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;

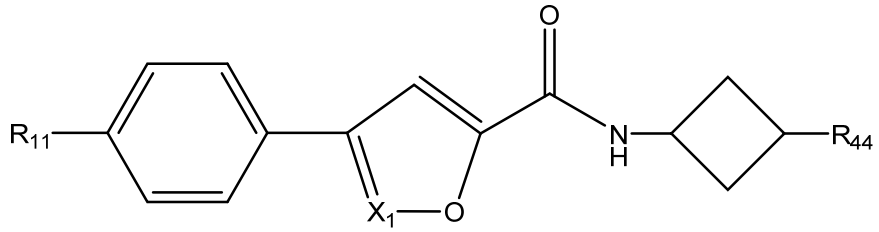
R_{ll} is selected for each occurrence from the group consisting of halogen, hydroxyl, C_{1-6} alkyl (optionally substituted by one, two, or three substituents each independently selected from halogen, hydroxyl, and C_{3-6} cycloalkyl) and heterocycle (optionally substituted by one, two or three substituents 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, the present disclosure refers to A compound represented by formula:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

X_1 is N;

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_{44} is a 5-6 membered monocyclic heteroaryl having one, two or three heteroatoms each selected from O, N, and S; wherein heteroaryl may be optionally substituted by one or two substituents each selected independently from R_{gg};

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;

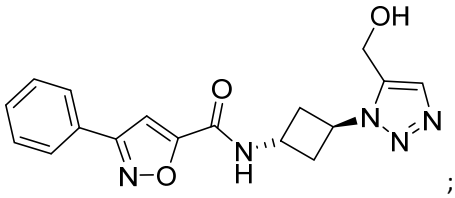
R_{ll} is selected for each occurrence from the group consisting of:

- 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; and

w is 0, 1 or 2.

[7b] In another aspect, the present disclosure refers to a compound selected from the group consisting of:



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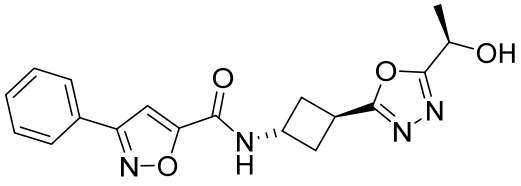

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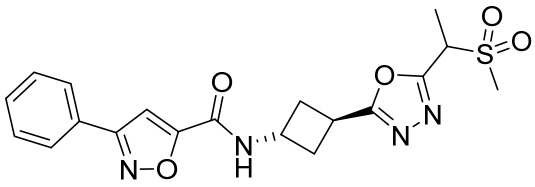
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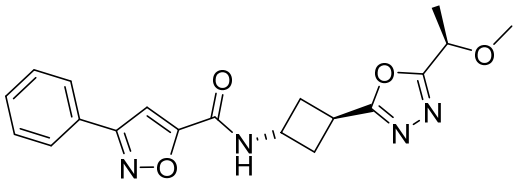
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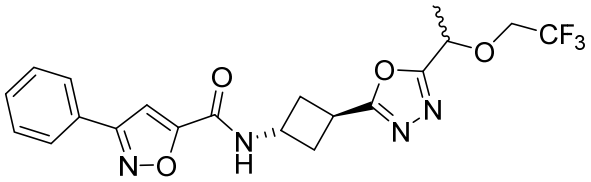
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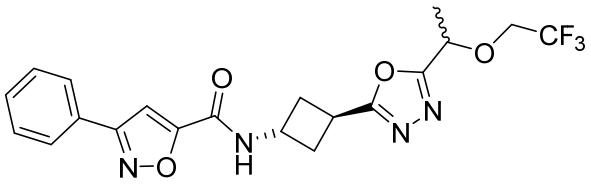
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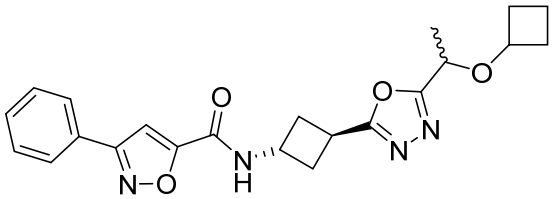
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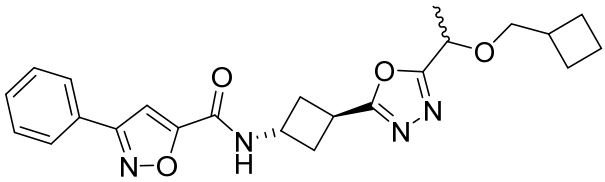
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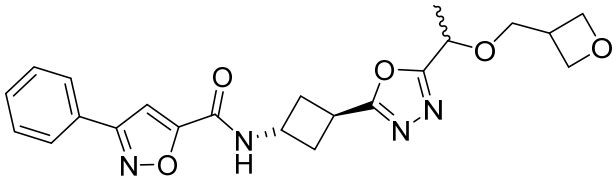
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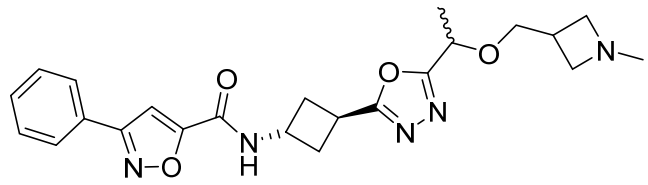
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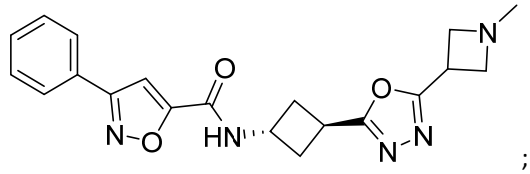
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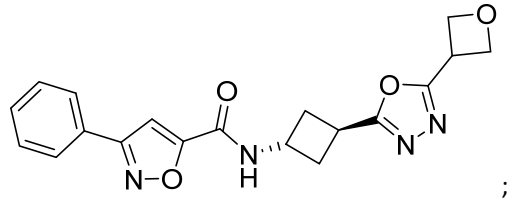
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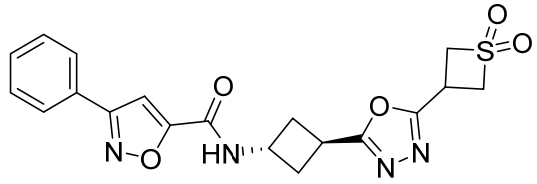
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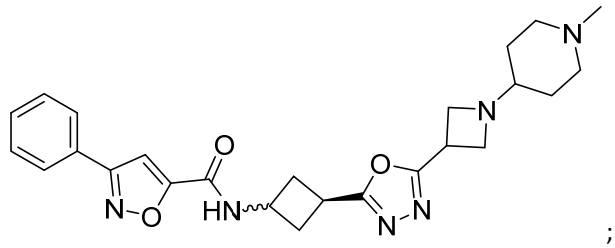
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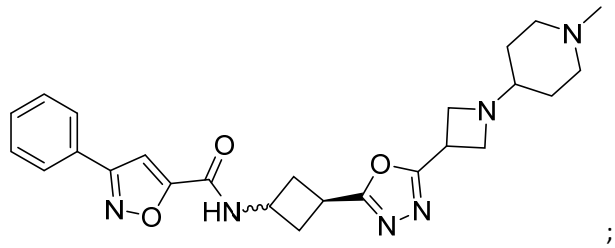
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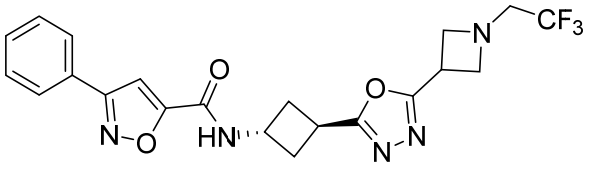
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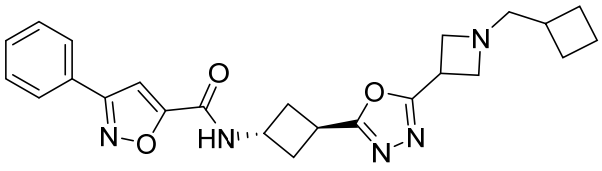
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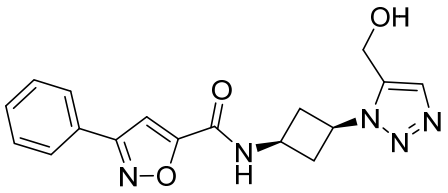
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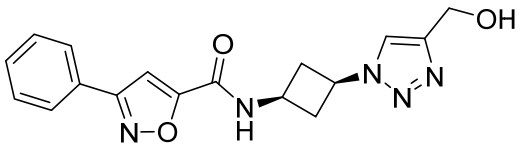
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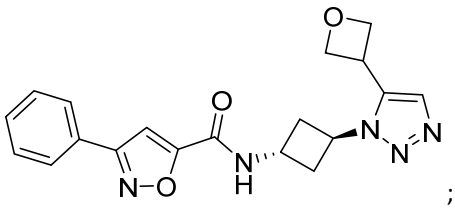
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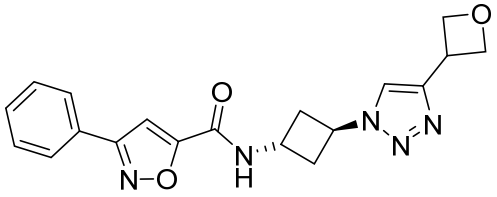
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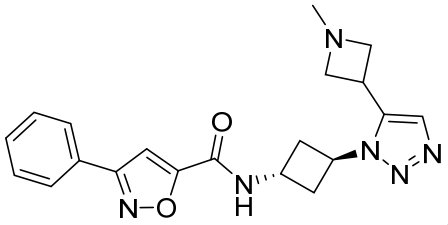
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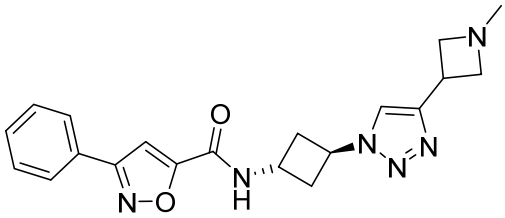
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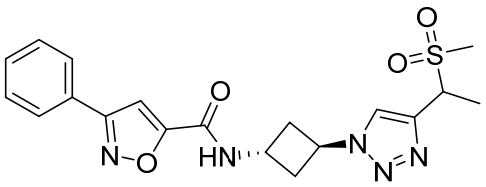
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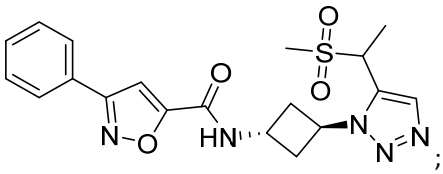
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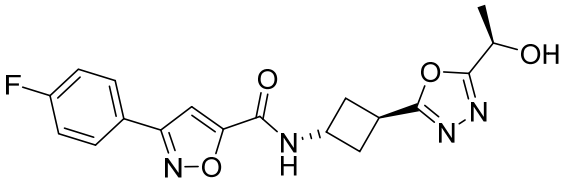
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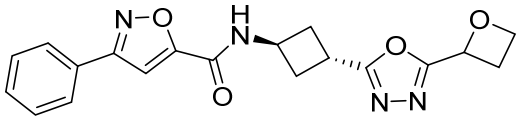
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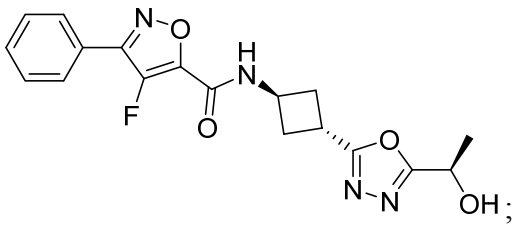

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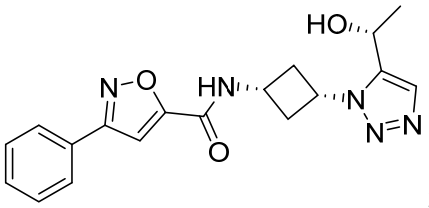

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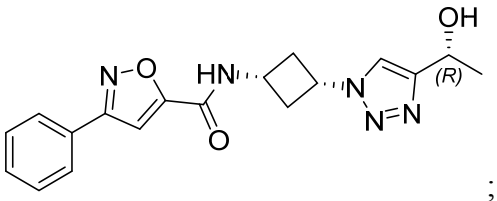

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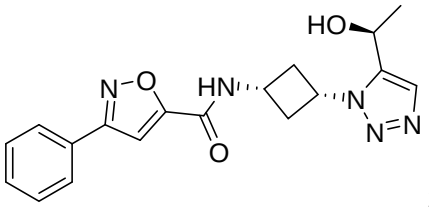

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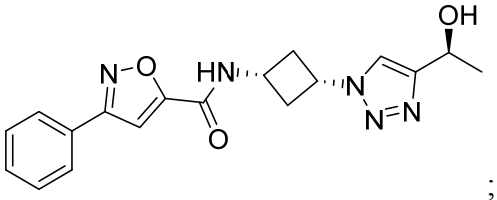

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and pharmaceutically acceptable salts thereof.

[7c] In a further aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier or excipient.

[7d] In another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease 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.

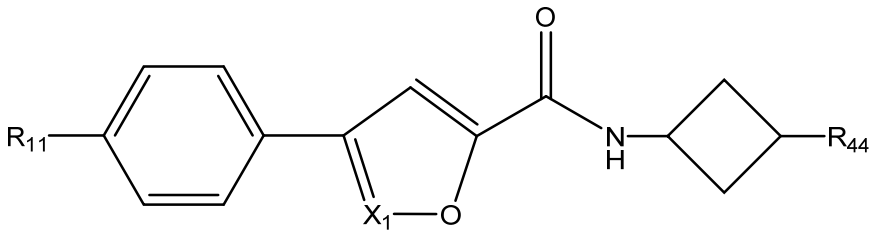
[8] Also contemplated herein are pharmaceutical compositions that include a disclosed compound (such as those compounds having disclosed formulas such as Formula (Ia), (IIa), (Ib), (IIb), (III), or (IV)) and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the compositions 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:



or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

X_1 is N;

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_{44} is a 5-6 membered monocyclic heteroaryl having one, two or three heteroatoms each selected from O, N, and S; wherein heteroaryl may be optionally substituted by one or two substituents each selected independently from R_{gg};

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;

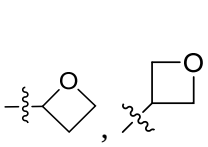
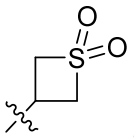
R_{ll} is selected for each occurrence from the group consisting of:

- 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;

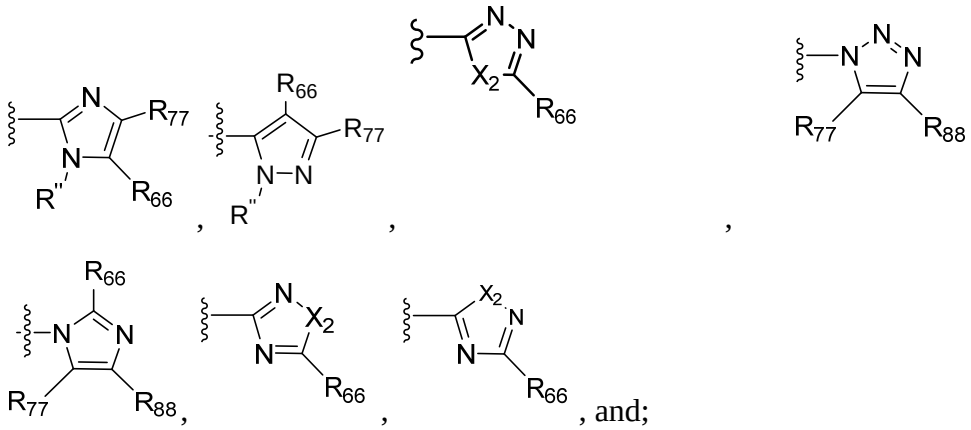
R’ and R’’ are each independently selected for each occurrence from H, C_{1-4} alkyl, phenyl and heterocycle; and

w is 0, 1 or 2.

2. The compound of claim 1, wherein R_{gg} is selected from the group consisting of:

, , and .

3. The compound of any one of claims 1-2, wherein R_{44} is selected from the group consisting of:



wherein X independently for each occurrence is selected from the group consisting of O, S, NR_{hh}, C, $C(R_{88})$, and $C(R_{88})(R_{99})$; X_2 independently for each occurrence is selected from the group consisting of O, S and NR_{hh}; R'' is H or C_{1-4}alkyl; and each R_{66}, R_{77}, R_{88} and R_{99} is independently selected for each occurrence from H and R_{gg}, and n is 0, 1, 2, or 3.

4. The compound of claim 3, wherein each R_{66}, R_{77}, R_{88} and R_{99} is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxyl, C_{1-6} alkyl, C_{3-6} cycloalkyl, and heterocycle,

wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, and heterocycle are optionally substituted by one, two or three substituents each independently selected from the group consisting of:

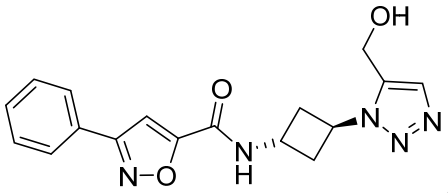
- hydroxyl, and

- C_{1-6} alkoxy optionally substituted by C_{3-6}cycloalkyl, heterocycle, -C_{1-2}alkyl-heterocycle and C_{1-2}alkyl- C_{3-6}cycloalkyl,

R' is independently selected for each occurrence from H and C_{1-4} alkyl.

5. The compound of any one of claims 1-4, wherein pp is 1 or 2, and R_{11} is selected from H, F, or methyl.

6. A compound selected from the group consisting of:



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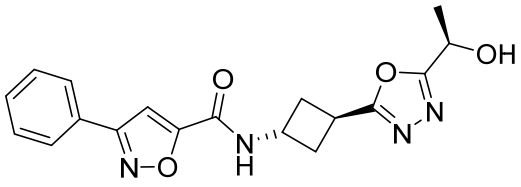

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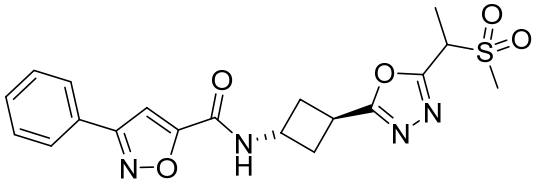
O
S
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O
N
O
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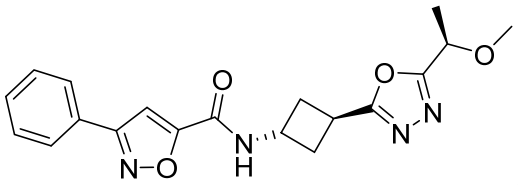
H
N
N
O

;


O
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H
N
N
O

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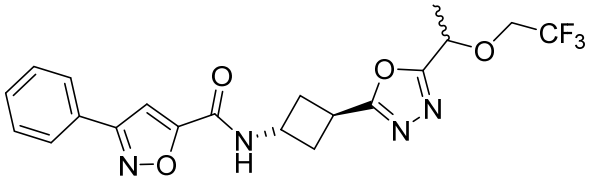
O
CF3
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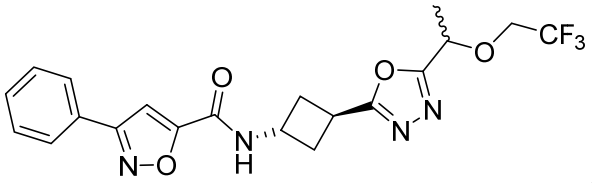
O
N
H
N
N
O

;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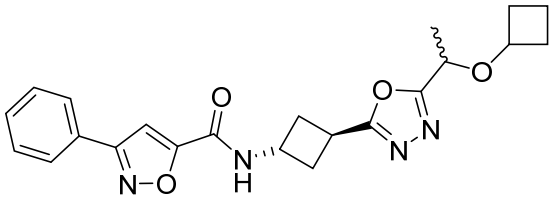
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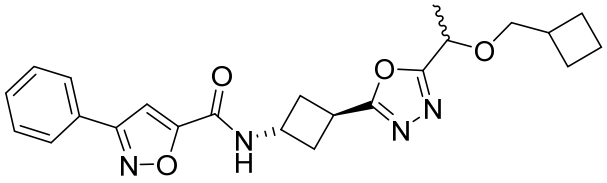
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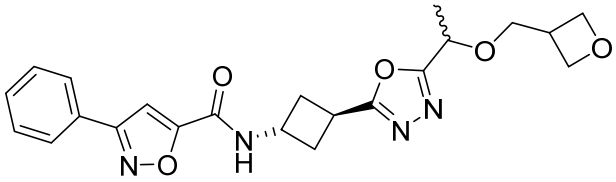
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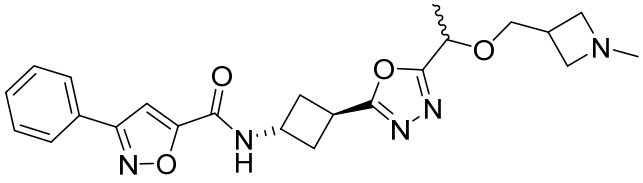
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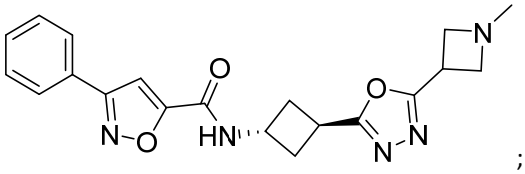
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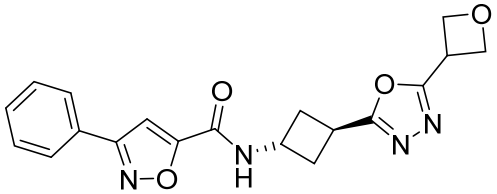
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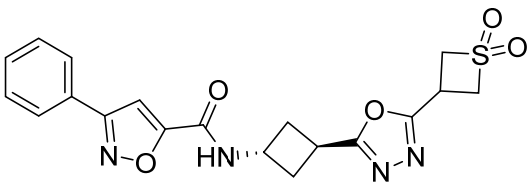
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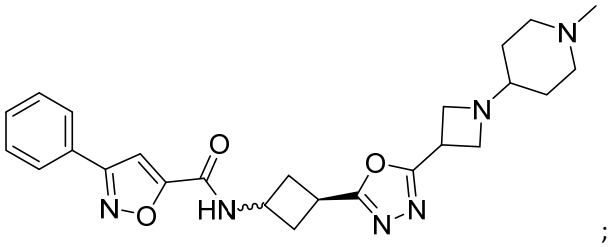
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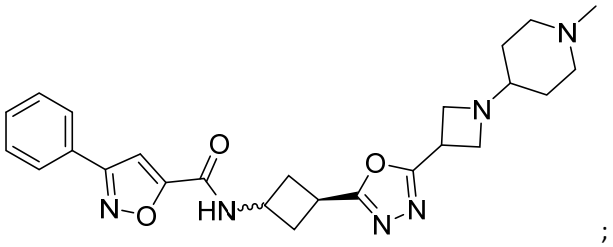
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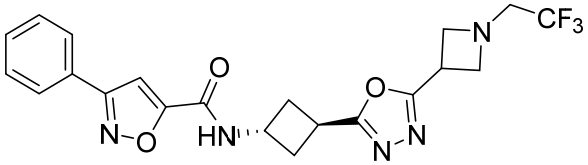
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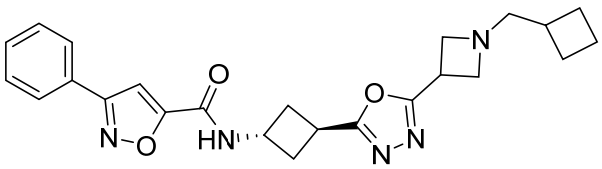
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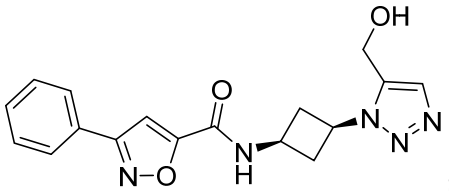
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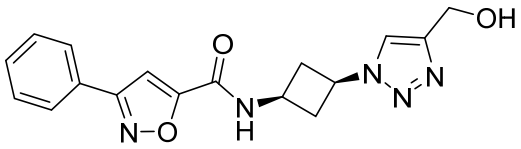
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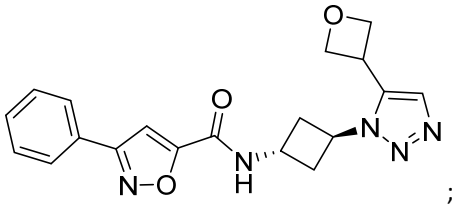
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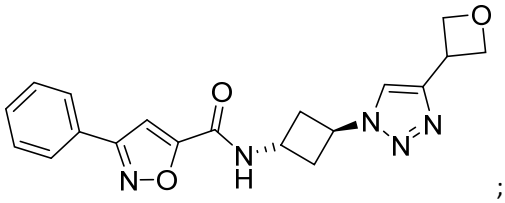
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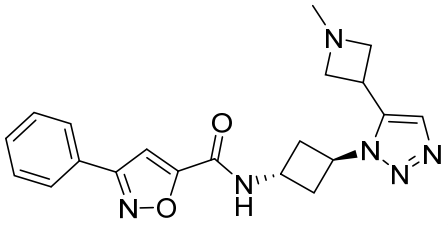
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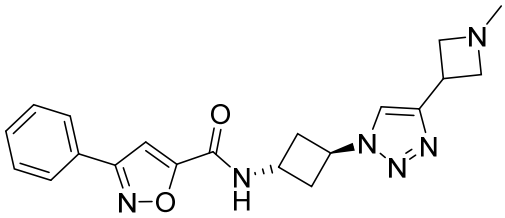
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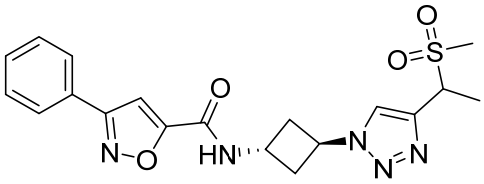
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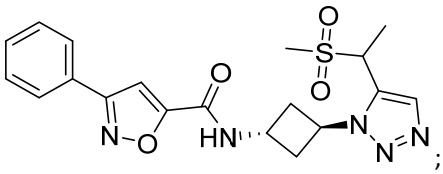
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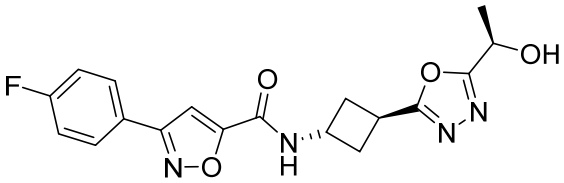
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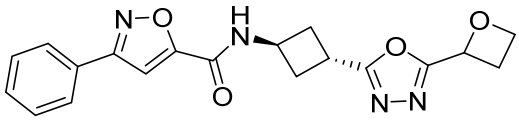
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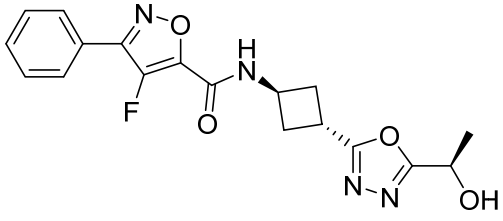
N–N
;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F
O
O
N–N
OH
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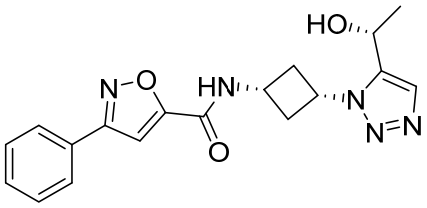
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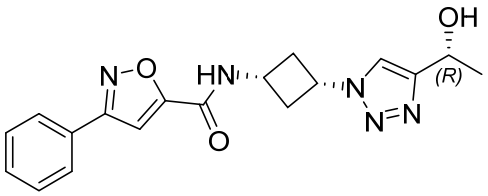
HN
O
N
N=N
;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HN
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N
N=N
(R)
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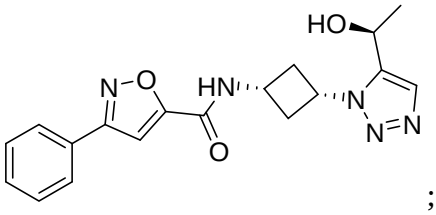
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N
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HN
O
N
N
N

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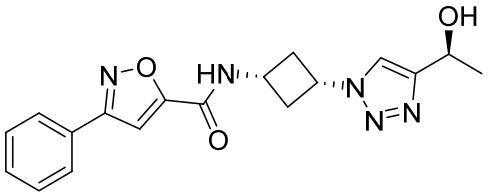
OH
N
O
HN
O
N
N
N

;

and pharmaceutically acceptable salts thereof.

7. A pharmaceutical composition comprising a compound of any one of claims 1 to 6 and a pharmaceutically acceptable carrier or excipient.

8. The pharmaceutical composition of claim 7, wherein the composition further comprises at least one additional CFTR modulator.

9. The pharmaceutical composition of claim 7, wherein the composition further comprises at least two additional CFTR modulators.

10. Use of a compound of any one of claims 1 to 6, or a pharmaceutical composition of any one claims 13-15, in the manufacture of a medicament for treating a disease 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.

11. The use of claim 10 wherein the disease is cystic fibrosis.

12. The use of claim 11, wherein the subject is a human patient.

13. The use of claim 12, wherein an additional CFTR modulator is to be further administered to said subject.

14. The use of claim 10, wherein at least two additional CFTR modulators are to be further administered to said subject.

15. The use of any one of claims 13 or 14, wherein at least one CFTR modulator is a CFTR corrector or potentiator.

16. The use of claim 15, 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.

17. The use of claim 15, 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.

18. The use of claim 16, wherein one of the at least two additional therapeutic agents is a CFTR corrector and the other is a CFTR potentiator.