from halogen, hydroxyl, and C_{1-6} alkyl), phenyl, heterocycle (optionally substituted by one, two or three substituents independently selected from halogen, hydroxyl, and C_{1-6} alkyl), and heteroaryl;

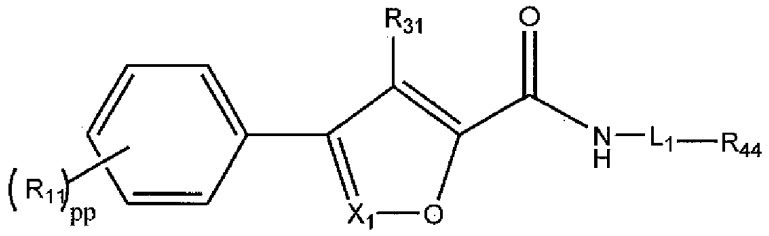
R_{ll} is selected for each occurrence from the group consisting of halogen, hydroxyl, C_{1-6} alkyl (optionally substituted by one, two, or three substituents each independently selected from halogen, hydroxyl, and C_{3-6} cycloalkyl) and heterocycle (optionally substituted by one, two or three substituents independently selected from halogen, hydroxyl, and C_{1-6} alkyl);

R' and R'' are each independently selected for each occurrence from H and C_{1-4} alkyl or taken together with the nitrogen to which they are attached form a heterocyclic ring;

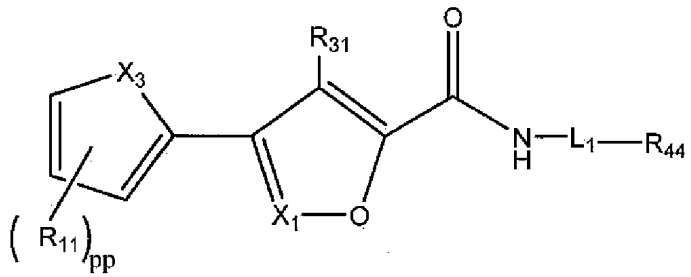
w is 0, 1 or 2; and

R_{hh} is selected for each occurrence from the group consisting of H, C_{1-6} alkyl and C_{3-6} cycloalkyl.

[7a] In one aspect of the present disclosure, there is provided a compound represented by formula III or IV:



III



IV

and pharmaceutically acceptable salts, stereoisomers, and prodrugs thereof, wherein:

X_1 is N or CR_{33};

X_3 is selected from the group consisting of O, S, and NR_{hh};

pp is 1, 2, or 3;

R_{11} is independently selected for each occurrence from the group consisting of hydrogen, halogen, and C_{1-4} alkyl (optionally substituted by one, two or three halogens);

R_{31} is selected from the group consisting of hydrogen, halogen, and C_{1-4} alkyl;

R_{33} is selected from the group consisting of H, halogen, C_{1-4} alkyl, and –NR'R'' wherein R' and R'' are each independently selected for each occurrence from H and C_{1-4} alkyl or taken together with the nitrogen to which they are attached form a heterocyclic ring;

L_1 is selected from the group consisting of C_{1-6} alkylene, C_{3-6} cycloalkylene, C_{3-6} cycloalkylene-C_{1-4} alkylene, C_{1-3} alkylene-NR_{hh}-$S(O)_w$-, - C_{1-3} alkylene-$S(O)_w$-NR_{hh}-, C_{3-6} cycloalkylene-C_{0-2} alkylene-$S(O)_w$-NR_{hh}, and C_{3-6} cycloalkylene- C_{0-2} alkylene NR_{hh}-$S(O)_w$-, wherein L_1 may be optionally substituted by one, two or three substituents selected from the group consisting of halogen, hydroxyl, and C_{1-3} alkyl (optionally substituted by one, two or three substituents each selected independently from R_{ff});

R_{44} is selected from the group consisting of H, halogen, hydroxyl, C_{1-3} alkoxy, phenyl, -O-phenyl, -NR'-phenyl, heterocycle, and a 5-6 membered monocyclic or 8-10 membered bicyclic heteroaryl having one, two or three heteroatoms each selected from O, N, and S; wherein phenyl, -O-phenyl, -NR'-phenyl, heterocycle and heteroaryl may be optionally substituted by one or two substituents each selected independently from R_{gg};

R_{ff} is selected for each occurrence from group consisting of halogen, hydroxyl, C_{1-4} alkyl, C_{1-4} alkyoxy, C_{2-4} alkenyl, C_{3-6} cycloalkyl, –NR'R'', -NR'-$S(O)_w$-C_{1-3} alkyl, $S(O)_w$-NR'R'', and -$S(O)_w$-C_{1-3} alkyl, where w is 0, 1, or 2, wherein C_{1-4} alkyl, C_{1-4} alkyoxy, C_{2-4} alkenyl and C_{3-6} cycloalkyl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, –NR'R'', -NR'-$S(O)_w$-C_{1-3} alkyl, $S(O)_w$-NR'R'', and -$S(O)_w$-C_{1-3} alkyl;

R_{gg} is selected for each occurrence from the group consisting of halogen, hydroxyl, cyano, -NR'R'', -NR'-$S(O)_w$-C_{1-3} alkyl, -$S(O)_w$-NR'R'', and -$S(O)_w$-C_{1-3} alkyl, where w is 0, 1, or 2; heterocycle, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} alkenyl, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} alkenyl are optionally substituted by one, two, or three substituents each independently selected from R_{jj}; and heterocycle is optionally substituted by one, two, or three substituents each independently selected from R_{ll};

R_{jj} is selected for each occurrence from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy (optionally substituted by one, two, or three substituents each independently selected from R_{kk}); C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, heterocycle, C(O)OH, -$C(O)OC_{1-6}$ alkyl, –NR'R'', -NR'-$S(O)_w$-C_{1-3} alkyl, -$S(O)_w$-NR'R'', and -$S(O)_w$-C_{1-3} alkyl, where w is 0, 1, or 2;

R_{kk} is selected for each occurrence from the group consisting of halogen, hydroxyl, C_{1-6} alkyl (optionally substituted by one, two, or three substituents each independently selected from halogen, hydroxyl, C_{3-6} cycloalkyl, and heterocycle (optionally substituted by C_{1-6} alkyl)), C_{3-6} cycloalkyl (optionally substituted by one, two, or three substituents each independently selected from halogen, hydroxyl, and C_{1-6} alkyl), phenyl, heterocycle (optionally substituted by one, two or three substituents independently selected from halogen, hydroxyl, and C_{1-6} alkyl), and heteroaryl;

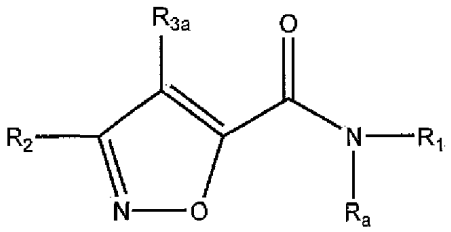
R_{ll} is selected for each occurrence from the group consisting of halogen, hydroxyl, C_{1-6} alkyl (optionally substituted by one, two, or three substituents each independently selected from halogen, hydroxyl, and C_{3-6} cycloalkyl) and heterocycle (optionally substituted by one, two or three substituents independently selected from halogen, hydroxyl, and C_{1-6} alkyl);

R' and R'' are each independently selected for each occurrence from H, C_{1-4} alkyl, phenyl and heterocycle;

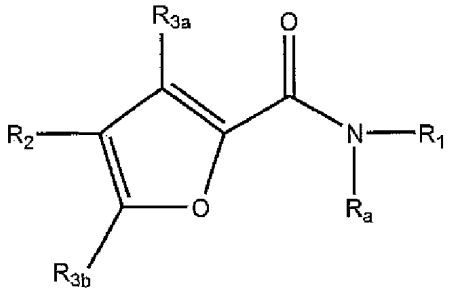
w is 0, 1 or 2; and

R_{hh} is selected for each occurrence from the group consisting of H, C_{1-6} alkyl and C_{3-6} cycloalkyl.

[07b] In another aspect of the present disclosure, there is provided a compound having the Formula (Ia) or the Formula (IIa):



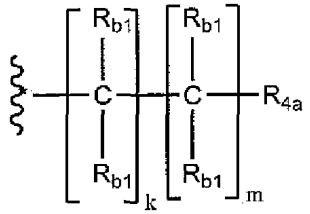
(Ia);



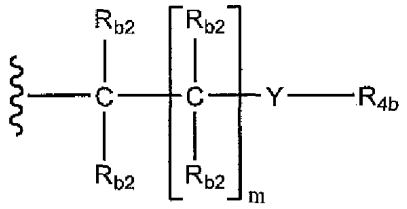
(IIa);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_1 is selected from the group consisting of:



and



;

R_2 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl;

R_{3a} and R_{3b} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted aryl, halo, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$, $(C=NR_d)R_c$, optionally substituted heterocyclic and optionally substituted heteroaryl;

R_{4a} is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted aryl, halo, OR_c, $S(O)_nR_c$, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)R_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nR_dR_d$, $NR_dS(O)_nR_c$, $S(O)NR_dR_d$, $OC(O)OR_c$, $(C=NR_d)R_c$, optionally substituted heterocyclic and optionally substituted heteroaryl;

R_{4b} is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted aryl, optionally substituted heterocyclic and optionally substituted heteroaryl;

R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_c$, $C(O)R_c$, $C(O)C(O)R_c$ and $S(O)_nR_c$;

or alternatively, R_a and the nitrogen atom to which it is attached is taken together with an adjacent $C(R_{b1})(R_{b1})$ or $C(R_{b2})(R_{b2})$ to form an optionally substituted, 4- to 12-membered heterocyclic ring containing one or more ring nitrogen atoms, wherein said heterocyclic ring optionally contains one or more ring heteroatoms selected from oxygen and sulfur;

each R_{b1} and R_{b2} is independently selected for each occurrence from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_c, NR_dR_d, $C(O)OR_c$, NO_2, CN, $C(O)R_c$, $C(O)C(O)R_c$, $C(O)NR_dR_d$, $NR_dC(O)R_c$, $NR_dS(O)_nR_c$, $N(R_d)(COOR_c)$, $NR_dC(O)C(O)R_c$, $NR_dC(O)NR_dR_d$, $NR_dS(O)_nNR_dR_d$, $NR_dS(O)_nR_c$, $S(O)_nR_c$, $S(O)_nNR_dR_d$, $OC(O)OR_c$ and $(C{=}NR_d)R_c$; or alternatively, two geminal R_{b1} groups or two geminal R_{b2} groups and the carbon to which they are attached are taken together to form a C(O) group, or yet alternatively, two geminal R_{b1} groups or two geminal R_{b2} groups are taken together with the carbon atom to which they are attached to form a spiro C_3-C_{12} cycloalkyl, a spiro C_3-C_{12} cycloalkenyl, a spiro heterocyclic, a spiro aryl or spiro heteroaryl, each optionally substituted;

Y is selected from the group consisting of $S(O)_n$, NR_d, $NR_dS(O)_n$, $NR_dS(O)_nNR_d$, $NR_dC(O)$, $NR_dC(O)O$, $NR_dC(O)C(O)$, $NR_dC(O)NR_d$, $S(O)_nNR_d$, and O;

each R_c is independently selected for each occurrence from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

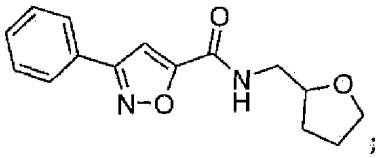
each R_d is independently selected for each occurrence from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_1-C_{10} alkoxy, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two geminal R_d groups are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl;

k is 0 or 1;

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

each n is independently 0, 1 or 2.

[7c] In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of: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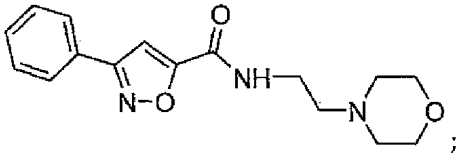
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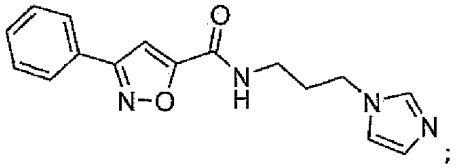
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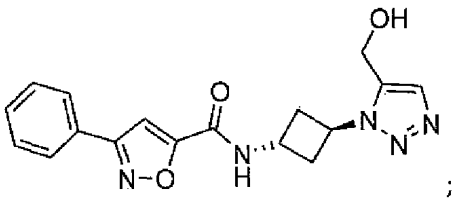
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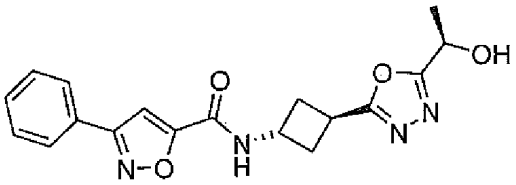
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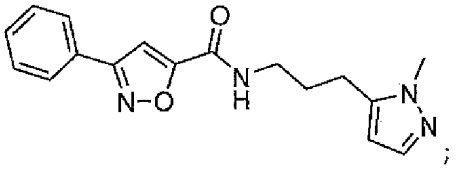
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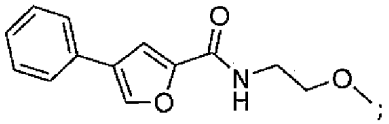
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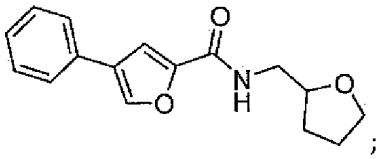
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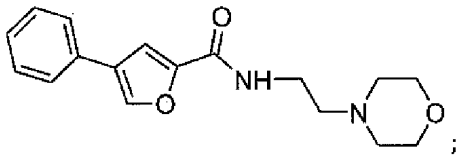
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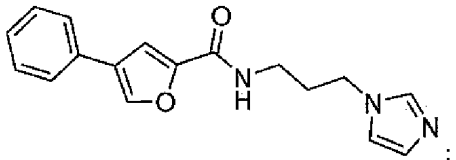
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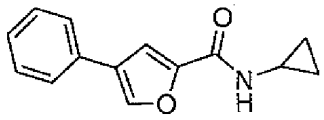
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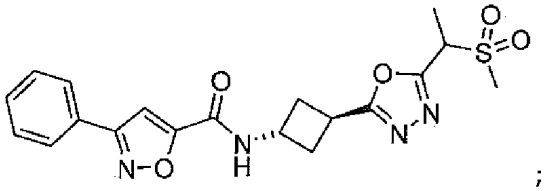
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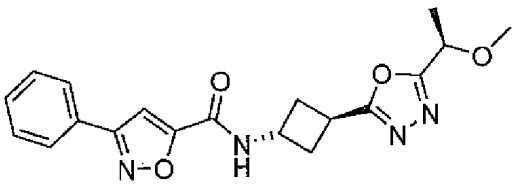
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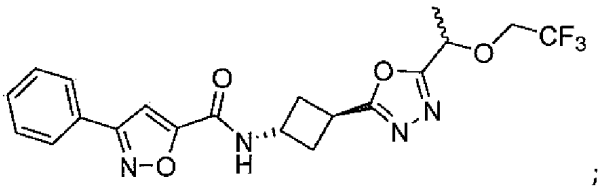
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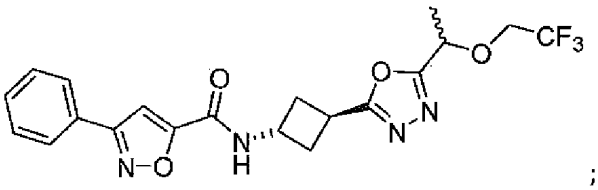
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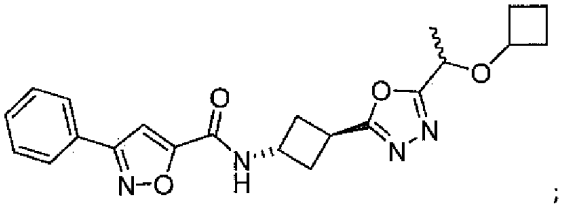
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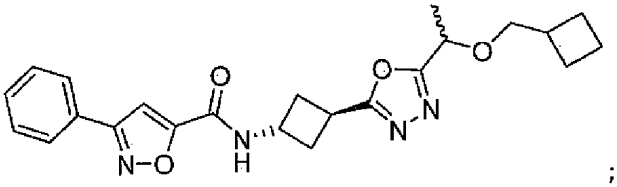
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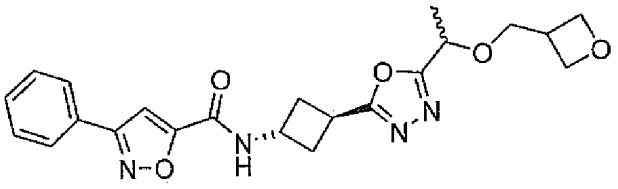
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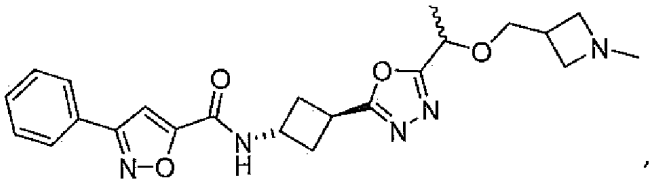
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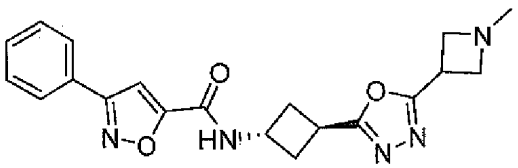
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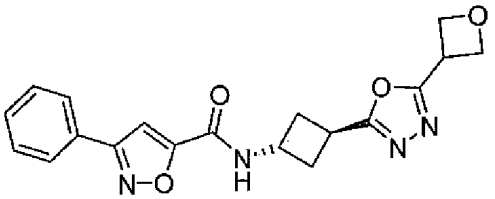
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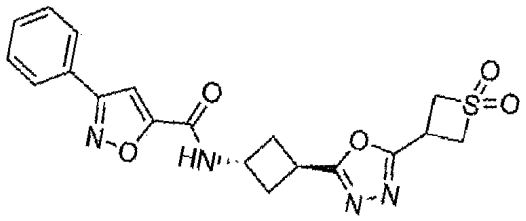

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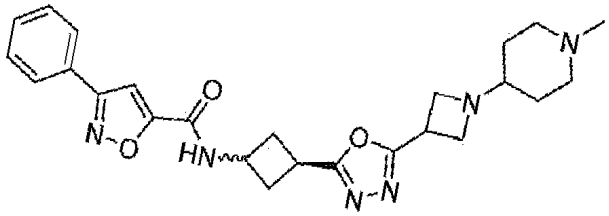

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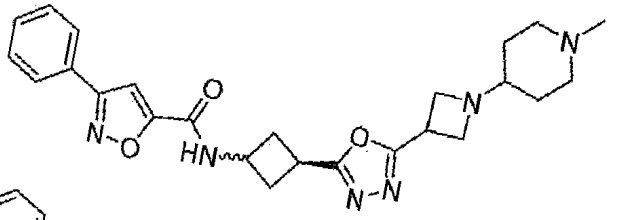

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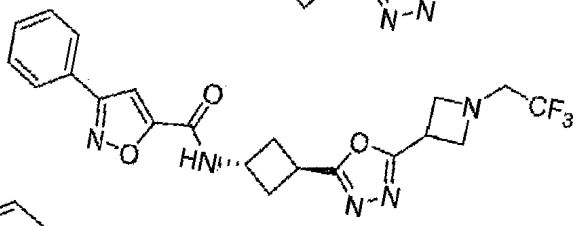

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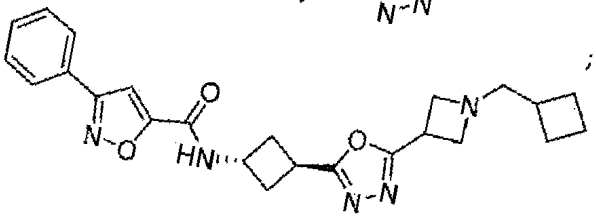

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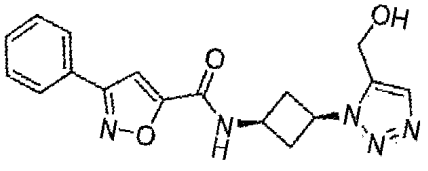

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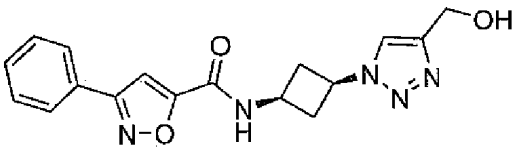
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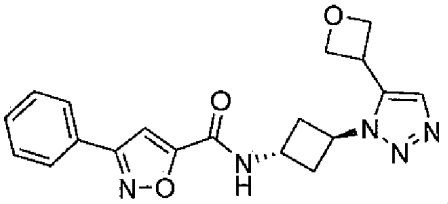
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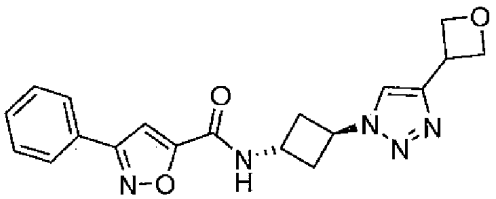
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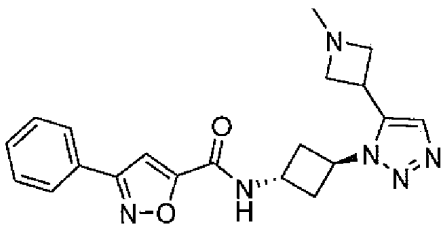
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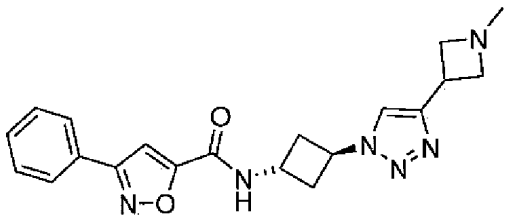
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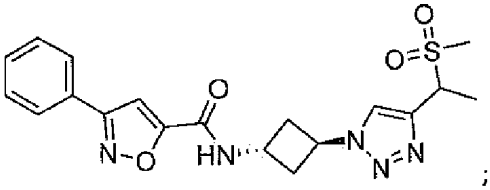
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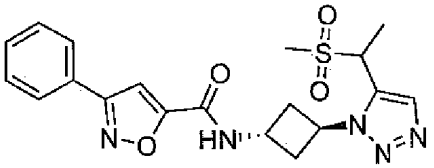
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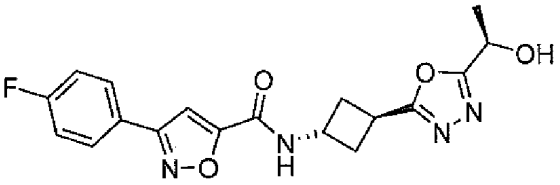
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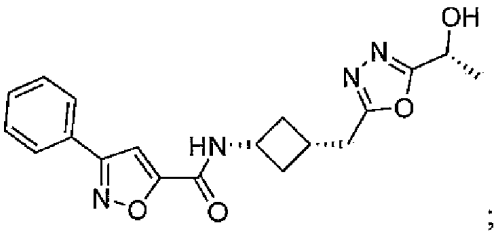
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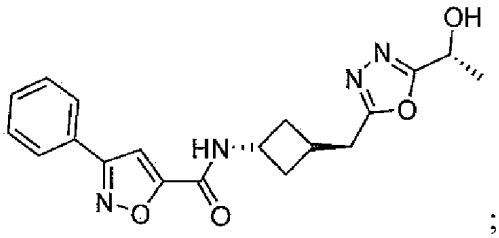
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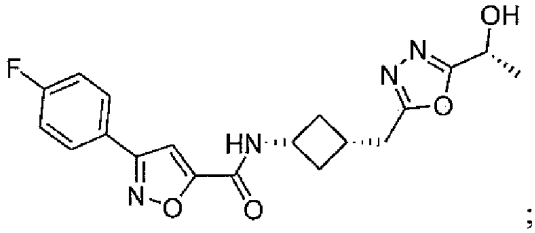
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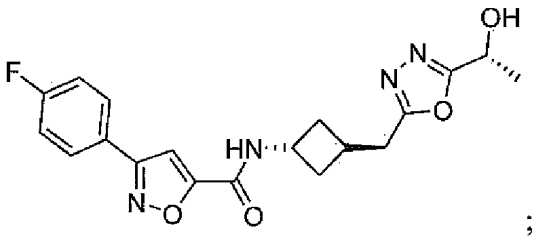
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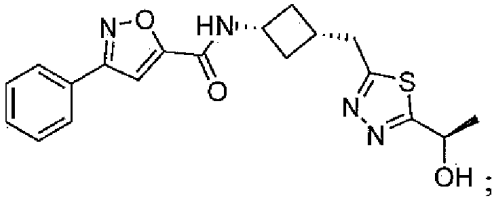
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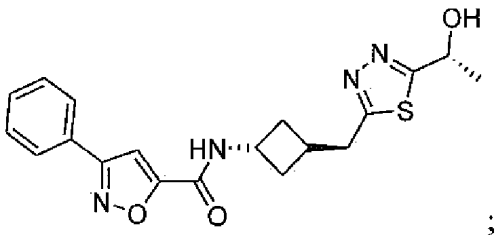
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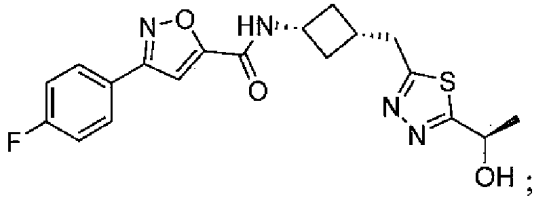
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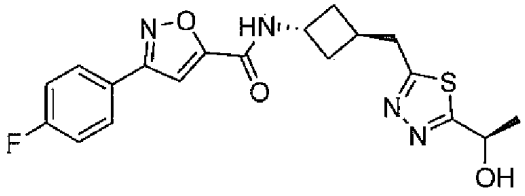
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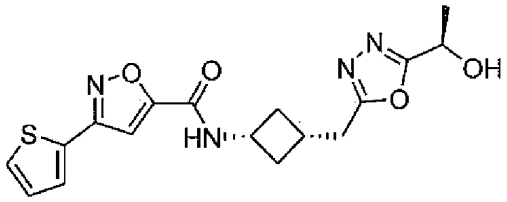
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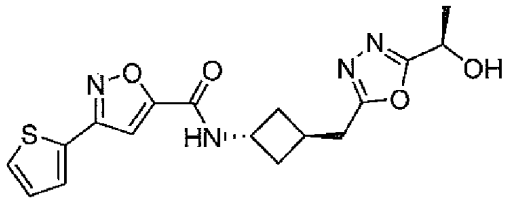
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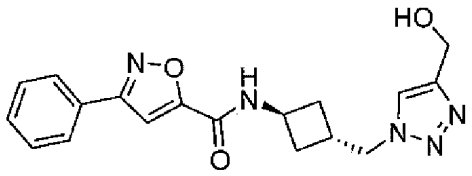
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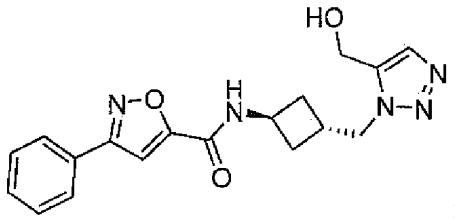
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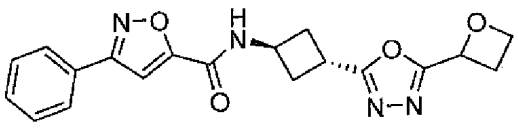
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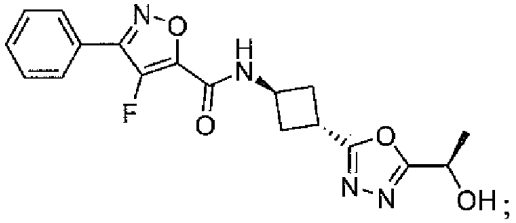
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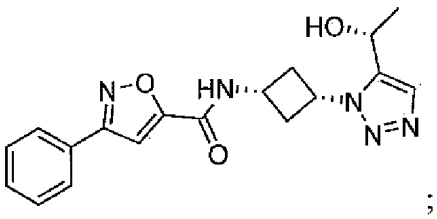
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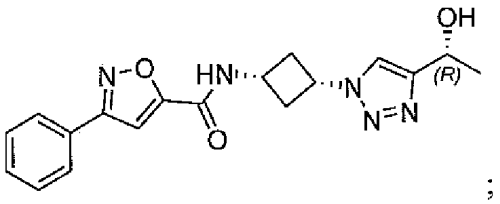
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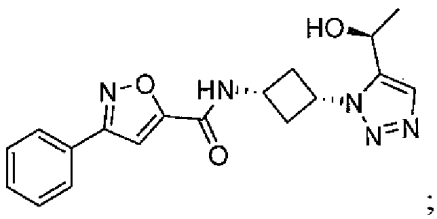
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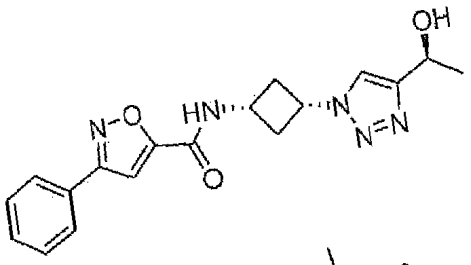
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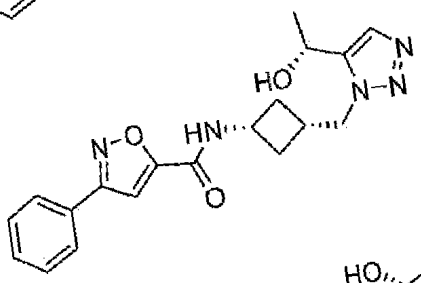
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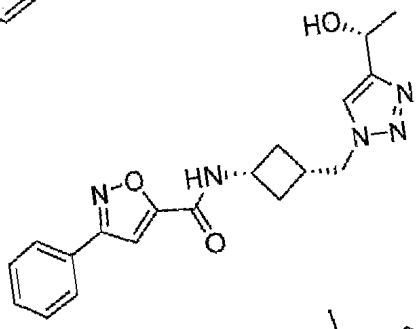
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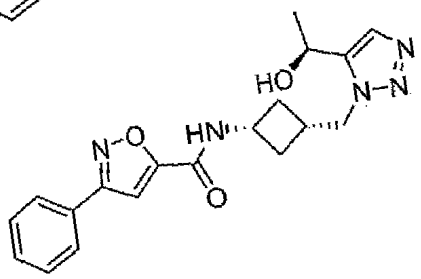
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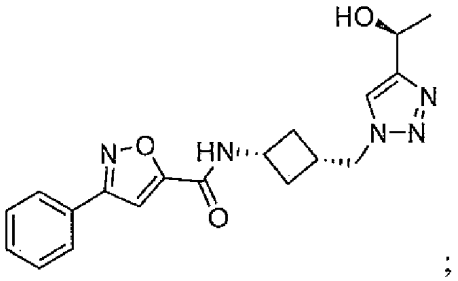
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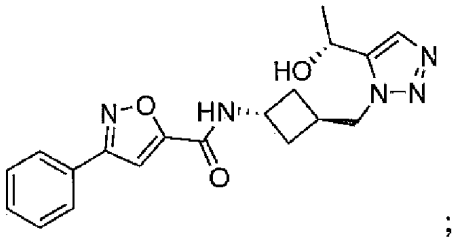
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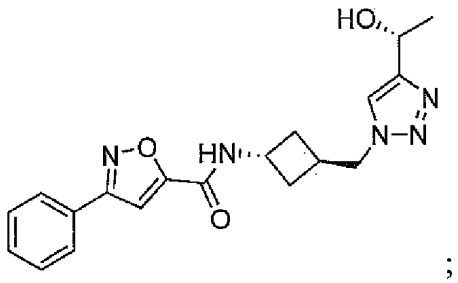
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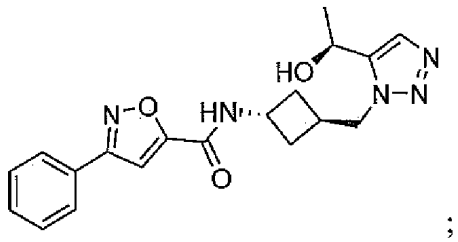
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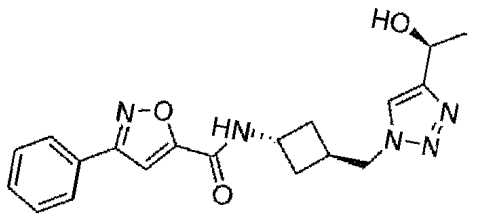

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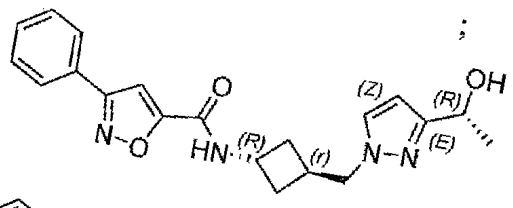

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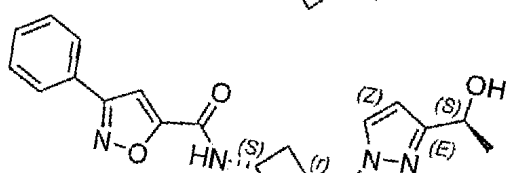

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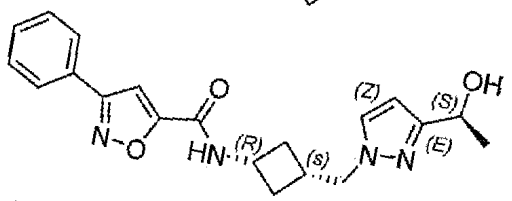

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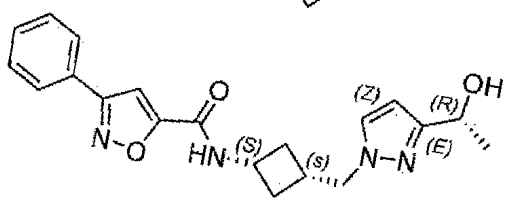

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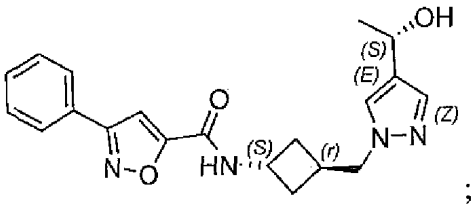
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(Z)
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(S)
(r)
N–N

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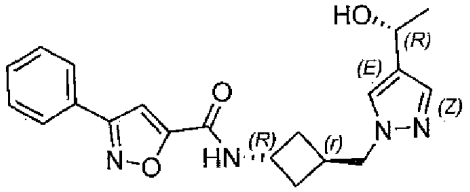
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(R)
(r)
N–N

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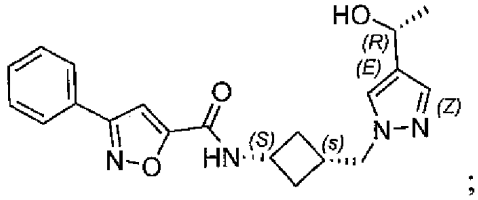
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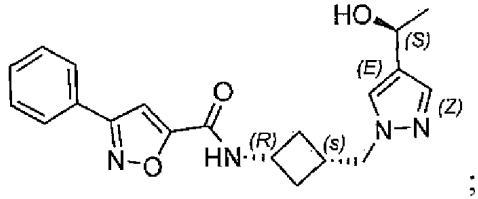
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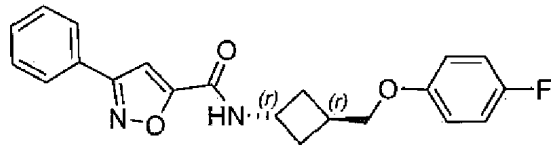
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(r)
O
F

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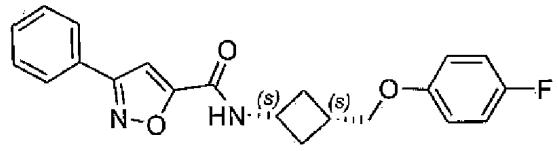
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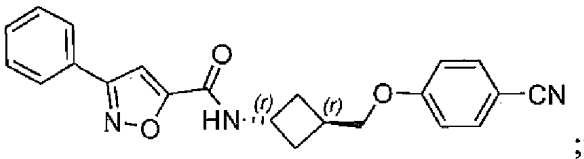

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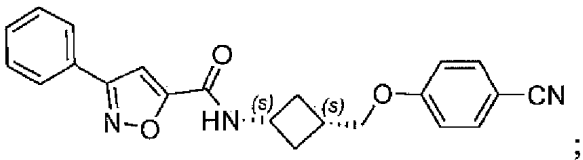

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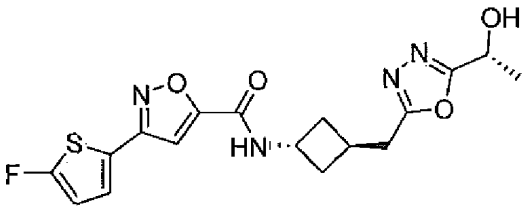

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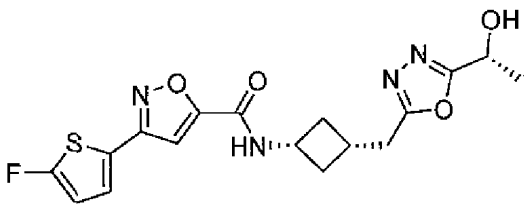


;

and pharmaceutically acceptable salts thereof. .

[7d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier or excipient.

[7e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof, wherein said medicament is to be administered to said subject.

[7f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.

[7g] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use in enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof.

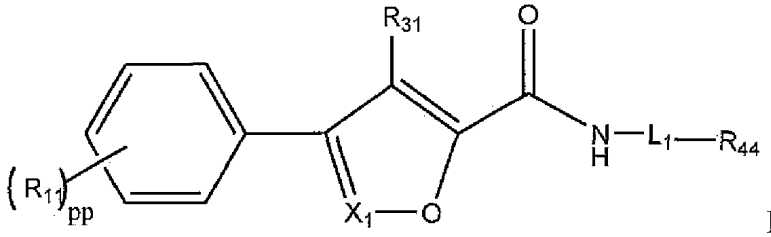
[8] Also contemplated herein are pharmaceutical compositions that include a disclosed compound (such as those compounds having disclosed formulas such as Formula (Ia), (IIa), (Ib), (IIb), (III), or (IV)) and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the compositions can include at least one additional CFTR modulator as described anywhere herein or at least two additional CFTR modulators, each independently as described anywhere herein.

[9] In additional embodiments, a method of enhancing (e.g., increasing) cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof is provided comprising administering to said subject an effective amount of a disclosed compound of e.g., Formula (Ia), (IIa), (Ib), (IIb), (III), or (IV).

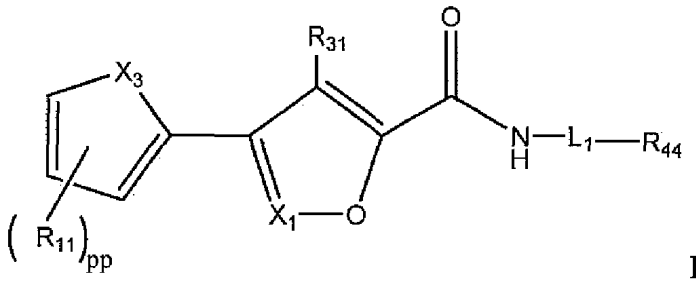
[10] In certain of these embodiments, the activity of one or more (e.g., one or two) mutant CFTRs (e.g., ΔF508, S549N, G542X, G551D, R117H, N1303K, W1282X, R553X, 621+1G>T, 1717-1G>A, 3849+10kbC>T, 2789+5G>A, 3120+1G>A, I507del, R1162X, 1898+1G>A, 3659delC, G85E, D1152H, R560T, R347P, 2184insA, A455E, R334W, Q493X, and 2184delA CFTR) is enhanced (e.g., increased). In certain embodiments, ΔF508 CFTR activity is enhanced (e.g., increased). In other embodiments, the activities of two mutant

What is claimed is:

1. A compound represented by formula III or IV:



III



IV

and pharmaceutically acceptable salts, stereoisomers, and prodrugs thereof, wherein:

X_1 is N or CR_{33};

X_3 is selected from the group consisting of O, S, and NR_{hh};

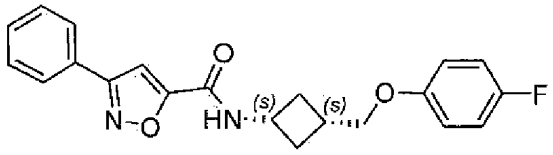
pp is 1, 2, or 3;

R_{11} is independently selected for each occurrence from the group consisting of hydrogen, halogen, and C_{1-4} alkyl (optionally substituted by one, two or three halogens);

R_{31} is selected from the group consisting of hydrogen, halogen, and C_{1-4} alkyl;

R_{33} is selected from the group consisting of H, halogen, C_{1-4} alkyl, and –NR'R'' wherein R' and R'' are each independently selected for each occurrence from H and C_{1-4} alkyl or taken together with the nitrogen to which they are attached form a heterocyclic ring;

L_1 is selected from the group consisting of C_{1-6} alkylene, C_{3-6} cycloalkylene, C_{3-6} cycloalkylene-C_{1-4} alkylene, C_{1-3} alkylene-NR_{hh}-$S(O)_w$-, - C_{1-3} alkylene-$S(O)_w$-NR_{hh}-, C_{3-6}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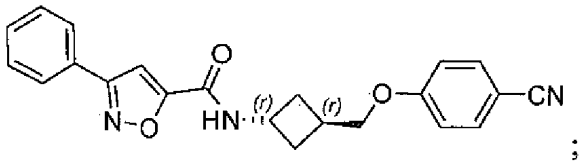
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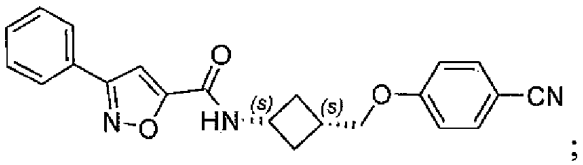
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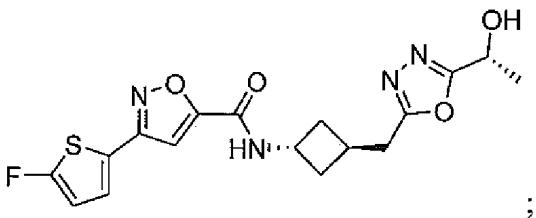
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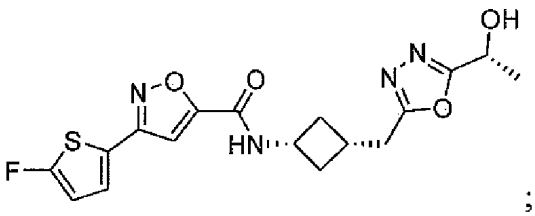
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and pharmaceutically acceptable salts thereof. .

37. A pharmaceutical composition comprising a compound of any one of claims 1 to 36 and a pharmaceutically acceptable carrier or excipient.

38. The pharmaceutical composition of claim 37, wherein the composition further comprises at least one additional CFTR modulator.

39. The pharmaceutical composition of claim 37, wherein the composition further comprises at least two additional CFTR modulators.

40. Use of a compound of any one of claims 1 to 36, or a pharmaceutical composition of any one claims 37-39, in the manufacture of a medicament for enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof, wherein said medicament is to be administered to said subject.

41. The use of claim 40, wherein the activity of a mutant CFTR is enhanced.

42. The use of claim 41, wherein the mutant CFTR is selected from the group consisting ΔF508, S549N, G542X, G551D, R117H, N1303K, W1282X, R553X, 621+1G>T, 1717-1G>A, 3849+10kbC>T, 2789+5G>A, 3120+1G>A, I507del, R1162X, 1898+1G>A, 3659delC, G85E, D1152H, R560T, R347P, 2184insA, A455E, R334W, Q493X, and 2184delA CFTR.

43. The use of claim 42, wherein ΔF508 CFTR activity is enhanced.

44. The use of any one of claims 40-43, wherein the subject is suffering from a disease associated with decreased CFTR activity.

45. The use of claim 44, wherein the disease is selected from the group consisting of cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, A-β-lipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolyis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, Sjogren's syndrome, familial hypercholesterolemia, I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, Huntington's disease, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidoluysian, myotonic dystrophy, hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, and Straussler-Scheinker syndrome.

46. The use of claim 45 wherein the disease is cystic fibrosis.

47. The use of claim 46, wherein the subject is a human patient.

48. The use of claim 47, wherein an additional CFTR modulator is to be further administered to said subject.

49. The use of claim 45, wherein at least two additional CFTR modulators are to be further administered to said subject.

50. The use of any one of claims 48 or 49, wherein at least one CFTR modulator is a CFTR corrector or potentiator.

51. The use of claim 50, wherein each CFTR corrector or potentiator is independently selected from the group consisting of VX-770 (Ivacaftor), VX-809 (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid, VX661 ((R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropane-1-carboxamide), VX-152, VX-440, GLPG-2222, GLPG2665, and GLPG-1837.

52. The use of claim 50, wherein the CFTR corrector is selected from the group consisting of VX-809, VX-661, GLPG-2222 and VX-983 and the CFTR potentiator is selected from the group consisting of GLPG-1837, ivacaftor and genistein.

53. The use of claim 51, wherein one of the at least two additional therapeutic agents is a CFTR corrector and the other is a CFTR potentiator.

54. A method of identifying a candidate agent that increases CFTR activity, comprising:

a) contacting a cell that expresses a CFTR protein with the candidate agent and a compound of any one of claims 1 to 36;

b) measuring the CFTR activity in the cell in the presence of the candidate agent and the compound of any one of claims 1 to 36; and

comparing the CFTR activity to that in the absence of the test agent, wherein an increase in CFTR activity in the presence of the test agent indicates that the agent increases CFTR activity.

55. The method of claim 54, wherein the cell expresses a mutant CFTR protein.

56. The method of any one of claims 54 and 55, wherein CFTR activity is measured by measuring chloride channel activity of the CFTR, and/or other ion transport activity.

57. The method of claim 56, wherein the method is high-throughput.

58. The method of any one of claims 53-56, wherein the candidate agent is a CFTR corrector or a CFTR potentiator.

59. Use of a compound of any one of claims 1-36, or a pharmaceutical composition of any one of claims 37-39, in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.

60. The compound of any one of claims 1 to 36, or a pharmaceutical composition of any one claims 37-39, for use in enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof.