scheme 1 comprises a step A, reacting a compound of formula (2)



with a compound of formula (3)

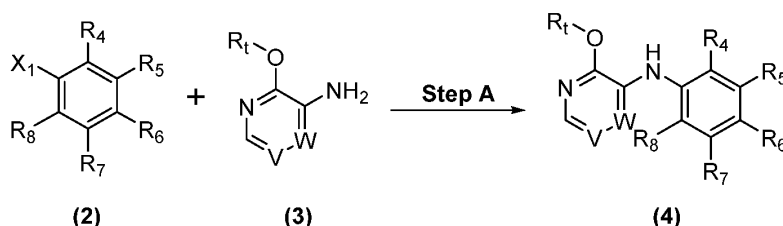


to produce a compound of formula (4)



wherein $R_4, R_5, R_6, R_7, R_8, V, W, X_1$, and R_t are as defined above.

[0091] Step A is shown below.



[0092] In some embodiments, step A comprises reacting a compound of formula (2) with a compound of formula (3) in the presence of reagents selected from the group consisting of solvents, bases, and mixtures thereof.

[0093] Suitable solvents for use in step A may be selected from the group consisting of amides, such as dimethylformamide (DMF), dimethylacetamide (DMA), 1-methyl-2-pyrrolidone (NMP), 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF), dimethoxyethane (DME), methyl *tert*-butyl ether (MTBE), 1,4-dioxane, and mixtures thereof; esters, such as methyl acetate (MeOAc), ethyl acetate (EtOAc), *n*-propyl acetate (*n*PrOAc), isopropyl acetate (*i*PrOAc), *n*-butyl acetate (*n*BuOAc), *sec*-butyl acetate (*sec*-BuOAc), *tert*-butyl acetate (*t*BuOAc), and isobutyl acetate (*i*BuOAc); halogenated alkanes, such as dichloromethane (DCM), chloroform (CHCl₃), carbon tetrachloride (CCl₄), 1,2-dichloroethane, and mixtures thereof; nitriles, such as acetonitrile (MeCN), propionitrile, benzonitrile, and mixtures thereof; and mixtures thereof.

[0094] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof.

[0095] In some embodiments, the solvent is DMF.

[0096] Suitable bases for use in step A may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts,

such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; and mixtures thereof.

[0097] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0098] In some embodiments, the base is sodium hydride.

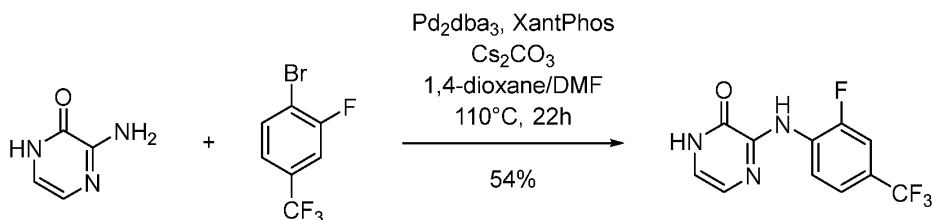
[0099] In some embodiments, step A is carried out in the presence of a solvent and a base. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof. In some embodiments, the solvent is DMF and the base is sodium hydride.

[0100] In some embodiments, step A is carried out from about 0 °C to about 200 °C. In some embodiments, step A is carried out from about 25 °C to about 150 °C. In some embodiments, step A is carried out from about 50 °C to about 100 °C. In some embodiments, step A is carried out from about 75 °C to about 85 °C.

[0101] In some embodiments, the amount of compound of formula (3) to the amount of compound of formula (2) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

[0102] In some embodiments, the amount of base to the amount of compound of formula (2) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

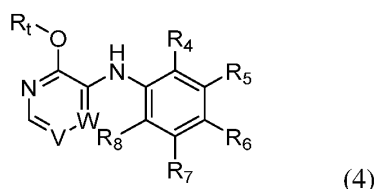
[0103] Step A can also be carried out by Buchwald coupling such as



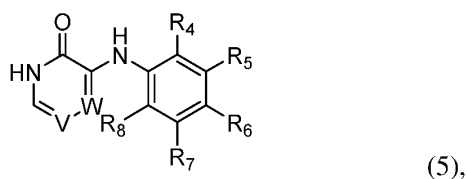
[0104] Step A may proceed by transition metal-catalyzed reaction to produce 3-((2-

fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one in 26-54% yield, such as by palladium catalysis, including such catalysts such as Pd₂(dba)₃/Xantphos, Pd(OAc)₂/Xantphos, XantPhos-Pd-G3, and BrettPhos-Pd-Ge.

[0105] Scheme 1 further comprises a step B, reacting a compound of formula (4)

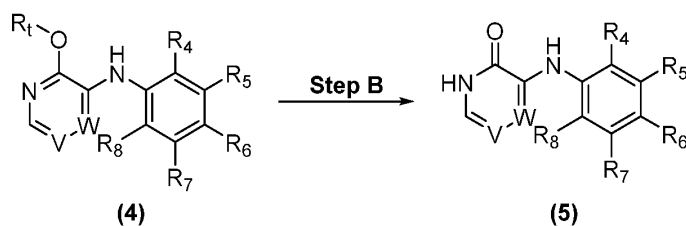


with an acid to produce a compound of formula (5)



wherein R₄, R₅, R₆, R₇, R₈, V, W, and R_t are as defined above.

[0106] Step B is shown below.



[0107] In some embodiments, step B comprises reacting a compound of formula (4) with an acid in the presence of a solvent.

[0108] Suitable solvents for use in step B may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as methanol (MeOH), ethanol (EtOH), *n*-propanol (*n*PrOH), isopropanol (*i*PrOH), ethylene glycol, diethylene glycol, and mixtures thereof; organic acids, such as formic acid, acetic acid (AcOH); water; and mixtures thereof.

[0109] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof.

[0110] In some embodiments, the solvent is AcOH.

[0111] Suitable acids for use in step B may be selected from the group consisting of organic acids, such as formic acid, AcOH, trifluoroacetic acid (TFA), and mixtures thereof; inorganic acids, such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof; and mixtures thereof.

[0112] In some embodiments, the acid is selected from the group consisting of AcOH, TFA, hydrochloric acid, hydrobromic acid, and mixtures thereof.

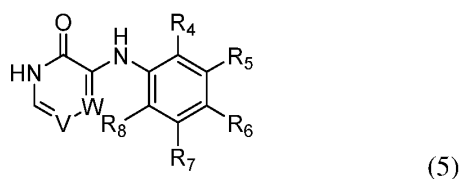
[0113] In some embodiments, the acid is hydrobromic acid.

[0114] In some embodiments, step B is carried out in the presence of a solvent and an acid. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and the acid is selected from the group consisting of AcOH, TFA, hydrochloric acid, hydrobromic acid, and mixtures thereof. In some embodiments, the solvent is AcOH and the acid is hydrobromic acid.

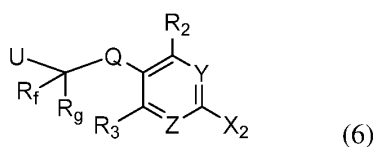
[0115] In some embodiments, step B is carried out from about 0 °C to about 200 °C. In some embodiments, step B is carried out from about 5 °C to about 100 °C. In some embodiments, step B is carried out from about 10 °C to about 50 °C. In some embodiments, step B is carried out from about 15 °C to about 35 °C. In some embodiments, step B is carried out at about room temperature (rt).

[0116] In some embodiments, the amount of acid to the amount of compound of formula (4) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

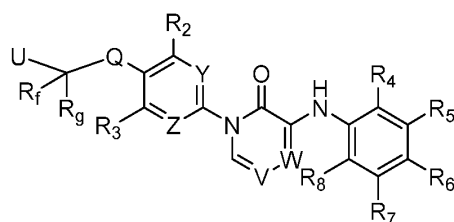
[0117] Scheme 1 further comprises a step 1-C, reacting a compound of formula (5)



with a compound of formula (6)



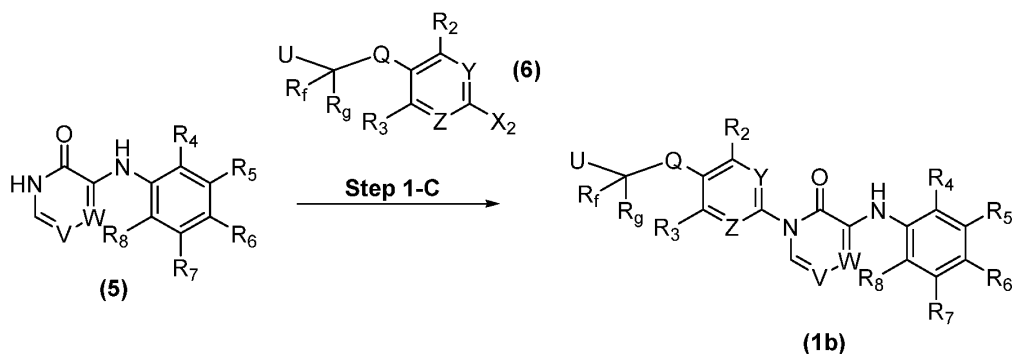
to produce a compound of formula (1b)



(1b),

wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, U, V, W, X₂, Y, Z, R_f, R_g, and R_t are as defined above.

[0118] Step 1-C is shown below.



(1b)

[0119] In some embodiments, step 1-C comprises reacting a compound of formula (5) with a compound of formula (6) in the presence of reagents selected from the group consisting of solvents, copper salts, bases, ligands, and mixtures thereof.

[0120] Suitable solvents for use in step 1-C may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; and mixtures thereof.

[0121] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof.

[0122] In some embodiments, the solvent is selected from the group consisting of DMF, 1,4-dioxane, and mixtures thereof. In some embodiments, the solvent is a mixture of DMF and 1,4-dioxane, or 1,4-dioxane alone.

[0123] Suitable copper salts for use in step 1-C may be selected from the group consisting of copper (I) fluoride (CuF), copper (I) chloride (CuCl), copper (I) bromide (CuBr), copper (I) iodide (CuI), and mixtures thereof.

[0124] In some embodiments, the copper salt is CuI.

[0125] Suitable bases for use in step 1-C may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; phosphates, such as monosodium phosphate (NaH_2PO_4), disodium phosphate (Na_2HPO_4), trisodium phosphate (Na_3PO_4), monopotassium phosphate (KH_2PO_4), dipotassium phosphate (K_2HPO_4), tripotassium phosphate (K_3PO_4), and mixtures thereof; and mixtures thereof.

[0126] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof.

[0127] In some embodiments, the base is tripotassium phosphate (K_3PO_4).

[0128] Suitable ligands for use in step 1-C are selected from the group consisting of diamines, such as *N,N'*-dimethylethylenediamine (*N,N'*-DMEDA), *N,N'*-diisopropylethylenediamine, *N,N'*-dimethyl-6-hexanediamine, and mixtures thereof; phenanthrolines, such as 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, 4,7-dimethoxy-1,10-phenanthroline, and mixtures thereof; bipyridines, such as 2,2'-bipyridine; and mixtures thereof.

[0129] In some embodiments, the ligand is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

[0130] In some embodiments, the ligand is *N,N'*-DMEDA.

[0131] In some embodiments, step 1-C is carried out in the presence of a solvent, a copper salt, a base, and a ligand. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; the copper salt is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; the base is selected from the group consisting of

ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and the ligand is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof. In some embodiments, the solvent is DMF, 1,4-dioxane, and mixtures thereof; the copper salt is CuI; the base is tripotassium phosphate; and the ligand is *N,N'*-DMEDA. In some embodiments, the solvent is a mixture of DMF and 1,4-dioxane, the copper salt is CuI, the base is tripotassium phosphate, and the ligand is *N,N'*-DMEDA.

[0132] In some embodiments, step 1-C is carried out from about 0 °C to about 200 °C. In some embodiments, step 1-C is carried out from about 25 °C to about 150 °C. In some embodiments, step 1-C is carried out from about 50 °C to about 125 °C. In some embodiments, step 1-C is carried out from about 80 °C to about 100 °C.

[0133] In some embodiments, the amount of compound of formula (6) to the amount of compound of formula (5) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

[0134] In some embodiments, the amount of copper salt to the amount of compound of formula (5) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.05 to 20 molar equivalents. In some embodiments, the range is 0.1 to 15 molar equivalents. In some embodiments, the range is 0.1 to 10 molar equivalents. In some embodiments, the range is 0.5 to 5 molar equivalents.

[0135] In some embodiments, the amount of base to the amount of compound of formula (5) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0136] In some embodiments, the amount of ligand to the amount of compound of formula (5) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0137] In some embodiments, step 1-C in Scheme 1 is followed by a dealkylation step 1-D, comprising removing the unsubstituted C₁-C₆ straight or branched alkyl in a compound of formula (1b), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is unsubstituted C₁-C₆ straight or branched alkyl, by reacting the compound of formula (1b)

with at least one dealkylation reagent to produce a compound of formula (1c), wherein U is $-\text{COOR}_e$, $-\text{COSR}_e$, or $-\text{CON}(\text{R}_e)_2$, and wherein R_e is H.

[0138] In some embodiments, step 1-D comprises reacting a compound of formula (1b), wherein U is $-\text{COOR}_e$, $-\text{COSR}_e$, or $-\text{CON}(\text{R}_e)_2$, and wherein R_e is unsubstituted C_1 - C_6 straight or branched alkyl, to form a compound of formula (1c), wherein R_e is H, in the presence of reagents selected from the group consisting of solvents, dealkylation reagents, and mixtures thereof.

[0139] Suitable solvents for use in step 1-D may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl_3 , carbon tetrachloride, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; organic acids, such as formic acid, and AcOH; water; and mixtures thereof.

[0140] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof.

[0141] In some embodiments, the solvent is selected from the group consisting of THF, water, and mixtures thereof. In some embodiments, the solvent is a mixture of water and THF.

[0142] Suitable dealkylation reagents for use in step 1-D may be selected from the group consisting of bases, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; acids, such as formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof; haloalkyl silanes, such as trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof; and mixtures thereof.

[0143] In some embodiments, the dealkylation reagent is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate,

sodium carbonate, potassium carbonate, cesium carbonate, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof.

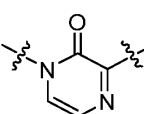
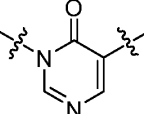
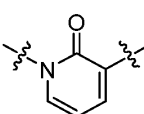
[0144] In some embodiments, the dealkylation reagent is lithium hydroxide.

[0145] In some embodiments, step 1-D is carried out in the presence of a solvent and a dealkylation reagent. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and the dealkylation reagent is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof. In some embodiments, the solvent is THF, water, and mixtures thereof; and the dealkylation reagent is lithium hydroxide. In some embodiments, the solvent is a mixture of water and THF, and the dealkylation reagent is lithium hydroxide.

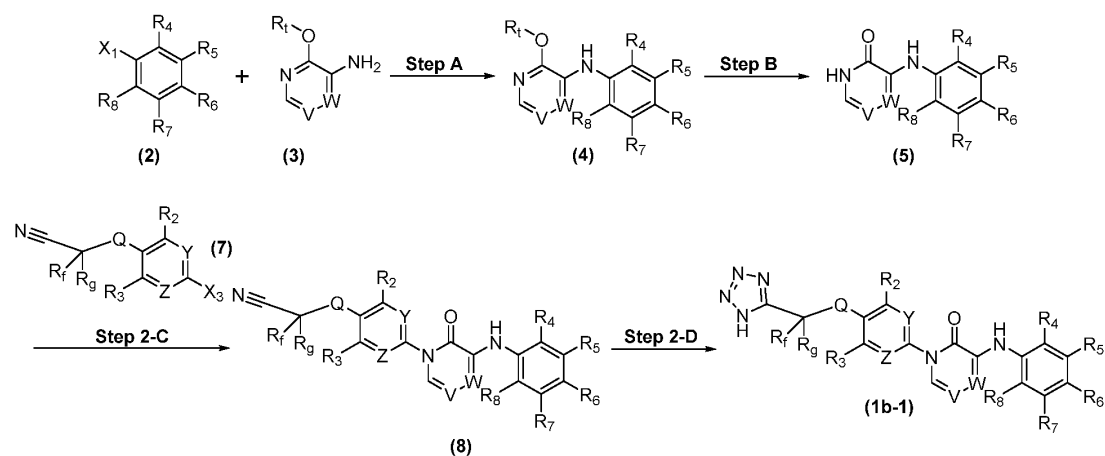
[0146] In some embodiments, step 1-D is carried out from about 0 °C to about 200 °C. In some embodiments, step 1-D is carried out from about 5 °C to about 100 °C. In some embodiments, step 1-D is carried out from about 10 °C to about 50 °C. In some embodiments, step 1-D is carried out from about 15 °C to about 35 °C. In some embodiments, step 1-D is carried out at about rt.

[0147] In some embodiments, the amount of dealkylation reagent to the amount of compound of formula (1b), wherein U is $-\text{COOR}_e$, $-\text{COSR}_e$, or $-\text{CON}(\text{R}_e)_2$, and wherein R_e is unsubstituted C_1 - C_6 straight or branched alkyl, is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0148] Compounds of formula (1) or (1a), wherein  is selected from the group

consisting of , , and , or an enantiomer, racemate, or

pharmaceutically acceptable salt thereof, are also prepared using the process shown in Scheme 2.



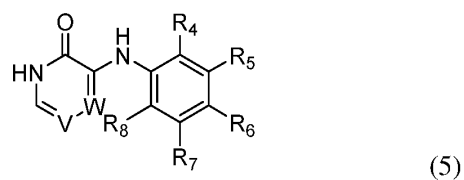
wherein:

R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, V, W, X₁, Y, Z, R_f, R_g, and R_t are as defined above; and X₃ is F, Cl, Br, or I.

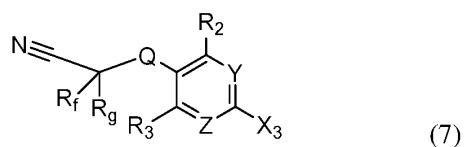
[0149] Scheme 2 comprises a Step A, which is as described above in Scheme 1.

[0150] Scheme 2 further comprises a Step B, which is as described above in Scheme 1.

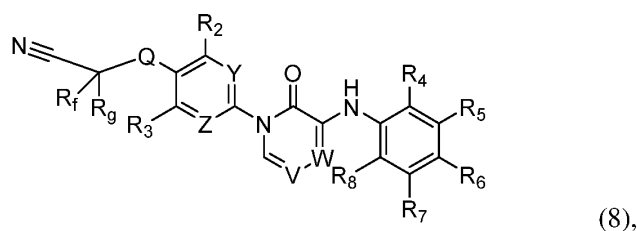
[0151] Scheme 2 further comprises a step 2-C, reacting a compound of formula (5)



with a compound of formula (7)

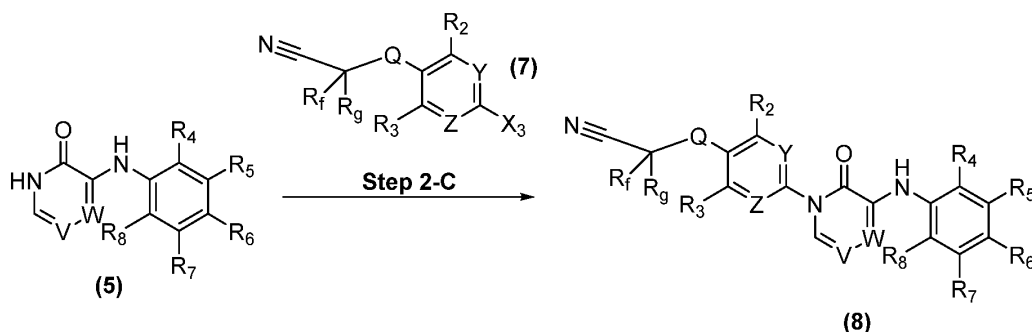


to produce a compound of formula (8)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, V, W, X₃, Y, Z, R_f, R_g, and R_t are as defined above.

[0152] Step 2-C is shown below.



[0153] In some embodiments, step 2-C comprises reacting a compound of formula (5) with a compound of formula (7) in the presence of reagents selected from the group consisting of solvents, copper salts, bases, ligands, and mixtures thereof.

[0154] Suitable solvents for use in step 2-C may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; and mixtures thereof.

[0155] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof.

[0156] In some embodiments, the solvent is selected from the group consisting of DMF, 1,4-dioxane, and mixtures thereof. In some embodiments, the solvent is a mixture of DMF and 1,4-dioxane.

[0157] Suitable copper salts for use in step 2-C may be selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof.

[0158] In some embodiments, the copper salt is CuI.

[0159] Suitable bases for use in step 2-C may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof;

hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; phosphates, such as NaH_2PO_4 , disodium phosphate Na_2HPO_4 , Na_3PO_4 , KH_2PO_4 , K_2HPO_4 , K_3PO_4 , and mixtures thereof; and mixtures thereof.

[0160] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof.

[0161] In some embodiments, the base is tripotassium phosphate.

[0162] Suitable ligands for use in step 2-C are selected from the group consisting of diamines, such as *N,N'*-DMEDA, *N,N'*-diisopropylethylenediamine, *N,N'*-dimethyl-6-hexanediamine, and mixtures thereof; phenanthrolines, such as 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, 4,7-dimethoxy-1,10-phenanthroline, and mixtures thereof; bipyridines, such as 2,2'-bipyridine; and mixtures thereof.

[0163] In some embodiments, the ligand is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

[0164] In some embodiments, the ligand is *N,N'*-DMEDA.

[0165] In some embodiments, step 2-C is carried out in the presence of a solvent, a copper salt, a base, and a ligand. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; the copper salt is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and the ligand is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof. In some embodiments, the solvent is DMF, 1,4-dioxane, and mixtures thereof; the copper salt is CuI; the base is tripotassium phosphate; and the ligand is *N,N'*-DMEDA. In some embodiments, the solvent is a mixture

of DMF and 1,4-dioxane, the copper salt is CuI, the base is tripotassium phosphate, and the ligand is *N,N'*-DMEDA.

[0166] In some embodiments, step 2-C is carried out from about 0 °C to about 200 °C. In some embodiments, step 2-C is carried out from about 25 °C to about 150 °C. In some embodiments, step 2-C is carried out from about 50 °C to about 125 °C. In some embodiments, step 2-C is carried out from about 80 °C to about 100 °C.

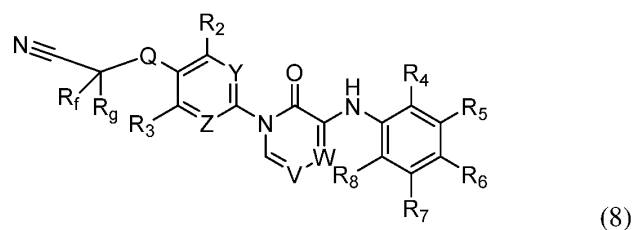
[0167] In some embodiments, the amount of compound of formula (7) to the amount of compound of formula (5) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

[0168] In some embodiments, the amount of copper salt to the amount of compound of formula (5) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.05 to 20 molar equivalents. In some embodiments, the range is 0.1 to 15 molar equivalents. In some embodiments, the range is 0.1 to 10 molar equivalents. In some embodiments, the range is 0.5 to 5 molar equivalents.

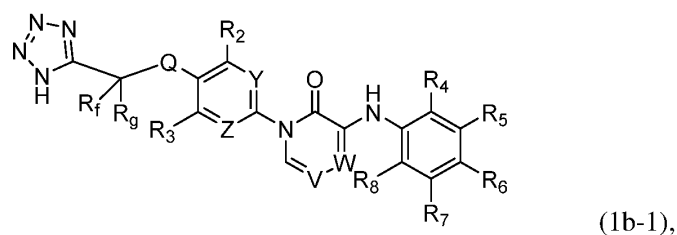
[0169] In some embodiments, the amount of base to the amount of compound of formula (5) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0170] In some embodiments, the amount of ligand to the amount of compound of formula (5) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0171] Scheme 2 further comprises a step 2-D, reacting a compound of formula (8)

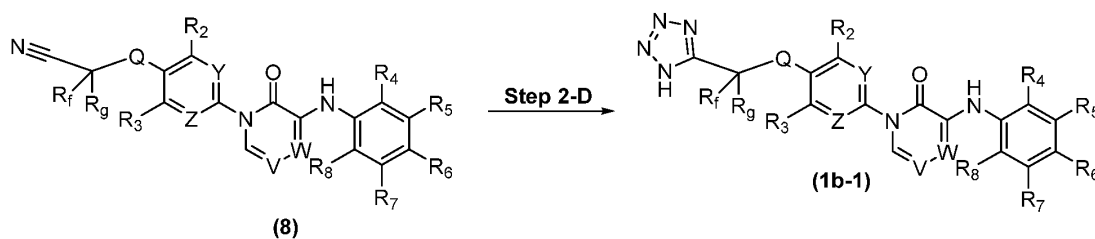


with an azide reagent to produce a compound of formula (1b-1)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, V, W, Y, Z, R_f, R_g, and R_i are as defined above.

[0172] Step 2-D is shown below.



[0173] In some embodiments, step 2-D comprises reacting a compound of formula (8) with an azide reagent in the presence of a solvent.

[0174] Suitable solvents for use in step 2-D may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; aromatic hydrocarbons, such as benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, mesitylene, pseudocumene (1,2,4-trimethylbenzene), hemimellitene (1,2,3-trimethylbenzene), and mixtures thereof; and mixtures thereof.

[0175] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof.

[0176] In some embodiments, the solvent is toluene.

[0177] Suitable azide reagents for use in step 2-D may be selected from the group consisting of lithium azide, sodium azide, potassium azide, silver azide, barium azide, trimethyltin azide, triethyltin azide, tripropyltin azide (tri(*n*-propyl)tin azide), triisopropyltin azide, tributyltin azide (tri(*n*-butyl)tin azide), tri(*sec*-butyl)tin azide, tri(isobutyl)tin azide, tri(*tert*-butyl)tin azide, and mixtures thereof.

[0178] In some embodiments, the azide reagent is selected from the group consisting of trimethyltin azide, triethyltin azide, tripropyltin azide, tributyltin azide, and mixtures thereof.

[0179] In some embodiments, the azide reagent is tributyltin azide.

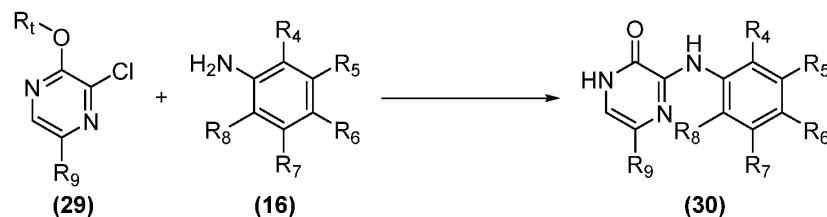
[0180] In some embodiments, step 2-D is carried out in the presence of a solvent and an azide reagent. In some embodiments, the solvent is selected from the group consisting of

DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof; and the azide reagent is selected from the group consisting of trimethyltin azide, triethyltin azide, tripropyltin azide, tributyltin azide, and mixtures thereof. In some embodiments, the solvent is toluene and the azide reagent is tributyltin azide.

[0181] In some embodiments, step 2-D is carried out from about 0 °C to about 200 °C. In some embodiments, step 2-D is carried out from about 25 °C to about 175 °C. In some embodiments, step 2-D is carried out from about 50 °C to about 150 °C. In some embodiments, step 2-D is carried out from about 75 °C to about 125 °C. In some embodiments, step 2-D is carried out from about 100 °C to about 120 °C.

[0182] In some embodiments, the amount of azide reagent to the amount of compound of formula (8) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0183] Alternatively to step 2-A, compounds of formula (30), or an enantiomer, racemate, or pharmaceutically acceptable salt thereof, may be prepared using the process shown in Scheme 3.1.



Scheme 2.1

wherein R_t, R₄, R₅, R₆, R₇, R₈, and R₉ are as defined above.

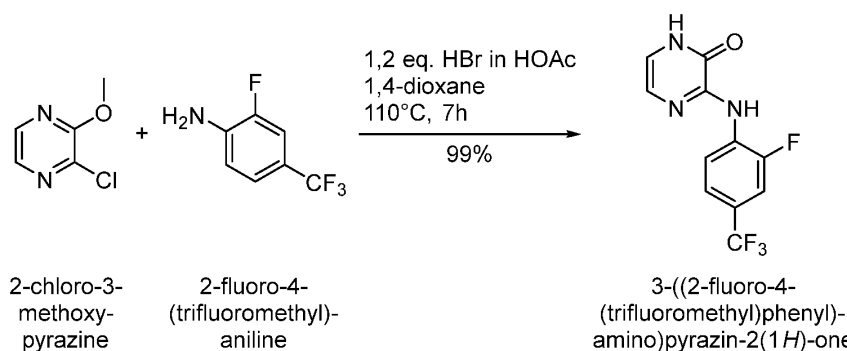
[0184] In an example, a compound of formula (30) was prepared from compounds of formula (29) and formula (16) in the presence of a solvent and an acid.

[0185] In some embodiments, suitable solvents may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; aromatic hydrocarbons, such as benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, mesitylene, pseudocumene (1,2,4-trimethylbenzene), hemimellitene (1,2,3-

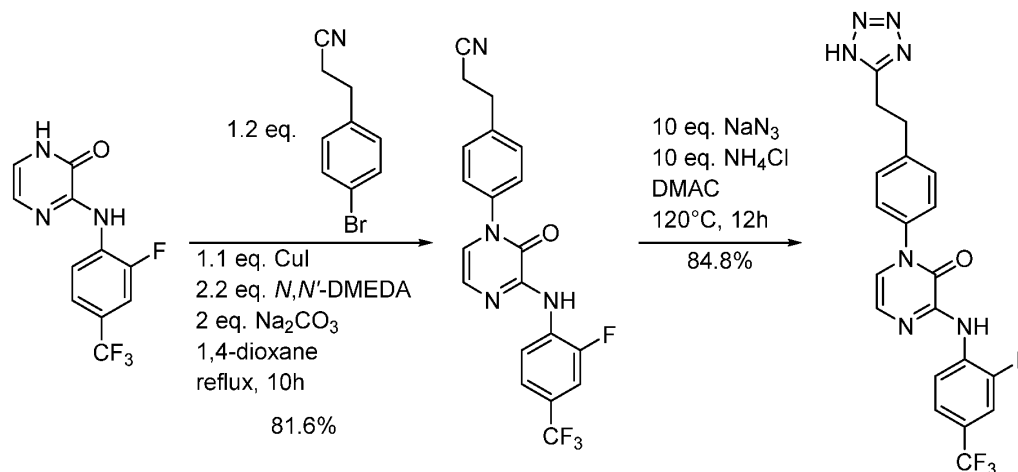
trimethylbenzene), and mixtures thereof; and mixtures thereof.

[0186] In some embodiments, suitable acids for the preparation of compounds of formula (30) may be selected from the group consisting of organic acids, such as formic acid, AcOH, trifluoroacetic acid (TFA), 10-camphorsulfonic acid (10-CSA), and mixtures thereof; inorganic acids, such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof; and mixtures thereof.

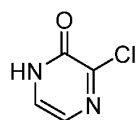
[0187] In an example, 3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one was prepared from 2-chloro-3-methoxypyrazine and 2-fluoro-4-(trifluoromethyl)aniline in the presence of hydrobromic acid (HBr) in HOAc and 1,4-dioxane according to the reaction shown below:



3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one may then be reacted with 3-(4-bromophenyl)propanenitrile to prepare 3-(4-(3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2H)-yl)phenyl)propanenitrile, which may then be reacted with sodium azide to prepare 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (compound 3).



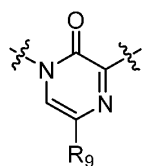
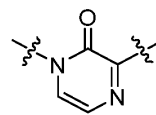
[0188] In another example, a pyrazinone such as 3-chloropyrazin-2(1H)-one, shown below, may be used in the place of 2-chloro-3-methoxypyrazine.

3-chloropyrazin-2(1*H*)-one

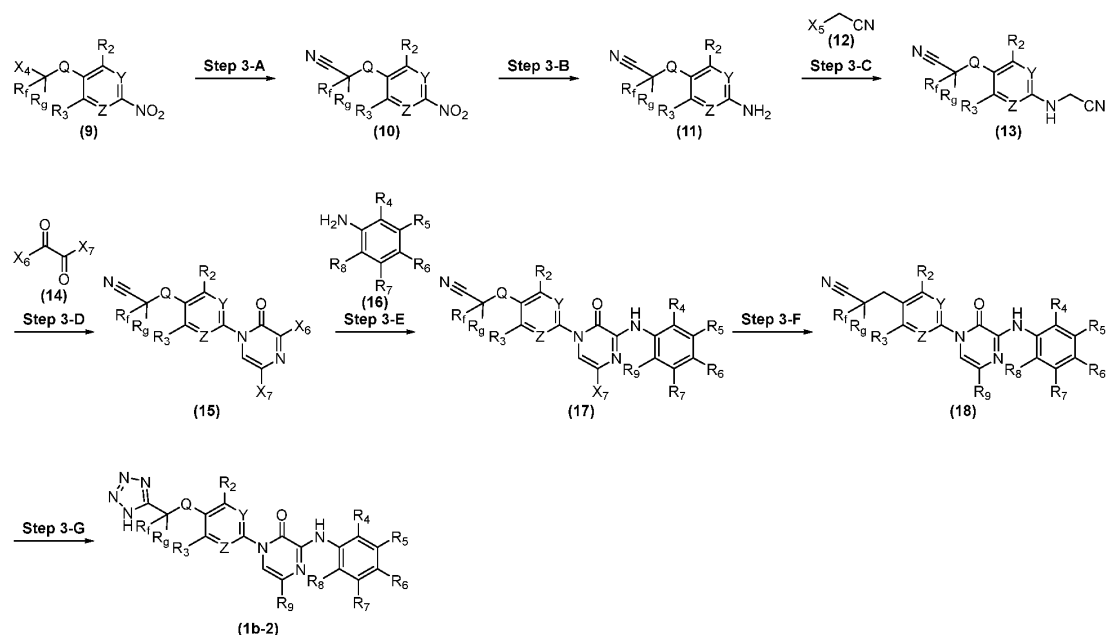
[0189] Compounds of formula (1) or (1a), wherein



is



, or an enantiomer, racemate, or pharmaceutically acceptable salt thereof, are also prepared using the process shown in Scheme 3.



Scheme 3

wherein:

R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , Q , Y , Z , R_f , and R_g , are as defined above;

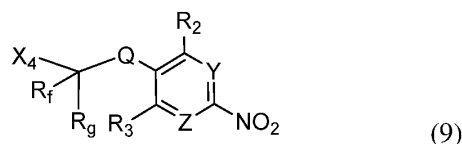
X_4 is F, Cl, Br, or I;

X_5 is F, Cl, Br, I, or a leaving group L_1 that is capable of being substituted by a nucleophile and may be selected from the group consisting of sulfonates such as *p*-toluenesulfonate (TsO[−]) or methanesulfonate (MsO[−]), perfluoroalkylsulfonates such as trifluoromethanesulfonate (−OSO₂CF₃); nitrate (−ONO₂); and phosphates (−OPO(OR)₂), wherein R may be an alkyl group);

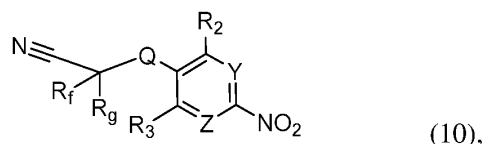
X₆ is F, Cl, Br, or I; and

X₇ is F, Cl, Br, or I.

[0190] Scheme 3 comprises a step 3-A, reacting a compound of formula (9)

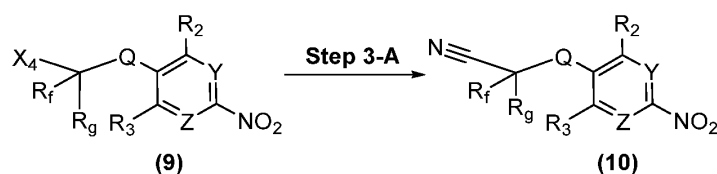


with a cyanide reagent to produce a compound of formula (10)



wherein R₂, R₃, Q, X₄, Y, Z, R_f, and R_g are as defined above.

[0191] Step 3-A is shown below.



[0192] In some embodiments, step 3-A comprises reacting a compound of formula (9) with cyanide reagent in the presence of a solvent.

[0193] Suitable solvents for use in step 3-A may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; organosulfur, such as DMSO; and mixtures thereof.

[0194] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, DMSO, and mixtures thereof.

[0195] In some embodiments, the solvent is DMSO.

[0196] Suitable cyanide reagents for use in step 3-A may be selected from the group consisting of lithium cyanide, sodium cyanide, potassium cyanide, and mixtures thereof.

[0197] In some embodiments, the cyanide reagent is selected from the group consisting of sodium cyanide, potassium cyanide, and mixtures thereof.

[0198] In some embodiments, the cyanide reagent is sodium cyanide.

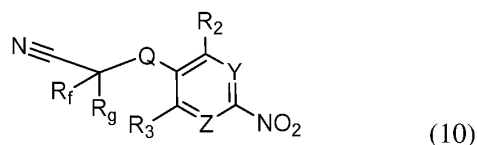
[0199] In some embodiments, step 3-A is carried out in the presence of a solvent and a cyanide reagent.

[0200] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, DMSO, and mixtures thereof; and the cyanide reagent is selected from the group consisting of sodium cyanide, potassium cyanide, and mixtures thereof. In some embodiments, the solvent is DMSO, and the cyanide reagent is sodium cyanide.

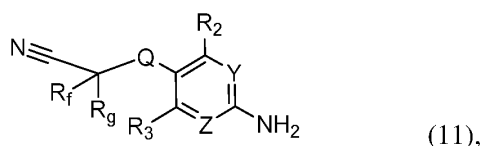
[0201] In some embodiments, step 3-A is carried out from about 0 °C to about 200 °C. In some embodiments, step 3-A is carried out from about 10 °C to about 150 °C. In some embodiments, step 3-A is carried out from about 20 °C to about 100 °C. In some embodiments, step 3-A is carried out from about 30 °C to about 75 °C. In some embodiments, step 3-A is carried out from about 40 °C to about 60 °C.

[0202] In some embodiments, the amount of cyanide reagent to the amount of compound of formula (9) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0203] Scheme 3 further comprises a step 3-B, reacting a compound of formula (10)

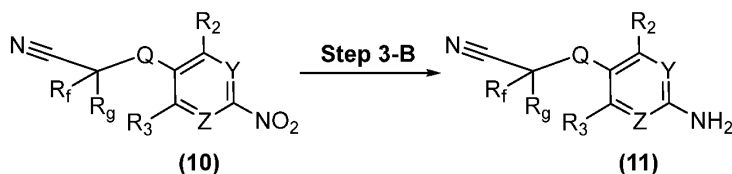


with a hydrogenation reagent to produce a compound of formula (11)



wherein R_2 , R_3 , Q , X_4 , Y , Z , R_f , and R_g are as defined above.

[0204] Step 3-B is shown below.



[0205] In some embodiments, step 3-B comprises reacting a compound of formula (10) with hydrogenation reagent in the presence of a solvent, a catalyst, and mixtures thereof.

[0206] Suitable solvents for use in step 3-B may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers,

such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; and mixtures thereof.

[0207] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof.

[0208] In some embodiments, the solvent is selected from the group consisting of EtOH, EtOAc, and mixtures thereof. In some embodiments, the solvent is a mixture of EtOH and EtOAc.

[0209] Suitable hydrogenation reagents for use in step 3-B may be selected from the group consisting of hydrogen (H₂), formic acid, isopropanol, dihydroanthracene, and mixtures thereof.

[0210] In some embodiments, the hydrogenation reagent is selected from the group consisting of hydrogen (H₂), formic acid, isopropanol, and mixtures thereof.

[0211] In some embodiments, the hydrogenation reagent is hydrogen (H₂).

[0212] Suitable catalysts for use in step 3-B may be selected from homogeneous catalysts, such as chloridotris(triphenylphosphine)rhodium(I) (RhCl(PPh₃)₃, Wilkinson's catalyst); and heterogeneous catalysts, such as platinum(0), palladium(0), rhodium(0), ruthenium(0), Raney Nickel, platinum on carbon (Pt/C), palladium on carbon (Pd/C), rhodium on carbon (Rh/C), ruthenium on carbon (Ru/C), and mixtures thereof; and mixtures thereof.

[0213] In some embodiments, the catalyst is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof.

[0214] In some embodiments, the catalyst is palladium(0).

[0215] In some embodiments, step 3-B is carried out in the presence of a solvent, a hydrogenation reagent, and a catalyst.

[0216] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; the hydrogenation reagent is selected from the group consisting of hydrogen (H₂), formic acid, isopropanol, and mixtures thereof; and the catalyst is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof. In some embodiments, the solvent is selected from the

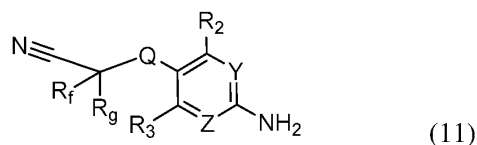
group consisting of EtOH, EtOAc, and mixtures thereof; the hydrogenation reagent is hydrogen (H₂); and the catalyst is palladium(0). In some embodiments, the solvent is a mixture of EtOH and EtOAc; the hydrogenation reagent is hydrogen (H₂); and the catalyst is palladium(0). .

[0217] In some embodiments, step 3-B is carried out from about 0 °C to about 200 °C. In some embodiments, step 3-B is carried out from about 5 °C to about 100 °C. In some embodiments, step 3-B is carried out from about 10 °C to about 50 °C. In some embodiments, step 3-B is carried out from about 15 °C to about 35 °C. In some embodiments, step 3-B is carried out at about rt.

[0218] In some embodiments, the amount of hydrogenation reagent to the amount of compound of formula (10) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0219] In some embodiments, the amount of catalyst to the amount of compound of formula (10) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

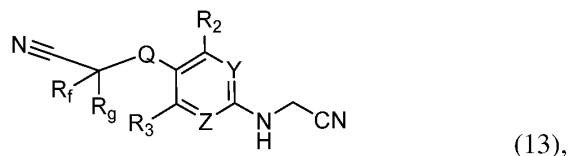
[0220] Scheme 3 further comprises a step 3-C, reacting a compound of formula (11)



with a compound of formula (12)

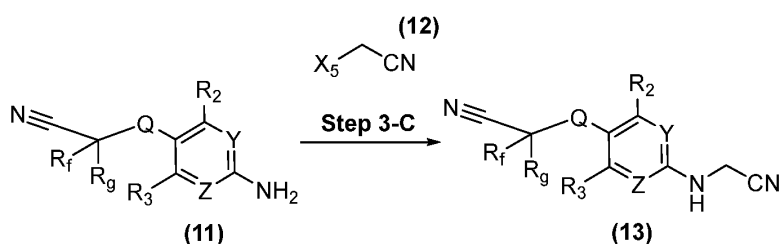


to produce a compound of formula (13)



wherein R₂, R₃, Q, X₅, Y, Z, R_f, and R_g are as defined above.

[0221] Step 3-C is shown below.



[0222] In some embodiments, step 3-C comprises reacting a compound of formula (11) with a compound of formula (12) in the presence of a solvent, a base, and mixtures thereof.

[0223] Suitable solvents for use in step 3-C may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl_3 , CCl_4 , 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; and mixtures thereof.

[0224] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof.

[0225] In some embodiments, the solvent is MeCN.

[0226] Suitable bases for use in step 3-C may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; and mixtures thereof.

[0227] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0228] In some embodiments, the base is potassium carbonate.

[0229] In some embodiments, step 3-C is carried out in the presence of a solvent and a base.

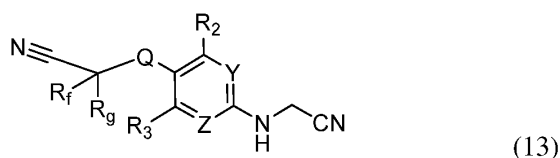
[0230] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof. In some embodiments, the solvent is MeCN, and the base is potassium carbonate.

[0231] In some embodiments, step 3-C is carried out from about 0 °C to about 200 °C. In some embodiments, step 3-C is carried out from about 25 °C to about 100 °C. In some embodiments, step 3-C is carried out from about 50 °C to about 75 °C. In some embodiments, step 3-C is carried out from about 55 °C to about 65 °C.

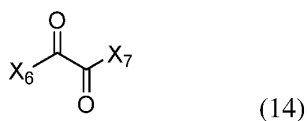
[0232] In some embodiments, the amount of compound of formula (12) to the amount of compound of formula (11) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

[0233] In some embodiments, the amount of base to the amount of compound of formula (11) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

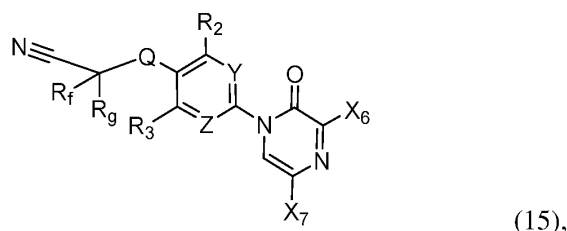
[0234] Scheme 3 further comprises a step 3-D, reacting a compound of formula (13)



with a compound of formula (14)

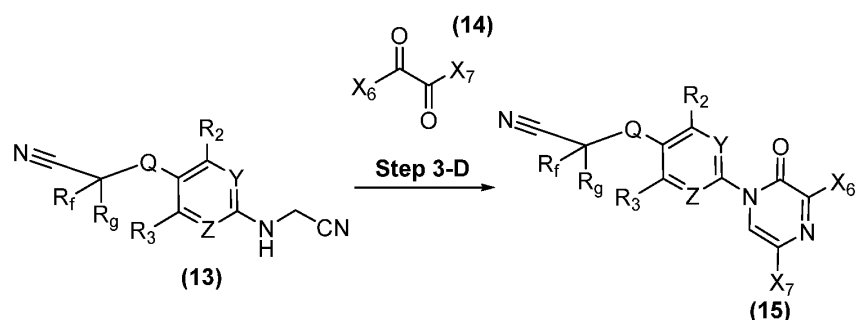


to produce a compound of formula (15)



wherein R_2 , R_3 , Q , X_6 , X_7 , Y , Z , R_f , and R_g are as defined above.

[0235] Step 3-D is shown below.



[0236] In some embodiments, step 3-D comprises reacting a compound of formula (13) with a compound of formula (14) in the presence of a solvent.

[0237] Suitable solvents for use in step 3-D may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl_3 , CCl_4 , 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; aromatic hydrocarbons, such as benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, mesitylene, pseudocumene (1,2,4-trimethylbenzene), hemimellitene (1,2,3-trimethylbenzene), chlorobenzene, and mixtures thereof; and mixtures thereof.

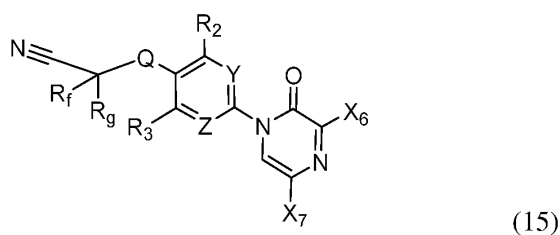
[0238] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof.

[0239] In some embodiments, the solvent is selected from the group consisting of DMF, chlorobenzene, and mixtures thereof. In some embodiments, the solvent is a mixture of DMF and chlorobenzene.

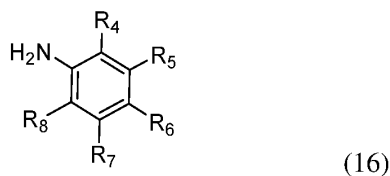
[0240] In some embodiments, step 3-D is carried out from about 0 °C to about 200 °C. In some embodiments, step 3-D is carried out from about 25 °C to about 175 °C. In some embodiments, step 3-D is carried out from about 50 °C to about 150 °C. In some embodiments, step 3-D is carried out from about 75 °C to about 125 °C. In some embodiments, step 3-D is carried out from about 95 °C to about 105 °C.

[0241] In some embodiments, the amount of compound of formula (14) to the amount of compound of formula (13) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

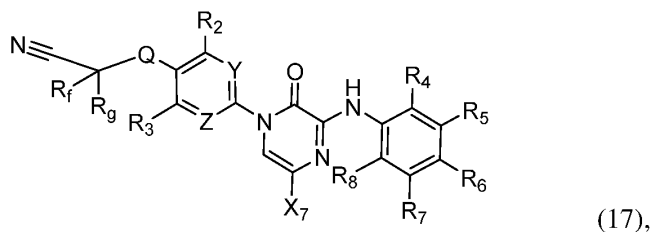
[0242] Scheme 3 further comprises a step 3-E, reacting a compound of formula (15)



with a compound of formula (16)

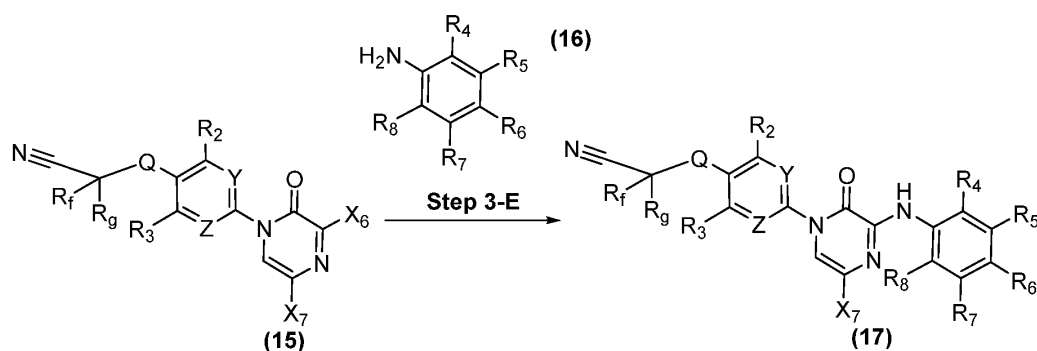


to produce a compound of formula (17)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, X₆, X₇, Y, Z, R_f, and R_g are as defined above.

[0243] Step 3-E is shown below.



[0244] In some embodiments, step 3-E comprises reacting a compound of formula (15) with a compound of formula (16) in the presence of a solvent, a base, and mixtures thereof.

[0245] Suitable solvents for use in step 3-E may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; aromatic hydrocarbons, such as benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, mesitylene, pseudocumene (1,2,4-trimethylbenzene), hemimellitene (1,2,3-trimethylbenzene), chlorobenzene, and mixtures thereof; and mixtures thereof.

[0246] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof.

[0247] In some embodiments, the solvent is THF.

[0248] Suitable bases for use in step 3-E may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium

carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; and mixtures thereof.

[0249] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0250] In some embodiments, the base is sodium hydride.

[0251] In some embodiments, step 3-E is carried out in the presence of a solvent and a base. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof. In some embodiments, the solvent is THF and the base is sodium hydride.

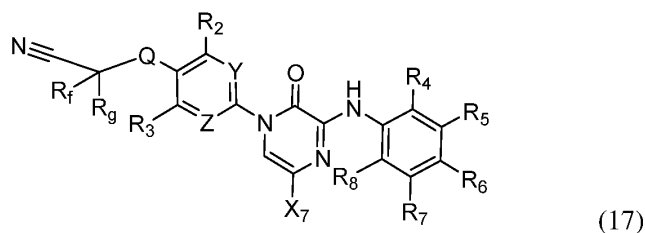
[0252] In other embodiments, step 3-E is carried out in the presence of an acid. In some embodiments the acid is camphorsulfonic acid (CSA). In some embodiments, step 3-E is carried out in the presence of a solvent and an acid. In some embodiments the solvent is 1,4-dioxane.

[0253] In some embodiments, step 3-E is carried out from about 0 °C to about 200 °C. In some embodiments, step 3-E is carried out from about 5 °C to about 100 °C. In some embodiments, step 3-E is carried out from about 10 °C to about 50 °C. In some embodiments, step 3-E is carried out from about 15 °C to about 35 °C. In some embodiments, step 3-E is carried out at about rt.

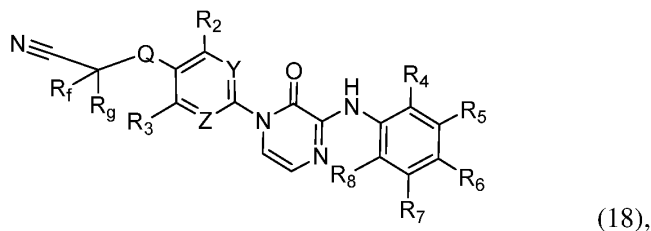
[0254] In some embodiments, the amount of compound of formula (16) to the amount of compound of formula (15) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

[0255] In some embodiments, the amount of base to the amount of compound of formula (15) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0256] Scheme 3 further comprises a step 3-F, reacting a compound of formula (17)

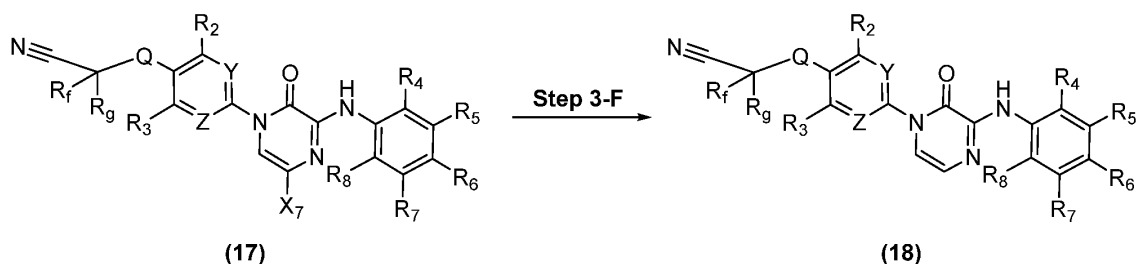


with a hydrogenation reagent to produce a compound of formula (18)



wherein R₂, R₃, Q, X₄, Y, Z, R_f, and R_g are as defined above.

[0257] Step 3-F is shown below.



[0258] In some embodiments, step 3-F comprises reacting a compound of formula (17) with hydrogenation reagent in the presence of a solvent, a catalyst, a base, and mixtures thereof.

[0259] Suitable solvents for use in step 3-F may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; and mixtures thereof.

[0260] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof.

[0261] In some embodiments, the solvent is MeOH.

[0262] Suitable hydrogenation reagents for use in step 3-F may be selected from the group consisting of hydrogen (H₂), formic acid, isopropanol, dihydroanthracene, and mixtures thereof.

[0263] In some embodiments, the hydrogenation reagent is selected from the group consisting of hydrogen (H₂), formic acid, isopropanol, mixtures thereof.

[0264] In some embodiments, the hydrogenation reagent is hydrogen (H₂).

[0265] Suitable catalysts for use in step 3-F may be selected from homogeneous catalysts, such as chloridotris(triphenylphosphine)rhodium(I) (RhCl(PPh₃)₃, Wilkinson's catalyst); and heterogeneous catalysts, such as platinum(0), palladium(0), rhodium(0), ruthenium(0), Raney Nickel, platinum on carbon (Pt/C), palladium on carbon (Pd/C), rhodium on carbon (Rh/C), ruthenium on carbon (Ru/C), and mixtures thereof; and mixtures thereof.

[0266] In some embodiments, the catalyst is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof.

[0267] In some embodiments, the catalyst is Pd/C.

[0268] Suitable bases for use in step 3-F may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; and mixtures thereof.

[0269] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0270] In some embodiments, the base is potassium carbonate.

[0271] In some embodiments, step 3-F is carried out in the presence of a solvent, a hydrogenation reagent, a catalyst, and a base.

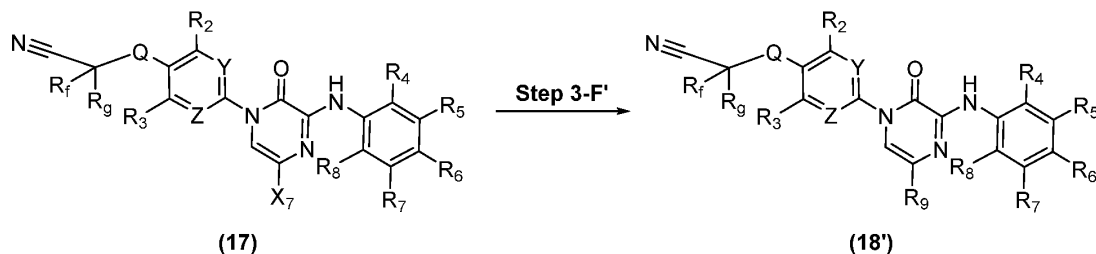
[0272] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; the hydrogenation reagent is selected from the group consisting of hydrogen (H_2), formic acid, isopropanol, mixtures thereof; the catalyst is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof. In some embodiments, the solvent is MeOH; the hydrogenation reagent is hydrogen (H_2); the catalyst is palladium(0); and the base is potassium carbonate.

[0273] In some embodiments, step 3-F is carried out from about 0 °C to about 200 °C. In some embodiments, step 3-F is carried out from about 5 °C to about 100 °C. In some embodiments, step 3-F is carried out from about 10 °C to about 50 °C. In some embodiments, step 3-F is carried out from about 15 °C to about 35 °C. In some embodiments, step 3-F is carried out at about rt.

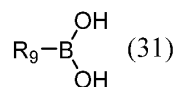
[0274] In some embodiments, the amount of hydrogenation reagent to the amount of compound of formula (17) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0275] In some embodiments, the amount of catalyst to the amount of compound of formula (17) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0276] In some embodiments, the amount of base to the amount of compound of formula (17) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.



[0277] Alternatively, in other embodiments, step 3-F' (also presented herein as step 7-F) comprises reacting a compound of formula (17) a compound of formula (31)



in the presence of a palladium catalyst, a solvent, a base, and mixtures thereof.

[0278] Suitable solvents for use in step 3-F' may be selected from the group consisting of water; amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, *i*BuOAc, and mixtures thereof; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; and mixtures thereof.

[0279] In some embodiments, the solvent is selected from the group consisting of water, DMF, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof.

[0280] In some embodiments, the solvent is a mixture of 1,4-dioxane and water.

[0281] Suitable palladium catalysts for use in step 3-F' may be selected from the group consisting of palladium(II) acetate (Pd(OAc)₂), palladium(II) acetylacetonate (Pd(acac)₂), tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃), dichlorobis(triphenylphosphine)palladium(II) (PdCl₂(PPh₃)₂), tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄), palladium(0) (Pd), palladium(0) on carbon (Pd/C), dichloro(1,1'-bis(di-*tert*-butylphosphino)ferrocene)palladium(II) (Pd(dtbpf)Cl₂), and mixtures thereof.

[0282] In some embodiments, the palladium catalyst is selected from the group consisting of Pd(OAc)₂, Pd(acac)₂, Pd₂(dba)₃, PdCl₂(PPh₃)₂, Pd(PPh₃)₄, Pd(dtbpf)Cl₂, and mixtures thereof.

[0283] In some embodiments, the palladium catalyst is Pd(dtbpf)Cl₂.

[0284] Suitable bases for use in step 3-F' may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide,

lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; and mixtures thereof.

[0285] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0286] In some embodiments, the base is potassium carbonate.

[0287] In some embodiments, step 3-F' is carried out in the presence of a solvent, a compound of formula (31), a palladium catalyst, and a base.

[0288] In some embodiments, the solvent is selected from the group consisting of water, DMF, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; the palladium catalyst is selected from the group consisting of Pd(OAc)₂, Pd(acac)₂, Pd₂(dba)₃, PdCl₂(PPh₃)₂, Pd(PPh₃)₄, Pd(dtbpf)Cl₂, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof. In some embodiments, the solvent is a mixture of 1,4-dioxane and water; the palladium catalyst is Pd(dtbpf)Cl₂; and the base is potassium carbonate.

[0289] In some embodiments, step 3-F' is carried out from about 0 °C to about 200 °C. In some embodiments, step 3-F' is carried out from about 50 °C to about 150 °C. In some embodiments, step 3-F' is carried out from about 75 °C to about 125 °C. In some embodiments, step 3-F' is carried out from about 90 °C to about 110 °C.

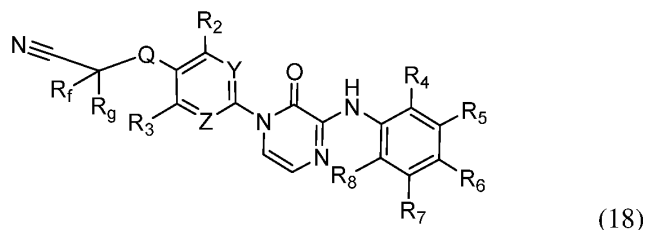
[0290] In some embodiments, the amount of the compound of formula (31) to the amount of compound of formula (17) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0291] In some embodiments, the amount of the palladium catalyst to the amount of compound of formula (17) is in the range of 0.01 to 25 molar equivalents. In some

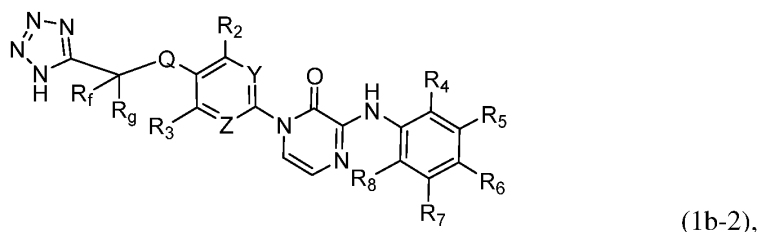
embodiments, the range is 0.05 to 20 molar equivalents. In some embodiments, the range is 0.1 to 15 molar equivalents. In some embodiments, the range is 0.5 to 10 molar equivalents.

[0292] In some embodiments, the amount of the base to the amount of compound of formula (17) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0293] Scheme 3 further comprises a step 3-G, reacting a compound of formula (18)

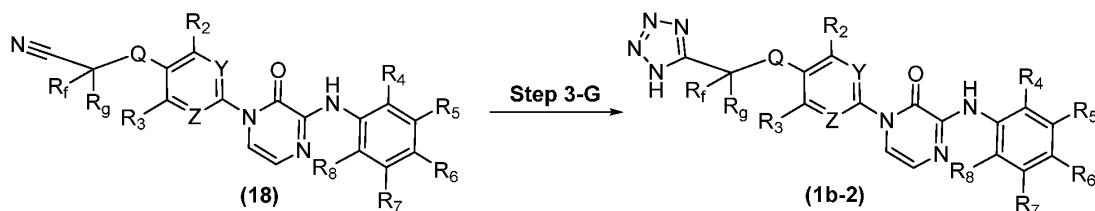


with an azide reagent to produce a compound of formula (1b-2)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, Y, Z, R_f, and R_g are as defined above.

[0294] Step 3-G is shown below.



[0295] In some embodiments, step 3-G comprises reacting a compound of formula (18) with an azide reagent in the presence of a solvent, a salt, and mixtures thereof.

[0296] Suitable solvents for use in step 3-G may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, carbon tetrachloride, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; aromatic hydrocarbons, such as benzene, toluene, *o*-xylene, *m*-

xylene, *p*-xylene, mesitylene, pseudocumene (1,2,4-trimethylbenzene), hemimellitene (1,2,3-trimethylbenzene), and mixtures thereof; and mixtures thereof.

[0297] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof.

[0298] In some embodiments, the solvent is DMF.

[0299] Suitable azide reagents for use in step 3-G may be selected from the group consisting of lithium azide, sodium azide, potassium azide, silver azide, barium azide, trimethyltin azide, triethyltin azide, tripropyltin azide (tri(*n*-propyl)tin azide), triisopropyltin azide, tributyltin azide (tri(*n*-butyl)tin azide), tri(*sec*-butyl)tin azide, tri(isobutyl)tin azide, tri(*tert*-butyl)tin azide, and mixtures thereof.

[0300] In some embodiments, the azide reagent is selected from the group consisting of lithium azide, sodium azide, potassium azide, trimethyltin azide, triethyltin azide, tripropyltin azide, tributyltin azide, and mixtures thereof.

[0301] In some embodiments, the azide reagent is sodium azide.

[0302] Suitable salts for use in step 3-G may be selected from the group consisting of lithium fluoride, sodium fluoride, potassium fluoride, ammonium fluoride, lithium chloride, sodium chloride, potassium chloride, ammonium chloride, lithium bromide, sodium bromide, potassium bromide, ammonium bromide, lithium iodide, sodium iodide, potassium iodide, ammonium iodide, lithium nitrate, sodium nitrate, potassium nitrate, and mixtures thereof.

[0303] In some embodiments, the salt is selected from the group consisting of ammonium fluoride, ammonium chloride, ammonium bromide, ammonium iodide, and mixtures thereof.

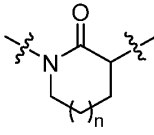
[0304] In some embodiments, the salt is ammonium chloride.

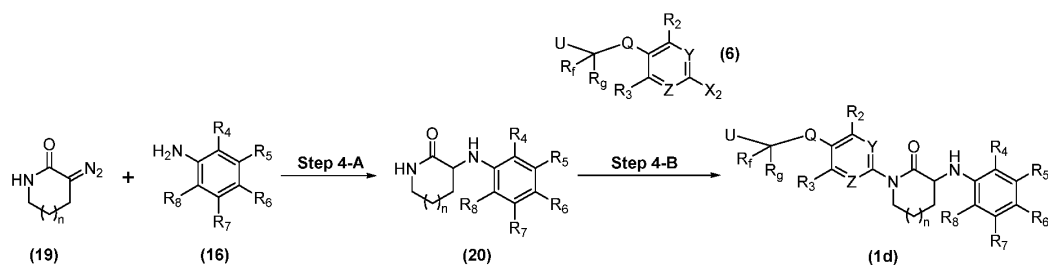
[0305] In some embodiments, step 3-G is carried out in the presence of a solvent, an azide reagent, and a salt. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof; the azide reagent is selected from the group consisting of lithium azide, sodium azide, potassium azide, trimethyltin azide, triethyltin azide, tripropyltin azide, tributyltin azide, and mixtures thereof; and the salt is selected from the group consisting of ammonium fluoride, ammonium chloride, ammonium bromide, ammonium iodide, and mixtures thereof. In some embodiments, the solvent is DMF, the azide reagent is sodium azide, and the salt is ammonium chloride.

[0306] In some embodiments, step 3-G is carried out from about 0 °C to about 200 °C. In some embodiments, step 3-G is carried out from about 50 °C to about 175 °C. In some embodiments, step 3-G is carried out from about 75 °C to about 150 °C. In some embodiments, step 3-G is carried out from about 100 °C to about 140 °C. In some embodiments, step 3-G is carried out from about 125 °C to about 135 °C.

[0307] In some embodiments, the amount of azide reagent to the amount of compound of formula (18) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0308] In some embodiments, the amount of salt to the amount of compound of formula (18) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

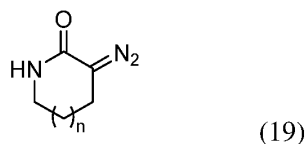
[0309] Compounds of formula (1) or (1a), wherein  is , or an enantiomer, racemate, or pharmaceutically acceptable salt thereof, are prepared using the process shown in Scheme 4.



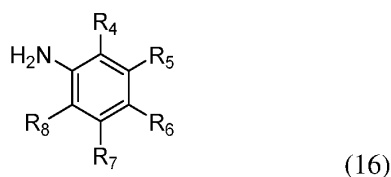
wherein

R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, U, X₂, Y, Z, R_f, R_g, and n are as defined above.

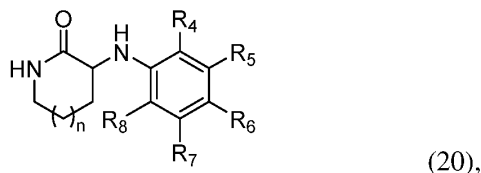
[0310] Scheme 4 comprises a step 4-A, reacting a compound of formula (19)



with a compound of formula (16)

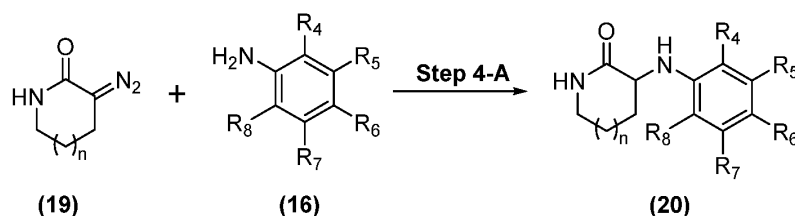


to produce a compound of formula (20)



wherein R₄, R₅, R₆, R₇, R₈, and n are as defined above.

[0311] Step 4-A is shown below.



[0312] In some embodiments, step 4-A comprises reacting a compound of formula (19) with a compound of formula (16) in the presence of reagents selected from the group consisting of solvents, catalysts, and mixtures thereof.

[0313] Suitable solvents for use in step 4-A may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; and mixtures thereof.

[0314] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof.

[0315] In some embodiments, the solvent is DCM.

[0316] Suitable catalysts for step 4-A may be selected from the group consisting of rhodium(II) acetate dimer (Rh₂(OAc)₄), rhodium(III) acetate (Rh(OAc)₃), palladium(II) acetate (Pd(OAc)₂), rhodium(III) acetylacetonate (Rh(acac)₃), ruthenium(III) acetylacetonate (Ru(acac)₃), palladium(II) acetylacetonate (Pd(acac)₂), nickel(II) acetylacetonate (Ni(acac)₂), platinum(II) acetylacetonate (Pt(acac)₂), tris(dibenzylideneacetone)dipalladium(0)

(Pd₂(dba)₃), dichlorobis(triphenylphosphine)palladium(II) (PdCl₂(PPh₃)₂), tetrakis(triphenylphosphine) palladium(0) (Pd(PPh₃)₄), palladium(0) (Pd), palladium(0) on carbon (Pd/C), and mixtures thereof.

[0317] In some embodiments, the catalyst is selected from the group consisting of Rh₂(OAc)₄, Rh(OAc)₃, Rh(acac)₃, and mixtures thereof.

[0318] In some embodiments, the catalyst is Rh₂(OAc)₄.

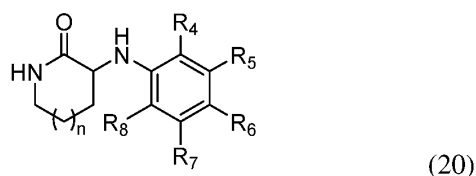
[0319] In some embodiments, step 4-A is carried out in the presence of a solvent and a catalyst.

[0320] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; and the catalyst is selected from the group consisting of Rh₂(OAc)₄, Rh(OAc)₃, Rh(acac)₃, and mixtures thereof. In some embodiments, the solvent is DCM, and the catalyst is Rh₂(OAc)₄.

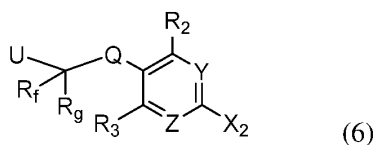
[0321] In some embodiments, step 4-A is carried out from about 0 °C to about 200 °C. In some embodiments, step 4-A is carried out from about 5 °C to about 100 °C. In some embodiments, step 4-A is carried out from about 10 °C to about 50 °C. In some embodiments, step 4-A is carried out from about 15 °C to about 35 °C. In some embodiments, step 4-A is carried out at about rt.

[0322] In some embodiments, the amount of catalyst to the amount of compound of formula (19) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.05 to 20 molar equivalents. In some embodiments, the range is 0.1 to 15 molar equivalents. In some embodiments, the range is 0.1 to 10 molar equivalents. In some embodiments, the range is 0.5 to 5 molar equivalents.

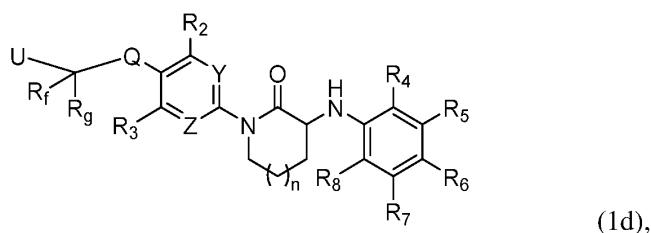
[0323] Scheme 4 further comprises a step 4-B, reacting a compound of formula (20)



with a compound of formula (6)

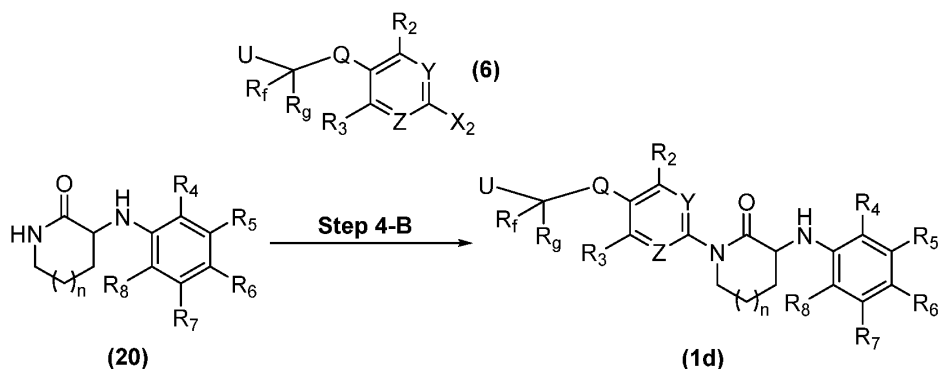


to produce a compound of formula (1c)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, U, X₂, Y, Z, R_f, R_g, and n are as defined above.

[0324] Step 4-B is shown below.



[0325] In some embodiments, step 4-B comprises reacting a compound of formula (20) with a compound of formula (6) in the presence of reagents selected from the group consisting of solvents, copper salts, bases, ligands, and mixtures thereof.

[0326] Suitable solvents for use in step 4-B may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; and mixtures thereof.

[0327] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof.

[0328] In some embodiments, the solvent is selected from the group consisting of DMF, 1,4-dioxane, and mixtures thereof. In some embodiments, the solvent is a mixture of DMF and 1,4-dioxane.

[0329] Suitable copper salts for use in step 4-B may be selected from the group consisting CuF, CuCl, CuBr, CuI, and mixtures thereof.

[0330] In some embodiments, the copper salt is CuI.

[0331] Suitable bases for use in step 4-B may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; phosphates, such as NaH_2PO_4 , Na_2HPO_4 , Na_3PO_4 , KH_2PO_4 , K_2HPO_4 , K_3PO_4 , and mixtures thereof; and mixtures thereof.

[0332] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, Na_3PO_4 , K_3PO_4 , and mixtures thereof.

[0333] In some embodiments, the base is K_3PO_4 .

[0334] Suitable ligands for use in step 4-B are selected from the group consisting of diamines, such as *N,N'*-dimethylethylenediamine (*N,N'*-DMEDA), *N,N'*-diisopropylethylenediamine, *N,N'*-dimethyl-6-hexanediamine, and mixtures thereof; phenanthrolines, such as 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, 4,7-dimethoxy-1,10-phenanthroline, and mixtures thereof; bipyridines, such as 2,2'-bipyridine; organophosphorous compounds, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 2,3-Bis(diphenylphosphino)butane (Chiraphos), 4,5-Bis(diphenyl phosphino)-9,9-dimethylxanthene (Xanthphos), Bis[(2-diphenylphosphino)phenyl] ether (DPEphos), 4,4,4',6,6'-Hexamethyl-2,2'-spirobichromane-8,8'-diylbis(diphenylphosphane) (SPANphos), 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane) (SEGPhos), 1,2-Bis(2,5-dimethylphospholano)benzene (Me-DuPhos), 1,1-Bis(diphenylphosphino)methane (dppm), 1,2-Bis(dimethylphosphino) ethane (dmpe), 1,2-Bis(diisopropylphosphino)ethane (dippe), 1,2-Bis(diphenylphosphino) benzene (dppbz), 1,2-Bis(diphenylphosphino)ethane (dppe), Bis(dicyclohexylphosphino)ethane (dcpe), 1,3-Bis(diphenylphosphino)propane (dppp), 1,4-Bis(diphenylphosphino)butane (dppb), and mixtures thereof; and mixtures thereof.

[0335] In some embodiments, the ligand is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, BINAP, Chiraphos, Xanthphos, DPEphos, SPANphos, Me-DuPhos, dppm, and mixtures thereof.

[0336] In some embodiments, the ligand is *N,N'*-DMEDA.

[0337] In some embodiments, step 4-B is carried out in the presence of a solvent, a copper salt, a base, and a ligand. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; the copper salt is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and the ligand is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof. In some embodiments, the solvent is DMF, 1,4-dioxane, and mixtures thereof; the copper salt is CuI; the base is tripotassium phosphate; and the ligand is *N,N'*-DMEDA. In some embodiments, the solvent is a mixture of DMF and 1,4-dioxane, the copper salt is CuI, the base is tripotassium phosphate, and the ligand is *N,N'*-DMEDA.

[0338] In some embodiments, step 4-B is carried out from about 0 °C to about 200 °C. In some embodiments, step 4-B is carried out from about 25 °C to about 150 °C. In some embodiments, step 4-B is carried out from about 50 °C to about 125 °C. In some embodiments, step 4-B is carried out from about 80 °C to about 100 °C.

[0339] In some embodiments, the amount of compound of formula (6) to the amount of compound of formula (20) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

[0340] In some embodiments, the amount of copper salt to the amount of compound of formula (20) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.05 to 20 molar equivalents. In some embodiments, the range is 0.1 to 15 molar equivalents. In some embodiments, the range is 0.1 to 10 molar equivalents. In some embodiments, the range is 0.5 to 5 molar equivalents.

[0341] In some embodiments, the amount of base to the amount of compound of formula (20) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0342] In some embodiments, the amount of ligand to the amount of compound of formula (20) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0343] In some embodiments, step 4-B in Scheme 4 is followed by a dealkylation step 4-C, comprising removing the unsubstituted C₁-C₆ straight or branched alkyl of R_e in a compound of formula (1d), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, by reacting the compound of formula (1d) with at least one dealkylation reagent to produce a compound of formula (1e), wherein R_e is H.

[0344] In some embodiments, step 4-C comprises reacting a compound of formula (1d), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is unsubstituted C₁-C₆ straight or branched alkyl, to form a compound of formula (1e), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is H, in the presence of reagents selected from the group consisting of solvents, dealkylation reagents, and mixtures thereof.

[0345] Suitable solvents for use in step 4-C may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; organic acids, such as formic acid, AcOH; water; and mixtures thereof.

[0346] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof.

[0347] In some embodiments, the solvent is selected from the group consisting of THF, water, and mixtures thereof. In some embodiments, the solvent is a mixture of water and THF.

[0348] Suitable dealkylation reagents for use in step 4-C may be selected from the group consisting of bases, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; acids, such as formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid,

hydrobromic acid, hydroiodic acid, and mixtures thereof; haloalkyl silanes, such as trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof; and mixtures thereof.

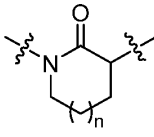
[0349] In some embodiments, the dealkylation reagent is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof.

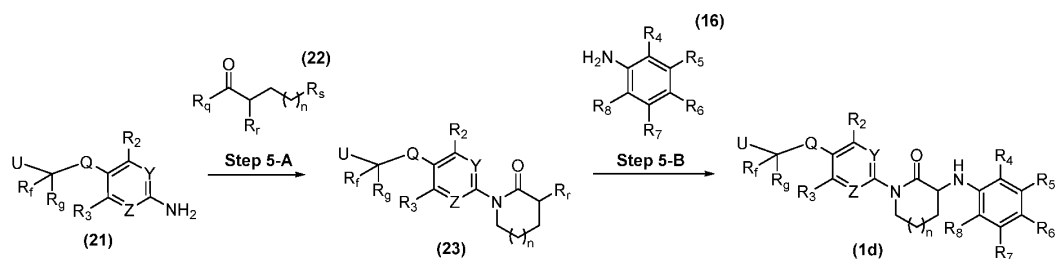
[0350] In some embodiments, the dealkylation reagent is lithium hydroxide.

[0351] In some embodiments, step 4-C is carried out in the presence of a solvent and a dealkylation reagent. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and the dealkylation reagent is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof. In some embodiments, the solvent is THF, water, and mixtures thereof; and the dealkylation reagent is lithium hydroxide. In some embodiments, the solvent is a mixture of water and THF, and the dealkylation reagent is lithium hydroxide.

[0352] In some embodiments, step 4-C is carried out from about 0 °C to about 200 °C. In some embodiments, step 4-C is carried out from about 5 °C to about 100 °C. In some embodiments, step 4-C is carried out from about 10 °C to about 50 °C. In some embodiments, step 4-C is carried out from about 15 °C to about 35 °C. In some embodiments, step 4-C is carried out at about rt.

[0353] In some embodiments, the amount of dealkylation reagent to the amount of compound of formula (1d), wherein U is $-\text{COOR}_e$, $-\text{COSR}_e$, or $-\text{CON}(\text{R}_e)_2$, and wherein R_e is unsubstituted C_1 - C_6 straight or branched alkyl, is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0354] Compounds of formula (1) or (1a), wherein  is , or an enantiomer, racemate, or pharmaceutically acceptable salt thereof, are prepared using the process shown in Scheme 5.



Scheme 5

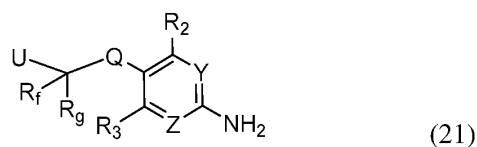
wherein:

R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , Q , U , Y , Z , R_f , R_g , and n , are as defined above;

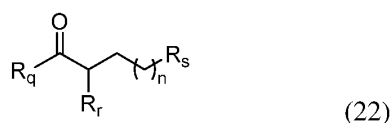
R_q , R_r , and R_s , are independently F, Cl, Br, I, OR_h , SR_h , or a leaving group L_2 that is capable of being substituted by a nucleophile and may be selected from the group consisting of sulfonates such as *p*-toluenesulfonate (TsO^-) or methanesulfonate (MsO^-), perfluoroalkylsulfonates such as trifluoromethanesulfonate ($-OSO_2CF_3$); nitrate ($-ONO_2$); and phosphates ($-OPO(OR_2)$, wherein R may be an alkyl group); and

R_h is H or an unsubstituted C_1 - C_6 straight or branched alkyl.

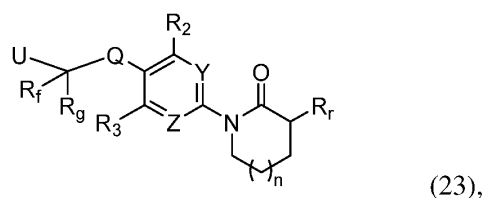
[0355] Scheme 5 comprises a step 5-A, reacting a compound of formula (21)



with a compound of formula (22)

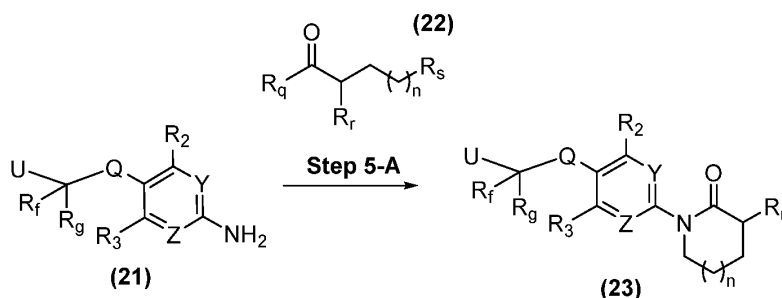


to produce a compound of formula (23)



wherein R_2 , R_3 , Q , U , Y , Z , R_f , R_g , R_q , R_r , R_s , and n are as defined above.

[0356] Step 5-A is shown below.



[0357] In some embodiments, step 5-A comprises reacting a compound of formula (21) with a compound of formula (22) in the presence of reagents selected from the group consisting of solvents, bases, and mixtures thereof.

[0358] Suitable solvents for use in step 5-A may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; and mixtures thereof.

[0359] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof.

[0360] In some embodiments, the solvent is MeCN.

[0361] Suitable bases for use in step 5-A may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; phosphates, such as monosodium phosphate, disodium phosphate, trisodium phosphate,

monopotassium phosphate, dipotassium phosphate, tripotassium phosphate, and mixtures thereof; and mixtures thereof.

[0362] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof.

[0363] In some embodiments, the base is selected from the group consisting of sodium hydride, tripotassium phosphate, and mixtures thereof. In some embodiments, the base is a mixture of sodium hydride and tripotassium phosphate.

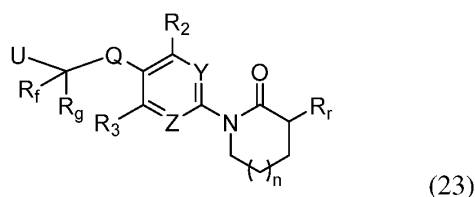
[0364] In some embodiments, step 5-A is carried out in the presence of a solvent and a base. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof. In some embodiments, the solvent is MeCN and the base is selected from the group consisting of sodium hydride, tripotassium phosphate, and mixtures thereof. In some embodiments, the solvent is MeCN and the base is a mixture of sodium hydride and tripotassium phosphate.

[0365] In some embodiments, step 5-A is carried out from about 0 °C to about 200 °C. In some embodiments, step 5-A is carried out from about 5 °C to about 100 °C. In some embodiments, step 5-A is carried out from about 10 °C to about 50 °C. In some embodiments, step 5-A is carried out from about 15 °C to about 35 °C. In some embodiments, step 5-A is carried out at about rt.

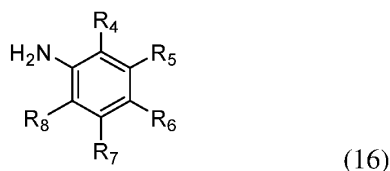
[0366] In some embodiments, the amount of compound of formula (22) to the amount of compound of formula (21) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

[0367] In some embodiments, the amount of base to the amount of compound of formula (21) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

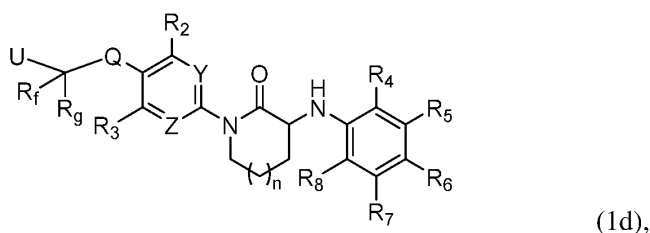
[0368] Scheme 5 further comprises a step 5-B, reacting a compound of formula (23)



with a compound of formula (16)

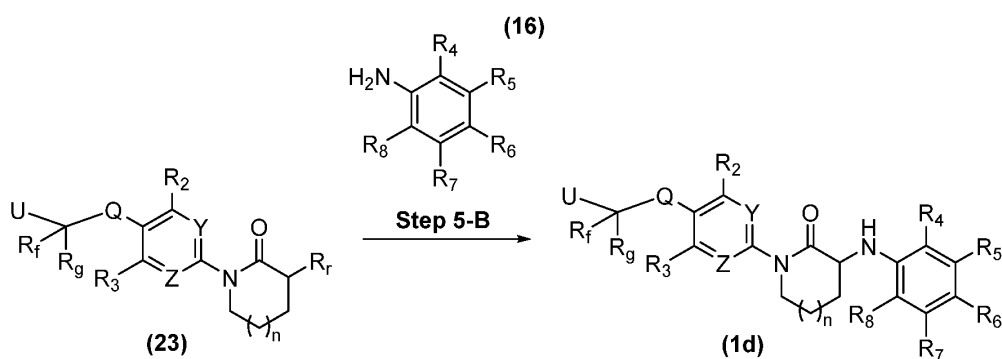


to produce a compound of formula (1d)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, U, Y, Z, R_f, R_g, R_r, and n, are as defined above.

[0369] Step 5-B is shown below.



[0370] In some embodiments, step 5-B comprises reacting a compound of formula (23) with a compound of formula (16) in the presence of reagents selected from the group consisting of solvents, bases, and mixtures thereof.

[0371] Suitable solvents for use in step 5-B may be selected from the group consisting of amides, such as DMF, DMA, NMP), 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; and mixtures thereof.

[0372] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof.

[0373] In some embodiments, the solvent is DMF.

[0374] Suitable bases for use in step 5-B may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; and mixtures thereof.

[0375] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0376] In some embodiments, the base is sodium hydride.

[0377] In some embodiments, step 5-B is carried out in the presence of a solvent and a base. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof. In some embodiments, the solvent is DMF and the base is sodium hydride.

[0378] In some embodiments, step 5-B is carried out from about -25 °C to about 100 °C. In some embodiments, step 5-B is carried out from about -20 °C to about 50 °C. In some embodiments, step 5-B is carried out from about -15 °C to about 25 °C. In some embodiments, step 5-B is carried out from about -10 °C to about 10 °C. In some embodiments, step 5-B is carried out from about -5 °C to about 5 °C.

[0379] In some embodiments, the amount of compound of formula (16) to the amount of compound of formula (23) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

[0380] In some embodiments, the amount of base to the amount of compound of formula (23) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0381] In some embodiments, step 5-B in Scheme 5 is followed by a dealkylation step 5-C, comprising removing the unsubstituted C₁-C₆ straight or branched alkyl of R_e in a compound of formula (1d), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, by reacting the compound of formula (1d) with at least one dealkylation reagent to produce a compound of formula (1e), wherein R_e is H.

[0382] In some embodiments, step 5-C comprises reacting a compound of formula (1d), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is unsubstituted C₁-C₆ straight or branched alkyl, to form a compound of formula (1e), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is H, in the presence of reagents selected from the group consisting of solvents, dealkylation reagents, and mixtures thereof.

[0383] Suitable solvents for use in step 5-C may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; organic acids, such as formic acid, AcOH; water; and mixtures thereof.

[0384] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof.

[0385] In some embodiments, the solvent is selected from the group consisting of THF, water, and mixtures thereof. In some embodiments, the solvent is a mixture of water and THF.

[0386] Suitable dealkylation reagents for use in step 5-C may be selected from the group consisting of bases, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium *tert*-butoxide,

sodium tert-butoxide, potassium tert-butoxide, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; acids, such as formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof; haloalkyl silanes, such as trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof; and mixtures thereof.

[0387] In some embodiments, the dealkylation reagent is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof.

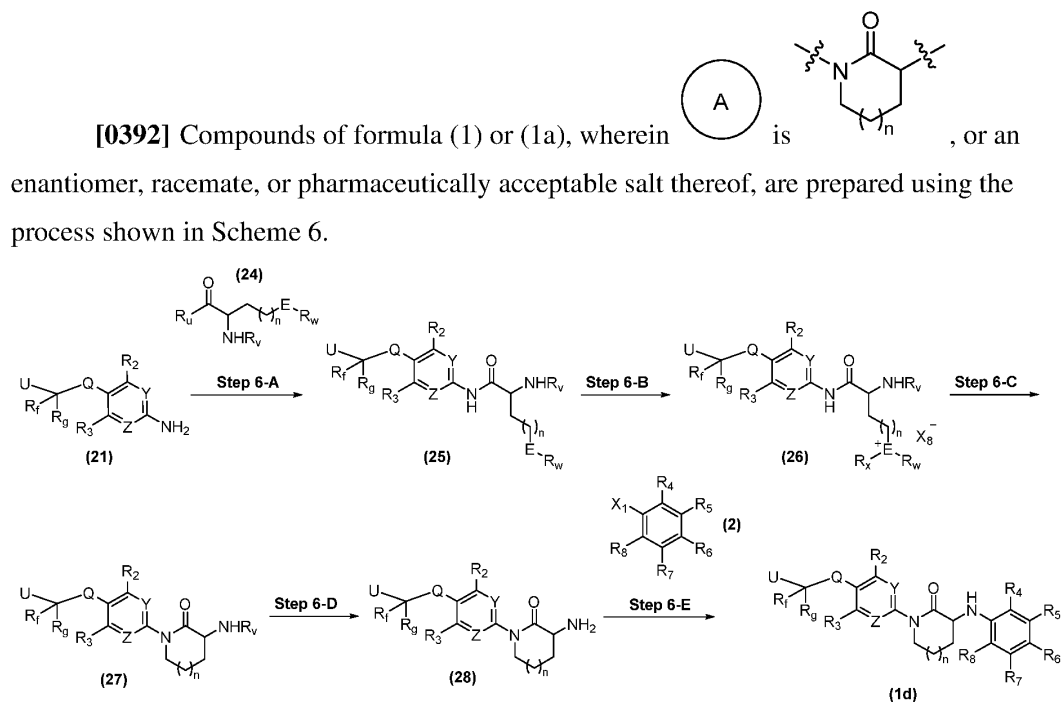
[0388] In some embodiments, the dealkylation reagent is lithium hydroxide.

[0389] In some embodiments, step 5-C is carried out in the presence of a solvent and a dealkylation reagent. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and the dealkylation reagent is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof. In some embodiments, the solvent is THF, water, and mixtures thereof; and the dealkylation reagent is lithium hydroxide. In some embodiments, the solvent is a mixture of water and THF, and the dealkylation reagent is lithium hydroxide.

[0390] In some embodiments, step 5-C is carried out from about 0 °C to about 200 °C. In some embodiments, step 5-C is carried out from about 5 °C to about 100 °C. In some embodiments, step 5-C is carried out from about 10 °C to about 50 °C. In some embodiments, step 5-C is carried out from about 15 °C to about 35 °C. In some embodiments, step 5-C is carried out at about rt.

[0391] In some embodiments, the amount of dealkylation reagent to the amount of compound of formula (1d), wherein U is $-\text{COOR}_e$, $-\text{COSR}_e$, or $-\text{CON}(\text{R}_e)_2$, and wherein R_e

is unsubstituted C₁-C₆ straight or branched alkyl, is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.



Scheme 6

wherein:

R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, U, Y, Z, R_f, R_g, and n, are as defined above;

X₈ is F, Cl, Br, or I;

E is O or S;

R_u is F, Cl, Br, I, OR_p, or SR_p;

R_v is unsubstituted C₁-C₆ straight or branched alkyl, or a protecting group selected from a variety of groups, including but not limited to those mentioned in Greene, Chapter 7: Protection for the Amino Group; and

R_w is H or unsubstituted C₁-C₆ straight or branched alkyl;

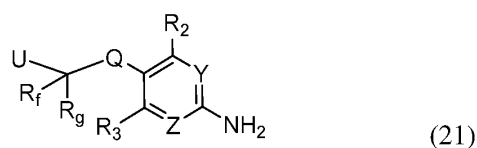
R_x is H or unsubstituted C₁-C₆ straight or branched alkyl; and

R_p is H or unsubstituted C₁-C₆ straight or branched alkyl.

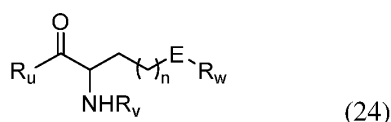
[0393] Suitable protecting groups R_v may be selected from *N*-alkylenearyls, such as a benzyl (Bn) group, a (diphenyl)methylene group, a trityl (triphenylmethyl, Tr) group, or a (4-methoxyphenyl)diphenylmethylene (methoxytrityl, MMT) group; amides, such as a formyl group, an acetyl (Ac) group, or a benzoyl (Bz) group; carbamates, such as a *tert*-

butyloxycarbonyl (BOC) group, a carbobenzyloxy (Cbz) group, a *p*-methoxybenzylcarbonyl (Moz) group, or a 9-fluorenylmethyloxycarbonyl (Fmoc) group; and N—P and N-sulfonyl protecting groups, such as a dialkyl phosphoramidate group, a methanesulfonyl (mesyl, Ms) group, or a *p*-toluenesulfonyl (tosyl, Ts) group. The protecting group in R_v may be introduced by methods known in the art whereby a compound of formula (24), wherein R_v is H, is reacted with a corresponding protecting group providing reagent to deliver a protected amine. Suitable reagents to be used for introducing the protecting group are known in the art and are commercially available. For example, di-*tert*-butyl-dicarbonate may be used for introducing a *tert*-butyloxycarbonyl (BOC) group.

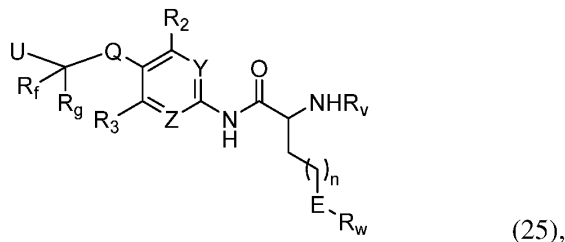
[0394] Scheme 6 comprises a step 6-A, reacting a compound of formula (21)



with a compound of formula (24)

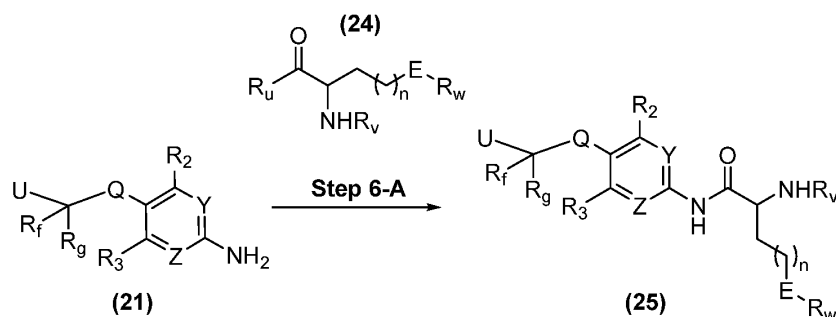


to produce a compound of formula (25)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, U, Y, Z, R_f, R_g, R_p, R_u, R_v, R_w, E, and n are as defined above.

[0395] Step 6-A is shown below.



[0396] In some embodiments, step 6-A comprises reacting a compound of formula (21) with a compound of formula (24) in the presence of reagents selected from the group consisting of solvents, peptide coupling reagents, bases, and mixtures thereof.

[0397] Suitable solvents for use in step 6-A may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; and mixtures thereof.

[0398] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof.

[0399] In some embodiments, the solvent is DCM.

[0400] Suitable peptide coupling reagents for use in step 6-A may be selected from the group consisting of carbodiimides, such as N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC), N-cyclohexyl, N'-isopropylcarbodiimide (CIC), and mixtures thereof; phosphonium salts, such as benzotriazol-1-yloxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tri-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), (7-azabenzotriazol-1-yloxy)-tris-(dimethylamino)-phosphonium hexafluorophosphate (AOP), (7-azabenzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyAOP), and mixtures thereof; aminium salts, such as 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU), 1-[(dimethylamino)(morpholino)methylene]-1*H*-[1,2,3]triazolo[4,5-*b*]pyridine-1-ium 3-oxide hexafluorophosphate (HDMA), and mixtures thereof; phosphonic acid anhydrides, such as propanephosphonic acid anhydride (T3P); and mixtures thereof. Additional examples of suitable peptide coupling reagents may be found in *Chem. Rev.* 2011, 111, 11, 6557–6602, which is incorporated herein in its entirety.

[0401] In some embodiments, the peptide coupling reagent is selected from the group consisting of DCC, DIC, CIC, BOP, PyBOP, AOP, PyAOP, HBTU, TBTU, HATU, HDMA, T3P, and mixtures thereof.

[0402] In some embodiments, the peptide coupling reagent is PyBOP.

[0403] Suitable bases for use in step 6-A may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; phosphates, such as NaH_2PO_4 , disodium phosphate Na_2HPO_4 , Na_3PO_4 , KH_2PO_4 , K_2HPO_4 , K_3PO_4 , and mixtures thereof; and mixtures thereof.

[0404] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof.

[0405] In some embodiments, the base is *N,N*-diisopropylethylamine.

[0406] In some embodiments, step 6-A is carried out in the presence of a solvent, a peptide coupling reagent, and a base. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; the peptide coupling reagent is selected from the group consisting of DCC, DIC, CIC, BOP, PyBOP, AOP, PyAOP, HBTU, TBTU, HATU, HDMA, T3P, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof. In some embodiments, the solvent is DCM, the peptide coupling reagent is PyBOP, and the base is *N,N*-diisopropylethylamine.

[0407] In some embodiments, step 6-A is carried out from about 0 °C to about 200 °C. In some embodiments, step 6-A is carried out from about 5 °C to about 100 °C. In some embodiments, step 6-A is carried out from about 10 °C to about 50 °C. In some

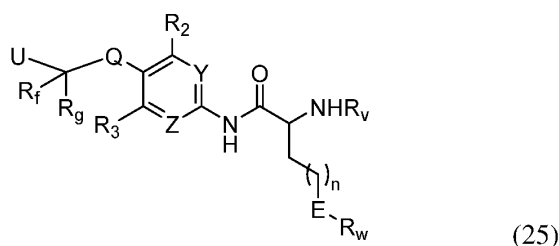
embodiments, step 6-A is carried out from about 15 °C to about 35 °C. In some embodiments, step 6-A is carried out at about rt.

[0408] In some embodiments, the amount of compound of formula (24) to the amount of compound of formula (21) is in the range of 0.5 to 20 molar equivalents. In some embodiments, the range is 0.67 to 10 molar equivalents. In some embodiments, the range is 0.75 to 5 molar equivalents.

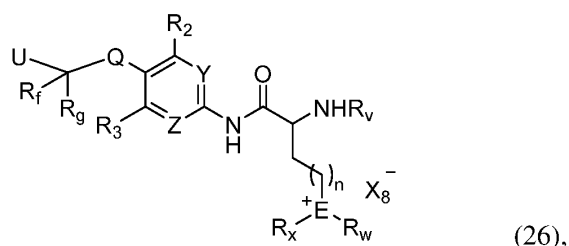
[0409] In some embodiments, the amount of peptide coupling reagent to the amount of compound of formula (21) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.05 to 20 molar equivalents. In some embodiments, the range is 0.1 to 15 molar equivalents. In some embodiments, the range is 0.1 to 10 molar equivalents. In some embodiments, the range is 0.5 to 5 molar equivalents.

[0410] In some embodiments, the amount of base to the amount of compound of formula (21) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0411] Scheme 6 further comprises a step 6-B, reacting a compound of formula (25)

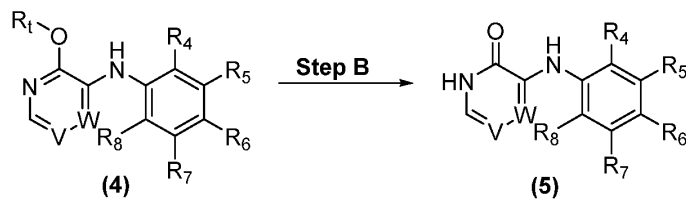


with an alkylating reagent to produce a compound of formula (26)



wherein R₂, R₃, Q, U, X₈, Y, Z, R_f, R_g, R_v, R_w, E, and n are as defined above.

[0412] Step 6-B is shown below.



[0413] In some embodiments, step 6-B comprises reacting a compound of formula (25) with an alkylating reagent in the presence of a solvent.

[0414] Suitable solvents for use in step 6-B may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, carbon tetrachloride, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; and mixtures thereof.

[0415] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof.

[0416] In some embodiments, the solvent is DCM.

[0417] Suitable alkylating reagents for use in step 6-B may be selected from the group consisting of alkyl halides, such as methyl fluoride, methyl chloride, methyl bromide, methyl iodide, ethyl fluoride, ethyl chloride, ethyl bromide, ethyl iodide, *n*-propyl fluoride, *n*-propyl chloride, *n*-propyl bromide, *n*-propyl iodide, isopropyl fluoride, isopropyl chloride, isopropyl bromide, isopropyl iodide, and mixtures thereof.

[0418] In some embodiments, the alkylating reagent is selected from the group consisting of methyl bromide, methyl iodide, ethyl bromide, ethyl iodide, *n*-propyl bromide, *n*-propyl iodide, isopropyl bromide, isopropyl iodide, and mixtures thereof.

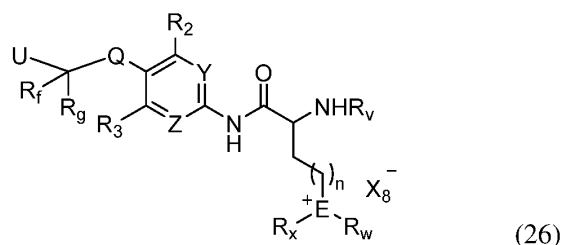
[0419] In some embodiments, the alkylating reagent is methyl iodide.

[0420] In some embodiments, step 6-B is carried out in the presence of a solvent and an alkylating reagent. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the alkylating reagent is selected from the group consisting of methyl bromide, methyl iodide, ethyl bromide, ethyl iodide, *n*-propyl bromide, *n*-propyl iodide, isopropyl bromide, isopropyl iodide, and mixtures thereof. In some embodiments, the solvent is DCM and the alkylating reagent is methyl iodide.

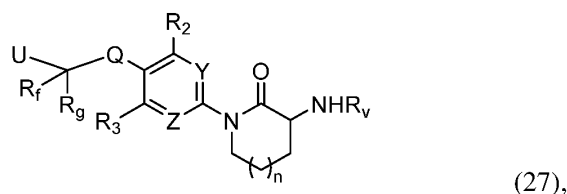
[0421] In some embodiments, step 6-B is carried out from about 0 °C to about 200 °C. In some embodiments, step 6-B is carried out from about 5 °C to about 100 °C. In some embodiments, step 6-B is carried out from about 10 °C to about 50 °C. In some embodiments, step 6-B is carried out from about 15 °C to about 35 °C. In some embodiments, step 6-B is carried out at about rt.

[0422] In some embodiments, the amount of alkylating reagent to the amount of compound of formula (25) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0423] Scheme 6 further comprises a step 6-C, reacting a compound of formula (26)

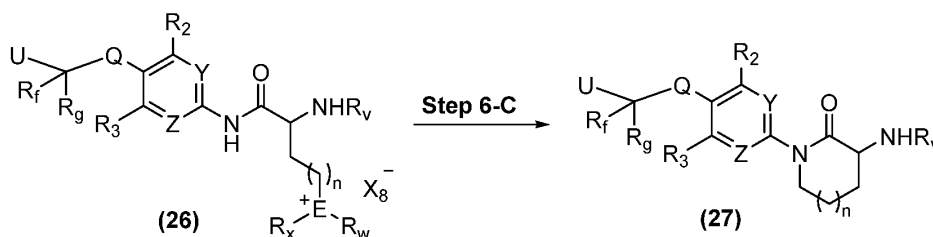


with a non-nucleophilic base to produce a compound of formula (27)



wherein R_2 , R_3 , Q , U , X_8 , Y , Z , R_f , R_g , R_v , R_x , R_w , E , and n are as defined above.

[0424] Step 6-C is shown below.



[0425] In some embodiments, step 6-C comprises reacting a compound of formula (26) with a non-nucleophilic base in the presence of a solvent.

[0426] Suitable solvents for use in step 6-C may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, $CHCl_3$, CCl_4 , 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; and mixtures thereof.

[0427] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof.

[0428] In some embodiments, the solvent is THF.

[0429] Suitable non-nucleophilic bases for use in step 6-C are organic bases that are poor nucleophiles and may be selected from the group consisting of phosphazenes, such as cyclodiphosphazane, hexachlorophosphazene, polyphosphazene, and mixtures thereof; amines, such as N,N-diisopropylethylamine, triisopropylamine, 2,6-di-*tert*-butylpiperidine, 1,8-Diazabicycloundec-7-ene (DBU), 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN), and mixtures thereof; alkoxide salts, such as lithium *tert*-butoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, and mixtures thereof; amine anions, such as lithium diisopropylamide (LDA), sodium diisopropylamide, potassium diisopropylamide, lithium tetramethylpiperidine (LiTMP), sodium tetramethylpiperidine (NaTMP), potassium tetramethylpiperidine (KTMP), lithium bis(trimethylsilyl)amide (LiHMDS), sodium bis(trimethylsilyl)amide (NaHMDS), potassium bis(trimethylsilyl)amide (KHMDS), and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; and mixtures thereof.

[0430] In some embodiments, the non-nucleophilic base is selected from the group consisting of N,N-diisopropylethylamine, 2,6-di-*tert*-butylpiperidine, DBU, DBN, potassium *tert*-butoxide, LDA, LiTMP, NaTMP, KTMP, LiHMDS, NaHMDS, KHMDS, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

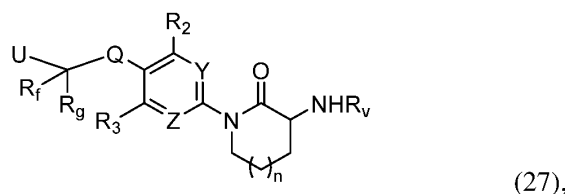
[0431] In some embodiments, the non-nucleophilic base is LiHMDS.

[0432] In some embodiments, step 6-C is carried out in the presence of a solvent and a non-nucleophilic base. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the non-nucleophilic base is selected from the group consisting of N,N-diisopropylethylamine, 2,6-di-*tert*-butylpiperidine, DBU, DBN, potassium *tert*-butoxide, LDA, LiTMP, NaTMP, KTMP, LiHMDS, NaHMDS, KHMDS, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof. In some embodiments, the solvent is THF and the non-nucleophilic base is LiHMDS.

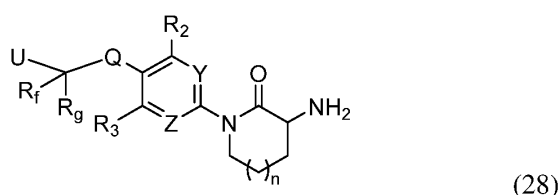
[0433] In some embodiments, step 6-C is carried out from about -25 °C to about 100 °C. In some embodiments, step 6-C is carried out from about -20 °C to about 50 °C. In some embodiments, step 6-C is carried out from about -15 °C to about 25 °C. In some embodiments, step 6-C is carried out from about -10 °C to about 10 °C. In some embodiments, step 6-C is carried out from about -5 °C to about 5 °C.

[0434] In some embodiments, the amount of non-nucleophilic base to the amount of compound of formula (26) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0435] Scheme 6 further comprises a step 6-D, reacting a compound of formula (27)

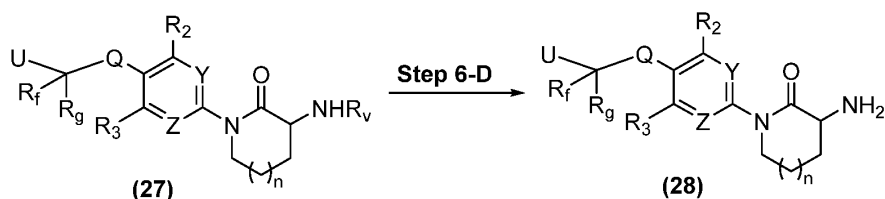


with a deprotecting reagent to produce a compound of formula (28)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, U, Y, Z, R_f, R_g, R_v, and n are as defined above.

[0436] Step 6-D is shown below:



[0437] In some embodiments, step 6-D comprises reacting a compound of formula (27) with a deprotecting reagent in the presence of a solvent.

[0438] Suitable solvents for use in step 6-D may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; organic acids, such as formic acid, AcOH; water; and mixtures thereof.

[0439] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof.

[0440] In some embodiments, the solvent is 1,4-dioxane.

[0441] Suitable deprotection reagents for use in step 6-D may be selected from the group consisting of acyl halides, such as acyl chloride, acyl bromide, acyl iodide, and mixtures thereof; acid anhydrides, such as acetic anhydride, formic anhydride, acetic formic anhydride, trifluoroacetic anhydride, trimethylacetic anhydride, hexanoic anhydride, benzoic anhydride, and mixtures thereof; organic acids, such as formic acid, AcOH, TFA, and mixtures thereof; inorganic acids, such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof; and mixtures thereof.

[0442] In some embodiments, the deprotection reagent is selected from the group consisting of formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof.

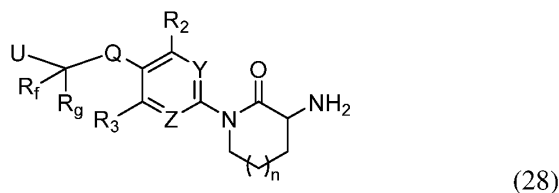
[0443] In some embodiments, the deprotection reagent is hydrochloric acid.

[0444] In some embodiments, step 6-D is carried out in the presence of a solvent and a deprotection reagent. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and the deprotection reagent is selected from the group consisting of formic acid, AcOH, TFA, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof. In some embodiments, the solvent is 1,4-dioxane, and the deprotection reagent is hydrochloric acid.

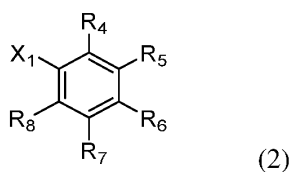
[0445] In some embodiments, step 6-D is carried out from about 0 °C to about 200 °C. In some embodiments, step 6-D is carried out from about 5 °C to about 100 °C. In some embodiments, step 6-D is carried out from about 10 °C to about 50 °C. In some embodiments, step 6-D is carried out from about 15 °C to about 35 °C. In some embodiments, step 6-D is carried out at about rt.

[0446] In some embodiments, the amount of deprotection reagent to the amount of compound of formula (27) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

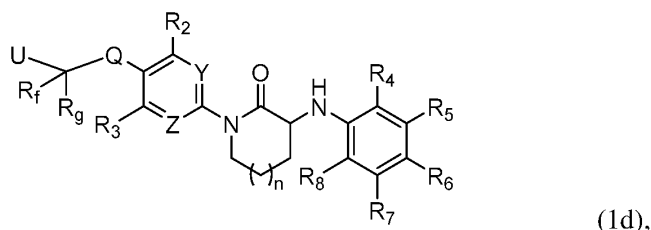
[0447] Scheme 6 further comprises a step 6-E, reacting a compound of formula (28)



with a compound of formula (2)

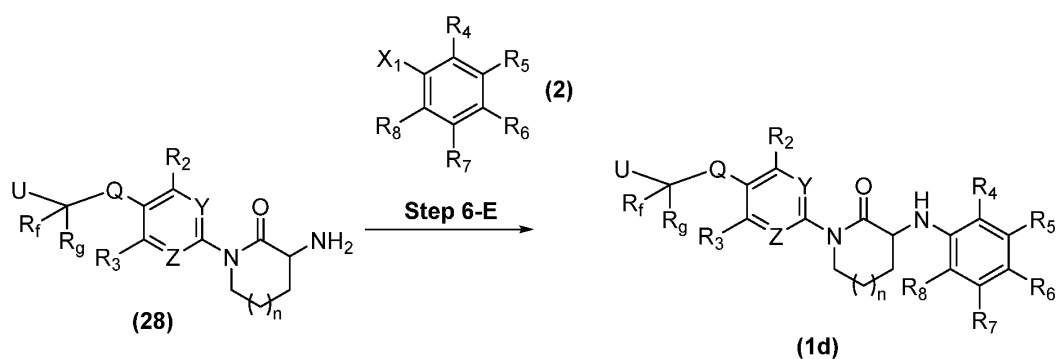


to produce a compound of formula (1d)



wherein R₂, R₃, R₄, R₅, R₆, R₇, R₈, Q, U, X₁, Y, Z, R_f, R_g, and n are as defined above.

[0448] Step 6-E is shown below.



[0449] In some embodiments, step 6-E comprises reacting a compound of formula (28) with a compound of formula (2) in the presence of a solvent, a catalyst, a ligand, and a base.

[0450] Suitable solvents for use in step 6-E may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; aromatic hydrocarbons, such as benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, mesitylene, pseudocumene (1,2,4-trimethylbenzene), hemimellitene (1,2,3-trimethylbenzene), and mixtures thereof; and mixtures thereof.

[0451] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof.

[0452] In some embodiments, the solvent is toluene.

[0453] Suitable catalysts for step 6-E may be selected from the group consisting of rhodium(II) acetate dimer (Rh₂(OAc)₄), rhodium(III) acetate (Rh(OAc)₃), palladium(II) acetate (Pd(OAc)₂), rhodium(III) acetylacetonate (Rh(acac)₃), ruthenium(III) acetylacetonate (Ru(acac)₃), palladium(II) acetylacetonate (Pd(acac)₂), nickel(II) acetylacetonate (Ni(acac)₂), platinum(II) acetylacetonate (Pt(acac)₂), tris(dibenzylideneacetone)dipalladium(0) (Pd₂(dba)₃), dichlorobis(triphenylphosphine)palladium(II) (PdCl₂(PPh₃)₂), tetrakis(triphenylphosphine) palladium(0) (Pd(PPh₃)₄), palladium(0) (Pd), palladium(0) on carbon (Pd/C), and mixtures thereof.

[0454] In some embodiments, the catalyst is selected from the group consisting of Pd₂(dba)₃, PdCl₂(PPh₃)₂, Pd(PPh₃)₄, and mixtures thereof.

[0455] In some embodiments, the catalyst is Pd₂(dba)₃.

[0456] Suitable ligands for use in step 6-E are selected from the group consisting of diamines, such as *N,N'*-dimethylethylenediamine (*N,N'*-DMEDA), *N,N'*-diisopropylethylenediamine, *N,N'*-dimethyl-6-hexanediamine, and mixtures thereof; phenanthrolines, such as 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, 4,7-dimethyl-1,10-phenanthroline, 4,7-dimethoxy-1,10-phenanthroline, and mixtures thereof; bipyridines, such as 2,2'-bipyridine; organophosphorous compounds, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 2,3-Bis(diphenylphosphino)butane (Chiraphos), 4,5-Bis(diphenyl phosphino)-9,9-dimethylxanthene (Xanthphos), Bis[(2-diphenylphosphino)phenyl] ether (DPEphos), 4,4,4',4',6,6'-Hexamethyl-2,2'-spirobichromane-8,8'-diylbis(diphenylphosphane) (SPANphos), 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane) (SEGPhos), 1,2-Bis(2,5-dimethylphospholano)benzene (Me-DuPhos), 1,1-Bis(diphenylphosphino)methane (dppm), 1,2-Bis(dimethylphosphino)ethane (dmpe), 1,2-Bis(diisopropylphosphino)ethane (dippe), 1,2-Bis(diphenylphosphino)benzene (dppbz), 1,2-Bis(diphenylphosphino)ethane (dppe), Bis(dicyclohexylphosphino)ethane (dcpe), 1,3-Bis(diphenylphosphino)propane (dppp), 1,4-Bis(diphenylphosphino)butane (dppb), and mixtures thereof; and mixtures thereof.

[0457] In some embodiments, the ligand is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, BINAP, Chiraphos, Xanthphos, DPEphos, SPANphos, Me-DuPhos, dppm, and mixtures thereof.

[0458] In some embodiments, the ligand is BINAP.

[0459] Suitable bases for use in step 6-E may be selected from the group consisting of amine bases, such as ammonia, methyl amine, dimethyl amine, trimethyl amine, ethyl amine, diethyl amine, triethyl amine, propyl amine, dipropyl amine, tripropyl amine, isopropyl amine, diisopropyl amine, triisopropyl amine, *N,N*-diisopropylethylamine, pyridine, imidazole, and mixtures thereof; alkoxide salts, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, and mixtures thereof; hydroxide salts, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and mixtures thereof; carbonate salts, such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, and mixtures thereof; bicarbonate salts, such as lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; hydride salts, such as lithium hydride, sodium hydride, potassium hydride, and mixtures thereof; phosphates, such as NaH_2PO_4 , Na_2HPO_4 , Na_3PO_4 , KH_2PO_4 , K_2HPO_4 , K_3PO_4 , and mixtures thereof; and mixtures thereof.

[0460] In some embodiments, the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, Na_3PO_4 , K_3PO_4 , and mixtures thereof.

[0461] In some embodiments, the base is cesium carbonate.

[0462] In some embodiments, step 6-E is carried out in the presence of a solvent, a catalyst, a ligand, and a base. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof; the catalyst is selected from the group consisting of $\text{Pd}_2(\text{dba})_3$, $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{Pd}(\text{PPh}_3)_4$, and mixtures thereof; the ligand is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, BINAP, Chiraphos, Xanthphos, DPEphos, SPANphos, Me-DuPhos, dppm, and mixtures thereof; and the base is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof. In some embodiments, the solvent is toluene, the catalyst is $\text{Pd}_2(\text{dba})_3$, the ligand is BINAP, and the base is cesium carbonate.

[0463] In some embodiments, step 6-E is carried out from about 0 °C to about 200 °C. In some embodiments, step 6-E is carried out from about 25 °C to about 175 °C. In some embodiments, step 6-E is carried out from about 50 °C to about 150 °C. In some

embodiments, step 6-E is carried out from about 75 °C to about 125 °C. In some embodiments, step 6-E is carried out from about 85 °C to about 100 °C.

[0464] In some embodiments, the amount of catalyst to the amount of compound of formula (28) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0465] In some embodiments, the amount of ligand to the amount of compound of formula (28) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0466] In some embodiments, the amount of base to the amount of compound of formula (28) is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

[0467] In some embodiments, step 6-E in Scheme 5 is followed by a dealkylation step 6-F, comprising removing the unsubstituted C₁-C₆ straight or branched alkyl in a compound of formula (1d), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is unsubstituted C₁-C₆ straight or branched alkyl, by reacting the compound of formula (1d) with at least one dealkylation reagent to produce a compound of formula (1e), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is H.

[0468] In some embodiments, step 6-F comprises reacting a compound of formula (1d), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is unsubstituted C₁-C₆ straight or branched alkyl, to form a compound of formula (1e), wherein U is -COOR_e, -COSR_e, or -CON(R_e)₂, and wherein R_e is H, in the presence of reagents selected from the group consisting of solvents, dealkylation reagents, and mixtures thereof.

[0469] Suitable solvents for use in step 6-F may be selected from the group consisting of amides, such as DMF, DMA, NMP, 2-pyrrolidone, and mixtures thereof; ethers, such as diethyl ether, THF, 2-MeTHF, DME, MTBE, 1,4-dioxane, and mixtures thereof; esters, such as MeOAc, EtOAc, *n*PrOAc, *i*PrOAc, *n*BuOAc, *sec*-BuOAc, *t*BuOAc, and *i*BuOAc; halogenated alkanes, such as DCM, CHCl₃, CCl₄, 1,2-dichloroethane, and mixtures thereof; nitriles, such as MeCN, propionitrile, benzonitrile, and mixtures thereof; alcohols, such as MeOH, EtOH, *n*PrOH, *i*PrOH, ethylene glycol, diethylene glycol, and mixtures thereof; organic acids, such as formic acid, AcOH; water; and mixtures thereof.

[0470] In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof.

[0471] In some embodiments, the solvent is selected from the group consisting of THF, water, and mixtures thereof. In some embodiments, the solvent is a mixture of water and THF.

[0472] Suitable dealkylation reagents for use in step 6-F may be selected from the group consisting of bases, such as lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, and mixtures thereof; acids, such as formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof; haloalkyl silanes, such as trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof.

[0473] In some embodiments, the dealkylation reagent is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof.

[0474] In some embodiments, the dealkylation reagent is lithium hydroxide.

[0475] In some embodiments, step 6-F is carried out in the presence of a solvent and a dealkylation reagent. In some embodiments, the solvent is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and the dealkylation reagent is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate, formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, trimethylsilyl fluoride, trimethylsilyl chloride, trimethylsilyl bromide, trimethyl silyl iodide, triethylsilyl fluoride, triethylsilyl chloride, triethylsilyl bromide, triethyl silyl iodide, and mixtures thereof. In some embodiments, the solvent is THF, water, and mixtures thereof; and the

dealkylation reagent is lithium hydroxide. In some embodiments, the solvent is a mixture of water and THF, and the dealkylation reagent is lithium hydroxide.

[0476] In some embodiments, step 6-F is carried out from about 0 °C to about 200 °C. In some embodiments, step 6-F is carried out from about 5 °C to about 100 °C. In some embodiments, step 6-F is carried out from about 10 °C to about 50 °C. In some embodiments, step 6-F is carried out from about 15 °C to about 35 °C. In some embodiments, step 6-F is carried out at about rt.

[0477] In some embodiments, the amount of dealkylation reagent to the amount of compound of formula (1d), wherein U is $-\text{COOR}_e$, $-\text{COSR}_e$, or $-\text{CON}(\text{R}_e)_2$, and wherein R_e is unsubstituted C_1 - C_6 straight or branched alkyl, is in the range of 0.01 to 25 molar equivalents. In some embodiments, the range is 0.1 to 20 molar equivalents. In some embodiments, the range is 0.5 to 15 molar equivalents. In some embodiments, the range is 1 to 10 molar equivalents.

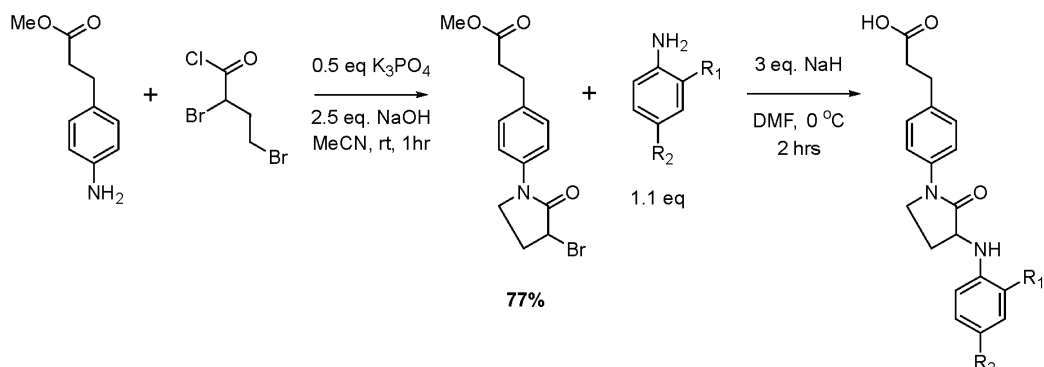
[0478] The compositions and methods described above may be better understood in connection with the following Examples. In addition, the following non-limiting examples are an illustration. The procedures described as general methods describe what is believed will be typically effective to prepare the compositions indicated. However, the person skilled in the art will appreciate that it may be necessary to vary the procedures for any given example of the present disclosure, for example, vary the order or steps and/or the chemical reagents used.

Examples

[0479] The preparation of exemplary compounds of formula (1) or (1a) using the processes of the invention is detailed below.

Example 1

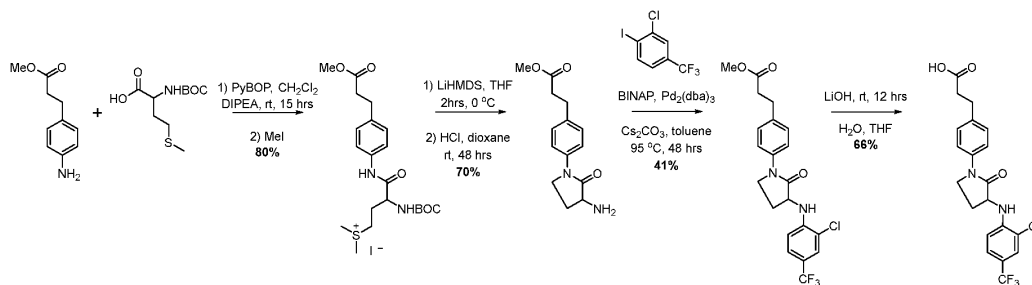
Synthesis of 3-(4-(3-((2,4-Disubstitutedphenyl)amino)-2-Oxopyrrolidin-1-yl)Phenyl)Propanoic Acid Compounds of Formula (1a)



[0480] Methyl 3-(4-aminophenyl)propanoate is reacted with 2,4-dibromobutanoyl chloride in the presence of potassium phosphate (0.5 eq.), sodium hydroxide (2.5 eq.) and acetonitrile. The reaction mixture is stirred at rt for 1 hour. The resulting intermediate, methyl 3-(4-(3-bromo-2-oxopyrrolidin-1-yl)phenyl)propanoate, is achieved in 77% yield. Methyl 3-(4-(3-bromo-2-oxopyrrolidin-1-yl)phenyl)propanoate is reacted with a 2,4-disubstituted aniline in the presence of sodium hydride (3 eq.) and DMF. The reaction mixture is stirred at 0 °C for 2 hours to provide the product, 3-(4-(3-((2,4-disubstitutedphenyl)amino)-2-oxopyrrolidin-1-yl)phenyl)propanoic acid.

Example 2

Synthesis of 3-(4-(3-((2-Chloro-4-(Trifluoromethyl)Phenyl)Amino)-2-Oxopyrrolidin-1-yl)Phenyl)Propanoic acid (Compound 11)

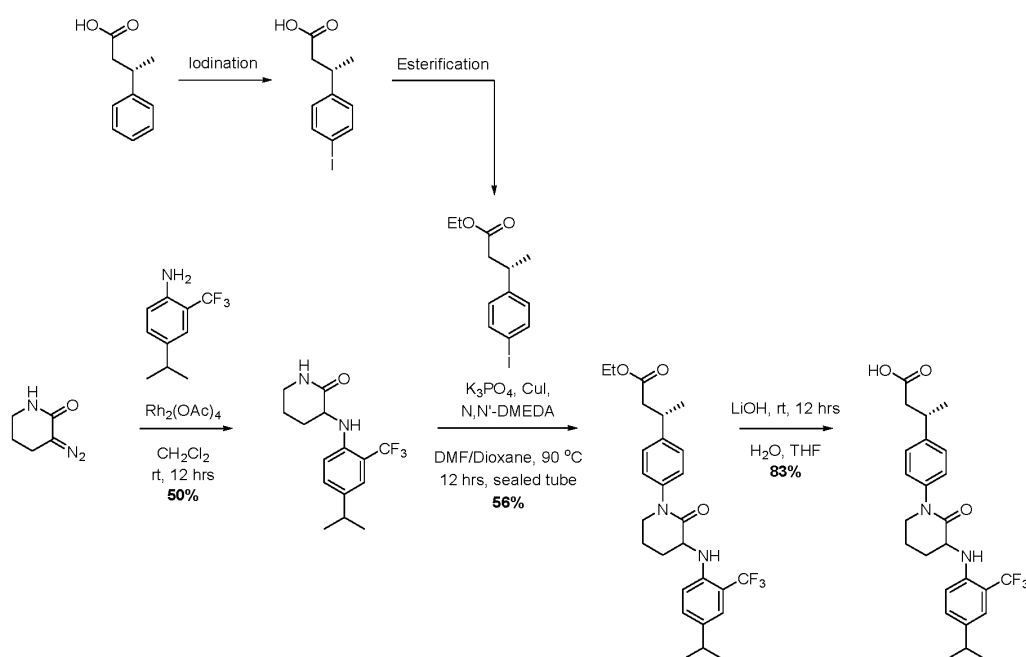


[0481] Methyl 3-(4-aminophenyl)propanoate was first reacted with 2-((tert-butoxycarbonyl)amino)-4-(methylthio)butanoic acid in the presence of PyBOP, DCM, and *N,N*-diisopropylethylamine (DIPEA). The reaction mixture was stirred at room temperature for 15 hours. After workup, the residue was treated with methyl iodide to give 3-((tert-butoxycarbonyl)amino)-4-((4-(3-methoxy-3-oxopropyl)phenyl)amino)-4-oxobutyl dimethyl sulfonium in 80% yield, which was first reacted with LiHMDS in the presence of THF at 0 °C for 2 hours. Then, hydrochloric acid and 1,4-dioxane were added to the reaction

mixture, and the reaction mixture was stirred at rt for 48 hours. The resulting intermediate, methyl 3-(4-(3-amino-2-oxopyrrolidin-1-yl)phenyl)propanoate was achieved in 70% yield. Methyl 3-(4-(3-amino-2-oxopyrrolidin-1-yl)phenyl)propanoate was reacted with 2-chloro-1-iodo-4-(trifluoromethyl) benzene in the presence of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), tris(dibenzylideneacetone) dipalladium(0), cesium carbonate, and toluene. The reaction mixture was stirred at 95 °C for 48 hours. The resulting intermediate, methyl 3-(4-(3-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrrolidin-1-yl)phenyl)propanoate was achieved in 41% yield. Methyl 3-(4-(3-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrrolidin-1-yl)phenyl)propanoate was then reacted with lithium hydroxide in the presence of water and THF. The reaction mixture was stirred at rt for 12 hours. The resulting product, 3-(4-(3-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrrolidin-1-yl)phenyl)propanoic acid, was achieved in 66% yield.

Example 3

Synthesis of (3S)-3-(4-(3-((4-Isopropyl-2-(Trifluoromethyl)Phenyl)Amino)-2-Oxopiperidin-1-yl)Phenyl)Butanoic Acid (Compound 14-(3S))



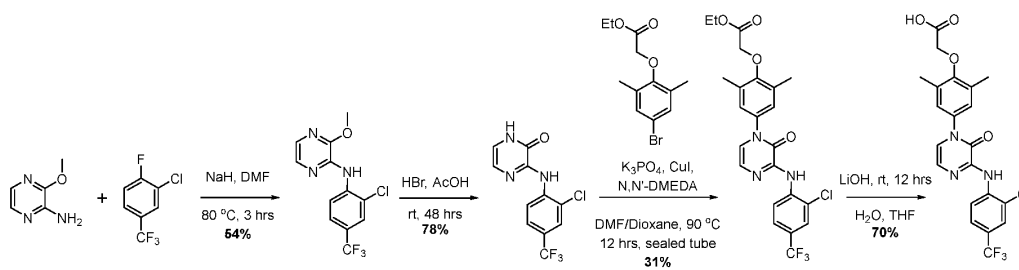
[0482] 3-Diazopiperidin-2-one was reacted with 4-isopropyl-2-(trifluoromethyl)aniline in the presence of rhodium(II) acetate and dichloromethane. The reaction mixture was stirred at rt for 12 hours. The resulting intermediate, 3-((4-isopropyl-2-(trifluoromethyl)phenyl)amino)piperidin-2-one, was achieved in 50% yield. 3-((4-Isopropyl-2-(trifluoromethyl)phenyl)amino)piperidin-2-one was then reacted with (*S*)-ethyl 3-(4-iodophenyl)butanoate in the presence of K₃PO₄, CuI, *N,N'*-DMEDA, DMF, and 1,4-dioxane.

The reaction mixture was stirred at 90 °C for 12 hours in a sealed tube. The resulting intermediate, (3*S*)-ethyl 3-(4-(3-((4-isopropyl-2-(trifluoromethyl)phenyl)amino)-2-oxopiperidin-1-yl)phenyl)butanoate, was achieved in 56% yield. (3*S*)-Ethyl 3-(4-(3-((4-isopropyl-2-(trifluoromethyl)phenyl)amino)-2-oxopiperidin-1-yl)phenyl)butanoate was reacted with lithium hydroxide in the presence of water and THF. The reaction mixture was stirred at rt for 12 hours. The resulting product, (3*S*)-3-(4-(3-((4-isopropyl-2-(trifluoromethyl)phenyl)amino)-2-oxopiperidin-1-yl)phenyl)butanoic acid, was achieved in 83% yield.

[0483] The reagent (*S*)-ethyl 3-(4-iodophenyl)butanoate was prepared in 2 steps, a first iodination step and a second esterification step, from (*S*)-3-phenyl-butyric acid.

Example 4

*Synthesis of 2-(4-(3-((2-Chloro-4-(Trifluoromethyl)Phenyl)Amino)-2-Oxopyrazin-1(2*H*)-yl)-2,6-Dimethylphenoxy)Acetic Acid (Compound 2)*



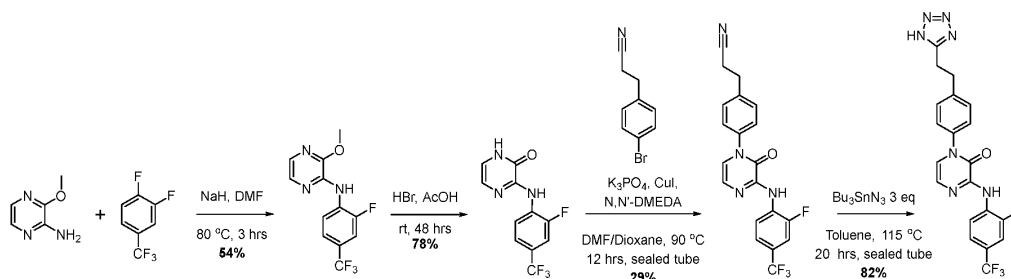
[0484] 3-Methoxypyrazin-2-amine and 2-chloro-4-(trifluoromethyl)benzene were reacted in the presence of sodium hydride and DMF. The reaction mixture was stirred at 80 °C for 3 hours. The resulting intermediate, *N*-(2-chloro-4-(trifluoromethyl)phenyl)-3-methoxypyrazin-2-amine, was achieved in 54% yield. *N*-(2-Chloro-4-(trifluoromethyl)phenyl)-3-methoxypyrazin-2-amine was reacted with 33% hydrobromic acid in the presence of AcOH. The reaction mixture was stirred at rt for 48 hours. The resulting intermediate, 3-((2-chloro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one, was achieved in 78% yield. 3-((2-Chloro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one was reacted with ethyl 2-(4-bromo-2,6-dimethylphenoxy)acetate in the presence of K₃PO₄, CuI, *N,N'*-DMEDA, DMF, and 1,4-dioxane. The reaction mixture was stirred at 90 °C for 12 hours in a sealed tube. The resulting intermediate, ethyl 2-(4-(3-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2*H*)-yl)-2,6-dimethylphenoxy)acetate, was achieved in 31% yield. Ethyl 2-(4-(3-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2*H*)-yl)-2,6-dimethylphenoxy)acetate was reacted with lithium hydroxide in the presence of water and THF. The reaction mixture was stirred at rt for 12 hours. The

resulting product, 2-(4-(3-((2-chloro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2H)-yl)-2,6-dimethylphenoxy)acetic acid, was achieved in 70% yield.

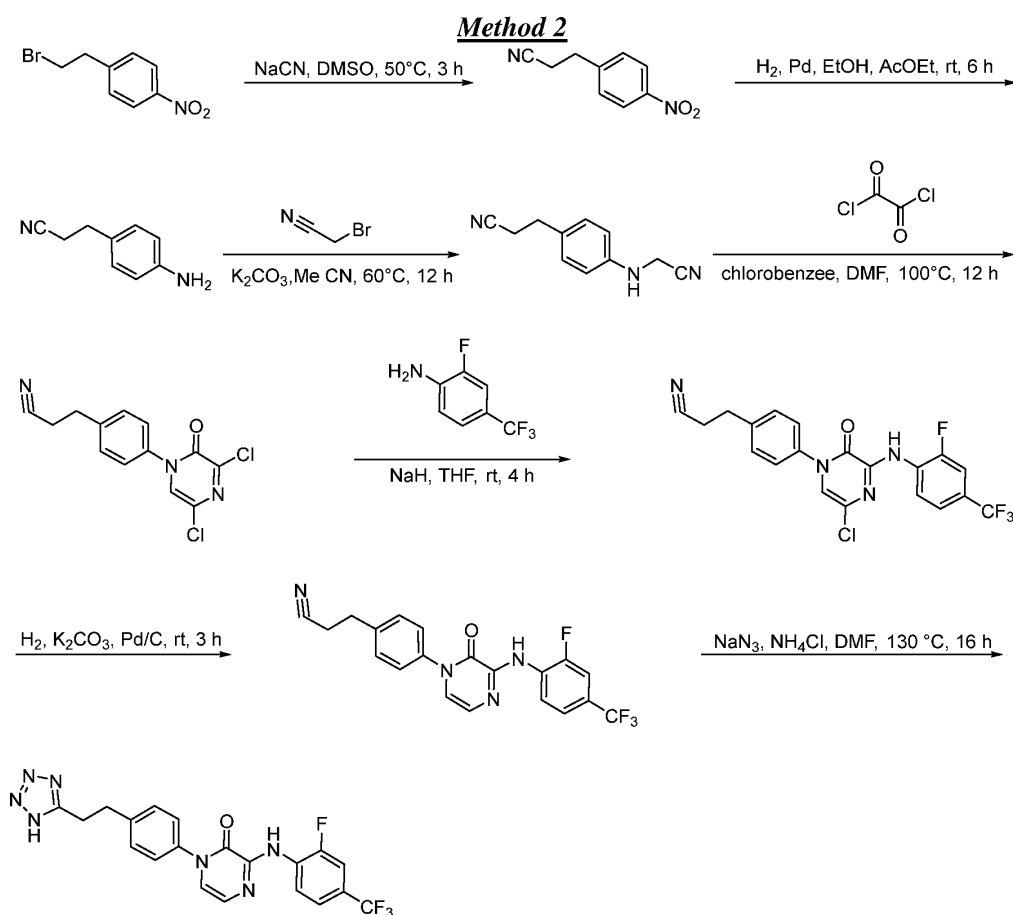
Example 5

Synthesis of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-(Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one (Compound 3)

Method 1



[0485] 3-Methoxypyrazin-2-amine was reacted with 1,2-difluoro-4-(trifluoromethyl)benzene in the presence of sodium hydride and DMF. The reaction mixture was stirred at 80 °C for 3 hours. The resulting intermediate, N-(2-fluoro-4-(trifluoromethyl)phenyl)-3-methoxypyrazin-2-amine, was achieved in 54% yield. N-(2-Fluoro-4-(trifluoromethyl)phenyl)-3-methoxypyrazin-2-amine was reacted with 33% hydrobromic acid in the presence of AcOH. The reaction mixture was stirred at room temperature for 48 hours. The resulting intermediate, 3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one, was achieved in 78% yield. 3-((2-Fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one was reacted with 3-(4-bromophenyl)propanenitrile in the presence of K₃PO₄, CuI, N,N'-DMEDA, DMF, and 1,4-dioxane. The reaction mixture was stirred at 90 °C for 12 hours in a sealed tube. The resulting intermediate, 3-(4-(3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2H)-yl)phenyl)propanenitrile, was achieved in 29% yield. 3-(4-(3-((2-Fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2H)-yl)phenyl)propanenitrile was reacted with tributyltin azide in the presence of toluene. The reaction mixture was stirred at 115 °C for 20 hours in a sealed tube. The resulting product, 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one, was achieved in 82% yield.



[0486] To a stirred solution of 1-(2-bromoethyl)-4-nitrobenzene (4 g, 17.39 mmol) in DMSO (40 mL) was added NaCN (980 mg, 20.00 mmol) at 25 °C. The reaction mixture was stirred at 50 °C for 3 h. The resulting intermediate, 3-(4-nitrophenyl)propanenitrile was achieved as an off-white solid in 63% yield (2 g). MS (ESI): 177.1.

[0487] To a stirred solution of 3-(4-nitrophenyl)propanenitrile (2 g, 11.35 mmol) in MeOH (50 mL) was added Pd/C (423 mg, 3.97 mmol). The reaction mixture was stirred at 25 °C for 6 h under H₂. The resulting intermediate, 3-(4-aminophenyl)propanenitrile, was achieved as a white solid in 87% yield (1.6 g). MS (ESI): 147.1.

[0488] To a stirred solution of 3-(4-aminophenyl)propanenitrile (1.6 g, 10.94 mmol) and 2-bromoacetonitrile (3.3 g, 27.36 mmol) in MeCN (20 mL) was added K₂CO₃ (3 g, 21.89 mmol) at 25 °C. The reaction mixture was stirred at 60 °C for 12 h. The resulting intermediate, 3-{4-[(cyanomethyl)amino]phenyl}propanenitrile was achieved as a white solid in 71% yield (1.6 g). MS (ESI): 186.1.

[0489] To a stirred solution of 3-{4-[(cyanomethyl)amino]phenyl}propanenitrile (1.6 g, 8.64 mmol) in chlorobenzene (40 mL) was added oxalic dichloride (5.5 g, 43.19 mmol).

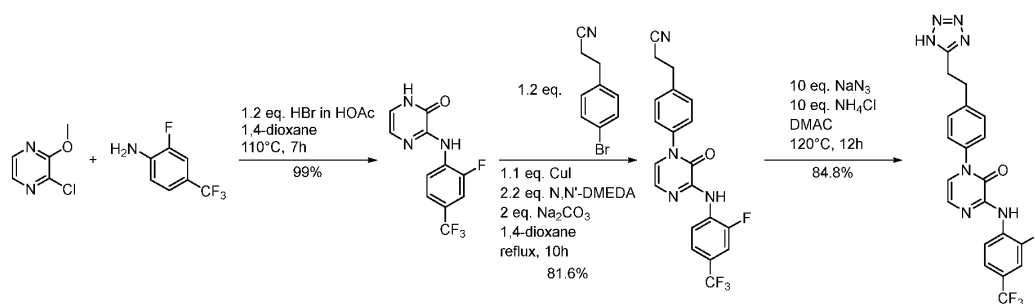
The reaction mixture was stirred at 100 °C for 1 h, then DMF was added (126 mg, 1.73 mmol). The reaction mixture was stirred at 100 °C for 12 h. The resulting intermediate, 3-[4-(3,5-dichloro-2-oxopyrazin-1-yl)phenyl]propanenitrile, was achieved as a white solid in 33% yield (900 mg). MS (ESI): 294.0.

[0490] To a stirred solution of 4-trifluoromethyl-2-fluoroaniline (398 mg, 13.60 mmol) in THF (11 mL) was added NaH (544 mg, 13.60 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. To the resulting mixture was added 3-[4-(3,5-dichloro-2-oxopyrazin-1-yl)phenyl]propanenitrile (500 mg, 1.02 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h. The resulting intermediate, 3-(4-(5-chloro-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2*H*)-yl)phenyl)propanenitrile, was achieved as an off-white solid in 25% yield (210 mg). MS (ESI): 437.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 8.30 (t, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 10.0 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.47 (m, 4H), 7.43 (s, 1H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.88 (dd, *J* = 10.8, 4.0 Hz, 2H).

[0491] To a stirred mixture of 3-(4-(5-chloro-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2*H*)-yl)phenyl)propanenitrile (110 mg, 0.25 mmol) and K₂CO₃ (35 mg, 0.25 mmol) in MeOH (20 mL) was added Pd/C (9 mg, 0.09 mmol). The reaction mixture was stirred at 25 °C for 3 h under H₂. The resulting intermediate, 3-(4-(3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2*H*)-yl)phenyl)propanenitrile, was achieved as a white solid in 73% yield (80 mg). MS (ESI): 403.1.

[0492] To a stirred mixture of 3-(4-(3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2*H*)-yl)phenyl)propanenitrile (70 mg, 0.17 mmol) and ammonium chloride (NH₄Cl, 93 mg, 1.74 mmol) in DMF (4 mL) was added sodium azide (NaN₃, 169 mg, 2.60 mmol). The reaction mixture was stirred at 130 °C for 16 h. The resulting product, 1-(4-(2-(1*H*-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one, was achieved as a yellow solid in 45% yield (37 mg). MS (ESI): 446.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (s, 1H), 8.61 (t, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 11.2 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.41 (m, 4H), 7.18 (d, *J* = 4.8 Hz, 1H), 7.05 (d, *J* = 4.8 Hz, 1H), 3.26 – 3.24 (m, 2H), 3.17 – 3.13 (m, 2H).

Method 3



[0493] A 300-mL flask was equipped with a condenser and loaded with 2-chloro-3-methoxypyrazine (10.99 g, 1 equiv., 76.0 mmol), 2-fluoro-4-(trifluoromethyl)aniline (16.25 g, 1.19 equiv., 90.7 mmol), and 1,4-dioxane (120 mL). HBr (16.0 mL, 22.37 g, 33% wt., 1.2 equiv., 91.2 mmol) in acetic acid was added to room temperature. White solid precipitated out of the mixture. The suspension was stirred at 120°C for 7 hours, cooled to room temperature, and added to ice water (1 L). The resulting suspension was cooled in an ice bath with stirring. Saturated Na₂CO₃ (125 mL) was added to adjust the pH of the mixture to 8-9. After stirring for 30 minutes, the resulting white precipitate was collected via filtration. The solid was washed with water, and dried at 50°C under vacuum for 2 days to give 3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one (21.47 g, 99% yield in 96% purity) as a white solid. LC-MS: 274.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.89 – 8.56 (m, 2H), 7.85 – 7.63 (m, 1H), 7.58 (ddt, *J* = 8.6, 2.0, 0.9 Hz, 1H), 7.10 – 6.81 (m, 2H).

[0494] Alternatively, Pd-catalyzed Buchwald reactions produced 3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one in 26-54% yield by using various catalysts including Pd₂(dba)₃/Xantphos, Pd(OAc)₂/Xantphos, XantPhos-Pd-G3, and BrettPhos-Pd-G3.

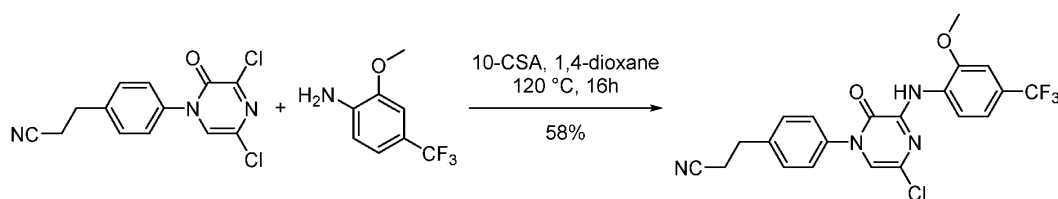
[0495] In a 500-mL flask was loaded 3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one (10.9 g, 1 equiv., 39.9 mmol), 3-(4-bromophenyl)propanenitrile (10.0 g, 1.19 equiv., 47.6 mmol), and 1,4-dioxane (160 mL). To the suspension was added CuI (8.36 g, 1.1 equiv., 43.9 mmol). The mixture was stirred for 5 minutes, and then *N,N'*-dimethylethane-1,2-diamine (7.7 g, 9.4 mL, 2.2 equiv., 87.8 mmol) was added. After stirring for 5 minutes, sodium carbonate (8.46 g, 2 equiv., 79.8 mmol) was added. The reaction mixture was heated under reflux for 10 hours, then filtered through Celite. The filtrate was evaporated. The solid pad was washed with DCM until all product was washed out. The residue and the washing were combined and washed with brine (400 mL), and then with saturated aqueous NH₄Cl (200 mL). The washings were extracted with DCM three times. The organic phase was dried over Na₂SO₄, filtered, and evaporated. The residue was crystallized with EtOAc/heptane to give 3-(4-(3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2*H*)-yl)phenyl)propanenitrile (11.1 g), with

more product (2.0 g) obtained from the mother liquor) as a white solid in 81.6% overall yield. LC-MS: 403.19.

[0496] In a 300-mL flask was loaded 3-(4-(3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2*H*)-yl)phenyl)propanenitrile (13.1 g, 1 equiv., 32.6 mmol), sodium azide (21.3 g, 10 equiv., 326 mmol), ammonium chloride (17.4 g, 10 equiv., 326 mmol), and N,N-dimethylacetamide ("DMAC," 110 mL). The reaction mixture was heated at 120°C for 12 h. The mixture was cooled to room temperature, poured into saturated NH₄Cl (550 mL), and stirred for 10 minutes. The resulting white solid was collected via filtration. The solid was suspended in water (400 mL), stirred, and filtered. The filtration was slow. The solid was suspended in water (400 mL) again, resulting in a gel-like material that was suspended in EtOAc (500 mL). The suspension was heated to help separation. The organic phase was separated. The aqueous phase was re-extracted with EtOAc. The hot organic phase was dried with Na₂SO₄, filtered, and evaporated. The residue was crystallized with EtOAc. More product was obtained from the filtrate. Both products were combined, and dried under high vacuum for 3 days to give 1-(4-(2-(1*H*-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one (11.1 g, 76.5% yield, Compound 3 in Table 29) as an off-white solid. The remaining mother liquor was purified by flash chromatography (40 g silica gel, MeOH/DCM 0-10%). The relatively pure fractions were combined and crystallized in EtOAc to give additional desired product (1.42 g). The overall yield was 84.8%. LC-MS: 446.1. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.86 (d, *J* = 2.7 Hz, 1H), 8.61 (t, *J* = 8.3 Hz, 1H), 7.63 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.76 (dd, *J* = 11.3, 2.1 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 4.6 Hz, 1H), 7.04 (d, *J* = 4.6 Hz, 1H), 3.25 (t, *J* = 7.7 Hz, 2H), 3.14 (t, *J* = 7.7 Hz, 2H).

Example 6

*Synthesis of 5-chloro-1-(4-(2-isocyanoethyl)phenyl)-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one*

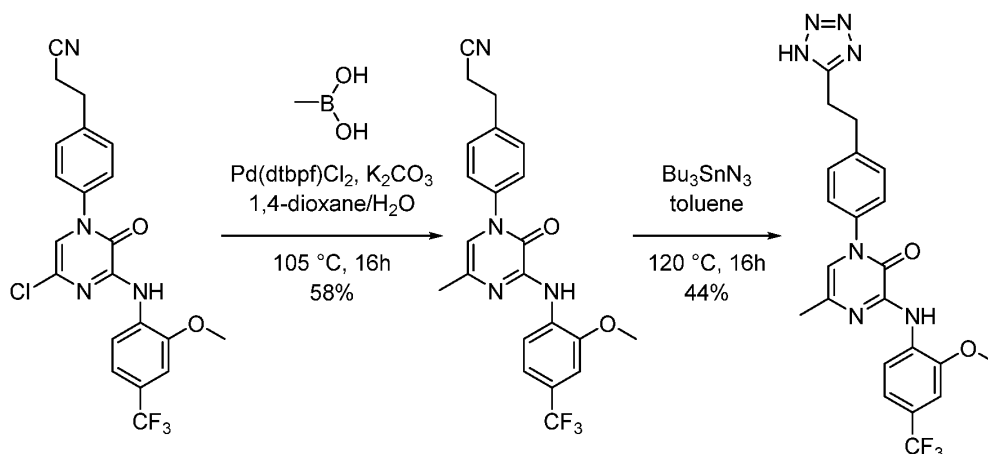


[0497] To a mixture of 3-(4-(3,5-dichloro-2-oxopyrazin-1(2*H*)-yl)phenyl)propanenitrile (4.82 g, 0.02 mol) in 1,4-dioxane (150 mL) was added 2-methoxy-4-(trifluoromethyl)aniline (4.10 g, 0.02 mol) and 10-camphorsulfonic acid (10-CS, 4.96 g, 0.02 mol) at 25 °C. The reaction mixture was stirred at 120 °C for 16h, cooled to rt, quenched with water (30 mL), and extracted with EtOAc (50 mL x 3). The combined organic layers

were washed with brine (50 mL), concentrated under reduced pressure. The residue was purified by flash chromatography (FC) to afford 5-chloro-1-(4-(2-isocyanoethyl)phenyl)-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (5.60 g, 58%) as a yellow solid. MS (ESI): 449.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.66 (d, *J* = 8.4 Hz, 1H), 7.54 – 7.42 (m, 6H), 7.39 (s, 1H), 4.01 (s, 3H), 3.01 – 2.85 (m, 4H).

Example 7

Synthesis of 1-(4-(2-1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-5-methylpyrazin-2(1H)-one (Compound 17)



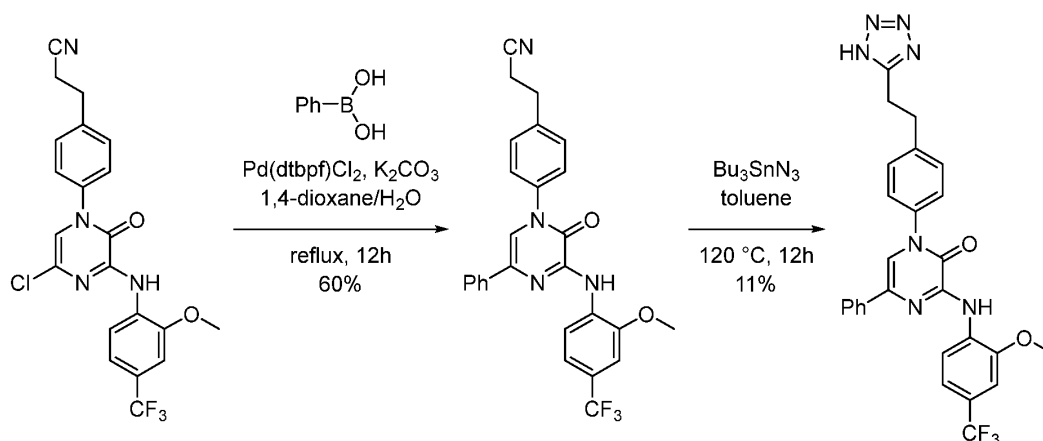
[0498] To the mixture of 3-(4-(5-chloro-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2H)-yl)phenyl)propanenitrile (200 mg, 0.45 mmol) in 1,4-dioxane (5 mL) and H₂O (1 mL) was added methylboronic acid (667 mg, 11.14 mmol), K₂CO₃ (185 mg, 1.34 mmol), and Pd(dtbpf)Cl₂ (58 mg, 0.09 mmol) at 25 °C. The reaction mixture was stirred under N₂ at 105 °C for 16h. The reaction mixture was quenched with water (20 mL), extracted with EtOAc (30 mL x 3), and washed with brine (20 mL x 2). The combined organic layers were concentrated under reduced pressure and the residue was purified by FC to afford 3-(4-(3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-5-methyl-2-oxopyrazin-1(2H)-yl)phenyl)propanenitrile (110 mg, 58%) as a yellow solid. MS (ESI): 429.1.

[0499] To the mixture of 3-(4-(3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-5-methyl-2-oxopyrazin-1(2H)-yl)phenyl)propanenitrile (110 mg, 0.26 mmol) in toluene (2 mL) was added azidotriphenyltin (256 mg, 0.77 mmol) at rt. The reaction mixture was stirred at 120 °C for 16h, then concentrated under reduced pressure. The residue was purified by prep-high-performance liquid chromatography (HPLC) to afford 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-5-methylpyrazin-2(1H)-one (53.0 mg, 44%) as a white solid. MS (ESI): 472.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.00 (s, 1H), 8.89 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.37 (m, 5H), 7.34 (d, *J* = 1.6 Hz, 1H), 7.01

(d, $J = 1.2$ Hz, 1H), 4.00 (s, 3H), 3.24 – 3.20 (m, 2H), 3.15 – 3.10 (m, 2H), 2.20 (d, $J = 0.8$ Hz, 3H).

Example 8

Synthesis of 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-5-phenylpyrazin-2(1H)-one (Compound 21)

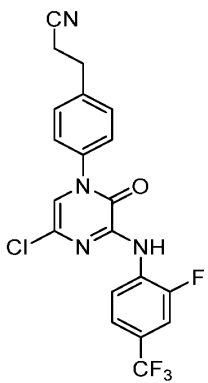
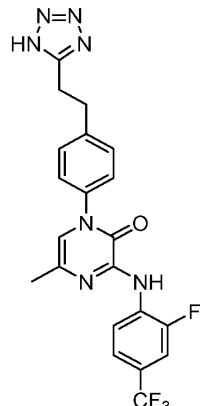
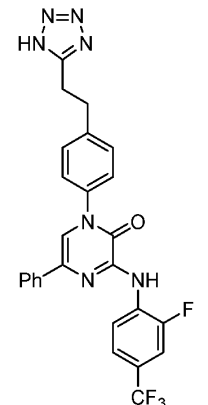


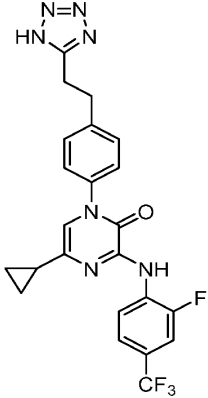
[0500] To a solution of 5-chloro-1-(4-(2-isocyanoethyl)phenyl)-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (300 mg, 0.67 mmol) in 1,4-dioxane (4 mL) and H₂O (1 mL) were added phenylboronic acid (415 mg, 3.4 mmol), Pd(dtbpf)Cl₂ (39 mg, 0.06 mmol) and K₂CO₃ (179 mg, 1.3 mmol). The reaction mixture was refluxed under nitrogen for 12h. The mixture was quenched with water (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by FC to afford 3-(4-(3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-2-oxo-5-phenylpyrazin-1(2H)-yl)phenyl)propanenitrile (200 mg, 60%) as a yellow solid. MS (ESI): 491.2 [M+H]⁺.

[0501] To a solution of 3-(4-(3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-2-oxo-5-phenylpyrazin-1(2H)-yl)phenyl)propanenitrile (100 mg, 0.21 mmol) in toluene (2 mL) was added tributylstannanylium azide (2120 mg, 0.63 mmol). The reaction mixture was stirred at 120 °C for 12h. The mixture was quenched with water (30 mL), and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-5-phenylpyrazin-2(1H)-one (16.6 mg, 11%) as a yellow solid. MS (ESI): 534.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 9.03 (d, $J = 8.4$ Hz, 1H), 8.00 – 7.95 (m, 2H), 7.77 (s, 1H), 7.55 (d, $J = 8.4$ Hz, 3H), 7.45 (d, $J = 8.0$ Hz, 4H), 7.41 – 7.31 (m, 3H), 4.03 (s, 3H), 3.24 (d, $J = 7.2$ Hz, 2H), 3.15 (d, $J = 8.0$ Hz, 2H).

[0502] The following compounds were synthesized similarly to 1-(4-(2-(1H-tetrazol-

5-yl)ethyl)phenyl)-3-((2-methoxy-4-(trifluoromethyl)phenyl)amino)-5-phenylpyrazin-2(1*H*)-one:

3-(4-(5-chloro-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-2-oxopyrazin-1(2 <i>H</i>)-yl)phenyl)propanenitrile		MS (ESI): 437.0. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.27 (s, 1H), 8.30 (t, <i>J</i> = 8.2 Hz, 1H), 7.83 (d, <i>J</i> = 10.0 Hz, 1H), 7.70 (d, <i>J</i> = 8.4 Hz, 1H), 7.53 – 7.47 (m, 4H), 7.43 (s, 1H), 2.97 (t, <i>J</i> = 6.8 Hz, 2H), 2.88 (dd, <i>J</i> = 10.8, 4.0 Hz, 2H).
1-(4-(2-(1 <i>H</i> -tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-5-methylpyrazin-2(1 <i>H</i>)-one (Compound 18)		MS (ESI): 460.0. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 (d, <i>J</i> = 2.8 Hz, 1H), 8.71 (t, <i>J</i> = 8.0 Hz, 1H), 8.14 (s, 1H), 7.78 (d, <i>J</i> = 11.2 Hz, 1H), 7.65 (d, <i>J</i> = 8.8 Hz, 1H), 7.43 (q, <i>J</i> = 8.4 Hz, 4H), 7.04 (d, <i>J</i> = 0.8 Hz, 1H), 3.23 (d, <i>J</i> = 7.6 Hz, 2H), 3.16 – 3.11 (m, 2H), 2.17 (s, 3H).
1-(4-(2-(1 <i>H</i> -tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-(trifluoromethyl)phenyl)amino)-5-phenylpyrazin-2(1 <i>H</i>)-one (Compound 20)		MS (ESI): 522.2. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.99 (s, 1H), 8.77 (t, <i>J</i> = 8.0 Hz, 1H), 7.97 – 7.89 (m, 2H), 7.83 (d, <i>J</i> = 11.2 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.55 (d, <i>J</i> = 8.4 Hz, 2H), 7.47 – 7.40 (m, 4H), 7.34 – 7.30 (m, 1H), 3.26 (t, <i>J</i> = 7.6 Hz, 2H), 3.18 (t, <i>J</i> = 8.0 Hz, 2H).

1-(4-(2-(1 <i>H</i> -tetrazol-5-yl)ethyl)phenyl)-5-cyclopropyl-3-((2-fluoro-4-(trifluoromethyl)phenyl)-amino)pyrazin-2(1 <i>H</i>)-one (Compound 19)		MS (ESI): 486.1. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.82 (d, <i>J</i> = 2.8 Hz, 1H), 8.55 (t, <i>J</i> = 8.0 Hz, 1H), 8.14 (s, 1H), 7.77 (d, <i>J</i> = 11.6 Hz, 1H), 7.66 (d, <i>J</i> = 8.8 Hz, 1H), 7.51 – 7.38 (m, 4H), 7.14 (s, 1H), 3.23 (d, <i>J</i> = 7.2 Hz, 2H), 3.16 – 3.12 (m, 2H), 1.94 – 1.82 (m, 1H), 0.80 (d, <i>J</i> = 6.4 Hz, 4H).
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[0503] The following examples include descriptions of studies undertaken to evaluate the efficacies of examples of compounds of formula (1) or (1a).

[0504] Reagents used in the following examples include the reagents listed below in Table 1:

TABLE 1

Compound	Vendor	Catalog Number
Terfenadine	Sigma-Aldrich	T9652
Tolbutamide	Sigma-Aldrich	T0891
K ₂ HPO ₄	SCR	20032117
NADPH	ACROS	328742500
Dextromethorphan	Sigma-Aldrich	D9684
Willaims E Medium	Gibco	A12176-01
Percoll	GE Healthcare	17-0891-09
DPBS	Gibco	14190-144
Glutamax	Gibco	35050-061
HEPES	Gibco	15630-080
L-Glutamine	Gibco	25030081
Fetal bovine serum	Gibco	10091-148
Human recombinant insulin	YEASEN	40112ES25
Dexamethasone	Alfa Aesar	A17590

Midazolam	National Institutes for Food and Drug Control	171265
Diclofenac	Sigma-Aldrich	D6899
Omeprazole	Sigma-Aldrich	19329
Phenacetin	Sigma-Aldrich	101690303
7-Ethoxycoumarin	Sigma-Aldrich	E13793
NaH ₂ PO ₄ ·2H ₂ O	Sigma-Aldrich	13472-35-0
Na ₂ HPO ₄ ·12H ₂ O	Sigma-Aldrich	10039-32-4
NaCl	Sigma-Aldrich	7647-14-5
Warfarin	International Laboratory USA	2151159
PEG400	Sigma-Aldrich	81172-1L
Ethanol	Damas-beta	73537L-4L

[0505] Equipment used in the following examples include the equipment listed below in Table 2:

TABLE 2

Equipment	Model	Vendor
Mass spectrometer	Q Trap 5500	AB Sciex
	Q Trap 5000	
	Q Trap 4500	
	API 5500+	
	API 4000	
	Triple Quad 5500	
	Triple Quad 6000	
Centrifuge	Multifuge X3R	Thermo Scientific
Analytical balance	TB-25	Denver Instrument
CO ₂ incubator	MCO-15AC	SANYO
Shaker	TS-2 Orbital Shaker	Kylin-Bell Lab Instrument

Dialysis Membranes	MWCO 12-14K	HTDialysis
HTD 96b	1006	HTDialysis
24 Well Cell Culture Plate	3524	Corning
1.1 mL, 12 STRIP	AXYGEN	MTS-11-12-C

Example 9

In vitro metabolic kinetics of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one (Compound 3) in rat and human liver microsomal fractions

[0506] The metabolic stability of 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (“Compound 3” in Table 29 below) was measured in rat and human microsomes. The liver microsome samples used in this example are listed below in Table 3:

TABLE 3

Species	Gender	Vendor	Catalog #	Lot #	Storage Conditions
Human	Mixed	Corning	452117	38295	-80 °C
Rat	Male	BioreclamationIVT	M00001	UDX	-80 °C

[0507] Phosphate buffer was prepared by dissolving 8.709 g of K₂HPO₄ in 950 mL of water. The pH of the solution was adjusted to 7.4 with aqueous HCl solution. The solution was adjusted with water to a final total volume of 1000 mL. The buffer was filtered through 0.22 µm filter, and stored in a refrigerator at 4 °C for future use.

[0508] A quenching solution was prepared by making a terfenadine/tolbutamide (1 mg/mL each) stock solution with DMSO, then diluting the stock solution in acetonitrile to a quenching solution containing 5/10 ng/mL (terfenadine/tolbutamide).

[0509] A stock solution of Compound 3 (molecular weight, 445.4 g/mol) was prepared in DMSO at a molarity of 10 mM. A working solution of Compound 3 at a molarity of 200 µM in DMSO was prepared from the stock solution.

[0510] Liver microsome was thawed in a 37 °C water bath. Liver microsome working solutions having a volume of 1669.5 µL were prepared according to Table 4 below:

TABLE 4

Liver microsome stock concentration (mg/mL)	Liver microsome stock volume (μL)	Working solution concentration (mg/mL)	Final concentration in incubation (mg/mL)	Phosphate buffer volume (μL)
20	53	0.629	0.5	1617

[0511] A 5 mM NADPH working solution was prepared with phosphate buffer.

[0512] Incubation was performed by adding 1.5 μL of control or Compound 3 working solution to 238.5 μL liver microsome working solution in a 1.1 mL mini tube, followed by gentle mixing. The mixture was pre-incubated in a 37 °C shaking water bath for 5 minutes. Reaction was initiated by adding 60 μL NADPH working solution. The solutions were mixed by pipetting up and down. At each of 0, 5, 15, 30, and 60 minutes, 30 μL of reaction mixture was transferred to 300 μL quenching solution, with mixing by pipetting. The samples were vortexed vigorously for 1 minute and centrifuged at 4000 rpm at 4 °C for 15 minutes. 100 μL of the supernatant of each sample was mixed with 100 μL of distilled water for LC-MS/MS analysis.

[0513] Mass spectrometry was performed by multiple reaction monitoring (MRM) of *m/z* values of 446.082 and 418.000 for Compound 3, using a Kinetex 2.6 μm C18 100 Å column (2.6 mm x 50 mm). Mobile phase A: 0.1% formic acid in H₂O, Mobile phase B: 0.1% formic acid in acetonitrile for a run time of 2 minutes.

[0514] The percent remaining was calculated according to the following equation (1):

$$\% \text{ remaining (at appointed time)} = \frac{\text{Peak area ratio of test compound at appointed time}}{\text{Peak area ratio of test compound at 0 minutes}} \times 100\% \quad (1)$$

[0515] The equation of first order kinetics was used to calculate half-life (“*t*_{1/2}”) and intrinsic clearance (“CL_{int}”). The equation of first order kinetics is equation (2) below, from which the equation (3) to provide half-life may be derived:

$$C_t = C_0 \times e^{-k_e \cdot t} \quad (2)$$

$$t_{1/2} = \frac{\ln 2}{k_e} \quad (3)$$

[0516] The equation for *in vitro* intrinsic clearance is provided below according to equation (4). The equations for intrinsic clearance and hepatic clearance are provided below as equations (5) and (6) respectively. In equation (6), *F*_{u,B} refers to the fraction of unbound drug in blood, which is assumed to be 1.

$$\text{In vitro CL}_{\text{int}} = k_e \times \frac{\text{Incubation volume}}{\text{Microsomal protein amount}} \quad (4)$$

$$\text{CL}_{\text{int}} = \text{In vitro CL}_{\text{int}} \times \frac{\text{Liver weight (g)}}{\text{Body weight (kg)}} \times \frac{\text{Microsomal protein (mg)}}{\text{Liver weight (g)}} \quad (5)$$

$$CL_{int} = \frac{Q_{hep} \times F_{u,B} \times CL_{int}}{Q_{hep} + F_{u,B} \times CL_{int}} \quad (6)$$

[0517] Physiological variable predictions used to calculate intrinsic clearance and hepatic clearance are provided below in Table 5:

TABLE 5

Species	Microsomal protein	Liver weight	Liver blood flow
	(mg/g liver weight)	(g/kg body weight)	(Q_{hep} , mL/min/kg)
Human	45	25.7	20.7
Rat	45	40	55.2

[0518] The data for human liver microsome samples is provided below in Table 6 for samples incubated with Compound 3 or with dextromethorphan. A plot of % dextromethorphan remaining over time with NADPH in human liver microsome samples is illustrated in FIG. 1. A plot of % Compound 3 remaining over time with NADPH in human liver microsome samples is illustrated in FIG. 2.

TABLE 6

Time (min)	Peak area ratio	% Remaining	Ln (%) remaining)	R ²	ke (min ⁻¹)	T _{1/2} (min)	<i>In vitro</i> CL _{int} (μL/min/mg protein)	CL _{int} (mL/min/kg)	CL _{hep} (mL/min/kg)
Dextromethorphan									
0	1.86	100.00	4.61	0.99	0.02	37.67	36.80	42.56	13.93
5	1.59	85.48	4.45						
15	1.28	68.82	4.23						
30	1.04	55.91	4.02						
60	0.592	31.83	3.46						
Compound 3									
0	3.22	100.00	4.61	-	-	>186.4	<7.44	<8.6	<6.08
5	3.30	102.48	4.63						
15	3.19	99.07	4.60						
30	3.18	98.76	4.59						

60	2.83	87.89	4.48	
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[0519] The data for rat liver microsome samples is provided below in Table 7 for samples incubated with Compound 3 or with dextromethorphan. A plot of % dextromethorphan remaining over time with NADPH in rat liver microsome samples is illustrated in FIG. 3. A plot of % Compound 3 remaining over time with NADPH in rat liver microsome samples is illustrated in FIG. 4.

TABLE 7

Time (min)	Peak area ratio	% Remaining	Ln (%) remaining)	R ²	ke (min ⁻¹)	T _{1/2} (min)	<i>In vitro</i> CL _{int} (μL/min/mg protein)	CL _{int} (mL/min/kg)	CL _{hep} (mL/min/kg)
Dextromethorphan									
0	4.01	100.00	4.61	0.99	0.13	5.24	264.57	476.22	49.47
5	2.36	58.85	4.08						
15	0.415	10.35	2.34						
30	0.0835	2.08	0.73						
60	0.0131	0.33	-1.12						
Compound 3									
0	1.32	100.00	4.61	0.88	0.01	63.93	21.68	39.03	22.86
5	1.28	96.97	4.57						
15	1.30	98.48	4.59						
30	1.17	88.64	4.48						
60	0.685	51.89	3.95						

[0520] The data for human and rat intrinsic and hepatic clearance is summarized below in Table 8 for Compound 3 and dextromethorphan.

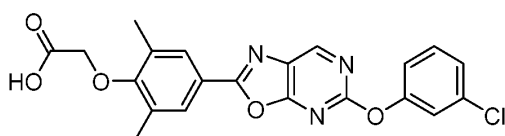
TABLE 8

Compound	Human			Rat		
	T _{1/2} (min)	<i>In vitro</i> CL _{int} (μL/min/ mg protein)	CL _{hep} (mL/min/ kg)	T _{1/2} (min)	<i>In vitro</i> CL _{int} (μL/min/ mg protein)	CL _{hep} (mL/min/ kg)
Compound 3	>186.3 8	<7.44	<6.08	63.9	21.7	22.9
Dextro- methorphan	37.7	36.8	13.9	5.2	264.6	49.5

Example 10

Tissue Binding Determination Study of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one (Compound 3) and 2-(4-(5-(3-Chlorophenoxy)oxazolo[5,4-d]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid (Compound A) in Rat Heart Tissue

[0521] The tissue binding of 1-(4-(2-(1*H*-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1*H*)-one (“Compound 3” in Table 29 below) was measured in rat heart tissue in comparison to 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid (“Compound A”), the structure of which is disclosed below:



2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid
(Compound A).

[0522] The rat heart tissue samples used in this example are listed below in Table 9:

TABLE 9

Species	Gender	Tissue	Vendor	Storage
SD Rat	Male	Heart	Bioduro	-20 °C

[0523] Phosphate buffer was prepared by dissolving 3.12 g of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 28.64 g of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$, and 5.844 g of NaCl in 950 mL of water. The pH of the solution was adjusted to 7.4 with aqueous 12 N NaOH solution. The solution was adjusted with water to a

final total volume of 1000 mL. The buffer was filtered through 0.22 µm filter, and stored in a refrigerator at 4 °C for future use.

[0524] A 4-fold weight of phosphate buffer solution was added to tissue to get tissue homogenate.

[0525] A quenching solution was prepared by making a terfenadine/tolbutamide (1 mg/mL each) stock solution with DMSO, then diluting the stock solution in methanol/acetonitrile (1:1, v/v) to prepare the quenching solution containing 5/10 ng/mL terfenadine/tolbutamide.

[0526] A stock solution of Compound 3 (molecular weight, 445.4 g/mol) was prepared in DMSO at a molarity of 10 mM. A working solution of Compound 3 at a molarity of 1 mM was prepared from the stock solution. A dosing solution at a molarity of 5 µM was prepared with tissue homogenate from the working solution. A stock solution of 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid ("Compound A," molecular weight, 425.1 g/mol) was prepared in DMSO at a molarity of 10 mM. A working solution of Compound A was prepared from the stock solution. A dosing solution at a molarity of 5 µM was prepared with tissue homogenate from the working solution.

[0527] A control compound dosing solution was prepared by making a 10 mM diclofenac stock solution. A 0.2 mM working solution was prepared from the diclofenac stock solution with DMSO. A 1 µM dosing solution was prepared from the working solution with tissue homogenate.

[0528] Equilibrium dialysis was performed according to the following procedure. A dialysis plate was prepared by adding 120 µL buffer to the buffer chamber, and 120 µL of dosing solution to the tissue side. The dialysis plate was sealed with an adhesive film to prevent evaporation. The dialysis plate was incubated in a 37 °C CO₂ incubator (5% CO₂) for 5 hours, shaking at 100 rpm. After five hours, the incubation plate was transferred to the bench from the incubator. 30 µL aliquot samples were taken from the tissue side and the buffer side of the dialysis plate for further analysis.

[0529] After the preparation of the dosing solutions, 30 µL aliquots of the dosing solutions were taken as the T0 samples. The remaining dosing solutions were placed in a 37 °C CO₂ incubator for 5 hours, then 30 µL aliquots were taken as the T5 samples.

[0530] To prepare the samples, blank tissue homogenate and blank phosphate buffer were prepared for use. 30 µL of sample from the tissue side, T0 samples, and T5 samples were each mixed with 30 µL of blank phosphate buffer. 180 µL of quenching solution was added. The samples were vortexed for 1 minute then centrifuged at 4000 rpm for 15 minutes. 30 µL of sample from the buffer side was mixed with 30 µL of blank tissue homogenate. 180

μL of quenching solution was added, and the sample was vortexed for 1 minute then centrifuged at 4000 rpm for 15 minutes. A 100 μL aliquot of supernatant was taken and mixed well with 100 μL of water for LC-MS/MS analysis.

[0531] Mass spectrometry was performed by multiple reaction monitoring (MRM) of *m/z* values for 446.082 and 418.000 for Compound 3 and 426.009 and 367.000 for 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid, using a Kinetex 2.6 μm C18 100 Å column (2.1 mm x 50 mm). Mobile phase A: 0.1% formic acid in H₂O, Mobile phase B: 0.1% formic acid in acetonitrile, for a run time of 2 minutes.

[0532] The Bound (%), Recovery (%), and Stability (%) were calculated according to the following equations (7) – (9):

$$\text{Bound (\%)} = 100 \% - F_{u,100\%} (\%) \quad (7)$$

$$\text{Recovery (\%)} = \frac{(C_t + C_b)}{C_{T0}} \times 100 \% \quad (8)$$

$$\text{Stability (\%)} = \frac{C_{T5}}{C_{T0}} \times 100 \% \quad (9).$$

$F_{u,100\%} (\%)$ was calculated according to equation (10):

$$F_{u,100\%} (\%) = \frac{F_{u,20\%}}{5 - 4 \times F_{u,20\%}} \times 100 \% \quad (10).$$

$F_{u,20\%} (\%)$ was calculated according to equation (11):

$$F_{u,20\%} (\%) = \frac{C_b}{C_t} \times 100 \% \quad (11).$$

In equations (7) – (11), C_t refers to the concentration of the test compound from the tissue side; C_b refers to the concentration of the test compound from the buffer side; C_{T5} refers to the concentration of the test compound from the T5 sample; and C_{T0} refers to the concentration of the test compound from the T0 sample.

[0533] The results of the tissue binding study for each of Compound 3 and 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid are provided below in Table 10.

TABLE 10

$F_{u,20\%} (\%)$	$F_{u,100\%} (\%)$	Bound (%)		Stability (%)		Recovery (%)	
Replicate	Replicate	Replicate	Mean	Replicate	Mean	Replicate	Mean
2-(4-(5-(3-chlorophenoxy)oxazolo[5,4- <i>d</i>]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid							
3.99	0.83	99.17	99.16	87.32	87.07	91.34	93.12
4.10	0.85	99.15		86.81		94.90	

Compound 3							
2.87	0.59	99.41	99.42	99.25	103.30	80.21	82.02
2.82	0.58	99.42		107.34		83.84	

Example 11

Plasma Protein Binding Determination Study of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one (Compound 3) in Human and Rat Plasma Protein

[0534] The plasma protein binding of 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (“Compound 3” in Table 29 below) was measured in rat and human plasma protein in comparison to warfarin.

[0535] The plasma protein samples used in this example are listed below in Table 10:

TABLE 11

Species	Gender	Vendor	Catalog #	Storage
Human	Male	澳能	FTS-P-100	-20 °C
Rat	Male	BIOIVT	RAI470507	-20 °C

[0536] Phosphate buffer was prepared by dissolving 3.12 g of NaH₂PO₄·2H₂O, 28.64 g of Na₂HPO₄·12H₂O, and 5.844 g of NaCl in 950 mL of water. The pH of the solution was adjusted to 7.4 with aqueous 12 N NaOH solution. The solution was adjusted with water to a final total volume of 1000 mL. The buffer was filtered through 0.22 μm filter, and stored in a refrigerator at 4 °C for future use.

[0537] The plasma was thawed in a 37 °C water bath. The pH of the plasma was adjusted to 7.4.

[0538] A quenching solution was prepared by making a terfenadine/tolbutamide (1 mg/mL each) stock solution with DMSO, then diluting the stock solution in acetonitrile to prepare the quenching solution containing 5/10 ng/mL terfenadine/tolbutamide.

[0539] A stock solution of Compound 3 (molecular weight, 445.4 g/mol) was prepared in DMSO at a molarity of 10 mM. A working solution of Compound 3 at a molarity of 1 mM was prepared from the stock solution. A dosing solution at a molarity of 5 μM was prepared with plasma from the working solution.

[0540] A control compound dosing solution was prepared by making a 10 mM warfarin stock solution. A 1 mM working solution was prepared from the warfarin stock

solution with DMSO. A 5 μ M dosin solution was prepared from the working solution with plasma.

[0541] Equilibrium dialysis was performed according to the following procedure. A dialysis plate was prepared by adding 120 μ L buffer to the buffer chamber, and 120 μ L of dosing solution to plasma side. The dialysis plate was sealed with an adhesive film to prevent evaporation. The dialysis plate was incubated in a 37 °C incubator for 5 hours, shaking at 100 rpm. After five hours, the incubation plate was transferred to the bench from the incubator. 30 μ L aliquot samples were taken from the tissue side and the buffer side of the dialysis plate for further analysis.

[0542] After the preparation of the dosing solution, 30 μ L aliquots of the dosing solution were taken as the T0 samples. The remaining dosing solutions were placed in a 37 °C incubator for 5 hours, then 30 μ L aliquots were taken as the T5 samples.

[0543] To prepare the samples, blank plasma and blank phosphate buffer were prepared for use. A 30 μ L of sample of plasma from the plasma side, T0 samples, and T5 samples were each mixed with 30 μ L of blank phosphate buffer. 180 μ L of quenching solution was added. The samples were vortexed for 1 minute then centrifuged at 4000 rpm for 15 minutes. 30 μ L of sample from the buffer side was mixed with 30 μ L of blank plasma. 180 μ L of quenching solution was added, and the sample was vortexed for 1 minute then centrifuged at 4000 rpm for 15 minutes. A 100 μ L aliquot of supernatant was taken and mixed well with 100 μ L of water for LC-MS/MS analysis.

[0544] Mass spectrometry was performed by multiple reaction monitoring (MRM) of m/z values for 446.082 and 418.000 for Compound 3, using a Kinetex 2.6 μ m C18 100 Å column 92.1 mm x 50 mm). Mobile phase A: 0.1% formic acid in H₂O, Mobile phase B: 0.1% formic acid in acetonitrile, for a run time of 2 minutes.

[0545] The Bound (%) and Recovery (%) were calculated according to the following equations (12) and (13). The Stability (%) was calculated according to equation (9) above.

$$\text{Bound (\%)} = 100 \% - \text{Free (\%)} \quad (12)$$

$$\text{Recovery (\%)} = \frac{C_p + C_b}{C_{T0}} \times 100 \% \quad (13)$$

The Free (%) was calculated according to the following equation (14):

$$\text{Free (\%)} = \frac{C_b}{C_p} \times 100 \% \quad (14)$$

In equations (12) – (14) and (9), C_p refers to the concentration of the test compound from the plasma side; C_b refers to the concentration of the test compound from the buffer side; C_{T5} refers to the concentration of the test compound from the T5 sample; and C_{T0} refers to the concentration of the test compound from the T0 sample.

[0546] The results of the plasma protein binding study for Compound 3 in human plasma is provided below in Table 12 relative to warfarin.

TABLE 12

Free %	Bound %		Stability (%)		Recovery (%)	
Replicate	Replicate	Mean	Replicate	Mean	Replicate	Mean
Compound 3						
0.18	99.82	99.81	109.04	104.86	102.23	98.66
0.19	99.81		100.68		96.10	
Warfarin						
0.68	99.32	99.31	107.75	103.88	92.09	94.45
0.70	99.30		100.00		96.80	

[0547] The results of the plasma protein binding study for Compound 3 in rat plasma is provided below in Table 13 relative to warfarin.

TABLE 13

Free (%)	Bound (%)		Stability (%)		Recovery (%)	
Replicate	Replicate	Mean	Replicate	Mean	Replicate	Mean
Compound 3						
0.69	99.20	99.39	100.35	98.16	85.55	91.38
0.54	99.46		95.98		97.20	
Warfarin						
0.80	99.20	99.16	107.63	101.91	87.72	86.98
0.88	99.12		96.18		86.25	

Example 12

In vitro Cytochrome P450 ("CYP") Enzyme Inhibition Studies of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one (Compound 3) in Human Liver Microsomal Fractions

[0548] The metabolic stability of 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one ("Compound 3" in Table 29 below) was measured in human microsomes. The liver microsome samples used in this

example are listed below in Table 14:

TABLE 14

Species	Gender	Vendor	Catalog #	Lot #	Storage
Human	Mixed	Corning	452117	38295	-80 °C

[0549] Phosphate buffer was prepared by dissolving 8.71 g of K₂HPO₄ in 950 mL of water. The pH of the solution was adjusted to 7.4 with aqueous HCl solution. The solution was adjusted with water to a final total volume of 1000 mL. The buffer was filtered through 0.22 µm filter, and stored in a refrigerator at 4 °C for future use.

[0550] A quenching solution was prepared by making a terfenadine/tolbutamide (1 mg/mL each) stock solution with DMSO, then diluting the stock solution in acetonitrile to a quenching solution containing 5/10 ng/mL (terfenadine/tolbutamide).

[0551] Positive working control stock solution was prepared according to Table 15:

TABLE 15

CYP isoform	Inhibitor	Stock Conc. (mM)	Max Working Conc. (µM)	Max Incubation Conc. (µM)	Stock solution Volume (µL)	Total Working Solution Volume (µL)	Format
1A2	β-Naphtho-flavone	2	400	2	10	50	5-in-1
2C9	Sulfa-phenazole	6	1200	6	10		5-in-1
2C19	Tranyl-cypromine	60	12000	60	10		5-in-1
2D6	Quinidine	0.6	120	0.6	10		5-in-1
3A4/5	Ketoconazole	2	400	2	10		5-in-1
2B6	Ticlopidine	1.2	1200	6	50	50	Individual
2C8	Quercetin	4	4000	20	50	50	Individual

[0552] Controls working solutions (4-fold dilution, 6 non-zero concentrations) with DMSO from the above stock solutions.

[0553] Substrate working control stock solution was prepared according to Table 16:

TABLE 16

CYP iso-form	Substrate	Stock Conc. (mM)	Working Conc. (μ M)	Incubation Conc. (μ M)	Solution Volume (μ L)	Total Working Solution Volume (μ L)	Format
1A2	Phenacetin	250	50	50	2	10	5-in-1
2C9	Diclofenac	50	10	10	2		5-in-1
2C19	Mephenytoin	125	25	25	2		5-in-1
2D6	Dextro-methorphan	25	5	5	2		5-in-1
3A4/5	Midazolam	12.5	2.5	2.5	2		5-in-1
2B6	Bupropion	80	80	80	5	5	Individual
2C8	Amodiaquine	2	2	2	5	5	Individual

[0554] Liver microsome was thawed in a 37 °C water bath. Liver microsome working solutions having a volume of 8.395 mL were prepared according to Table 17 below:

TABLE 17

Liver microsome stock concentration (mg/mL)	Liver microsome stock volume (μ L)	Substrate working solution volume (μ L)	Phosphate buffer volume (mL)
20	52.8	10.6	8.332

[0555] A 5 mM NADPH working solution was prepared with phosphate buffer.

[0556] A working solution of Compound 3 was prepared from a stock solution of 10 mM by 4-fold dilution of the stock solution (6 non-zero concentrations) with DMSO.

[0557] Incubation was performed by adding 1.5 μ L of control or Compound 3 working solution to 238.5 μ L liver microsome working solution in a 1.1 mL tube, with mixing by pipetting several times. The mixture was pre-incubated in a 37 °C shaking water bath for 5 minutes. Reaction was initiated by adding 60 μ L NADPH working solution. The solutions were mixed by pipetting several times. The incubation proceeded in the 37 °C shaking water bath for 10 minutes. Following the incubation, 300 μ L of quenching solution was immediately added, followed by vortexing for about 20 seconds. All samples were

centrifuged at 4000 rpm for 15 minutes at 4 °C, then the supernatant was transferred for LC-MS/MS analysis.

[0558] Mass spectrometry was performed by multiple reaction monitoring (MRM) of the analytes according to Table 18 below, using a Kinetex 2.6 µm C18 100 Å column (2.6 mm x 50 mm). Mobile phase A: 0.1% formic acid in H₂O, Mobile phase B: 0.1% formic acid in acetonitrile, for a run time of 2.5 minutes.

TABLE 18

Analyte	Ionization mode	MRM
Acetaminophen	ESI, positive	152.1 / 110.0
4'-Hydroxydiclofenac	ESI, positive	312.1 / 230.0
4'-Hydroxymephenytion	ESI, positive	235.0 / 150.0
Dextrophan	ESI, positive	258.2 / 199.1
1'-Hydroxymidazolam	ESI, positive	342.1 / 203.0
Hydroxybupropion	ESI, positive	256.0 / 139.0
N-desethylamodiaquine	ESI, positive	328.1 / 255.1

[0559] The CYP inhibition data for Compound 3 and positive control are provided below in Table 19. Plots of enzyme inhibition for each of the CYP isoforms by Compound 3 at various concentrations of Compound 3 are illustrated in FIGs. **5 – 11**. Plots of enzyme inhibition for each of the CYP isoforms by a positive control at various concentrations of the positive control are illustrated in FIGs. **12 – 18**. Half maximal inhibitory concentration is indicated on each of FIGs. **5 – 18**.

TABLE 19

Test Conc (µM)	1A2		2C9		2C19		2D6		3A4/5		2B6		2C8	
	Control (%)		Control (%)		Control (%)		Control (%)		Control (%)		Control (%)		Control (%)	
	Raw	Mean	Raw	Mean	Raw	Mean	Raw	Mean	Raw	Mean	Raw	Mean	Raw	Mean
Compound 3														
50	52.72	52.82	42.46	41.91	73.28	75.21	77.00	75.96	62.09	62.24	34.67	35.33	25.11	24.68
	52.92		41.36		77.13		74.91		62.39		34.00		24.24	
12.5	92.31	91.38	81.14	80.43	100.83	101.10	109.06	107.49	87.16	86.57	106.33	99.00	76.05	72.82
	90.46		79.72		101.38		105.92		85.97		91.67		69.58	
3.1	104.41	105.23	96.61	98.03	104.68	104.13	109.76	109.76	95.52	95.82	118.67	122.33	94.50	97.90

	106.05		99.45		103.58		109.76		96.12		126.00		101.29	
0.78	102.36	103.08	99.13	98.97	104.68	103.58	195.92	105.23	99.40	98.21	112.00	109.33	93.53	95.31
	103.79		98.82		102.48		104.53		97.01		106.67		97.09	
0.20	98.67	100.10	96.92	97.87	98.62	102.75	105.23	104.70	97.31	98.21	101.33	105.83	109.06	106.63
	101.54		98.82		106.89		104.18		99.10		110.33		104.21	
0.049	102.97	104.00	100.24	101.34	98.07	100.28	105.23	103.83	99.40	101.04	100.33	106.33	107.77	105.50
	105.03		102.45		102.48		102.44		102.69		112.33		103.24	
0	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Positive Control														
–	6.51	6.25	10.60	10.96	5.71	6.64	9.60	9.62	2.94	2.87	3.95	3.92	17.65	17.33
	5.99		11.31		7.57		9.64		2.79		3.89		17.02	
–	17.14	16.84	32.60	33.33	29.91	27.57	27.80	27.44	5.66	5.77	8.31	8.29	57.62	59.44
	16.53		34.06		25.24		27.07		5.87		8.27		61.26	
–	46.03	46.37	69.76	71.31	63.09	64.67	59.27	60.04	13.16	13.25	19.33	19.41	80.79	89.40
	46.71		72.86		66.25		60.80		13.33		19.50		98.01	
–	88.44	86.62	99.64	97.36	100.32	99.05	92.93	91.78	33.40	33.28	67.34	60.13	86.42	93.71
	84.81		95.08		97.79		90.63		33.16		52.93		100.99	
–	106.35	104.31	110.38	107.83	111.67	109.46	107.46	104.97	73.23	72.54	88.11	90.28	97.68	98.01
	102.27		105.28		107.26		102.49		71.85		92.46		98.34	
–	109.07	111.79	111.11	113.66	110.41	112.62	108.99	109.37	99.48	102.25	100.50	99.16	91.39	92.88
	114.51		116.21		114.83		109.75		105.01		97.82		94.37	
0	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Example 13

Metabolic Stability Assay and Intrinsic Clearance of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one (Compound 3) in Rat and Human Hepatocyte Incubations

[0560] The metabolic stability and intrinsic clearance of 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (“Compound 3” in Table 29 below) was measured in rat and human hepatocyte incubations. The hepatocyte samples used in this example are listed below in Table 20:

TABLE 20

Species	Gender	Vendor	Catalog #	Lot #
---------	--------	--------	-----------	-------

Human	Mixed	BioIVT	X008000	YEU
Sprague-Dawley Rat	Male	RILD	LH-DS-02M	KIO

[0561] Human recombinant insulin solution (4 mg/mL) was prepared by diluting acetic acid 100-fold with distilled water, then adding human recombinant insulin such that when dissolved in the dilute acetic acid, the final concentration is 4 mg/mL.

[0562] Dexamethasone solution at a concentration of 10 mM was prepared by dissolving dexamethasone in DMSO.

[0563] The thawing medium was prepared according to the reagents listed in Table 21:

TABLE 21

Reagents	Volume (mL)	Final Concentration
Williams E medium	700	–
Isotonic percoll	270	–
10% DPBS	30.0	–
Glutamax	10.00	2 mM
HEPES	15.00	15 mM
Fetal bovine serum	50.0	0.05 mM
Human recombinant insulin	1.00	4.0 µg/mL
Dexamethasone	0.100	1.0 µM

[0564] An incubation medium was prepared by adding 6.122 mL glutamine to 300 mL of Williams E medium to achieve a final glutamine concentration of 4.0 mM. The incubation medium was thoroughly mixed, and an aliquot of 15 mL of the incubation solution was transferred to each 15 mL tube and stored at 4 °C for up to 30 days.

[0565] Stock solutions at 1 mg/mL of terfenadine and tolbutamide were prepared by dissolving appropriate amounts of terfenadine or tolbutamide in DMSO. A quenching solution containing 5 and 10 ng/mL of terfenadine and tolbutamide, respectively, was prepared from the stock solutions with dilution with acetonitrile.

[0566] The hepatocytes were prepared according to the following thawing procedure. 50 mL of cryopreserved hepatocyte recovery medium (“CHRM”) was pre-warmed in a 37 °C

water bath incubator for at least 25 minutes prior to use. A vial of rat or human hepatocytes was removed from a liquid nitrogen tank. The vial was immediately immersed in the 37 °C water bath incubator. The vial was gently shaken until it was thoroughly thawed. The pre-warmed CHRM was aliquoted in a EP tube for future use (1 mL per vial of hepatocytes). The thawed hepatocytes were immediately added to the pre-warmed CHRM. 1 mL of CHRM was added to the emptied vial to re-suspend the remaining cells. The suspension was combined with the hepatocyte/CHRM solution. The hepatocytes were resuspended by gently inverting the hepatocyte/CHRM solution several times. The hepatocytes were centrifuged at room temperature (100 x g for 10 minutes). The supernatant was discarded. 1.5 mL of pre-warmed incubation medium was added to pellets from each vial, with gentle swirling to mix.

[0567] Cell counting was performed under a microscope after diluting 50 µL of cells by adding 400 µL incubation medium and 50 µL trypan blue. 12 µL diluted cell suspension was removed for counting. The cells may only be used when cell viability is greater than 70%. The cells were diluted to 2 million viable cells/mL in the incubation medium. The cell counting data is reported below in Table 22.

TABLE 22

	Human		Rat	
	Living cell	Dead cell	Living cell	Dead cell
Cell No. of top 4	111	26	139	56
Cell No. of bottom 4	109	3	136	50
Average cell No.	110	29	138	53
Viability (%)	79.4		72.2	
Total cell No. per mL	$2.75 \cdot 10^6$		$3.44 \cdot 10^6$	
Dilution factor	1.38		1.72	
Original volume of cell (mL)	1.85		1.90	
Final total volume (mL)	2.54		3.27	
Medium volume (mL)	0.69		1.37	

[0568] A stock solution of Compound 3 (molecular weight, 445.4 g/mol) in DMSO at a molarity of 10 mM. A working solution of Compound 3 at a molarity of 2 μ M was prepared with the incubation medium.

[0569] Incubation was performed according to the following procedure. The hepatocyte suspensions were pre-incubated in the 37 °C CO₂ incubator for 20 minutes. 400 μ L of positive control or Compound 3 solution was added into wells on a 24-well plate. The reaction was initiated by adding 400 μ L of hepatocytes (2 million cells/mL) into wells containing the control or Compound 3 solution. The plate was gently agitated on the orbital shaker at 100 rpm speed to mix. The plates were incubated in the CO₂ incubator. At each time point (0, 15, 30, 60, 90, and 120 minutes), 30 μ L of the reaction mixture was removed from the plate and added to 300 μ L of quenching solution, and vortexed for 1 minute to mix. The samples were centrifuged at 4000 rpm for 15 minutes at 4 °C. 100 μ L of supernatant was removed to a 96-well plate and mixed with 100 μ L of distilled water for LC-MS/MS analysis.

[0570] Mass spectrometry was performed by multiple reaction monitoring (MRM) of analytes according to Table 23 below, using a Kinetex 2.6 μ m C18 100 Å column (3.0 mm x 30 mm). Mobile phase A: 0.1% formic acid in H₂O, Mobile phase B: 0.1% formic acid in acetonitrile for a run time of 2 minutes.

[0571] The percent remaining was calculated according to equation (1). The equation of first order kinetics (equation (2)) was used to calculate half-life (“t_{1/2}”) and intrinsic clearance (“CL_{int}”), from which equation (3) to provide half-life may be derived.

[0572] The equation for *in vitro* intrinsic clearance is provided below according to equation (15). The equations for intrinsic clearance and hepatic clearance are provided below as equations (16) and (17) respectively. In equation (17), F_u refers to the fraction of unbound drug in plasma, which is assumed to be 1.

$$\text{In vitro CL}_{\text{int}} = \frac{0.693}{t_{1/2}} \times \frac{\text{Incubation volume } (\mu\text{L})}{\text{Cells number (million)}} \quad (15)$$

$$\text{CL}_{\text{int}} = \text{In vitro CL}_{\text{int}} \times \frac{\text{liver weight (g)}}{\text{body weight (kg)}} \times \frac{\text{cell numbers (millions)}}{\text{liver weight (g)}} \quad (16)$$

$$\text{CL}_{\text{hepatic}} = \frac{Q_{\text{hep}} \times F_u \times \text{CL}_{\text{int}}}{Q_{\text{hep}} + F_u \times \text{CL}_{\text{int}}} \quad (17)$$

[0573] Physiological variable predictions used to calculate intrinsic clearance and hepatic clearance are provided below in Table 23.

TABLE 23

Species	Hepatocellularity	Liver weight	Liver blood flow (Q_{hep})
	Million cells/g liver weight	g/kg body weight	mL/min/kg
Human	120	25.7	20.7
Monkey	120	30	43.6
Dog	240	32	30.9
Rat	120	40	55.2
Mouse	120	87.5	90
Rabbit	120	30.8	70.8
Mini-pig	120	16.7	38.9

[0574] The data for human hepatocyte samples is provided below in Table 24 for samples incubated with Compound 3, phenacetin, diclofenac, dextromethorphan, omeprazole, midazolam, and 7-ethoxycoumarin. Plots of each of % remaining of each of phenacetin, diclofenac, dextromethorphan, omeprazole, midazolam, 7-ethoxycoumarin, and Compound 3 in human hepatocyte samples are illustrated in FIGs. 19 – 25.

TABLE 24

Time (min)	Area ratio	% Remaining	Ln (%) remaining)	R ²	ke (min ⁻¹)	T _{1/2} (min)	<i>In vitro</i> CL _{int} (μL/min/10 ⁶ cells)	CL _{int} (mL/min/kg)	CL _{hep} (mL/min/kg)
Phenacetin									
0	0.564	100.0	4.61	0.99	0.01	52.03	13.32	41.09	13.76
15	0.416	73.8	4.30						
30	0.316	56.0	4.03						
60	0.247	43.8	3.78						
90	0.166	29.4	3.38						
120	0.103	18.3	2.90						
Diclofenac									
0	0.147	100.0	4.61	0.99	0.06	10.79	64.23	198.10	18.74

15	0.0656	44.6	3.80						
30	0.0214	14.6	2.68						
60	0	0.0	–						
90	0	0.0	–						
120	0	0.0	–						
Dextromethorphan									
0	1.27	100.0	4.61	1.00	0.04	19.34	35.84	110.52	17.43
15	0.899	70.8	4.26						
30	0.534	42.8	3.74						
60	0.164	12.9	2.56						
90	0.0492	3.9	1.35						
120	0.0206	1.6	0.48						
Omeprazole									
0	0.823	100.0	4.61	0.95	0.01	53.33	13.00	40.08	13.65
15	0.696	84.6	4.44						
30	0.567	68.9	4.23						
60	0.505	61.4	4.12						
90	0.305	37.1	3.61						
120	0.155	18.8	2.94						
Midazolam									
0	1.63	100.0	4.61	1.00	0.03	23.97	28.92	89.20	16.80
15	1.19	73.0	4.29						
30	0.806	49.4	3.90						
60	0.324	19.9	2.99						
90	0.126	7.7	2.05						
120	0.0551	3.4	1.22						
7-Ethoxycoumarin									
0	0.846	100.0	4.61	0.96	0.06	11.01	62.95	194.14	18.71

15	0.461	54.5	4.00						
30	0.128	15.1	2.72						
60	0	0.0	–						
90	0	0.0	–						
120	0	0.0	–						
Compound 3									
0	1.15	100.0	4.61	–	–	>3.72.8	<1.9	<5.7	<4.5
15	1.28	111.3	4.71						
30	1.24	107.8	4.68						
60	1.24	107.8	4.68						
90	1.25	108.7	4.69						
120	1.15	100.0	4.61						

[0575] The data for rat hepatocyte samples is provided below in Table 25 for samples incubated with Compound 3, phenacetin, diclofenac, dextromethorphan, omeprazole, midazolam, and 7-ethoxycoumarin. Plots of each of % remaining of each of phenacetin, diclofenac, dextromethorphan, omeprazole, midazolam, 7-ethoxycoumarin, and Compound 3 in rat hepatocyte samples are illustrated in FIGs. **26 – 32**.

TABLE 25

Time (min)	Area ratio	% Remaining	Ln (% Remain)	R ²	ke (min ⁻¹)	T _{1/2} (min)	<i>In vitro</i> CL _{int} (μL/min/10 ⁶ cells)	CL _{int} (mL/min/kg)	CL _{hep} (mL/min/kg)
Phenacetin									
0	0.671	100.0	4.61	0.97	0.05	14.44	48.00	230.38	44.53
15	0.413	61.5	4.12						
30	0.159	23.7	3.17						
60	0	0.0	–						
90	0	0.0	–						
120	0	0.0	–						
Diclofenac									

0	0.328	100.0	4.61	0.99	0.06	10.79	64.27	308.48	46.82
15	0.105	32.0	3.47						
30	0.0325	9.9	2.29						
60	0.00683	2.1	0.73						
90	0	0.0	–						
120	0	0.0	–						
Dextromethorphan									
0	1.15	100.0	4.61	–	0.25	2.72	254.45	1221.35	52.81
15	0.0253	2.2	0.79						
30	0.00673	0.6	-0.54						
60	0	0.0	–						
90	0	0.0	–						
120	0	0.0	–						
Omeprazole									
0	0.546	100.0	4.61	1.00	0.11	6.36	108.92	522.83	49.93
15	0.0926	17.0	2.83						
30	0.0208	3.8	1.34						
60	0	0.0	–						
90	0	0.0	–						
120	0	0.0	–						
Midazolam									
0	1.04	100.0	4.61	–	0.24	2.91	238.19	1143.30	52.66
15	0.0292	2.8	1.03						
30	0	0.0	–						
60	0	0.0	–						
90	0	0.0	–						
120	0	0.0	–						
7-Ethoxycoumarin									

0	0.678	100.0	4.61	0.94	0.06	10.71	64.71	310.62	46.87
15	0.395	58.3	4.06						
30	0.0973	14.4	2.66						
60	0	0.0	–						
90	0	0.0	–						
120	0	0.0	–						
Compound 3									
0	20.8	100.0	4.61	–	–	>372.8	<1.9	<8.9	<7.7
15	20.7	99.5	4.60						
30	22.7	109.1	4.69						
60	20.8	100.0	4.61						
90	20.7	99.5	4.60						
120	16.8	80.8	4.39						

Example 14

Study of Induced Temporary Lymphopenia Upon Administration of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one (Compound 3) in Rats

[0576] The ability of 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (“Compound 3” in Table 29 below) to induce temporary lymphopenia in rats was evaluated.

[0577] Male Sprague Dawley rats (300 g) were separated into four groups and administered, by oral gavage, (1) vehicle (solutol 20% in water); (2) Compound 3 at 8 mg/kg in vehicle (pH 7.4); (3) Compound 3 at 60 mg/kg in vehicle (pH 7.4); and (4) 100 mg/kg in vehicle (pH 7.4). Blood was collected in EDTA tubes at 0, 2, 6, 24, and 48 hours. All rats were sampled. Samples were analyzed for lymphocyte percent, change from baseline, and total counts of lymphocytes.

[0578] The maximum reduction in circulating lymphocytes was obtained 6 hours after administration of Compound 4, as with administration of 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid, with a return to normal levels by 24 hours after administration for lower doses matching 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid. Further,

there was no difference in reduction observed between administration of 8 mg/kg and 60 mg/kg at all timepoints assessed.

[0579] Additionally, the 100 mg/kg dose of Compound 3 demonstrated a maximum temporary reduction of lymphocytes and delayed recovery to normal values, which matched the dynamics of administration of 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid. FIGs. 33 and 34 illustrates temporary lymphopenia with full recovery by measure of circulating lymphocyte. FIG. 35 illustrates the circulating lymphocyte number for administration of vehicle over time. FIGs. 36 – 38 illustrate the circulating lymphocyte number for administration of 8 mg/kg, 60 mg/kg, and 100 mg/kg Compound 3, respectively, over time.

Example 15

Cellular Assays Upon Adminsitration of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one (Compound 3) with Comparison to Adminsitration of other Compounds

[0580] PathHunter CHO-K1 EDG1(S1P1R) cell lines were submitted to cellular assays to measure β -arrestin recruitment and cyclic adenosine monophosphate (cAMP) accumulation so as to test relative S1P₁ agonism of 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (“Compound 3” in Table 29 below), 2-(4-(5-(3-chlorophenoxy)oxazolo[5,4-*d*]pyrimidin-2-yl)-2,6-dimethylphenoxy)acetic acid, sphingosine-1-phosphate (“S1P”), Ponesimod, and Siponimod.

[0581] β -Arrestin recruitment is a luminescence-based assay, in which the S1P₁ receptor and β -arrestin may each be tagged with the complementing fragments of the β -galactosidase (“ β -gal”) enzyme. Recruitment of β -arrestin to the S1P₁ receptor may result in an active β -gal enzyme, which, in the presence of the substrate, generates light.

[0582] As illustrated in FIGs. 39 and 40, which summarize β -arrestin recruitment for two respective experimental trials, Compound 3 and Compound A demonstrate very similar response curves, which may be clearly distinguished from functional antagonists S1P, Ponesimod, and Siponimod. Further, Table 26 demonstrates the similar EC₅₀ values for β -arrestin recruitment for Compound A and Compound 3.

TABLE 26EC₅₀ Values (nM) for β -Arrestin Recruitment by Various Substrates

Experiment	Compound A	Ponesimod	S1P	Siponimod	Compound 3
1	52.6	1.48	28.5	0.774	38.9
2	54.8	1.97	58.5	0.941	38.7
Average	53.7	1.721	43.485	0.8569	38.8

[0583] cAMP recruitment is a homogeneous time-resolved fluorescence (“HTRF”)-based assay. G_{ai} protein-coupled receptors (“GPCRs”) may inhibit the activity of adenylyl cyclase (“AC”) enzyme, which is responsible for cAMP production. The assay measures total accumulation of cAMP in cells after S1P₁ receptor is activated in the presence of an AC activator, Forskolin, and a non-selective phosphodiesterase (“PDE”) inhibitor, 3-isobutyl-1-methylxanthine (“IBMX”).

[0584] As illustrated in FIGs. **41** and **42**, which summarize G_{ai}-protein activation response curves for two respective experimental trials, Compound 3 and Compound A demonstrate very similar response curves, which may be clearly distinguished from functional antagonists S1P, Ponesimod, and Siponimod. Further, Table 27 demonstrates the similar EC₅₀ values for G_{ai}-protein activation for Compound A and Compound 3.

TABLE 27EC₅₀ Values (nM) for G_{ai}-Protein Activation by Various Substrates

Experiment	Compound A	Ponesimod	S1P	Siponimod	Compound 3
1	1.62	0.131	2.10	0.0609	1.13
2	1.98	0.263	5.48	0.117	1.42
Average	1.8005	0.197	3.7865	0.08895	1.276

[0585] A ratio of β -arrestin to G_{ai}-protein activation may indicate the G_{ai}-protein biased activity on the S1P₁ receptor. As demonstrated in Table 28, the ratio of β -arrestin to G_{ai}-protein activation indicates that Compound 3 has nearly identical G_{ai}-protein biased activity on the S1P₁ receptor as Compound A.

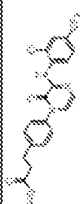
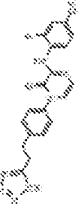
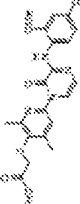
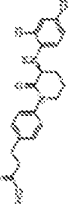
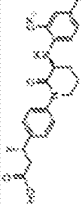
TABLE 28

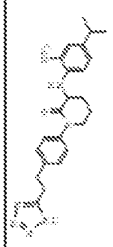
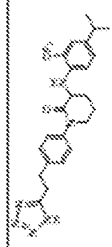
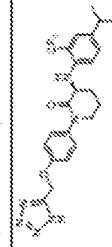
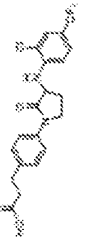
Ratios of β -arrestin to G_{ai} -Protein Activation for Various Substrates

Experiment	Compound A	Ponesimod	S1P	Siponimod	Compound 3
1	32	11	14	13	34
2	28	7	11	8	27
Average	30	9	11	10	30

[0586] The S1P₁ modulation activity was further tested for exemplary compounds 1-13. The results of these tests are set forth in Table 29.

TABLE 29

#	Structure	ΔAMP EC ₅₀	P-30733 EC ₅₀	Ratio	HUYEC Ago/degus (Ratio)	Caco-2 P _t	Met Libb h/m/r	hHES CL	hHep CL (% CYP3A4)	Subst @ pH 7.4	CYP3A4 INS IC ₅₀ nM	hERG IC ₅₀
1		6 nM	91 nM	14	63 nM (583 nM) (1:9)	162	24/31/24	--	0.371 (21%)	18 nM	>30 nM	--
2		74 nM	414 nM	6	92 nM (644 nM) (1:1)	36	29/20<20	--	0.001 (0%)	3725 nM	>30 nM	--
3		21 nM	126 nM	6	76 nM (814 nM) (1:4)	91	<20<20<20	--	0.012 (ND)	22 nM	>30 nM	--
4		31 nM	228 nM	7.4	ND	30	<20<20<20	--	0.002	1169 nM	ND	--
5		40 nM	344 nM	8.6	ND	30	<20<20<20	--	0.014	ND	ND	--
6 (5)		47 nM	810 nM	17	658 nM (>10 nM) (~27)	163	29/23>20	3.58	--	4536 nM	>30 nM >30 nM	>30 nM
7		14 nM	106 nM	7.5	ND	138	<20<20<20	--	ND	ND	ND	ND
8		49 nM	312 nM	6.3	2.5 nM (17.4 nM) (5)	191	29/23<20	ND	0.05	1.29 mg/mL 2782 nM	ND	>30 nM

#	Structure	γ -AMP EC ₅₀	P-arr ₁ EC ₅₀	Ratio	HLVEC Agon:desegs (Ratio)	Caco-2 P _t	Met Lib ^b h/m/r	hHES CL	hHsp CL (% CYP3A4)	Solub. @ pH 7.4	CYP 3A4 ENS IC ₅₀ MT	MERG IC ₅₀
9		14 nM	77 nM	5.5	ND	42	31<20/43	--	ND	0.22 mg/mL 455 μ M	ND	ND
10	 (Enantiomer 1)	6 nM	76 nM	10.9	ND	42	34<20<20	--	0.079 0.195	ND	ND	> 30 μ M
11	 (Enantiomer 2)	201 nM	NoVal	ND	ND	29	<20<20/43	--	0.304	ND	ND	ND
12 (S)		9 nM	210 nM	23.3	ND	ND	ND	--	ND	--	--	--
13		253 nM	1240 nM	5	--	--	--	--	--	--	--	--

^a Catep/Kinase panel (373 K) clean/clean; hGPR40 IC₅₀ > 10 μ M; selec. vs. S1P family high; MNT/Ames II Neg.
^b Catep/Kinase panel (373 K) clean/clean; hGPR40 IC₅₀ > 10 μ M; selec. vs. S1P family; S1P₂ IC₅₀ = 3.8 μ M (ant); S1P₄ IC₅₀ = 6.0 μ M (ant); MNT/Ames II Neg.

Example 16

Pharmacokinetic Study of Oral and Intravenous Administration of 1-(4-(2-(1H-Tetrazol-5-yl)Ethyl)Phenyl)-3-((2-Fluoro-4-Trifluoromethyl)Phenyl)Amino)Pyrazin-2(1H)-one in Rats

[0587] The plasma concentration of 1-(4-(2-(1H-tetrazol-5-yl)ethyl)phenyl)-3-((2-fluoro-4-trifluoromethyl)phenyl)amino)pyrazin-2(1H)-one (Compound 3) were measured over time as administered orally or intravenously to rats.

[0588] For intravenous administration, the dose of Compound 3 in a vehicle of 90% PEG400/10% EtOH at a concentration of 0.20 mg/mL was 1.00 mg/kg, at a dosing volume of 5.00 mL/kg.

[0589] The formulation of Compound 3 for intravenous administration is according to Table 30 below:

TABLE 30

Compound	Formulation	Designed Formulation Concentration (mg/mL)	Mass of Compound (mg)	Final Total Volume (mL)	Volume of PEG400 (mL)	Volume of EtOH (mL)
Compound 3	90% PEG400/10% EtOH	0.20	1.45	6.907	6.216	0.691

[0590] The intravenous formulation was prepared on the day of administration, by weighing a known amount of Compound 3 into a 12 mL glass vial. 6.216 mL of PEG400 was added, and the mixture was vortexed and sonicated to solution. 0.691 mL of EtOH was added, and the mixture was vortexed and sonicated to solution. The dosing solution was filtered using a 0.22 µm filter (Millipore, Durapore®, PVDF). 50 µL of dosing solution was pipetted into a 20 mL glass vial, and 10 mL of MeOH was added for dose concentration verification.

[0591] For oral administration, the dose of Compound 3 in a vehicle of 90% PEG400/10% EtOH at a concentration of 0.50 mg/mL was 5.0 mg/kg, at a dosing volume of 10.0 mL/kg.

[0592] The formulation of Compound 3 for oral administration is according to Table 31 below:

TABLE 31

Compound	Formulation	Designed Formulation Concentration (mg/mL)	Mass of Compound (mg)	Final Total Volume (mL)	Volume of PEG400 (mL)	Volume of EtOH (mL)
Compound 3	90% PEG400/10% EtOH	0.50	5.72	10.899	9.809	1.090

[0593] The oral formulation was prepared on the day of administration, by weighing a known amount of Compound 3 into a 12 mL glass vial. 9.809 mL of PEG400 was added, and the mixture was vortexed and sonicated to solution. 1.090 mL of EtOH was added, and the mixture was vortexed and sonicated to solution. 50 μ L of dosing solution was pipetted into a 20 mL glass vial, and 10 mL of MeOH was added for dose concentration verification.

[0594] The administration doses were tested to be within criteria (and for oral administration, were retested, and confirmed) by ultra-high performance liquid chromatography-MS/MS (“UPLC-MS/MS”).

[0595] The doses were tested by preparing dosing solutions based on the designed formulations. The dose formulations were tested (total 2000x dilution for intravenous and oral doses from the original dosing formulations) by (1) pipetting 50 μ L intravenous and oral dose formulations into 10 mL MeOH for concentration verification (200x dilution), then (2) adding 5 μ L of the intravenous and oral doses from (1) into 50 μ L of blank plasma (10x dilution). The calculated concentrations of Compound 3 in the intravenous and oral doses are provided below in Table 32.

TABLE 32

Route	Nominal Dose Concentration (mg/mL)	Dilution Factor	Determined Concentration (ng/mL)	Calculated Concentration (mg/mL)	Mean Calculated Concentration
Intravenous	0.200	2000	98.3	0.197	0.186
		2000	94.6	0.189	
		2000	85.7	0.171	
Oral	0.500	2000	197	0.394	0.392
		2000	194	0.388	
		2000	197	0.394	

[0596] The calculated concentrations of intravenous dose were within the criteria

($\pm 20\%$) compared with the nominal dose concentrations (0.200 mg/mL). The calculated concentrations of oral dose were not within the criteria ($\pm 20\%$) compared with the nominal dose concentrations (0.500 mg/mL), so the oral dose was retested using neat solvent.

[0597] The oral doses were retested by preparing dosing solutions based on the designed formulations. Rat pharmacokinetic dose formulations were tested (total 1000x dilution for oral doses from the original dosing formulations) by (1) pipetting 100 μL of oral dose formulation into 900 μL MeOH for concentration verification (10x dilution), (2) pipetting 10 μL of oral dose from (1) was added into 990 μL MeOH for concentration verification (100x dilution), and (3) adding 5 μL of the oral dose from (2) into 100 μL of IS and 100 μL of MeOH/H₂O (1:1, v/v) with 0.1% FA. The calculated concentrations of Compound 3 in the oral doses are provided below in Table 33.

TABLE 33

Route	Nominal Dose Concentration (mg/mL)	Dilution Factor	Determined Concentration (ng/mL)	Calculated Concentration (mg/mL)	Mean Calculated Concentration
Oral	0.500	1000	446	0.446	0.467
		1000	465	0.465	
		1000	490	0.490	

[0598] The calculated concentrations of oral doses within the criteria ($\pm 20\%$) compared with the nominal dose concentrations (0.200 mg/mL). The calculated concentrations of oral dose were not consistent with the initial testing, so the oral doses were retested.

[0599] The retests of the oral doses were confirmed by preparing dosing solution based on the designed formulations. Rat pharmacokinetic dose formulations were tested again (total 1000x dilution for oral doses from the original dosing formulations) by (1) pipetting 100 μL of oral dose formulation into 900 μL MeOH for concentration verification (10x) dilution), (2) pipetting 10 μL of oral dose from (1) was added into 990 μL MeOH for concentration verification (100x dilution), and (3) adding 5 μL of the oral dose from (2) into 100 μL of IS and 100 μL of MeOH/H₂O (1:1, v/v) with 0.1% FA. The calculated concentrations of Compound 3 in the oral doses are provided below in Table 34.

TABLE 34

Route	Nominal Dose Concentration (mg/mL)	Dilution Factor	Determined Concentration (ng/mL)	Calculated Concentration (mg/mL)	Mean Calculated Concentration
Oral	0.500	1000	435	0.435	0.439
		1000	450	0.450	
		1000	433	0.433	

[0600] The calculated concentrations for oral doses were within the criteria ($\pm 20\%$) compared with the nominal dose concentrations.

[0601] The LC/MS/MS Conditions used in this Example were as follows:

LC/MS/MS Instrumentation Type: AB Sciex APi 5500+ (JS #2)

LC/MS/MS Quantitation Software and Version #: Analyst Software 1.7.2.

Ionization Mode: Electrospray, Positive ions

Scan Mode: Multiple reaction monitoring (MRM)

MRM of Analyte: 446.08/418.00 (MW: 445.38)

MRM of Internal Standard: 472.40/436.40 (Terfenadine)

LC Method Pump: Shimadzu LC-40D XS

LC Column: Kinetex® C18 2.6 μm 100 Å (50 mm * 2.10 mm) Column

LC Mobile Phase A: 2mM NH₄OAc in water (with 0.1% FA)

LC Mobile Phase B: Acetonitrile (with 0.1% Fa)

Column Temperature: Room temperature

Injection Volume: 1 μL

UPLC Gradient:

Time (min)	Flow Rate (mL/min)	A (%)	B (%)
0.40	0.600	75.0	25.0
1.30	0.600	10.0	90.0
2.20	0.600	10.0	90.0
2.21	0.600	75.0	25.0
3.00	0.600	75.0	25.0

[0602] Plasma samples were prepared according to the following procedure. The samples were in an amount of 50 μL for plasma. Protein precipitation (PPT) by internal standard (ISTD) was performed in MeOH:Acetonitrile (1:1, v/v): (1) 5 μL MeOH was added

to samples; (2) 200 µL of 5 ng/mL ISTD (Terfenadine) in MeOH:Acetonitrile (1:1, v/v) was added to samples; (3) the samples were vortexed for 1 minute and centrifuged at 4000 rpm for 15 minutes; and (4) supernatant was diluted 3x with MeOH:H₂O (1:1, v/v, with 0.1% FA) for injection. The sample matrix and the blank matrix were male Sprague-Dawley Rat plasma:

Matrix	Plasma
Standard Range	1-2000 ng/mL & 5-5000 ng/mL
Regression	Linear
Weighting	1 / (x * x)
Lower Limit of Quantitation ("LLOQ")	1 ng/mL
Internal Standard	Terfenadine (5 ng/mL) in MeOH/Acetonitrile (1:1, v/v)

[0603] The pharmacokinetic data for intravenous administration at 1 mg/kg dose of Compound 3 in 90% PEG400/10% EtOH is provided in Table 35:

TABLE 35

Animal	No. pts used for t _{1/2}	t _{1/2} (hr)	C ₀ (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{Inf} (hr*ng/mL)	AUC _{Extr} (%)	V _z (L/kg)	V _{ss} (L/kg)	CL (mL/min/kg)	MRT _{Inf} (hr)
Rat #7	3	3.95	858	5251	5324	1.37	1.07	0.951	3.13	5.06
Rat #8 Redose	3	3.43	948	6103	6146	0.713	0.805	0.871	2.71	5.35
Rat #9	3	4.36	695	3302	3364	1.84	1.87	1.50	4.95	5.04
N	3	3	3	3	3	3	3	3	3	3
Mean		3.91	834	4885	4945	1.31	1.25	1.11	3.6	5.15
SD		0.47	129	1436	1430	0.57	0.56	0.34	1.2	0.18
CV%		12.0	15.4	29.4	28.9	43.4	44.5	30.8	33.1	3.41

[0604] The pharmacokinetic data for oral administration at 5 mg/kg dose of Compound 3 in 90% PEG400/10% EtOH is provided in Table 36:

TABLE 36

Animal	No. pts used for t _{1/2}	t _{1/2} (hr)	t _{max} (hr)	C _{max} (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	AUC Extr (%)	MRT _{inf} (hr)	AUC _{inf} /D (hr*kg*ng/mL/mg)	F (%)
Rat #10	2	3.27	8.00	1730	22512	22789	1.21	7.65	4558	92.2
Rat #11	2	3.63	8.00	2170	28159	28692	1.86	7.99	5738	116
Rat #12	2	5.20	8.00	2680	37381	39757	5.98	9.47	7951	161
N	3	3	3	3	3	3	3	3	3	3
Mean		4.03	8.00	2193	29351	30413	3.02	8.37	6083	123
SD		1.02	0.00	475	7506	8614	2.58	0.97	1723	35
CV%		25.4	0.00	21.7	25.6	28.3	85.7	11.5	28.3	28.3

[0605] The mean $\pm$ SD concentration of rat plasma concentration of Compound 3 administered orally and intravenously was illustrated in FIG. 43. Individual rat plasma concentrations over time of Compound 3 administered intravenously were illustrated in FIG. 44. Individual and mean plasma concentrations over time for intravenous administration are provided below in Table 37. Rat #8 chewed the tape at the injection site, causing the tape to fall off, excessive bleeding, and measured data anomalies. Another rat was redosed and the retested data was used for the pharmacokinetic parameters calculation.

TABLE 37

Time (h)	Calculated Concentration (ng/mL)						
	Rat #7	Rat #8	Rat #8 Redose	Rat #9	Mean	SD	CV (%)
0.083	858	19.8	913	677	816	123	15.1
0.25	1080	30.3	846	643	856	219	25.5
0.5	751	28.2	728	525	668	124	18.6
1	683	46.6	676	489	616	110	17.9
2	523	96.6	524	394	480	75	15.6
4	464	203	452	257	391	116	29.7
8	181	206	278	105	188	87	46.1
24	12.8	25.8	8.85	9.84	10.5	2.1	19.6

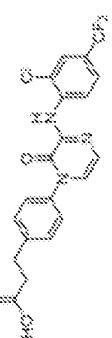
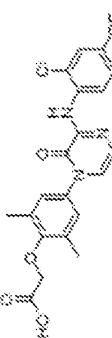
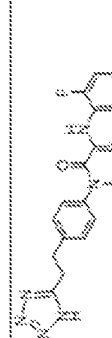
[0606] Individual rat plasma concentrations over time of Compound 3 administered orally were illustrated in FIG. 45. Individual and mean plasma concentrations over time for intravenous administration are provided below in Table 38.

TABLE 38

Time (h)	Calculated Concentration (ng/mL)					
	Rat #10	Rat #11	Rat #12	Mean	SD	CV (%)
0.25	27.5	40.2	100	55.8	38.5	69.0
0.5	89.1	118	251	153	86	56.5
1	270	225	648	381	232	61.0
2	481	4531	1320	751	493	65.6
4	1260	1580	1820	1553	281	18.1
8	1730	2170	2680	2193	475	21.7
24	58.5	102	317	159	138	87.0

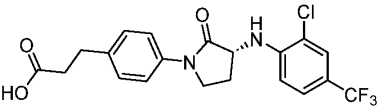
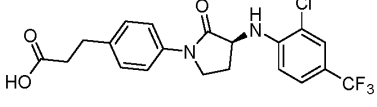
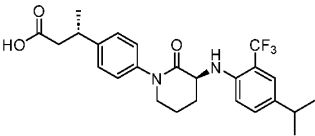
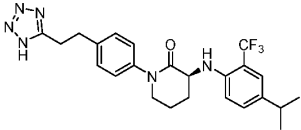
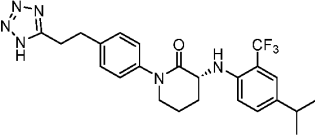
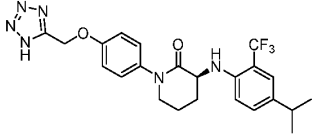
[0607] Further, the pharmacokinetic profiles of exemplary compounds 1-3 and 6 were obtained. The pharmacokinetic profiles are set forth in Table 39.

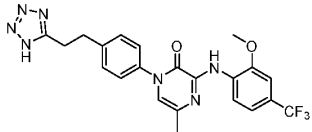
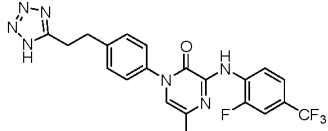
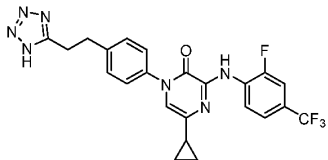
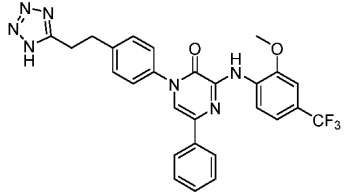
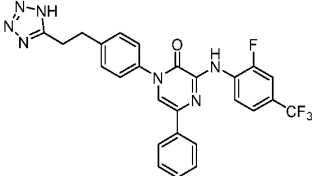
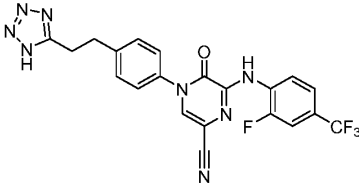
TABLE 39

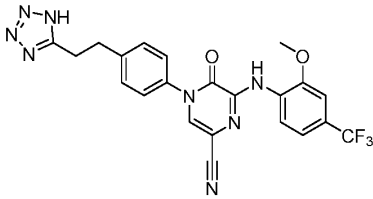
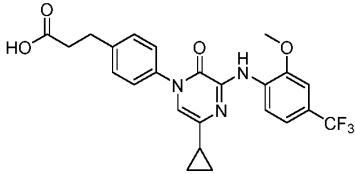
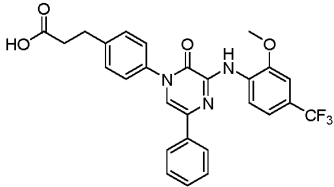
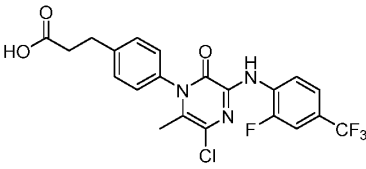
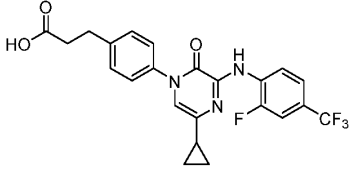
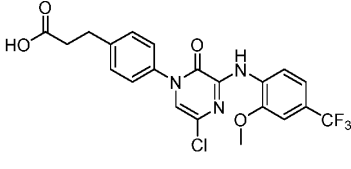
#	Structure	IV Route						PO Route				
		mg/kg	C ₀ (µg/mL)	AUC ₀₋₂₄ (µg·h/mL)	CL (L/h/kg)	V _d (L/kg)	C _{max} (µg/mL)	t _{max} (h)	AUC ₀₋₂₄ (µg·h/mL)	n ² (h)	F (%)	HP ratio (3 mg/kg; t ₀ µg/kg)
1		iv: 3 po: 10	3.4	0.557	5.37	2.27	0.411	1	1.19	6	63	..
2		iv: 1 po: 3	3.05	1.85	0.6	0.4	0.58	1	0.89	1	16	..
3		iv: 1 po: 3	2.47	3.49	0.29	0.8	1.68	2	12.9	4	100	1
6 (S)		iv: 1 po: 2	4.6	1.14	0.9	0.29	0.357	2	1.43	8	64	..

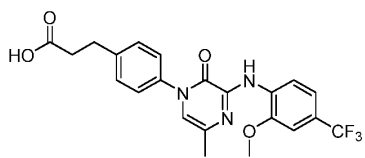
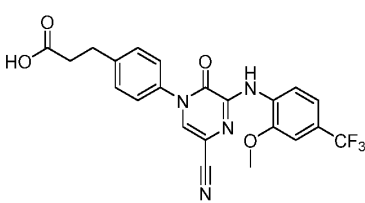
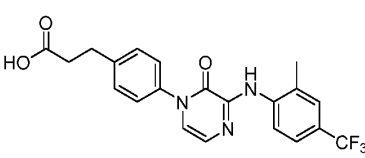
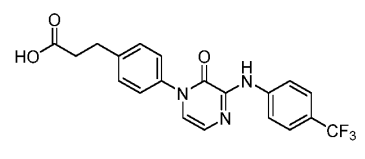
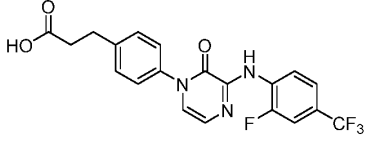
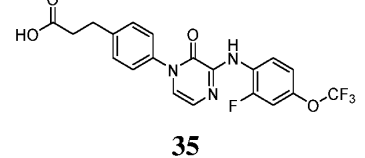
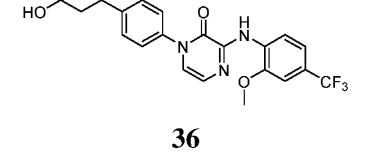
[0608] The pharmacokinetic profiles of additional exemplary compounds are set forth below in Table 40.

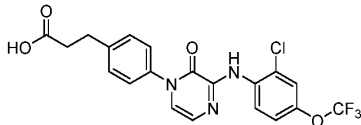
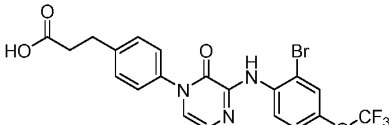
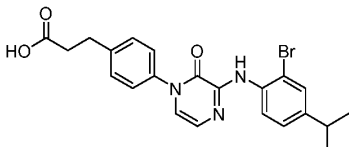
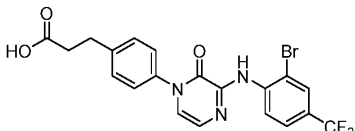
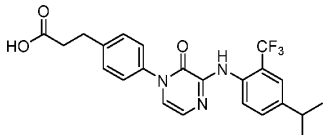
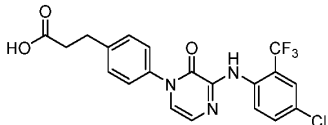
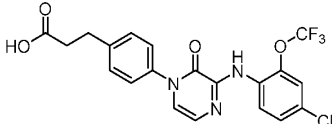
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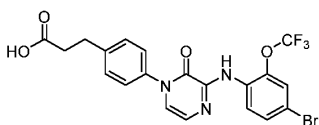
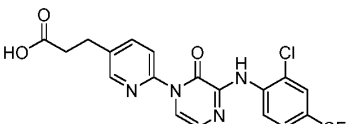
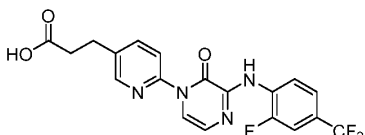
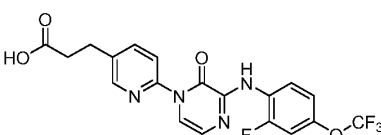
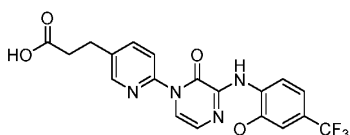
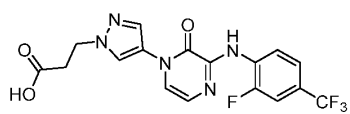
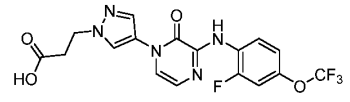
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 11-(R)	42	450
 11-(S)	88	890
 14-(S,S)	49	312
 15-(S)	6	70
 15-(R)	201	-
 16-(S)	9	210

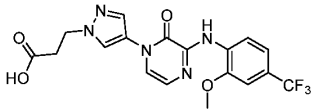
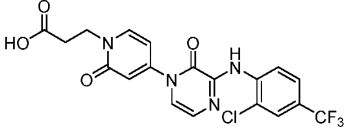
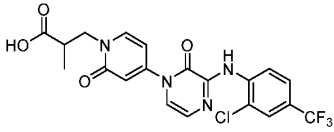
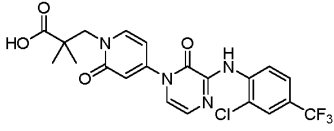
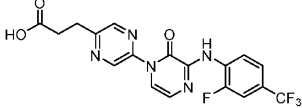
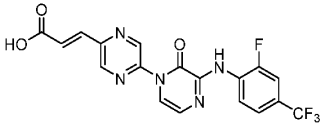
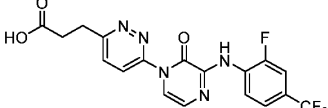
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 17	78	1865
 18	56	1200
 20	>1000	>10000
 21	137	3845
 22	5.5	134
 23	>1000	>10000

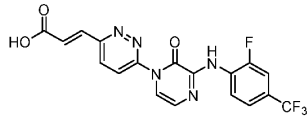
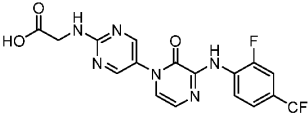
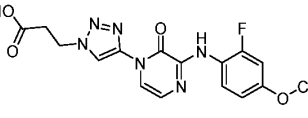
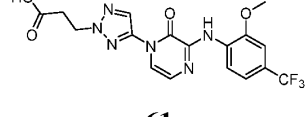
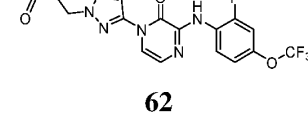
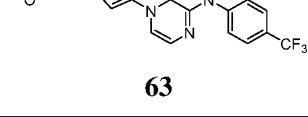
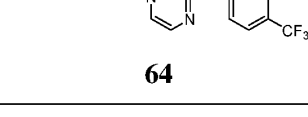
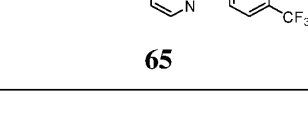
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 24	186	6729
 25	28	692
 26	90	2602
 27	>1000	>10000
 28	308	>10000
 29	215	>10000

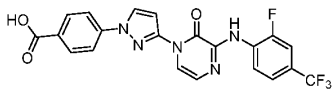
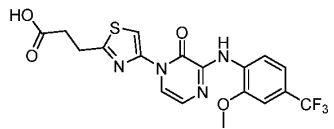
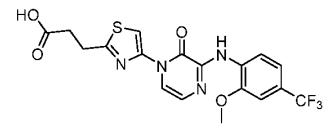
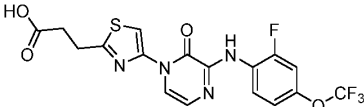
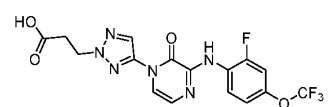
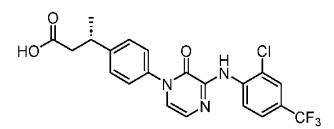
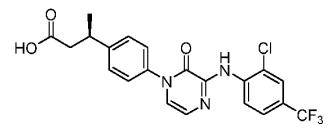
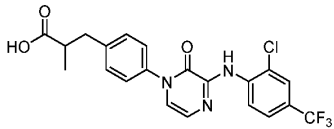
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 30	283	>10000
 31	777	>10000
 32	38	302
 33	89	2380
 34	4	94
 35	6	133
 36	0.4	15

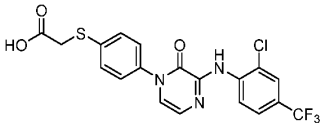
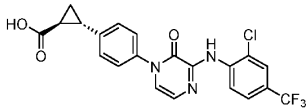
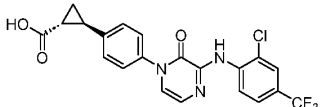
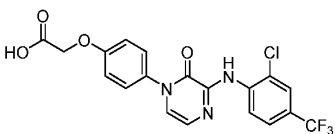
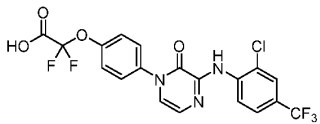
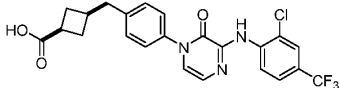
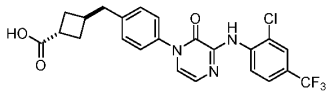
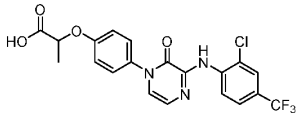
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 37	18	131
 38	79	563
 39	68	306
 40	5	177
 41	12	128
 42	37	349
 43	16	120

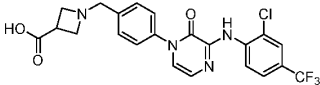
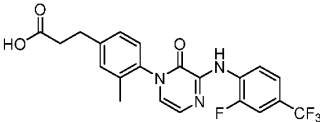
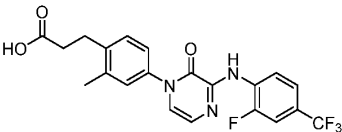
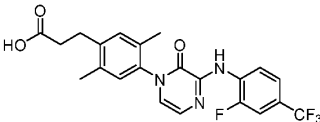
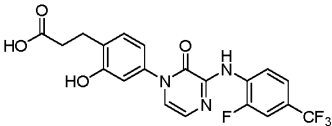
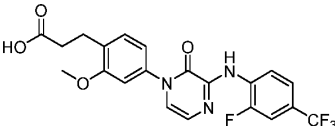
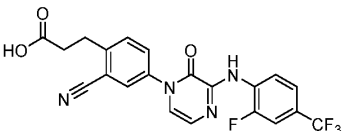
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 44	21	159
 45	11	85
 46	4	105
 47	7.6	203
 48	0.7	21
 49	370	5940
 50	201	4940

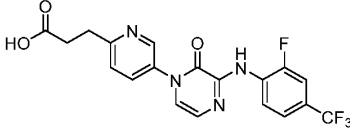
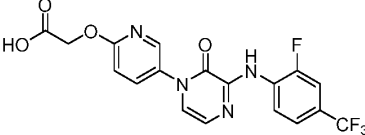
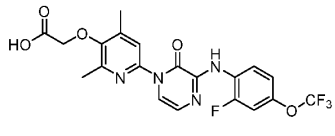
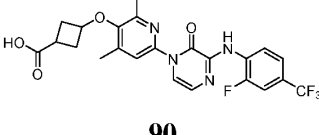
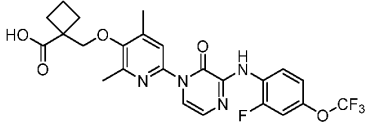
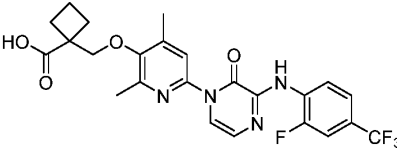
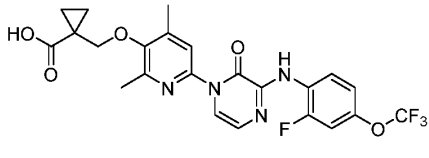
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 51	36	880
 52	52	1230
 53	600	>10000
 54	400	>10000
 55	13	333
 56	14	355
 57	393	>10000

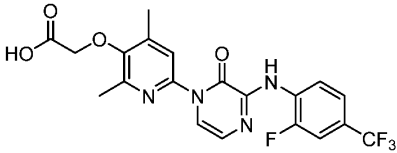
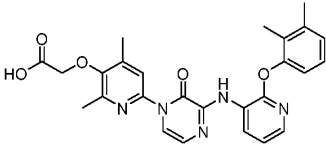
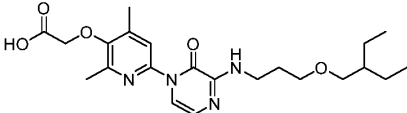
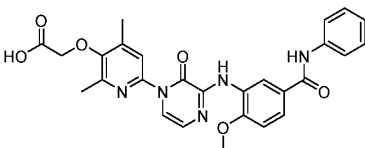
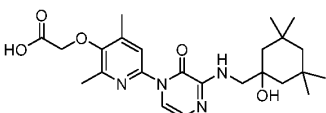
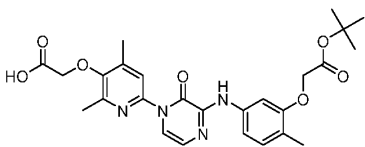
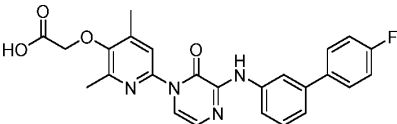
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 58	>1000	>10000
 59	>1000	>10000
 60	>1000	>10000
 61	3.6	114
 62	28	633
 63	>1000	>10000
 64	>1000	>10000
 65	36	1320

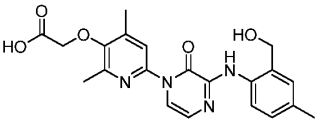
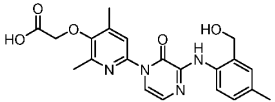
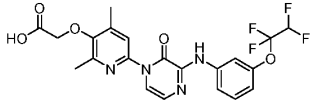
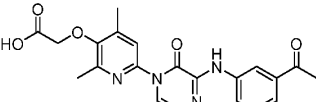
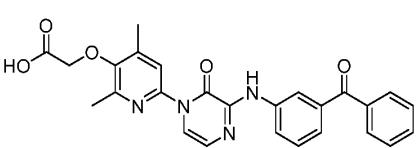
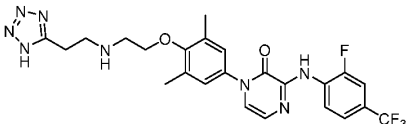
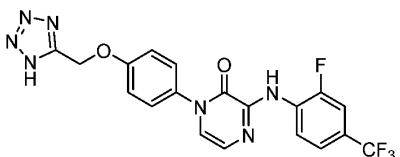
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 66	344	>10000
 67	10	233
 68	103	2680
 69	51	1654
 70	28	633
 71	91	408
 72	56	280
 73	33	427

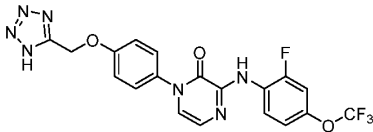
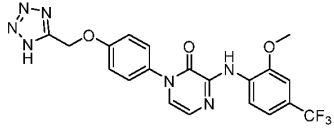
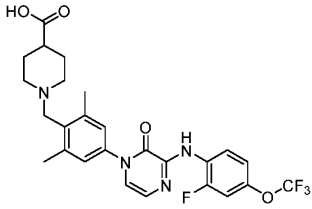
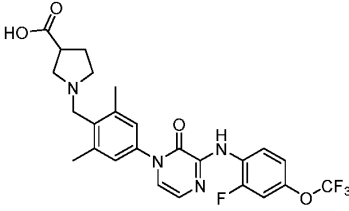
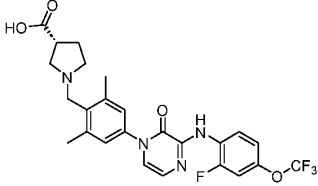
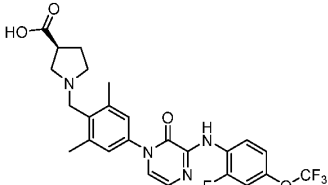
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 74	22	177
 75-(S,S)	62	738
 75-(R,R)	45	-
 76	63	430
 77	35	391
 Cis-78	17	145
 Trans-78	22	202
 79	102	1810

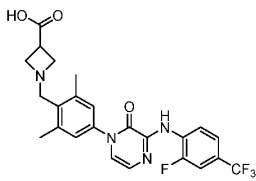
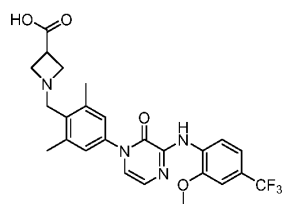
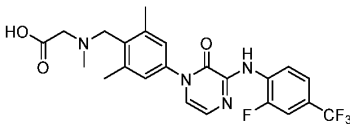
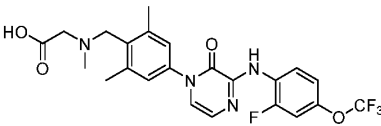
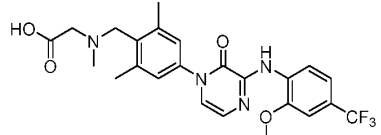
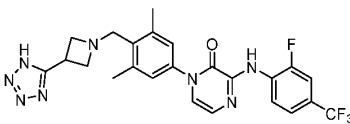
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 80	37	412
 81	57	650
 82	1.9	48
 83	10	292
 84	3.7	8.6
 85	2.1	53
 86	9.9	233

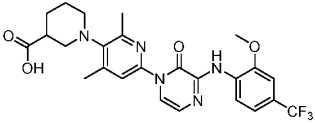
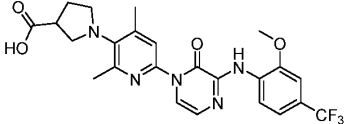
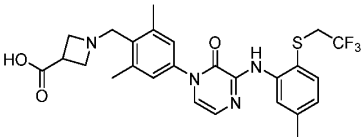
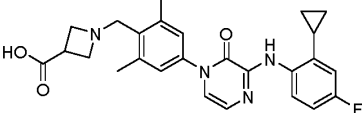
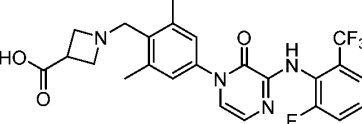
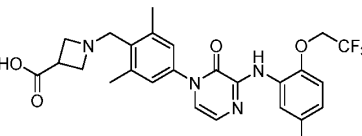
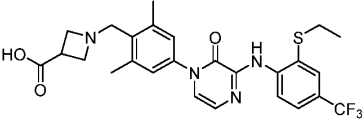
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 87	27	1020
 88	>1000	>10000
 89	70	1600
 90	2	67
 91	>1000	>10000
 92	561	>10000
 93	223	>10000

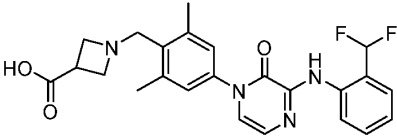
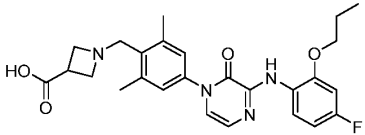
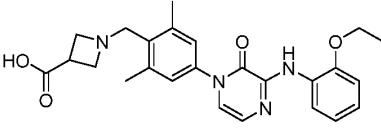
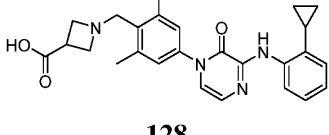
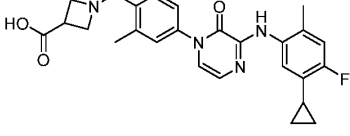
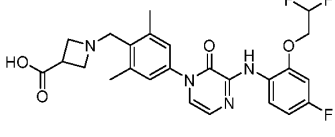
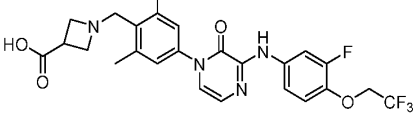
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 94	23	772
 95	>1000	>10000
 96	>1000	>10000
 97	>1000	>10000
 98	>1000	>10000
 99	>1000	>10000
 100	>1000	>10000

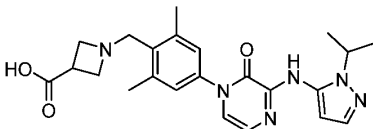
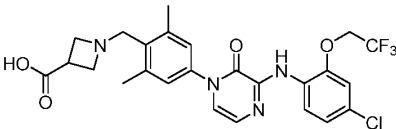
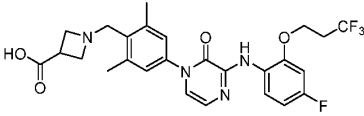
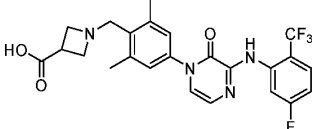
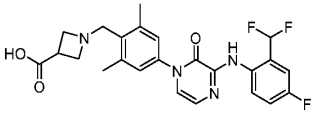
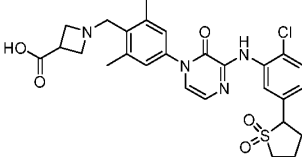
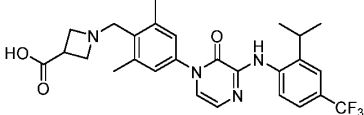
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 101	>1000	>10000
 102	>1000	>10000
 103	>1000	>10000
 104	>1000	>10000
 105	>1000	>10000
 106	6.5	135
 107	7	124

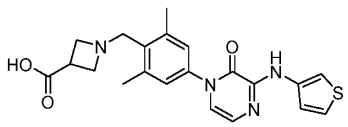
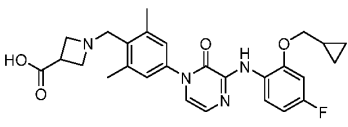
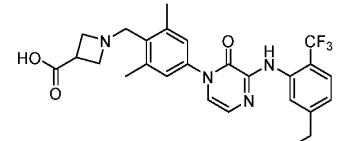
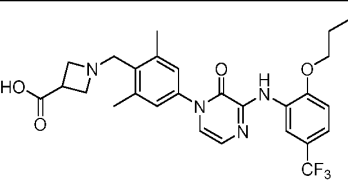
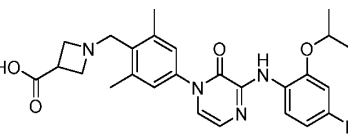
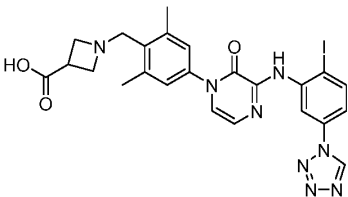
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 108	24	680
 109	2.5	74
 110	41	809
 111	9.4	164
 111-(R)	4.2	93
 111-(S)	5.1	100

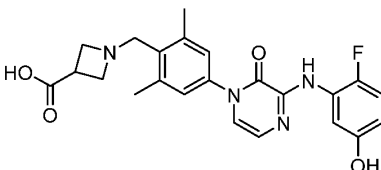
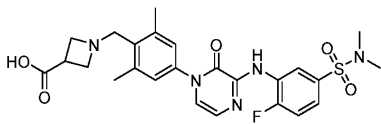
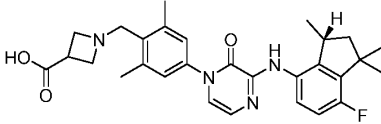
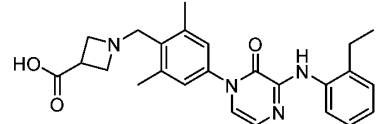
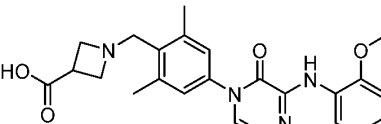
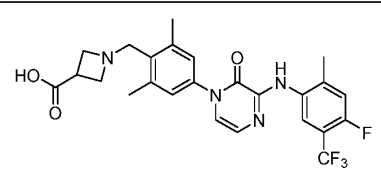
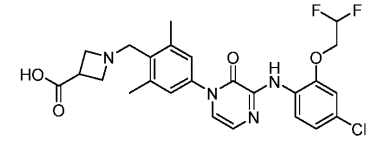
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 112	7.1	125
 113	17	411
 114	57	1540
 115	102	3550
 116	11	291
 117	19	531

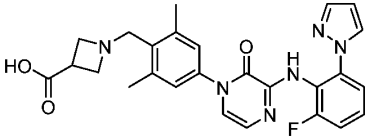
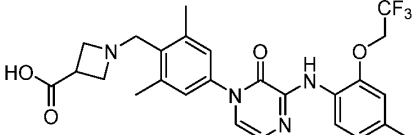
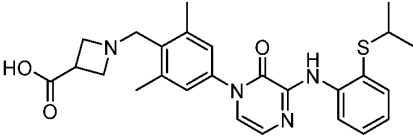
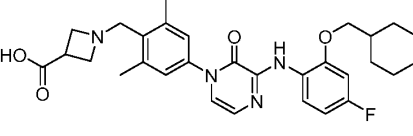
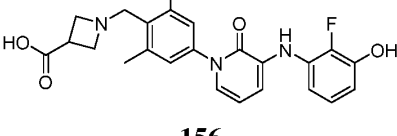
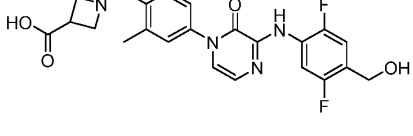
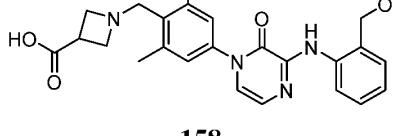
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 118	17	336
 119	3.7	7.5
 120	495	>10000
 121	64	1490
 122	>1000	>10000
 123	725	>10000
 124	1	22

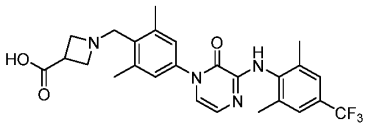
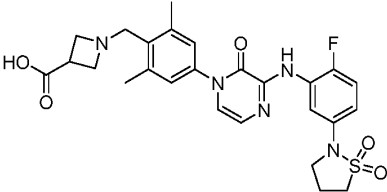
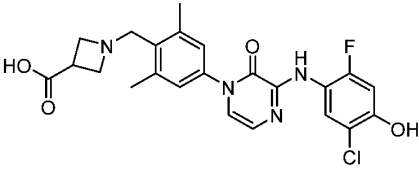
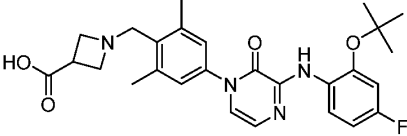
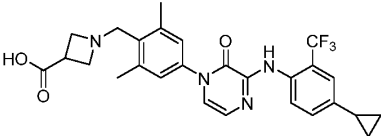
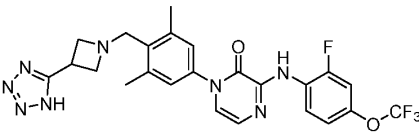
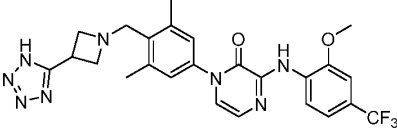
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 125	>1000	>10000
 126	25	430
 127	208	4980
 128	134	4120
 129	>1000	>10000
 130	476	5520
 131	2.6	87

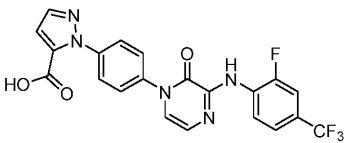
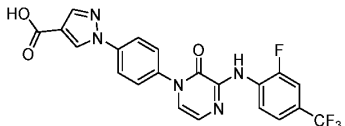
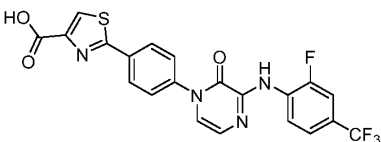
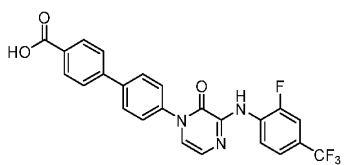
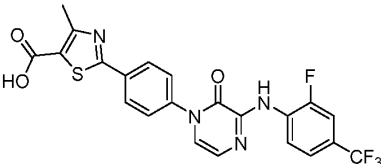
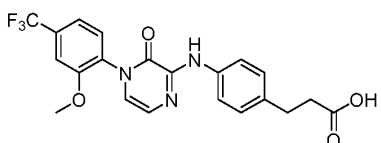
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 132	>1000	>10000
 133	992	2020
 134	656	>10000
 135	>1000	>10000
 136	660	>10000
 137	>1000	>10000
 138	4.6	129

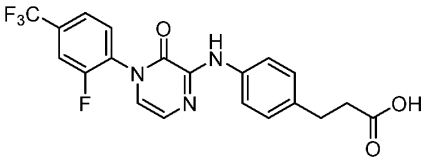
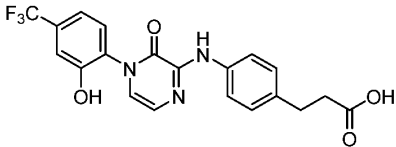
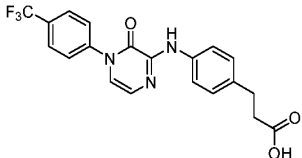
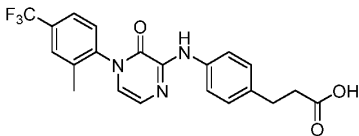
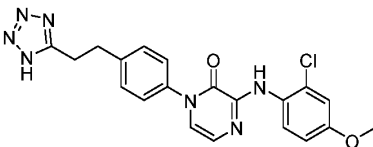
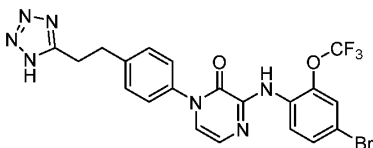
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 139	>1000	>10000
 140	85	1170
 141	240	>10000
 142	164	3300
 143	185	2400
 144	>1000	>10000

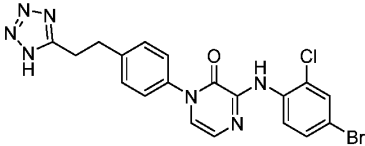
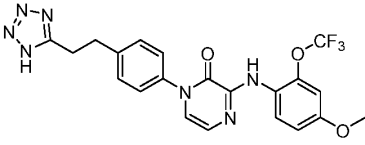
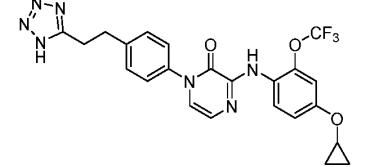
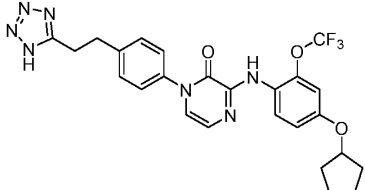
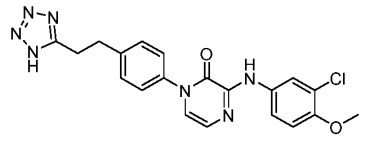
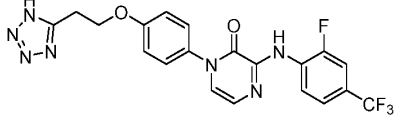
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 145	>1000	>10000
 146	>1000	>10000
 147	850	>10000
 148	>1000	>10000
 149	>1000	>10000
 150	>1000	>10000
 151	54	1140

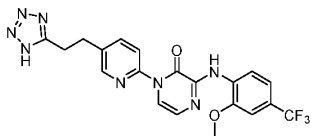
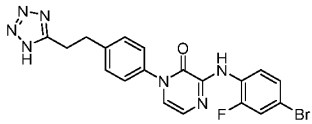
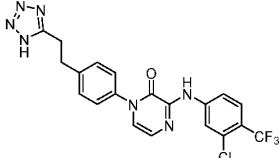
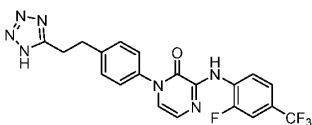
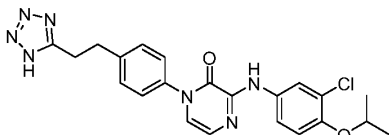
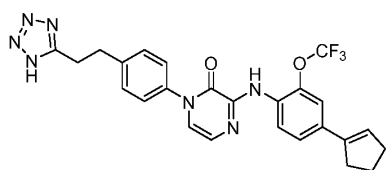
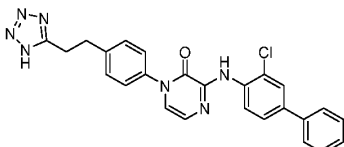
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 152	>1000	>10000
 153	20	285
 154	206	2640
 155	>1000	>10000
 156	>10000	>10000
 157	>1000	>10000
 158	>1000	>10000

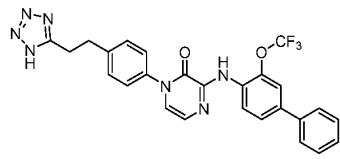
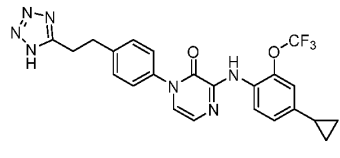
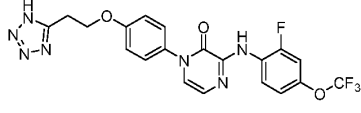
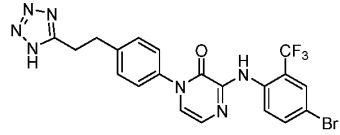
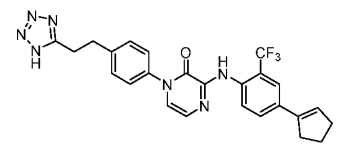
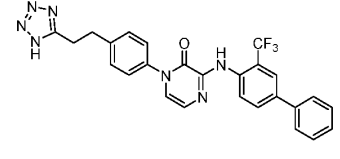
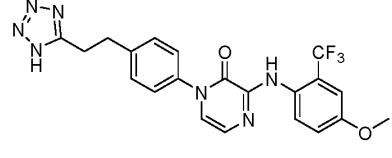
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 159	440	>10000
 160	>1000	>10000
 161	>1000	>10000
 162	369	>10000
 163	7.5	162
 164	12	445
 165	25	628

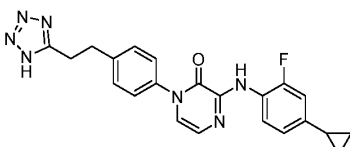
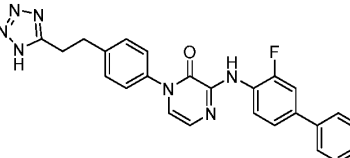
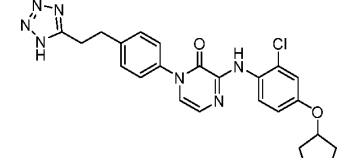
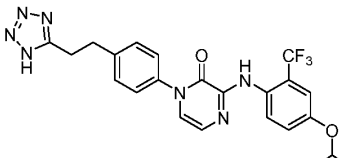
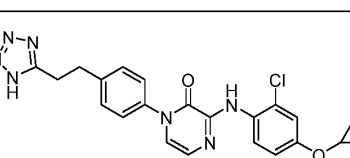
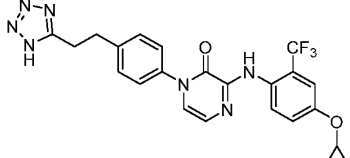
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 166	>1000	>10000
 167	56	1530
 168	203	>10000
 169	28	954
 170	359	>10000
 171	>1000	>10000

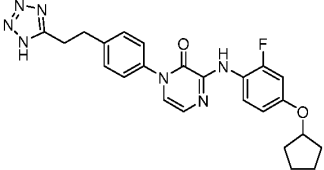
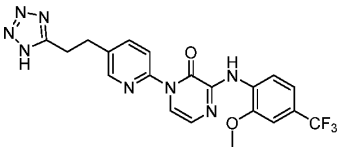
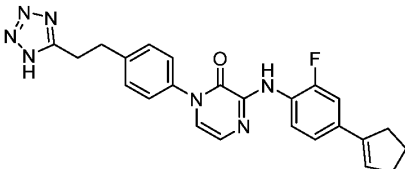
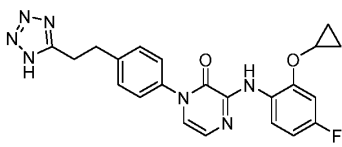
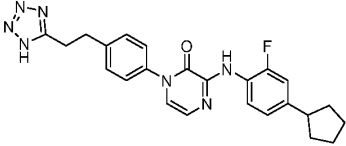
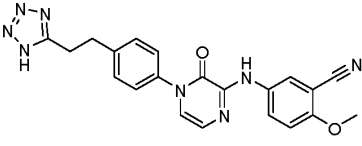
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 172	>1000	>10000
 173	>1000	>10000
 174	>1000	>10000
 175	>1000	>10000
 176	75	2400
 177	0.8	22

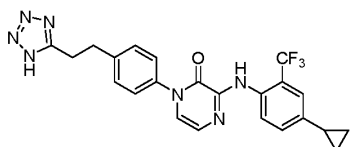
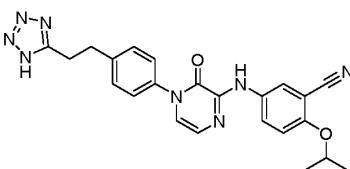
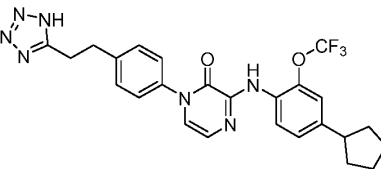
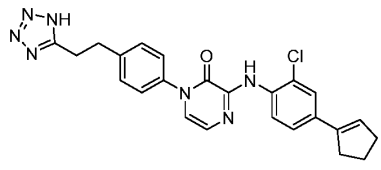
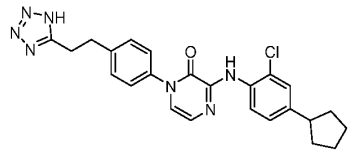
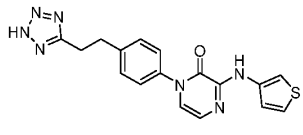
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 178	3.9	134
 179	7	223
 180	4.2	94
 181	6.4	171
 182	>1000	>10000
 183	12	419

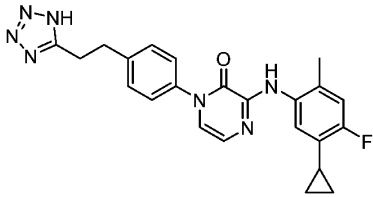
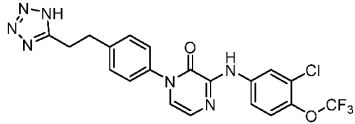
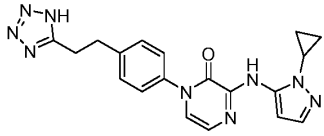
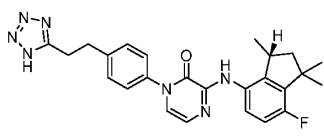
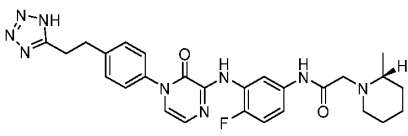
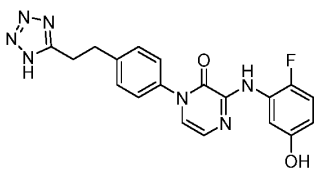
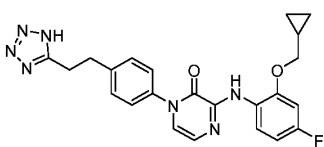
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 184	1	15
 185	11	253
 186	270	>10000
 187	1.4	48
 188	8.6	196
 189	29	506
 190	15	489

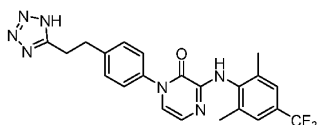
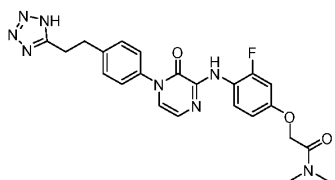
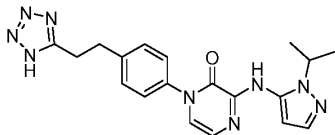
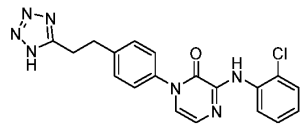
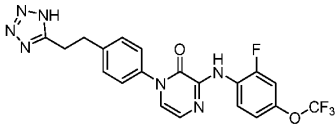
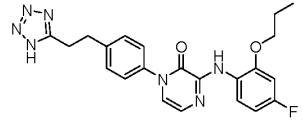
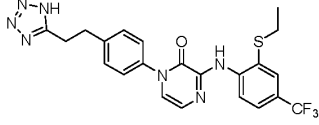
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 191	3	77
 192	2.3	8.7
 193	36	1160
 194	1.5	42
 195	272	>10000
 196	4	150
 197	60	1630

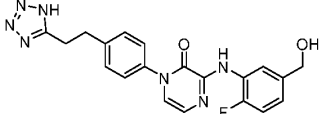
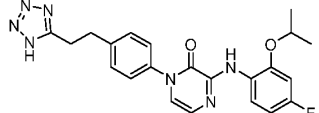
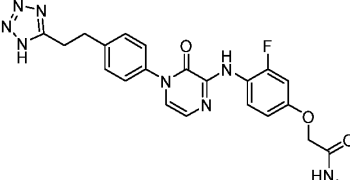
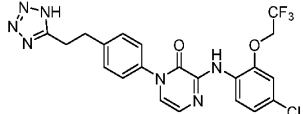
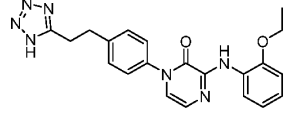
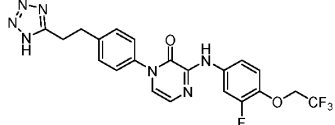
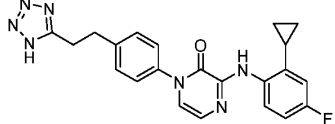
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 198	13	382
 199	34	651
 200	84	3030
 201	23	759
 202	16	620
 203	15	482

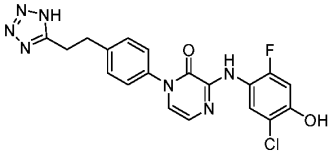
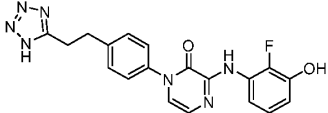
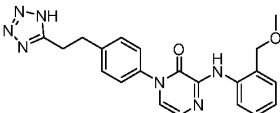
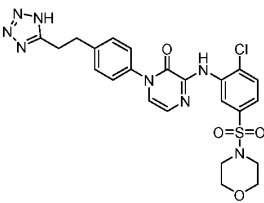
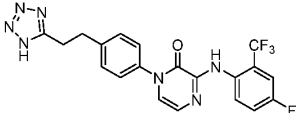
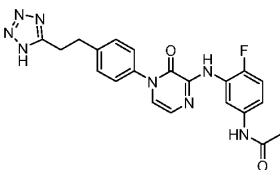
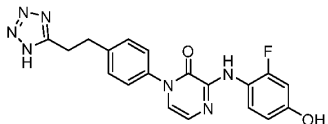
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 204	242	7350
 205	1	15
 206	23	650
 207	39	1270
 208	14	564
 209	>1000	>10000

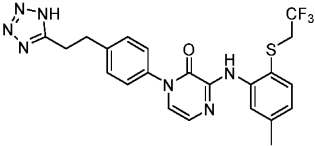
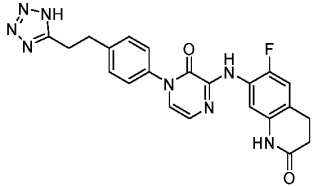
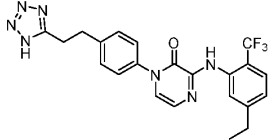
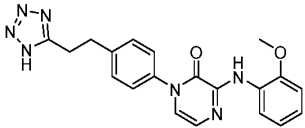
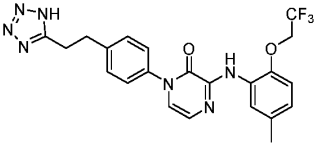
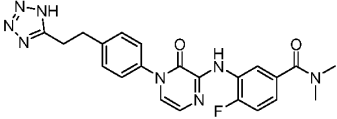
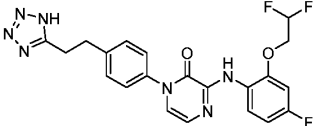
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 210	1.4	38
 211	14	468
 212	1.6	36
 213	70	2480
 214	8.5	309
 215	>1000	>10000

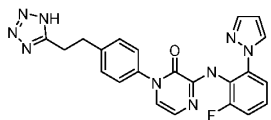
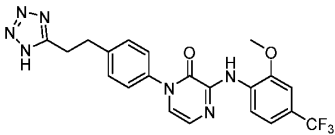
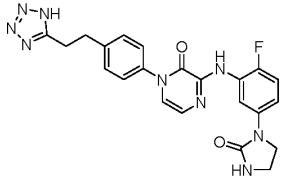
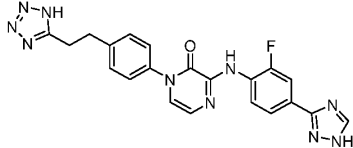
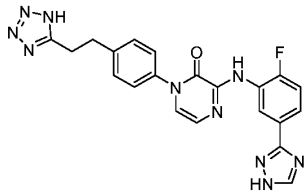
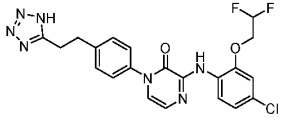
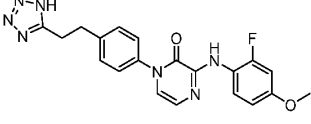
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 216	>1000	>10000
 217	34	>10000
 218	>1000	>10000
 219	>1000	>10000
 220	>1000	>10000
 221	>1000	>10000
 222	24	521

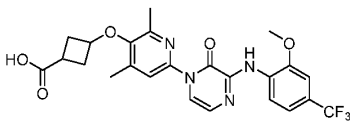
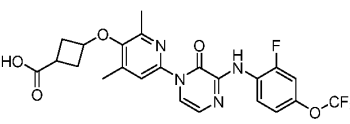
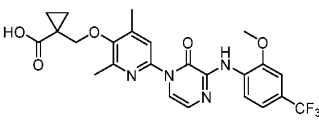
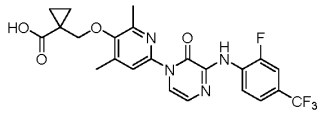
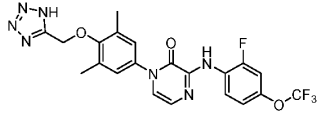
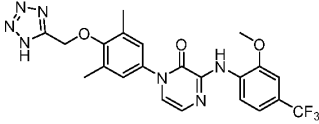
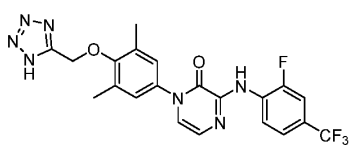
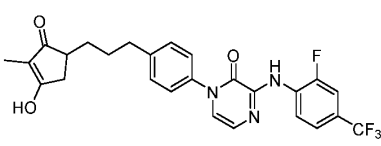
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 223	>1000	>10000
 224	>1000	>10000
 225	>1000	>10000
 226	>1000	>10000
 227	7	110
 228	13.5	252
 229	0.1	1.3

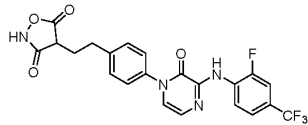
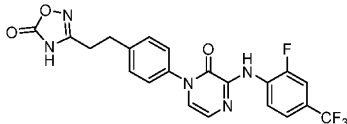
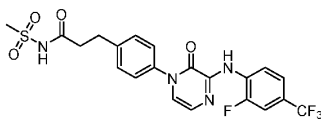
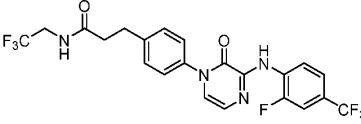
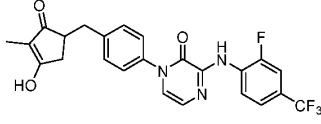
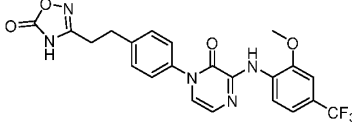
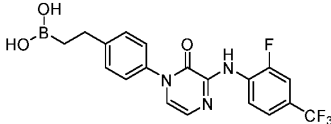
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 230	>1000	>10000
 231	>1000	>10000
 232	>1000	>10000
 233	8	132
 234	690	>10000
 235	16	200
 236	802	>10000

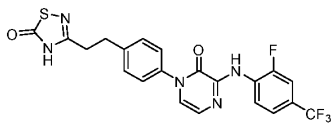
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 237	>1000	>10000
 238	>1000	>10000
 239	>1000	>10000
 240	>1000	>10000
 241	700	>10000
 242	>1000	>10000
 243	>1000	>10000

Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 244	580	>10000
 245	>1000	>10000
 246	>1000	>10000
 247	>1000	>10000
 248	>1000	>10000
 249	>1000	>10000
 250	100	3150

Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 251	>1000	>10000
 252	8.9	19.2
 253	>1000	>10000
 254	>1000	>10000
 255	>1000	>10000
 256	3.6	60
 257	41	7808

Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 258	0.8	13
 259	6.2	179
 260	19	556
 261	105	4637
 262	34	825
 263	5	100
 264	17	515
 265	26	751

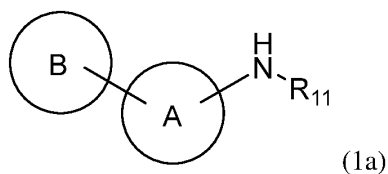
Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 266	23	665
 267	3.6	133
 268	8.6	236
 269	8	361
 270	19	443
 271	1.2	22
 272	17	227

Compound	cAMP EC ₅₀ (nM)	β-arrestin EC ₅₀ (nM)
 273	31	547

[0609] The foregoing description and examples have been set forth merely to illustrate the invention and are not meant to be limiting. Since modifications of the described embodiments incorporating the spirit and the substance of the invention may occur to persons skilled in the art, the invention should be construed broadly to include all variations within the scope of the claims and equivalents thereof.

[0610] The subject-matter of the disclosure may also relate, among others, to the following aspects:

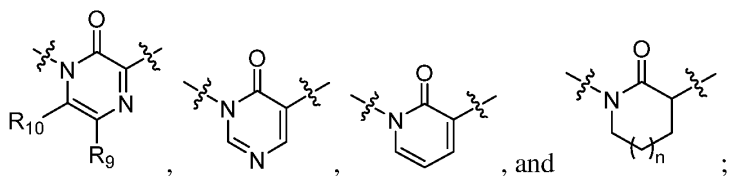
[0611] A first aspect relates to a compound of formula (1a):



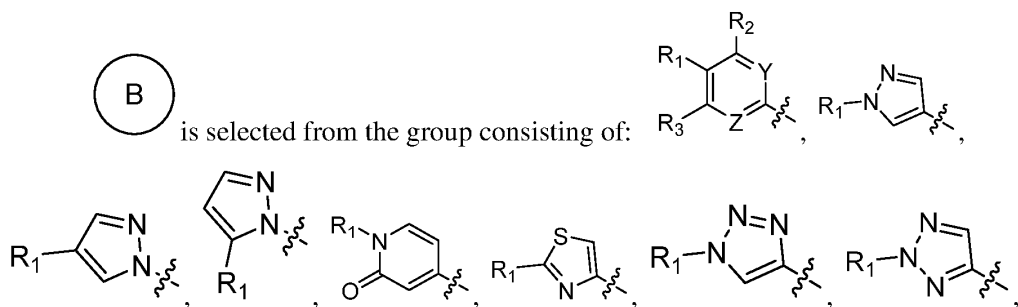
wherein

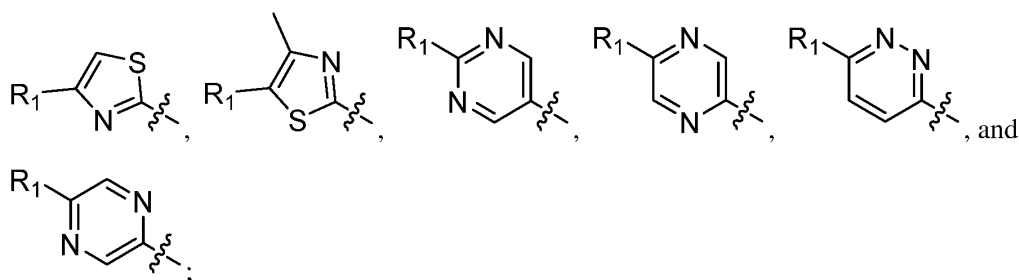


is selected from the group consisting of:



is selected from the group consisting of:

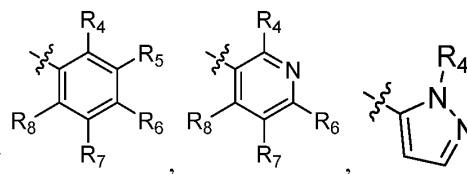




R_1 is $(T)_w-(CR_gR_f)_m-Q-(CR_gR_f)_m-U$;

R_2 and R_3 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, and CN;

R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} , are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $S(O)_2R_j$, $S(O)_2N(R_c)_2$, $N(R_c)_2$, CN, $C(O)R_j$, $N(R_c)C(O)R_j$, $C(O)N(R_c)_2$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted cycloalkenyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;



R_{11} is selected from the group consisting of H, $OCH_2C(O)_2R_c$, an unsubstituted C_1 - C_6 straight or branched alkyl, a substituted C_1 - C_6 straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group;

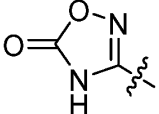
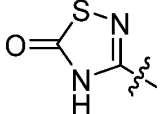
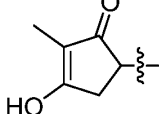
Y is CR_a or N;

Z is CR_b or N;

Q is O, S, NR_i , or $-(CR_hR_d)_p-$;

T is O, S, NR_i , or $-(CR_hR_d)_p-$;

U is $-COOR_e$, $-COS(O)_pR_e$, $-CONHS(O)_pR_e$, $-CONHR_e$, $-CON(R_e)_2$, vinyl, a substituted C_1 - C_6 straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a

substituted or unsubstituted heteroaryl group, , , ,
or B(OH)₂;

n is 0, 1, or 2;

each m is independently 0, 1, 2, 3, 4, or 5;

p is 0, 1, or 2;

w is 0, 1, or 2;

R_a and R_b are independently selected from the group consisting of H, unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OR_c, SR_c, N(R_c)₂, and CN;

R_c is H, unsubstituted C₁-C₆ straight or branched alkyl, or substituted C₁-C₆ straight or branched alkyl;

R_d is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_e is H, unsubstituted C₁-C₆ straight or branched alkyl, or C₁-C₆ straight or branched alkyl substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OR_c, SR_c, N(R_c)₂, and CN;

R_f is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_g is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_h is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_i is H, D, F, Cl, Br, I, unsubstituted C₁-C₆ straight or branched alkyl, or unsubstituted cycloalkyl;

R_j is a substituted or unsubstituted C₁-C₆ straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaryl group;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, R₄ and R₅, R₆ and R₇, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OC₄alkyl, OC₅alkyl, OC₆alkyl, unsubstituted cycloalkyl, substituted heterocyclyl, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂,

NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, CONMe₂, CONHMe, and CONH₂;

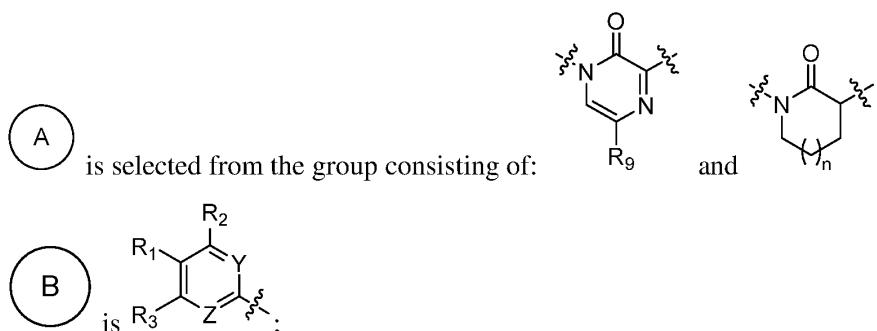
wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

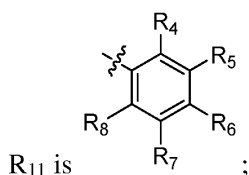
wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, an unsubstituted heterocyclyl group, an unsubstituted heteroaryl group, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, CONH₂, and CONHPh; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; or an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0612] A second aspect relates to the compound of aspect 1, wherein:





R₁ is $-Q-(CHR_f)_m-U$;

R₂ and R₃ are independently selected from the group consisting of H, unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OR_c, SR_c, CN, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

Y is CR_a or N;

Z is CR_b or N;

Q is O, S, or $-(CHR_d)_p-$;

U is $-COOR_e$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, and OR_c;

R_c is H, unsubstituted C₁-C₆ straight or branched alkyl, or substituted C₁-C₆ straight or branched alkyl;

R_d is H, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_e is H or unsubstituted C₁-C₆ straight or branched alkyl;

R_f is H, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or

more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

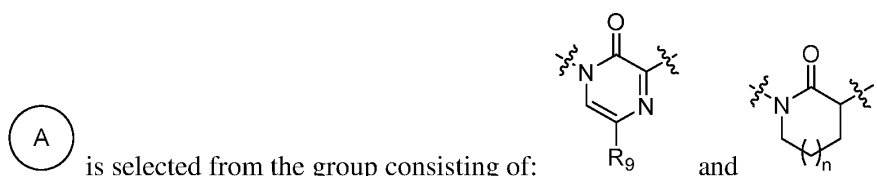
wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, CF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or unsubstituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂; or

an enantiomer, racemate, or pharmaceutically acceptable salt thereof.

[0613] A third aspect relates to the compound of any preceding aspect, wherein:



R₁ is -Q-(CHR_f)_m-U;

R₂ and R₃ are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, OR_c, CN, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

Y is CR_a or N;

Z is CR_b or N;

Q is O or $-(\text{CHR}_d)_p-$;

U is $-\text{COOR}_e$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, and OR_c;

R_c is H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, or substituted isopropyl;

R_d is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

R_e is H, methyl, ethyl *n*-propyl, or isopropyl;

R_f is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted methyl, ethyl, *n*-propyl, or isopropyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂;

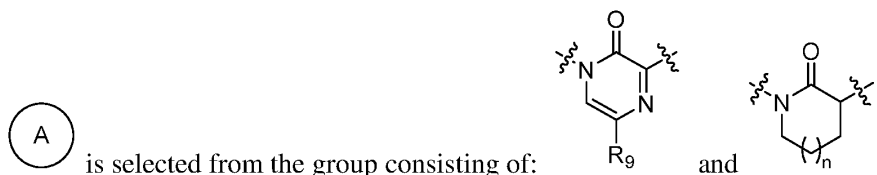
wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH,

OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0614] A fourth aspect relates to the compound of any preceding aspect, wherein:



R₁ is -Q-(CHR_f)_m-U;

R₂ and R₃ are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, OR_c, CN, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl;

Y is CR_a or N;

Z is CR_b or N;

Q is O or -(CHR_d)_p-;

U is -COOR_e, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c;

R_c is H, methyl, CH₂F, CHF₂, CF₃, ethyl, *n*-propyl, or isopropyl;

R_d is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

R_e is H, methyl, ethyl, *n*-propyl, or isopropyl;

R_f is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

wherein R_1 and R_2 , R_1 and R_3 , R_2 and R_a , or R_3 and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted methyl, ethyl, *n*-propyl, or isopropyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, NH_2 , and $COOH$;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH_2F , $OCHF_2$, OCF_3 , NH_2 , NMe_2 , NEt_2 , $N(nPr)_2$, $N(iPr)_2$, CH_2COOH , carbonyl, and $COOH$;

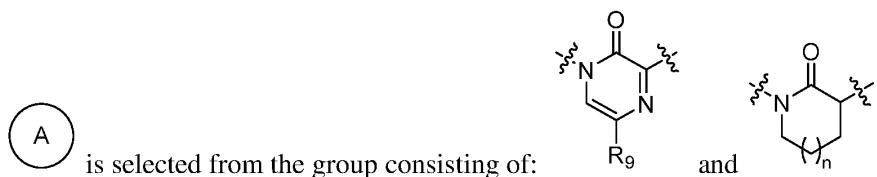
wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH_2F , $OCHF_2$, OCF_3 , NH_2 , NMe_2 , NEt_2 , $N(nPr)_2$, $N(iPr)_2$, CH_2COOH , carbonyl, and $COOH$;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH_2F , $OCHF_2$, OCF_3 , NH_2 , NMe_2 , NEt_2 , $N(nPr)_2$, $N(iPr)_2$, CH_2COOH , carbonyl, and $COOH$; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH_2F , $OCHF_2$, OCF_3 , NH_2 , NMe_2 , NEt_2 , $N(nPr)_2$, $N(iPr)_2$, CH_2COOH , carbonyl, and $COOH$; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0615] A fifth aspect relates to the compound of any preceding aspect, wherein:



R_1 is $-Q-(CHR_t)_m-U$;

R_2 and R_3 are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c ;

R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are independently selected from the group consisting of H, methyl, CF_3 , ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OR_c , CN, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl;

Y is CR_a or N;

Z is CR_b or N;

Q is O or $-(\text{CHR}_d)_p-$;

U is $-\text{COOH}$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or $\text{B}(\text{OH})_2$;

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

R_a is H or methyl;

R_b is H or methyl;

R_c is H, methyl, or CF_3 ;

R_d is H, F, Cl, Br, or methyl;

R_f is H, F, Cl, Br, or methyl;

wherein R₁ and R₂ or R₁ and R₃ together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ;

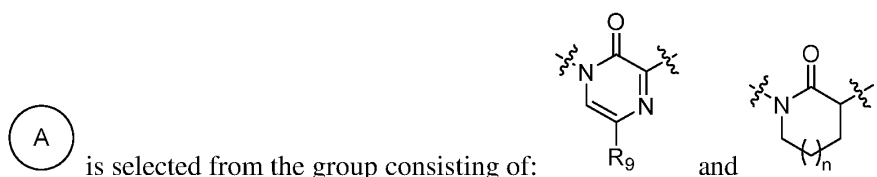
wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0616] A sixth aspect relates to the compound of any preceding aspect, wherein:



R_1 is $-Q-(CHR_f)_m-U$;

R_2 and R_3 are independently H or methyl;

R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are independently selected from the group consisting of H, methyl, isopropyl, CF_3 , F, Cl, Br, OMe, OCF_3 , CN, cyclopropyl, cyclopentyl, and phenyl;

Y is CH or N;

Z is CH or N;

Q is O or $-(CHR_d)_p-$;

U is $-COOH$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or $B(OH)_2$;

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

R_d is H, F, or methyl;

R_f is H, F, or methyl;

wherein R_1 and R_2 or R_1 and R_3 together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and $COOH$;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and $COOH$;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and $COOH$; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl,

Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH; or
an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0617] A seventh aspect relates to the compound of any preceding aspect, wherein U is a cycloalkyl group selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cyclooctenyl, cyclooctadienyl, and cyclooctatrienyl;

wherein the cycloalkyl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

[0618] An eighth aspect relates to the compound of aspects **1** to **6**, wherein U is a heterocyclyl group selected from the group consisting of azetidiny, pyrrolidinyl, pyrrolinyl, pyrazolidinyl, imidazoliny, imidazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, oxetanyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiophene, dihydrothiophene, tetrahydrothiopyranyl, and dihydrothiopyranyl;

wherein the heterocyclyl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

[0619] A ninth aspect relates to the compound of aspects **1** to **6**, wherein U is an aryl group selected from the group consisting of phenyl, naphthalenyl, cyclobutadienyl,

cyclopentadienyl, indenyl, anthracenyl, phenanthrenyl, terphenylenyl, fluorenyl, and pyrenyl;

wherein the aryl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, CF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

[0620] A tenth aspect relates to the compound of aspects **1** to **6**, wherein U is a heteroaryl group selected from the group consisting of pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, 5(4*H*)-oxo-1,2,4-thiadiazolyl, oxazolyl, 5(4*H*)-oxo-1,2,4-oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, 1*H*-indolyl, 3*H*-indolyl, 2*H*-isoindolyl, indolizynyl, quinolynyl, isoquinolynyl, quinoxalynyl, cinnolynyl, quinazolynyl, phthalazinyl, purinyl, indazolyl, benzimidazolyl, benzo[*d*]oxazole, benzo[*d*]thiazole, benzo[*c*]isoxazole, benzo[*d*]isoxazole, benzo[*c*]isothiazole, benzo[*d*]isothiazole, quinoline-2(1*H*)-one, isoquinoline-1(2*H*)-one, indolin-2-one, isoindolin-1-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-thione, furanyl, carbazolyl, benzofuranyl, isobenzofuranyl, dibenzofuranyl, benzofuran-2(3*H*)-one, isobenzofuran-1(3*H*)-one, thiophenyl, benzo[*b*]thiophenyl, benzo[*c*]thiophenyl, benzo[*b*]thiophen-2(3*H*)-one, and benzo[*c*]thiophen-1(3*H*)-one;

wherein the heteroaryl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

[0621] An eleventh aspect relates to the compound of any preceding aspect, wherein

R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cycloalkyl group selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cyclooctenyl, cyclooctadienyl, and cyclooctatrienyl;

wherein the cycloalkyl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

[0622] A twelfth aspect relates to the compound of aspects **1** to **10**, wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a heterocyclyl group selected from the group consisting of azetidiny, pyrrolidiny, pyrroliny, pyrazolidiny, imidazolinyl, imidazolidiny, pyrazolinyl, piperidiny, piperazinyl, oxetanyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiophene, dihydrothiophene, tetrahydrothiopyranyl, 3,5-dioxoisoxazolidiny, and dihydrothiopyranyl;

wherein the heterocyclyl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

[0623] A thirteenth aspect relates to the compound of aspects **1** to **10**, wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form an aryl group selected from the group consisting of phenyl, naphthalenyl, cyclobutadienyl, cyclopentadienyl, indenyl, anthracenyl, phenanthrenyl, terphenylenyl, fluorenyl, and pyrenyl;

wherein the aryl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

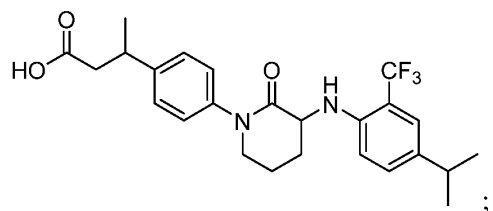
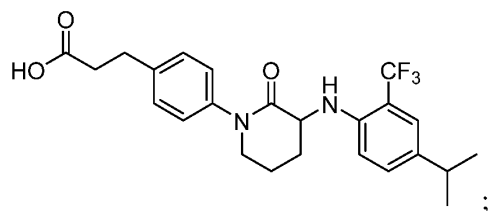
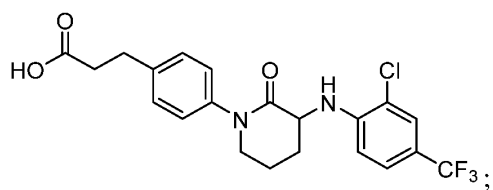
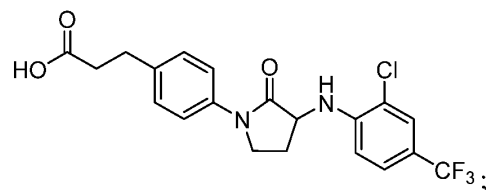
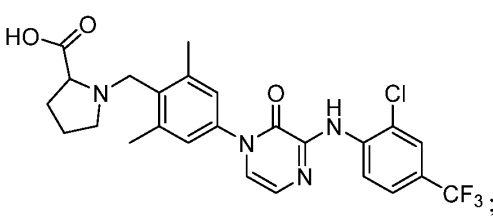
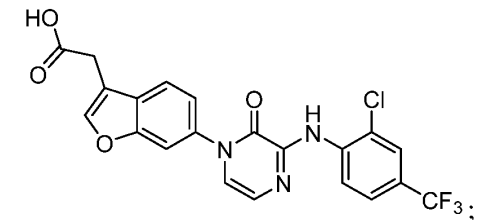
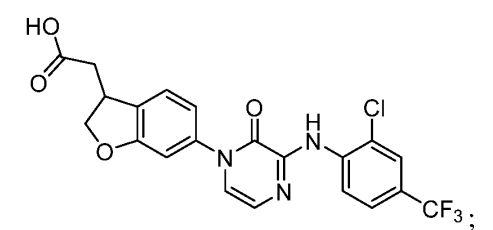
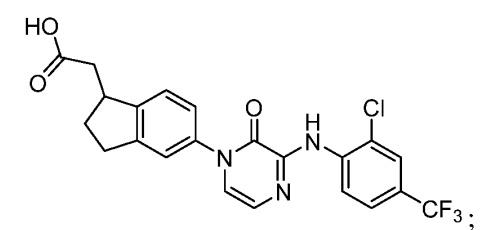
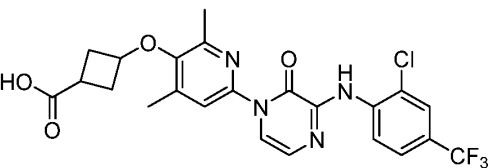
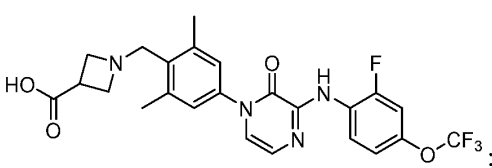
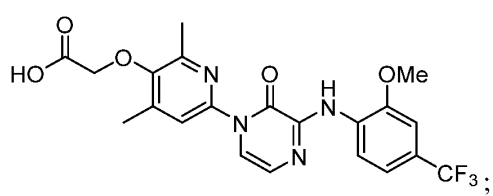
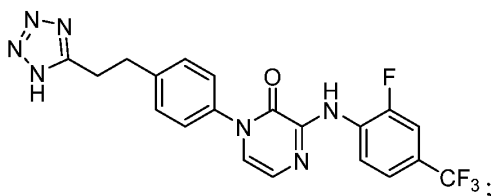
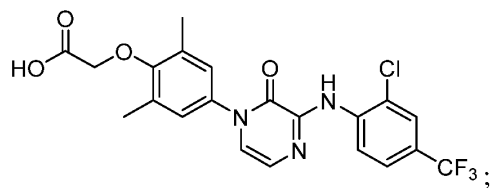
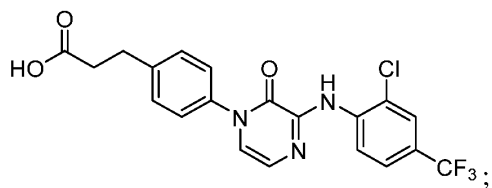
[0624] A fourteenth aspect relates to the compound of aspects **1** to **10**, wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a heteroaryl group selected from the group consisting of pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, 5(4*H*)-oxo-1,2,4-thiadiazolyl, oxazolyl, 5(4*H*)-oxo-1,2,4-oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, 1*H*-indolyl, 3*H*-indolyl, 2*H*-isoindolyl, indolizynyl, quinolynyl, isoquinolynyl, quinoxalynyl, cinnolynyl, quinazolinyl, phthalazinyl, purinyl, indazolyl, benzimidazolyl, benzo[*d*]oxazole, benzo[*d*]thiazole, benzo[*c*]isoxazole, benzo[*d*]isoxazole, benzo[*c*]isothiazole, benzo[*d*]isothiazole, quinoline-2(1*H*)-one, isoquinoline-1(2*H*)-one, indolin-2-one, isoindolin-1-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-thione, furanyl, carbazolyl, benzofuranyl, isobenzofuranyl, dibenzofuranyl, benzofuran-2(3*H*)-one, isobenzofuran-1(3*H*)-one, thiophenyl, benzo[*b*]thiophenyl, benzo[*c*]thiophenyl, benzo[*b*]thiophen-2(3*H*)-one, and benzo[*c*]thiophen-1(3*H*)-one;

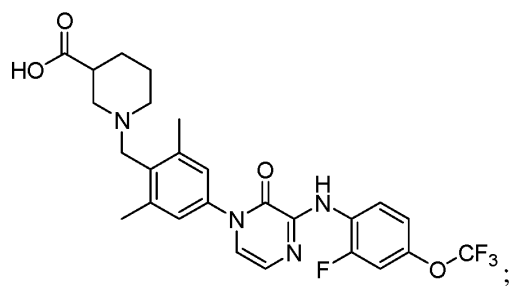
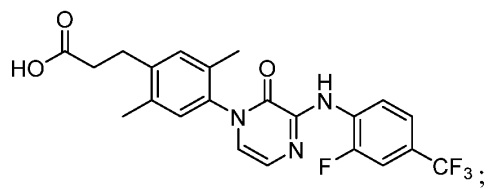
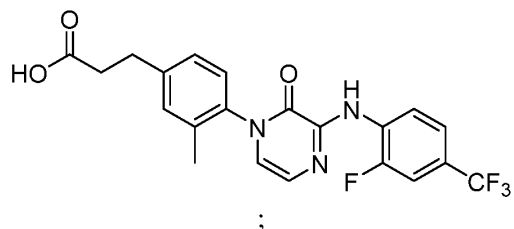
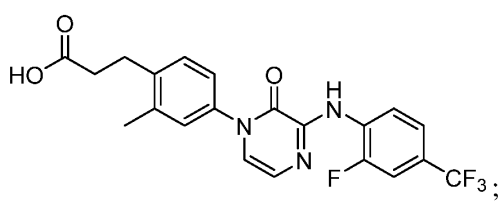
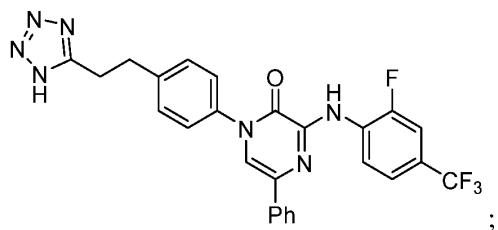
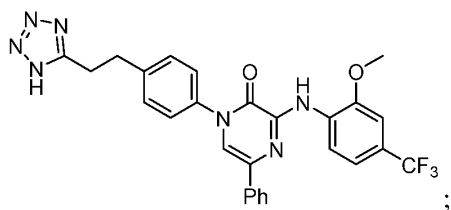
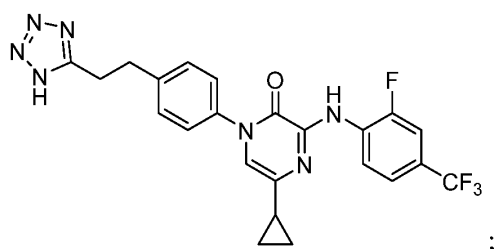
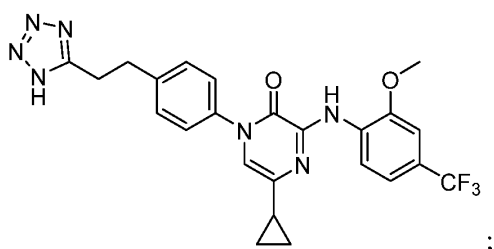
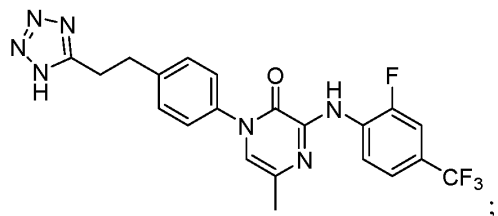
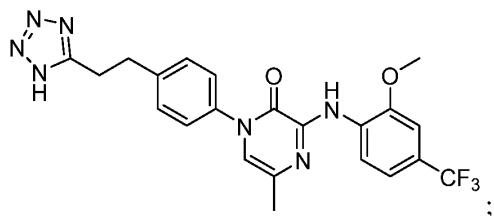
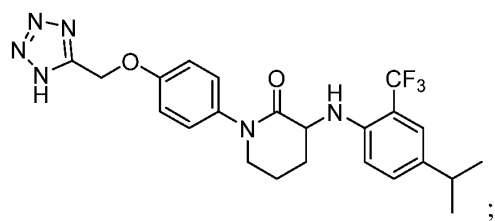
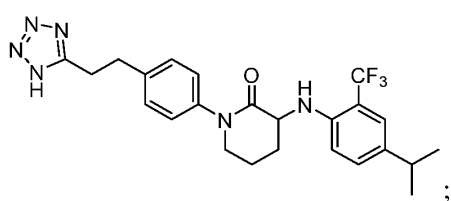
wherein the heteroaryl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

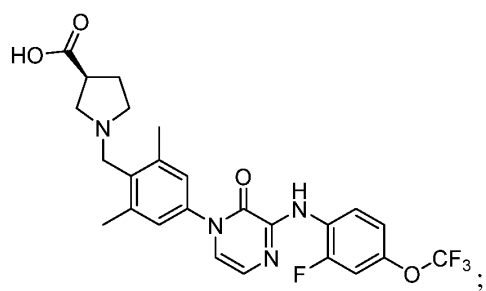
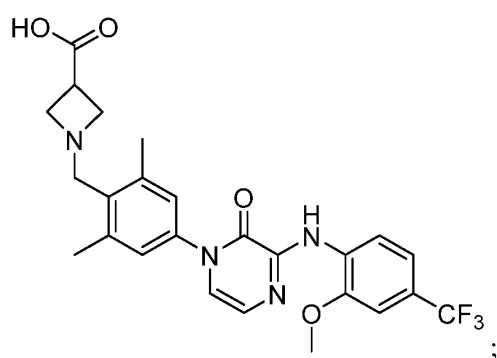
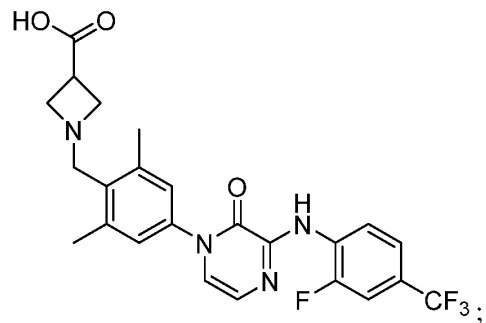
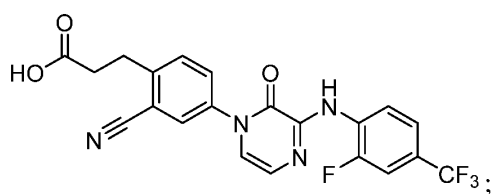
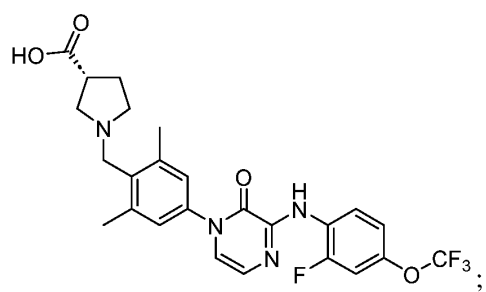
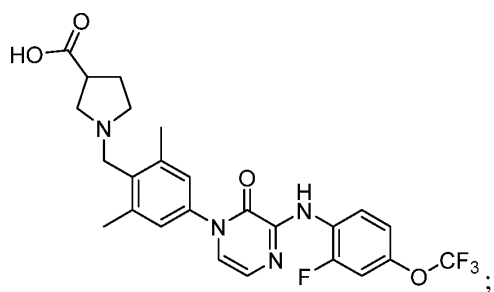
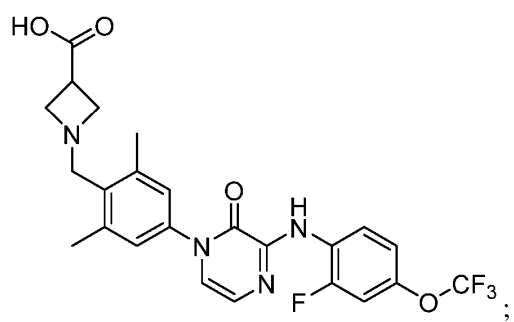
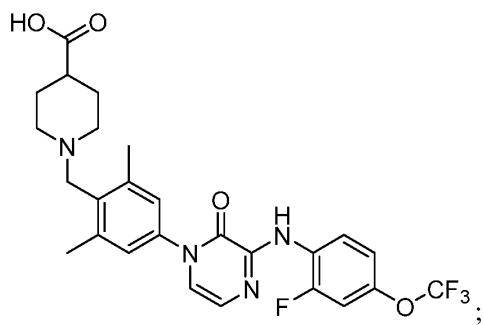
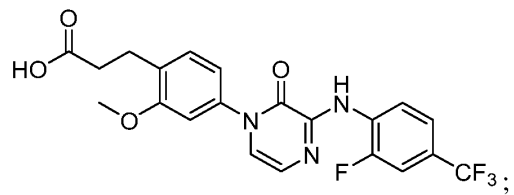
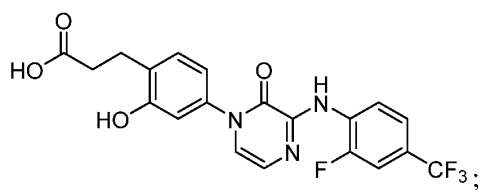
wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

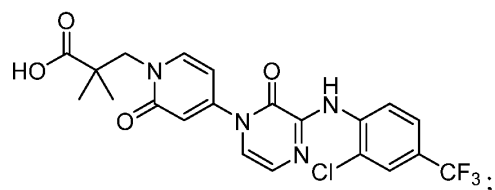
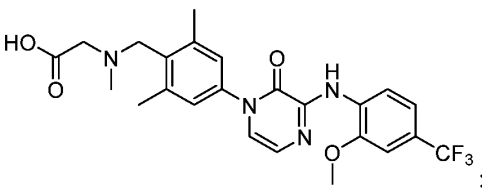
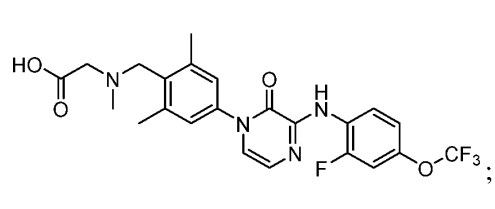
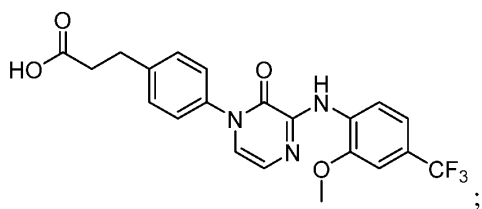
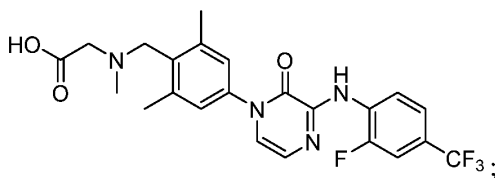
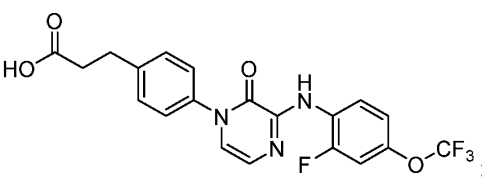
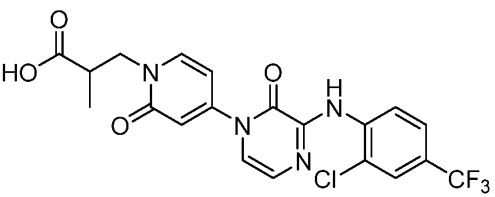
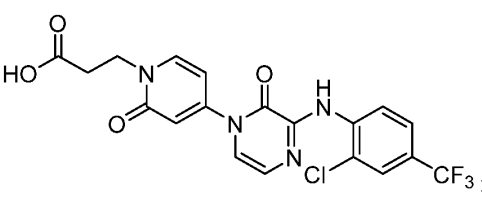
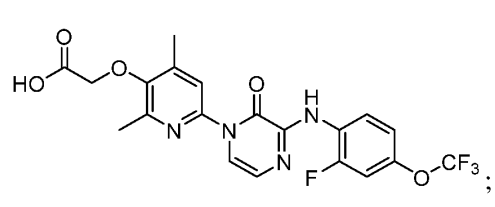
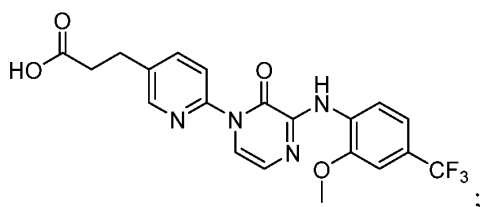
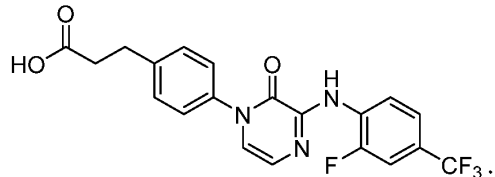
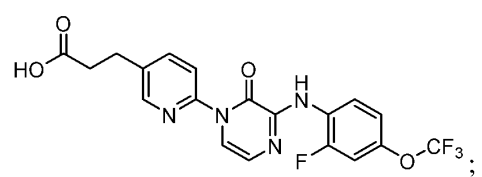
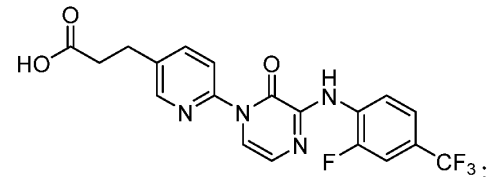
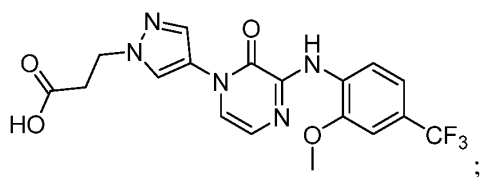
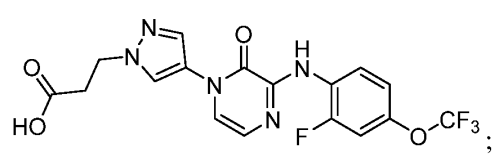
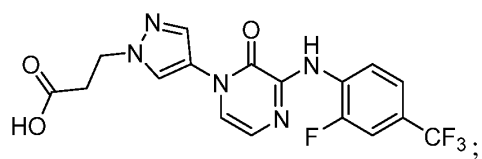
[0625] A fifteenth aspect relates to the compound of any preceding aspect, wherein

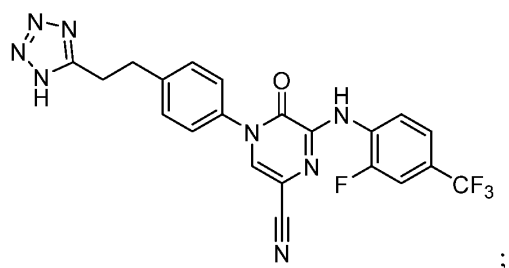
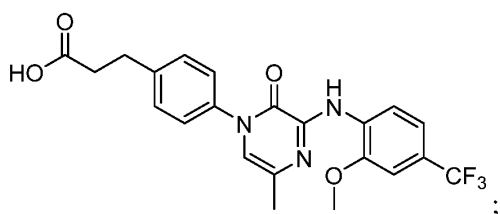
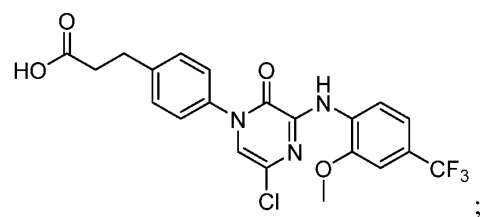
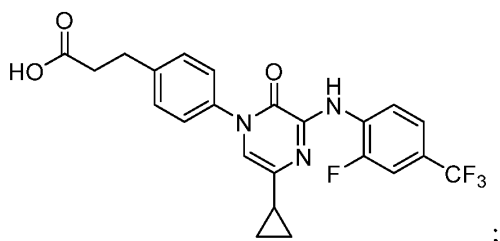
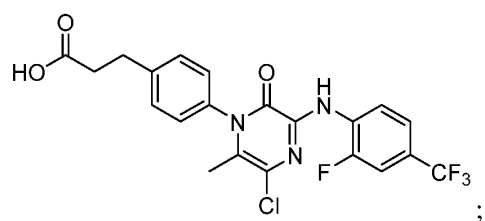
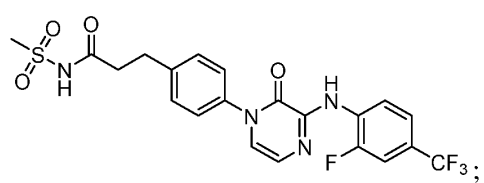
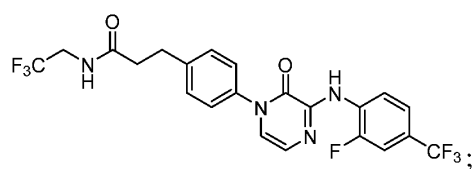
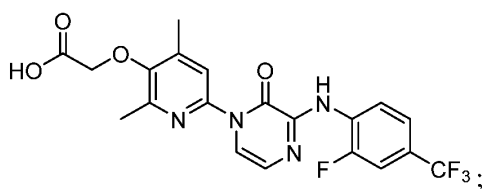
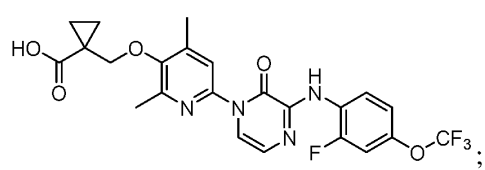
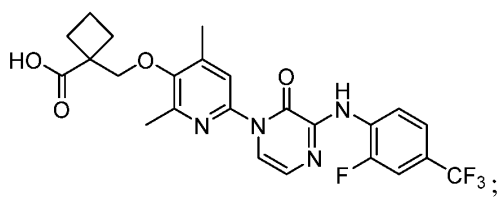
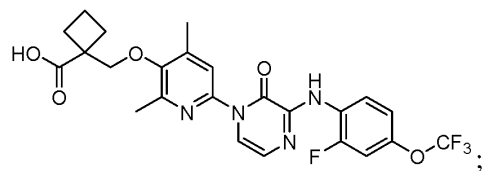
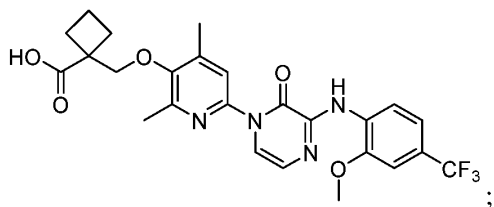
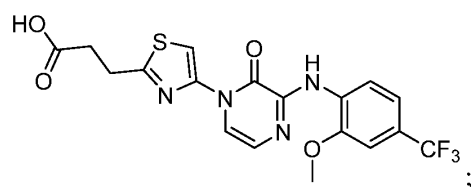
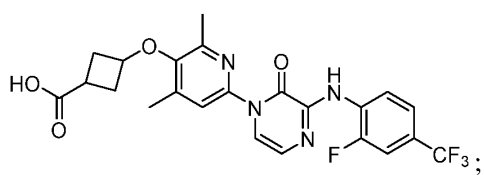
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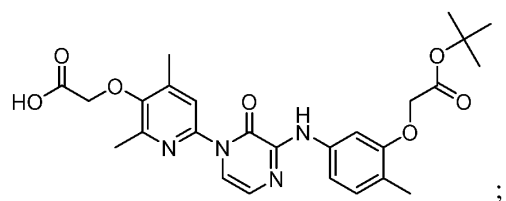
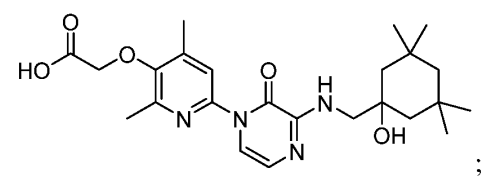
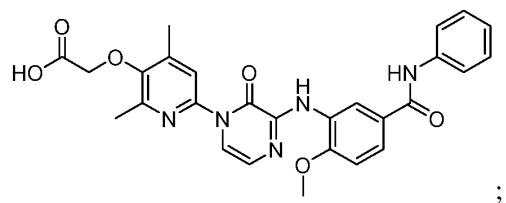
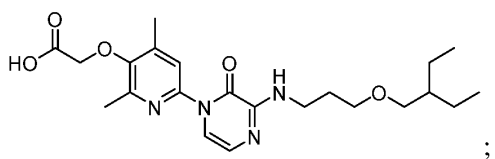
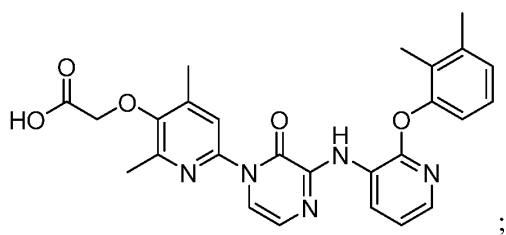
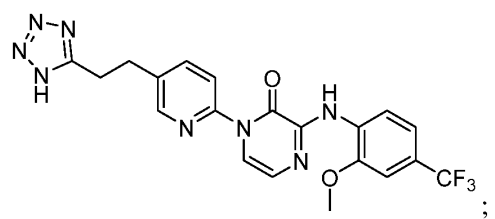
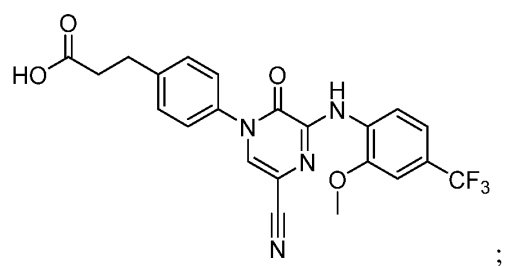
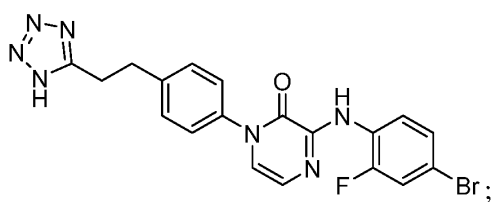
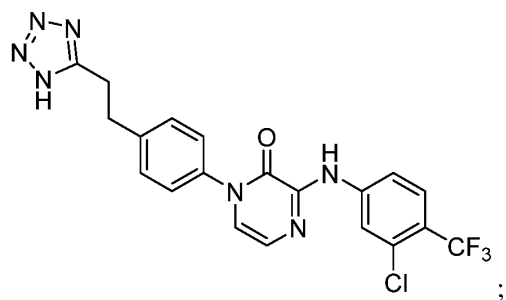
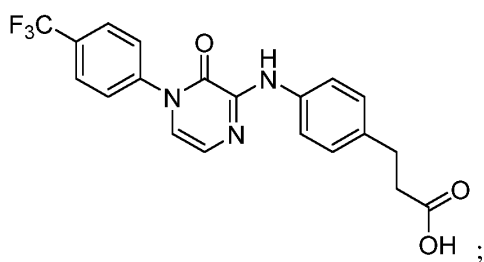
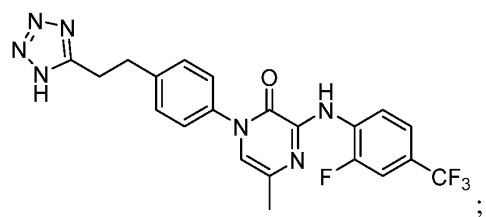
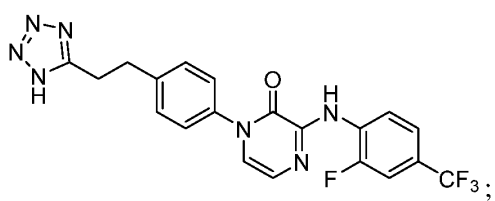


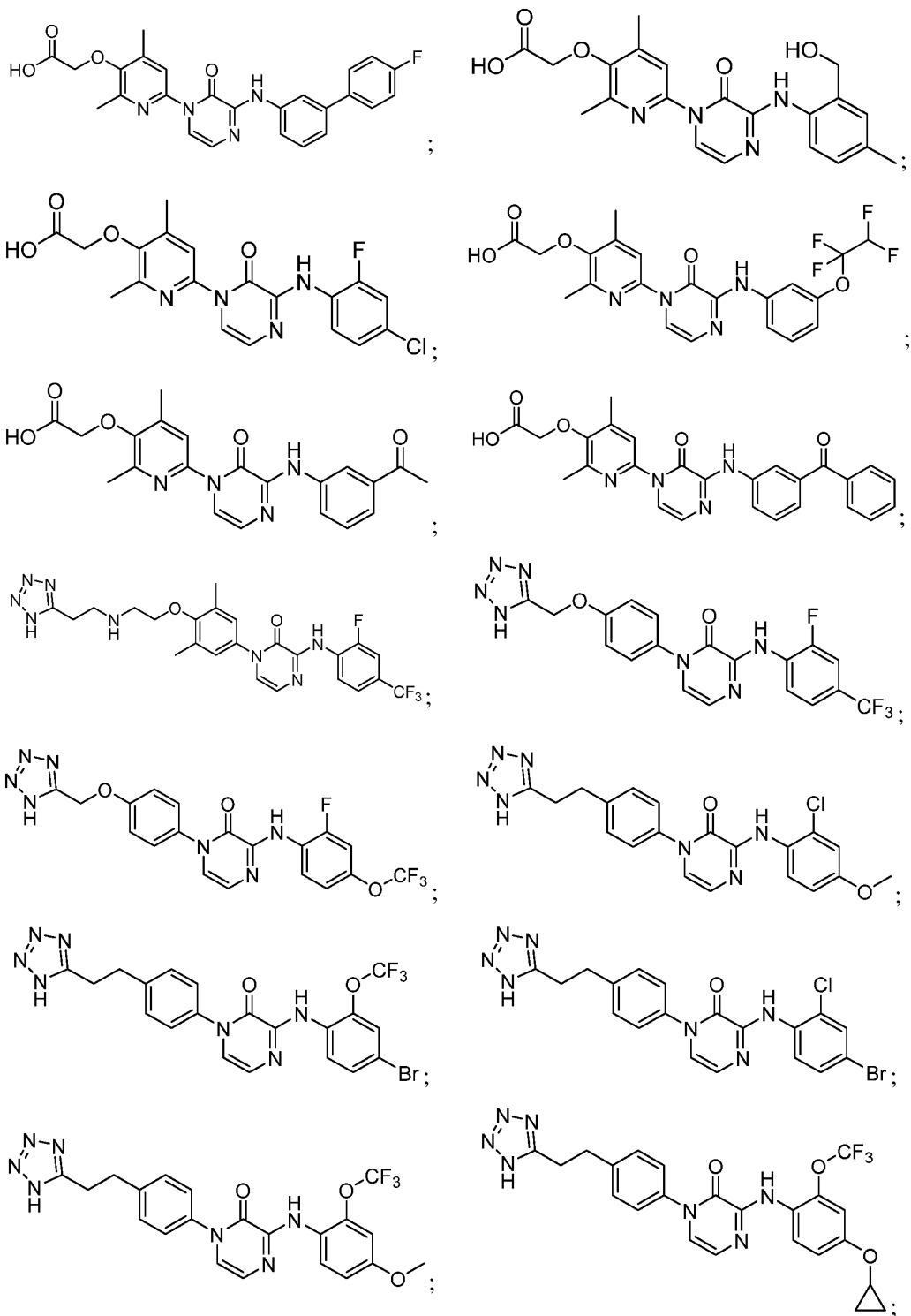


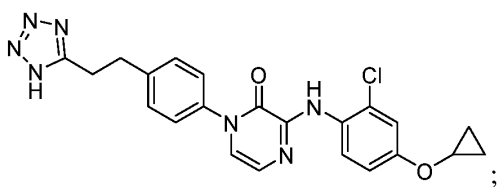
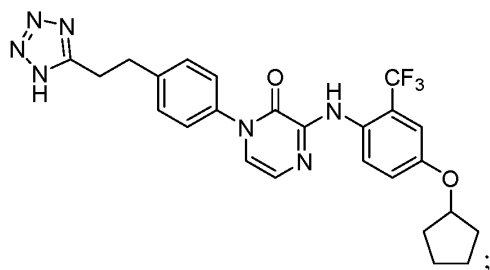
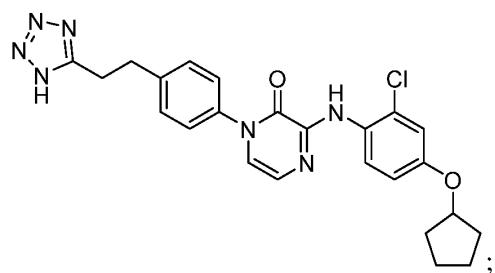
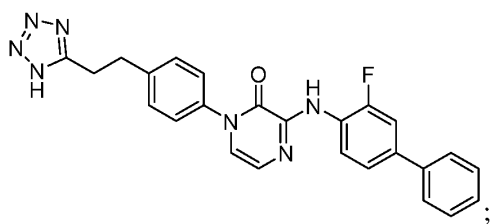
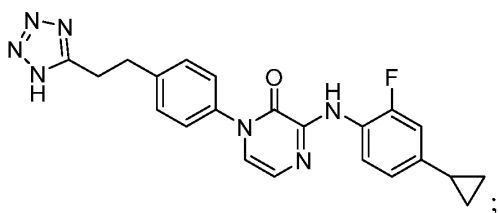
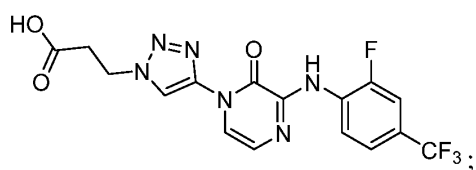
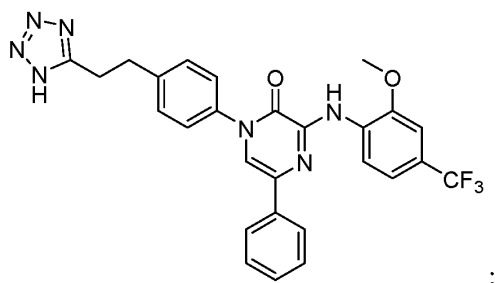
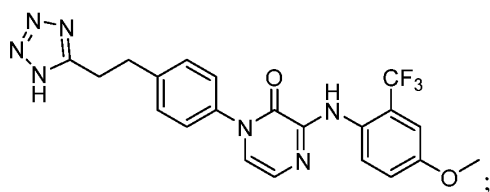
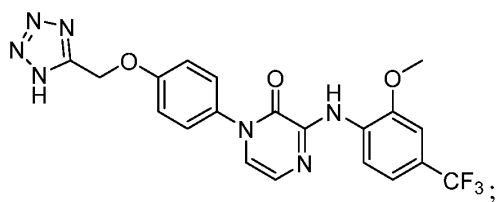
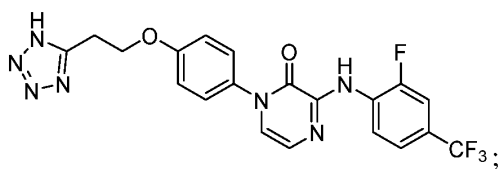
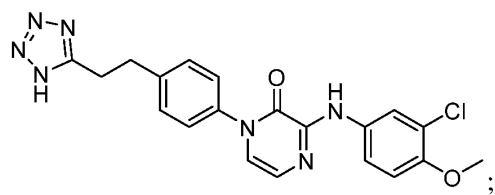
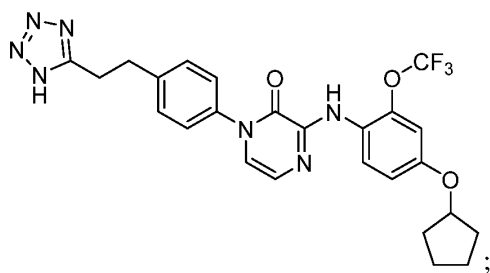


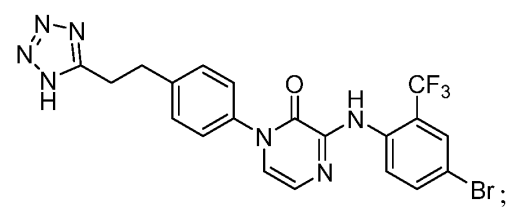
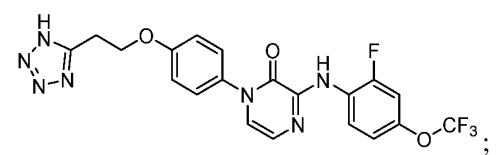
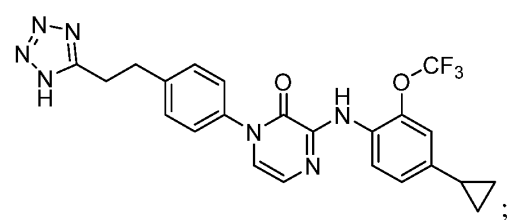
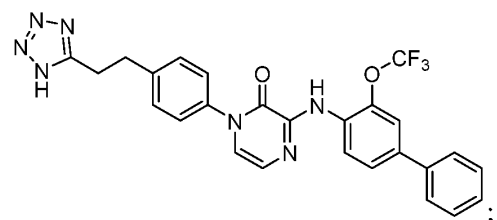
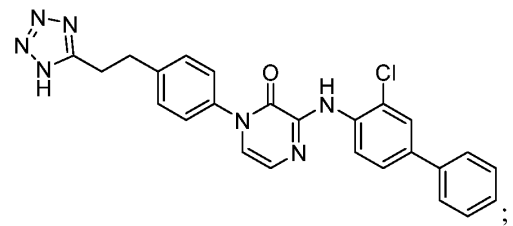
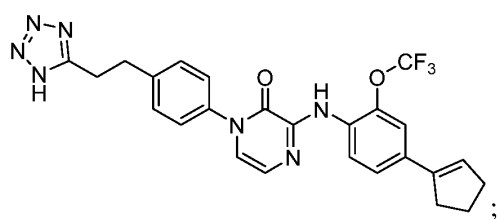
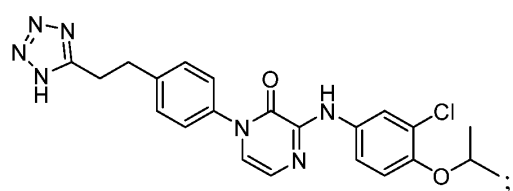
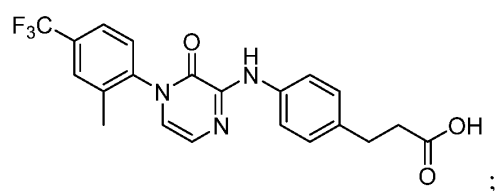
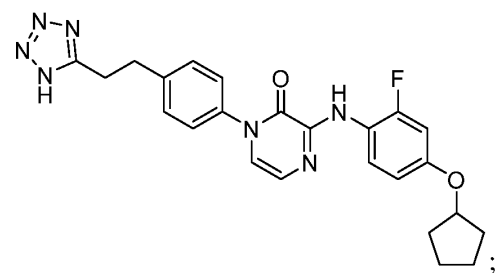
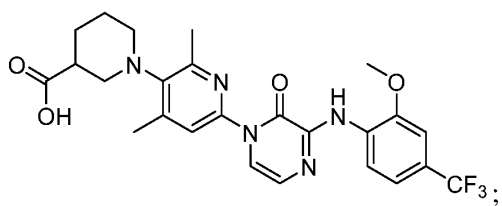
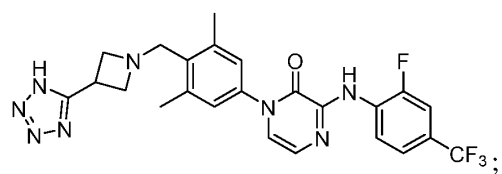
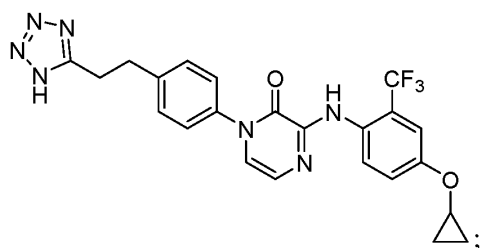


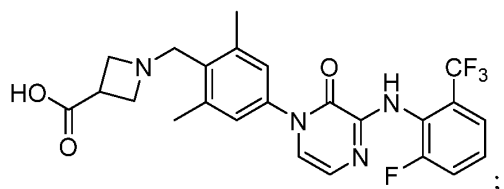
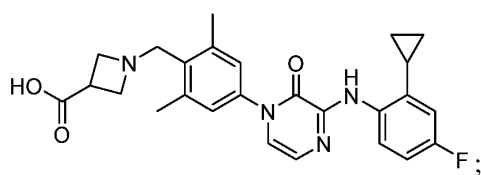
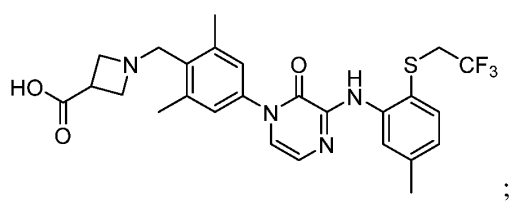
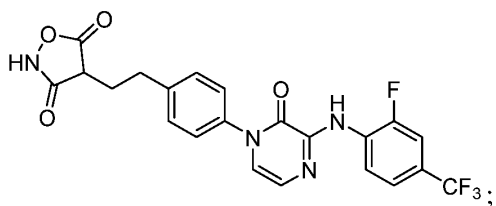
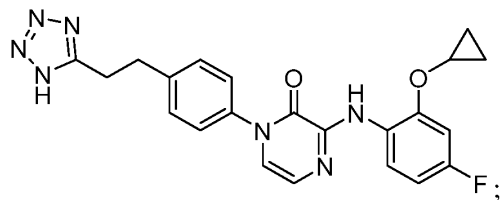
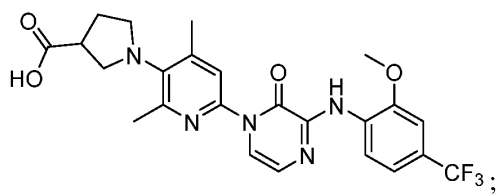
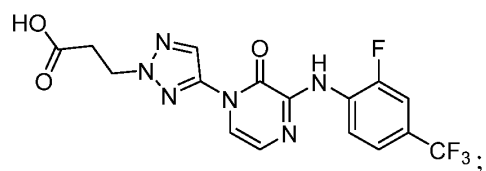
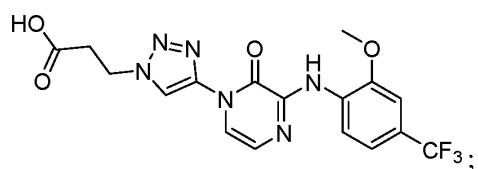
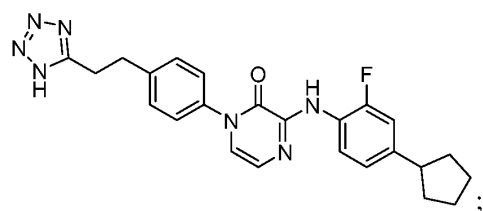
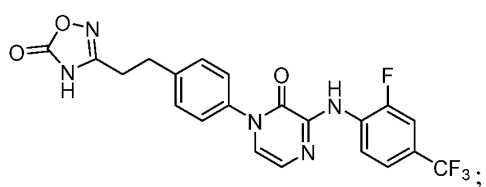
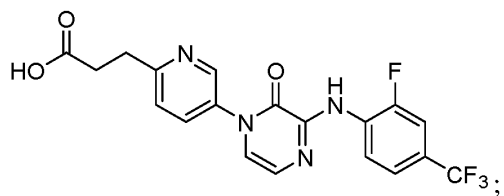
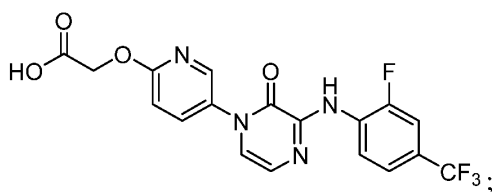
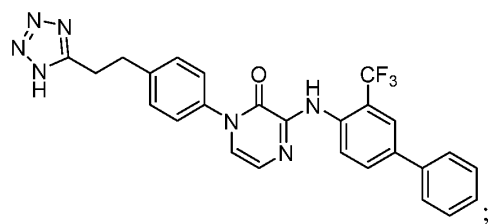
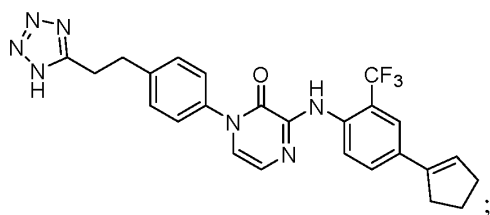


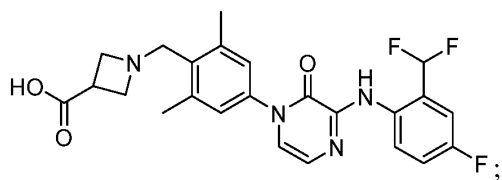
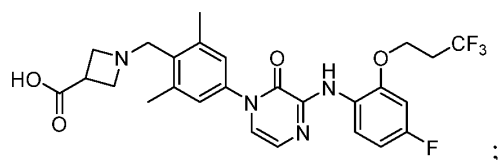
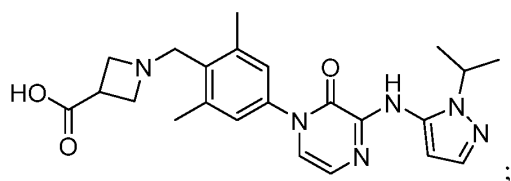
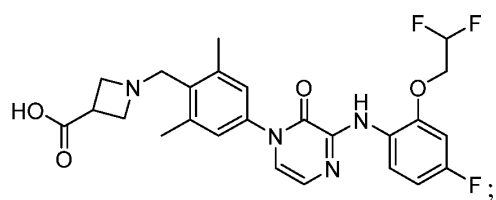
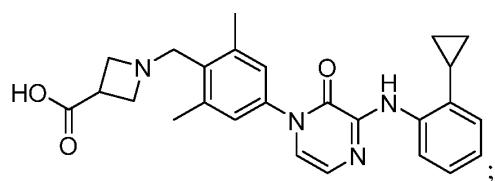
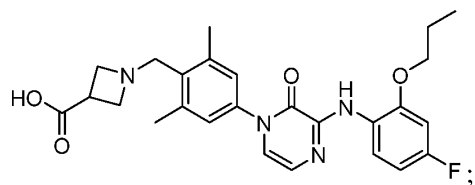
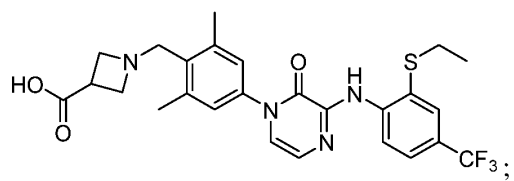


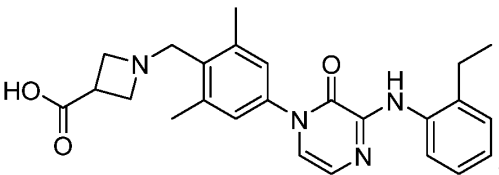
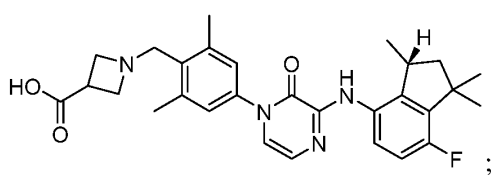
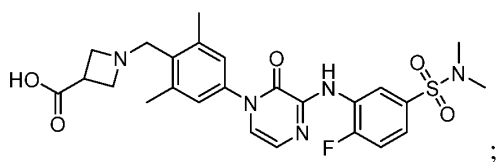
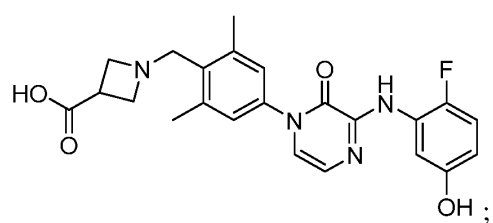
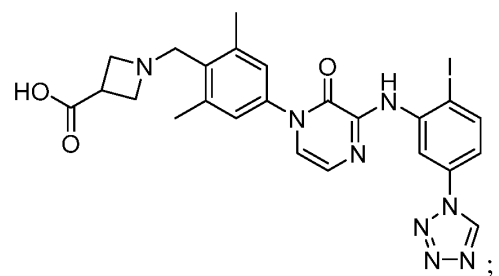
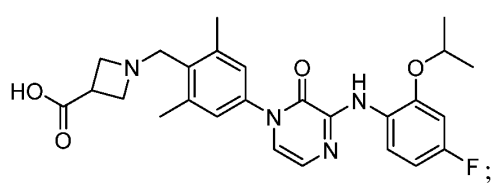
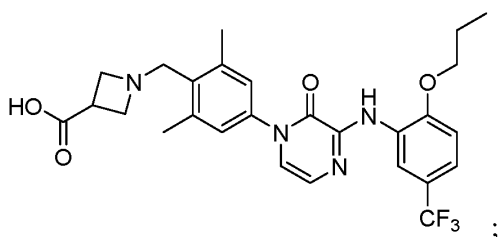
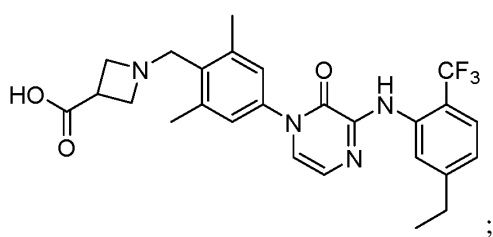
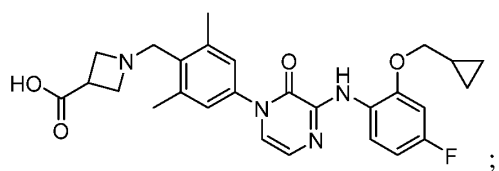
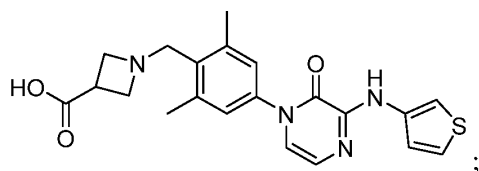
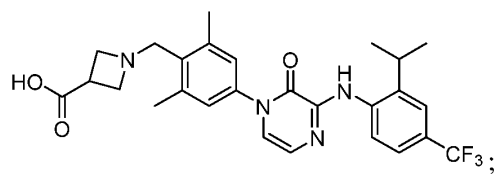
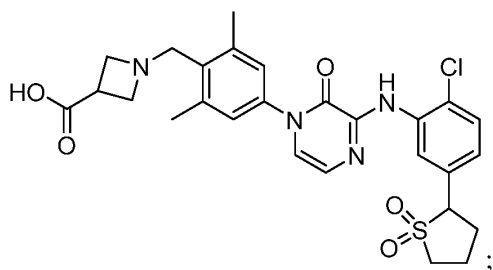


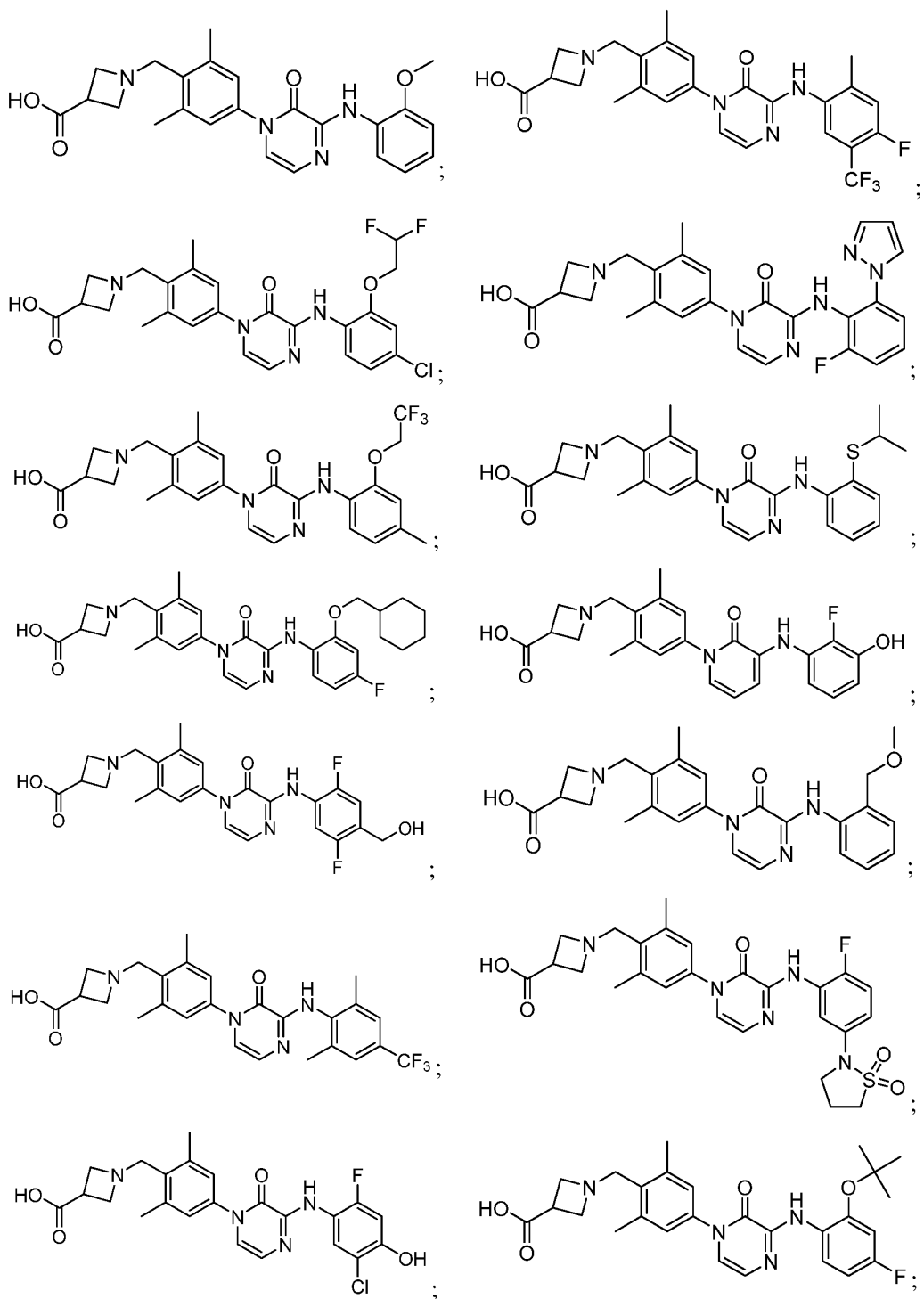


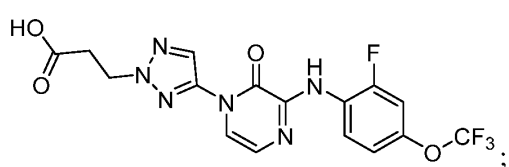
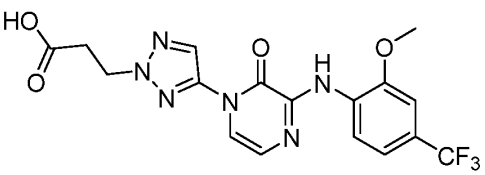
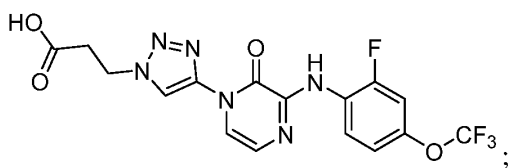
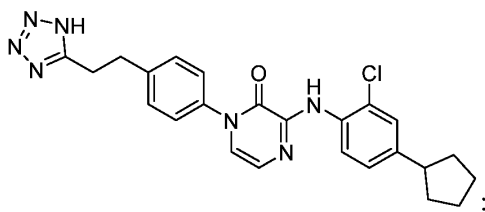
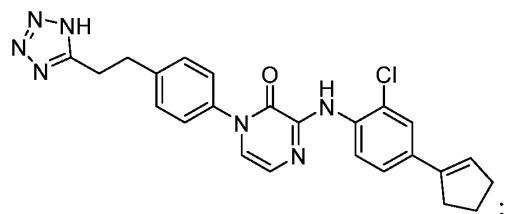
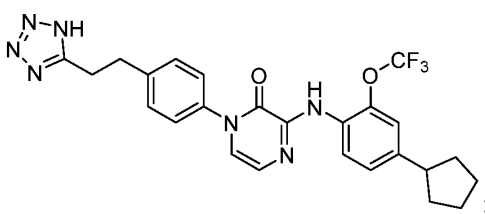
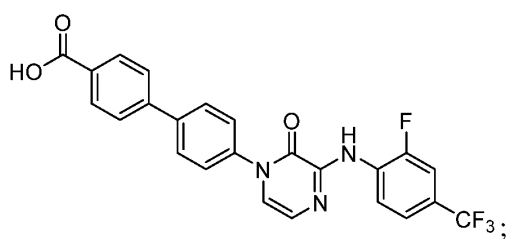
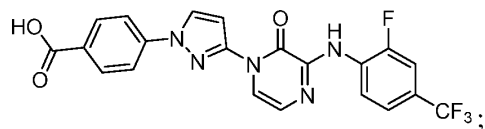
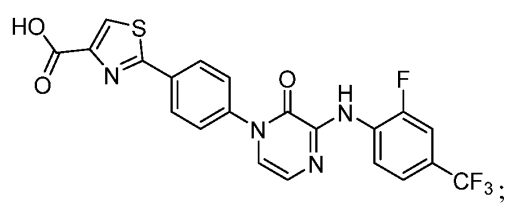
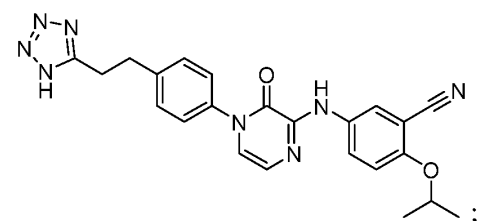
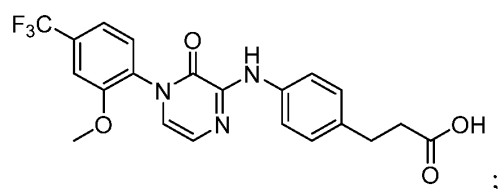
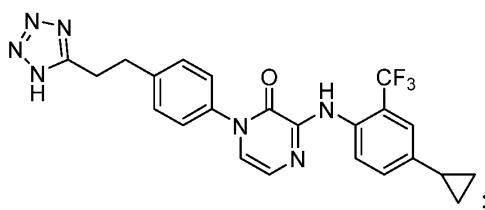
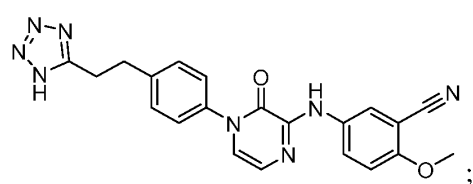
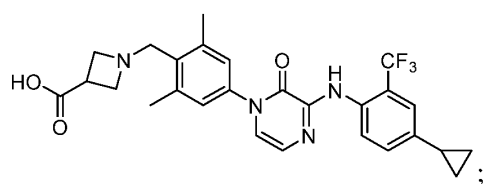


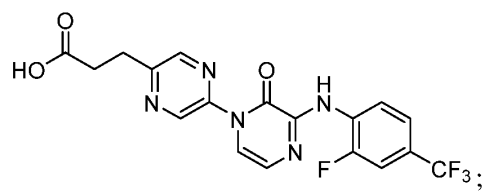
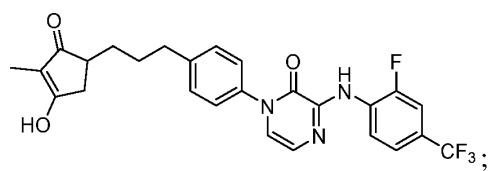
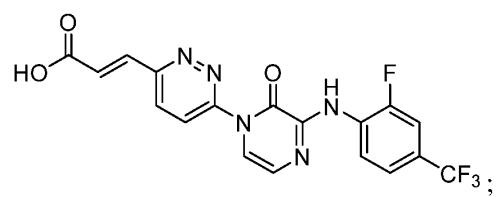
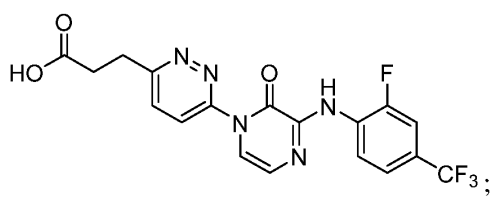
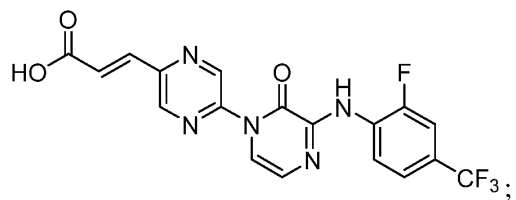
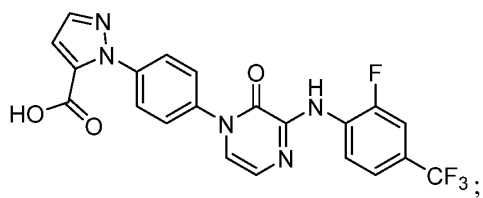
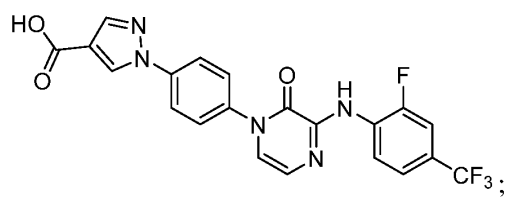
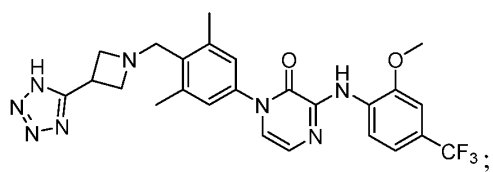
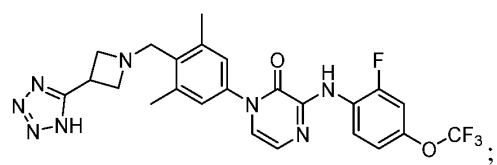
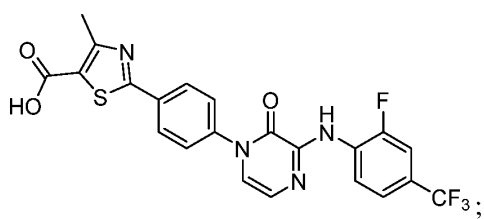
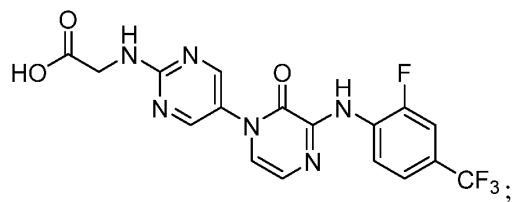
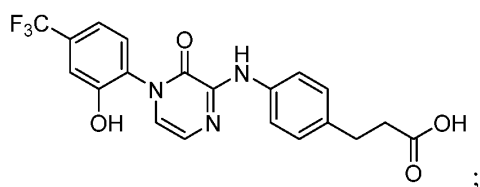
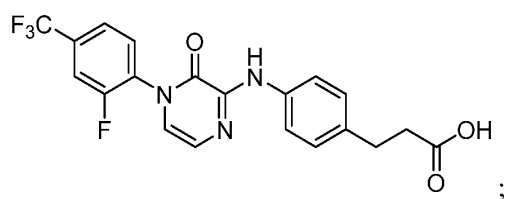
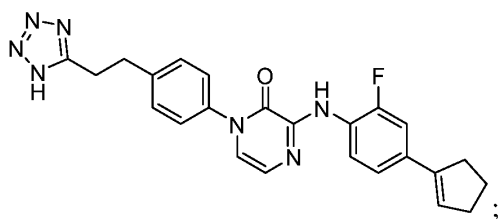


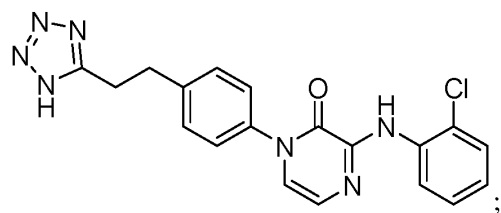
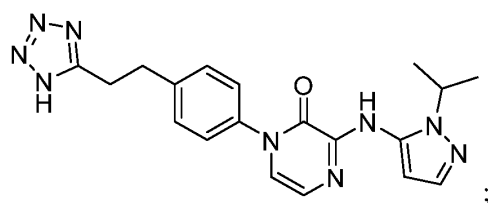
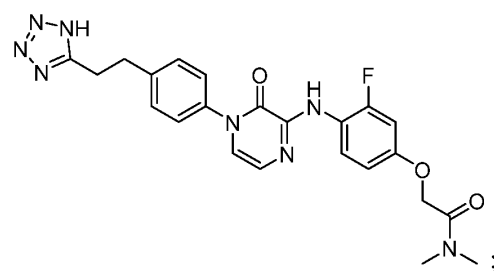
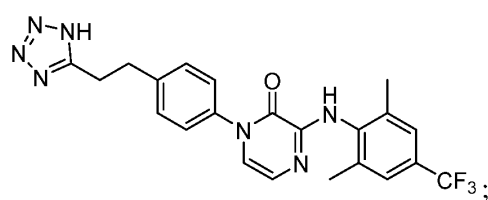
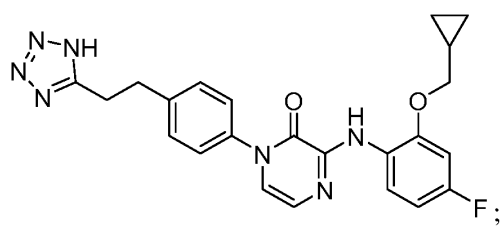
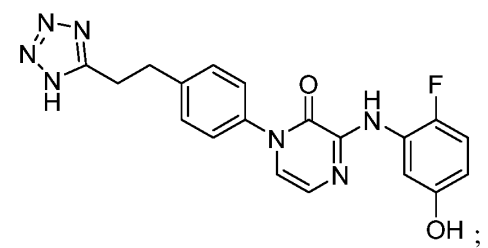
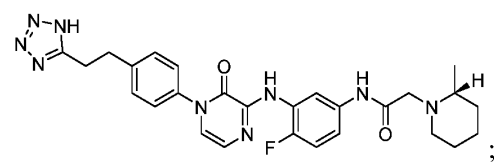
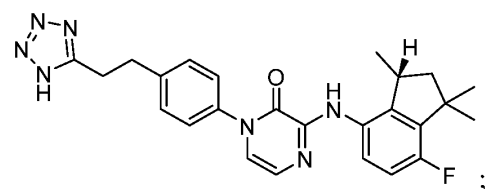
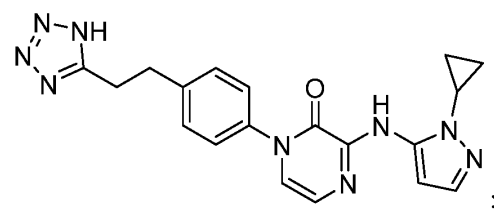
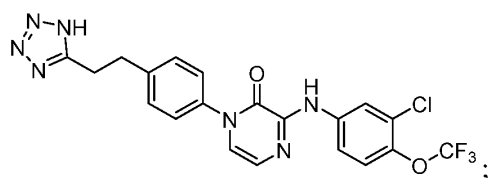
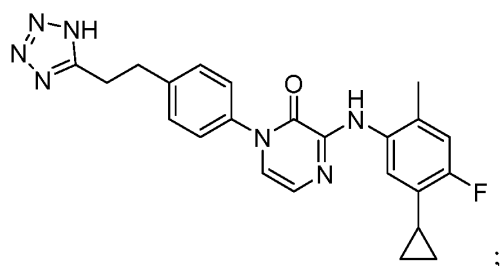
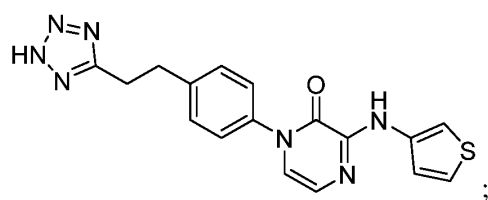


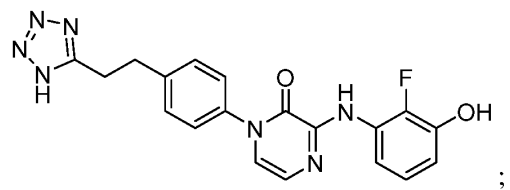
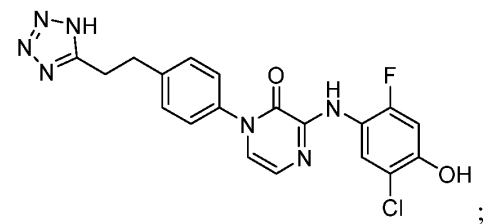
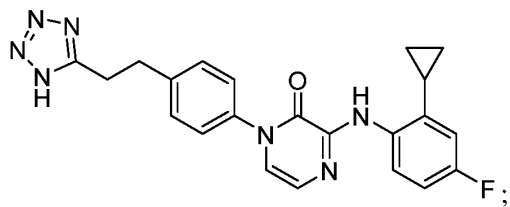
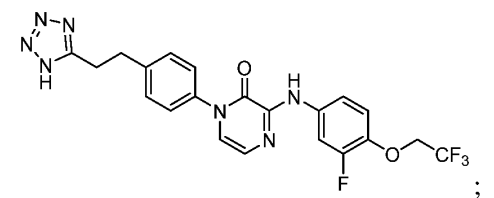
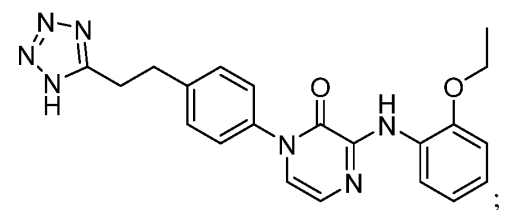
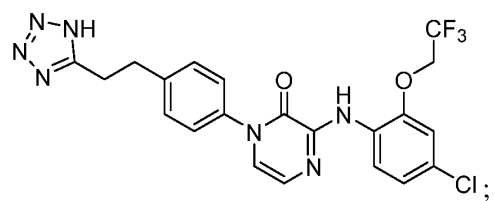
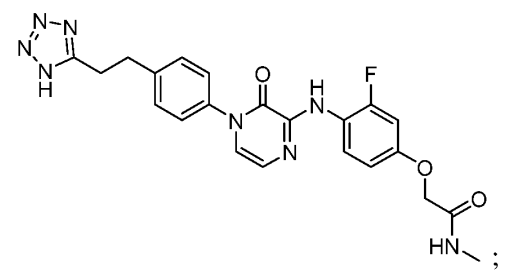
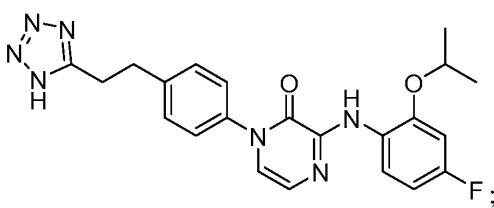
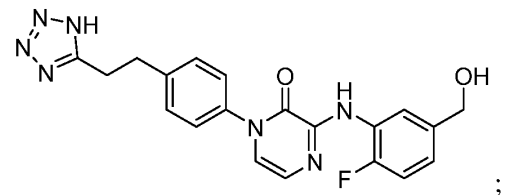
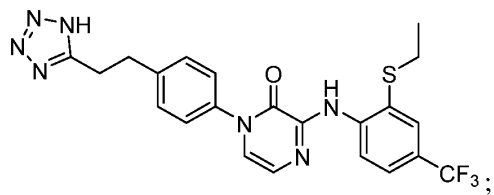
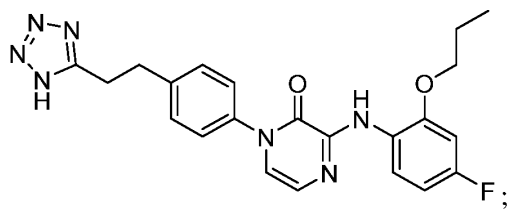
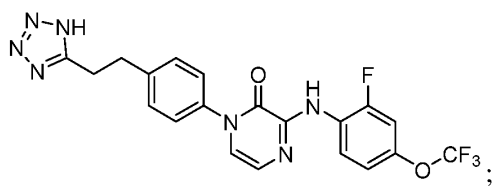


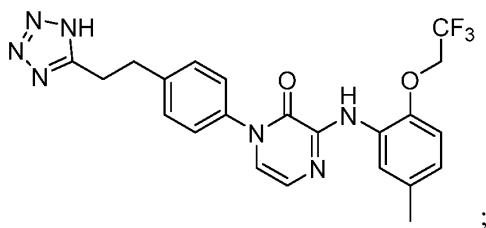
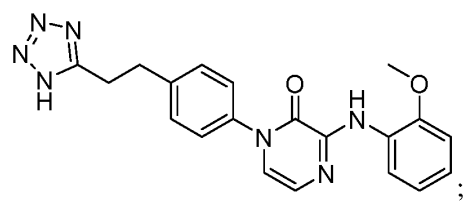
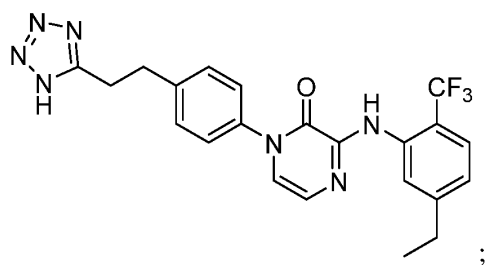
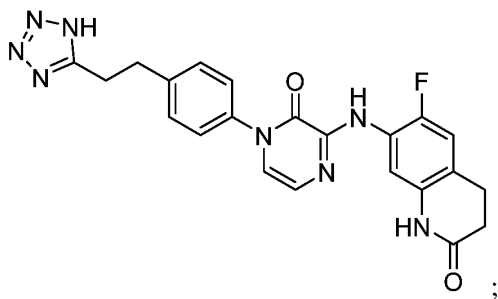
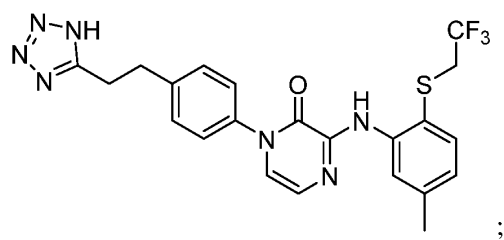
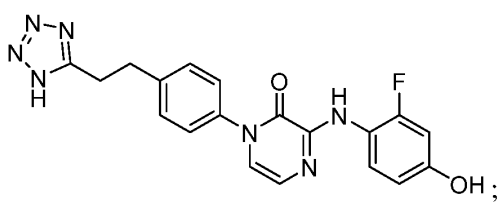
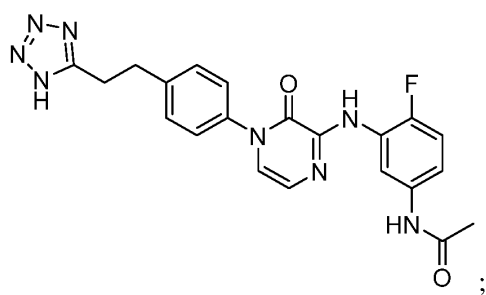
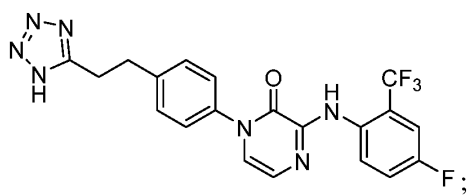
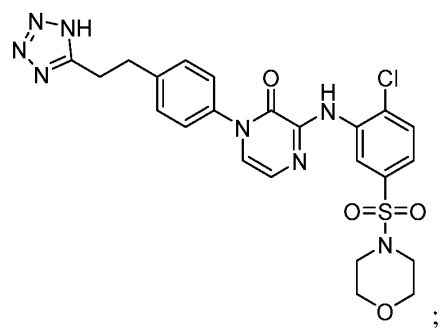
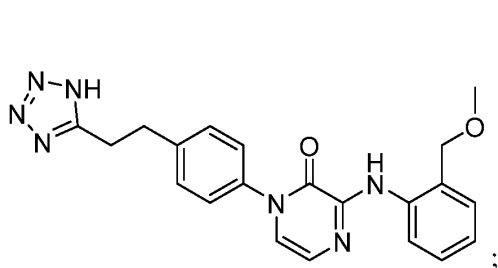


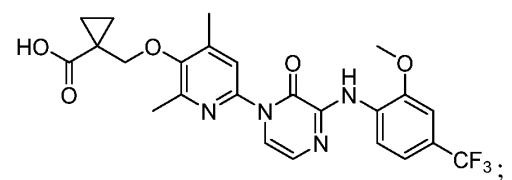
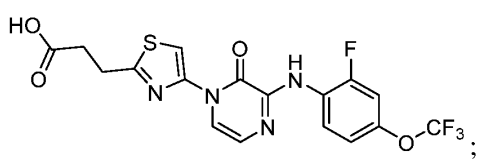
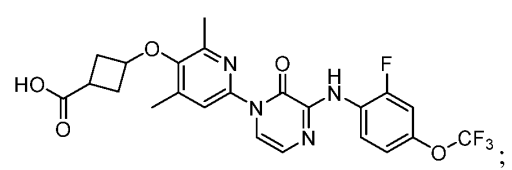
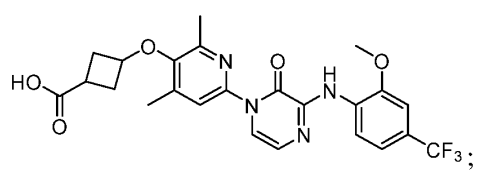
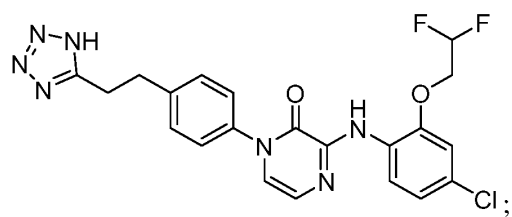
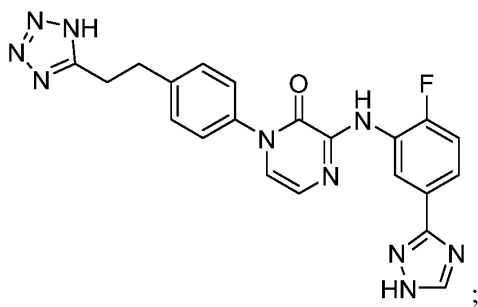
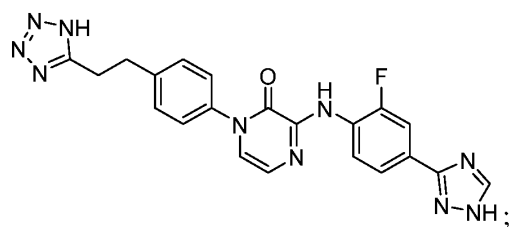
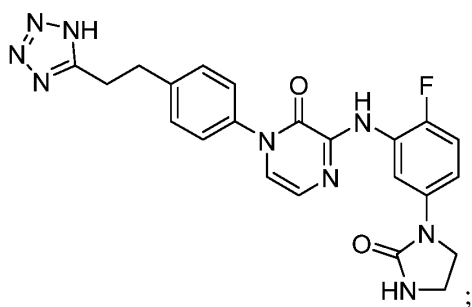
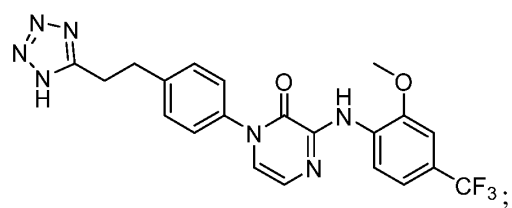
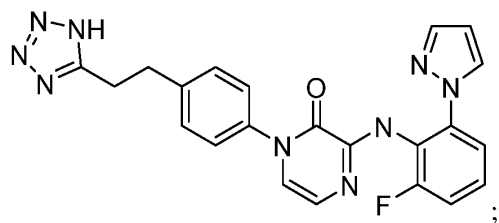
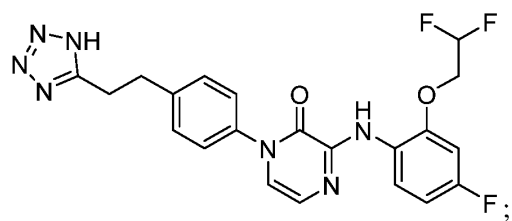
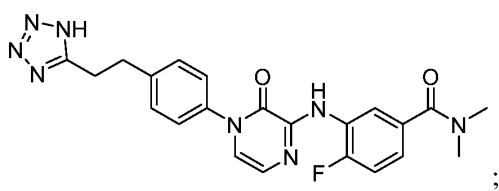


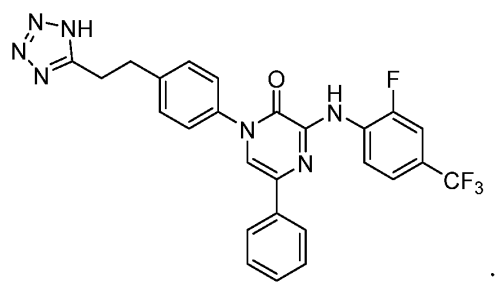
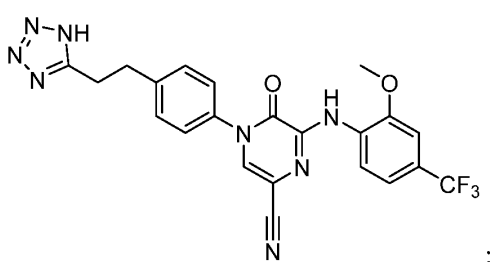
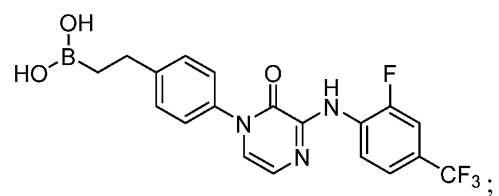
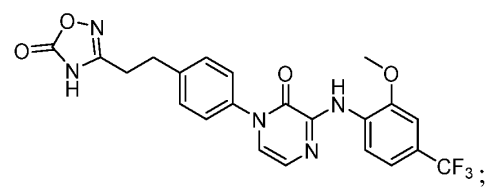
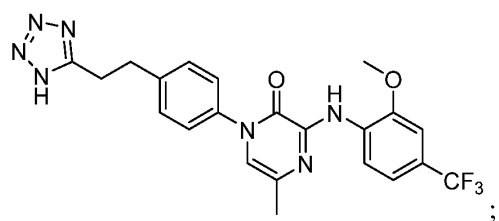
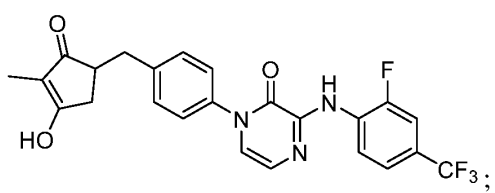
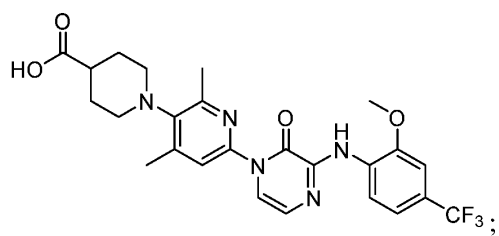
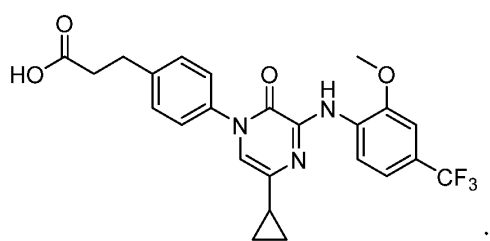
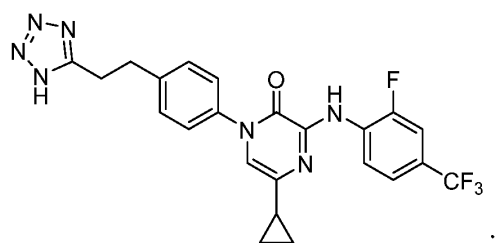
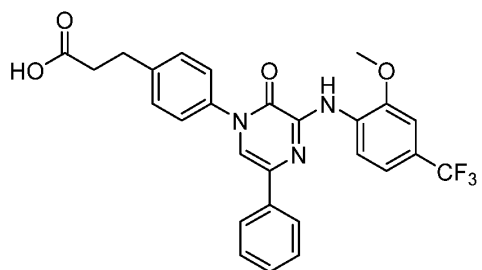
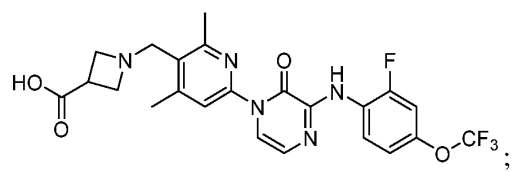
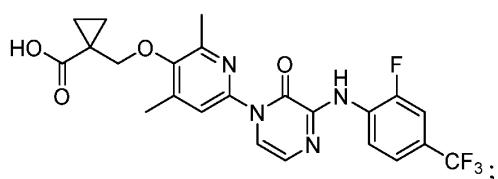


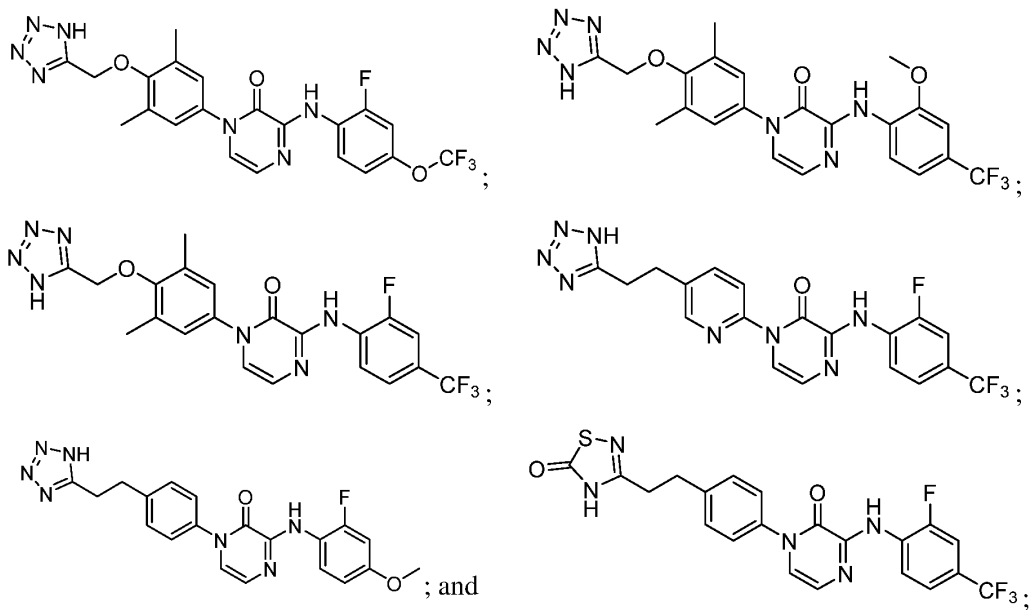






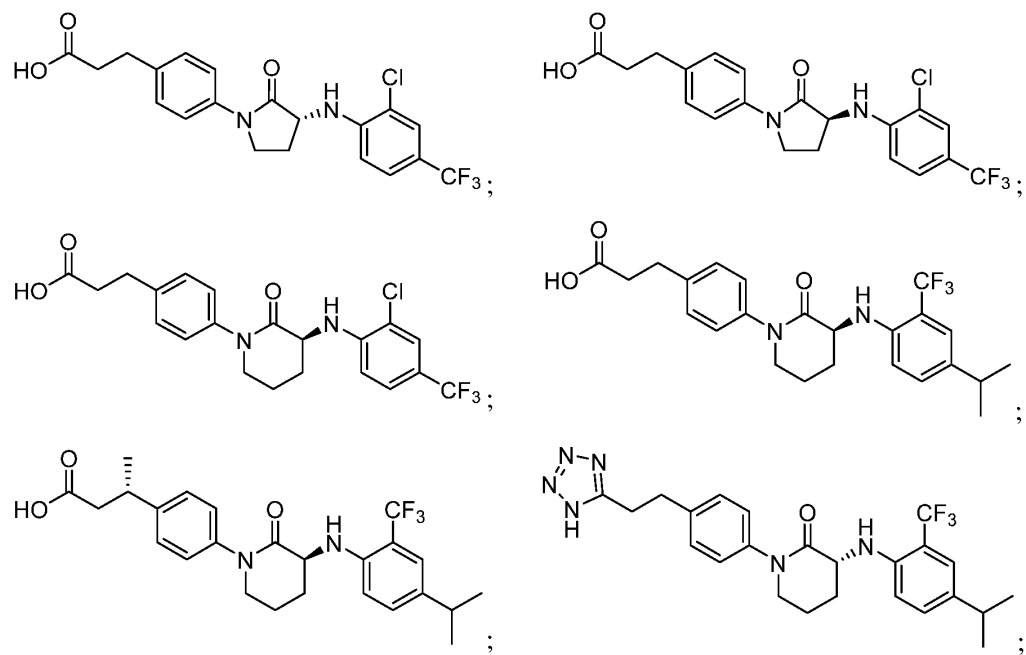


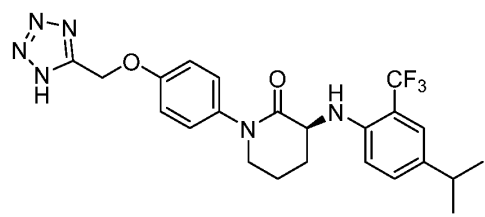
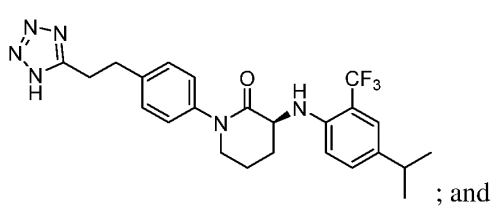




or an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0626] A sixteenth aspect relates to the compound of aspect **15**, wherein the compound is selected from the group consisting of:

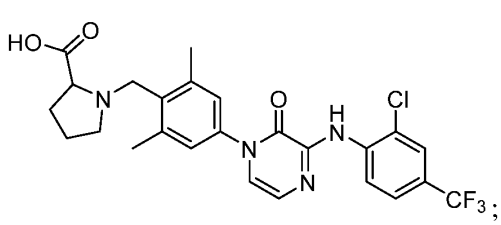
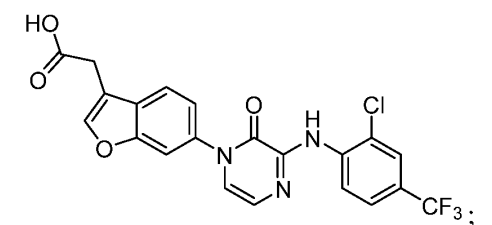
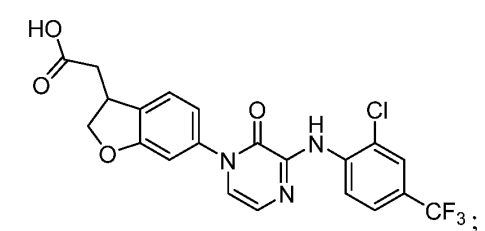
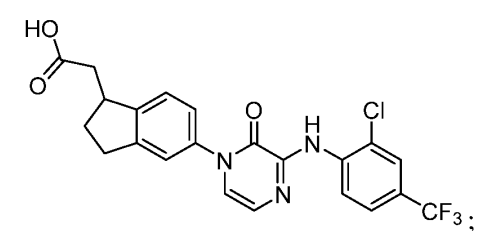
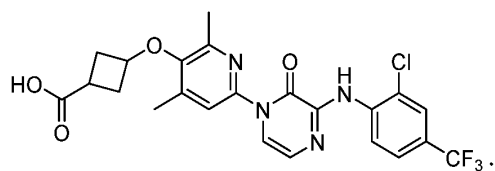
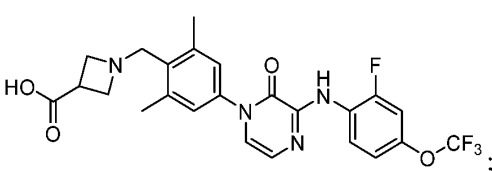
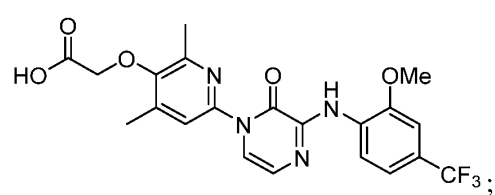
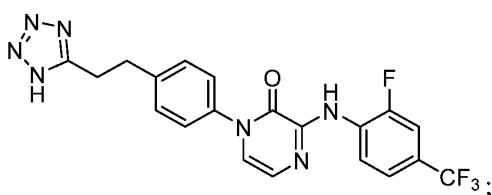
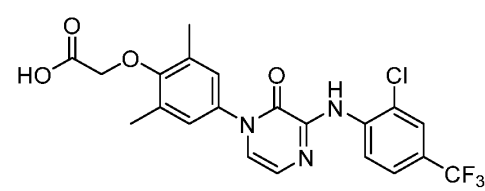
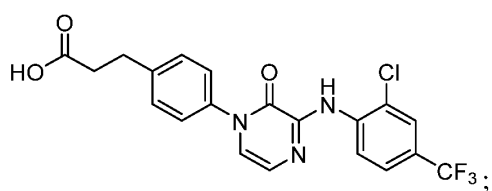


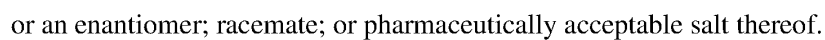


; and
or a pharmaceutically acceptable salt thereof.

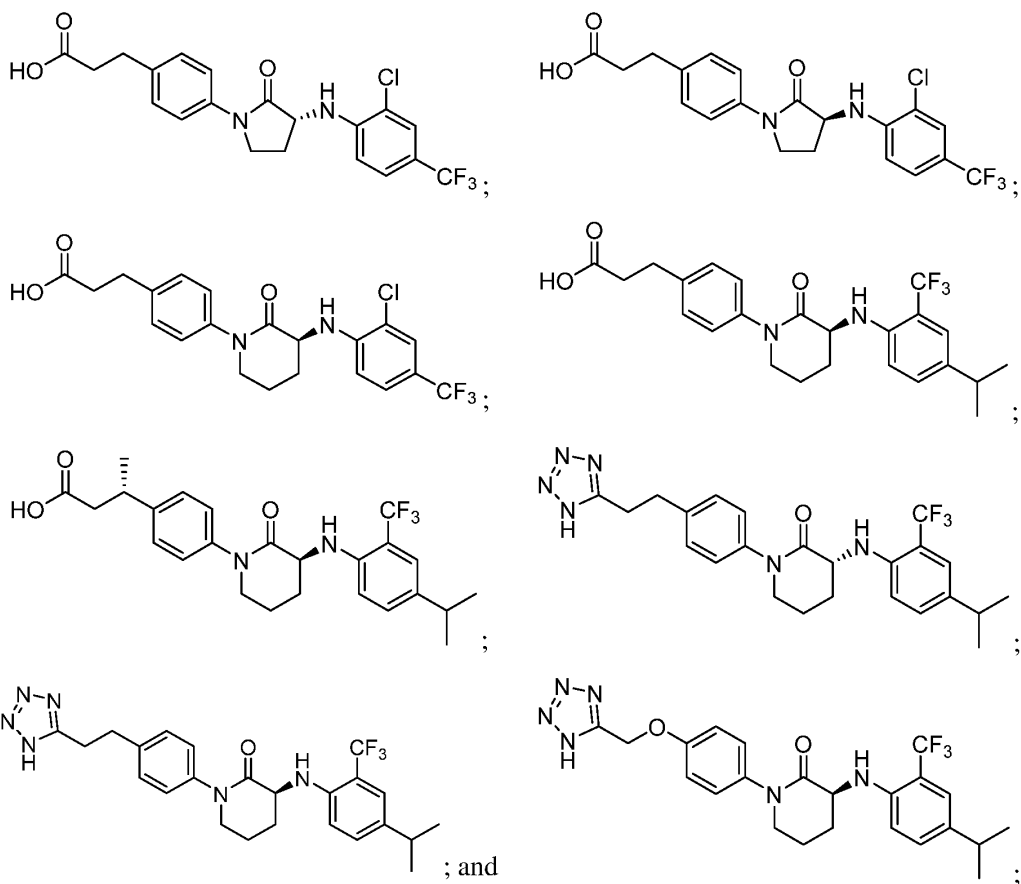
[0627] A seventeenth aspect relates to a pharmaceutical composition comprising the compound of any preceding aspect and one or more pharmaceutically acceptable excipients.

[0628] An eighteenth aspect relates to the pharmaceutical composition of aspect 17, wherein the compound is selected from the group consisting of:





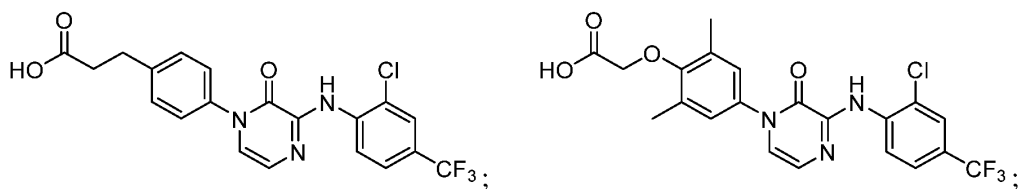
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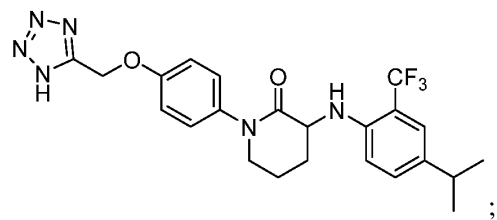
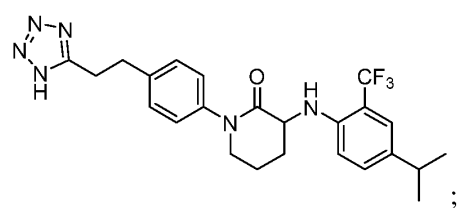
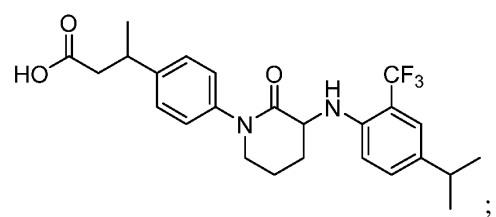
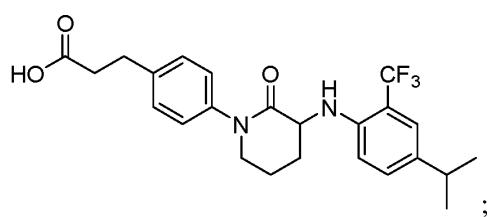
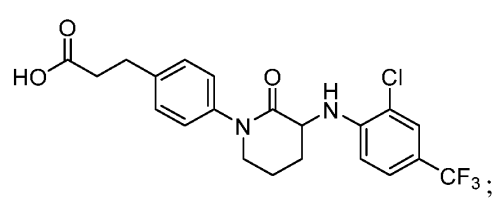
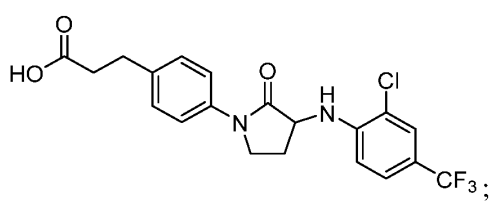
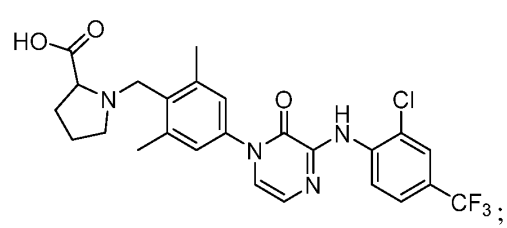
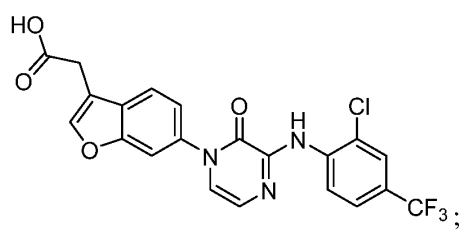
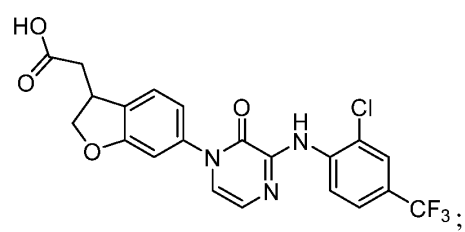
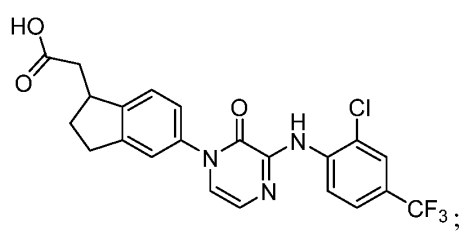
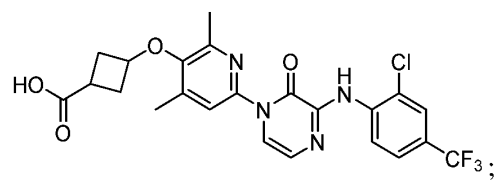
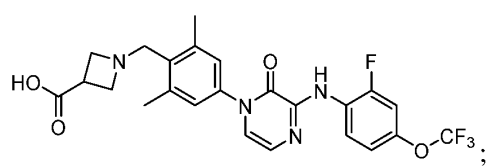
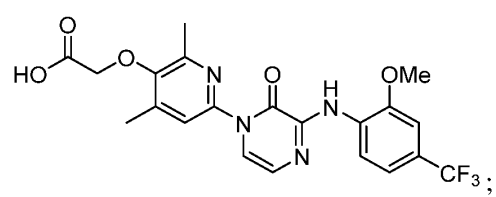
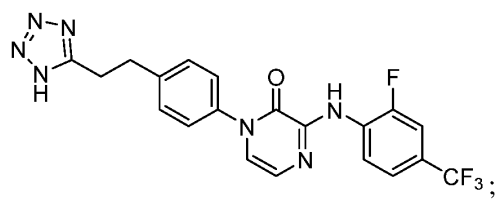


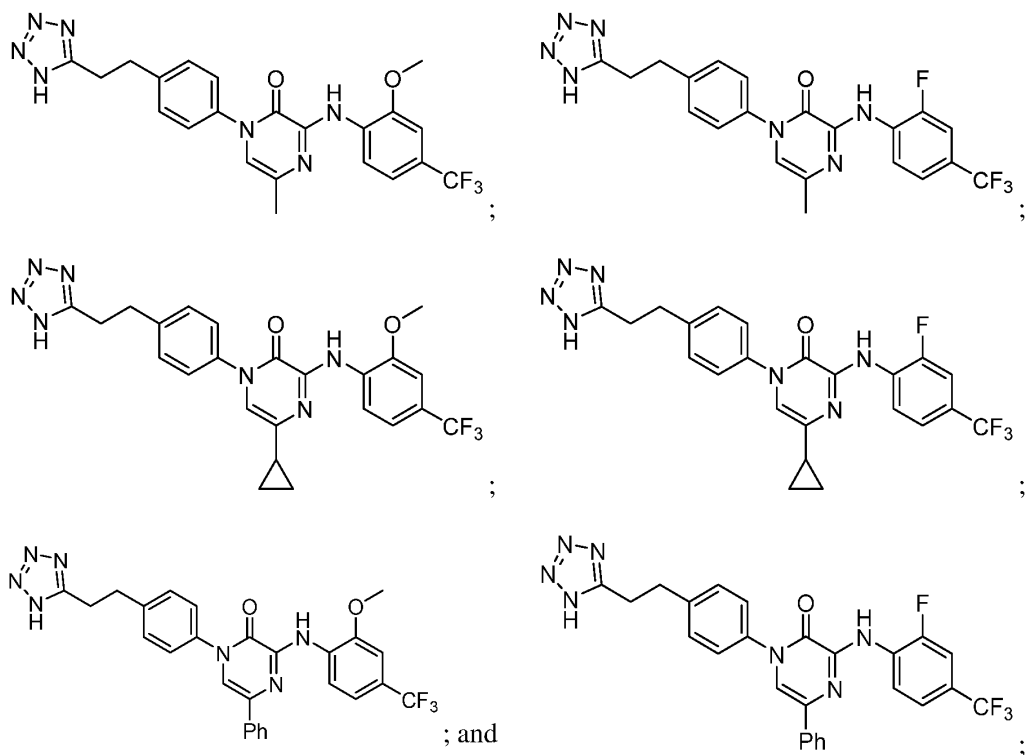
or a pharmaceutically acceptable salt thereof.

[0630] A twentieth aspect relates to a method of treating multiple sclerosis, relapsing-remitting multiple sclerosis, amyotrophic lateral sclerosis, psoriasis, systemic lupus erythematosus, ulcerative colitis, Crohn's disease, and lymphopenia, wherein the method comprises the step of administering to an individual in need thereof a pharmaceutical composition of aspects **17** to **19**.

[0631] A twenty-first aspect relates to the method of aspect **20**, wherein the compound is selected from the group consisting of:

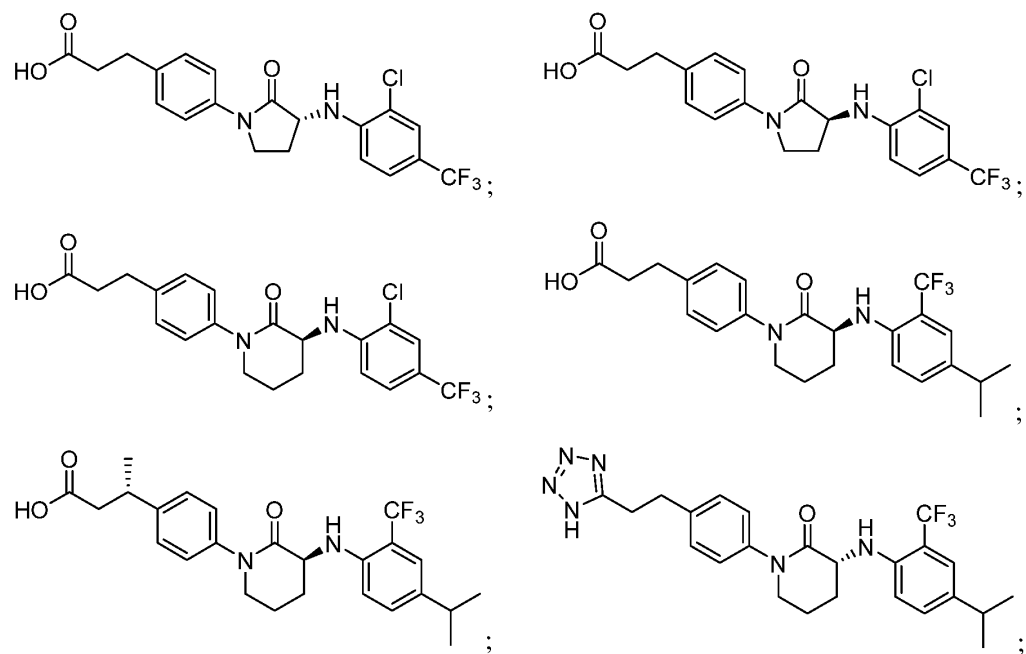


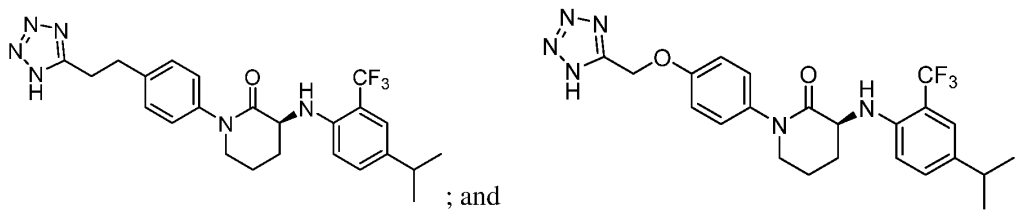




or an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

[0632] A twenty-second aspect relates to the method of aspect 20 or 21, wherein the compound is selected from the group consisting of:

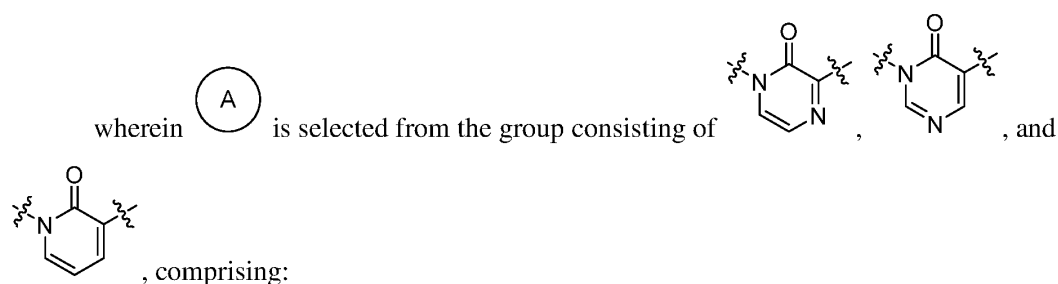




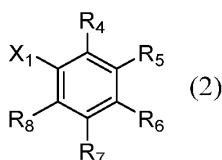
or a pharmaceutically acceptable salt thereof.

[0633] A twenty-third aspect relates to the method of aspects **20** to **22**, wherein the pharmaceutical composition is administered to the individual intranasally; intrapulmonarily; topically; orally; intravenously as an infusion or injection; subcutaneously as an infusion, injection, or depot formulation; transdermally; intraperitoneally; or rectally.

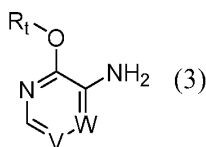
[0634] A twenty-fourth aspect relates to a process for preparing compounds of aspects **1** to **16**,



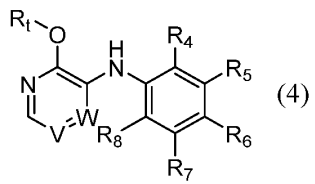
a step 1-A, reacting a compound of formula (2)



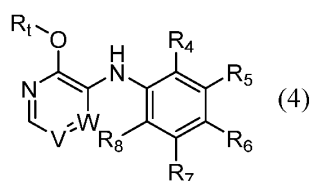
with a compound of formula (3)



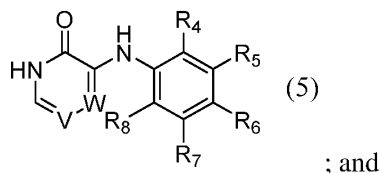
to produce a compound of formula (4)



a step 1-B, reacting a compound of formula (4)

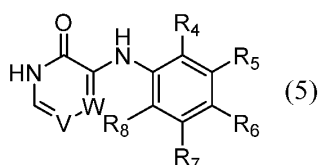


with an acid to produce a compound of formula (5)

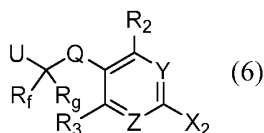


; and

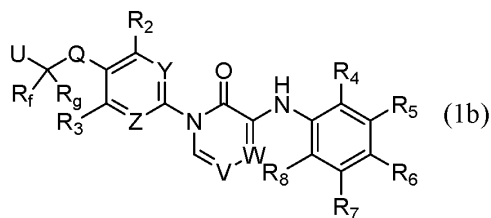
a step 1-C, reacting a compound of formula (5)



with a compound of formula (6)



to produce a compound of formula (1b)



wherein X₁ is F, Cl, Br, or I; X₂ is F, Cl, Br, or I; V is N or CH; W is N or CH; and R_f is H or unsubstituted C₁-C₆ straight or branched alkyl.

[0635] A twenty-fifth aspect relates to the process of aspect **24**, wherein step A is carried out from about 50 °C to about 100 °C; step B is carried out from about 50 °C to about 100 °C; and step 1-C is carried out from about 50 °C to about 125 °C.

[0636] A twenty-sixth aspect relates to the process of aspect **24** or **25**, wherein step A is carried out in the presence of a solvent and a base; step B is carried out in the presence of a solvent and an acid; and step 1-C is carried out in the presence of a solvent, a copper salt, a base, and a ligand.

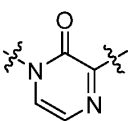
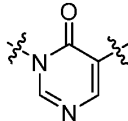
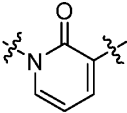
[0637] A twenty-seventh aspect relates to the process of aspect **26**, wherein the

solvent in step A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; and wherein the base in step A is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

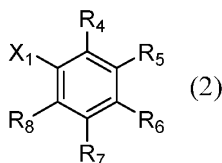
[0638] A twenty-eighth aspect relates to the process of aspect **26** or **27**, wherein the solvent in step B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and wherein the acid in step B is selected from the group consisting of AcOH, TFA, hydrochloric acid, hydrobromic acid, and mixtures thereof.

[0639] A twenty-ninth aspect relates to the process of aspects **26** to **28**, wherein the solvent in step 1-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; wherein the copper salt in step 1-C is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; wherein the base in step 1-C is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and wherein the ligand in step 1-C is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

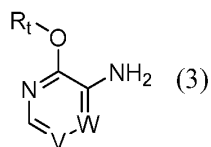
[0640] A thirtieth aspect relates to a process for preparing compounds of aspects **1** to **16**,

wherein  is selected from the group consisting of , , and , comprising:

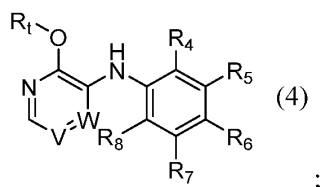
a step A, reacting a compound of formula (2)



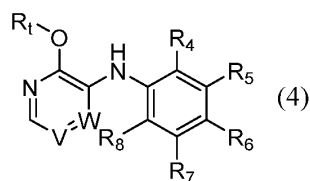
with a compound of formula (3)



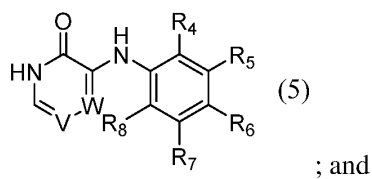
to produce a compound of formula (4)



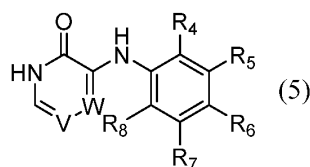
a step B, reacting a compound of formula (4)



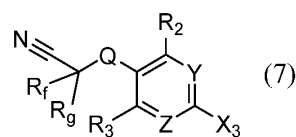
with an acid to produce a compound of formula (5)



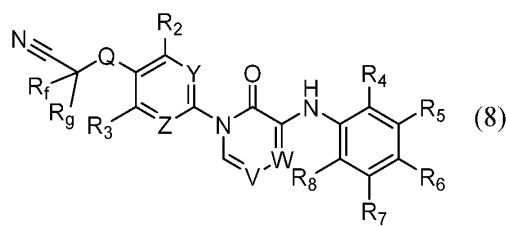
a step 2-C, reacting a compound of formula (5)



with a compound of formula (7)



to produce a compound of formula (8)



wherein X_3 is F, Cl, Br, or I;

V is N or CH;

W is N or CH; and

and R_t is H or unsubstituted C_1 - C_6 straight or branched alkyl.

[0641] A thirty-first aspect relates to the process of aspect **30**, wherein step A is carried out from about 50 °C to about 100 °C; step B is carried out from about 50 °C to about 100 °C; and step 2-C is carried out from about 50 °C to about 125 °C.

[0642] A thirty-second aspect relates to the process of aspect **30** or **31**, wherein step A is carried out in the presence of a solvent and a base; step B is carried out in the presence of a solvent and an acid; and step 2-C is carried out in the presence of a solvent, a copper salt, a base, and a ligand.

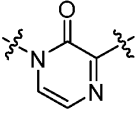
[0643] A thirty-third aspect relates to the process of aspect **32**, wherein the solvent in step A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, $CHCl_3$, MeCN, and mixtures thereof; and wherein the base in step A is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0644] A thirty-fourth aspect relates to the process of aspect **32** or **33**, wherein the solvent in step B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, $CHCl_3$, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and wherein the acid in step B is selected from the group consisting of AcOH, TFA, hydrochloric acid, hydrobromic acid, and mixtures thereof.

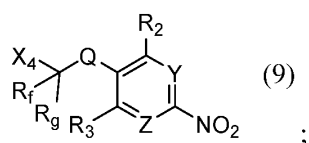
[0645] A thirty-fifth aspect relates to the process of aspects **32** to **34**, wherein the solvent in step 2-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, $CHCl_3$, MeCN, and mixtures thereof; wherein the copper salt in step 2-C is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; wherein the base in step 2-C is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium

hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and wherein the ligand in step 2-C is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

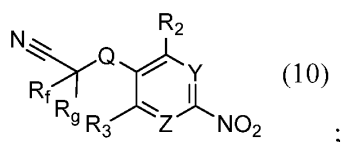
[0646] A thirty-sixth aspect relates to a process for preparing compounds of aspects 1 to 16,

wherein  is , comprising:

a step 3-A, reacting a compound of formula (9)



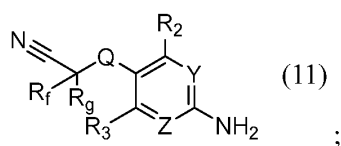
with a cyanide reagent to produce a compound of formula (10)



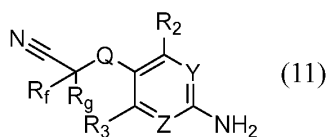
a step 3-B, reacting a compound of formula (10)



with a hydrogenation reagent to produce a compound of formula (11)



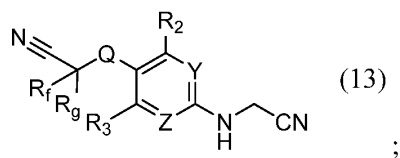
a step 3-C, reacting a compound of formula (11)



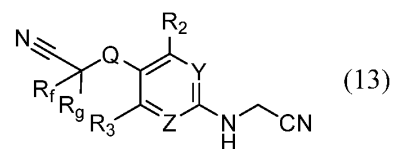
with a compound of formula (12)



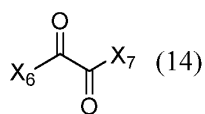
to produce a compound of formula (13)



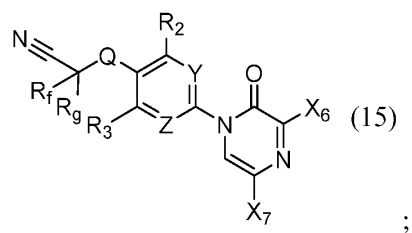
a step 3-D, reacting a compound of formula (13)



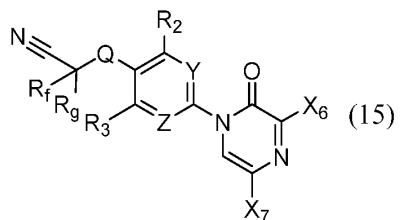
with a compound of formula (14)



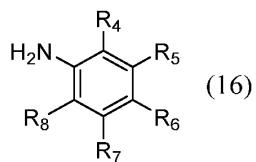
to produce a compound of formula (15)



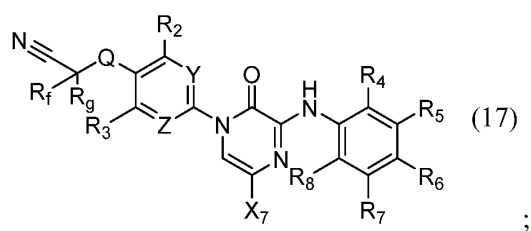
a step 3-E, reacting a compound of formula (15)



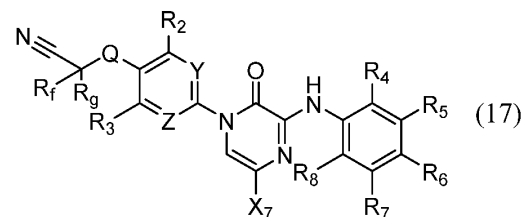
with a compound of formula (16)



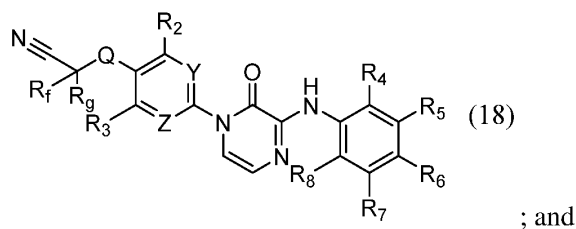
to produce a compound of formula (17)



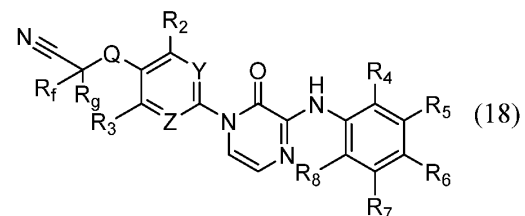
a step 3-F, reacting a compound of formula (17)



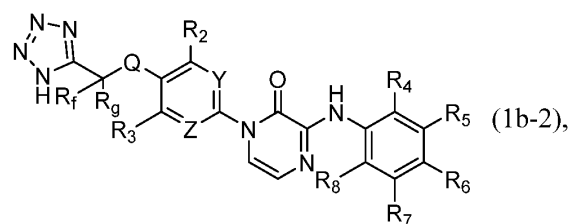
with a hydrogenation reagent to produce a compound of formula (18)



a step 3-G, reacting a compound of formula (18)



with an azide reagent to produce a compound of formula (1b-2)



wherein X₄ is F, Cl, Br, or I; X₅ is F, Cl, Br, I, or a leaving group L₁ selected from the group consisting of *p*-toluenesulfonate (-OTs), methanesulfonate (-OMs), trifluoromethanesulfonate (-SO₃CF₃), nitrate (-ONO₂), and phosphates (-OPO(OR)₂), wherein R is an alkyl group; X₆ is F, Cl, Br, or I; and X₇ is F, Cl, Br, or I.

[0647] A thirty-seventh aspect relates to the process of aspect **36**, wherein step 3-A is carried out from about 30 °C to about 75 °C; step 3-B is carried out from about 15 °C to about 35 °C; step 3-C is carried out from about 50 °C to about 75 °C; step 3-D is carried out from about 75 °C to about 125 °C; step 3-E is carried out from about 15 °C to about 35 °C; step 3-F is carried out from about 15 °C to about 35 °C; and step 3-G is carried out from about 100 °C to about 140 °C.

[0648] A thirty-eighth aspect relates to the process of aspect **36** or **37**, wherein step 3-A is carried out in the presence of a solvent and a cyanide reagent; step 3-B is carried out in the presence of a solvent, a hydrogenation reagent, and a catalyst; step 3-C is carried out in the presence of a solvent and a base; step 3-D is carried out in the presence of a solvent; step 3-E is carried out in the presence of a solvent and a base; step 3-F is carried out in the presence of a solvent, a hydrogenation reagent, a catalyst, and a base; and step 3-G is carried out in the presence of a solvent, an azide reagent, and a salt.

[0649] A thirty-ninth aspect relates to the process of aspect **38**, wherein the solvent in step 3-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, DMSO, and mixtures thereof; and wherein the cyanide reagent in step 3-A is selected from the group consisting of sodium cyanide, potassium cyanide, and mixtures thereof.

[0650] A fortieth aspect relates to the process of aspect **38** or **39**, wherein the solvent in step 3-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; wherein the hydrogenation reagent in step 3-B is selected from the group consisting of hydrogen (H₂), formic acid, isopropanol, and mixtures thereof; and wherein the catalyst is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof.

[0651] A forty-first aspect relates to the process of aspects **38** to **40**, wherein the solvent in step 3-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the base in step 3-C is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0652] A forty-second aspect relates to the process of aspects **38** to **41**, wherein the solvent in step 3-D is selected from the group consisting of DMF, DMA, NMP, THF, 2-

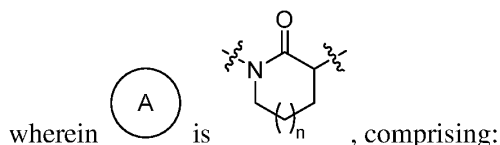
MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof.

[0653] A forty-third aspect relates to the process of aspects 38 to 42, wherein the solvent in step 3-E is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof; and wherein the base in step 3-E is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

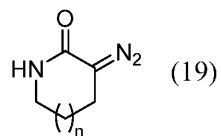
[0654] A forty-fourth aspect relates to the process of aspects 38 to 43, wherein the solvent in step 3-F is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; wherein the hydrogenation reagent in step 3-F is selected from the group consisting of hydrogen (H_2), formic acid, isopropanol, and mixtures thereof; wherein the catalyst in step 3-F is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof; and wherein the base in step 3-F is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0655] A forty-fifth aspect relates to the process of aspects 38 to 44, wherein the solvent in step 3-G is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof; wherein the azide reagent in step 3-G is selected from the group consisting of lithium azide, sodium azide, potassium azide, trimethyltin azide, triethyltin azide, tripropyltin azide, tributyltin azide, and mixtures thereof; and wherein the salt in step 3-G is selected from the group consisting of ammonium fluoride, ammonium chloride, ammonium bromide, ammonium iodide, and mixtures thereof.

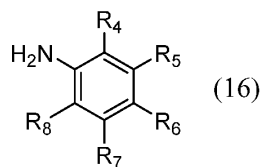
[0656] A forty-sixth aspect relates to a process for preparing compounds of aspects 1 to 16,



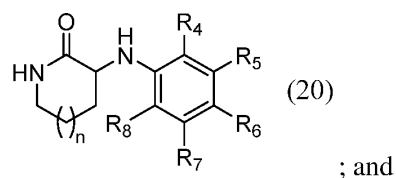
a step 4-A, reacting a compound of formula (19)



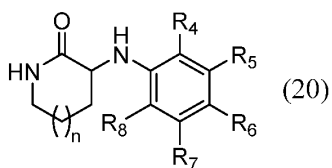
with a compound of formula (16)



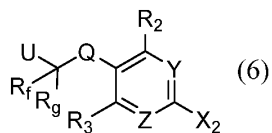
to produce a compound of formula (20)



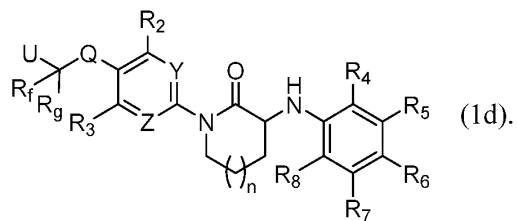
a step 4-B, reacting a compound of formula (20)



with a compound of formula (6)



to produce a compound of formula (1d)



[0657] A forty-seventh aspect relates to the process of aspect **46**, wherein step 4-A is

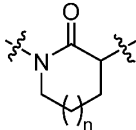
carried out from about 15 °C to about 35 °C; and step 4-B is carried out from about 50 °C to about 125 °C.

[0658] A forty-eighth aspect relates to the process of aspect **46** or **47**, wherein step 4-A is carried out in the presence of a solvent and a catalyst; and step 4-B is carried out in the presence of a solvent, a copper salt, a base, and a ligand.

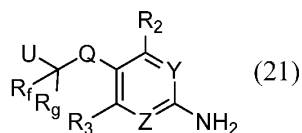
[0659] A forty-ninth aspect relates to the process of aspect **48**, wherein the solvent in step 4-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; and wherein the catalyst in step 4-A is selected from the group consisting of Rh₂(OAc)₄, Rh(OAc)₃, Rh(acac)₃, and mixtures thereof.

[0660] A fiftieth aspect relates to the process of aspect **48** or **49**, wherein the solvent in step 4-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; wherein the copper salt in step 4-B is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; wherein the base in step 4-B is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and wherein the ligand in step 4-B is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

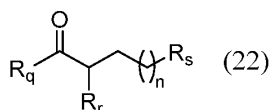
[0661] A fifty-first aspect relates to a process for preparing compounds of aspects **1** to **16**,

wherein  is , comprising:

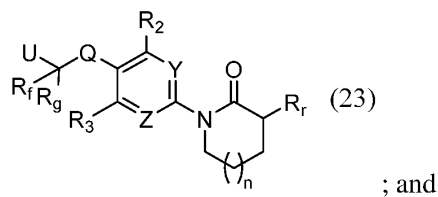
a step 5-A, reacting a compound of formula (21)



with a compound of formula (22)

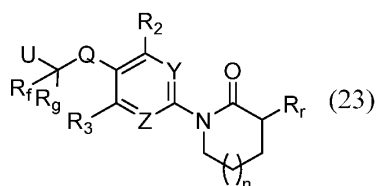


to produce a compound of formula (23)

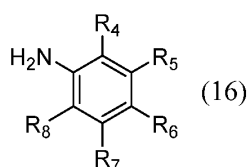


; and

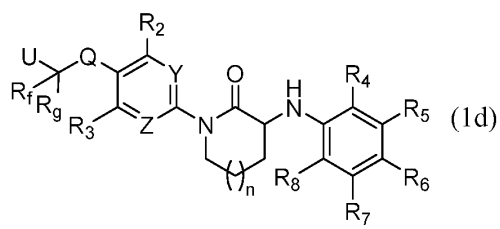
a step 5-B, reacting a compound of formula (23)



with a compound of formula (16)



to produce a compound of formula (1d)



wherein R_q , R_r , and R_s , are independently F, Cl, Br, I, OR_h , SR_h , or a leaving group L_2 selected from the group consisting of *p*-toluenesulfonate (-OTs), methanesulfonate (-OMs), trifluoro-methanesulfonate (-SO₃CF₃), nitrate (-ONO₂), and phosphates (-OPO(OR)₂), wherein R is an alkyl group, and R_h is H or an unsubstituted C₁-C₆ straight or branched alkyl.

[0662] A fifty-second aspect relates to the process of aspect **51**, wherein step 5-A is carried out from about 15 °C to about 35 °C; and step 5-B is carried out from about -10 °C to about 10 °C.

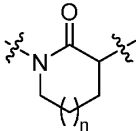
[0663] A fifty-third aspect relates to the process of aspect **51** or **52**, wherein step 5-A is carried out in the presence of a solvent and a base; and step 5-B is carried out in the presence of a solvent and a catalyst.

[0664] A fifty-fourth aspect relates to the process of aspect **53**, wherein the solvent in step 5-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF,

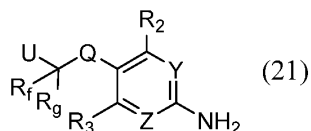
EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; and wherein the base in step 5-A is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0665] A fifty-fifth aspect relates to the process of aspect **53** or **54**, wherein the solvent in step 5-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; and wherein the base in step 5-B is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

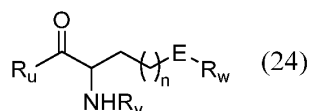
[0666] A fifty-sixth aspect relates to a process for preparing compounds of aspects **1** to **16**,

wherein  is , comprising:

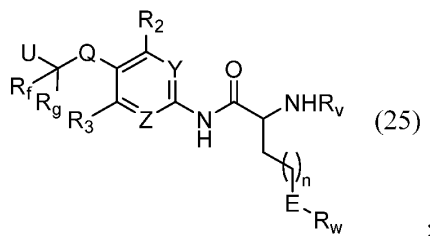
a step 6-A, reacting a compound of formula (21)



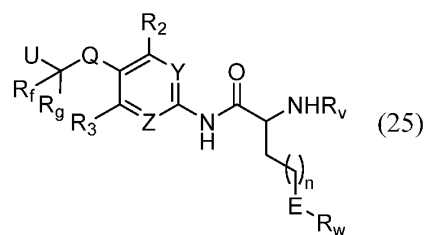
with a compound of formula (24)



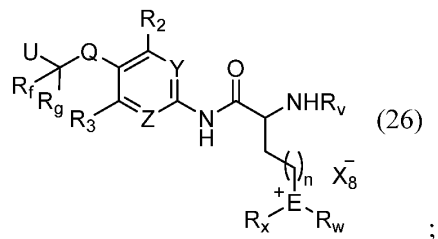
to produce a compound of formula (25)



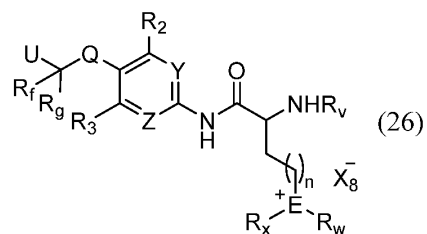
a step 6-B, reacting a compound of formula (25)



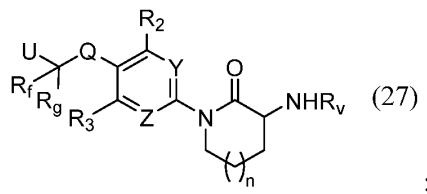
with an alkylating reagent to produce a compound of formula (26)



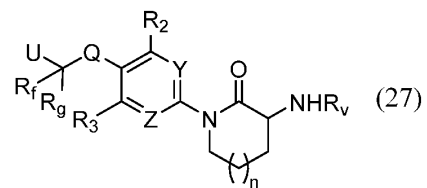
a step 6-C, reacting a compound of formula (26)



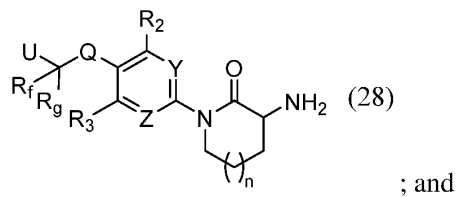
with a non-nucleophilic base to produce a compound of formula (27)



a step 6-D, reacting a compound of formula (27)

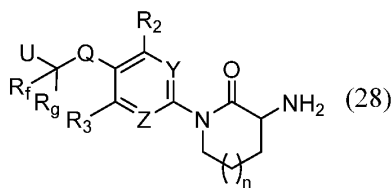


with a deprotecting reagent to produce a compound of formula (28)

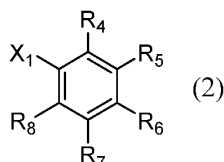


; and

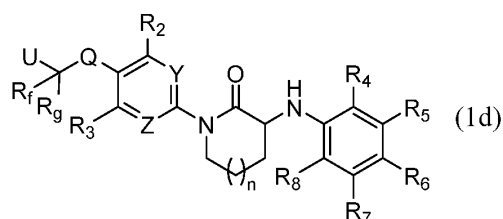
a step 6-E, reacting a compound of formula (28)



with a compound of formula (2)



to produce a compound of formula (1d)



wherein X_8 is F, Cl, Br, or I; E is O or S; R_u is F, Cl, Br, I, OR_p , or S_p ; R_v is unsubstituted C_1 - C_6 straight or branched alkyl, or a protecting group selected from the group consisting of a benzyl (Bn) group, a (diphenyl)methylene group, a trityl (triphenylmethyl, Tr) group, a (4-methoxyphenyl)diphenylmethylene (methoxytrityl, MMT) group, a formyl group, an acetyl (Ac) group, a benzoyl (Bz) group, a *tert*-butoxycarbonyl (BOC) group, a carbobenzyloxy (Cbz) group, a *p*-methoxybenzylcarbonyl (Moz) group, a 9-fluorenylmethoxycarbonyl (Fmoc) group, a dialkyl phosphoramidate group, a methanesulfonyl (mesyl, Ms) group, and a *p*-toluenesulfonyl (tosyl, Ts) group; R_w is H or unsubstituted C_1 - C_6 straight or branched alkyl; R_x is H or unsubstituted C_1 - C_6 straight or branched alkyl; and R_p is H or unsubstituted C_1 - C_6 straight or branched alkyl.

[0667] A fifty-seventh aspect relates to the process of aspect **56**, wherein step 6-A is carried out from about 15 °C to about 35 °C; step 6-B is carried out from about 15 °C to about 35 °C; step 6-C is carried out from about -10 °C to about 10 °C; step 6-D is carried out from about 15 °C to about 35 °C; and step 6-E is carried out from about 75 °C to about 125 °C.

[0668] A fifty-eighth aspect relates to the process of aspect **56** or **57**, wherein step 6-A is carried out in the presence of a solvent, a peptide coupling reagent, and a base; step 6-B is carried out in the presence of a solvent and an alkylating reagent; step 6-C is carried out in

the presence of solvent and a non-nucleophilic base; step 6-D is carried out in the presence of a solvent and a deprotection reagent; and step 6-E is carried out in the presence of a solvent, a catalyst, a ligand, and a base.

[0669] A fifty-ninth aspect relates to the process of aspect **58**, wherein the solvent in step 6-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; wherein the peptide coupling reagent in step 6-A is selected from the group consisting of DCC, DIC, CIC, BOP, PyBOP, AOP, PyAOP, HBTU, TBTU, HATU, HDMA, T3P, and mixtures thereof; and wherein the base in step 6-A is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof.

[0670] A sixtieth aspect relates to the process of aspect **58** or **59**, wherein the solvent in step 6-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and wherein the alkylating reagent in step 6-B is selected from the group consisting of methyl bromide, methyl iodide, ethyl bromide, ethyl iodide, *n*-propyl bromide, *n*-propyl iodide, isopropyl bromide, isopropyl iodide, and mixtures thereof.

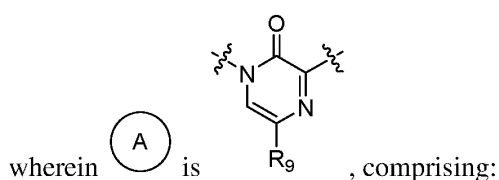
[0671] A sixty-first aspect relates to the process of aspects **58** to **60**, wherein the solvent in step 6-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the non-nucleophilic base in step 6-C is selected from the group consisting of *N,N*-diisopropylethylamine, 2,6-di-*tert*-butylpiperidine, DBU, DBN, potassium tert-butoxide, LDA, LiTMP, NaTMP, KTMP, LiHMDS, NaHMDS, KHMDS, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0672] A sixty-second aspect relates to the process of aspects **58** to **61**, wherein the solvent in step 6-D is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and wherein the deprotection reagent in step 6-D is selected from the group consisting of formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof.

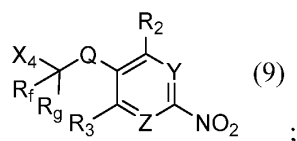
[0673] A sixty-third aspect relates to the process of aspects **58** to **62**, wherein the solvent in step 6-E is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene,

m-xylene, *p*-xylene, and mixtures thereof; wherein the catalyst in step 6-E is selected from the group consisting of Pd₂(dba)₃, PdCl₂(PPh₃)₂, Pd(PPh₃)₄, and mixtures thereof; wherein the ligand in step 6-E is selected from the group consisting of N,N'-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, BINAP, Chiraphos, Xanthphos, DPEphos, SPANphos, Me-DuPhos, dppm, and mixtures thereof; and wherein the base in step 6-E is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof.

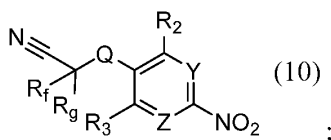
[0674] A sixty-fourth aspect relates to a process for preparing compounds of aspects 1 to 16,



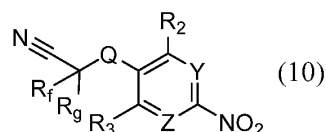
a step 7-A, reacting a compound of formula (9)



with a cyanide reagent to produce a compound of formula (10)



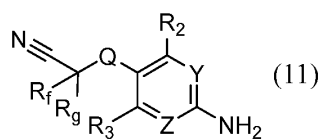
a step 7-B, reacting a compound of formula (10)



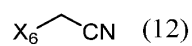
with a hydrogenation reagent to produce a compound of formula (11)



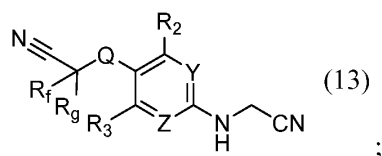
a step 7-C, reacting a compound of formula (11)



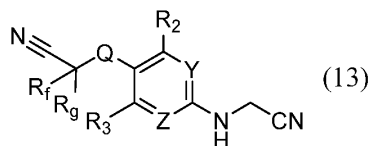
with a compound of formula (12)



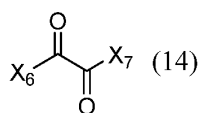
to produce a compound of formula (13)



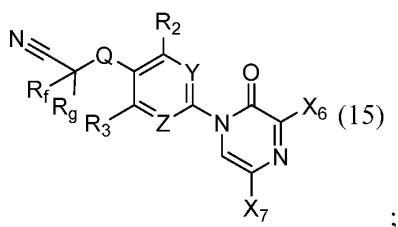
a step 7-D, reacting a compound of formula (13)



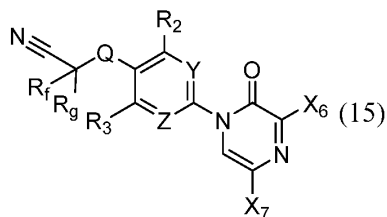
with a compound of formula (14)



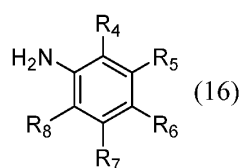
to produce a compound of formula (15)



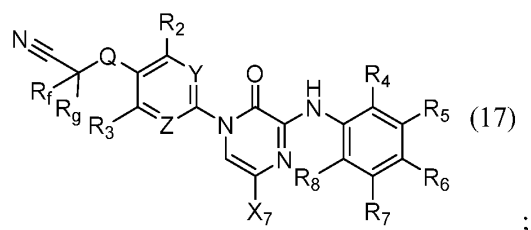
a step 7-E, reacting a compound of formula (15)



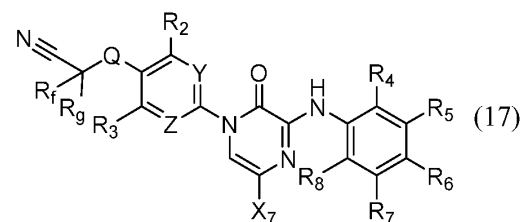
with a compound of formula (16)



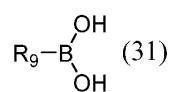
to produce a compound of formula (17)



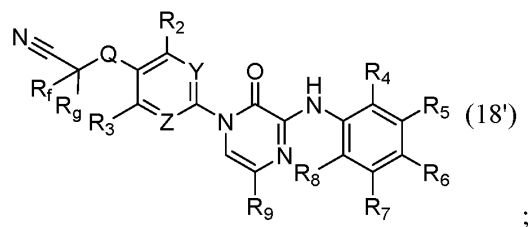
a step 7-F, reacting a compound of formula (17)



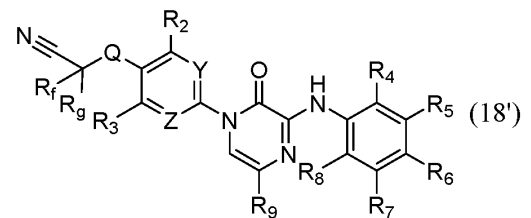
with a palladium catalyst and a compound of formula (31)



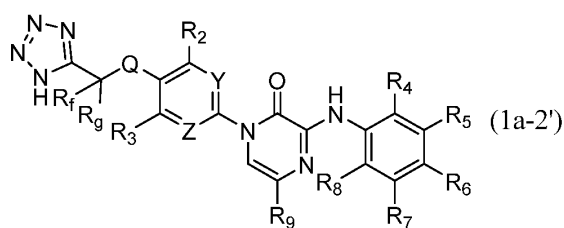
to produce a compound of formula (18')



a step 7-G, reacting a compound of formula (18')



with an azide reagent to produce a compound of formula (1a-2')



wherein X_4 is F, Cl, Br, or I; X_5 is F, Cl, Br, I, or a leaving group L_1 selected from the group consisting of *p*-toluenesulfonate ($-OTs$), methanesulfonate ($-OMs$), trifluoromethanesulfonate ($-OSO_2CF_3$), nitrate ($-ONO_2$), and phosphates ($-OPO(OR)_2$), wherein R is an alkyl group; X_6 is F, Cl, Br, or I; and X_7 is F, Cl, Br, or I.

[0675] A sixty-fifth aspect relates to the process of aspect **64**, wherein step 7-A is carried out from about 30 °C to about 75 °C; step 7-B is carried out from about 15 °C to about 35 °C; step 7-C is carried out from about 50 °C to about 75 °C; step 7-D is carried out from about 75 °C to about 125 °C; step 7-E is carried out from about 15 °C to about 35 °C; step 7-F is carried out from about 50 °C to about 140 °C; and step 7-G is carried out from about 100 °C to about 140 °C.

[0676] A sixty-sixth aspect relates to the process of aspect **64** or **65**, wherein step 7-A is carried out in the presence of a solvent and a cyanide agent; step 7-B is carried out in the presence of a solvent, a hydrogenation reagent, and a catalyst; step 7-C is carried out in the presence of a solvent and a base; step 7-D is carried out in the presence of a solvent; step 7-E is carried out in the presence of a solvent and a base; step 7-F is carried out in the presence of a solvent; and step 7-G is carried out in the presence of a solvent, an azide reagent, and a salt.

[0677] A sixty-seventh aspect relates to the process of aspect **66**, wherein the solvent in step 7-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, $CHCl_3$, MeCN, DMSO, and mixtures thereof; and wherein the cyanide reagent in step 7-A is selected from the group consisting of sodium cyanide, potassium cyanide, and mixtures thereof.

[0678] A sixty-eighth aspect relates to the process of aspect **66** or **67**, wherein the solvent in step 7-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, $CHCl_3$, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; wherein the hydrogenation reagent in step 7-B is selected from the group consisting of hydrogen (H_2), formic acid, isopropanol, and mixtures thereof; and wherein the catalyst is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof.

[0679] A sixty-ninth aspect relates to the process of aspects **66** to **68**, wherein the solvent in step 7-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the base in step 7-C is selected from the group consisting of ammonia, triethylamine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

[0680] A seventieth aspect relates to the process of aspects **66** to **69**, wherein the solvent in step 7-D is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof.

[0681] A seventy-first aspect relates to the process of aspects **66** to **70**, wherein the solvent in step 7-E is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof; and wherein the base in step 7-E is selected from the group consisting of ammonia, triethylamine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

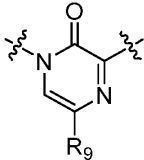
[0682] A seventy-second aspect relates to the process of aspects **66** to **71**, wherein the solvent in step 7-F is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, water, and mixtures thereof.

[0683] A seventy-third aspect relates to the process of aspects **64** to **72**, wherein the palladium catalyst in step 7-F is selected from the group consisting of palladium(II) acetate ($\text{Pd}(\text{OAc})_2$), palladium(II) acetylacetonate ($\text{Pd}(\text{acac})_2$), tris(dibenzylideneacetone)dipalladium(0) ($\text{Pd}_2(\text{dba})_3$), dichlorobis(triphenylphosphine)palladium(II) ($\text{PdCl}_2(\text{PPh}_3)_2$), tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$), palladium(0) (Pd), palladium(0) on carbon (Pd/C), dichloro(1,1'-bis(di-*tert*-butylphosphino)ferrocene)palladium(II) ($\text{Pd}(\text{dtbpf})\text{Cl}_2$), and mixtures thereof.

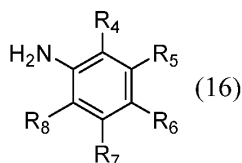
[0684] A seventy-fourth aspect relates to the process of aspects **66** to **73**, wherein the solvent in step 7-G is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene,

m-xylene, *p*-xylene, and mixtures thereof; wherein the azide reagent in step 7-G is selected from the group consisting of lithium azide, sodium azide, potassium azide, trimethyltin azide, triethyltin azide, tripropyltin azide, tributyltin azide, and mixtures thereof; and wherein the salt in step 7-G is selected from the group consisting of ammonium fluoride, ammonium chloride, ammonium bromide, ammonium iodide, and mixtures thereof.

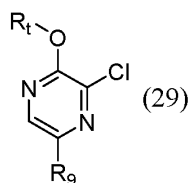
[0685] A seventy-fifth aspect relates to a process for preparing compounds of aspects

1 to 16, wherein  is , comprising:

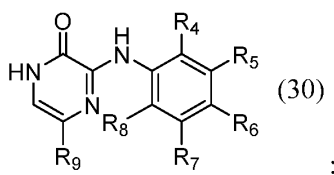
a step 8-A, reacting a compound of formula (16)



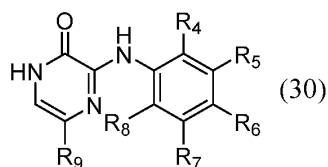
with a compound of formula (29)



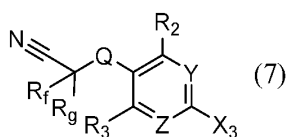
to produce a compound of formula (30)



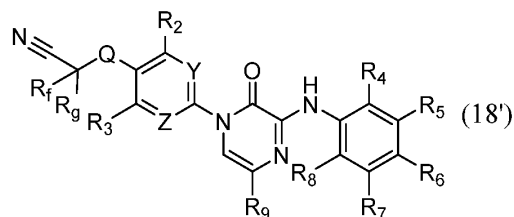
a step 8-B, reacting a compound of formula (30)



with a compound of formula (7)



to produce a compound of formula (18')



wherein X₃ is F, Cl, Br, or I; and

R_t is H or unsubstituted C₁-C₆ straight or branched alkyl.

[0686] A seventy-sixth aspect relates to the process of aspect **75**, wherein step 8-A is carried out from about 50 °C to about 125 °C; and step 8-B is carried out from about 50 °C to about 125 °C.

[0687] A seventy-seventh aspect relates to the process of aspect **75** or **76**, wherein step 8-A is carried out in the presence of a solvent and an acid; step 8-B is carried out in the presence of a solvent, a copper salt, a base, and a ligand.

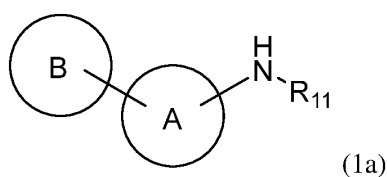
[0688] A seventy-eighth aspect relates to the process of aspect **77**, wherein the solvent in step 8-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, 1,4-dioxane, DCM, CHCl₃, MeCN, AcOH, and mixtures thereof; and wherein the acid in step 8-A is selected from the group consisting of formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof.

[0689] A seventy-ninth aspect relates to the process of aspect **77** or **78**, wherein the solvent in step 8-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; wherein the copper salt in step 8-B is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; wherein the base in step 8-B is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and wherein the ligand in step 8-B is selected from the group consisting of *N,N*'-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

[0690] In addition to the features mentioned in each of the independent aspects enumerated above, some examples may show, alone or in combination, the optional features mentioned in the dependent aspects and/or as disclosed in the description above and shown in the figures.

CLAIMS

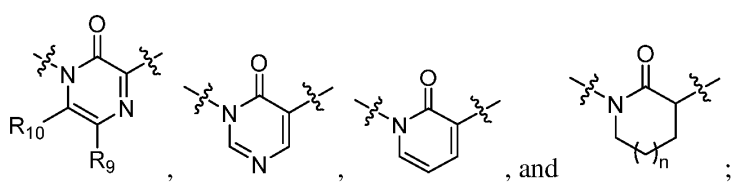
1. A compound of formula (1a):



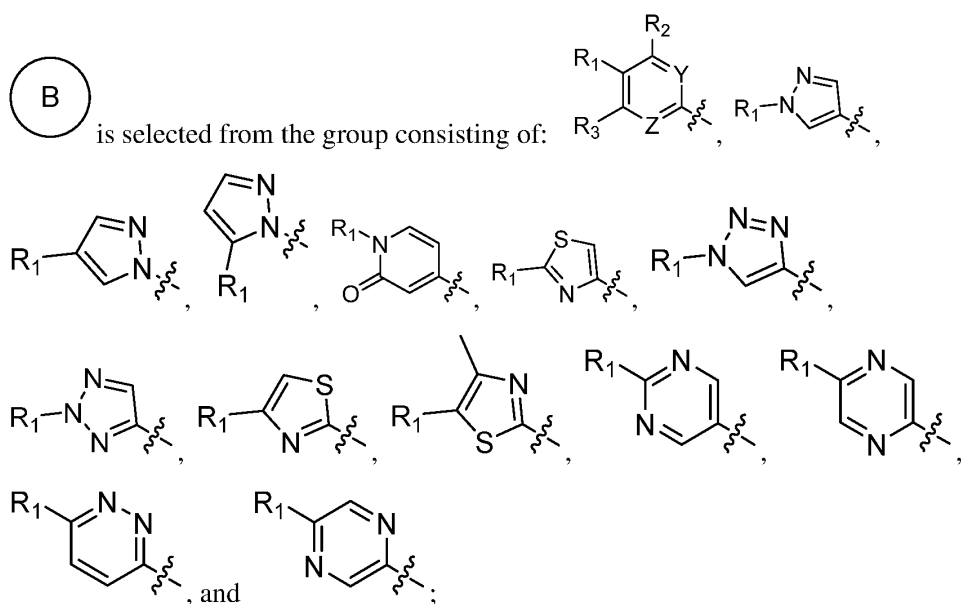
wherein



is selected from the group consisting of:



is selected from the group consisting of:

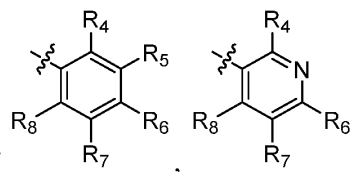


R_1 is $(T)_w-(CR_gR_f)_m-Q-(CR_gR_f)_m-U$;

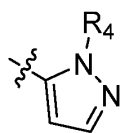
R_2 and R_3 are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $N(R_c)_2$, and CN;

R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} , are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $S(O)_2R_j$, $S(O)_2N(R_c)_2$, $N(R_c)_2$, CN, $C(O)R_j$, $N(R_c)C(O)R_j$, $C(O)N(R_c)_2$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted

cycloalkenyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;



R_{11} is selected from the group consisting of



, H, $\text{OCH}_2\text{C}(\text{O})_2\text{R}_c$, an unsubstituted C_1 - C_6 straight or branched alkyl, a substituted C_1 - C_6 straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

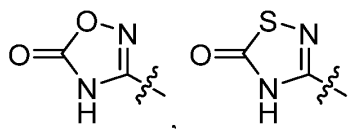
Y is CR_a or N;

Z is CR_b or N;

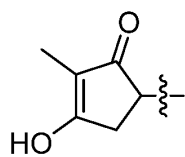
Q is O, S, NR_i , or $-(\text{CR}_h\text{R}_d)_p-$;

T is O, S, NR_i , or $-(\text{CR}_h\text{R}_d)_p-$;

U is $-\text{COOR}_e$, $-\text{COS}(\text{O})_p\text{R}_e$, $-\text{CONHS}(\text{O})_p\text{R}_e$, $-\text{CONHR}_e$, $-\text{CON}(\text{R}_e)_2$, vinyl, a substituted C_1 - C_6 straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a



substituted or unsubstituted heteroaryl group,



, or $\text{B}(\text{OH})_2$;

n is 0, 1, or 2;

each m is independently 0, 1, 2, 3, 4, or 5;

p is 0, 1, or 2;

w is 0, 1, or 2;

R_a and R_b are independently selected from the group consisting of H, unsubstituted C_1 - C_6 straight or branched alkyl, substituted C_1 - C_6 straight or branched alkyl, F, Cl, Br, I, OR_c , SR_c , $\text{N}(\text{R}_c)_2$, and CN;

R_c is H, unsubstituted C₁-C₆ straight or branched alkyl, or substituted C₁-C₆ straight or branched alkyl;

R_d is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_e is H, unsubstituted C₁-C₆ straight or branched alkyl, or C₁-C₆ straight or branched alkyl substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OR_c, SR_c, N(R_c)₂, and CN;

R_f is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_g is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_h is H, D, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_i is H, D, F, Cl, Br, I, unsubstituted C₁-C₆ straight or branched alkyl, or unsubstituted cycloalkyl;

R_j is a substituted or unsubstituted C₁-C₆ straight or branched alkyl, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted heteroaryl group;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, R₄ and R₅, R₆ and R₇, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OC₄alkyl, OC₅alkyl, OC₆alkyl, unsubstituted cycloalkyl, substituted heterocyclyl, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, CONMe₂, CONHMe, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, an unsubstituted heterocyclyl group, an unsubstituted heteroaryl group, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr,

SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, CONH₂, and CONHPh; and

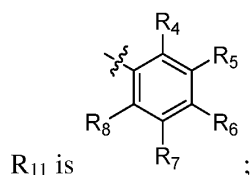
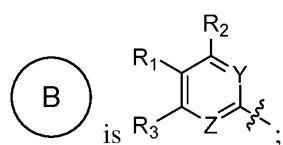
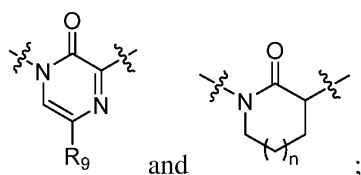
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein:



is selected from the group consisting of:



R₁ is -Q-(CHR_f)_m-U;

R₂ and R₃ are independently selected from the group consisting of H, unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OR_c, SR_c, CN, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

Y is CR_a or N;

Z is CR_b or N;

Q is O, S, or -(CHR_d)_p-;

U is -COOR_e, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, unsubstituted C₁-C₆ straight or branched alkyl, substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, and OR_c;

R_c is H, unsubstituted C₁-C₆ straight or branched alkyl, or substituted C₁-C₆ straight or branched alkyl;

R_d is H, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

R_e is H or unsubstituted C₁-C₆ straight or branched alkyl;

R_f is H, F, Cl, Br, I, or unsubstituted C₁-C₆ straight or branched alkyl;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂; and

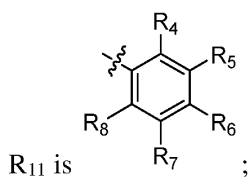
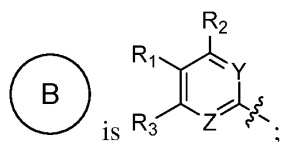
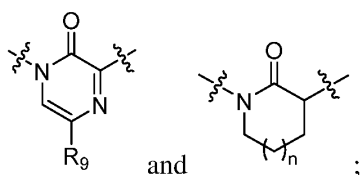
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein:



is selected from the group consisting of:



R₁ is -Q-(CHR_f)_m-U;

R₂ and R₃ are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, OR_c, CN, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

Y is CR_a or N;

Z is CR_b or N;

Q is O or $-(\text{CHR}_d)_p-$;

U is $-\text{COOR}_e$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, substituted isopropyl, F, Cl, Br, I, and OR_c;

R_c is H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl, or substituted isopropyl;

R_d is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

R_e is H, methyl, ethyl, *n*-propyl, or isopropyl;

R_f is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted methyl, ethyl, *n*-propyl, or isopropyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, carbonyl, COOH, and CONH₂;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, COOH, CH₂CONH₂, and CONH₂; and

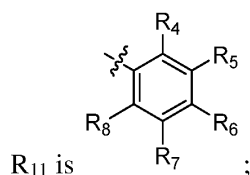
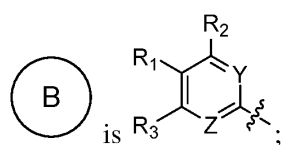
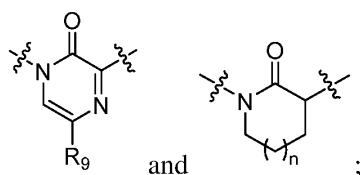
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, COOH, CH₂CONH₂, and CONH₂; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein:



is selected from the group consisting of:



R₁ is -Q-(CHR_f)_m-U;

R₂ and R₃ are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, substituted methyl, ethyl, substituted ethyl, *n*-propyl, substituted *n*-propyl, isopropyl,

substituted isopropyl, F, Cl, Br, I, OR_c, CN, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl;

Y is CR_a or N;

Z is CR_b or N;

Q is O or $-(\text{CHR}_d)_p-$;

U is $-\text{COOR}_e$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

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

p is 0 or 1;

R_a and R_b are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c;

R_c is H, methyl, CH₂F, CHF₂, CF₃, ethyl, *n*-propyl, or isopropyl;

R_d is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

R_e is H, methyl, ethyl, *n*-propyl, or isopropyl;

R_f is H, F, Cl, Br, I, methyl, ethyl, *n*-propyl, or isopropyl;

wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted methyl, ethyl, *n*-propyl, or isopropyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, NH₂, and COOH;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, and COOH;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, and COOH;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH,

OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, and COOH; and

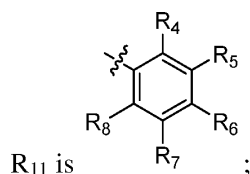
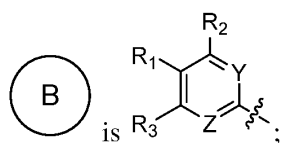
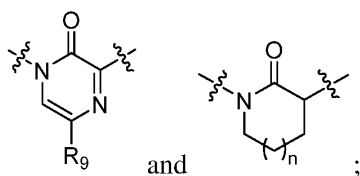
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, CH₂COOH, carbonyl, and COOH; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

5. The compound of claim 1, wherein:



is selected from the group consisting of:



R₁ is -Q-(CHR_t)_m-U;

R₂ and R₃ are independently selected from the group consisting of H, methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, and OR_c;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, CF₃, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OR_c, CN, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, 2-pyridyl, 3-pyridyl, and 4-pyridyl;

Y is CR_a or N;

Z is CR_b or N;

Q is O or -(CHR_d)_p-;

U is $-\text{COOH}$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or $\text{B}(\text{OH})_2$;

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

R_a is H or methyl;

R_b is H or methyl;

R_c is H, methyl, or CF_3 ;

R_d is H, F, Cl, Br, or methyl;

R_f is H, F, Cl, Br, or methyl;

wherein R_1 and R_2 or R_1 and R_3 together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ; and

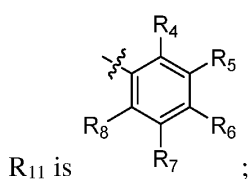
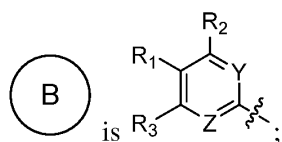
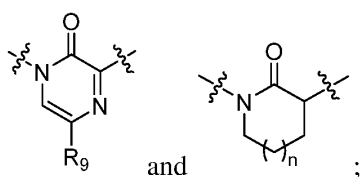
wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF_3 , NH_2 , NMe_2 , CH_2COOH , carbonyl, and COOH ; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein:



is selected from the group consisting of:



R₁ is $-Q-(CHR_t)_m-U$;

R₂ and R₃ are independently H or methyl;

R₄, R₅, R₆, R₇, R₈, and R₉ are independently selected from the group consisting of H, methyl, isopropyl, CF₃, F, Cl, Br, OMe, OCF₃, CN, cyclopropyl, cyclopentyl, and phenyl;

Y is CH or N;

Z is CH or N;

Q is O or $-(CHR_d)_p-$;

U is $-COOH$, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or B(OH)₂;

n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

R_d is H, F, or methyl;

R_f is H, F, or methyl;

wherein R₁ and R₂ or R₁ and R₃ together form a cyclic structure selected from the group consisting of a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heteroaryl group;

wherein the substituted cycloalkyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH;

wherein the substituted heterocyclyl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH;

wherein the substituted aryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH; and

wherein the substituted heteroaryl groups are substituted with one or more substituents selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, F, Cl, Br, I, OH, OMe, OCF₃, NH₂, NMe₂, CH₂COOH, carbonyl, and COOH; or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

7. The compound of claim **1**, wherein U is a cycloalkyl group selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cyclooctenyl, cyclooctadienyl, and cyclooctatrienyl;

wherein the cycloalkyl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

8. The compound of claim **1**, wherein U is a heterocyclyl group selected from the group consisting of azetidiny, pyrrolidiny, pyrroliny, pyrazolidiny, imidazolinyl, imidazolidiny, pyrazolinyl, piperidiny, piperazinyl, oxetanyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiophene, dihydrothiophene, tetrahydrothiopyranyl, and dihydrothiopyranyl;

wherein the heterocyclyl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH,

SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

9. The compound of claim 1, wherein U is an aryl group selected from the group consisting of phenyl, naphthalenyl, cyclobutadienyl, cyclopentadienyl, indenyl, anthracenyl, phenanthrenyl, terphenylenyl, fluorenyl, and pyrenyl;

wherein the aryl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

10. The compound of claim 1, wherein U is a heteroaryl group selected from the group consisting of pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, 5(4*H*)-oxo-1,2,4-thiadiazolyl, oxazolyl, 5(4*H*)-oxo-1,2,4-oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, 1*H*-indolyl, 3*H*-indolyl, 2*H*-isoindolyl, indoliziny, quinolinyl, isoquinolinyl, quinoxalinyl, cinnolinyl, quinazolinyl, phthalazinyl, purinyl, indazolyl, benzimidazolyl, benzo[*d*]oxazole, benzo[*d*]thiazole, benzo[*c*]isoxazole, benzo[*d*]isoxazole, benzo[*c*]isothiazole, benzo[*d*]isothiazole, quinoline-2(1*H*)-one, isoquinoline-1(2*H*)-one, indolin-2-one, isoindolin-1-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-thione, furanyl, carbazolyl, benzofuranyl, isobenzofuranyl, dibenzofuranyl, benzofuran-2(3*H*)-one, isobenzofuran-1(3*H*)-one, thiophenyl, benzo[*b*]thiophenyl, benzo[*c*]thiophenyl, benzo[*b*]thiophen-2(3*H*)-one, and benzo[*c*]thiophen-1(3*H*)-one;

wherein the heteroaryl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

11. The compound of claim 1, wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a cycloalkyl group selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cyclooctenyl, cyclooctadienyl, and cyclooctatrienyl;

wherein the cycloalkyl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

12. The compound of claim 1, wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a heterocyclyl group selected from the group consisting of azetidiny, pyrrolidiny, pyrroliny, pyrazolidiny, imidazolidiny, imidazolidiny, pyrazolidiny, piperidiny, piperaziny, oxetany, tetrahydrofurany, dihydrofurany, tetrahydropyrany, dihydropyrany, tetrahydrothiophene, dihydrothiophene, tetrahydrothiopyrany, 3,5-dioxoisoxazolidiny, and dihydrothiopyrany;

wherein the heterocyclyl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

13. The compound of claim 1, wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form an aryl group selected from the group consisting of phenyl, naphthalenyl, cyclobutadienyl, cyclopentadienyl, indenyl, anthracenyl, phenanthrenyl, terphenylenyl, fluorenyl, and pyrenyl;

wherein the aryl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

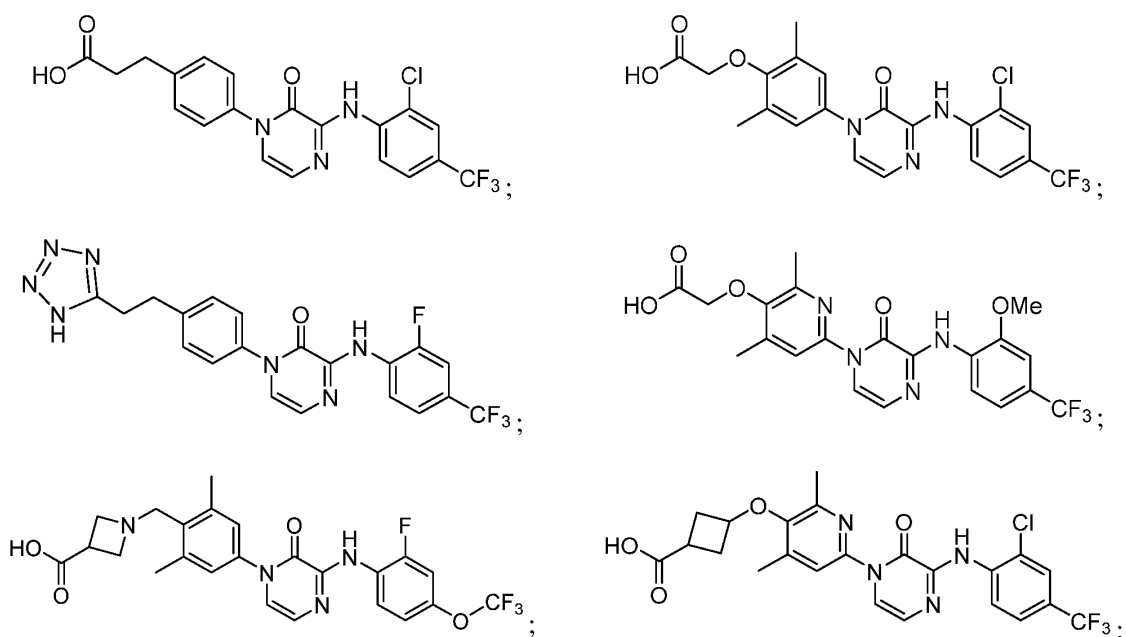
14. The compound of claim 1, wherein R₁ and R₂, R₁ and R₃, R₂ and R_a, or R₃ and R_b together form a heteroaryl group selected from the group consisting of pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, 5(4*H*)-oxo-1,2,4-thiadiazolyl, oxazolyl, 5(4*H*)-oxo-1,2,4-oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, 1*H*-indolyl, 3*H*-indolyl, 2*H*-isoindolyl, indolizynyl, quinolynyl, isoquinolynyl, quinoxalynyl, cinnolynyl, quinazolinyl, phthalazinyl, purinyl, indazolyl, benzimidazolyl, benzo[*d*]oxazole, benzo[*d*]thiazole, benzo[*c*]isoxazole, benzo[*d*]isoxazole, benzo[*c*]isothiazole, benzo[*d*]isothiazole, quinoline-2(1*H*)-one, isoquinoline-1(2*H*)-one, indolin-2-one, isoindolin-

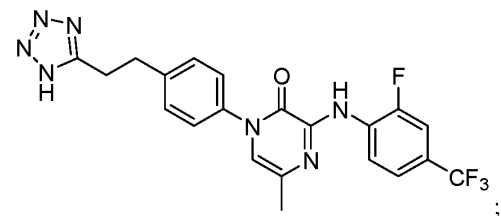
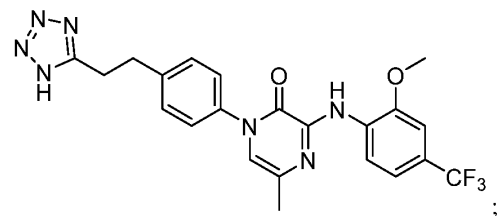
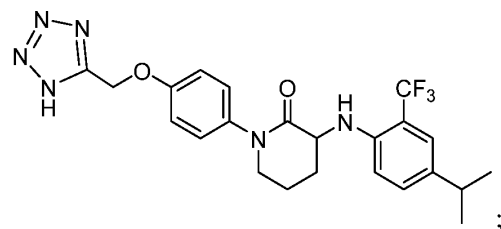
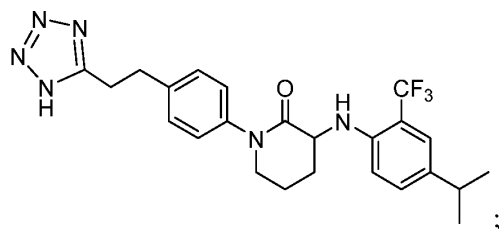
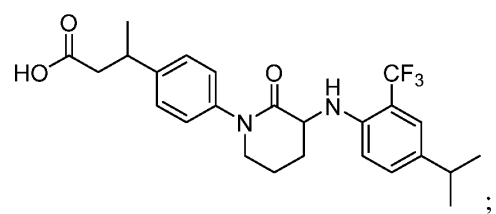
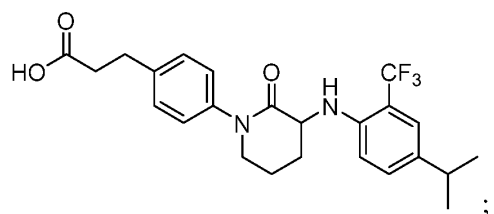
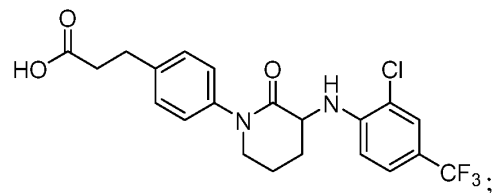
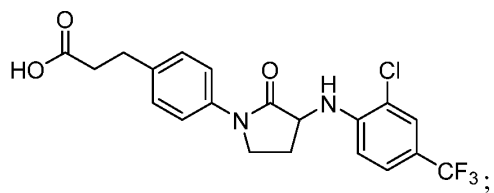
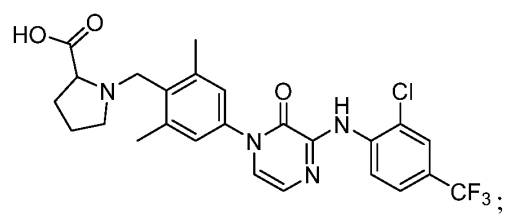
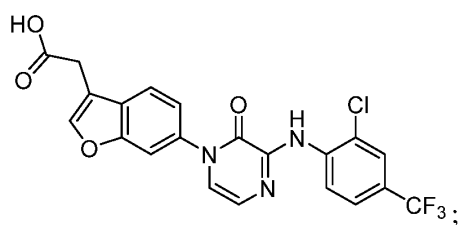
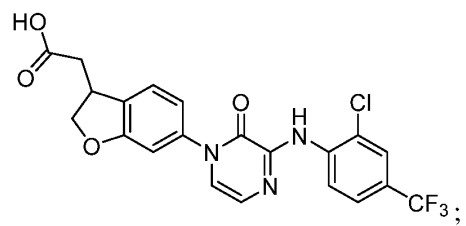
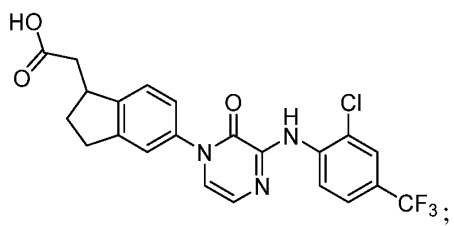
1-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-one, 1*H*-benzo[*d*]imidazole-2(3*H*)-thione, furanyl, carbazolyl, benzofuranyl, isobenzofuranyl, dibenzofuranyl, benzofuran-2(3*H*)-one, isobenzofuran-1(3*H*)-one, thiophenyl, benzo[*b*]thiophenyl, benzo[*c*]thiophenyl, benzo[*b*]thiophen-2(3*H*)-one, and benzo[*c*]thiophen-1(3*H*)-one;

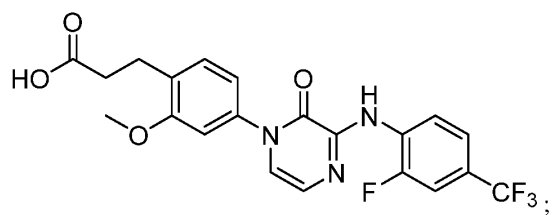
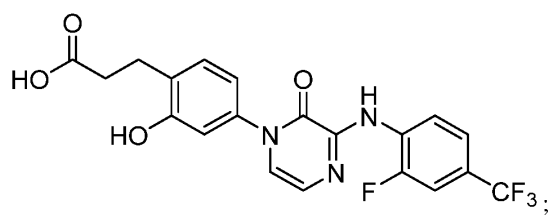
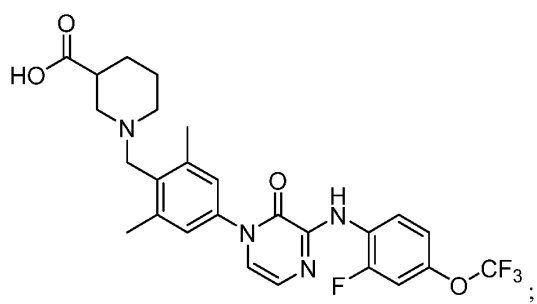
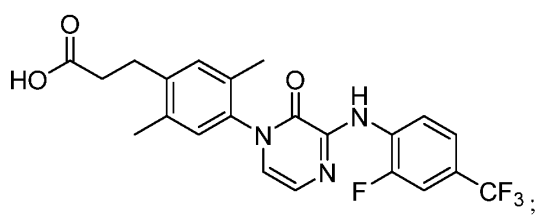
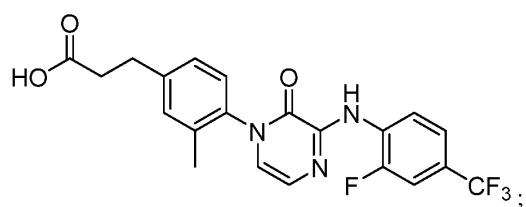
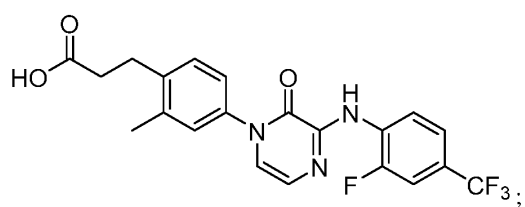
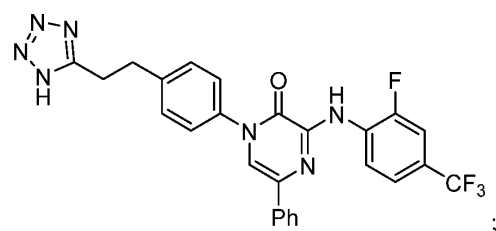
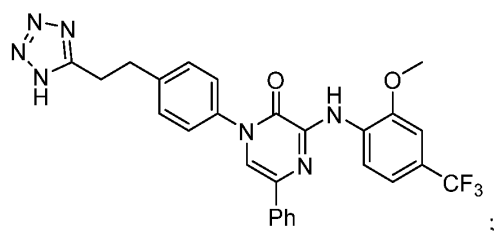
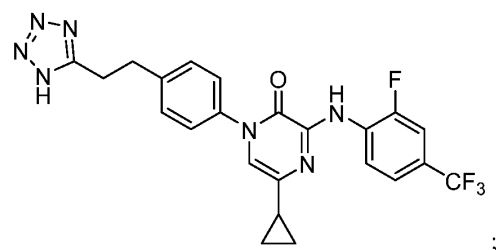
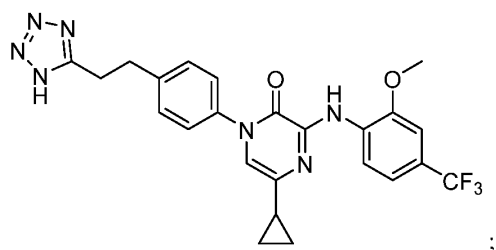
wherein the heteroaryl group is unsubstituted or is substituted with one or more substituents selected from the group consisting of unsubstituted or substituted C₁-C₆ straight or branched alkyl, F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂; and

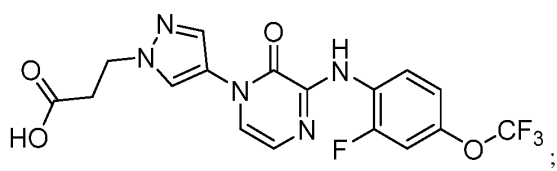
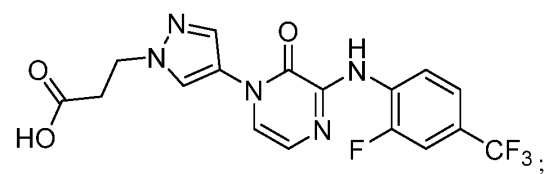
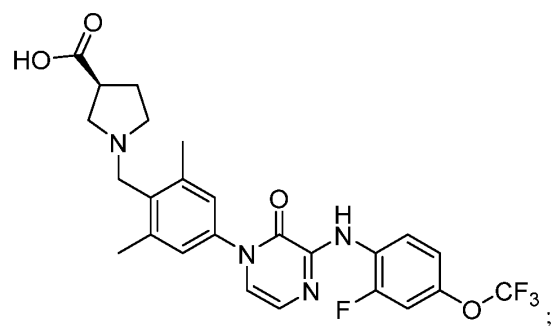
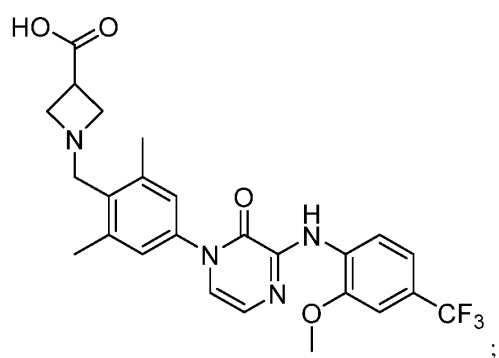
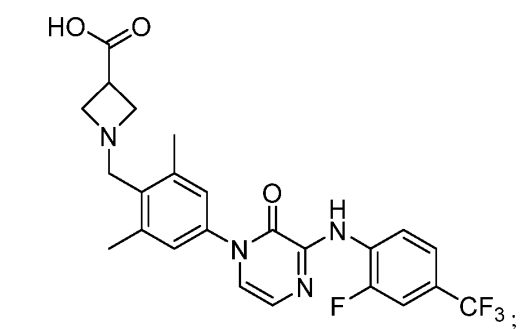
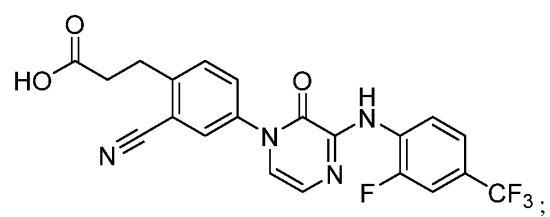
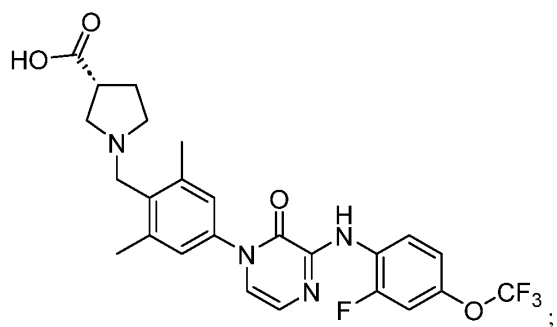
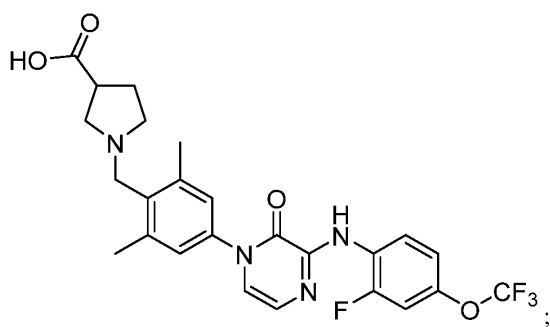
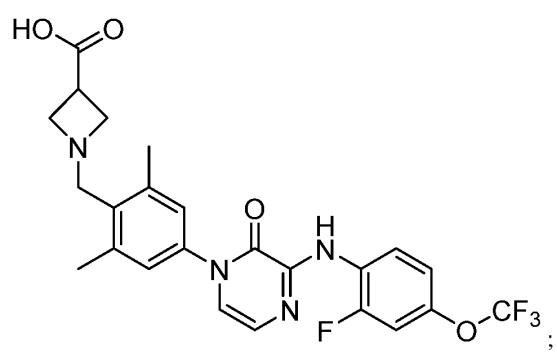
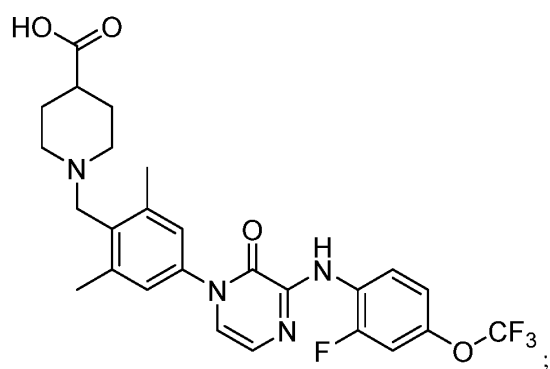
wherein the substituted C₁-C₆ straight or branched alkyl are substituted with one or more substituents selected from the group consisting of F, Cl, Br, I, OH, OMe, OEt, O-*n*Pr, O-*i*Pr, OCH₂F, OCHF₂, OCF₃, SH, SMe, SEt, S-*n*Pr, S-*i*Pr, SCH₂F, SCHF₂, SCF₃, NH₂, NMe₂, NEt₂, N(*n*Pr)₂, N(*i*Pr)₂, N(CH₂F)₂, N(CHF₂)₂, N(CF₃)₂, carbonyl, COOH, COSH, and CONH₂.

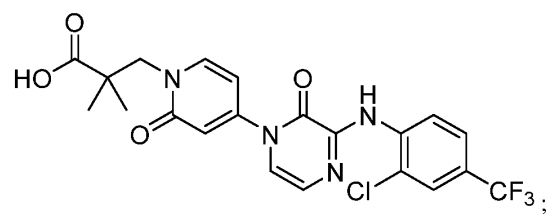
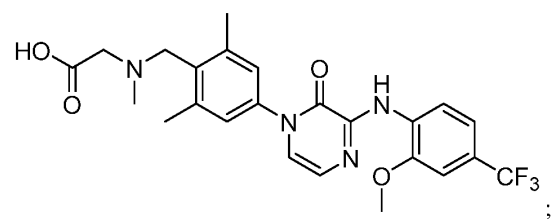
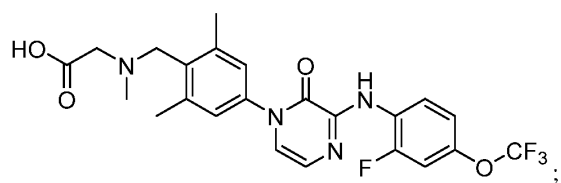
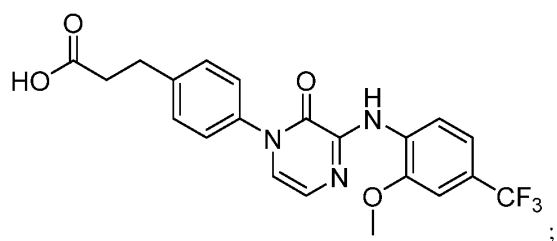
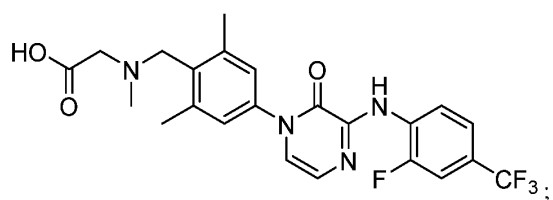
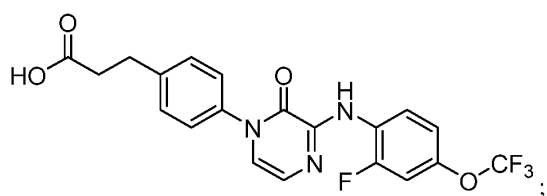
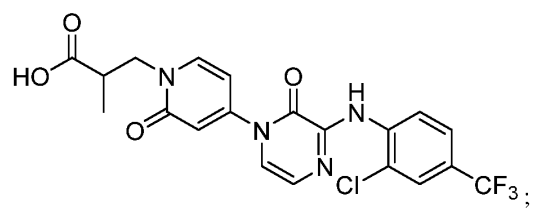
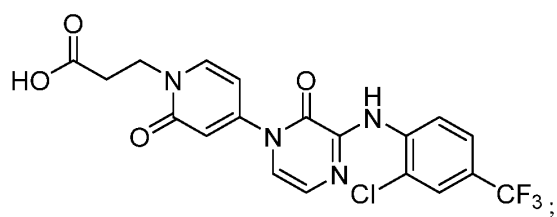
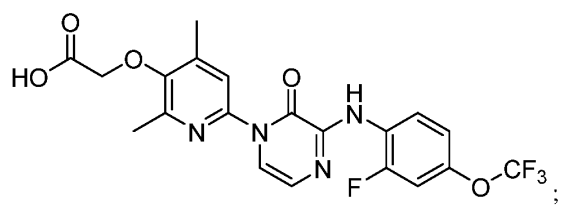
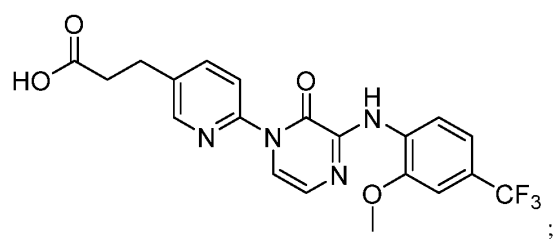
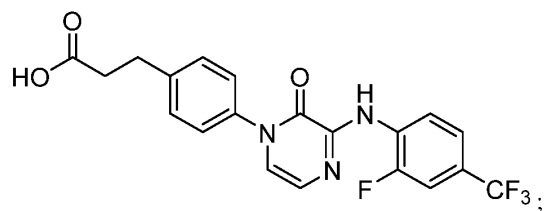
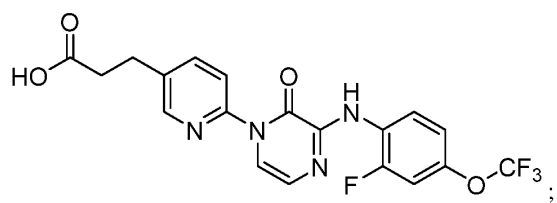
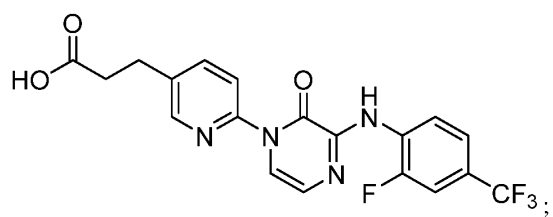
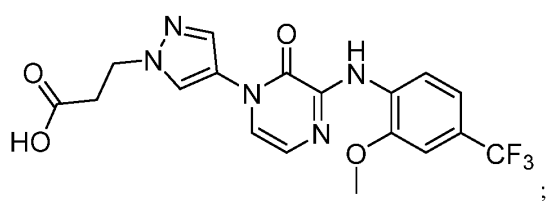
15. The compound of claim 1, wherein the compound is selected from the group consisting of:

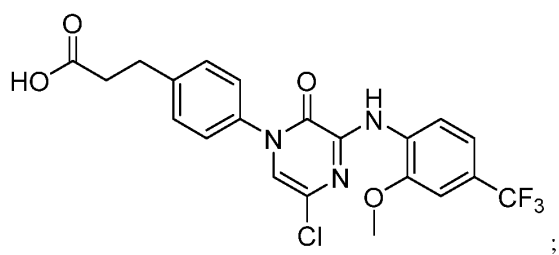
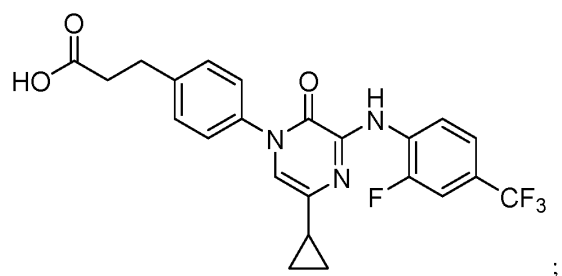
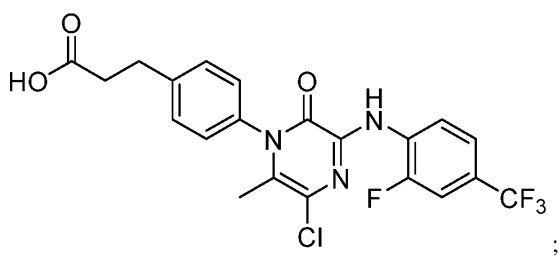
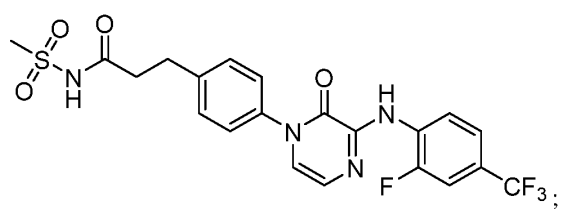
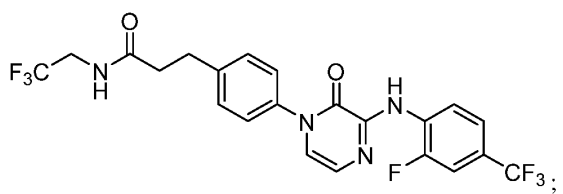
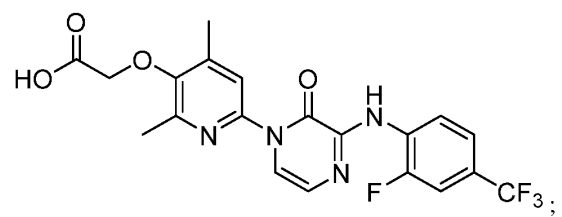
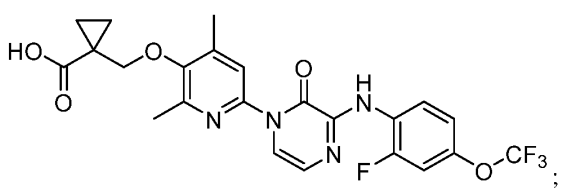
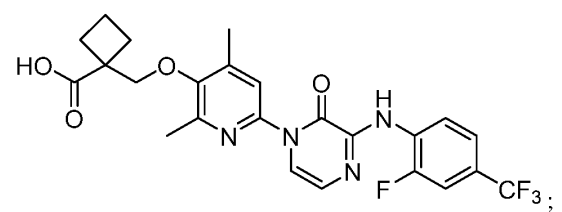
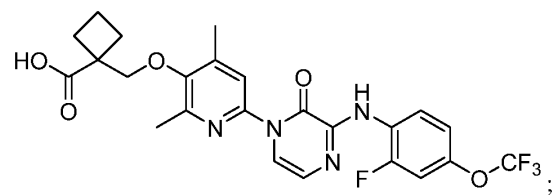
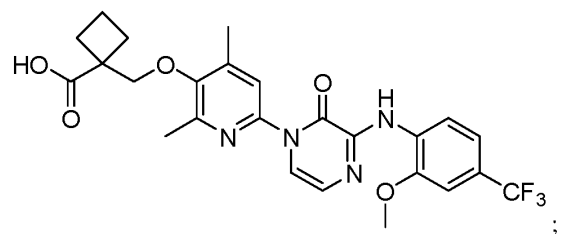
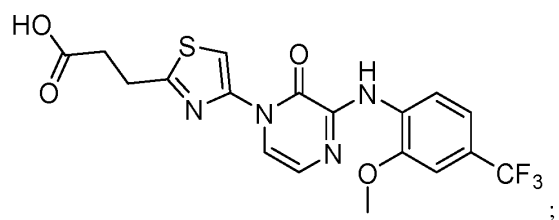
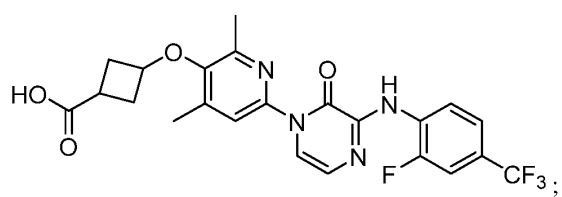


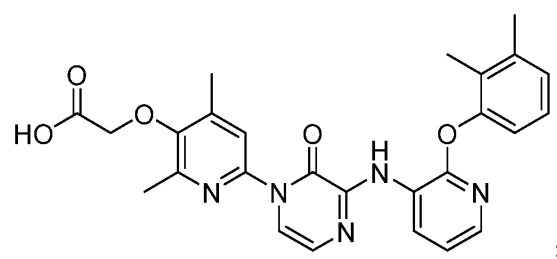
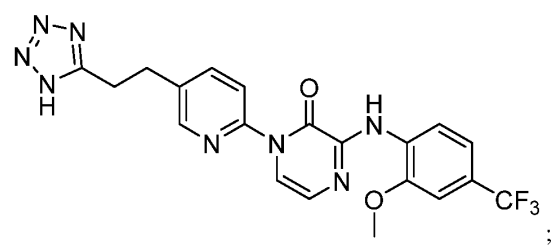
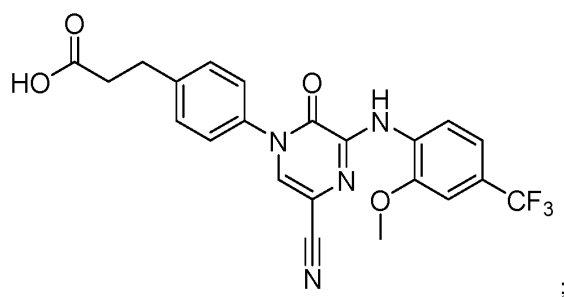
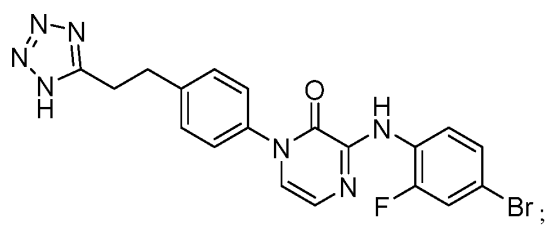
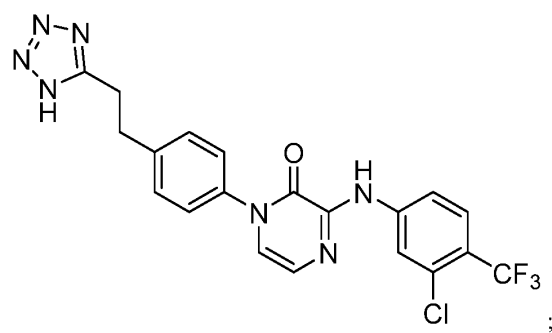
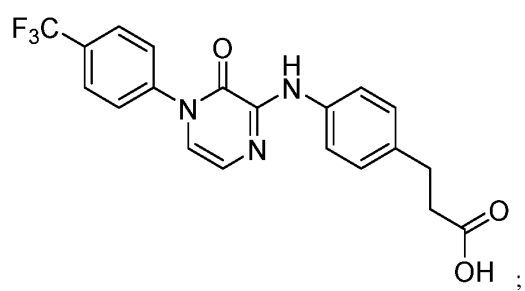
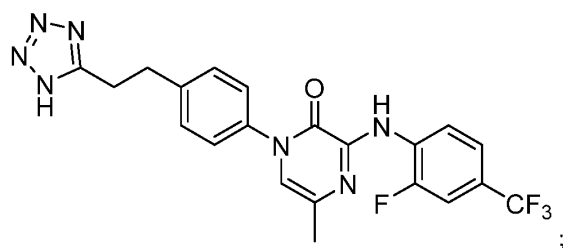
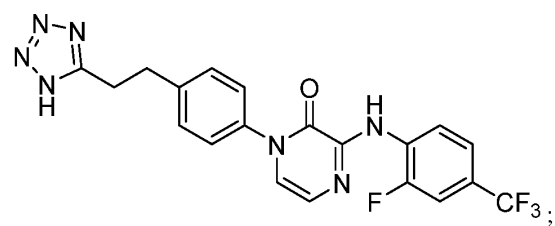
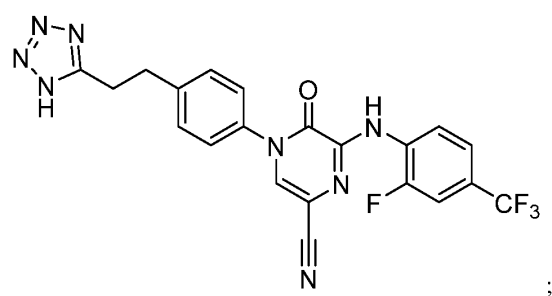
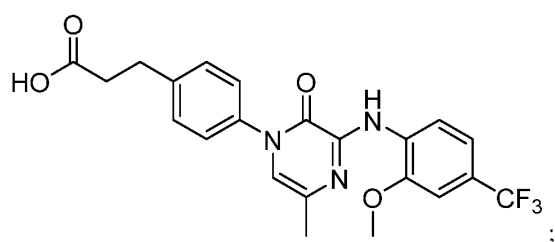


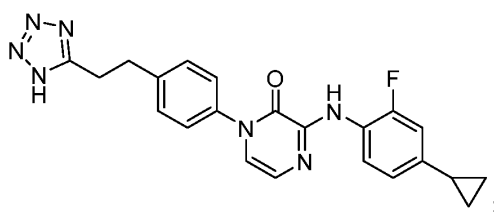
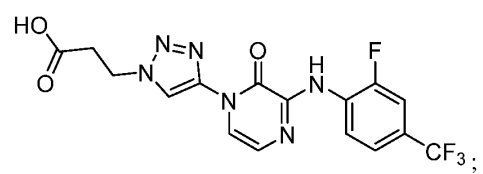
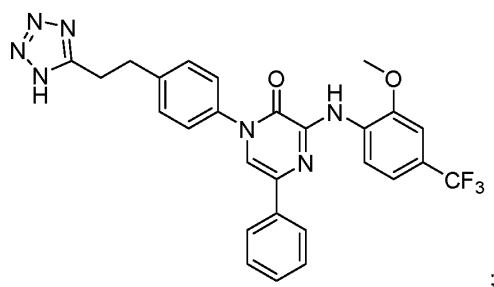
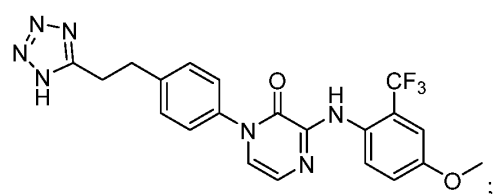
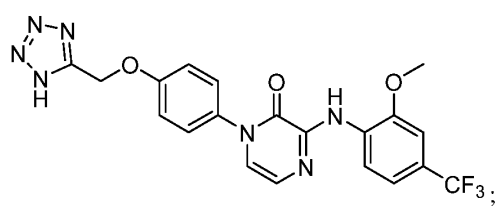
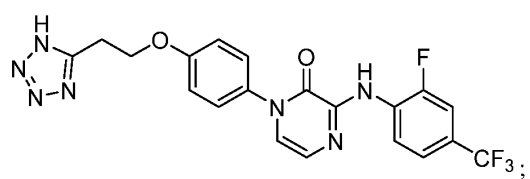
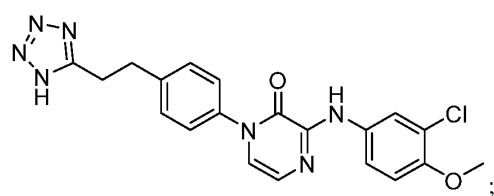
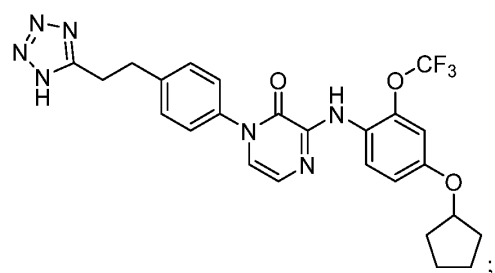
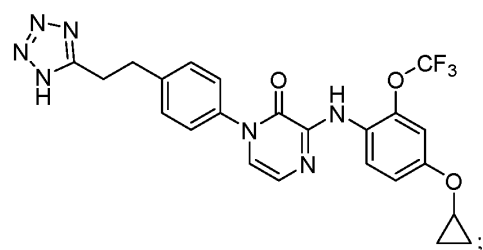
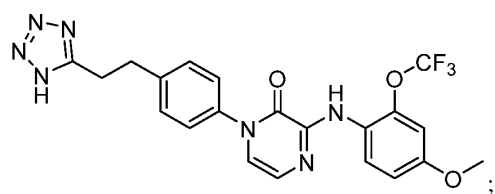
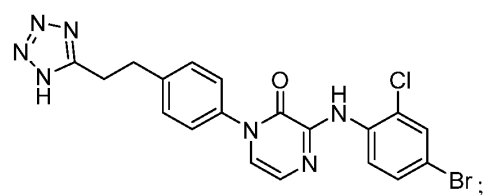
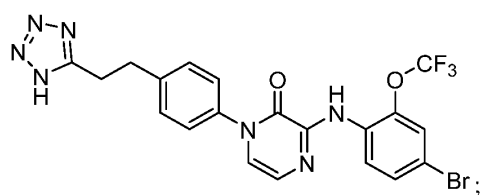


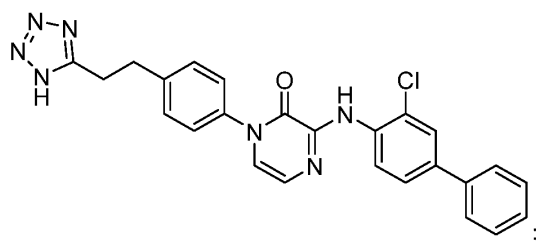
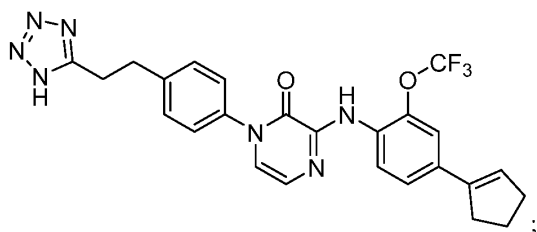
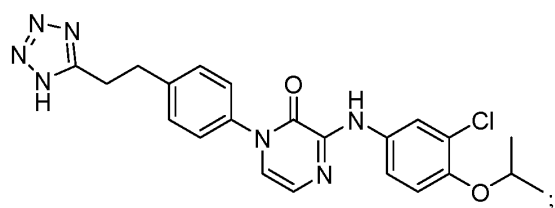
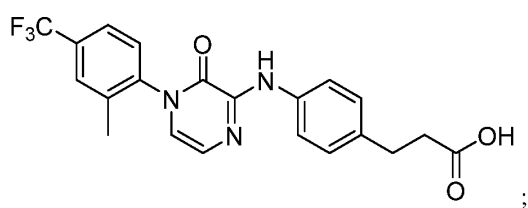
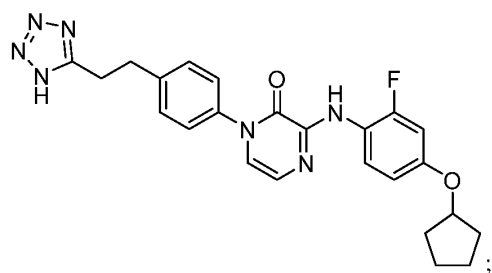
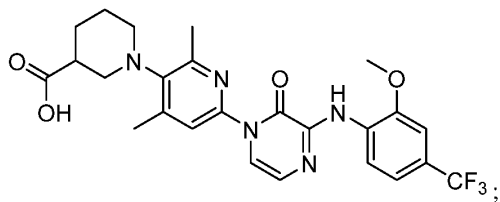
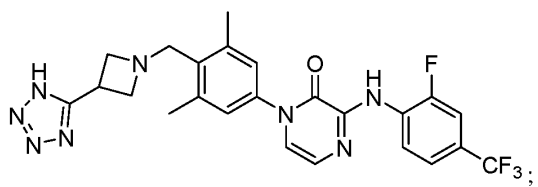
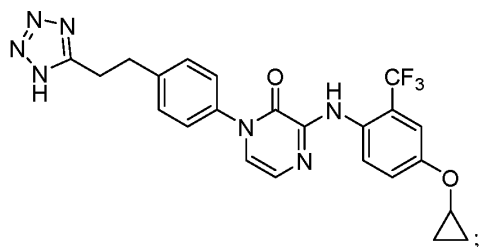
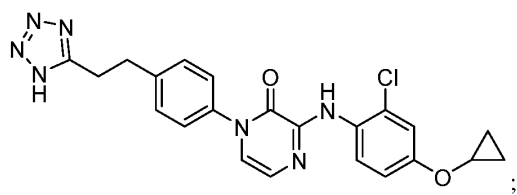
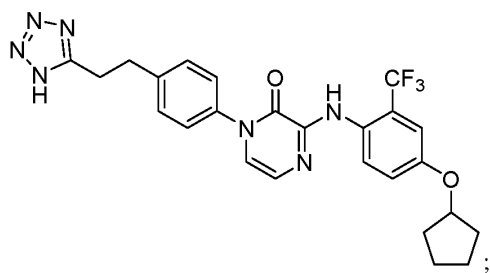
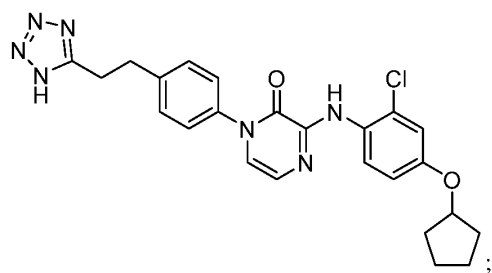
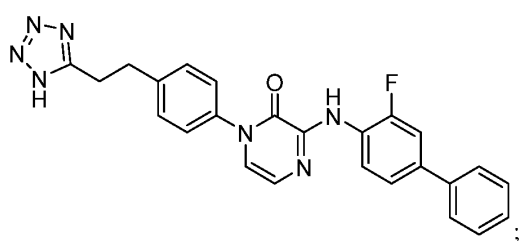


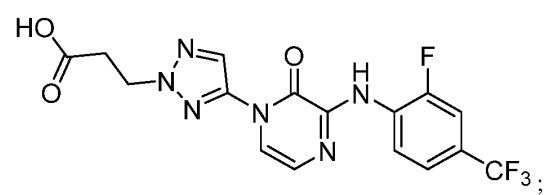
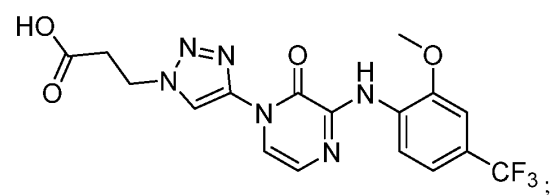
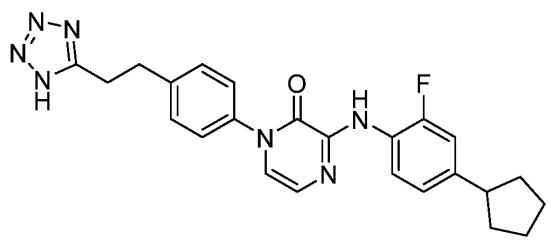
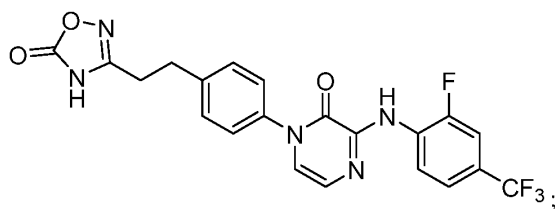
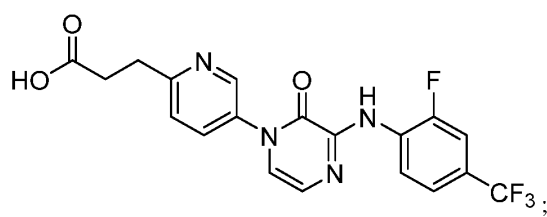
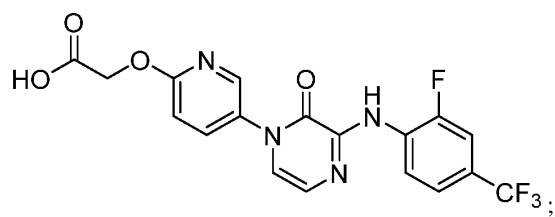
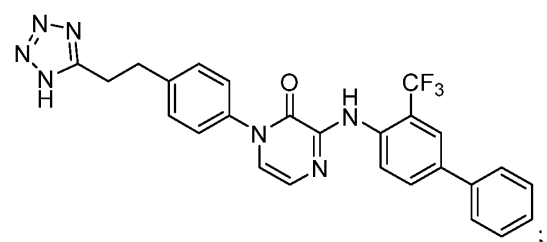
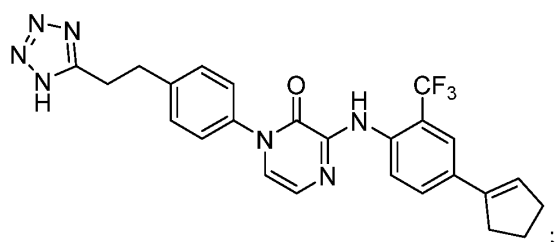
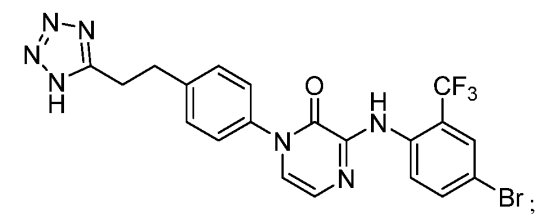
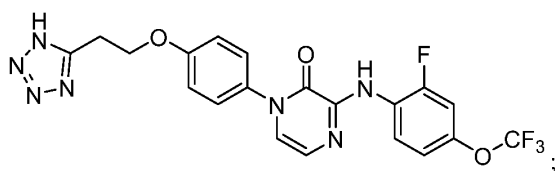
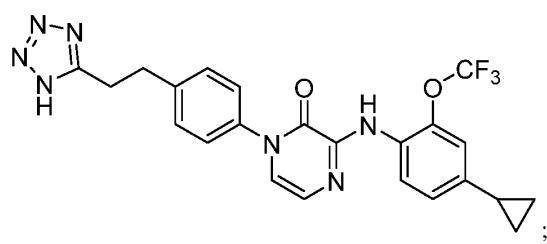
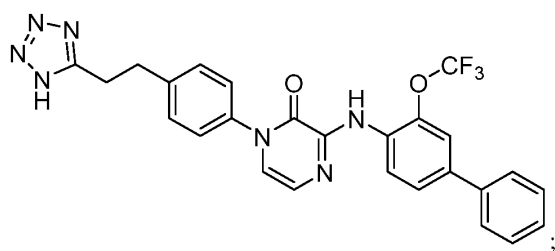


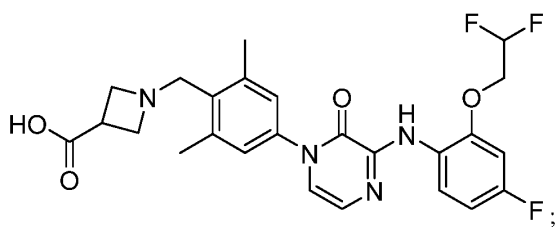
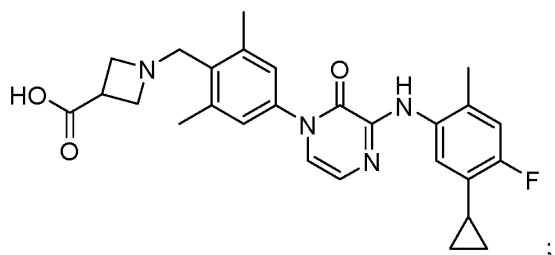
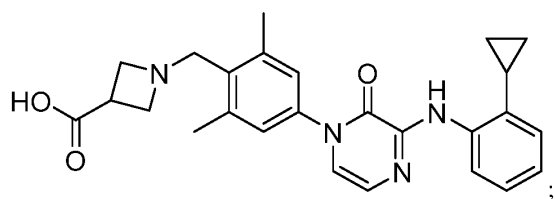
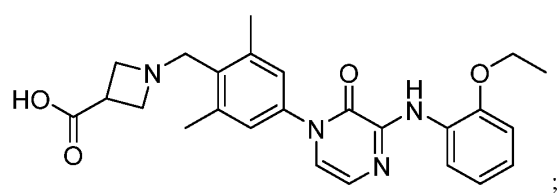
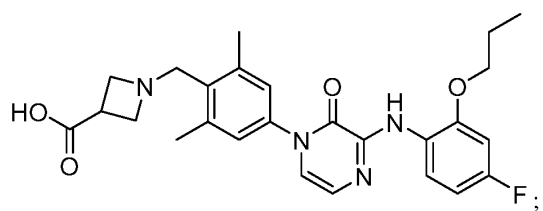
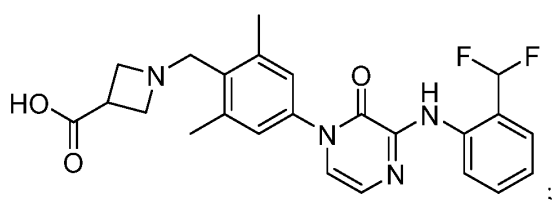
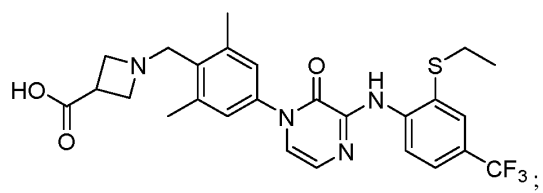
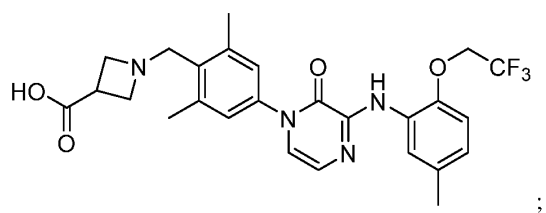
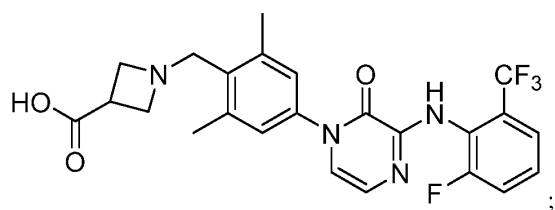
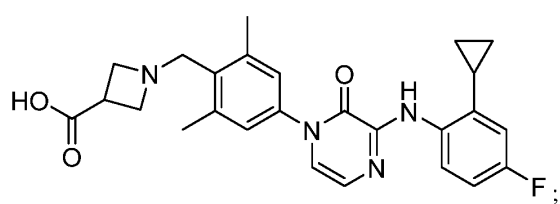
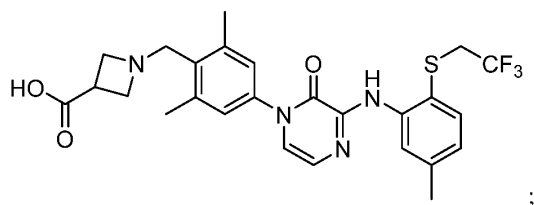
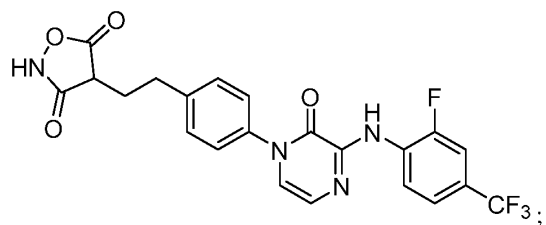
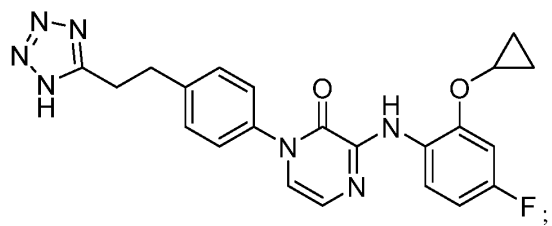
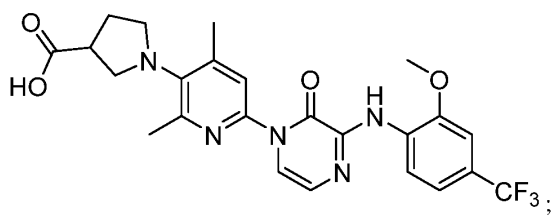


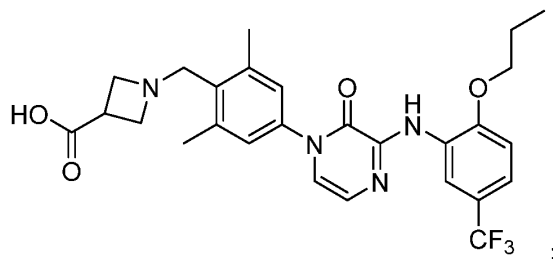
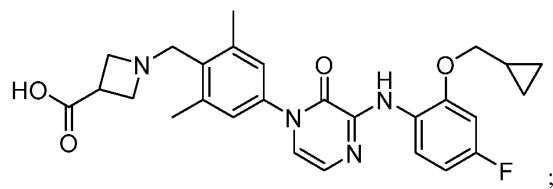
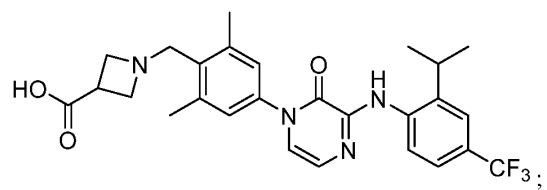
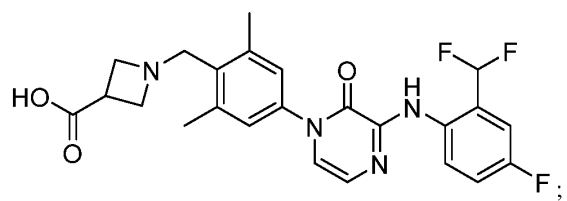
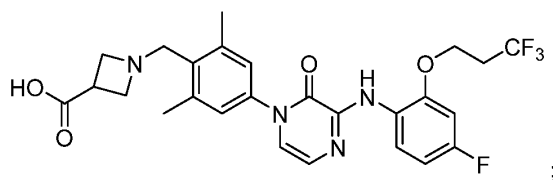
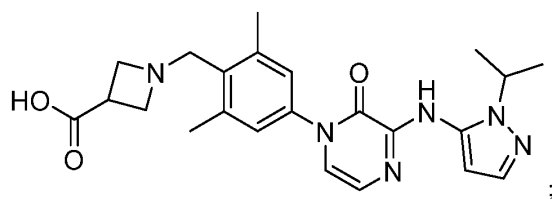


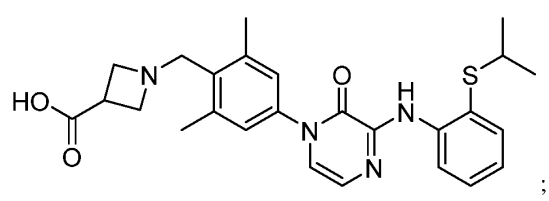
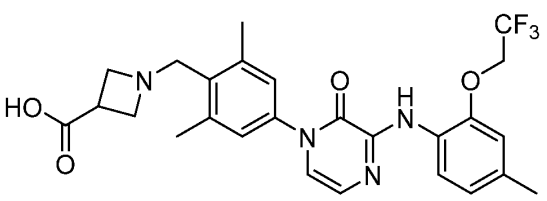
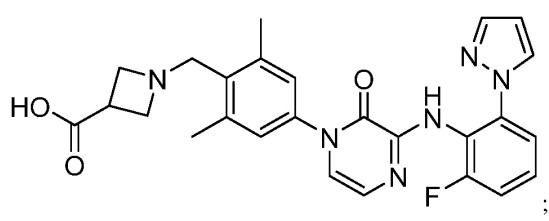
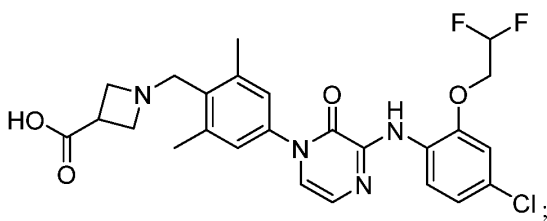
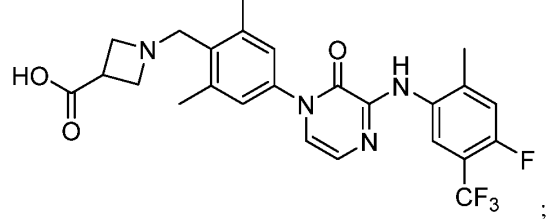
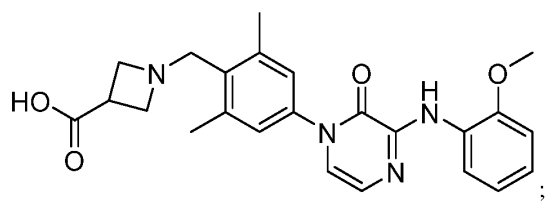
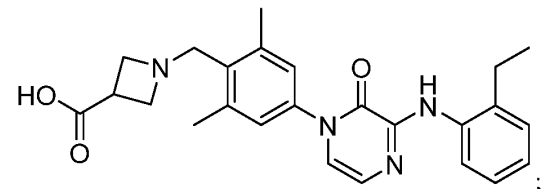
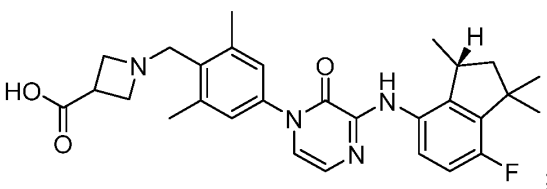
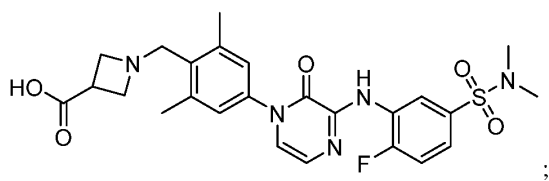
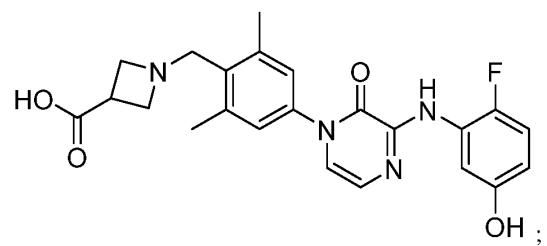
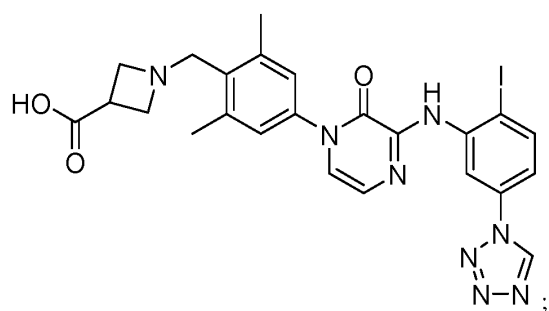
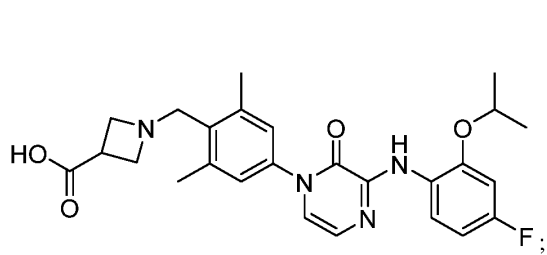


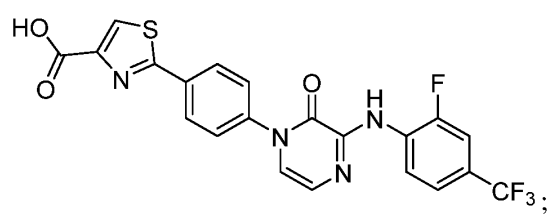
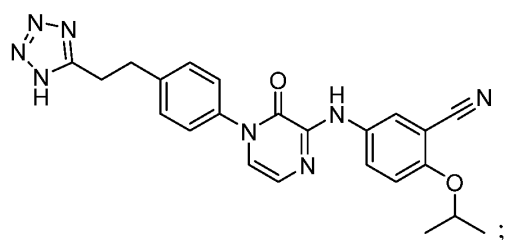
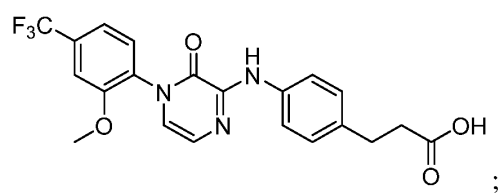
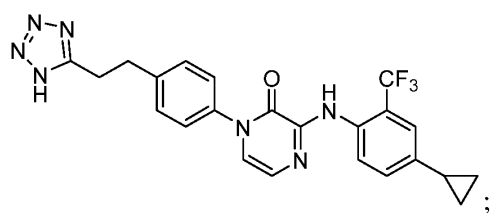
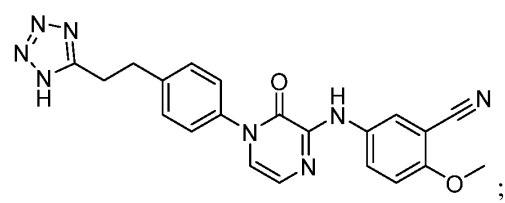
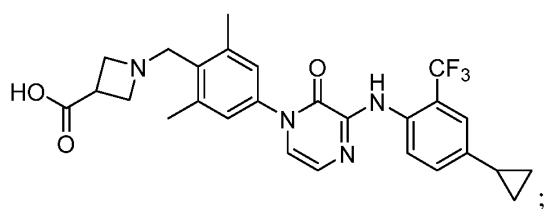
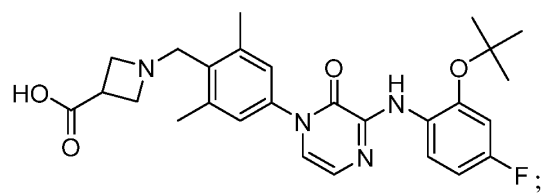
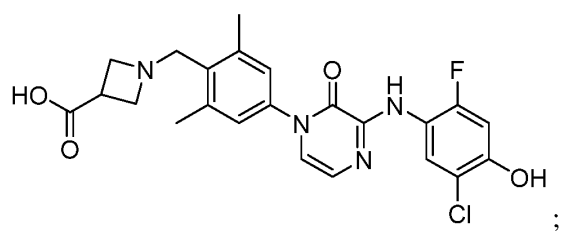
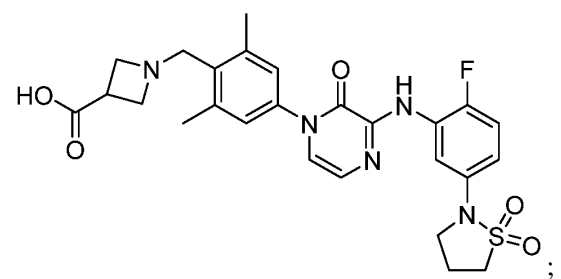
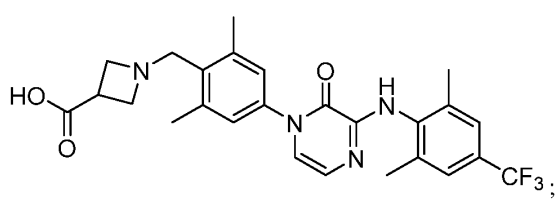
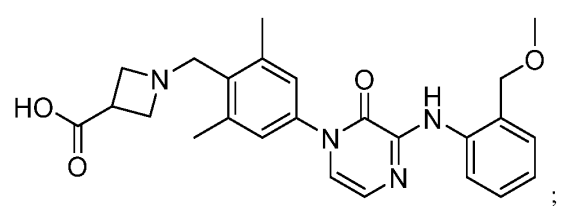
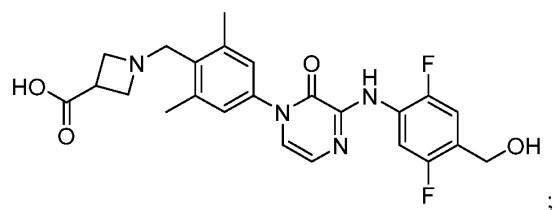
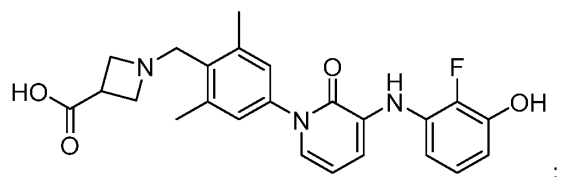
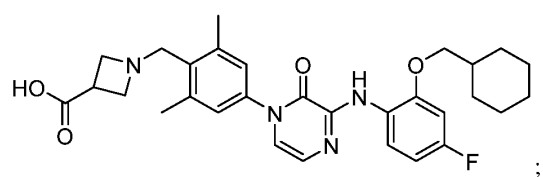


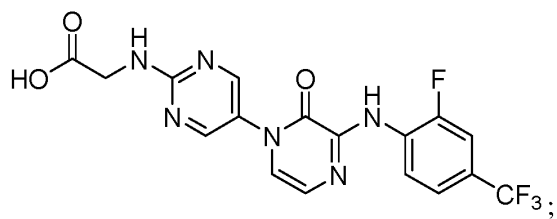
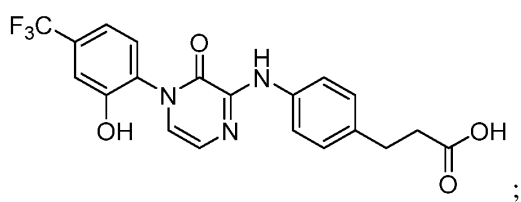
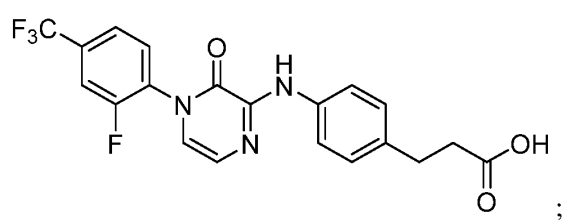
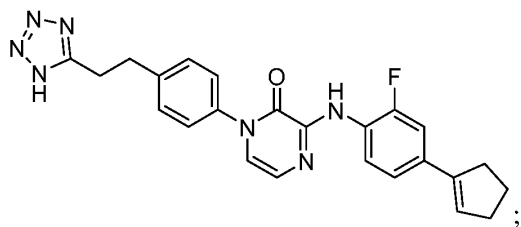
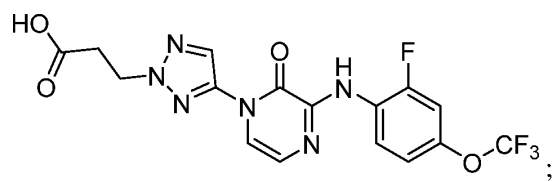
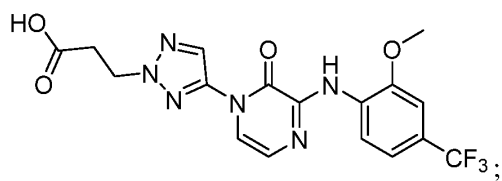
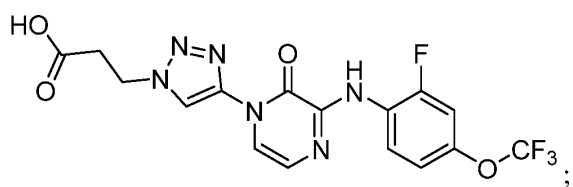
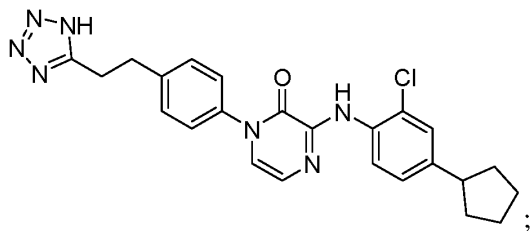
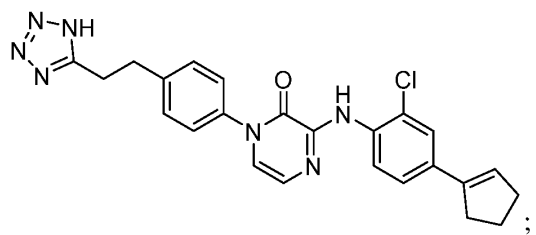
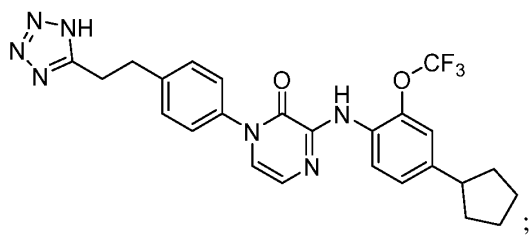
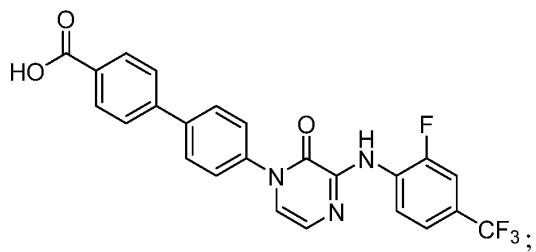
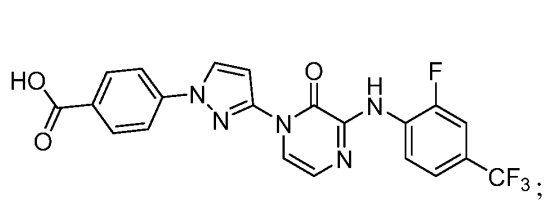


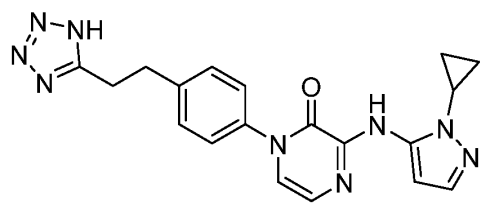
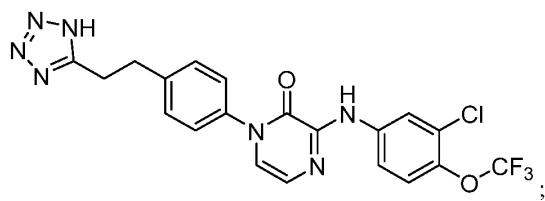
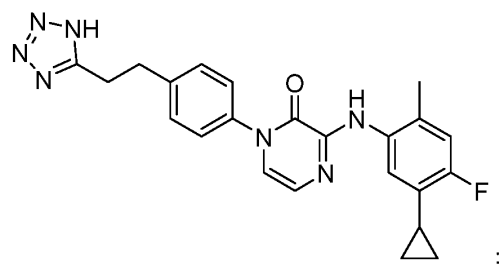
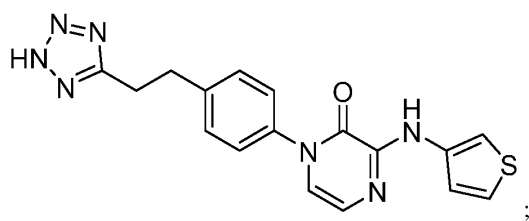
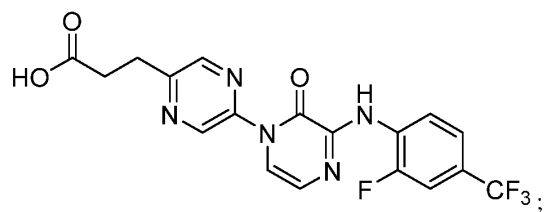
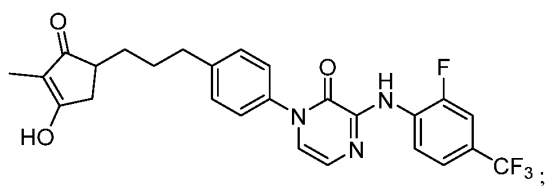
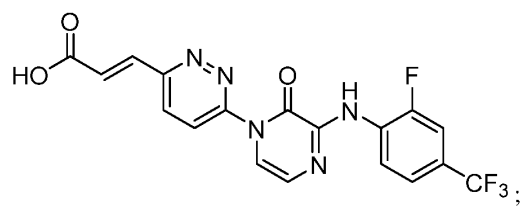
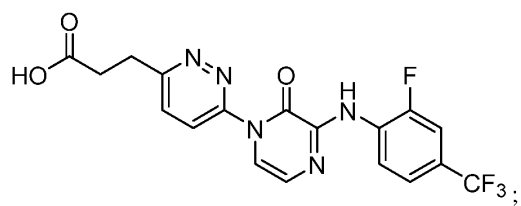
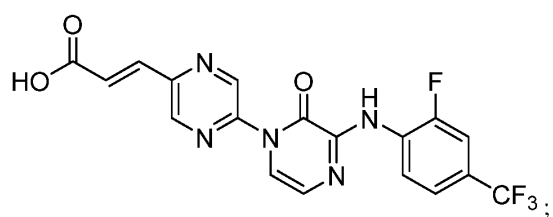
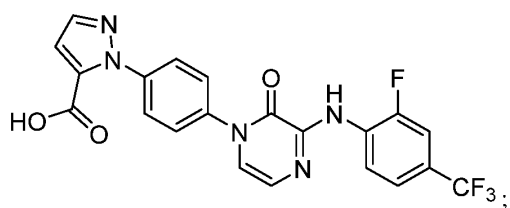
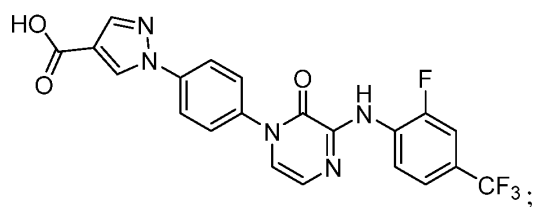
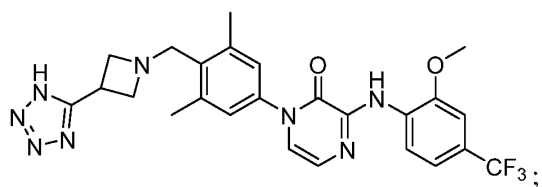
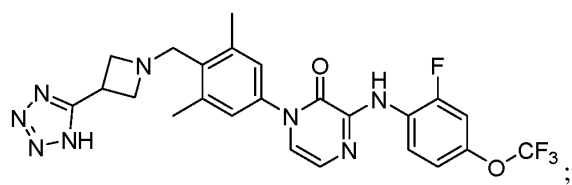
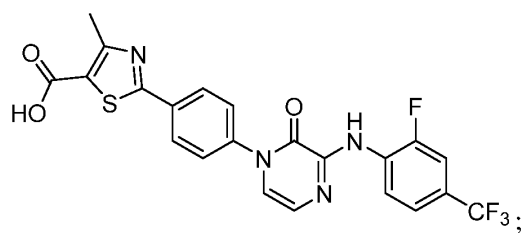


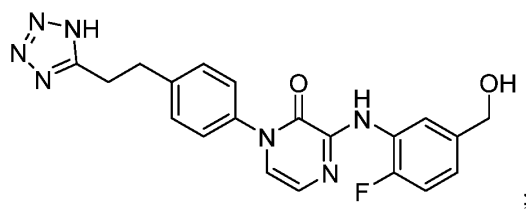
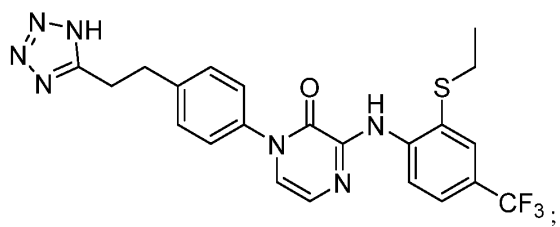
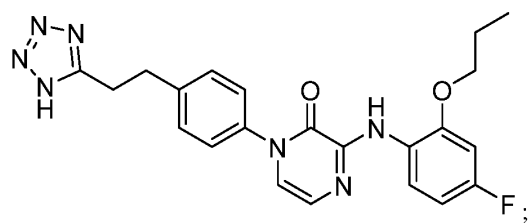
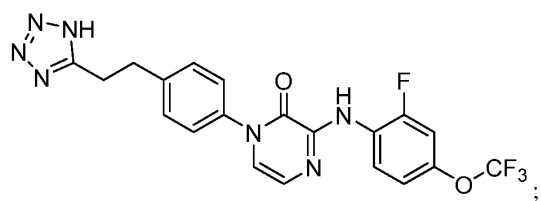
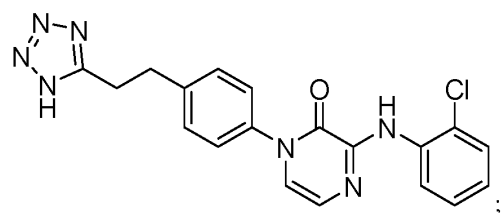
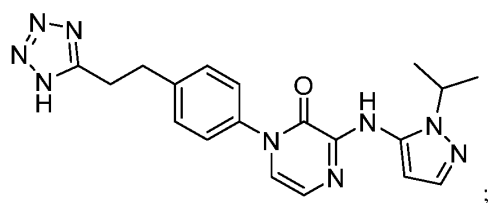
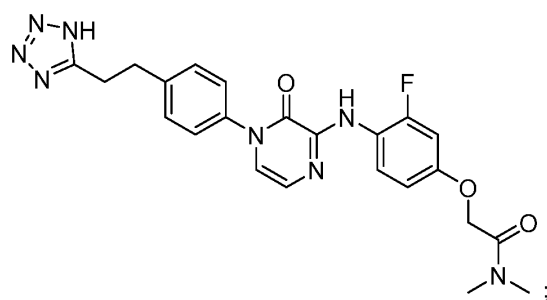
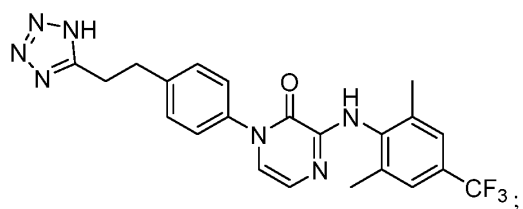
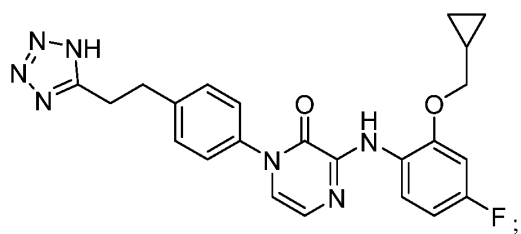
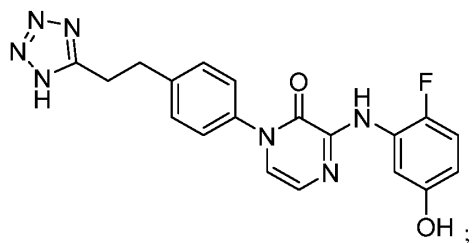
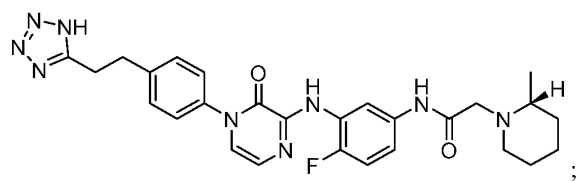
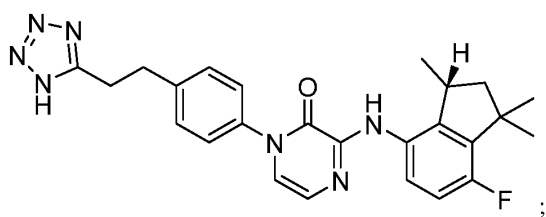


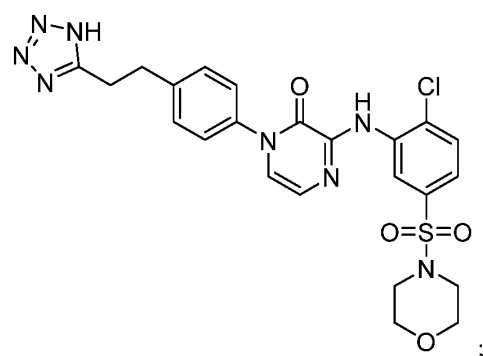
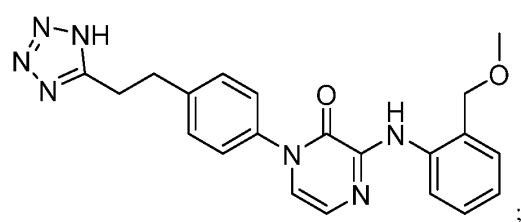
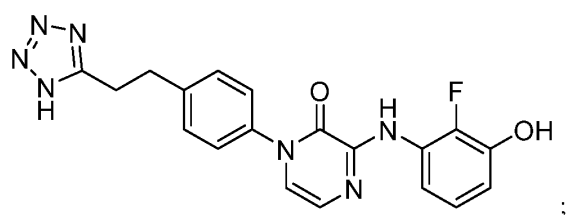
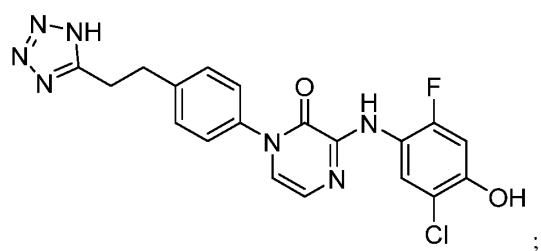
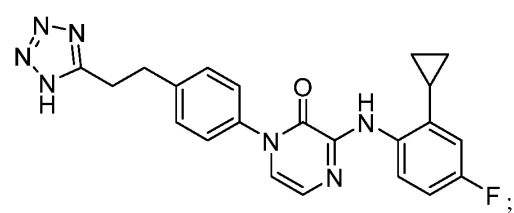
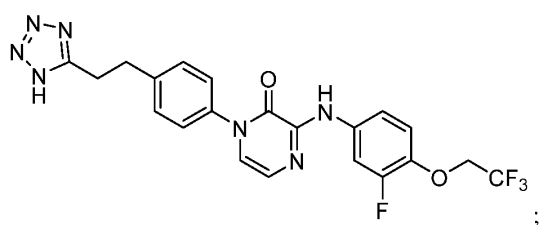
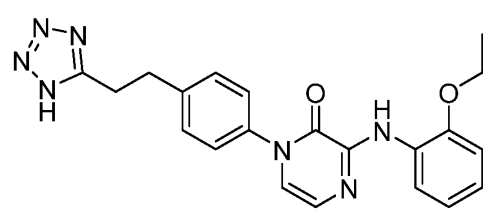
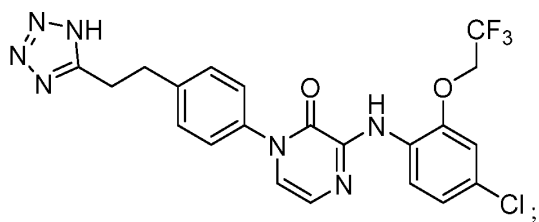
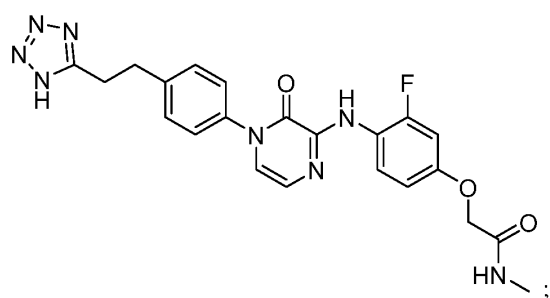
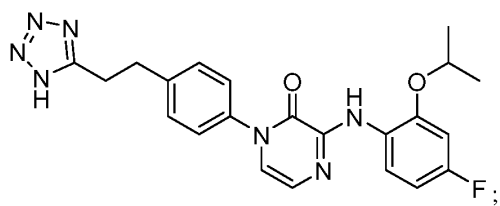


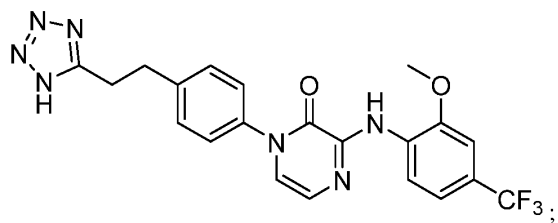
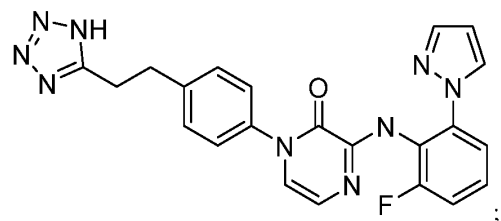
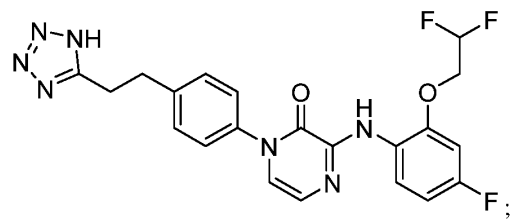
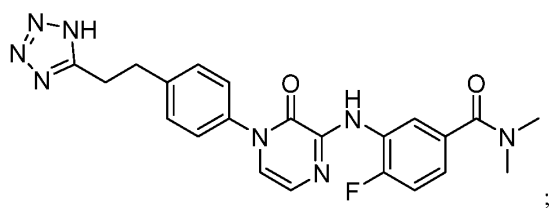
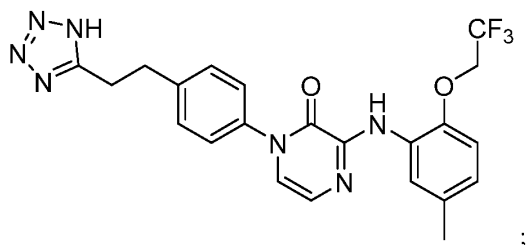
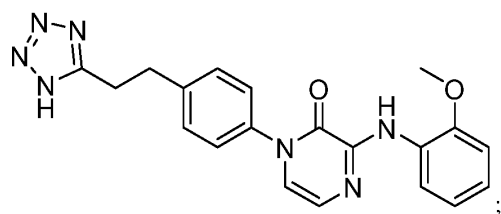
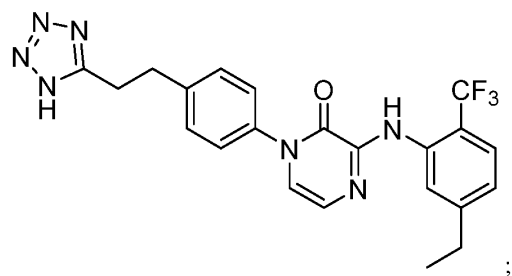
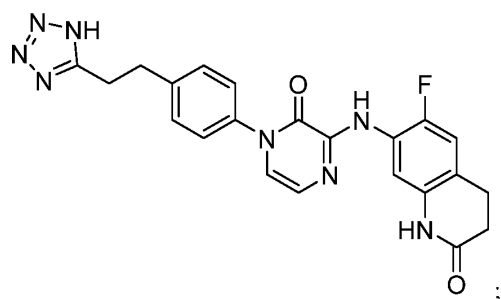
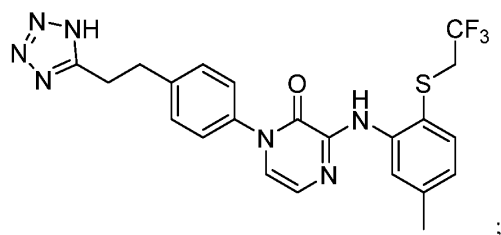
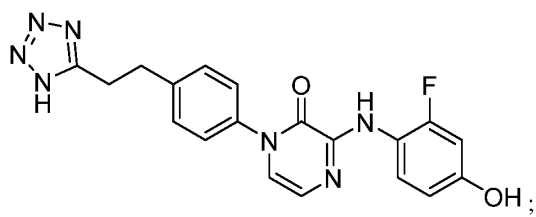
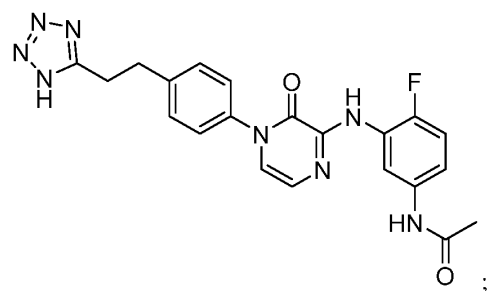
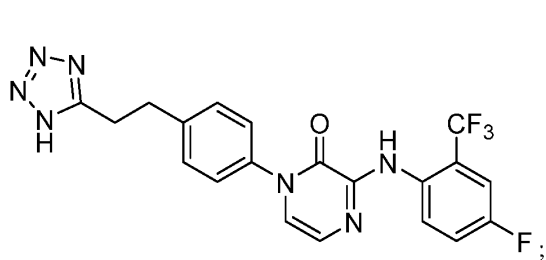


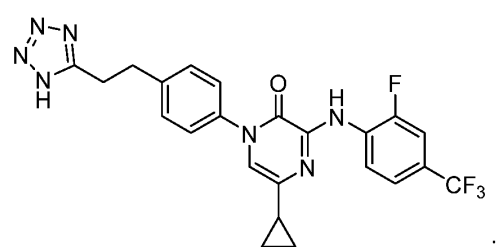
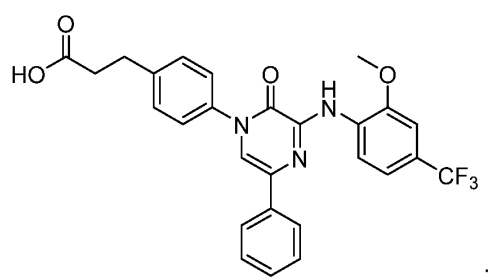
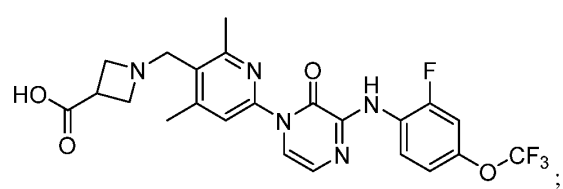
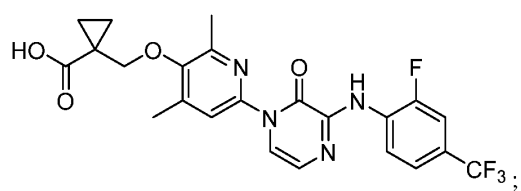
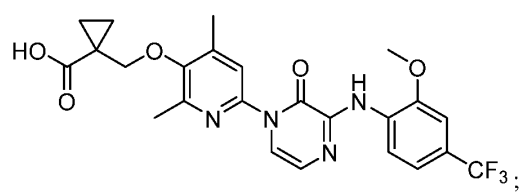
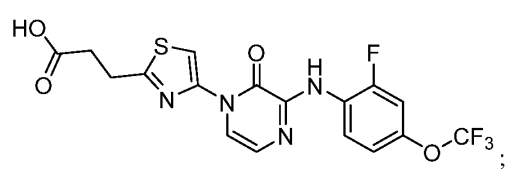
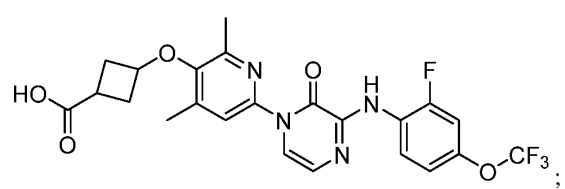
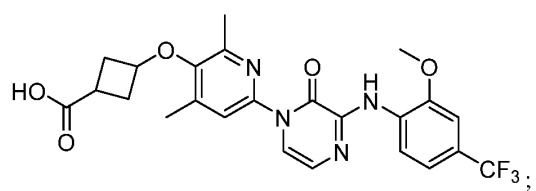
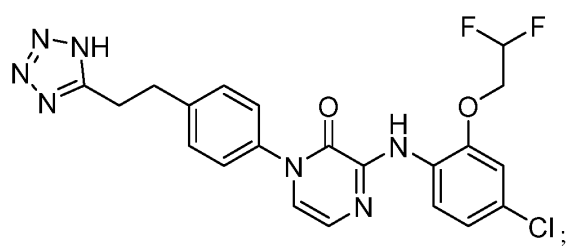
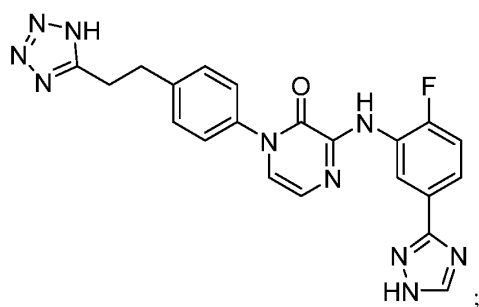
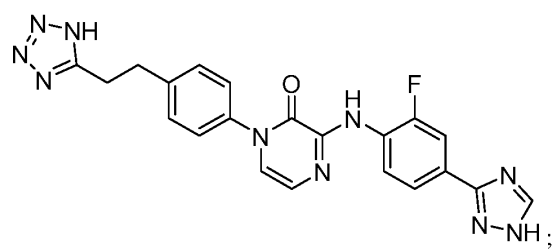
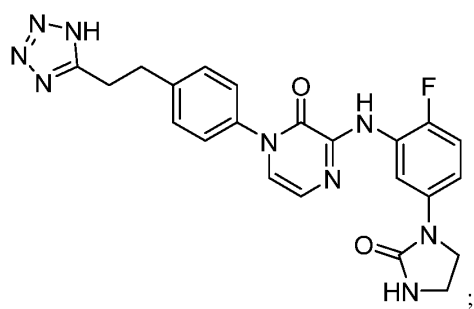


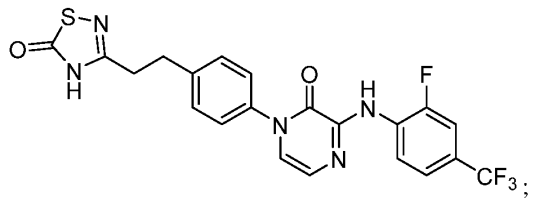
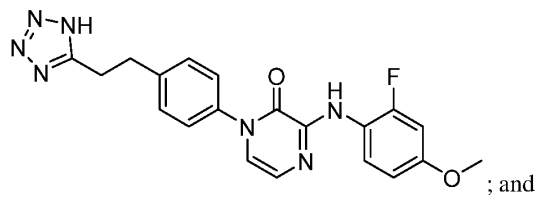
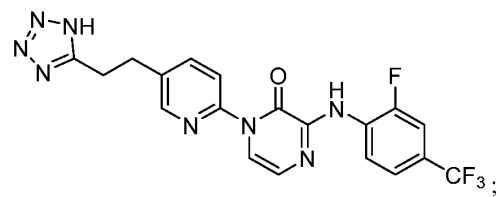
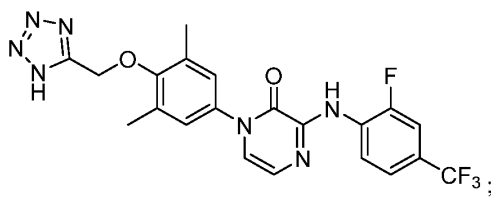
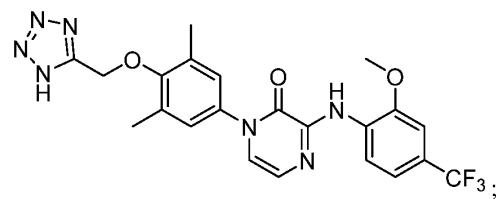
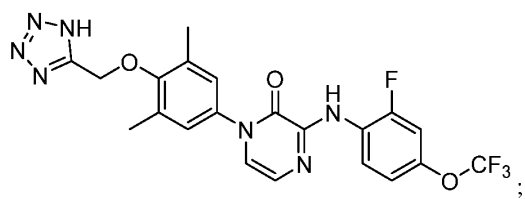
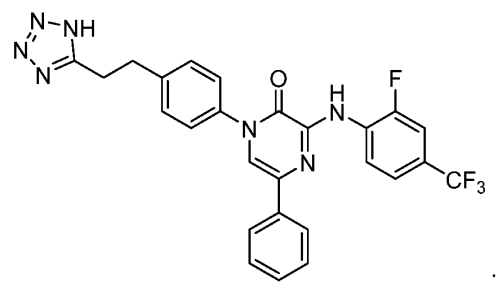
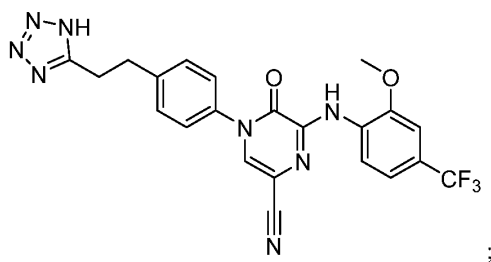
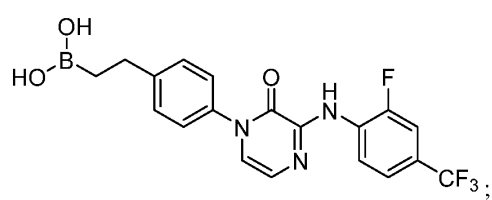
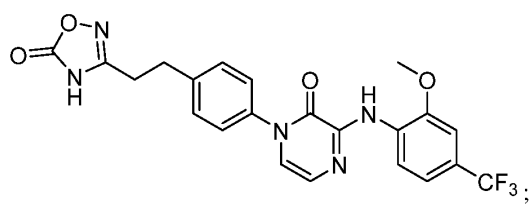
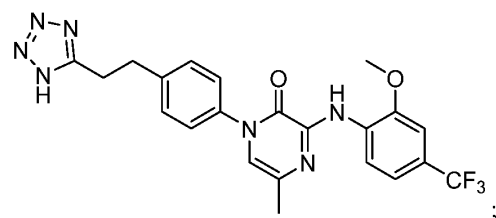
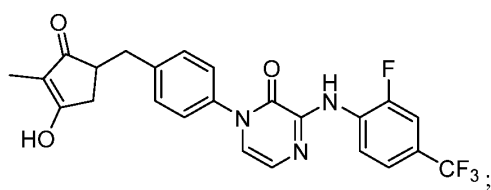
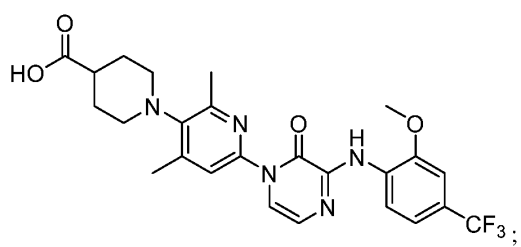
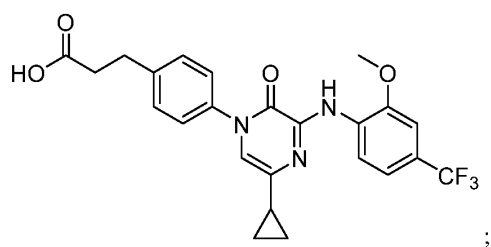


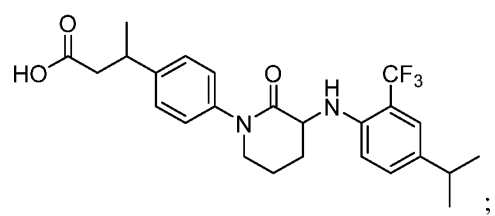
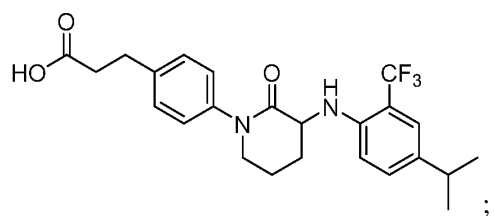
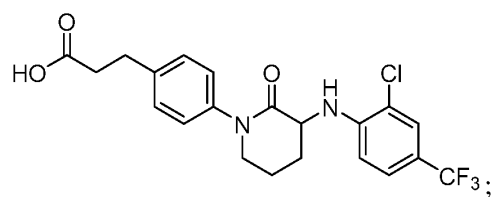
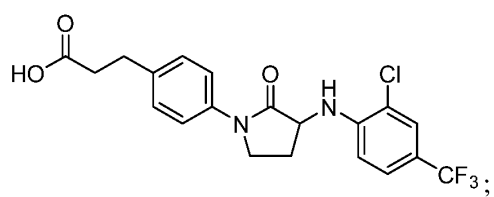
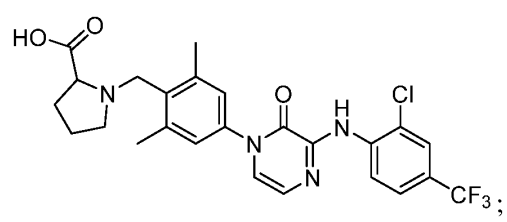
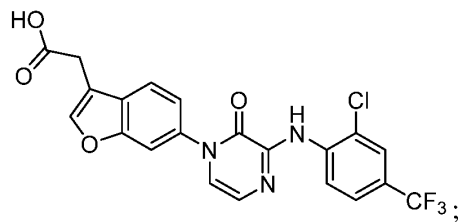
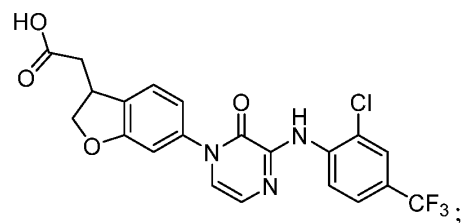
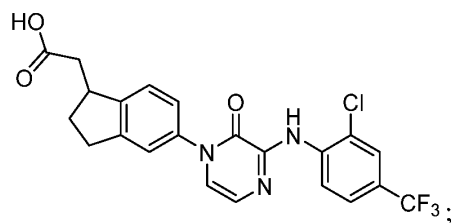
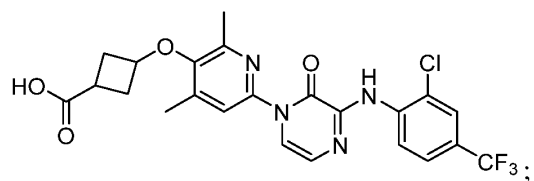
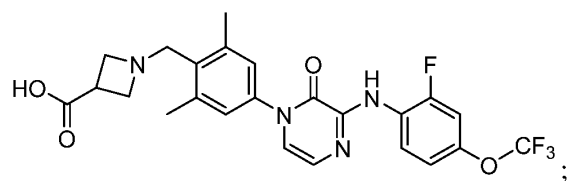
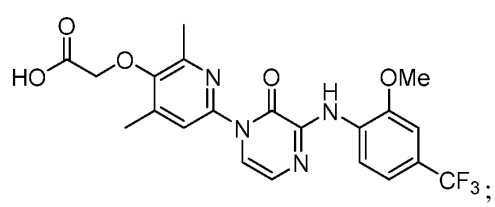
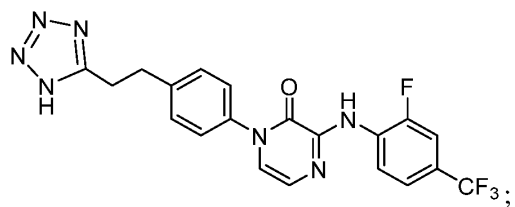
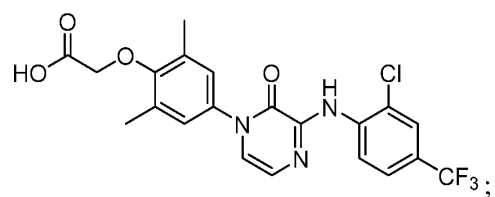
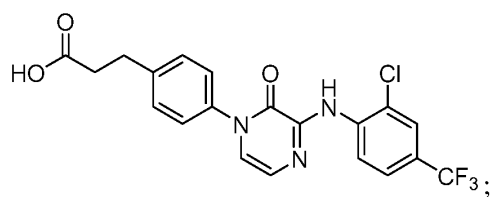


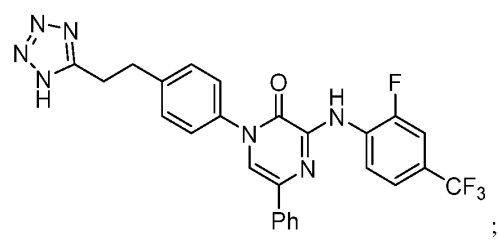
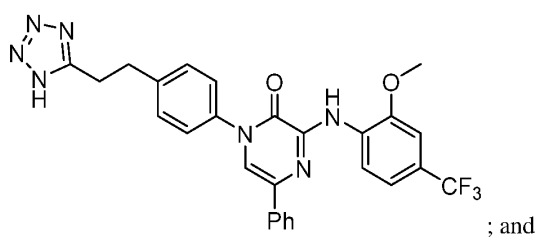
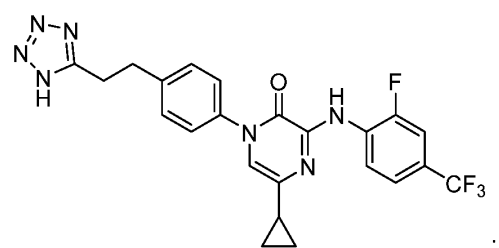
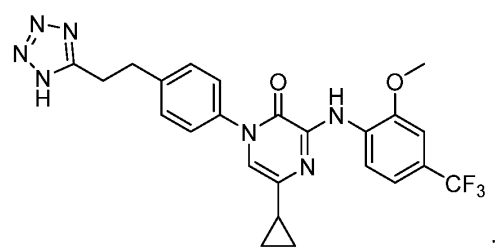
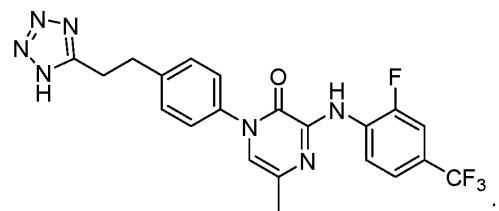
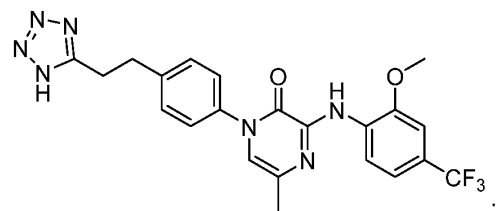
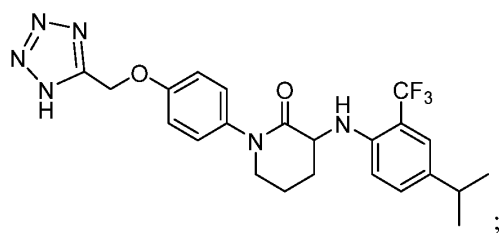
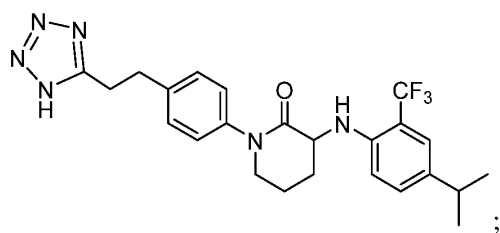








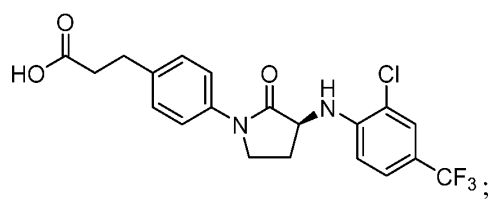
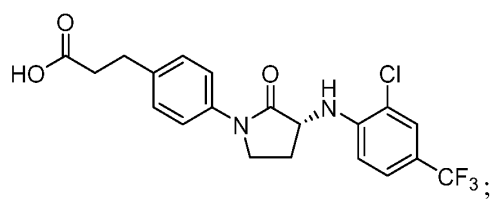


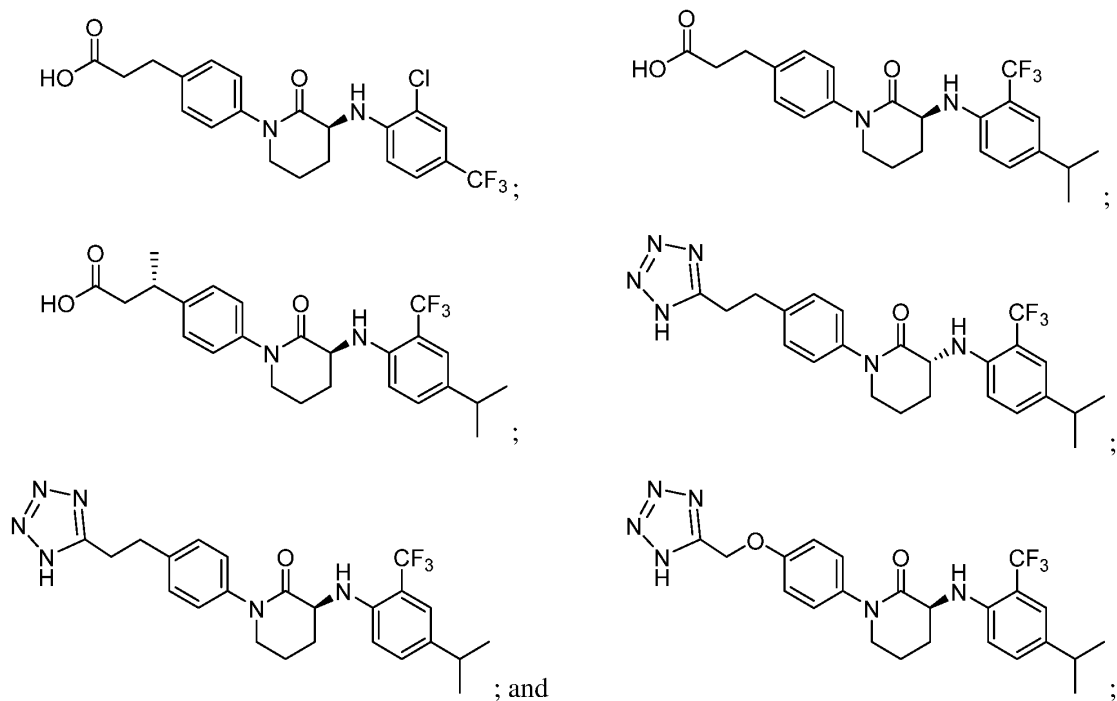


or

an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

19. The pharmaceutical composition of claim **18**, wherein the compound is selected from the group consisting of

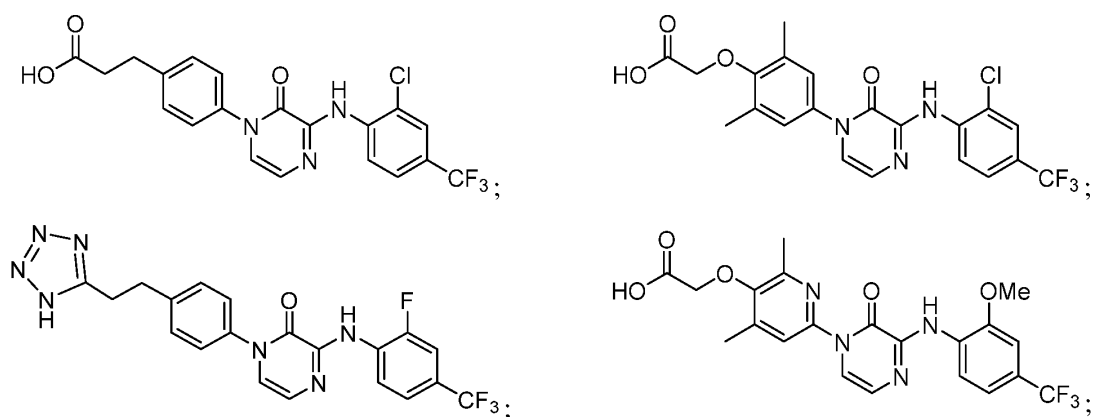


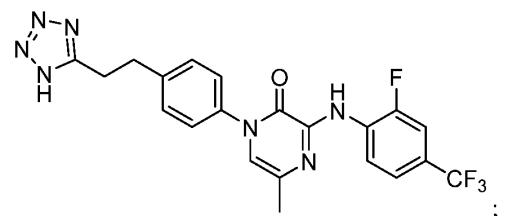
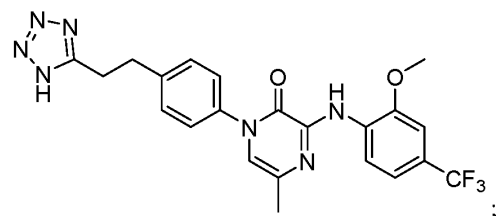
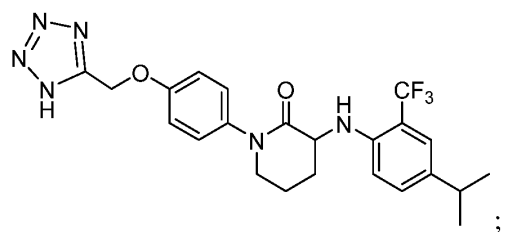
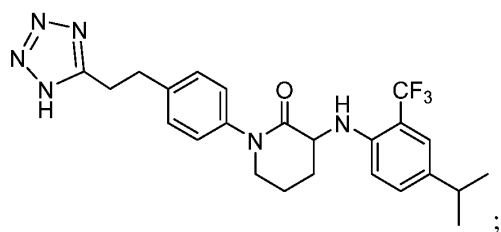
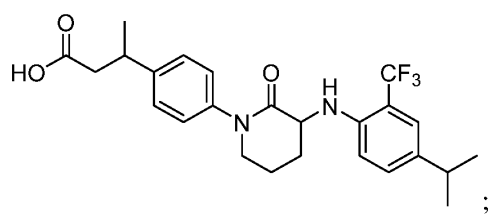
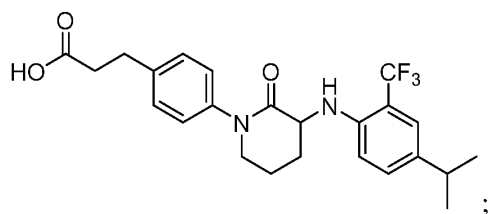
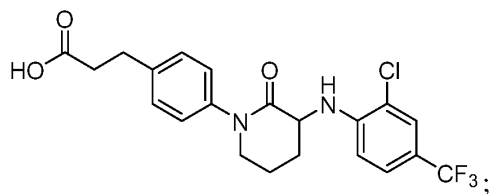
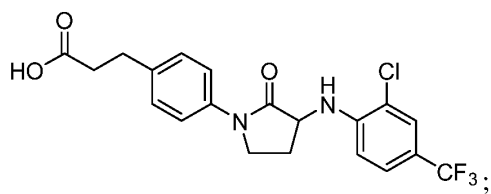
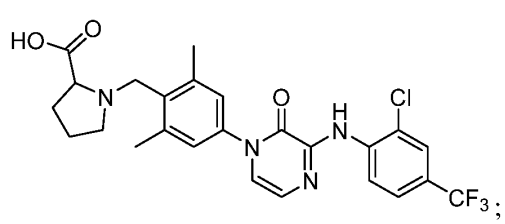
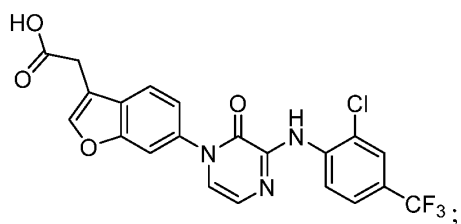
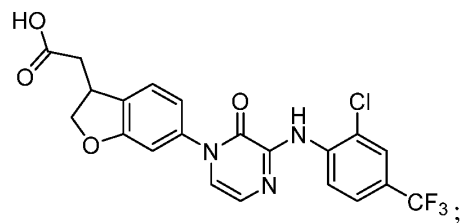
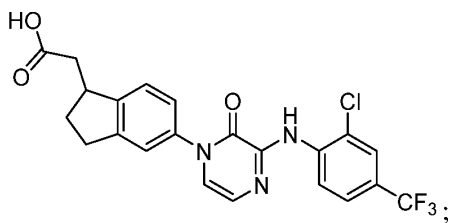
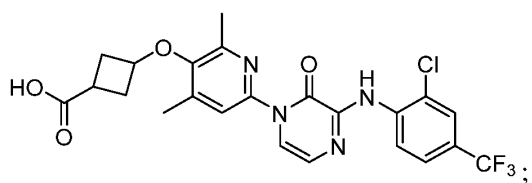
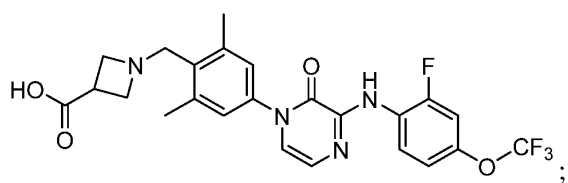


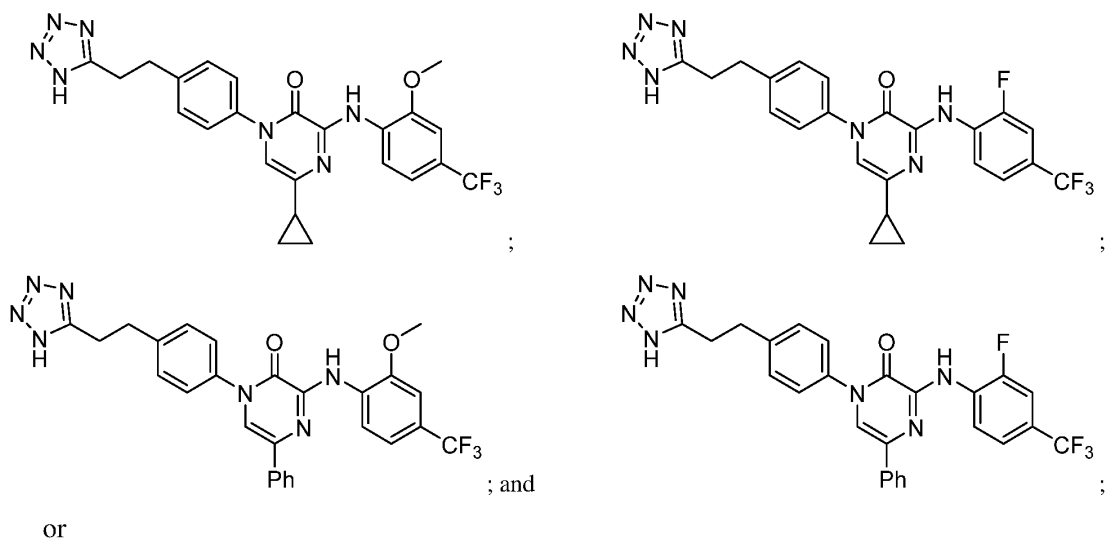
or a pharmaceutically acceptable salt thereof.

20. A method of treating multiple sclerosis, relapsing-remitting multiple sclerosis, amyotrophic lateral sclerosis, psoriasis, systemic lupus erythematosus, ulcerative colitis, Crohn's disease, and lymphopenia, wherein the method comprises the step of administering to an individual in need thereof a pharmaceutical composition of claim **17**.

21. The method of claim **20**, wherein the compound is selected from the group consisting of:

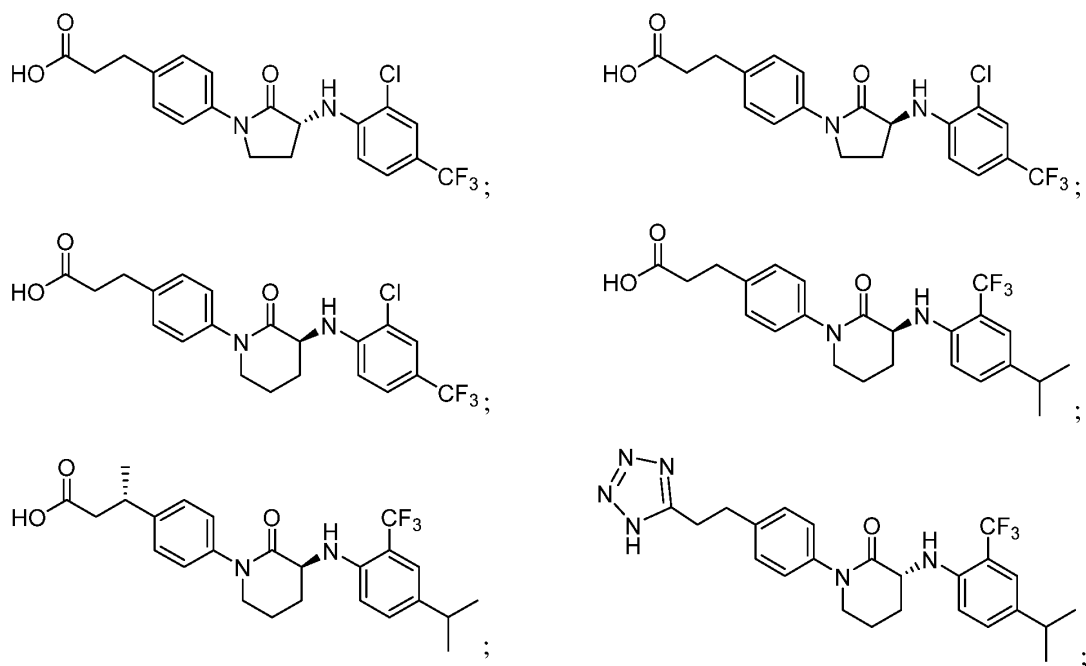


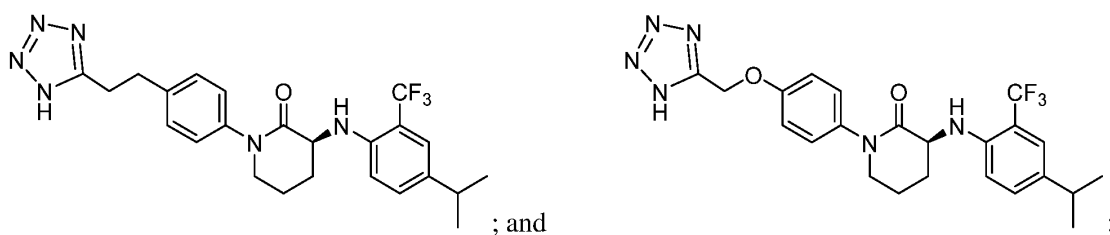




an enantiomer; racemate; or pharmaceutically acceptable salt thereof.

22. The method of claim **21**, wherein the compound is selected from the group consisting of

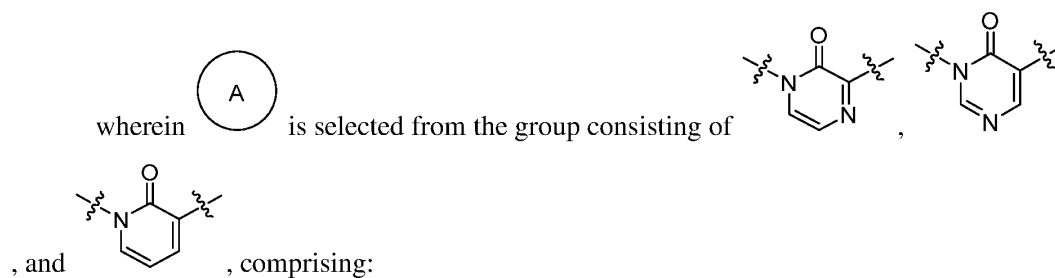




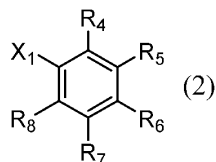
or a pharmaceutically acceptable salt thereof.

23. The method of claim **22**, wherein the pharmaceutical composition is administered to the individual intranasally; intrapulmonarily; topically; orally; intravenously as an infusion or injection; intramuscularly as an infusion or injection; subcutaneously as an infusion, injection, or depot formulation; transdermally; intraperitoneally; or rectally.

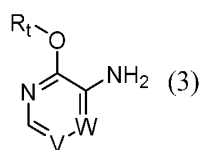
24. A process for preparing compounds of claim **1**,



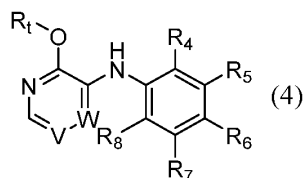
a step A, reacting a compound of formula (2)



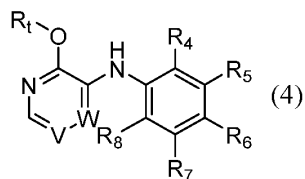
with a compound of formula (3)



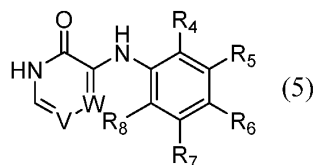
to produce a compound of formula (4)



a step B, reacting a compound of formula (4)

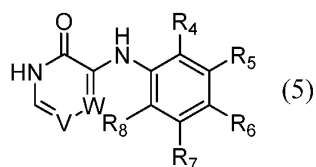


with an acid to produce a compound of formula (5)

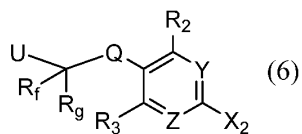


; and

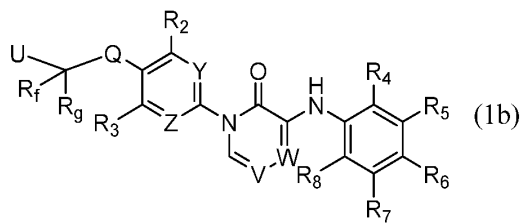
a step 1-C, reacting a compound of formula (5)



with a compound of formula (6)



to produce a compound of formula (1b)



wherein X₁ is F, Cl, Br, or I; X₂ is F, Cl, Br, or I; V is N or CH; W is N or CH; and R_t is H or unsubstituted C₁-C₆ straight or branched alkyl.

25. The process of claim **24**, wherein step A is carried out from about 50 °C to about 100 °C; step B is carried out from about 50 °C to about 100 °C; and step 1-C is carried out from about 50 °C to about 125 °C.

26. The process of claim **24**, wherein step A is carried out in the presence of a solvent and a base; step B is carried out in the presence of a solvent and an acid; and step 1-C is carried out in the presence of a solvent, a copper salt, a base, and a ligand.

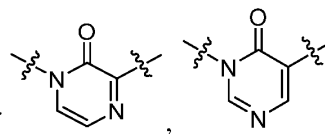
27. The process of claim **26**, wherein the solvent in step A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; and wherein the base in step A is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

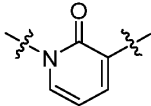
28. The process of claim **26**, wherein the solvent in step B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and wherein the acid in step B is selected from the group consisting of AcOH, TFA, hydrochloric acid, hydrobromic acid, and mixtures thereof.

29. The process of claim **26**, wherein the solvent in step 1-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; wherein the copper salt in step 1-C is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; wherein the base in step 1-C is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and wherein the ligand in step 1-C is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

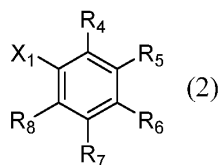
30. A process for preparing compounds of claim **1**,

wherein  is selected from the group consisting of

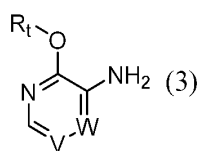


, and , comprising:

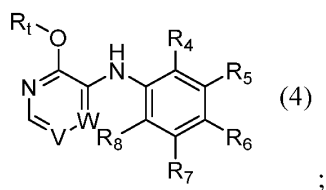
a step A, reacting a compound of formula (2)



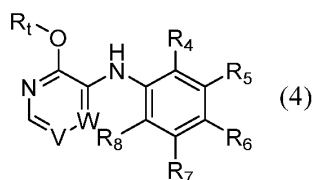
with a compound of formula (3)



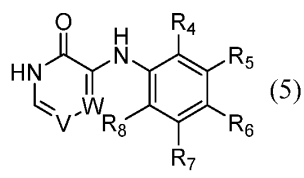
to produce a compound of formula (4)



a step B, reacting a compound of formula (4)

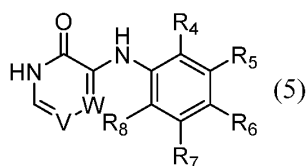


with an acid to produce a compound of formula (5)

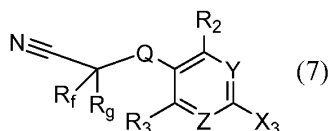


; and

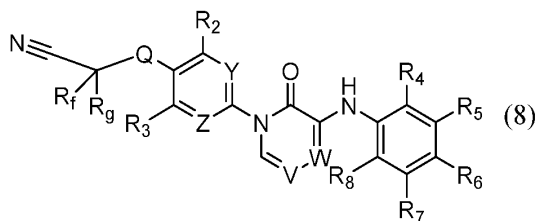
a step 2-C, reacting a compound of formula (5)



with a compound of formula (7)



to produce a compound of formula (8)



wherein X_3 is F, Cl, Br, or I; V is N or CH; W is N or CH; and R_i is H or unsubstituted C_1 - C_6 straight or branched alkyl.

31. The process of claim **30**, wherein step A is carried out from about 50 °C to about 100 °C; step B is carried out from about 50 °C to about 100 °C; and step 2-C is carried out from about 50 °C to about 125 °C.

32. The process of claim **30**, wherein step A is carried out in the presence of a solvent and a base; step B is carried out in the presence of a solvent and an acid; and step 2-C is carried out in the presence of a solvent, a copper salt, a base, and a ligand.

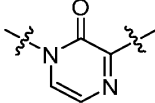
33. The process of claim **32**, wherein the solvent in step A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, $CHCl_3$, MeCN, and mixtures thereof; and wherein the base in step A is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

34. The process of claim **32**, wherein the solvent in step B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, $CHCl_3$, MeCN, MeOH,

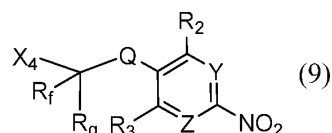
EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and wherein the acid in step B is selected from the group consisting of AcOH, TFA, hydrochloric acid, hydrobromic acid, and mixtures thereof.

35. The process of claim **32**, wherein the solvent in step 2-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; wherein the copper salt in step 2-C is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; wherein the base in step 2-C is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and wherein the ligand in step 2-C is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

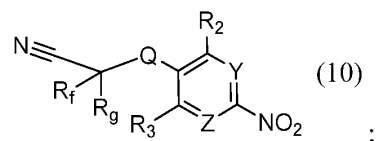
36. A process for preparing compounds of claim **1**,

wherein  is , comprising:

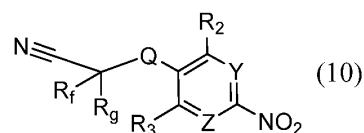
a step 3-A, reacting a compound of formula (9)



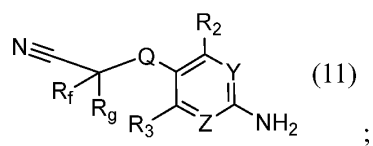
with a cyanide reagent to produce a compound of formula (10)



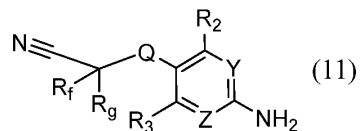
a step 3-B, reacting a compound of formula (10)



with a hydrogenation reagent to produce a compound of formula (11)



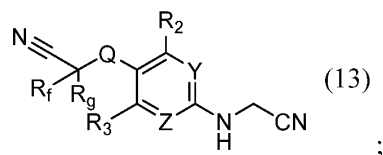
a step 3-C, reacting a compound of formula (10)



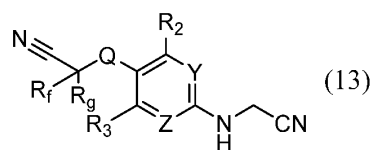
with a compound of formula (12)



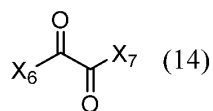
to produce a compound of formula (13)



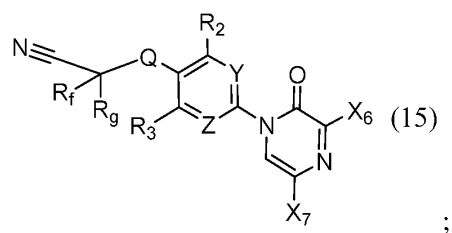
a step 3-D, reacting a compound of formula (13)



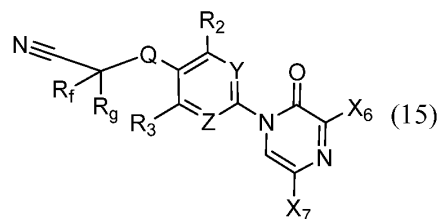
with a compound of formula (14)



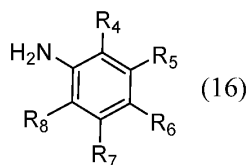
to produce a compound of formula (15)



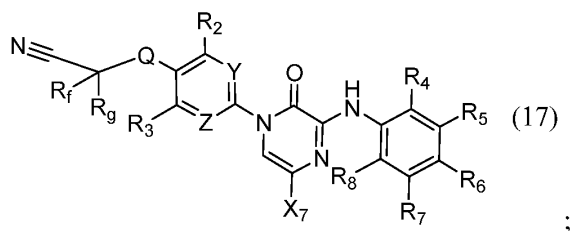
a step 3-E, reacting a compound of formula (15)



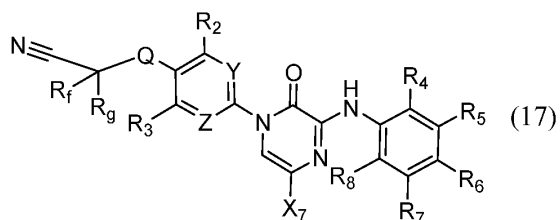
with a compound of formula (16)



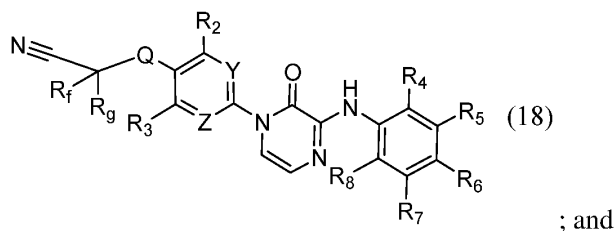
to produce a compound of formula (17)



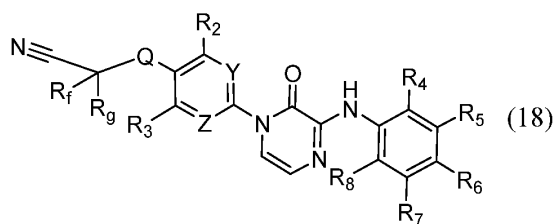
a step 3-F, reacting a compound of formula (17)



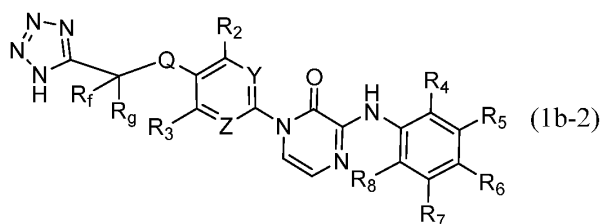
with a hydrogenation reagent to produce a compound of formula (18)



a step 3-G, reacting a compound of formula (18)



with an azide reagent to produce a compound of formula (1b-2)



wherein X₄ is F, Cl, Br, or I; X₅ is F, Cl, Br, I, or a leaving group L₁ selected from the group consisting of *p*-toluenesulfonate (-OTs), methanesulfonate (-OMs), trifluoromethanesulfonate (-SO₃CF₃), nitrate (-ONO₂), and phosphates (-OPO(OR)₂), wherein R is an alkyl group; X₆ is F, Cl, Br, or I; and X₇ is F, Cl, Br, or I.

37. The process of claim **36**, wherein step 3-A is carried out from about 30 °C to about 75 °C; step 3-B is carried out from about 15 °C to about 35 °C; step 3-C is carried out from about 50 °C to about 75 °C; step 3-D is carried out from about 75 °C to about 125 °C; step 3-E is carried out from about 15 °C to about 35 °C; step 3-F is carried out from about 15 °C to about 35 °C; and step 3-G is carried out from about 100 °C to about 140 °C.

38. The process of claim **36**, wherein step 3-A is carried out in the presence of a solvent and a cyanide reagent; step 3-B is carried out in the presence of a solvent, a hydrogenation reagent, and a catalyst; step 3-C is carried out in the presence of a solvent and a base; step 3-D is carried out in the presence of a solvent; step 3-E is carried out in the presence of a solvent and a base; step 3-F is carried out in the presence of a solvent, a hydrogenation reagent, a catalyst, and a base; and step 3-G is carried out in the presence of a solvent, an azide reagent, and a salt.

39. The process of claim **38**, wherein the solvent in step 3-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, DMSO, and mixtures thereof; and wherein the cyanide reagent in step 3-A is selected from the group consisting of sodium cyanide, potassium cyanide, and mixtures thereof.

40. The process of claim **38**, wherein the solvent in step 3-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; wherein the hydrogenation reagent in step 3-B is selected from the group consisting of hydrogen (H_2), formic acid, isopropanol,

and mixtures thereof; and wherein the catalyst is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof.

41. The process of claim **38**, wherein the solvent in step 3-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the base in step 3-C is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

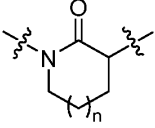
42. The process of claim **38**, wherein the solvent in step 3-D is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof.

43. The process of claim **38**, wherein the solvent in step 3-E is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof; and wherein the base in step 3-E is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

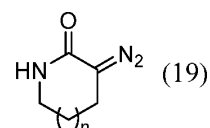
44. The process of claim **38**, wherein the solvent in step 3-F is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; wherein the hydrogenation reagent in step 3-F is selected from the group consisting of hydrogen (H₂), formic acid, isopropanol, and mixtures thereof; wherein the catalyst in step 3-F is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof; and wherein the base in step 3-F is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

45. The process of claim 38, wherein the solvent in step 3-G is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof; wherein the azide reagent in step 3-G is selected from the group consisting of lithium azide, sodium azide, potassium azide, trimethyltin azide, triethyltin azide, tripropyltin azide, tributyltin azide, and mixtures thereof; and wherein the salt in step 3-G is selected from the group consisting of ammonium fluoride, ammonium chloride, ammonium bromide, ammonium iodide, and mixtures thereof.

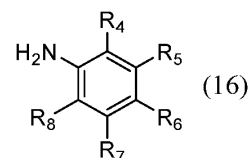
46. A process for preparing compounds of claim 1,

wherein  is , comprising:

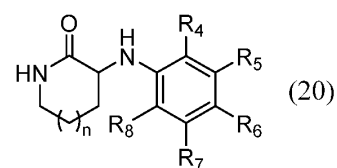
a step 4-A, reacting a compound of formula (19)



with a compound of formula (16)

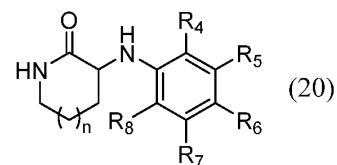


to produce a compound of formula (20)

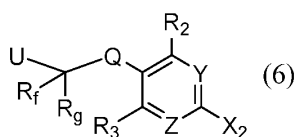


; and

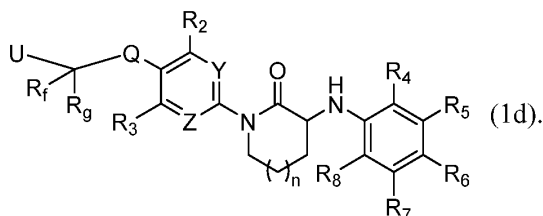
a step 4-B, reacting a compound of formula (20)



with a compound of formula (6)



to produce a compound of formula (1d)



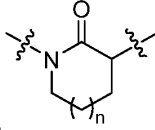
47. The process of claim **46**, wherein step 4-A is carried out from about 15 °C to about 35 °C; and step 4-B is carried out from about 50 °C to about 125 °C.

48. The process of claim **46**, wherein step 4-A is carried in the presence of a solvent and a catalyst; and step 4-B is carried out in the presence of a solvent, a copper salt, a base, and a ligand.

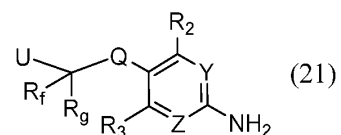
49. The process of claim **48**, wherein the solvent in step 4-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; and wherein the catalyst in step 4-A is selected from the group consisting of $\text{Rh}_2(\text{OAc})_4$, $\text{Rh}(\text{OAc})_3$, $\text{Rh}(\text{acac})_3$, and mixtures thereof.

50. The process of claim **48**, wherein the solvent in step 4-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, and mixtures thereof; wherein the copper salt in step 4-B is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof; wherein the base in step 4-B is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and wherein the ligand in step 4-B is selected from the group consisting of *N,N*'-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.

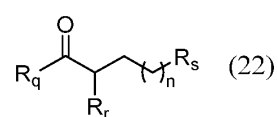
51. A process for preparing compounds of claim 1,

wherein  is , comprising:

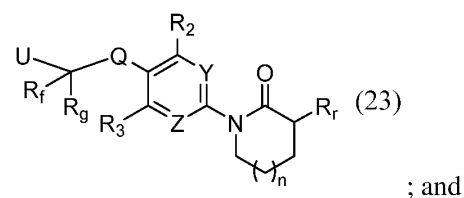
a step 5-A, reacting a compound of formula (21)



with a compound of formula (22)

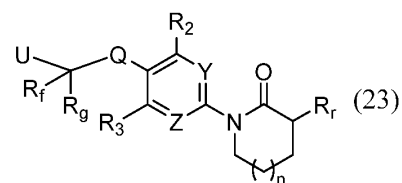


to produce a compound of formula (23)

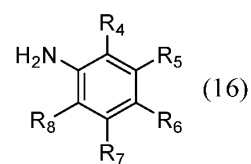


; and

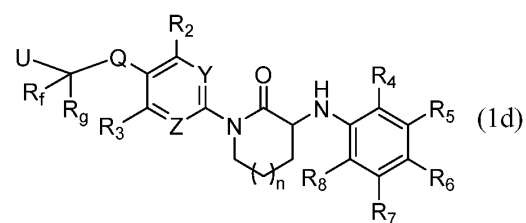
a step 5-B, reacting a compound of formula (23)



with a compound of formula (16)



to produce a compound of formula (1d)



wherein R_q, R_r, and R_s, are independently F, Cl, Br, I, OR_h, SR_h, or a leaving group L₂ selected from the group consisting of *p*-toluenesulfonate (-OTs), methanesulfonate (-OMs), trifluoromethanesulfonate (-OSO₂CF₃), nitrate (-ONO₂), and phosphates (-OPO(OR)₂), wherein R is an alkyl group; and R_h is H or an unsubstituted C₁-C₆ straight or branched alkyl.

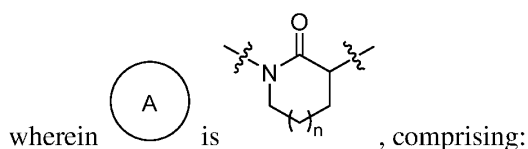
52. The process of claim **51**, wherein step 5-A is carried out from about 15 °C to about 35 °C; and step 5-B is carried out from about -10 °C to about 10 °C.

53. The process of claim **51**, wherein step 5-A is carried out in the presence of a solvent and a base; and step 5-B is carried out in the presence of a solvent and a catalyst.

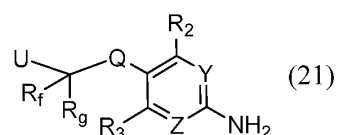
54. The process of claim **53**, wherein the solvent in step 5-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; and wherein the base in step 5-A is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

55. The process of claim **53**, wherein the solvent in step 5-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; and wherein the base in step 5-B is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

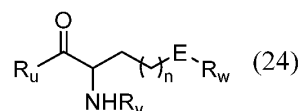
56. A process for preparing compounds of claim 1,



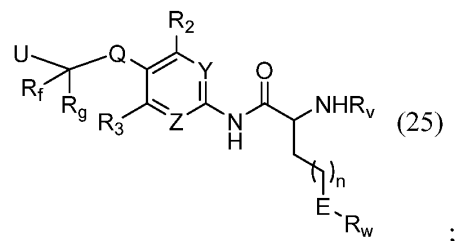
a step 6-A, reacting a compound of formula (21)



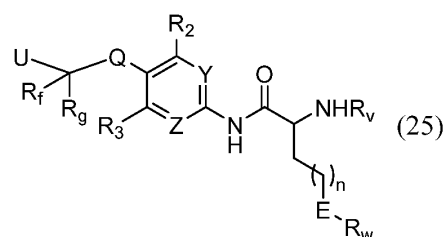
with a compound of formula (24)



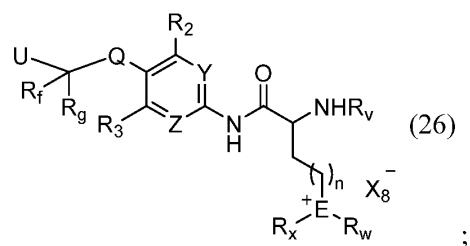
to produce a compound of formula (25)



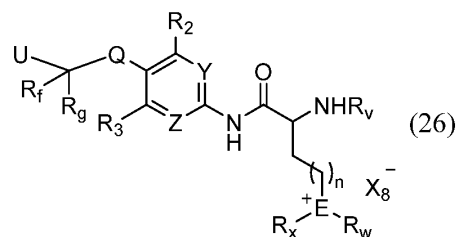
a step 6-B, reacting a compound of formula (25)



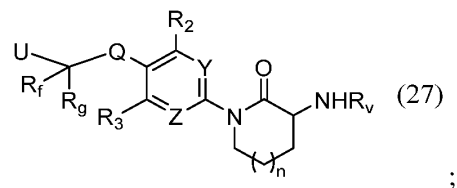
with an alkylating reagent to produce a compound of formula (26)



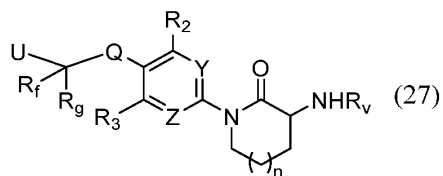
a step 6-C, reacting a compound of formula (26)



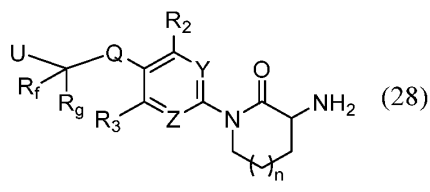
with a non-nucleophilic base to produce a compound of formula (27)



a step 6-D, reacting a compound of formula (27)

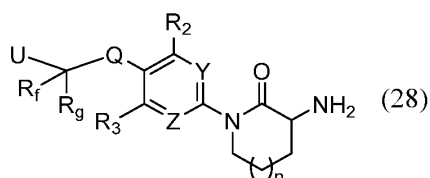


with a deprotecting reagent to produce a compound of formula (28)

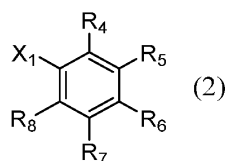


; and

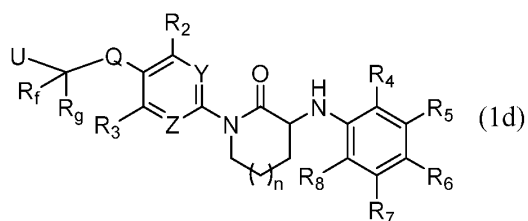
a step 6-E, reacting a compound of formula (28)



with a compound of formula (2)



to produce a compound of formula (1d)



wherein X_8 is F, Cl, Br, or I; E is O or S; R_u is F, Cl, Br, I, OR_p , or SR_p ; R_v is unsubstituted C_1 - C_6 straight or branched alkyl, or a protecting group selected from the group consisting of a benzyl (Bn) group, a (diphenyl)methylene group, a trityl (triphenylmethyl, Tr) group, a (4-methoxyphenyl)diphenylmethylene (methoxytrityl, MMT) group, a formyl group, an acetyl (Ac) group, a benzoyl (Bz) group, a *tert*-butoxycarbonyl (BOC) group, a carbobenzyloxy (Cbz) group, a *p*-methoxybenzylcarbonyl (Moz) group, a 9-fluorenylmethoxycarbonyl (Fmoc) group, a dialkyl phosphoramidate group, a methanesulfonyl

(mesyl, Ms) group, and a *p*-toluenesulfonyl (tosyl, Ts) group; R_w is H or unsubstituted C₁-C₆ straight or branched alkyl; R_x is H or unsubstituted C₁-C₆ straight or branched alkyl; and R_p is H or unsubstituted C₁-C₆ straight or branched alkyl.

57. The process of claim 56, wherein step 6-A is carried out from about 15 °C to about 35 °C; step 6-B is carried out from about 15 °C to about 35 °C; step 6-C is carried out from about -10 °C to about 10 °C; step 6-D is carried out from about 15 °C to about 35 °C; and step 6-E is carried out from about 75 °C to about 125 °C.

58. The process of claim 56, wherein step 6-A is carried out in the presence of a solvent, a peptide coupling reagent, and a base; step 6-B is carried out in the presence of a solvent and an alkylating reagent; step 6-C is carried out in the presence of solvent and a non-nucleophilic base; step 6-D is carried out in the presence of a solvent and a deprotection reagent; and step 6-E is carried out in the presence of a solvent, a catalyst, a ligand, and a base.

59. The process of claim 58, wherein the solvent in step 6-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof; wherein the peptide coupling reagent in step 6-A is selected from the group consisting of DCC, DIC, CIC, BOP, PyBOP, AOP, PyAOP, HBTU, TBTU, HATU, HDMA, T3P, and mixtures thereof; and wherein the base in step 6-A is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof.

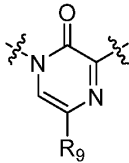
60. The process of claim 58, wherein the solvent in step 6-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl₃, MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and wherein the alkylating reagent in step 6-B is selected from the group consisting of methyl bromide, methyl iodide, ethyl bromide, ethyl iodide, *n*-propyl bromide, *n*-propyl iodide, isopropyl bromide, isopropyl iodide, and mixtures thereof.

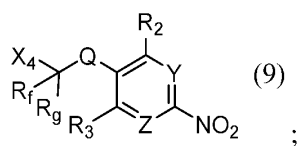
61. The process of claim 58, wherein the solvent in step 6-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the non-nucleophilic base in step 6-C is selected from the group consisting of *N,N*-diisopropylethylamine, 2,6-di-*tert*-butylpiperidine, DBU, DBN, potassium *tert*-butoxide, LDA, LiTMP, NaTMP, KTMP, LiHMDS, NaHMDS, KHMDS, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

62. The process of claim 58, wherein the solvent in step 6-D is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, AcOH, water, and mixtures thereof; and wherein the deprotection reagent in step 6-D is selected from the group consisting of formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof.

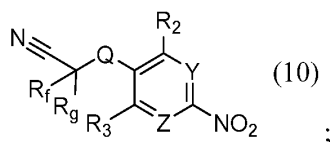
63. The process of claim 58, wherein the solvent in step 6-E is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof; wherein the catalyst in step 6-E is selected from the group consisting of $\text{Pd}_2(\text{dba})_3$, $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{Pd}(\text{PPh}_3)_4$, and mixtures thereof; wherein the ligand in step 6-E is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, BINAP, Chiraphos, Xanthphos, DPEphos, SPANphos, Me-DuPhos, dppm, and mixtures thereof; and wherein the base in step 6-E is selected from the group consisting of ammonia, triethylamine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof.

64. A process for preparing compounds of claim 1,

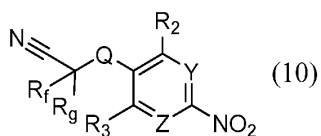
wherein  is , comprising:
a step 7-A, reacting a compound of formula (9)



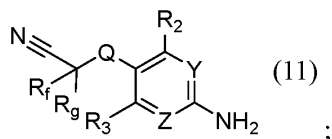
with a cyanide reagent to produce a compound of formula (10)



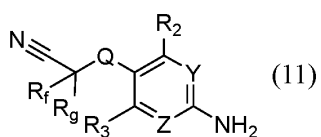
a step 7-B, reacting a compound of formula (10)



with a hydrogenation reagent to produce a compound of formula (11)



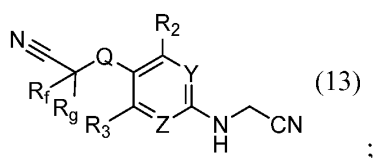
a step 7-C, reacting a compound of formula (11)



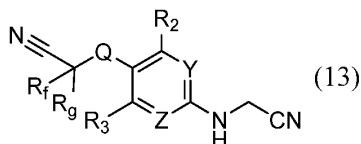
with a compound of formula (12)



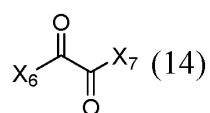
to produce a compound of formula (13)



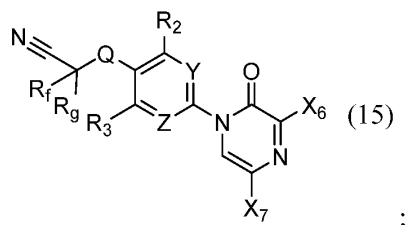
a step 7-D, reacting a compound of formula (13)



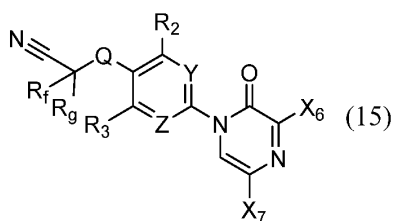
with a compound of formula (14)



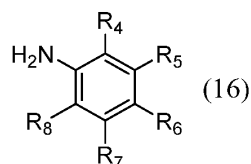
to produce a compound of formula (15)



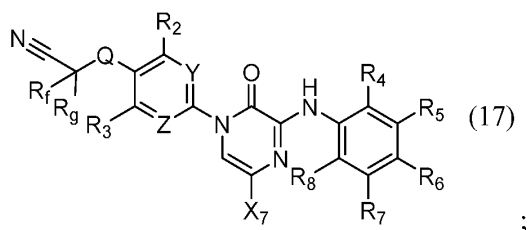
a step 7-E, reacting a compound of formula (15)



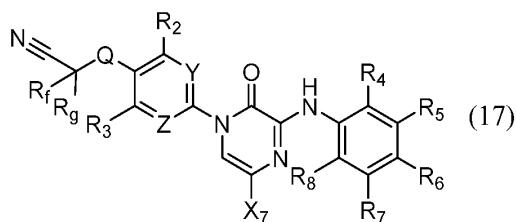
with a compound of formula (16)



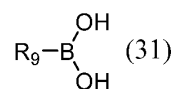
to produce a compound of formula (17)



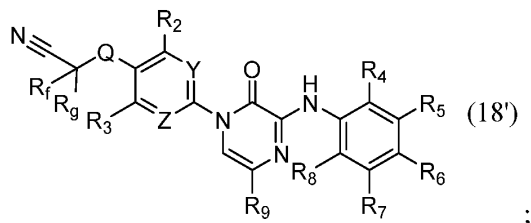
a step 7-F, reacting a compound of formula (17)



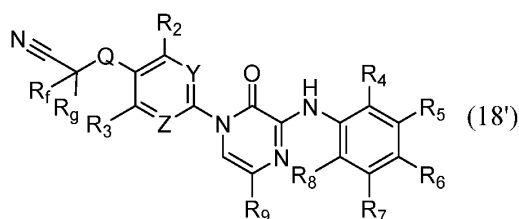
with a palladium catalyst and a compound of formula (31)



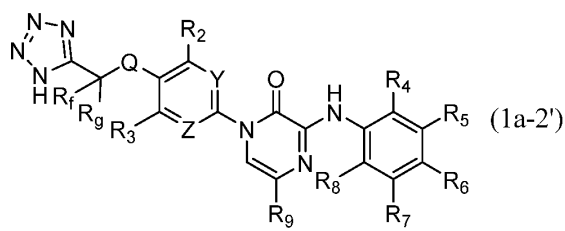
to produce a compound of formula (18')



a step 7-G, reacting a compound of formula (18')



with an azide reagent to produce a compound of formula (1a-2')



wherein X_4 is F, Cl, Br, or I; X_5 is F, Cl, Br, I, or a leaving group L_1 selected from the group consisting of *p*-toluenesulfonate ($-\text{OTs}$), methanesulfonate ($-\text{OMs}$), trifluoromethanesulfonate ($-\text{OSO}_2\text{CF}_3$), nitrate ($-\text{ONO}_2$), and phosphates ($-\text{OPO}(\text{OR})_2$), wherein R is an alkyl group; X_6 is F, Cl, Br, or I; and X_7 is F, Cl, Br, or I.

65. The process of claim **64**, wherein step 7-A is carried from about 30 °C to about 75 °C; step 7-B is carried out from about 15 °C to about 35 °C; step 7-C is carried out from about 50 °C to about 75 °C; step 7-D is carried out from about 75 °C to about 125 °C; step 7-E is carried out from about 15 °C to about 35 °C; step 7-F is carried out from about 50 °C to about 140 °C; and step 7-G is carried out from about 100 °C to about 140 °C.

66. The process of claim **64**, wherein step 7-A is carried out in the presence of a solvent and a cyanide agent; step 7-B is carried out in the presence of a solvent, a

hydrogenation reagent, and a catalyst; step 7-C is carried out in the presence of a solvent and a base; step 7-D is carried out in the presence of a solvent; step 7-E is carried out in the presence of a solvent and a base; step 7-F is carried out in the presence of a solvent; and step 7-G is carried out in the presence of a solvent, an azide reagent, and a salt.

67. The process of claim **66**, wherein the solvent in step 7-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, DMSO, and mixtures thereof; and wherein the cyanide reagent in step 7-A is selected from the group consisting of sodium cyanide, potassium cyanide, and mixtures thereof.

68. The process of claim **66**, wherein the solvent in step 7-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; wherein the hydrogenation reagent in step 7-B is selected from the group consisting of hydrogen (H_2), formic acid, isopropanol, and mixtures thereof; and wherein the catalyst is selected from the group consisting of Wilkinson's catalyst, platinum(0), palladium(0), Pt/C, Pd/C, and mixtures thereof.

69. The process of claim **66**, wherein the solvent in step 7-C is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, and mixtures thereof; and the base in step 7-C is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride potassium hydride, and mixtures thereof.

70. The process of claim **66**, wherein the solvent in step 7-D is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof.

71. The process of claim **66**, wherein the solvent in step 7-E is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, chlorobenzene, and mixtures thereof; and wherein the base in step 7-E is selected from the group consisting of ammonia, triethylamine, *N,N*-diisopropylethylamine, potassium *tert*-

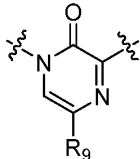
butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, lithium hydride, sodium hydride, potassium hydride, and mixtures thereof.

72. The process of claim **66**, wherein the solvent in step 7-F is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, water, and mixtures thereof.

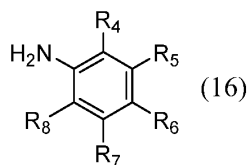
73. The process of claim **64**, wherein the palladium catalyst in step 7-F is selected from the group consisting of palladium(II) acetate ($\text{Pd}(\text{OAc})_2$), palladium(II) acetylacetonate ($\text{Pd}(\text{acac})_2$), tris(dibenzylideneacetone)dipalladium(0) ($\text{Pd}_2(\text{dba})_3$), dichlorobis(triphenylphosphine)palladium(II) ($\text{PdCl}_2(\text{PPh}_3)_2$), tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$), palladium(0) (Pd), palladium(0) on carbon (Pd/C), dichloro(1,1'-bis(di-*tert*-butylphosphino)ferrocene)palladium(II) ($\text{Pd}(\text{dtbpf})\text{Cl}_2$), and mixtures thereof.

74. The process of claim **66**, wherein the solvent in step 7-G is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, DCM, CHCl_3 , MeCN, MeOH, EtOH, *i*PrOH, benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mixtures thereof; wherein the azide reagent in step 7-G is selected from the group consisting of lithium azide, sodium azide, potassium azide, trimethyltin azide, triethyltin azide, tripropyltin azide, tributyltin azide, and mixtures thereof; and wherein the salt in step 7-G is selected from the group consisting of ammonium fluoride, ammonium chloride, ammonium bromide, ammonium iodide, and mixtures thereof.

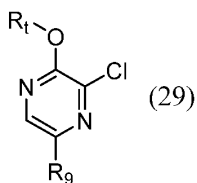
75. A process for preparing compounds of claim **1**,

wherein  is , comprising:

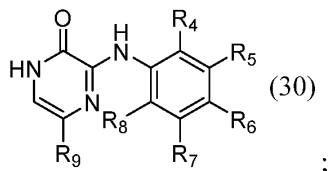
a step 8-A, reacting a compound of formula (16)



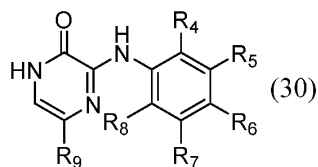
with a compound of formula (29)



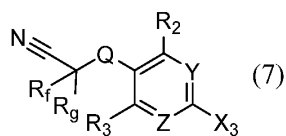
to produce a compound of formula (30)



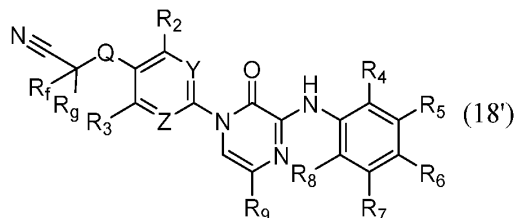
a step 8-B, reacting a compound of formula (30)



with a compound of formula (7)



to produce a compound of formula (18')



wherein X₃ is F, Cl, Br, or I; and

R_f is H or unsubstituted C₁-C₆ straight or branched alkyl.

76. The process of claim **75**, wherein step 8-A is carried out from about 50 °C to about 125 °C; and step 8-B is carried out from about 50 °C to about 125 °C.

77. The process of claim **75**, wherein step 8-A is carried out in the presence of a solvent and an acid; step 8-B is carried out in the presence of a solvent, a copper salt, a base, and a ligand.

78. The process of claim **77**, wherein the solvent in step 8-A is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, EtOAc, 1,4-dioxane, DCM, CHCl₃, MeCN, AcOH, and mixtures thereof; and

wherein the acid in step 8-A is selected from the group consisting of formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof.

79. The process of claim **77**, wherein the solvent in step 8-B is selected from the group consisting of DMF, DMA, NMP, THF, 2-MeTHF, 1,4-dioxane, EtOAc, DCM, CHCl₃, MeCN, and mixtures thereof;

wherein the copper salt in step 8-B is selected from the group consisting of CuF, CuCl, CuBr, CuI, and mixtures thereof;

wherein the base in step 8-B is selected from the group consisting of ammonia, triethyl amine, *N,N*-diisopropylethylamine, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, trisodium phosphate, tripotassium phosphate, and mixtures thereof; and

wherein the ligand in step 8-B is selected from the group consisting of *N,N'*-DMEDA, 1,10-phenanthroline, 2,2'-bipyridine, and mixtures thereof.