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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2017 (02.02.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/019589 A1

(51) International Patent Classification:

C07D 413/14 (2006.01)	***C07D 307/54*** (2006.01)
C07D 405/12 (2006.01)	***A61K 31/42*** (2006.01)
C07D 407/12 (2006.01)	***A61K 31/422*** (2006.01)
C07D 409/14 (2006.01)	***A61K 31/341*** (2006.01)
C07D 413/12 (2006.01)	***A61P 11/00*** (2006.01)
C07D 417/12 (2006.01)	***A61P 37/00*** (2006.01)
C07D 261/14 (2006.01)	

(21) International Application Number:
PCT/US2016/043835

(22) International Filing Date:
25 July 2016 (25.07.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/196,841	24 July 2015 (24.07.2015)	US
62/199,672	31 July 2015 (31.07.2015)	US
62/271,177	22 December 2015 (22.12.2015)	US
62/271,812	28 December 2015 (28.12.2015)	US
62/277,595	12 January 2016 (12.01.2016)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

WO 2017/019589 A1

(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS OF INCREASING CFTR ACTIVITY

(57) Abstract: The present disclosure features compounds such as those having the Formulae (I) and (II), which can increase cystic fibrosis transmembrane conductance regulator (CFTR) activity as measured in human bronchial epithelial (hBE) cells. The present disclosure also features methods of treating a condition associated with decreased CFTR activity or a condition associated with a dysfunction of proteostasis comprising administering to a subject an effective amount of a disclosed compound, such as a compound of Formula (I) or (II).

COMPOUNDS, COMPOSITIONS AND METHODS OF INCREASING CFTR ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. provisional application serial numbers 62/196,841, filed July 24, 2015; 62/199,672, filed July 31, 2015; 62/271,177, filed December 22, 2015; 62/271,812, filed December 28, 2015; and 62/277,595, filed January 12, 2016; the contents of each of which is hereby incorporated by reference herein in its entirety.

BACKGROUND

[0002] Cells normally maintain a balance between protein synthesis, folding, trafficking, aggregation, and degradation, referred to as protein homeostasis, utilizing sensors and networks of pathways (Sitia et al., *Nature* **426:** 891-894, 2003; Ron et al., *Nat Rev Mol Cell Biol* **8:** 519-529, 2007). The cellular maintenance of protein homeostasis, or proteostasis, refers to controlling the conformation, binding interactions, location and concentration of individual proteins making up the proteome. Protein folding *in vivo* is accomplished through interactions between the folding polypeptide chain and macromolecular cellular components, including multiple classes of chaperones and folding enzymes, which minimize aggregation (Wiseman et al., *Cell* **131:** 809-821, 2007). Whether a given protein folds in a certain cell type depends on the distribution, concentration, and subcellular localization of chaperones, folding enzymes, metabolites and the like. Cystic fibrosis and other maladies of protein misfolding arise as a result of an imbalance in the capacity of the protein homeostasis (proteostasis) environment to handle the reduced energetic stability of misfolded, mutated proteins that are critical for normal physiology (Balch et al., *Science* **319**, 916-9 (2008); Powers, et al., *Annu Rev Biochem* **78**, 959-91 (2009); Hutt et al., *FEBS Lett* **583**, 2639-46 (2009)).

[0003] Cystic Fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which encodes a multi-membrane spanning epithelial chloride channel (Riordan et al., *Annu Rev Biochem* **77**, 701-26 (2008)). Approximately ninety

percent of patients have a deletion of phenylalanine (Phe) 508 (ΔF508) on at least one allele. This mutation results in disruption of the energetics of the protein fold leading to degradation of CFTR in the endoplasmic reticulum (ER). The ΔF508 mutation is thus associated with defective folding and trafficking, as well as enhanced degradation of the mutant CFTR protein (Qu et al., *J Biol Chem* **272**, 15739-44 (1997)). The loss of a functional CFTR channel at the plasma membrane disrupts ionic homeostasis (Cl^-, Na^+, HCO_3^-) and airway surface hydration leading to reduced lung function (Riordan et al.). Reduced periciliary liquid volume and increased mucus viscosity impede mucociliary clearance resulting in chronic infection and inflammation, phenotypic hallmarks of CF disease (Boucher, *J Intern Med* 261, 5-16 (2007)). In addition to respiratory dysfunction, ΔF508 CFTR also impacts the normal function of additional organs (pancreas, intestine, gall bladder), suggesting that the loss-of-function impacts multiple downstream pathways that will require correction.

[0004] In addition to cystic fibrosis, mutations in the CFTR gene and/or the activity of the CFTR channel has also been implicated in other conditions, including for example, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, smoking-related lung diseases, such as chronic obstructive pulmonary disease (COPD), dry eye disease, Sjogren's syndrome and chronic sinusitis, (Sloane et al. (2012), PLoS ONE 7(6): e39809.doi:10.1371/journal. pone.0039809; Bombieri et al. (2011), J Cyst Fibros. 2011 Jun;10 Suppl 2:S86-102; (Albert et al. (2008). Clinical Respiratory Medicine, Third Ed., Mosby Inc.; Levin et al. (2005), Invest Ophthalmol Vis Sci., 46(4):1428-34; Froussard (2007), Pancreas 35(1): 94-5).

[0005] There remains a need in the art for compounds, compositions and methods of increasing CFTR activity as well as for methods of treating CF, other CFTR-related diseases, and other maladies of protein misfolding.

SUMMARY

[0006] The present disclosure is based, in part, on the discovery that disclosed compounds such as those having the Formulae (I) and (II) increase cystic fibrosis transmembrane conductance regulator (CFTR) activity as measured in human bronchial epithelial (hBE) cells.

[0007] In an embodiment, this disclosure is at least partially directed to a method of enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof is provided, which includes administering to said subject an effective amount of a compound having the formula (I) or (II) as disclosed herein.

[0008] 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 compound of Formula (I) and (II).

[0009] 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 CFTRs (e.g., ΔF508 and G551D; ΔF508 and A455E; or G542X and Δ508F) are enhanced (e.g., increased).

[0010] In certain of these embodiments, the subject (e.g., a human patient) is suffering from a disease associated with decreased CFTR activity (e.g., 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). In certain embodiments, the disease is cystic fibrosis.

[0011] In yet additional aspects, the disclosure is directed to treating a patient suffering from cystic fibrosis comprising administering to said patient an effective amount of a disclosed compound (e.g., a compound provided herein, .e.g., Formulas I, and II (e.g., a compound of Table 1) and optionally, administering to said patient a) CFTR potentiator and/or b) a CFTR corrector.

[0012] In certain embodiments, methods can include: administering to the patient an effective amount of a disclosed compound; and administering ivacaftor. In certain of these embodiments, methods can further include administering VX-661 or lumacaftor. In another aspect, this disclosure provides methods of treating a patient with F508del homozygous CFTR mutation, comprising: administering to the patient an effective amount of a disclosed compound; administering ivacaftor ; and/or administering lumacaftor or VX661. In a further aspect, this disclosure provides methods of treating a patient with a G542X class I CFTR mutation, comprising: administering to the patient an effective amount of a disclosed compound; and optionally administering NB124. In still another aspect, this disclosure provides methods of treating a patient with a A455E Class V CFTR mutation, comprising: administering to the patient an effective amount of a disclosed compound disclosed; administering ivacaftor; and administering a CFTR corrector selected from VX-661 and lumacaftor. In a further aspect, this disclosure provides methods of treating a patient with A455E/F508del CFTR mutation, comprising: administering to the patient an effective amount of a disclosed compound; administering ivacaftor; and administering a CFTR corrector selected from VX-661 and lumacaftor. In another aspect, this disclosure provides methods of treating a patient with a G551D Class III CFTR mutation, comprising: administering to the patient an effective amount of a disclosed compound; administering ivacaftor; and administering a CFTR corrector selected from VX-661 and lumacaftor. In a further aspect, this disclosure provides methods of treating a patient with G551D/F508del CFTR mutations, comprising: administering to the patient an effective amount of a disclosed compound; administering ivacaftor; and

administering a CFTR corrector selected from VX-661 and lumacaftor. Also provided herein is a method of treating a patient with 3849 + 10kb C>T/N1303 CFTR mutations, comprising administering to the patient an effective amount of a disclosed compound; and optionally administering ivacaftor.

[0013] In some embodiments, the methods described herein can further include administering an additional therapeutic agent or administering at least two additional CFTR therapeutic agents. In some embodiments, the methods described herein can further include administering an additional CFTR modulator or administering at least two additional CFTR modulators. In certain embodiments, at least one CFTR modulator is a CFTR corrector (e.g., VX-809, VX-661, VX-152, VX-440, VX-983, and GLPG2222) or potentiator (e.g., ivacaftor, genistein and GLPG1837). In certain of these embodiments, one of the at least two additional therapeutic agents is a CFTR corrector (e.g., VX-809, VX-661, VX-152, VX-440, and VX-983) and the other is a CFTR potentiator (e.g., ivacaftor and genistein). In certain of these embodiments, one of the at least two additional therapeutic agents is a CFTR corrector (e.g., GLPG2222) and the other is a CFTR potentiator (e.g., GLPG1837). In other embodiments, the methods described herein can further include administrating an epithelial sodium channel (ENaC) inhibitor (e.g., VX-371).

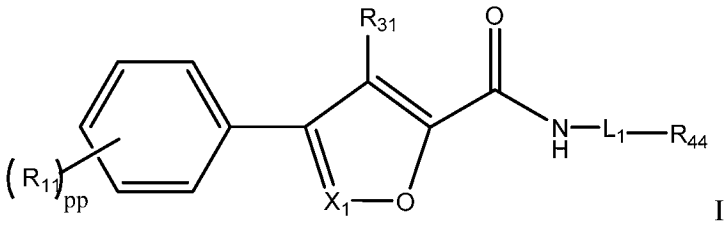
[0014] In a further aspect, a method of identifying a candidate agent that increases CFTR activity is provided, which includes: (i) contacting a cell that expresses a CFTR protein with the candidate agent and a disclosed compound; (ii) measuring the CFTR activity in the cell in the presence of the candidate agent and the disclosed compound; and (iii) 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. In certain embodiments, the cell expresses a mutant CFTR protein. In certain embodiments, CFTR activity is measured by measuring chloride channel activity of the CFTR, and/or other ion transport activity. In certain of these embodiments, the method is high-throughput. In certain of these embodiments, the candidate agent is a CFTR corrector or a CFTR potentiator.

DETAILED DESCRIPTION

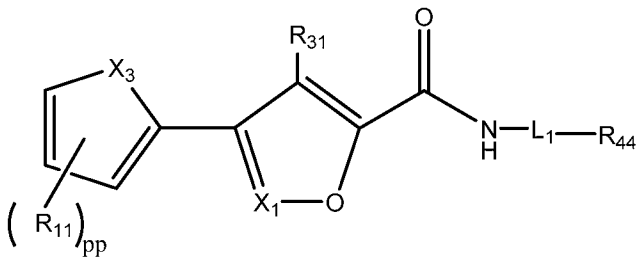
[0015] As used herein, the words "a" and "an" are meant to include one or more unless otherwise specified. For example, the term "an agent" encompasses both a single agent and a combination of two or more agents.

[0016] As discussed above, the present disclosure is directed in part to methods of treating CFTR that include administering compounds as described herein having the Formula (I) and (II) or a pharmaceutically acceptable salt, prodrug or solvate thereof, and in some embodiments, additionally administering another agent as described here.

[0017] In some embodiments, a compound for use in the disclosed methods has the formula (I). In other embodiments, a compound has the formula (II) as provided below.



I



II

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

X_1 is CR_{33} or N;

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;

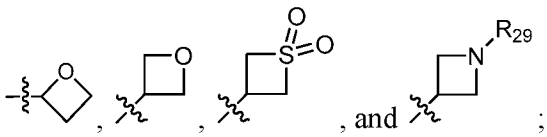
R_{ll} is selected for each occurrence from the group consisting of halogen, hydroxyl, C_{1-6} alkyl (optionally substituted by one, two, or three substituents each independently selected from halogen, hydroxyl, and C_{3-6} cycloalkyl) and heterocycle (optionally substituted by one, two or three substituents 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. L_1 is C_{1-3} alkylene, C_{3-5} cycloalkylene, or C_{3-6} cycloalkylene-C_{1-4} alkylene. For example, R_{31} may be H or F.

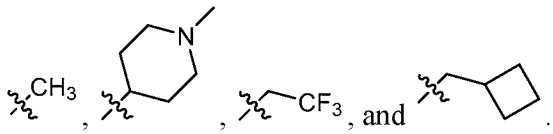
[0018] In certain embodiments, R_{gg} is selected from the group consisting of:



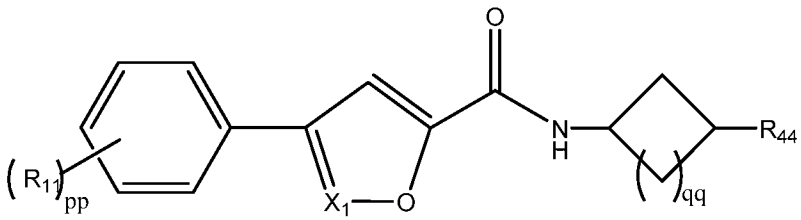
, and ;

wherein R_{29} is selected from C_{1-6} alkyl (optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkoxy, and cycloalkyl) and heterocycle (optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy).

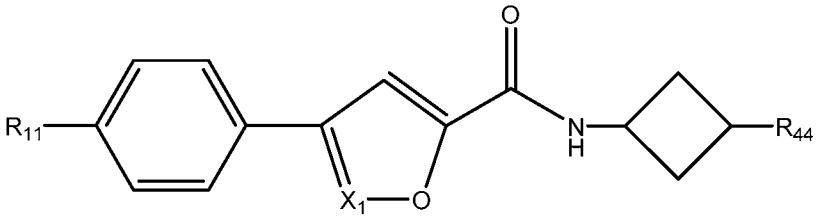
[0019] R_{29}, in certain embodiments, may be selected from the group consisting of:



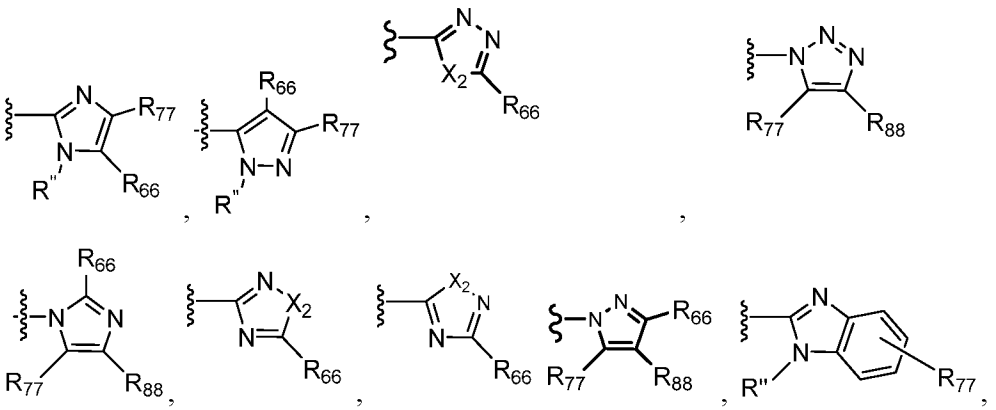
[0020] For example, provided herein is a compound:

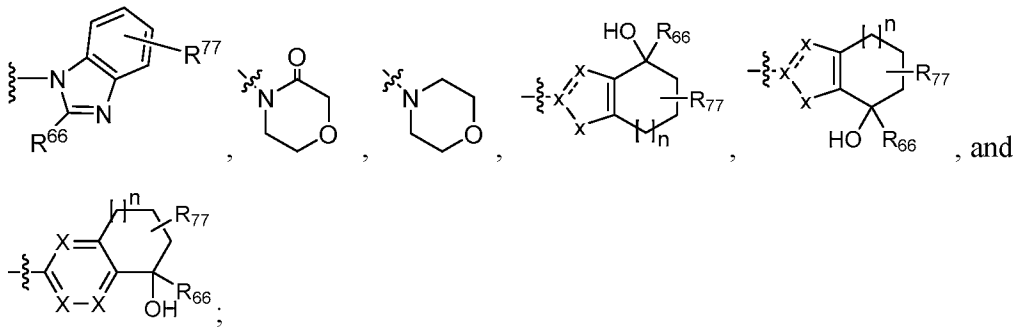


wherein qq is 0 or 1, for example a compound, represented by:



[0021] R_{44} may be selected, for example, from the group consisting of: pyrrolidinyl, piperidinyl, tetrahydropyranyl, and tetrahydrofuranyl, or may be 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.

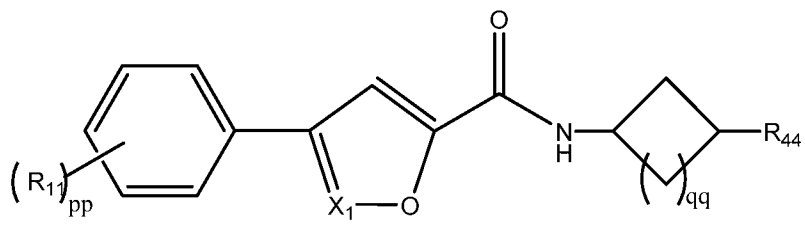
[0022] Each R_{66}, R_{77}, R_{88} and R_{99} may be independently selected for each occurrence in certain embodiments, from the group consisting of hydrogen, halogen, hydroxyl, C_{1-6} alkyl, C_{3-6} cycloalkyl, and heterocycle, wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, and heterocycle are optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, C_{1-6} alkyl, 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), -$S(O)_w$-C_{1-3} alkyl (w is 0,1, or 2) and –NR'$S(O)_2C_{1-6}$ alkyl; and R' is independently selected for each occurrence from H and C_{1-4} alkyl.

[0023] For example, pp is 0, 1 or 2, and R_{11} is selected from H, F, or methyl.

[0024] In certain of these embodiments, L_1 is C_{1-3} alkylene or C_{3-5} cycloalkylene.

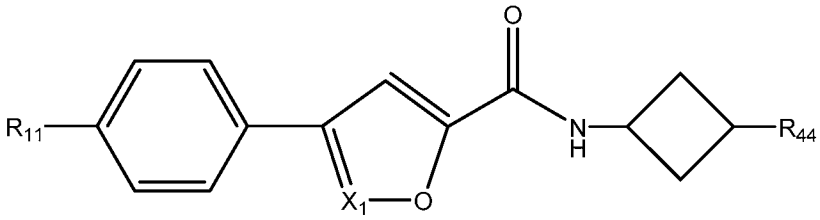
[0025] In certain of these embodiments, R_{31} is H or F.

[0026] In certain of these embodiments, a disclosed compound has the formula:



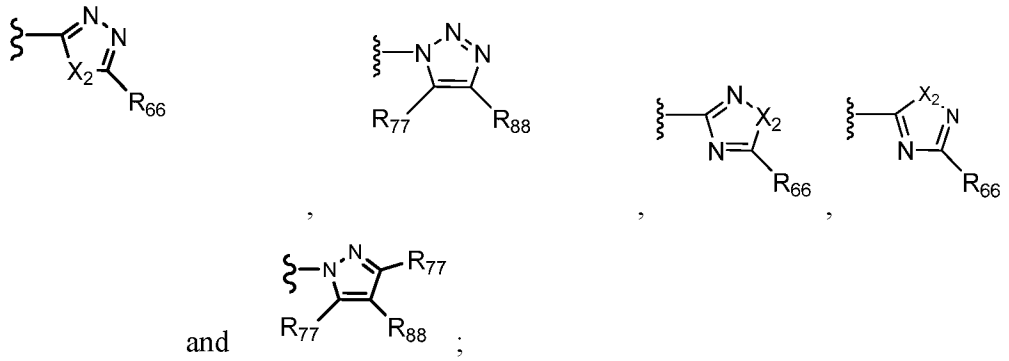
; wherein qq is 0 or 1.

[0027] For example, the compound can have the following formula:



[0028] In certain embodiments, R_{44} is selected from the group consisting of: pyrrolidinyl, piperidinyl, tetrahydropyranyl, and tetrahydofuranyl.

[0029] In other embodiments, R_{44} is selected from the group consisting of



wherein X_2 independently for each occurrence is selected from the group consisting of O, S or NR_{hh}; and each R_{66}, R_{77} and R_{88} is independently selected for each occurrence from R_{gg}.

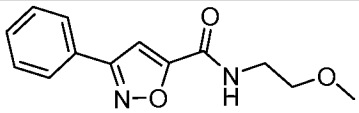
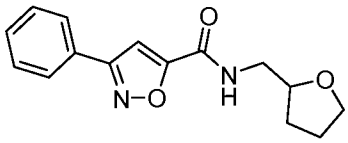
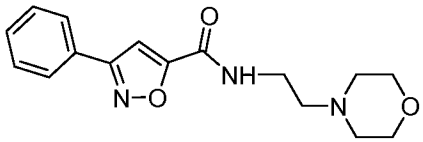
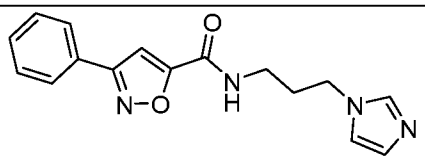
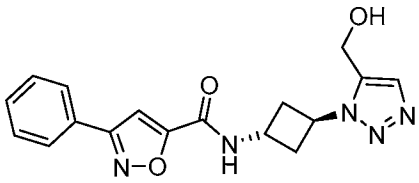
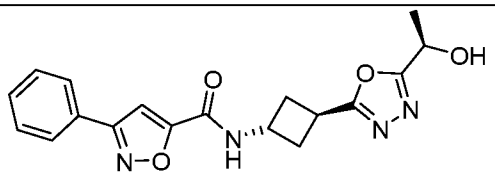
[0030] In certain of these embodiments, each of R_{66}, R_{77} and R_{88} is selected from the group consisting of H, halogen, methyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), ethyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), propyl ((optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), isopropyl ((optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), *n*-butyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), *t*-butyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), *s*-butyl (optionally substituted by one, two or three substituents each

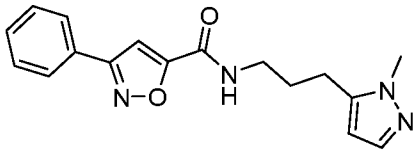
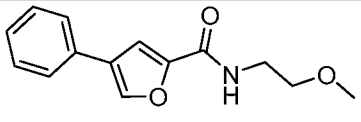
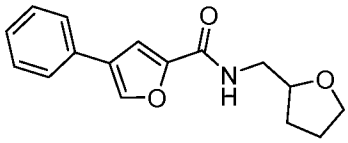
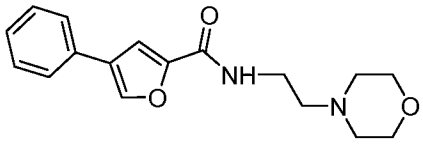
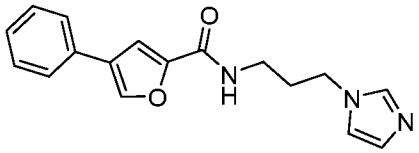
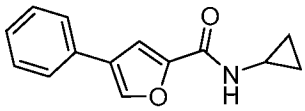
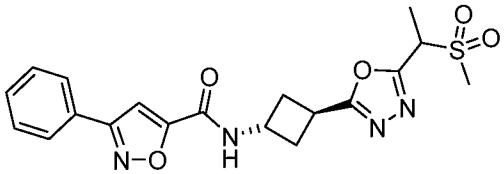
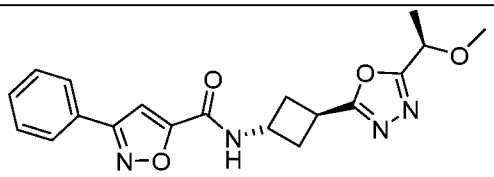
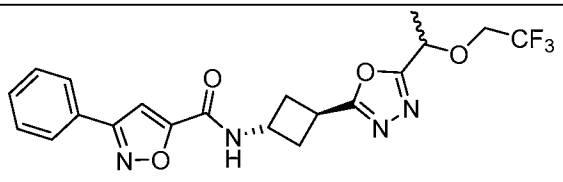
selected from halogen, hydroxyl, methoxy and ethoxy) and isobutyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy).

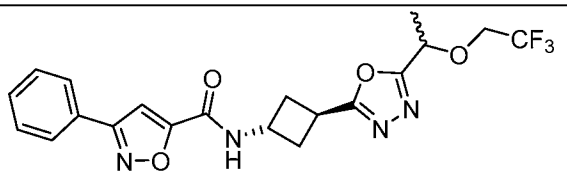
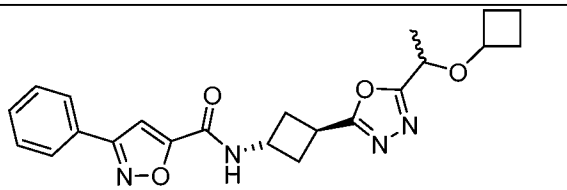
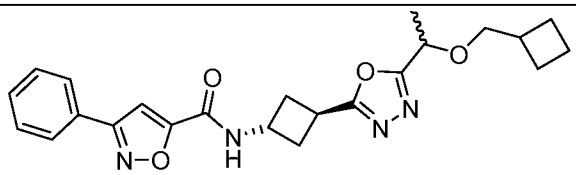
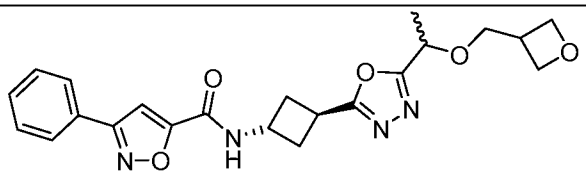
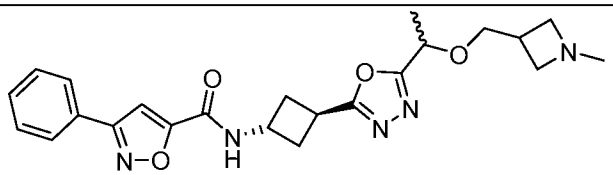
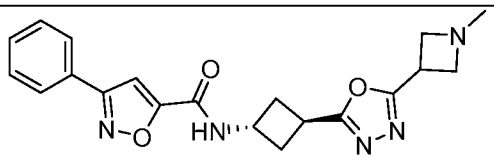
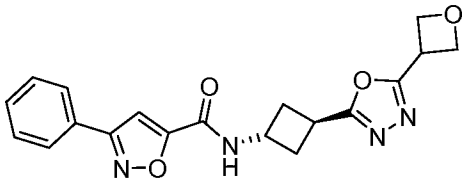
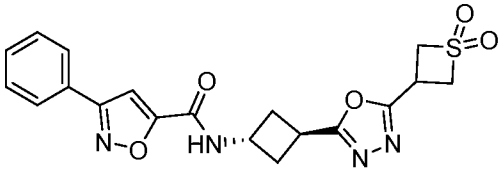
[0031] In certain embodiments, pp is 0, 1 or 2, and R_{11} is selected from H, F, or methyl.

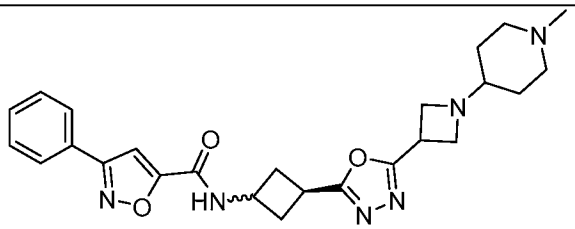
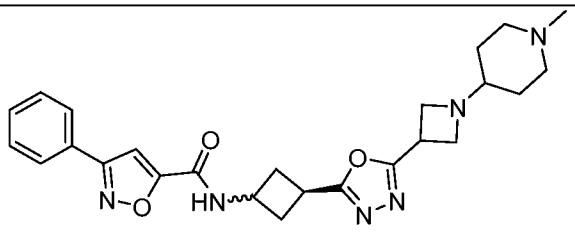
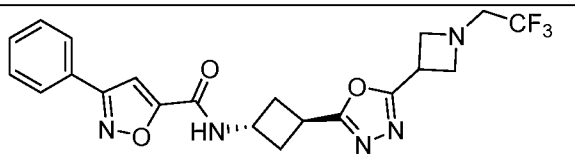
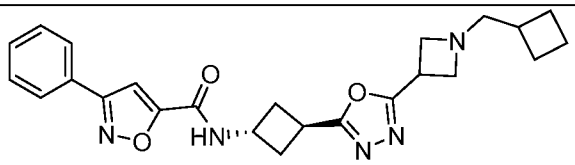
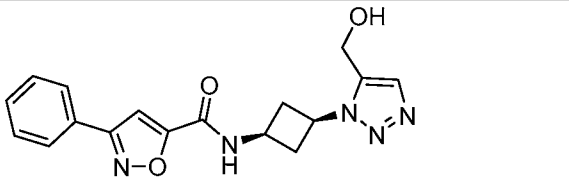
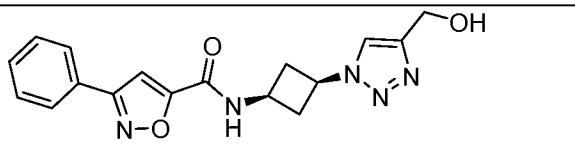
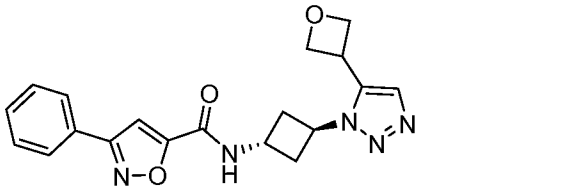
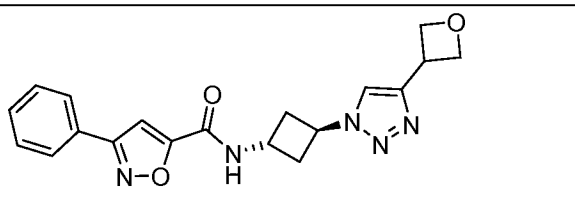
[0032] Exemplary compounds of Formulae (I) and (II) are shown below in Table 1 and throughout this disclosure, including the examples and the claims.

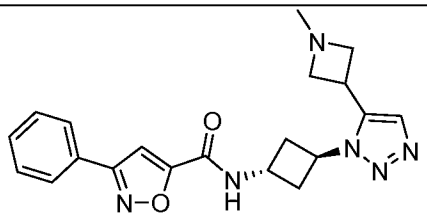
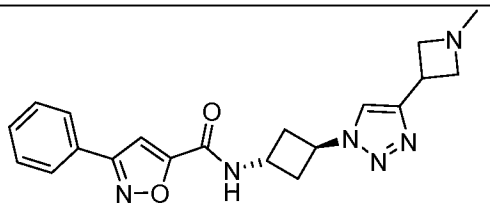
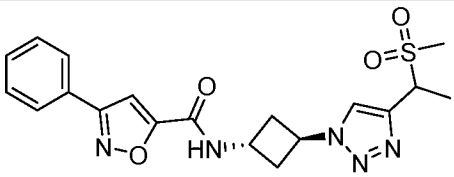
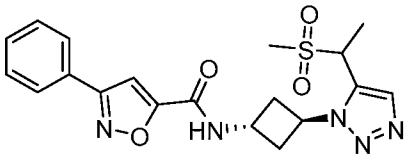
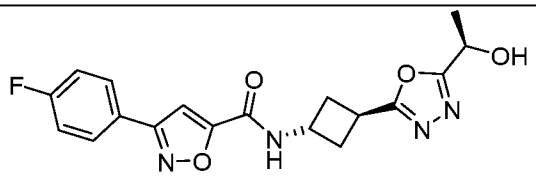
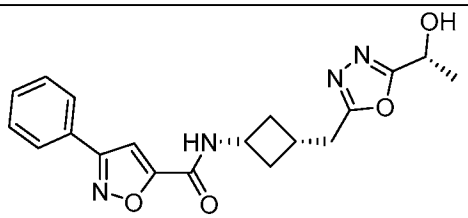
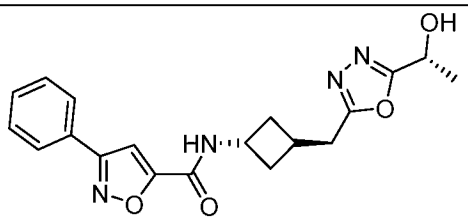
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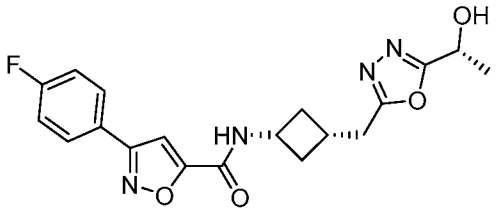
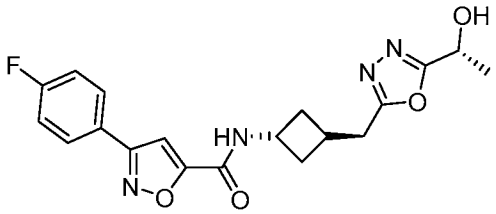
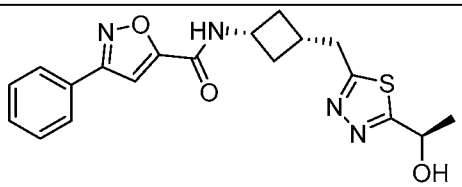
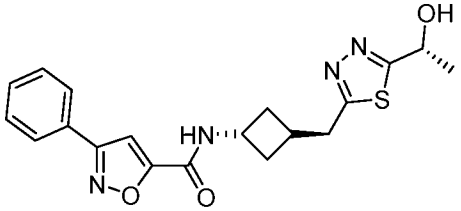
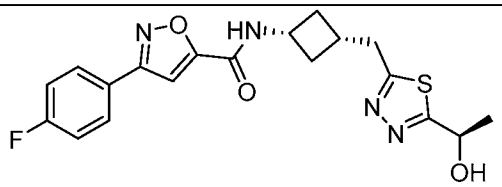
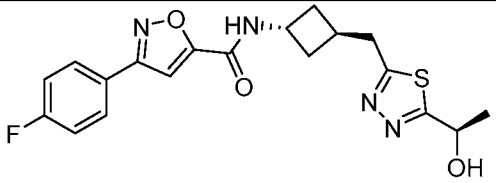
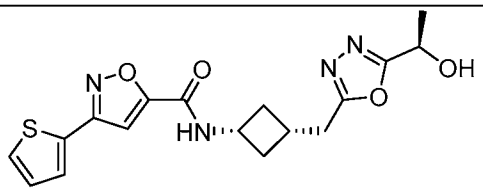
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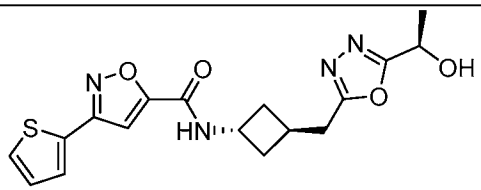
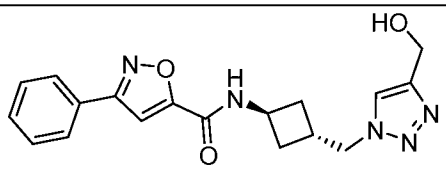
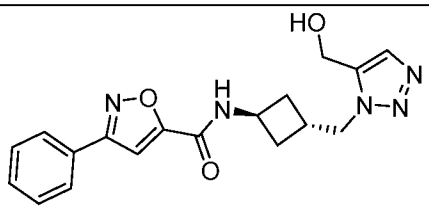
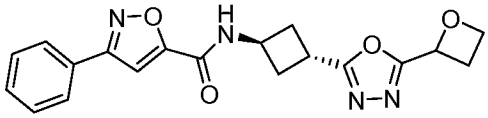
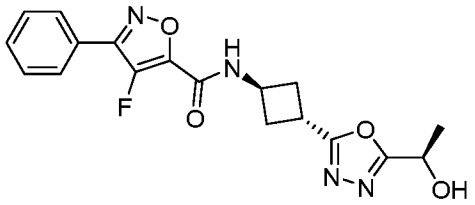
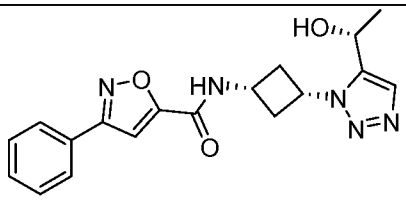
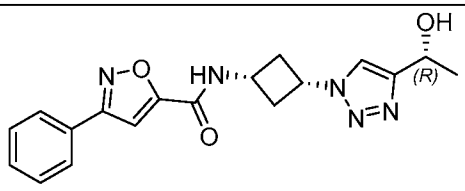
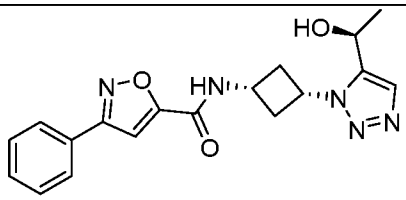
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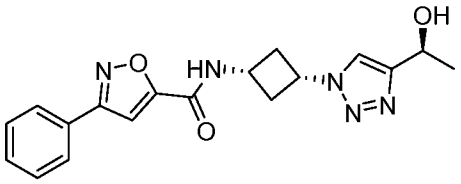
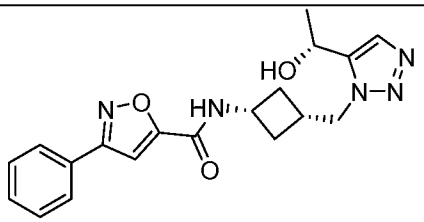
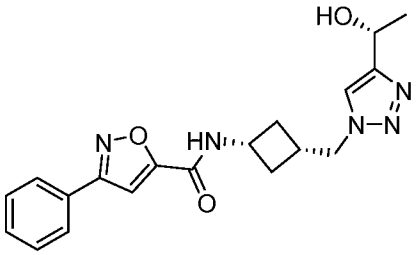
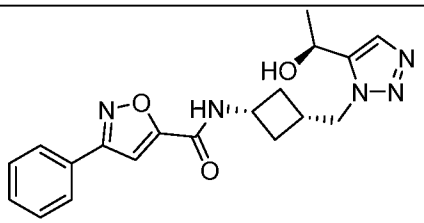
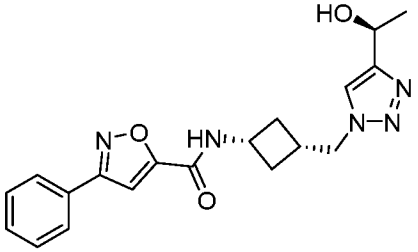
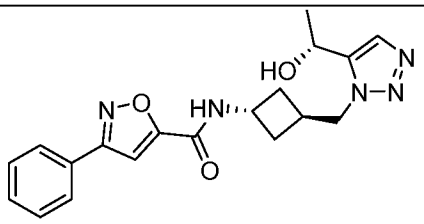
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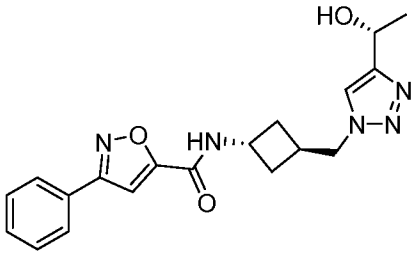
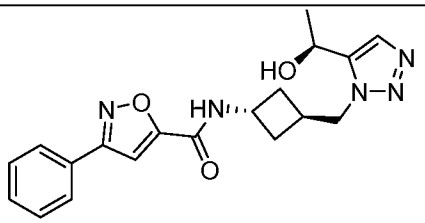
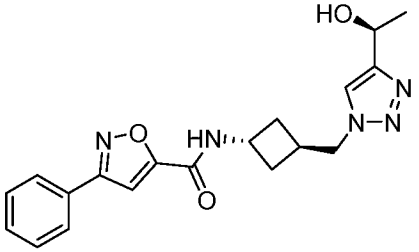
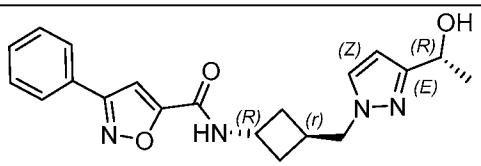
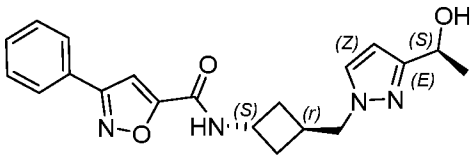
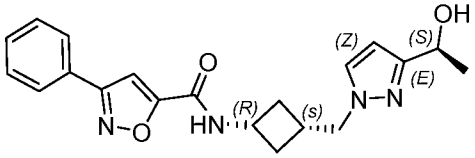
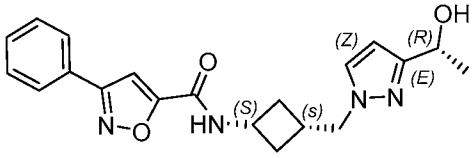
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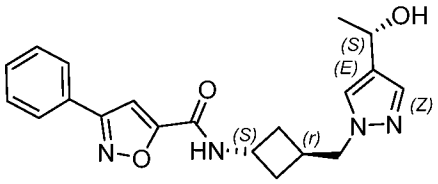
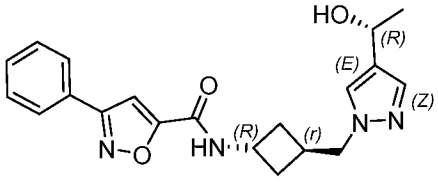
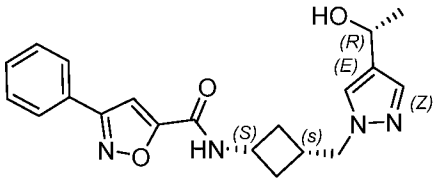
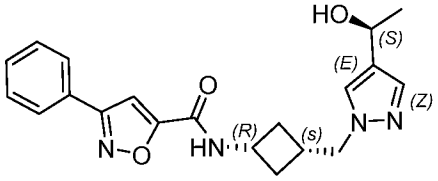
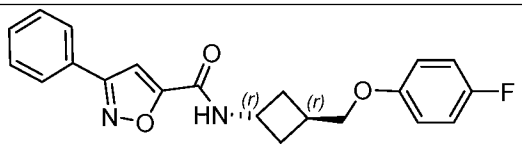
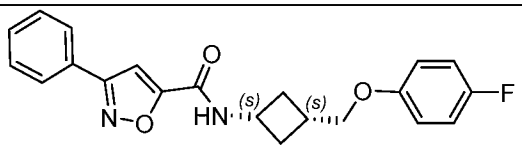
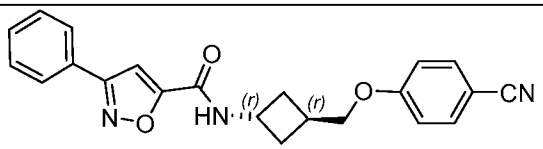
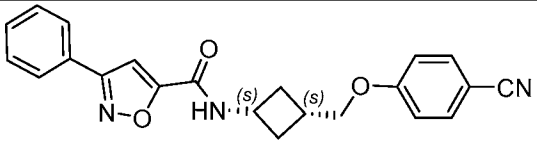
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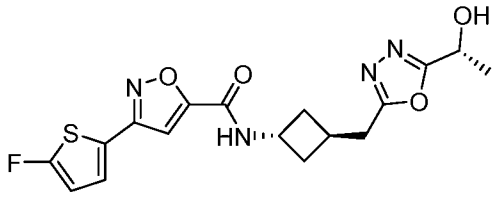
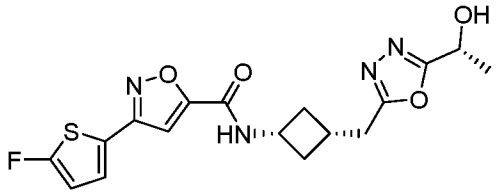
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[0033] Also contemplated herein are pharmaceutical compositions that include a disclosed compound such as those compounds having Formula (I) and (II) and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the compositions can include at least one additional CFTR modulator as described anywhere herein or at least two additional CFTR modulators, each independently as described anywhere herein.

[0034] It is to be understood that the specific embodiments described herein can be taken in combination with other specific embodiments delineated herein.

[0035] The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

[0036] It will be appreciated that the description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding.

[0037] The term "alkyl", as used herein, unless otherwise indicated, refers to both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; for example, "C_1-C_{10} alkyl" denotes alkyl having 1 to 10 carbon atoms, and straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C_{1-6} alkyl, C_{1-4} alkyl, and C_{1-3} alkyl, respectively. Examples of alkyl include, but are not limited to,

methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

[0038] The term, "alkenyl", as used herein, refers to both straight and branched-chain moieties having the specified number of carbon atoms and having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein as C_{2-6} alkenyl, and C_{3-4} alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

[0039] The term, "alkynyl", as used herein, refers to both straight and branched-chain moieties having the specified number or carbon atoms and having at least one carbon-carbon triple bond.

[0040] The term "cycloalkyl," as used herein, refers to saturated cyclic alkyl moieties having 3 or more carbon atoms, for example, 3-10, 3-6, or 4-6 carbons, referred to herein as C_{3-10} cycloalkyl, C_{3-6} cycloalkyl or C_{4-6} cycloalkyl, respectively for example, examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl.

[0041] The term "cycloalkenyl," as used herein, refers to cyclic alkenyl moieties having 3 or more carbon atoms.

[0042] The term "cycloalkynyl," as used herein, refers to cyclic alkynyl moieties having 5 or more carbon atoms.

[0043] "Alkylene" means a straight or branched, saturated aliphatic divalent radical having the number of carbons indicated. "Cycloalkylene" refers to a divalent radical of carbocyclic saturated hydrocarbon group having the number of carbons indicated.

[0044] The term "alkoxy" as used herein refers to a straight or branched alkyl group attached to oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C_{1-6} alkoxy, and C_{2-6} alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

[0045] The term "heterocyclic" or "heterocycle" encompasses heterocycloalkyl, heterocycloalkenyl, heterobicycloalkyl, heterobicycloalkenyl, heteropolycycloalkyl, heteropolycycloalkenyl, and the like unless indicated otherwise. Heterocycloalkyl refers to cycloalkyl groups containing one or more heteroatoms (O, S, or N) within the ring. Heterocycloalkenyl as used herein refers to cycloalkenyl groups containing one or more heteroatoms (O, S or N) within the ring. Heterobicycloalkyl refers to bicycloalkyl groups containing one or more heteroatoms (O, S or N) within a ring. Heterobicycloalkenyl as used herein refers to bicycloalkenyl groups containing one or more heteroatoms (O, S or N) within a ring. A heterocycle can refer to, for example, a saturated or partially unsaturated 4- to 12 or 4-10-membered ring structure, including bridged or fused rings, and whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, heterocyclic rings may be linked to the adjacent radical through carbon or nitrogen. Examples of heterocyclic groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran or dihydrofuran etc.

[0046] Cycloalkyl, cycloalkenyl, heterocyclic, groups also include groups similar to those described above for each of these respective categories, but which are substituted with one or more oxo moieties.

[0047] The term "aryl", as used herein, refers to mono- or polycyclic aromatic carbocyclic ring systems. A polycyclic aryl is a polycyclic ring system that comprises at least one aromatic ring. Polycyclic aryls can comprise fused rings, covalently attached rings or a combination thereof. The term "aryl" embraces aromatic radicals, such as, phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. An aryl group may be substituted or unsubstituted. In some embodiments, the aryl is a C_4-C_{10} aryl. Examples of optionally substituted aryl are phenyl, substituted phenyl, napthyl and substituted naphthyl.

[0048] The term "heteroaryl", as used herein, refers to aromatic carbocyclic groups containing one or more heteroatoms (O, S, or N) within a ring. A heteroaryl group, unless indicated otherwise, can be monocyclic or polycyclic. A heteroaryl group may additionally be substituted or unsubstituted. The heteroaryl groups of this disclosure can also include ring systems substituted with one or more oxo moieties. A polycyclic heteroaryl can comprise fused rings, covalently attached rings or a combination thereof. A polycyclic heteroaryl is a polycyclic ring system that comprises at least one aromatic ring containing one or more

heteroatoms within a ring. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, thiazolopyridinyl, oxazolopyridinyl and azaindolyl. The foregoing heteroaryl groups may be C-attached or heteroatom-attached (where such is possible). For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). In some embodiments, the heteroaryl is 4- to 12-membered heteroaryl. In yet other embodiments, the heteroaryl is a mono or bicyclic 4- to 10-membered heteroaryl.

[0049] The term "substituted" refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to, and unless indicated otherwise, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{12} cycloalkyl, -C_3-C_{12} cycloalkenyl, C_3-C_{12} cycloalkynyl, -heterocyclic, -F, -Cl, -Br, -I, -OH, -NO_2, -N_3, -CN, -NH_2, oxo, thioxo, -NHR_x, -NR_xR_x, dialkylamino, -diarylamino, -diheteroarylamino, -OR_x, -$C(O)R_y$, -$C(O)C(O)R_y$, -OCO_2R_y, -$OC(O)R_y$, $OC(O)C(O)R_y$, -$NHC(O)R_y$, -$NHCO_2R_y$, -$NHC(O)C(O)R_y$, $NHC(S)NH_2$, -$NHC(S)NHR_x$, -$NHC(NH)NH_2$, -$NHC(NH)NHR_x$, -$NHC(NH)R_x$, -$C(NH)NHR_x$, and $(C{=}NR_x)R_x$; -$NRxC(O)R_x$, -$NR_xC(O)N(R_x)_2$, -$NRxCO_2R_y$, -$NRxC(O)C(O)R_y$, -$NR_xC(S)NH_2$, -$NR_xC(S)NHR_x$, -$NR_xC(NH)NH_2$, -$NR_xC(NH)NHR_x$, -$NR_xC(NH)R_x$, -$C(NRx)NHR_x$ -$S(O)R_y$, -$NHSO_2R_x$, -CH_2NH_2, -$CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C_3-C_{12} cycloalkyl, -polyalkoxyalkyl, -polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-R_x, or -methylthiomethyl, wherein R_x is selected from the group consisting of hydrogen, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{12} cycloalkyl, -aryl, -heteroaryl and -heterocyclic and -R_y is selected from the group consisting of hydrogen, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{12} cycloalkyl, -aryl, -heteroaryl, -heterocyclic, -NH_2, -NH-C_1-C_{12} alkyl, -NH-C_2-C_{12} alkenyl, -NH-C_2-C_{12}-alkynyl, -NH-C_3-C_{12} cycloalkyl, -NH-aryl, -NH-heteroaryl and -NH-heterocyclic. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted.

[0050] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

[0051] The term "haloalkyl" as used herein refers to an alkyl group having 1 to (2n+1) substituent(s) independently selected from F, Cl, Br or I, where n is the maximum number of carbon atoms in the alkyl group. It will be understood that haloalkyl is a specific example of an optionally substituted alkyl.

[0052] The terms "hydroxy" and "hydroxyl" as used herein refers to the radical -OH.

[0053] As will be understood by the skilled artisan, "H" is the symbol for hydrogen, "N" is the symbol for nitrogen, "S" is the symbol for sulfur, "O" is the symbol for oxygen. "Me" is an abbreviation for methyl.

[0054] The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term "stereoisomers" when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols "(+)," "(-)," "*R*" or "*S*," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present disclosure encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[0055] The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol ═ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "*E*" and "*Z*" isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond.

[0056] Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the

ring. The arrangement of substituents around a carbocyclic or heterocyclic ring are designated as being in the *"Z"* or *"E"* configuration wherein the terms *"Z"* and *"E"* are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both *"Z"* and *"E"* isomers. Substituents around a carbocyclic or heterocyclic ring may also be referred to as "cis" or "trans", where the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0057] Individual enantiomers and diasterisomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations, and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009. Where a particular compound is described or depicted, it is intended to encompass that chemical structure as well as tautomers of that structure.

[0058] The term "enantiomerically pure" means a stereomerically pure composition of a compound. For example, a stereochemically pure composition is a composition that is free or substantially free of other stereoisomers of that compound. In another example, for a

compound having one chiral center, an enantiomerically pure composition of the compound is free or substantially free of the other enantiomer. In yet another example, for a compound having two chiral centers, an enantiomerically pure composition is free or substantially free of the other diastereomers.

[0059] Where a particular stereochemistry is described or depicted it is intended to mean that a particular enantiomer is present in excess relative to the other enantiomer. A compound has an R-configuration at a specific position when it is present in excess compared to the compound having an S-configuration at that position. A compound has an *S*-configuration at a specific position when it is present in excess compared to the compound having an *R*-configuration at that position.

[0060] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

[0061] The disclosure also embraces isotopically labeled compounds of the disclosure which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. For example, a compound of the disclosure may have one or more H atom replaced with deuterium.

[0062] Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly suitable for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be suitable in some circumstances. Isotopically labeled compounds of the disclosure can generally be prepared by following

procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0063] The disclosure additionally encompasses embodiments wherein one or more of the nitrogen atoms in a disclosed compound are oxidized to N-oxide.

[0064] Representative and exemplary synthetic routes for the preparation of compounds described herein are shown in the schemes below and throughout the Examples section. As will be understood by the skilled artisan, diastereomers can be separated from the reaction mixture using column chromatography.

[0065] Compounds of the disclosure can also be prepared using methods described in the literature, including, but not limited to, *J. Med. Chem.* **2011**, *54(13)*, 4350-64; *Russian Journal of Organic Chemistry* **2011**, *47*(8), 1199-1203; U.S. Patent Application Publication No. 2009/0036451 A1; WO2008/046072 A2, and U.S. Patent No. 4,336,264, the contents of each of which are expressly incorporated by reference herein.

[0066] As discussed above, the disclosure encompasses to a method of enhancing (e.g., increasing) CFTR activity in a subject (e.g., a subject suffering from any one or more of the conditions described herein) comprising administering a compound of the disclosure in an effective amount. The disclosure also encompasses a method of treating a patient suffering from a condition associated with CFTR activity comprising administering to said patient an effective amount of a compound described herein. In certain embodiments, the disease is cystic fibrosis.

[0067] "Treating" or "treatment" includes preventing or delaying the onset of the symptoms, complications, or biochemical indicia of a disease, alleviating or ameliorating the symptoms or arresting or inhibiting further development of the disease, condition, or disorder. A "subject" is an animal to be treated or in need of treatment. A "patient" is a human subject in need of treatment.

[0068] An "effective amount" refers to that amount of an agent that is sufficient to achieve a desired and/or recited effect. In the context of a method of treatment, an "effective amount" of the therapeutic agent that is sufficient to ameliorate of one or more symptoms of a disorder and/or prevent advancement of a disorder, cause regression of the disorder and/or to achieve a desired effect.

[0069] The term "modulating" encompasses increasing, enhancing, inhibiting, decreasing, suppressing, and the like. The terms "increasing" and "enhancing" mean to cause a net gain by either direct or indirect means. As used herein, the terms "inhibiting" and "decreasing" encompass causing a net decrease by either direct or indirect means.

[0070] In some examples, CFTR activity is enhanced after administration of a compound described herein when there is an increase in the CFTR activity as compared to that in the absence of the administration of the compound. CFTR activity encompasses, for example, chloride channel activity of the CFTR, and/or other ion transport activity (for example, HCO_3^- transport). 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). Contemplated patients may have a CFTR mutation(s) from one or more classes, such as without limitation, Class I CFTR mutations, Class II CFTR mutations, Class III CFTR mutations, Class IV CFTR mutations, Class V CFTR mutations, and Class VI mutations. Contemplated subject (e.g., human subject) CFTR genotypes include, without limitation, homozygote mutations (e.g., ΔF508 / ΔF508 and R117H / R117H) and compound heterozygote mutations (e.g., ΔF508 / G551D; ΔF508 / A455E; ΔF508 / G542X; Δ508F / W1204X; Δ508F / S549N; R553X / W1316X; W1282X/N1303K, 591Δ18 / E831X; F508del/R117H/ N1303K/ 3849+10kbC>T; Δ 303K/ 384 and DF508/G178R).

[0071] In certain embodiments, the mutation is a Class I mutation, e.g., a G542X; a Class II/ I mutation, e.g., a ΔF508 / G542X compound heterozygous mutation. In other embodiments, the mutation is a Class III mutation, e.g., a G551D; a Class II/ Class III mutation, e.g., a ΔF508 / G551D compound heterozygous mutation. In still other embodiments, the mutation is a Class V mutation, e.g., a A455E; Class II/ Class V mutation, e.g., a ΔF508 / A455E compound heterozygous mutation. Of the more than 1000 known mutations of the *CFTR* gene, ΔF508 is the most prevalent mutation of CFTR which results in misfolding of the protein and impaired trafficking from the endoplasmic reticulum to the apical membrane (Dormer et al. (2001), *J. Cell Sci.* 114, 4073-4081; http://www.genet.sickkids.on.ca/app). In certain embodiments, ΔF508 CFTR activity is enhanced (e.g., increased). In certain

embodiments, ΔF508 CFTR activity and/or G542X CFTR activity and/or G551D CFTR activity and/or A455E CFTR activity is enhanced (e.g., increased). An enhancement of CFTR activity can be measured, for example, using literature described methods, including for example, Ussing chamber assays, patch clamp assays, and hBE Ieq assay (Devor et al. (2000), *Am. J. Physiol. Cell Physiol.* 279(2): C461-79; Dousmanis et al. (2002), *J. Gen. Physiol.* 119(6): 545-59; Bruscia et al. (2005), *PNAS* 103(8): 2965-2971).

[0072] As discussed above, the disclosure also encompasses a method of treating cystic fibrosis. The present disclosure can also be used to treat other conditions associated with CFTR activity, including conditions associated with deficient CFTR activity.

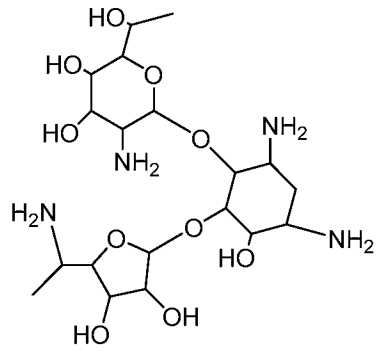
[0073] In some embodiments, the disclosure is directed to a method of treating a condition associated with deficient or decreased CFTR activity comprising administering an effective amount of a compound of Formula (Ia) or (Ib) that enhances CFTR activity. Non-limiting examples of conditions associated with deficient CFTR activity are cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, smoking-related lung diseases, such as chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, Aβ–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, and Sjogren's syndrome.

[0074] In some embodiments, disclosed methods of treatment further comprise administering an additional therapeutic agent. For example, in an embodiment, provided herein is a method of administering a disclosed compound and at least one additional therapeutic agent. In certain aspects, a disclosed method of treatment comprises administering a disclosed compound, and at least two additional therapeutic agents. Additional therapeutic agents include, for example, mucolytic agents, bronchodilators, antibiotics, anti-infective agents, anti-inflammatory agents, ion channel modulating agents, therapeutic agents used in gene therapy, CFTR correctors, and CFTR potentiators, or other agents that modulates CFTR activity. In some embodiments, at least one additional therapeutic agent is selected from the group consisting of a CFTR corrector and a CFTR potentiator. Non-limiting examples of CFTR

correctors and potentiators include VX-770 (Ivacaftor), deuterated Ivacaftor, GLPG2851, GLPG2737, GLPG2451, VX-809 (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid, VX-661 (1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-[1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(2-hydroxy-1,1-dimethylethyl)-1H-indol-5-yl]- cyclopropanecarboxamide), VX-983, VX-152, VX-440, and Ataluren (PTC124) (3-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]benzoic acid), FDL169, GLPG1837/ABBV-974 (for example, a CFTR potentiator), GLPG2665, GLPG2222 (for example, a CFTR corrector); and compounds described in, e.g., WO2014/144860 and 2014/176553, hereby incorporated by reference. Non-limiting examples of modulators include QBW-251, QR-010, NB-124, riociquat, and compounds described in, e.g., WO2014/045283; WO2014/081821, WO2014/081820, WO2014/152213; WO2014/160440, WO2014/160478, US2014027933; WO2014/0228376, WO2013/038390, WO2011/113894, WO2013/038386; and WO2014/180562, of which the disclosed modulators in those publications are contemplated as an additional therapeutic agent and incorporated by reference. Non-limiting examples of anti-inflammatory agents include N6022 (3-(5-(4-(1H-imidazol-1-yl) phenyl)-1-(4-carbamoyl-2-methylphenyl)-1H-pyrrol-2-yl) propanoic acid), CTX-4430, N1861, N1785, and N91115.

[0075] In some embodiments, the methods described herein can further include administering an additional therapeutic agent or administering at least two additional CFTR therapeutic agents. In some embodiments, the methods described herein can further include administering an additional CFTR modulator or administering at least two additional CFTR modulators. In certain embodiments, at least one CFTR modulator is a CFTR corrector (e.g., VX-809, VX-661, VX-983, VX-152, VX-440, and GLPG2222 or GLPG2665) or potentiator (e.g., ivacaftor, genistein and GLPG1837). In certain of these embodiments, one of the at least two additional therapeutic agents is a CFTR corrector (e.g., VX-809, VX-661, VX-152, VX-440, and VX-983) and the other is a CFTR potentiator (e.g., ivacaftor and genistein). In certain of these embodiments, one of the at least two additional therapeutic agents is a CFTR corrector (e.g., GLPG2222) and the other is a CFTR potentiator (e.g., GLPG1837). In certain of these embodiments, one of the at least two additional therapeutic agents is a CFTR corrector (e.g., VX-809 or VX-661) and the other is a CFTR potentiator (e.g., ivacaftor). In certain of

these embodiments, at least one CFTR modulator is an agent that enhances read-through of stop codons (e.g., NB124 or ataluren). NB124 has the structure:



[0076] In other embodiments, the methods described herein can further include administrating an epithelial sodium channel (ENaC) inhibitor (e.g., VX-371).

[0077] Accordingly, in another aspect, this disclosure provides a method of treating a condition associated with deficient or decreased CFTR activity (e.g., cystic fibrosis), which includes administering to a subject in need thereof (e.g., a human patient in need thereof) an effective amount of a disclosed compound and at least one or two additional CFTR therapeutic agent(s) (e.g., at least one or two additional CFTR therapeutic agents, e.g., in which one of the at least one or two additional therapeutic agents is optionally a CFTR corrector or modulator (e.g., VX-809, VX-661, VX-983, VX-152, VX-440, GLPG2222, NB124, ataluren) and/or the other is a CFTR potentiator (e.g., ivacaftor, genistein, and GLPG1837); e.g., one of the at least two additional therapeutic agents is GLPG2222, and the other is GLPG1837; or one of the at least two additional therapeutic agents is VX-809 or VX-661, and the other is a ivacaftor). In certain embodiments, the subject's CFTR genotype includes, without limitation, one or more Class I CFTR mutations, one or more Class II CFTR mutations, one or more Class III CFTR mutations, one or more Class IV CFTR mutations, or one or more Class V CFTR mutations, or one or more Class VI CFTR mutations. In certain embodiments, the subject's CFTR genotype includes, without limitation, one or more homozygote mutations (e.g., ΔF508 / ΔF508 or R117H / R117H) and/or one or more compound heterozygote mutations (e.g., ΔF508 / G551D; ΔF508 / A455E; ΔF508 / G542X; Δ508F / W1204X; Δ508F / S549N; R553X / W1316X; W1282X/N1303K; F508del/R117H; N1303K/ 3849+10kbC>T; ΔF508/R334W; DF508/G178R; and 591Δ18 / E831X). In certain embodiments, the subject's CFTR genotype

includes a Class I mutation, e.g., a G542X Class I mutation, e.g., a ΔF508 / G542X compound heterozygous mutation. In other embodiments, the subject's CFTR genotype includes a Class III mutation, e.g., a G551D Class III mutation, e.g., a ΔF508 / G551D compound heterozygous mutation. In still other embodiments, the subject's CFTR genotype includes a Class V mutation, e.g., a A455E Class V mutation, e.g., a ΔF508 / A455E compound heterozygous mutation. In certain embodiments, ΔF508 CFTR activity and/or G542X CFTR activity and/or G551D CFTR activity and/or A455E activity is enhanced (e.g., increased). In certain embodiments, the enhancement in activity (e.g., increase in activity) provided by the combination of the disclosed compound and one or two additional therapeutic agents is greater than additive when compared to the enhancement in activity provided by each therapeutic component individually.

Class	**Effect on CFTR protein**	**Example of mutation**
I	Shortened protein or no protein synthesized	W1282X Instead of inserting the amino acid tryptophan (W), the protein sequence is prematurely stopped (indicated by an X).
II	Protein fails to reach cell membrane	ΔF508 A phenylalanine amino acid (F) is deleted
III	Channel cannot be regulated properly	G551D A "missense" mutation: instead of a glycine amino acid (G), aspartate (D) is added
IV	Reduced chloride conductance	R117H Missense
V	Reduced levels of protein, for example, but not limited to, due to incorrect splicing of gene	3120+1G>A Splice-site mutation in gene intron 16
VI	Reduced due to protein instability	N287Y a A ->T at 991

Genotype	**Description**	**Possible Symptoms**
Δ508F / Δ508F	homozygote	Severe lung disease, pancreatic insufficient
R117H / R117H	homozygote	Congenital bilateral absence of the vas deferens, No lung or pancreas disease,

WT / Δ508F	heterozygote	Unaffected
WT / 3120+1 G>A	heterozygote	Unaffected
Δ508F / W1204X	compound heterozygote	No lung disease, pancreatic insufficient
R553X and W1316X	compound heterozygote	Mild lung disease, pancreatic insufficient
591Δ18 / E831X	compound heterozygote	No lung or pancreas disease, nasal polyps

[0078] For example, provided herein is a method of treating a patient having one or more of the following mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R , G970R, or R117H, and/or e.g., a patient with one or two copies of the F508del mutation, or one copy of the ΔF508 mutation and a second mutation that results in a gating effect in the CFTR protein (e.g., a patient that is heterozygous for ΔF508 and G551D mutation), a patient with one copy of the ΔF508 mutation and a second mutation that results in residual CFTR activity , or a patient with one copy of the ΔF508 mutation and a second mutation that results in residual CFTR activity, comprising administering an effective amount of a disclosed compound. As described herein, such exemplary methods (e.g., of a patient having one or mutations such as those described above) may include, for example, administering to such patient a combination therapy, e.g., administering (simultaneously or sequentially) an effective amount of ivacaftor to said patient and an effective amount of disclosed compound that may act as an amplifier. Such administration may result, for example, in increased chloride transport in human bronchial epithelial cells with e.g., one or two copies of mutations, e.g, ΔF508 mutation, as compared to administration of ivacaftor alone. Another combination therapy that includes a disclosed compound may also include an effective amount of a readthrough agent (e.g., ataluren, NB124) and an effect amount of disclosed compound that may act as an amplifier. Without being limited by theory, the increase in immature CFTR protein levels elicited by amplifiers such as those disclosed herein can result in CFTR mRNA

stabilization, which is consistent with a model that disclosed compounds work by enhancing CFTR efficiency. For example, acting at an early step in CFTR synthesis to provide more protein, amplifier (e.g., as disclosed herein) can be useful in combinations to boost the activity of additional CFTR modulators.

[0079] The phrase "combination therapy," as used herein, refers to an embodiment where a patient is co-administered a disclosed compound, a CFTR potentiator agent (e.g., ivacaftor) and optionally, one or more CFTR corrector agent(s) (e.g, VX-661 and/or lumacaftor) as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. For example, a beneficial effect of a combination may include, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. For example, administration of a disclosed compound with ivacaftor alone or with a CFTR corrector agent (e.g., lumacaftor or VX-661) may result in a level of function (e.g., as measured by chloride activity in HBE cells or patients that have a ΔF508 mutation, that achieves clinical improvement (or better) as compared to the chloride activity level in cells or patients with a G551D mutation receiving ivacaftor alone, or ivacaftor and a corrector agent (lumacaftor or VX-661; or for example, administration of a disclosed compound with ivacaftor alone or ivacaftor with a CFTR corrector agent (e.g., lumacaftor or VX-661) may result in a level of function (e.g., as measured by chloride activity in HBE cells or patients that have a A455E mutation, that achieves clinical improvement (or better) as compared to the chloride activity level at e.g., 50% or more of wild type cells; or upon administration of a disclosed compound and ivacaftor to a patient (e.g. having a G551D class III mutation) may show e.g., about two times or more improved activity of ivacaftor as compared to administration of ivacaftor alone. Administration of disclosed therapeutic agents in combination typically is carried out over a defined time period (usually a day, days, weeks, months or years depending upon the combination selected). Combination therapy is intended to embrace administration of multiple therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single tablet or capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential

or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, inhalational routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection or inhalation or nebulizer while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection, inhalation or nebulization.

[0080] Combination therapy also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies. Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by a day, days or even weeks.

[0081] The components of a disclosed combination may be administered to a patient simultaneously or sequentially. It will be appreciated that the components may be present in the same pharmaceutically acceptable carrier and, therefore, are administered simultaneously. Alternatively, the active ingredients may be present in separate pharmaceutical carriers, such as, conventional oral dosage forms, that can be administered either simultaneously or sequentially.

[0082] In a further aspect, a method of identifying a candidate agent that increases CFTR activity is provided, which includes: (i) contacting a cell that expresses a CFTR protein with the candidate agent and a disclosed compound; (ii) measuring the CFTR activity in the cell in the presence of the candidate agent and the disclosed compound; and (iii) 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. In certain embodiments, the cell expresses a mutant CFTR protein. In certain embodiments, CFTR activity is measured by measuring chloride channel activity of the CFTR, and/or other ion

transport activity. In certain of these embodiments, the method is high-throughput. In certain of these embodiments, the candidate agent is a CFTR corrector or a CFTR potentiator.

[0083] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in a disclosed compounds used in disclosed compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[0084] Also included in the present disclosure are methods that include administering prodrugs of the compounds described herein, for example, prodrugs of a compound of Formula (IIIa), (III), or (IV), or a pharmaceutical composition thereof or method of use of the prodrug.

[0085] The term “prodrug” refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such as in the intestinal lumen or upon transit of the intestine, blood or liver). Prodrugs are well known in the art (for example, see Rautio, Kumpulainen, *et al., Nature Reviews Drug Discovery* **2008**, *7*,

255). For example, if a compound of the disclosure or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_{1-8}) alkyl, (C_{2-12}) alkylcarbonyloxymethyl, 1-(alkylcarbonyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkylcarbonyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_{1-2})alkylamino(C_{2-3})alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_{1-2})alkyl, N,N-di(C_{1-2})alkylcarbamoyl-(C_{1-2})alkyl and piperidino-, pyrrolidino- or morpholino(C_{2-3})alkyl.

[0086] Similarly, if a compound of the disclosure contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkylcarbonyloxymethyl, 1-((C_{1-6})alkylcarbonyloxy)ethyl, 1-methyl-1-((C_{1-6})alkylcarbonyloxy)ethyl (C_{1-6})alkoxycarbonyloxymethyl, N-(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkylcarbonyl, α-amino(C_{1-4})alkylcarbonyl, arylalkylcarbonyl and α-aminoalkylcarbonyl, or α-aminoalkylcarbonyl-α-aminoalkylcarbonyl, where each α-aminoalkylcarbonyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_{1-6})alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0087] If a compound of the disclosure incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-alkylcarbonyloxyalkyl derivative, an (oxodioxolenyl)methyl derivative, an N-Mannich base, imine or enamine. In addition, a secondary amine can be metabolically cleaved to generate a bioactive primary amine, or a tertiary amine can metabolically cleaved to generate a bioactive primary or secondary amine. For examples, see Simplício, *et al., Molecules* **2008**, *13,* 519 and references therein.

[0088] The disclosure additionally includes use of clathrates of the compounds described herein, pharmaceutical compositions comprising the clathrates, and methods of use of the

clathrates. In some embodiments, the disclosure is directed to clathrates of a disclosed compound of e.g., Formula (IIIa), (III), or (IV), or a pharmaceutical composition thereof.

[0089] As discussed above, the disclosure includes administration of pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and a compound described herein. A disclosed compound, or a pharmaceutically acceptable salt, solvate, clathrate or prodrug thereof, can be administered in pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient. The excipient can be chosen based on the expected route of administration of the composition in therapeutic applications. The route of administration of the composition depends on the condition to be treated. For example, intravenous injection may be suitable for treatment of a systemic disorder and oral administration may be suitable to treat a gastrointestinal disorder. The route of administration and the dosage of the composition to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. A pharmaceutical composition comprising a disclosed compound or a pharmaceutically acceptable salt, solvate, clathrate or prodrug, can be administered by a variety of routes including, but not limited to, parenteral, oral, pulmonary, ophthalmic, nasal, rectal, vaginal, aural, topical, buccal, transdermal, intravenous, intramuscular, subcutaneous, intradermal, intraocular, intracerebral, intralymphatic, intraarticular, intrathecal and intraperitoneal. The compositions can also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the pharmacologic agent or composition. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like. Pharmaceutical compositions can also include large, slowly metabolized macromolecules such as proteins, polysaccharides such as chitosan, polylactic acids, polyglycolic acids and copolymers (such as latex functionalized

SEPHAROSE™, agarose, cellulose, and the like), polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes).

[0090] The compositions can be administered parenterally such as, for example, by intravenous, intramuscular, intrathecal or subcutaneous injection. Parenteral administration can be accomplished by incorporating a composition into a solution or suspension. Such solutions or suspensions may also include sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents. Parenteral formulations may also include antibacterial agents such as, for example, benzyl alcohol or methyl parabens, antioxidants such as, for example, ascorbic acid or sodium bisulfite and chelating agents such as EDTA. Buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose may also be added. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

[0091] Additionally, auxiliary substances, such as wetting or emulsifying agents, surfactants, pH buffering substances and the like can be present in compositions. Other components of pharmaceutical compositions are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, and mineral oil. In general, glycols such as propylene glycol or polyethylene glycol are suitable liquid carriers, particularly for injectable solutions.

[0092] Injectable formulations can be prepared either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The preparation also can also be emulsified or encapsulated in liposomes or micro particles such as polylactide, polyglycolide, or copolymer for enhanced adjuvant effect, as discussed above [Langer, *Science* 249: 1527, 1990 and Hanes, *Advanced Drug Delivery Reviews* 28: 97-119, 1997]. The compositions and pharmacologic agents described herein can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient.

[0093] Additional formulations suitable for other modes of administration include oral, intranasal, and pulmonary formulations, suppositories, transdermal applications and ocular delivery. For suppositories, binders and carriers include, for example, polyalkylene glycols or

triglycerides; such suppositories can be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10%, or about 1% to about 2%. Oral formulations include excipients, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, and magnesium carbonate. Topical application can result in transdermal or intradermal delivery. Transdermal delivery can be achieved using a skin patch or using transferosomes. [Paul et al., *Eur. J. Immunol.* 25: 3521-24, 1995; Cevc et al., *Biochem. Biophys. Acta* 1368: 201-15, 1998].

[0094] For the purpose of oral therapeutic administration, the pharmaceutical compositions can be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. Tablets, pills, capsules, troches and the like may also contain binders, excipients, disintegrating agent, lubricants, glidants, sweetening agents, and flavoring agents. Some examples of binders include microcrystalline cellulose, gum tragacanth or gelatin. Examples of excipients include starch or lactose. Some examples of disintegrating agents include alginic acid, corn starch and the like. Examples of lubricants include magnesium stearate or potassium stearate. An example of a glidant is colloidal silicon dioxide. Some examples of sweetening agents include sucrose, saccharin and the like. Examples of flavoring agents include peppermint, methyl salicylate, orange flavoring and the like. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used. In another embodiment, the composition is administered as a tablet or a capsule.

[0095] Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor, and the like. For vaginal administration, a pharmaceutical composition may be presented as pessaries, tampons, creams, gels, pastes, foams or spray.

[0096] The pharmaceutical composition can also be administered by nasal administration. As used herein, nasally administering or nasal administration includes administering the composition to the mucus membranes of the nasal passage or nasal cavity of the patient. As used herein, pharmaceutical compositions for nasal administration of a composition include therapeutically effective amounts of the compounds prepared by well-known methods to be

administered, for example, as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. Administration of the composition may also take place using a nasal tampon or nasal sponge.

[0097] For topical administration, suitable formulations may include biocompatible oil, wax, gel, powder, polymer, or other liquid or solid carriers. Such formulations may be administered by applying directly to affected tissues, for example, a liquid formulation to treat infection of conjunctival tissue can be administered dropwise to the subject's eye, or a cream formulation can be administered to the skin.

[0098] Rectal administration includes administering the pharmaceutical compositions into the rectum or large intestine. This can be accomplished using suppositories or enemas. Suppository formulations can easily be made by methods known in the art. For example, suppository formulations can be prepared by heating glycerin to about 120 ^{o}C, dissolving the pharmaceutical composition in the glycerin, mixing the heated glycerin after which purified water may be added, and pouring the hot mixture into a suppository mold.

[0099] Transdermal administration includes percutaneous absorption of the composition through the skin. Transdermal formulations include patches, ointments, creams, gels, salves and the like.

[0100] In addition to the usual meaning of administering the formulations described herein to any part, tissue or organ whose primary function is gas exchange with the external environment, for purposes of the present disclosure, "pulmonary" will also mean to include a tissue or cavity that is contingent to the respiratory tract, in particular, the sinuses. For pulmonary administration, an aerosol formulation containing the active agent, a manual pump spray, nebulizer or pressurized metered-dose inhaler as well as dry powder formulations are contemplated. Suitable formulations of this type can also include other agents, such as antistatic agents, to maintain the disclosed compounds as effective aerosols.

[0101] A drug delivery device for delivering aerosols comprises a suitable aerosol canister with a metering valve containing a pharmaceutical aerosol formulation as described and an actuator housing adapted to hold the canister and allow for drug delivery. The canister in the drug delivery device has a head space representing greater than about 15% of the total volume of the canister. Often, the compound intended for pulmonary administration is dissolved,

suspended or emulsified in a mixture of a solvent, surfactant and propellant. The mixture is maintained under pressure in a canister that has been sealed with a metering valve.

[0102] The disclosure also encompasses the treatment of a condition associated with a dysfunction in proteostasis in a subject comprising administering to said subject an effective amount of a disclosed compound that enhances, improves or restores proteostasis of a protein. Proteostasis refers to protein homeostasis. Dysfunction in protein homeostasis is a result of protein misfolding, protein aggregation, defective protein trafficking or protein degradation. For example, the disclosure encompasses administering a compound of Formula (Ia) or (Ib) that corrects protein misfolding, reduces protein aggregation, corrects or restores protein trafficking and/or affects protein degradation for the treatment of a condition associated with a dysfunction in proteostasis. In some aspects of the disclosure, a compound of Formula (Ia) or (Ib) that corrects protein misfolding and/or corrects or restores protein trafficking is administered. In cystic fibrosis, the mutated or defective enzyme is the cystic fibrosis transmembrane conductance regulator (CFTR). One of the most common mutations of this protein is ΔF508 which is a deletion (Δ) of three nucleotides resulting in a loss of the amino acid phenylalanine (F) at the 508th (508) position on the protein. As described above, mutated cystic fibrosis transmembrane conductance regulator exists in a misfolded state and is characterized by altered trafficking as compared to the wild type CFTR. Additional exemplary proteins of which there can be a dysfunction in proteostasis, for example that can exist in a misfolded state, include, but are not limited to, glucocerebrosidase, hexosamine A, aspartylglucosaminidase, α-galactosidase A, cysteine transporter, acid ceramidase, acid α-L-fucosidase, protective protein, cathepsin A, acid β-glucosidase, acid β-galactosidase, iduronate 2-sulfatase, α-L-iduronidase, galactocerebrosidase, acid α -mannosidase, acid β -mannosidase, arylsulfatase B, arylsulfatase A, *N*-acetylgalactosamine-6-sulfate sulfatase, acid β -galactosidase, *N*-acetylglucosamine-1-phosphotransferase, acid sphingmyelinase, NPC-1, acid α-glucosidase, β-hexosamine B, heparin *N*-sulfatase, α -*N*-acetylglucosaminidase, α -glucosaminide *N*-acetyltransferase, *N*-acetylglucosamine-6-sulfate sulfatase, α -*N*-acetylgalactosaminidase, α -neuramidase, β -glucuronidase, β-hexosamine A and acid lipase, polyglutamine, α -synuclein, TDP-43, superoxide dismutase (SOD), Aβ peptide, tau protein transthyretin and insulin. The disclosed compounds may be used to restore proteostasis (e.g., correct folding and/or alter trafficking) of the proteins described above.

[0103] Protein conformational diseases encompass gain of function disorders and loss of function disorders. In one embodiment, the protein conformational disease is a gain of function disorder. The terms "gain of function disorder," "gain of function disease," "gain of toxic function disorder" and "gain of toxic function disease" are used interchangeably herein. A gain of function disorder is a disease characterized by increased aggregation-associated proteotoxicity. In these diseases, aggregation exceeds clearance inside and/or outside of the cell. Gain of function diseases include, but are not limited to, neurodegenerative diseases associated with aggregation of polyglutamine, Lewy body diseases, amyotrophic lateral sclerosis, transthyretin-associated aggregation diseases, Alzheimer's disease, Machado-Joseph disease, cerebral B-amyloid angiopathy, retinal ganglion cell degeneration, tautopathies (progressive supranuclear palsy, corticobasal degeneration, frontotemporal lobar degeneration), cerebral hemorrhage with amyloidosis, Alexander disease, Serpinopathies, familial amyloidotic neuropathy, senile systemic amyloidosis, ApoAI amyloidosis, ApoAII amyloidosis, ApoAIV amyloidosis, familial amyloidosis of the Finnish type, lysozyme amyloidosis, fibrinogen amyloidosis, dialysis amyloidosis, inclusion body myositis/myopathy, cataracts, medullary thyroid carcinoma, cardiac atrial amyloidosis, pituitary prolactinoma, hereditary lattice corneal dystrophy, cutaneous lichen amyloidosis, corneal lactoferrin amyloidosis, corneal lactoferrin amyloidosis, pulmonary alveolar proteinosis, odontogenic tumor amyloid, seminal vesical amyloid, sickle cell disease, critical illness myopathy, von Hippel-Lindau disease, spinocerebellar ataxia 1, Angelman syndrome, giant axon neuropathy, inclusion body myopathy with Paget disease of bone, frontotemporal dementia (IBMPFD) and prion diseases. Neurodegenerative diseases associated with aggregation of polyglutamine include, but are not limited to, Huntington's disease, dentatorubral and pallidoluysian atrophy, several forms of spino-cerebellar ataxia, and spinal and bulbar muscular atrophy. Alzheimer's disease is characterized by the formation of two types of aggregates: extracellular aggregates of Aβ peptide and intracellular aggregates of the microtubule associated protein tau. Transthyretin-associated aggregation diseases include, for example, senile systemic amyloidoses and familial amyloidotic neuropathy. Lewy body diseases are characterized by an aggregation of α-synuclein protein and include, for example, Parkinson's disease, Lewy body dementia (LBD) and multiple system atrophy (SMA). Prion diseases (also known as transmissible spongiform encephalopathies or TSEs) are characterized by aggregation of prion proteins. Exemplary human prion diseases are Creutzfeldt-Jakob Disease (CJD), Variant Creutzfeldt-Jakob Disease,

Gerstmann-Straussler-Scheinker Syndrome, Fatal Familial Insomnia and Kuru. In another embodiment, the misfolded protein is alpha-1 anti-trypsin.

[0104] In a further embodiment, the protein conformation disease is a loss of function disorder. The terms "loss of function disease" and "loss of function disorder" are used interchangeably herein. Loss of function diseases are a group of diseases characterized by inefficient folding of a protein resulting in excessive degradation of the protein. Loss of function diseases include, for example, lysosomal storage diseases. Lysosomal storage diseases are a group of diseases characterized by a specific lysosomal enzyme deficiency which may occur in a variety of tissues, resulting in the build-up of molecules normally degraded by the deficient enzyme. The lysosomal enzyme deficiency can be in a lysosomal hydrolase or a protein involved in the lysosomal trafficking. Lysosomal storage diseases include, but are not limited to, aspartylglucosaminuria, Fabry's disease, Batten disease, Cystinosis, Farber, Fucosidosis, Galactasidosialidosis, Gaucher's disease (including Types 1, 2 and 3), Gm1 gangliosidosis, Hunter's disease, Hurler-Scheie's disease, Krabbe's disease, α-Mannosidosis, β-Mannosidosis, Maroteaux-Lamy's disease, Metachromatic Leukodystrophy, Morquio A syndrome, Morquio B syndrome, Mucolipidosis II, Mucolipidosis III, Neimann-Pick Disease (including Types A, B and C), Pompe's disease, Sandhoff disease, Sanfilippo syndrome (including Types A, B, C and D), Schindler disease, Schindler-Kanzaki disease, Sialidosis, Sly syndrome, Tay-Sach's disease and Wolman disease.

[0105] In another embodiment, the disease associated with a dysfunction in proteostasis is a cardiovascular disease. Cardiovascular diseases include, but are not limited to, coronary artery disease, myocardial infarction, stroke, restenosis and arteriosclerosis. Conditions associated with a dysfunction of proteostasis also include ischemic conditions, such as, ischemia/reperfusion injury, myocardial ischemia, stable angina, unstable angina, stroke, ischemic heart disease and cerebral ischemia.

[0106] In yet another embodiment, the disease associated with a dysfunction in proteostasis is diabetes and/or complications of diabetes, including, but not limited to, diabetic retinopathy, cardiomyopathy, neuropathy, nephropathy, and impaired wound healing.

[0107] In a further embodiment, the disease associated with a dysfunction in proteostasis is an ocular disease including, but not limited to, age-related macular degeneration (AMD),

diabetic macular edema (DME), diabetic retinopathy, glaucoma, cataracts, retinitis pigmentosa (RP) and dry macular degeneration.

[0108] In yet additional embodiments, the method of the disclosure is directed to treating a disease associated with a dysfunction in proteostasis, wherein the disease affects the respiratory system or the pancreas. In certain additional embodiments, the methods of the disclosure encompass treating a condition selected from the group consisting of polyendocrinopathy/hyperinsulinemia, diabetes mellitus, Charcot-Marie Tooth syndrome, Pelizaeus-Merzbacher disease, and Gorham's Syndrome.

[0109] Additional conditions associated with a dysfunction of proteostasis include hemoglobinopathies, inflammatory diseases, intermediate filament diseases, drug-induced lung damage and hearing loss. The disclosure also encompasses methods for the treatment of hemoglobinopathies (such as sickle cell anemia), an inflammatory disease (such as inflammatory bowel disease, colitis, ankylosing spondylitis), intermediate filament diseases (such as non-alcoholic and alcoholic fatty liver disease) and drug induced lung damage (such as methotrexate-induced lung damage). The disclosure additionally encompasses methods for treating hearing loss, such as noise-induced hearing loss, aminoglycoside-induced hearing loss, and cisplatin-induced hearing loss.

[0110] Additional conditions include those associated with a defect in protein trafficking and that can be treated according to methods of the disclosure include: PGP mutations, hERG trafficking mutations, nephrongenic diabetes insipidus mutations in the arginine-vasopressin receptor 2, persistent hyperinsulinemic hypoglycemia of infancy (PHH1) mutations in the sulfonylurea receptor 1, and α1AT.

[0111] The disclosure is illustrated by the following examples which are not meant to be limiting in any way.

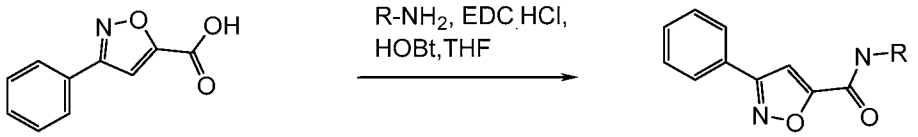
EXEMPLIFICATION

[0112] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that

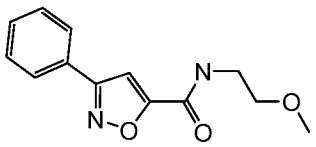
reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials. At least some of the compounds identified as "intermediates" herein are contemplated as compounds of the disclosure.

General procedure (1) for amide coupling:

[0113] EDC·HCl (1.98 mmol), HOBt·H_2O (1.32 mmol) and amine (1.45 mmol) were added to a solution of 3-phenylisoxazole-5-carboxylic acid (1.32 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 15 h at room temperature and concentrated to dryness. The crude solid was extracted with EtOAc (3 x 10 mL) and washed with water. The combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The crude compound was purified by Combiflash to give the corresponding amide.

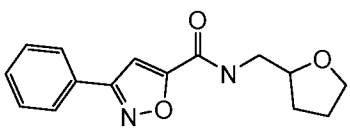


Example 1: N-(2-methoxyethyl)-3-phenylisoxazole-5-carboxamide:



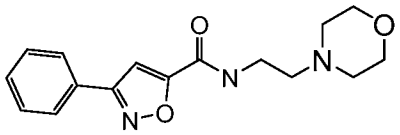
[0114] Compound 1 was obtained as an off white solid using the general procedure 1 (0.120 g, 37.0%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82-7.79 (m, 2H), 7.50-7.45 (m, 3H), 7.21 (s, 1H), 6.98-6.97 (br, 1H), 3.68-3.64 (m, 2H), 3.57-3.55 (t, 2H), 3.40 (s, 3H); LCMS $[M+H]^+$ 247.2, HPLC purity: 99.76% at 220 nm and 99.64% at 254 nm.

Example 2: 3-phenyl-N-((tetrahydrofuran-2-yl)methyl)isoxazole-5-carboxamide:



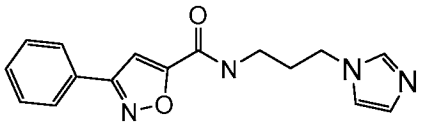
[0115] Compound 2 was obtained as a white solid using the general procedure 1 (0.110 g, 30.6%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.80 (m, 2H), 7.49-7.45 (m, 3H), 7.25-7.21 (d, J = 14.9Hz, 1H), 6.95 (br, 1H), 4.08-4.06 (m, 1H), 3.92-3.89 (m, 1H), 3.81-3.71 (m, 2H), 3.44-3.39 (m, 1H), 2.06-1.99 (m, 1H), 1.96-1.91(m, 2H), 1.63-1.58(m, 1H); LCMS $[M+H]^+$ 273.2. HPLC purity: 99.78% at 220 nm and 99.79% at 254 nm.

Example 3: N-(2-morpholinoethyl)-3-phenylisoxazole-5-carboxamide



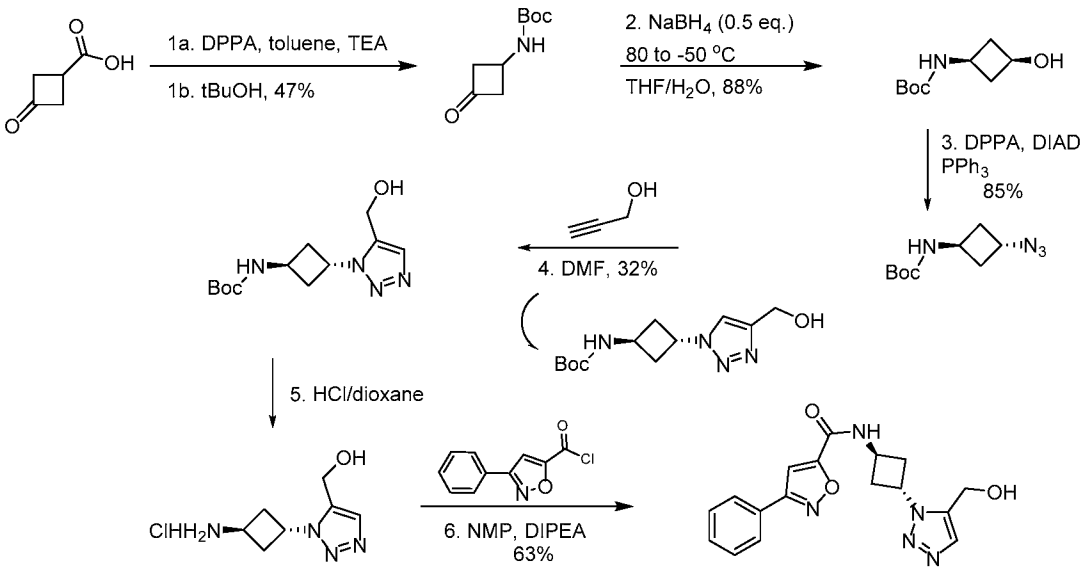
[0116] Compound 3 was obtained as a white solid using the general procedure 1 (0.125 g, 31.5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.80 (m, 2H), 7.49-7.46 (m, 3H), 7.21 (s, 2H), 3.75-3.72 (t, 4H), 3.58-3.53 (q, 2H), 2.61-2.58 (t, 2H), 2.51-2.50 (m, 4H); LCMS $[M+H]^+$ 302.1, HPLC purity: 99.81% at 220 nm and 99.87% at 254 nm.

Example 4: N-(3-(1H-imidazol-1-yl)propyl)-3-phenylisoxazole-5-carboxamide



[0117] Compound 4 was obtained as a white solid using the general procedure 1 (0.127 g, 32.6%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82-7.79 (m, 2H), 7.52 (s, 1H), 7.50-7.46 (m, 3H), 7.22 (s, 1H),7.08 (s, 1H), 6.98-6.97 (m, 1H), 6.79-6.76 (m, 1H), 4.08-4.04 (t, 2H), 3.52-3.47 (m, 2H), 2.18-2.11 (m, 2H); LCMS $[M+H]^+$ 297.2. HPLC purity: 98.05% at 220 nm and 97.78% at 254 nm.

Example 5: N-(trans-3-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0118] **Step 1: tert-butyl (3-oxocyclobutyl)carbamate**: DPPA (4.0 g, 1.1 eq.) was added dropwise to a cold (-5~5 °C) solution of 3-oxocyclobutanecarboxylic acid (1.5 g, 1.0 eq.) and TEA (1.5 g, 1.1 eq.) in toluene (30 mL), and the mixture stirred at -5~0 °C for 16 h. The reaction mixture was washed with $NaHCO_3$ (2 x 9 mL), water (1 x 9 mL) and NaCl aq. (1 x 4.5 mL) at 0~10 °C. The organic phase was dried over Na_2SO_4, filtered and t-BuOH (7.5 mL) added to the filtrate. The reaction mixture was heated at 90~100 °C for 16 h. The mixture was concentrated under vacuum at 60~70 °C and then suspended in TBME (4.5 mL), filtered and the solid dried in air to give 1.15 g (purity: 98.5%, yield: 47.2%) of product as a white solid.

[0119] **Step 2: tert-butyl (cis-3-hydroxycyclobutyl)carbamate**: a solution of tert-butyl (3-oxocyclobutyl)carbamate (200 mg, 1.0 eq.) in THF (1 mL) was added dropwise to a cold (below -70 °C) solution of $NaBH_4$ (20.4 mg, 0.5 eq.) in THF (1.8 mL) and water (2 mL), maintaining the temperature at -80~-70 °C (ca. for 2 h for completion of addition). The mixture was stirred at-60~-50 °C for 3 h, water (2 mL) was added to the reaction mixture and allowed to reach up to 15 °C. The reaction mixture is then extracted with ethyl acetate (2 mL, 2 x 1 mL) and the combined organic layers were washed with brine (1 mL). The organic layer was concentrated under vacuum at 35~40 °C, the solid dissolved in toluene (1 mL, 80~90 °C) and gradually cooled to 25-30 °C for 2.5 h. The mixture was stirred for 2 h at 25-30 °C, filtered, and the solid dried in air to give the product (177 mg with ratio of cis:trans (96.4:3.6), yield: 87.6%) as an off-white solid.

[0120] Step 3: tert-butyl (trans-3-azidocyclobutyl)carbamate: a solution of PPh_3 (315 mg) and DIAD (243 mg) in THF (3 mL) was stirred for 20 min at 0-10 °C. A solution of tert-butyl (cis-3-hydroxycyclobutyl)carbamate (150 mg, 1.0 eq.) and DPPA (265 mg, 1.2 eq.) in THF (1 ml) was added dropwise, the mixture warmed to 25-30 °C, and stirred for 2 h. Brine (3 mL) was added to the reaction mixture, extracted with ethyl acetate (3 mL) and the combined organic layers concentrated under vacuum to give a crude oil. The mixture was purified by SiO_2 column chromatography and eluted with ethyl acetate/petroleum ether (0%~10%) gradually. The product was suspended in *n*-heptane (0.3 mL) and stirred for 0.5 h at 20~25 °C. The mixture was filtered and the solid dried in air to give the product in 85% yield and ratio of cis/trans= 4:96 checked by ^1H NMR.

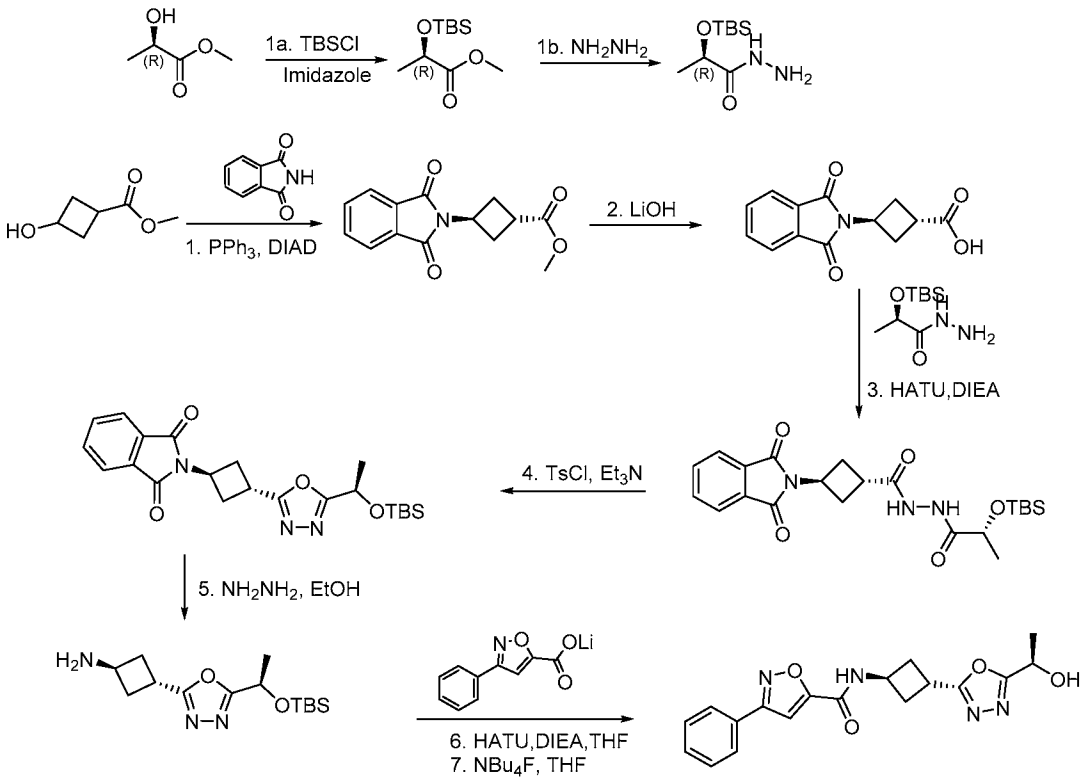
[0121] Step 4: tert-butyl (trans-3-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)carbamate: a solution of tert-butyl (trans-3-azidocyclobutyl)carbamate (246 mg, 1.0 eq.) and prop-2-yn-1-ol (326 mg, 5.0 eq.) in DMF (1.2 mL) was heated at 90~ 95 °C for 20 h. The mixture was concentrated under vacuum at 65 °C to give ~1:1 mixture of 4 and 5 regioisomers (353 mg). The mixture was purified by SFC to give tert-butyl (trans-3-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)carbamate (101 mg, P: 99.9% (205 nm), Y: 32%) as a solid.

[0122] Step 5: (1-(trans-3-aminocyclobutyl)-1H-1,2,3-triazol-5-yl)methanol hydrochloride: tert-butyl (trans-3-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)carbamate (101 mg, 1.0 eq.) was added slowly (5 portions) to a solution of HCl/dioxane (3.5 mol/L, 2 mL) at 20~30 °C and stirred for 18 h at 20~30 °C. The reaction mixture was concentrated under vacuum at 55 °C to give the product (93.4 mg, assay 67% based on free base, Y: 100%) as a solid.

[0123] Step 6: N-(trans-3-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide: DIPEA (388 mg, 3.00 mmol, 3.00 equiv) was added dropwise to a 0 °C solution of lithio 3-phenyl-1,2-oxazole-5-carboxylate (190 mg, 0.97 mmol, 1.00 equiv), [1-[trans-3-aminocyclobutyl]-1H-1,2,3-triazol-5-yl]methanol hydrochloride (204 mg, 1.00 mmol, 1.00 equiv) and HATU (684 mg, 1.80 mmol, 1.80 equiv) in DMF (5 mL). The resulting solution was stirred for 1 hour at room temperature and diluted with 50 mL of water/ice. The resulting solution was extracted with ethyl acetate (3 x 50 mL) and the organic

layers combined. The resulting mixture was washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, H_2O/CH_3CN=100:1 increasing to H_2O/CH_3CN=1:100 within 30 min; Detector, UV 254 nm to give 100 mg (30%) of 3-phenyl-N-[trans-3-[5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LC-MS (ES, *m/z*): $[M+1]^+$ = 340. ^1H NMR (400MHz, DMSO-d_6): δ 9.54-9.52 (d, *J* = 7.2 Hz, 1H), 7.96-7.94 (m, 2H), 7.69-7.63 (m, 2H), 7.56-7.54 (m, 3H), 5.45-5.42 (t, *J* = 5.6 Hz, 1H), 5.27-5.20 (m, 1H), 4.80-4.71 (m, 1H), 4.56-4.55 (d, *J* = 5.6 Hz, 2H), 2.93-2.87 (m, 2H), 2.81-2.75 (m, 2H).

Example 6: N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0124] **Step 1a: methyl (2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanoate**: into a 250-mL round-bottom flask, was placed a solution of methyl (2*R*)-2-hydroxypropanoate (5 g, 48.03 mmol, 1.00 equiv) and imidazole (6.5 g, 95.59 mmol, 2.00 equiv) in dichloromethane (100 mL). This was followed by the addition of a solution of tert-butyl(chloro)dimethylsilane (8.7 g, 57.72 mmol, 1.20 equiv) in dichloromethane (50 mL) dropwise with stirring at 0 °C. The

resulting solution was stirred for 2 hours at room temperature. The reaction was then quenched by the addition of 100 mL of water/ice. The resulting solution was extracted with dichloromethane (3 x 100 mL) and the organic layers combined. The resulting mixture was washed with brine (3 x 50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give 7 g (67%) of methyl (2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanoate as colorless oil.

[0125] Step 1b: (2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazide: into a 250-mL round-bottom flask, was placed a solution of methyl (2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanoate (7 g, 32.06 mmol, 1.00 equiv) in ethanol (100 mL). To the solution was added hydrazine (10 g, 159.81 mmol, 5.00 equiv, 80%). The resulting solution was stirred for 15 hours at 90 °C in an oil bath. The resulting solution was quenched by the addition of water/ice. The resulting solution was extracted with ethyl acetate (3 x 100 mL) and the organic layers combined. The resulting mixture was washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give 6.5 g (93%) of (2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazide as colorless oil. LC-MS (ES, *m/z*): $[M+1]^+$ = 219.

[0126] Step 1: methyl (trans-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylate : into a 250-mL round-bottom flask, under nitrogen, was placed a solution of methyl 3-cis-hydroxycyclobutane-1-carboxylate (8 g, 61.47 mmol, 1.00 equiv), 2,3-dihydro-1H-isoindole-1,3-dione (18.1 g, 123.02 mmol, 2.00 equiv) and triphenylphosphine (32.3 g, 123.15 mmol, 2.00 equiv) in THF (100 mL). This was followed by the addition of DIAD (24.9 g, 123.14 mmol, 2.00 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 2.5 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). The crude product was re-crystallized from petroleum ether/ethyl acetate in the ratio of 10:1 to give 7.2 g (45%) of methyl trans-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylate as a white solid. LC-MS (ES, *m/z*): $[M+1]^+$ = 260. ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.85-7.82 (m, 2H), 7.74-7.71 (m, 2H), 5.08-5.04 (m, 1H), 3.75 (s, 3H), 3.34-3.32 (m, 1H), 3.20-3.12 (m, 2H), 2.66-2.60 (m, 2H).

[0127] Step 2: trans-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylic acid: into a 100-mL round-bottom flask, was placed a solution of methyl trans-3-

(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylate (7.2 g, 27.77 mmol, 1.00 equiv) in 1,4-dioxane (100 mL). To the solution was added 5M hydrogen chloride aqueous (10 mL). The resulting solution was stirred for 4 hours at 80 °C in an oil bath. The resulting mixture was concentrated under vacuum to give 6.2 g (91%) of trans-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylic acid as a white solid. LC-MS (ES, *m/z*): $[M-1]^-$ = 244.

[0128] Step 3: (2*R*)-2-[(tert-butyldimethylsilyl)oxy]-N-[trans-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutyl]carbonyl]propanehydrazide: into a 250-mL round-bottom flask, was placed a solution of trans-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylic acid (6.2 g, 25.28 mmol, 1.00 equiv), (2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazide (6.61 g, 30.27 mmol, 1.20 equiv) and HATU (14.4 g, 37.89 mmol, 1.50 equiv) in THF (100 mL). This was followed by the addition of DIEA (9.81 g, 75.91 mmol, 3.00 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 1 hour at room temperature. The reaction was then quenched by the addition of 100 mL of water/ice. The resulting solution was extracted with ethyl acetate (3 x 50 mL) and the organic layers combined. The resulting mixture was washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:4) to give 7 g (62%) of (2*R*)-2-[(tert-butyldimethylsilyl)oxy]-N-[trans-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutyl]carbonyl]propanehydrazide as colorless oil. LC-MS (ES, *m/z*): $[M+1]^+$ = 446.

[0129] Step 4: 2-[trans-3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-2,3-dihydro-1H-isoindole-1,3-dione: into a 250-mL round-bottom flask, was placed a solution of (2*R*)-2-[(tert-butyldimethylsilyl)oxy]-N-[[trans-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutyl]carbonyl]propanehydrazide (6.95 g, 15.60 mmol, 1.00 equiv) and TEA (7.89 g, 77.97 mmol, 5.00 equiv) in dichloromethane (100 mL). This was followed by the addition of a solution of 4-methylbenzene-1-sulfonyl chloride (8.92 g, 46.79 mmol, 3.00 equiv) in dichloromethane (50 mL) dropwise with stirring at 0 °C. The resulting solution was stirred for 15 hours at room temperature. The reaction was then quenched by the addition of 100 mL of water/ice. The resulting solution was extracted with dichloromethane (2 x 50 mL) and the organic layers combined. The resulting mixture was washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude

product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, H_2O/CH_3CN=100:1 increasing to H_2O/CH_3CN=1:100 within 30 min; Detector, UV 254 nm to give 3.28 g (49%) of 2-[trans-3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-2,3-dihydro-1H-isoindole-1,3-dione as colorless oil. LC-MS (ES, *m/z*): $[M+1]^+$ = 428. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.72-7.70 (m, 2H), 7.60-7.58 (m, 2H), 5.04-4.96 (m, 2H), 3.83-3.78 (m, 1H), 3.26-3.24 (m, 2H), 2.67-2.62 (m, 2H), 1.49-1.48 (d, *J* = 6.8Hz, 3H), 0.76 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

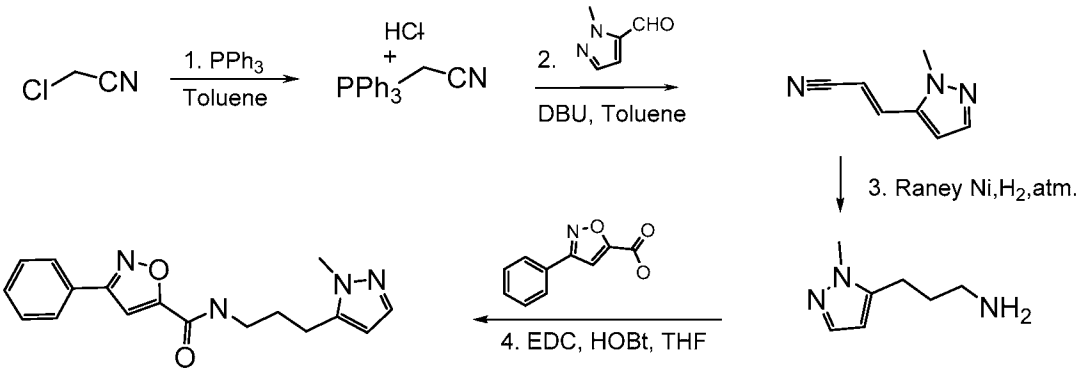
[0130] Step 5: trans-3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutan-1-amine: into a 250-mL round-bottom flask, was placed a solution of 2-[trans-3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-2,3-dihydro-1H-isoindole-1,3-dione (1.18 g, 2.76 mmol, 1.00 equiv) in ethanol (100 mL). To the solution was added hydrazine hydrate (3.45 g, 55.13 mmol, 20.00 equiv, 80%). The resulting solution was stirred for 3 hours at room temperature. The solids were filtered and the resulting mixture concentrated under vacuum to give 760 mg (crude) of trans-3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutan-1-amine as a colorless oil. LC-MS (ES, *m/z*): $[M+1]^+$ = 298.

[0131] Step 6: N-(trans-3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenyl-1,2-oxazole-5-carboxamide: into a 100-mL round-bottom flask, was placed a solution of lithio 3-phenyl-1,2-oxazole-5-carboxylate (300 mg, 1.54 mmol, 1.20 equiv), 3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutan-1-amine (380 mg, 1.28 mmol, 1.00 equiv) and HATU (728 mg, 1.92 mmol, 1.50 equiv) in THF (50 mL). This was followed by the addition of DIEA (500 mg, 3.87 mmol, 3.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 1 hour at room temperature. The resulting solution was diluted with 50 mL of water/ice. The resulting solution was extracted with ethyl acetate (3x50 mL) and the organic layers combined. The resulting mixture was washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give 300 mg (50%) of N-(trans-3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenyl-1,2-oxazole-5-carboxamide as an off-white crude solid. LC-MS (ES, *m/z*): $[M+1]^+$ = 469.

[0132] Step 7: N-(trans-3-[5-[(1*R*)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenyl-1,2-oxazole-5-carboxamide: into a 50-mL round-bottom flask, was placed a solution

of N-(3-[trans-5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenyl-1,2-oxazole-5-carboxamide (300 mg, 0.64 mmol, 1.00 equiv) and TBAF (1mol/L in tetrahydrofuran, 1 mL) in THF (5 mL). The resulting solution was stirred for 3 hours at room temperature, diluted with 20 mL of water. The resulting solution was extracted with ethyl acetate (3 x 30 mL) and the organic layers combined. The resulting mixture was washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, H_2O/CH_3CN=100:1 increasing to H_2O/CH_3CN=1:100 within 30 min; Detector, UV 254 nm to give 149.2 mg (66%) of N-(trans-3-[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenyl-1,2-oxazole-5-carboxamide (Compound A) as a white solid. LC-MS (ES, *m/z*): $[M+1]^+$ = 355. ^{1}H NMR (400MHz, DMSO-d_6): δ 9.48-9.46 (d, *J* = 7.6 Hz, 1H), 7.96-7.93 (m, 2H), 7.67 (s, 1H), 7.56-7.54 (m, 3H), 5.95-5.94 (d, *J* = 5.6Hz, 1H), 4.95-4.89 (m, 1H), 4.73-4.63 (m, 1H), 3.77-3.71 (m, 1H), 2.73-2.50 (m, 4H), 1.50-1.48 (d, *J* = 6.8Hz, 3H).

Example 7: N-(3-(1-methyl-1H-pyrazol-5-yl)propyl)-3-phenylisoxazole-5-carboxamide



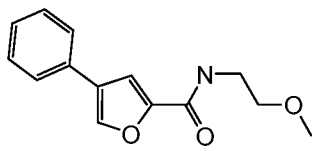
[0133] **Step 1: Cyanomethyl triphenylphosphonium chloride**: chloroacetonitrile (10 g, 0.132 mol) was added dropwise to a solution of triphenylphosphine (23.5 g, 0.0895 mol) in (120 mL) toluene and refluxed for 6 h. The reaction mixture was cooled to room temperature and the solids were filtered and washed with (2 x 20 mL) diethyl ether to give the product (15 g, 49.58%) as a white solid. ^{1}H-NMR (400 MHz, DMSO) δ 8.02-7.97 (m, 3H), 7.90-7.79 (m, 12H), 5.94 (s, 1H), 5.90 (s, 1H); LCMS $[M+H]^+$ 301.7.

[0134] Step 2: 3-(2-Methyl-2H-pyrazol-3-yl)-acrylonitrile (4): To a stirred solution of 2-Methyl-2H-pyrazole-3-carbaldehyde **3** (3.8 g, 0.0345 mol) in toluene (50 mL) was added cyanomethyl triphenylphosphonium chloride (12.8 g, 0.0389 mol) at room temperature. DBU (1.52 mL, 0.0099 mol) was then added dropwise and heated to reflux for 3 h. After completion of the reaction the toluene was distilled off completely under vacuum. The resulting crude product was purified on combi flash chromatography (the desired product eluting in 15% EtOAc:hexane) to afford the product (1.1 g, 24.01% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.46-7.45 (d, *J* = 176Hz, 1H), 7.3-7.25 (m, 1H), 6.56(s, 1H), 5.79-5.75 (d, *J* = 16.34Hz, 1H), 3.93 (s, 3H). LCMS $[M+H]^+$: 134.1.

[0135] Step 3: 3-(1-methyl-1H-pyrazol-5-yl)propan-1-amine: Raney Ni (1 g, 50 % in water suspension) was added to a solution of 3-(2-methyl-2H-pyrazol-3-yl)-acrylonitrile (1.0 g, 0.0075 mol) in ethanol (10 mL)at room temperature. The reaction mixture was then stirred under a hydrogen atmosphere for 16 h, filtered through a celite bed and was washed with ethanol (2 x 10 mL). The filtrate was evaporated under vacuum to afford the compound (0.9 g, 86.53 % yield) as a yellow oil. The crude product was used directly for amide coupling.

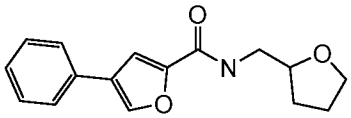
[0136] Step 4: N-(3-(1-methyl-1H-pyrazol-5-yl)propyl)-3-phenylisoxazole-5-carboxamide: EDC·HCl (0.220g, 0.00115 mole), HOBt.H_2O (0.129 g, 0.00084 mole) were added to a solution of 3-phenylisoxazole-5-carboxylic acid (0.150g, 0.00076 mol) in THF (5 mL) and stirred at room temperature for 20 minutes. To this reaction mixture was added 3-(1-methyl-1H-pyrazol-5-yl)propan-1-amine (0.16g, 0.00115mol) and DIPEA (0.590 mL, 0.0023 mole) and stirred for 16 h. The reaction mixture was concentrated on rotary evaporator and the mixture was purified using combiflash, desired product eluted in 35% EtOAc:hexane (0.115g, 47.23%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.53 (m, 1H), 7.50-7.48 (m, 1H), 7.38-7.37 (d, *J=1.84Hz* 1H), 7.15-7.14 (m, 1H), 6.88 (br, 1H), 6.81 (s, 1H), 3.79 (s, 3H), 3.56-3.51 (q, 2H), 2.71-2.67 (t, 2H), 2.02-1.95 (m, 2H); LCMS $[M+H]^+$ 316.9; HPLC purity: 95.83% at 220 nm and 98.85% at 254 nm.

Example 8: N-(2-methoxyethyl)-4-phenylfuran-2-carboxamide:



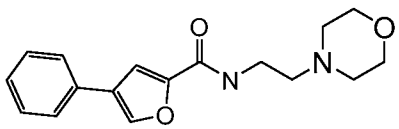
[0137] Compound 8 was obtained as an off white solid using the general procedure 1. Yield: 57%; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.42 (br, 1H), 8.35 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.57 (s, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 3.44 - 3.39 (m, 4H), 3.26 (s, 3H); LC-MS: $(M+H)^+$ 246.0; HPLC purity 99.32 % at 220 nm and 99.35 % at 254 nm.

Example 9: 4-phenyl-N-((tetrahydrofuran-2-yl)methyl)furan-2-carboxamide:



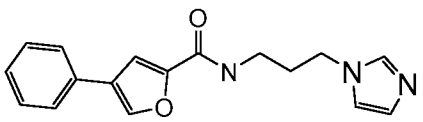
[0138] Compound 9 was obtained as an off white solid using the general procedure 1. Yield: 46%; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.42 (br, 1H), 8.35 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.59 (s, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 3.97 (m, 1H), 3.79 (m, 1H), 3.64 (m, 1H), 3.27 (s, 2H), 1.90 – 1.78 (m, 3H), 1.61 (m, 1H); LC-MS: $(M+H)^+$ 271.9; HPLC purity 98.21% at 220 nm and 98.35 % at 254 nm.

Example 10: N-(2-morpholinoethyl)-4-phenylfuran-2-carboxamide



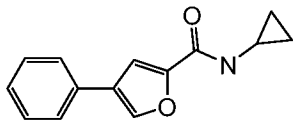
[0139] Compound 10 was obtained as an off white solid using the general procedure 1. Yield: 42%; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.35 (m, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.54 (s, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 3.56 (s, 4H), 3.36 (s, 2H), 2.46-2.40 (m, 6H); LC-MS: $(M+H)^+$ 300.7; HPLC purity 99.42 % at 220 nm and 99.36 % at 254 nm.

Example 11: N-(3-(1H-imidazol-1-yl)propyl)-4-phenylfuran-2-carboxamide:



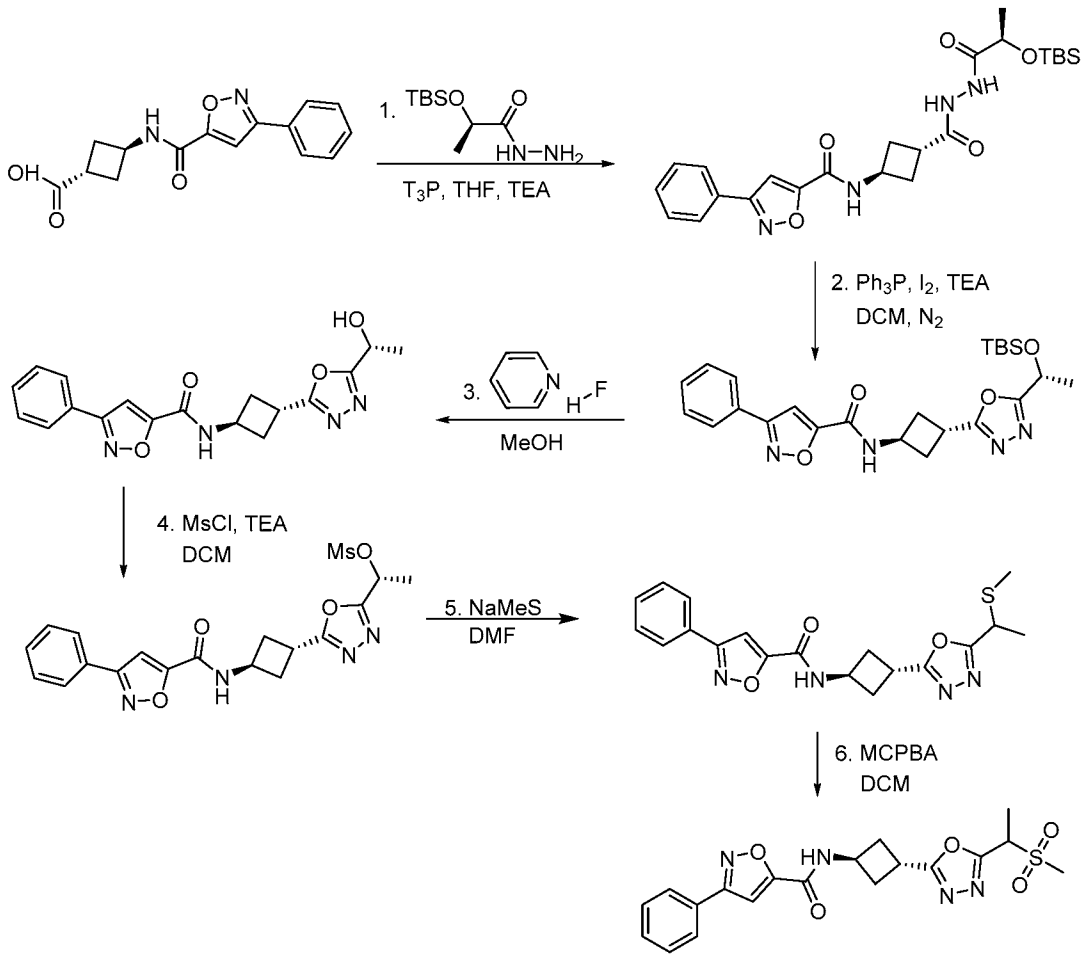
[0140] Compound 11 was obtained as an off white solid using the general procedure 1. Yield: 33%; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.54 (t, *J* = 5.6 Hz, 1H), 8.36 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.56 (s, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.21 (s, 1H), 6.89 (s, 1H), 4.02 (t, *J* = 6.8 Hz, 2H), 3.23 (q, *J* = 6.8 Hz, 2H), 1.97 (quintet, *J* = 6.8 Hz, 2H); LC-MS: $(M+H)^+$ 296.1; HPLC purity 99.51 % at 220 nm and 99.21 % at 254 nm.

Example 12: N-cyclopropyl-4-phenylfuran-2-carboxamide:



[0141] Compound 12 was obtained as an off white solid using the general procedure 1 (0.032 g, 19.04%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.666 (s, 1H), 7.48-7.46 (m, 2H), 7.41-7.36 (m, 3H), 7.31-7.24 (m, 1H), 6.44 (s, 1H), 2.89-2.85 (m, 1H), 0.89-0.84 (m, 2H), 0.65-0.61 (m, 2H); LCMS $[M+H]^+$ 228.1; HPLC purity: 99.57% at 220 nm and 99.02% at 254 nm.

Example 13: *N*-(*trans*-3-(5-(1-(methylsulfonyl)ethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0142] **Step 1: *N-trans*-(3-[[(2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazido]carbonyl]cyclobutyl)-3-phenylisoxazole-5-**

carboxamide: T_3P (50%) (55.6 g, 5.00 eq.), TEA (8.83 g, 87.26 mmol, 5.00 eq.) and (2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazide (4.95 g, 22.67 mmol, 1.30 eq.) were added to a solution of 3-(3-phenylisoxazole-5-amido)cyclobutane-1-carboxylic acid (5 g, 17.47 mmol, 1.00 eq.) in tetrahydrofuran (50 mL) and the solution was stirred for 1.5 hours at 30 °C. The reaction was then quenched by the addition of water, extracted with dichloromethane and the organic layers combined, dried and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1) to give 8.45 g (crude) of *N-trans*-(3-[[(2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazido]carbonyl]cyclobutyl)-3-phenylisoxazole-5-carboxamide as a light yellow solid; LC-MS (ES, *m/z*): $[M+1]^+ = 487.1$.

[0143] Step 2: *N-trans*-(3-[5-[(R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide: I_2 (20.74 g, 5.00 eq.) and TEA (9.98 g, 98.63 mmol, 6.00 eq.) were added to a solution of Ph_3P (21.56 g, 5.00 eq.) in dichloromethane (50 mL), followed by the dropwise addition of a solution of *N-trans*-(3-[[(2*R*)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazido]carbonyl]cyclobutyl)-3-phenylisoxazole-5-carboxamide (8 g, 16.44 mmol, 1.00 eq.) in dichloromethane (50 mL). The resulting solution was stirred for 2.5 hours at 0 °C, then quenched by the addition of water, and the solution was extracted with dichloromethane and the organic layers combined, dried and concentrated under vacuum to afford 3.19 g (41%) of *N-trans*-(3-[5-[(*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide as a brown solid; LC-MS (ES, *m/z*): $[M+1]^+ = 469.1$.

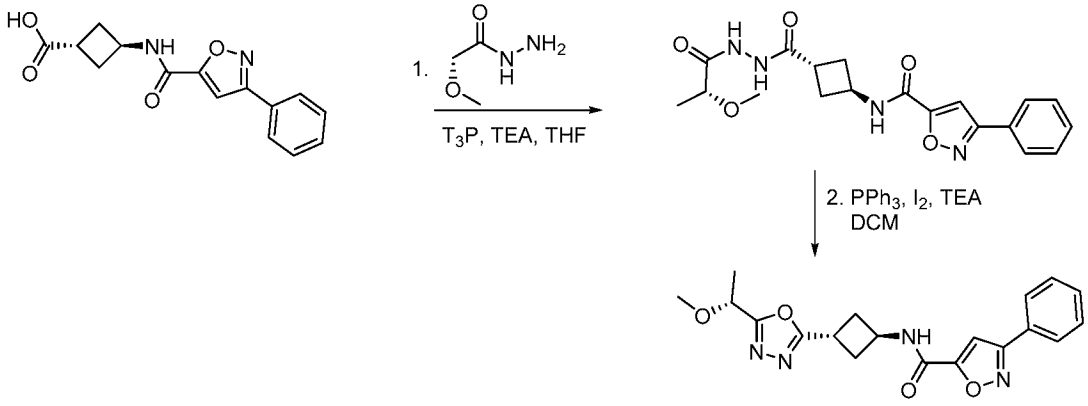
[0144] Step 3: *N-trans*-(3-[5-[(1*R*)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide: a solution of *N-trans*-(3-[5-[(1*R*)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide (25.3 g, 53.99 mmol, 1.00 eq.) and pyridine hydrofluoride (15 g, 151.35 mmol, 2.80 eq.) in methanol (50 mL) was stirred for 5 hours at room temperature. The reaction was then quenched by the addition of water, extracted with dichloromethane and the organic layers combined, dried and concentrated under vacuum. The residue was dissolved in 50 mL of toluene and the solids were collected by filtration to give 1.85 g (10%) of *N-trans*-(3-[5-[(1*R*)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide as a yellow solid; LC-MS (ES, *m/z*): $[M+1]^+ = 355.0$.

[0145] Step 4: (*R*)-1-[5-*trans*-[3-(3-phenylisoxazole-5-amido)cyclobutyl]-1,3,4-oxadiazol-2-yl]ethyl methanesulfonate: TEA (1.28 g, 12.65 mmol, 3.00 eq.) and MsCl (0.725 g, 1.50 eq.) were added to a solution of *N-trans*-(3-[5-[(R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide (1.5 g, 4.23 mmol, 1.00 eq.) in dichloromethane (50 mL) and the solution was stirred for 3 hours at 0 °C. The reaction was then quenched by the addition of 200 mL of saturation NH_4Cl, extracted with dichloromethane and the organic layers combined, dried and concentrated under vacuum to give 1.72 g (94%) of (*R*)-1-[5-*trans*-[3-(3-phenylisoxazole-5-amido)cyclobutyl]-1,3,4-oxadiazol-2-yl]ethyl methanesulfonate as a yellow solid; LC-MS (ES, *m/z*): $[M+1]^+ = 433.0$.

[0146] Step 5: *N-trans*-(3-[5-[1-(methylsulfanyl)ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide: a solution of (*R*)-1-[5-*trans*-[3-(3-phenylisoxazole-5-amido)cyclobutyl]-1,3,4-oxadiazol-2-yl]ethyl methanesulfonate (400 mg, 0.92 mmol, 1.00 eq.) and NaMeS (132 mg, 2.00 eq.) in DMF (3 mL) was stirred for 5 hours at 100 °C. The resulting mixture was concentrated under vacuum and the residue was applied onto a silica gel column with ethyl acetate/petroleum ether (4:5) to give 254 mg (71%) of *N-trans*-(3-[5-[1-(methylsulfanyl)ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide as a yellow solid; LC-MS (ES, *m/z*): $[M+1]^+ = 385.0$.

[0147] Step 6: *N*-(3-[5-*trans*-[1-methanesulfonylethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide: a solution of *N*-(3-[5-*trans*-[1-(methylsulfanyl)ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide (230 mg, 0.60 mmol, 1.00 eq.) and MCPBA (0.42 g, 4.00 eq.) in dichloromethane (5 mL) was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum and the residue was applied onto a silica gel column with dichloromethane/methanol (25:1) to give 80 mg (32%) of a racemic mixture of *N*-(3-[5-*trans*-[1-methanesulfonylethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl)-3-phenylisoxazole-5-carboxamide as a yellow solid; LC-MS (ES, *m/z*): $[M+1]^+ = 417.0$ ^1H NMR (DMSO-d_6, 400MHz, *ppm*): δ 9.44 (s, 1H), 7.93-7.91 (m, 2H), 7.65 (s,1H), 7.54-7.52 (m, 3H), 5.16-5.11 (m, 1H), 4.69-4.63 (m, 1H), 3.78-3.75 (m, 1H), 3.14 (s, 3H), 2.72-2.65 (m, 4H), 1.74-1.70 (m, 3H); HPLC purity: 97.1% at 254 nm.

Example 14: *N*-(*trans*-3-(5-((R)-1-methoxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide

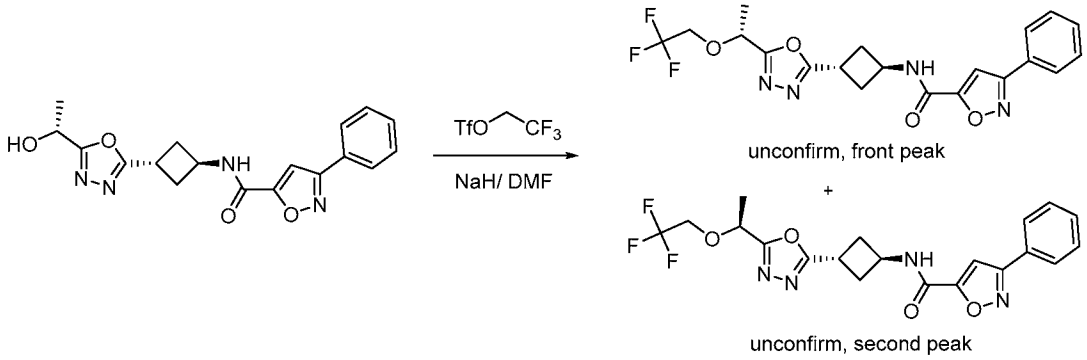


[0148] Step 1: 3-phenyl-*N*-[*trans*-3-[N-[(2*R*)-2-methoxypropanoyl]hydrazinecarbonyl]cyclobutyl]-1,2-oxazole-5-carboxamide: TEA (315 mg, 3.11 mmol, 2.97 eq.) and T_3P (667 mg) were added to a solution of trans-3-(3-phenylisoxazole-5-amido)cyclobutane-1-carboxylic acid (300 mg, 1.05 mmol, 1.00 eq.) and (2*R*)-2-methoxypropanehydrazide (185 mg, 1.57 mmol, 1.49 eq.) in tetrahydrofuran (5 mL) and the mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum, diluted with 5 mL of methanol. The solids were collected by filtration and dried in an oven under reduced pressure to give 200 mg (49%) of 3-phenyl-*N*-[*trans*-3-[N-[(2R)-2-methoxypropanoyl]hydrazinecarbonyl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LC-MS (ES, *m/z*): $[M+1]^+ = 387.2$.

[0149] Step 2: 3-phenyl-*N*-[*trans*-3-[5-[(1*S*)-1-methoxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide: 3-phenyl-*N*-[*trans*-3-[N-[(2*R*)-2-methoxypropanoyl]hydrazinecarbonyl]cyclobutyl]-1,2-oxazole-5-carboxamide (150 mg, 0.39 mmol, 1.00 eq.) was added to a solution of PPh_3 (150 mg, 0.57 mmol, 1.47 eq.), I_2 (150 mg) and TEA (120 mg, 1.19 mmol, 3.05 eq.) in dichloromethane (5 mL) and the mixture was stirred for 2 hours at 0 °C. The resulting mixture was washed with water (2x5 mL) and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Waters): Column: XBridge C18 OBD Prep Column 10 μm, 19 mm X 250 mm; mobile phase, water (0.5% NH_4HCO_3) and CH_3CN; Gradient; 40% of CH_3CN to 45% of CH_3CN in 10 min; Detector, UV 254 nm to give 101.8 mg (71%) of 3-phenyl-*N*-[*trans*-3-[5-[(1*S*)-1-methoxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as a light yellow solid. LC-MS (ES, *m/z*): $[M+1]^+ = 369.0$; ^1H NMR (DMSO-d_6, 300MHz, *ppm*): δ 9.46-9.44 (d, *J* = 7.2 Hz, 1H), 7.94-7.93 (m, 2H), 7.66 (s, 1H), 7.55-7.54 (m, 3H), 4.72-4.64 (m, 2H), 3.78-

3.73 (m, 1H), 3.29 (s, 3H), 2.73-2.61 (m, 4H), 1.51-1.49 (d, J = 6.8 Hz, 3H); HPLC purity: 99.1% at 254 nm.

Example 15 and 16: 3-phenyl-*N*-(*trans*-3-(5-((S)-1-(2,2,2-trifluoroethoxy)ethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)isoxazole-5-carboxamide and 3-phenyl-*N*-(*trans*-3-(5-((R)-1-(2,2,2-trifluoroethoxy)ethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)isoxazole-5-carboxamide

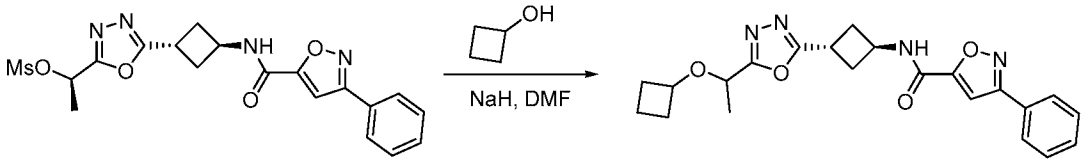


[0150] 2,2,2-trifluoroethyl trifluoromethanesulfonate (491 mg, 2.12 mmol, 1.50 eq.) was added to a solution of 3-phenyl-*N*-[*trans*-3-[5-[(1*R*)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-isoxazole-5-carboxamide (500 mg, 1.41 mmol, 1.00 eq.) and sodium hydride (85 mg, 2.12 mmol, 1.50 eq.) in DMF (10 mL) and the solution was stirred for 2 hours at room temperature. The reaction mixture was diluted with water (30 mL), extracted with ethyl acetate (3x30 mL) and the organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Waters): Column: XBridge C18 OBD Prep Column 10 μm, 19 mm X 250 mm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 15% B to 65% B in 8 min; 254/220 nm. The isomers were purified by Chiral-Prep-HPLC with the following conditions: Column: Chiralpak IA 2*25cm, 5um; Mobile Phase A: Hexane; HPLC, Mobile Phase B: EtOH, HPLC Flow rate: 18 mL/min; Gradient: 40 B to 40 B in 15 min; 254/220 nm; RT1: 9.505; RT2: 11.208. This resulted in 19.1 mg (3%) of front peak as a white solid and 16.8 mg of second peak as a white solid.

[0151] **Front Peak:** LC-MS (ES, *m/z*): $[M+1]^+$ = 437.1. ^{1}H-NMR (DMSO-d_6, 300MHz, *ppm*): δ 7.87-7.86 (m, 2H), 7.49-7.47 (m, 3H), 7.37 (s, 1H), 5.00-4.94 (m, 1H), 4.11-4.02 (m, 2H), 3.81-3.74 (m, 1H), 2.78-2.68 (m, 4H), 1.64-1.62 (d, J = 6.6 Hz, 3H); HPLC purity: 98.6% at 254 nm.

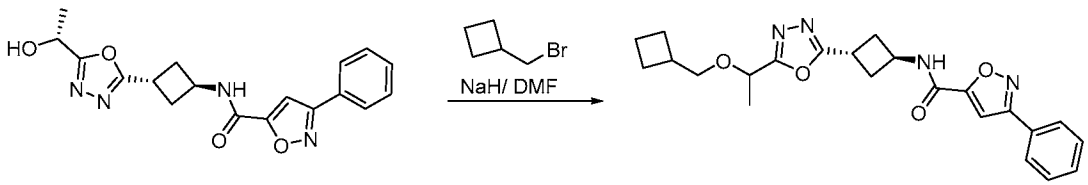
[0152] **Second Peak:** LC-MS (ES, *m/z*): $[M+1]^+ = 437.1$; ^{1}H NMR (DMSO-d_6, 300MHz, *ppm*): δ 7.86 (br, 2H), 7.48 (br, 3H), 7.37 (s, 1H), 5.00-4.94 (m, 1H), 4.10-4.02 (m, 2H), 3.79-3.77 (m, 1H), 2.78-2.69 (m, 4H), 1.64-1.62 (d, J = 6.6 Hz, 3H); HPLC purity: 98.9% at 254 nm.

Example 17: *N*-(*trans*-3-(5-(1-cyclobutoxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0153] Sodium hydride (84 mg, 2.10 mmol, 3.00 eq.) was added in portions to a cold (0 °C) solution of cyclobutanol (150 mg, 2.08 mmol, 3.00 eq.) in DMF (10 mL) and the resulting solution was stirred for 30 min at 0 °C. (R)-1-[5-*trans*-[3-(3-phenylisoxazole-5-amido)cyclobutyl]-1,3,4-oxadiazol-2-yl]ethyl methanesulfonate (300 mg, 0.69 mmol, 1.00 eq.) was added to the mixture and stirred for an additional 2 hours at 25 °C. The reaction was then quenched by the addition of 100 mL of water, extracted with ethyl acetate (2x100 mL) and the organic layers combined. The resulting mixture was washed with brine (2x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-TLC (petroleum ether:ethyl acetate = 1:1) to give 50.2 mg (18%) of 3-phenyl-*N*-[*trans*-3-[5-(1-cyclobutoxyethyl)-1,3,4-oxadiazol-2-yl]cyclobutyl]isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+ = 409.4$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.46-9.43 (d, J = 7.2 Hz, 1H), 7.95-7.92 (m, 2H), 7.65 (s, 1H), 7.56-7.54 (m, 3H), 4.78-4.64 (m, 2H), 4.04-3.99 (m, 1H), 3.77-3.74 (m, 1H), 2.71-2.50 (m, 4H), 2.18-2.14 (m, 1H), 1.97-1.85 (m, 2H), 1.75-1.57 (m, 2H), 1.49-1.47 (d, J = 6.6 Hz, 3H), 1.47-1.40 (m, 1H); HPLC purity: 98.0% at 254 nm.

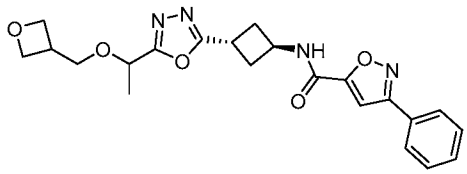
Example 18: *N*-(*trans*-3-(5-(1-(cyclobutylmethoxy)ethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0154] (Bromomethyl)cyclobutane (83 mg, 0.56 mmol, 2.00 eq.) was added to a solution of 3-phenyl-*N*-[*trans*-3-[5-(1-hydroxyethyl)-1,3,4-oxadiazol-2-yl]cyclobutyl]isoxazole-5-

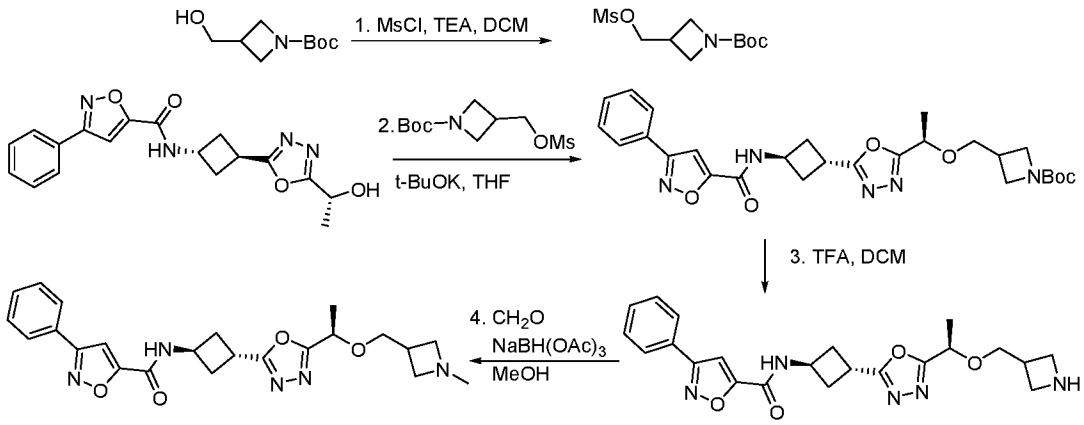
carboxamide (100 mg, 0.28 mmol, 1.00 eq.) and sodium hydride (17 mg, 0.42 mmol, 1.50 eq.) in DMF (2 mL). The resulting solution was stirred for 2 hours at room temperature, the reaction mixture was quenched by the addition of water (20 mL) and the solution was extracted with ethyl acetate (3x10 mL). The organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Waters): Column: XBridge Prep C18 OBD Column 19×150mm, 5um; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 40% B to 80% B in 8 min; 254 nm to give 21.2 mg (18%) of 3-phenyl-*N*-[*trans*-3-[5-[1-(cyclobutylmethoxy)ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+1]^+ = 421.0$; ^1H NMR (DMSO-d_6, 300MHz, *ppm*): δ 9.46-9.43 (d, *J* = 7.2 Hz, 1H), 7.94-7.93 (m, 2H), 7.66 (s, 1H), 7.57-7.54 (m, 3H), 4.81-4.74 (m, 1H), 4.72-4.64 (m, 1H), 3.77-3.74 (m, 1H), 3.49-3.36 (m, 2H), 2.70-2.65 (m, 4H), 1.96-1.91 (m, 2H), 1.88-1.80 (m, 2H), 1.75-1.67 (m, 2H), 1.50-1.48 (d, *J* = 6.6Hz, 3H); HPLC purity: 99.8% at 254 nm.

Example 19: *N*-(*trans*-3-(5-(1-(oxetan-3-ylmethoxy)ethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0155] The title compound was prepared using the method shown in example 18.

Example 20: *N*-(*trans*-3-(5-((R)-1-((1-methylazetidin-3-yl)methoxy)ethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0156] Step1: tert-butyl 3-[(methanesulfonyloxy)methyl]azetidine-1-carboxylate: MsCl (549 mg, 4.82 mmol, 1.20 eq.) and TEA (606 mg, 6.00 mmol, 1.50 eq.) were added to a solution of tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (750 mg, 4.01 mmol, 1.00 eq.) in dichloromethane (20 mL) and the solution was stirred for 3 hours at room temperature. The resulting solution was diluted with ethyl acetate (50 mL), washed with saturated sodium carbonate aq. (1 x 30 mL), water (1 x 30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give 980 mg (92%) of tert-butyl 3-[(methanesulfonyloxy)methyl]azetidine-1-carboxylate as colorless oil.

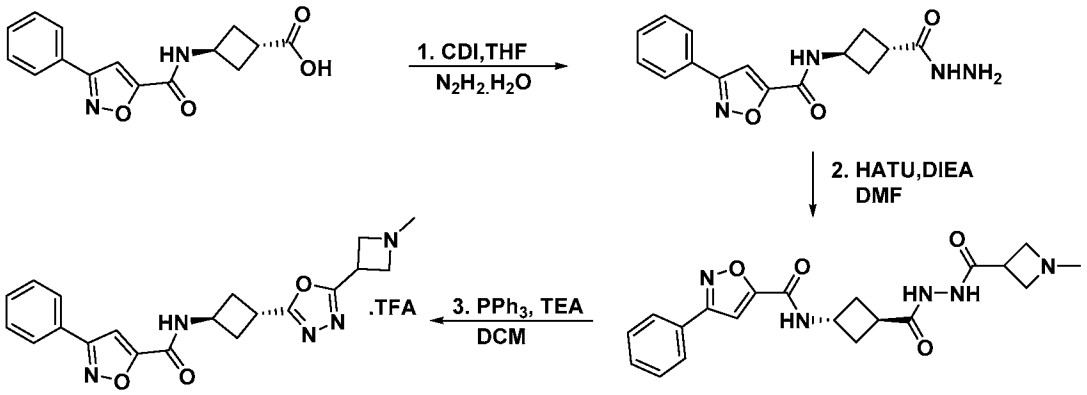
[0157] Step 2: tert-butyl 3-[(1-[5-[*trans*-3-(3-phenylisoxazole-5-amido)cyclobutyl]-1,3,4-oxadiazol-2-yl]ethoxy)methyl]azetidine-1-carboxylate: tert-butyl 3-[(methanesulfonyloxy)methyl]azetidine-1-carboxylate (670 mg, 2.53 mmol, 1.50 eq.) was added to a solution of 3-phenyl-*N*-[*trans*-3-[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-isoxazole-5-carboxamide (600 mg, 1.69 mmol, 1.00 eq.) and t-BuOK (570 mg, 5.08 mmol, 3.00 eq.) in THF (15 mL). The reaction was stirred for 16 hours at 80 °C in an oil bath then diluted with ethyl acetate (100 mL). The resulting solution was washed with water (2 x 30 mL), brine (1 x 30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10 up to 1:2) to give 287 mg (32%) of tert-butyl 3-[(1-[5-[*trans*-3-(3-phenylisoxazole-5-amido)cyclobutyl]-1,3,4-oxadiazol-2-yl]ethoxy)methyl]azetidine-1-carboxylate as a light yellow solid; LC-MS (ES, *m/z*): $[M+H]^+ = 524.2$.

[0158] Step 3: 3-phenyl-N-[*trans*-3-[5-[1-(azetidin-3-ylmethoxy)ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]isoxazole-5-carboxamide: a solution of tert-butyl 3-[(1-[5-[*trans*-3-(3-

phenylisoxazole-5-amido)cyclobutyl]-1,3,4-oxadiazol-2-yl]ethoxy)methyl]azetidine-1-carboxylate (237 mg, 0.45 mmol, 1.00 eq.) and TFA (1.5 mL) in DCM (4 mL) was stirred for 2 hours at room temperature. The reaction was quenched by addition of 20 mL of saturated sodium carbonate aqueous and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give 150 mg (78%) of 3-phenyl-N-[*trans*-3-[5-[1-(azetidin-3-ylmethoxy)ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]isoxazole-5-carboxamide as a yellow solid; LC-MS (ES, *m/z*): $[M+H]^+ = 424.2$.

[0159] Step 4: 3-phenyl-*N*-[trans3-**(5-[1-[(1-methylazetidin-3-yl)methoxy]ethyl]-1,3,4-oxadiazol-2-yl)cyclobutyl]-isoxazole-5-carboxamide**: HCHO (57 mg, 0.70 mmol, 1.50 eq.) was added to a solution of 3-phenyl-*N*-[*trans*-3-[5-[1-(azetidin-3-ylmethoxy)ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]isoxazole-5-carboxamide (150 mg, 0.35 mmol, 1.00 eq.) in methanol (3 mL) and stirred for 30min. $NaBH(OAc)_3$ (150 mg, 0.71 mmol, 2.00 eq.) was added to the reaction mixture and stirred16 hours at room temperature. After removing the solid by filtration, the crude product (3 mL) was purified by Prep-HPLC with the following conditions (Waters): Column: XBridge C18 OBD Prep Column 10 μm, 19 mm X 250 mm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 15% B to 45% B in 8 min; 220/254 nm to give 68.6 mg (44%) of 3-phenyl-*N*-[*trans*3-(5-[1-[(1-methylazetidin-3-yl)methoxy]ethyl]-1,3,4-oxadiazol-2-yl)cyclobutyl]-isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+ = 438.2$; ^1H NMR (CDOD, 400 MHz): δ 7.89-7.87 (m, 2H), 7.51-7.50 (m, 3H), 7.39 (s, 1H), 4.85-4.78 (m, 2H), 3.85-3.59 (m, 3H), 3.48-3.43 (m, 2H), 3.16-3.11 (m, 2H), 2.87-2.73 (m, 4H), 2.60-2.57 (m, 1H), 2.35-2.33 (m, 3H), 1.61-1.58 (m, 3H); HPLC purity: 97% at 254 nm.

Example 21: *N*-(*trans*-3-(5-(1-methylazetidin-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide trifluoroacetate



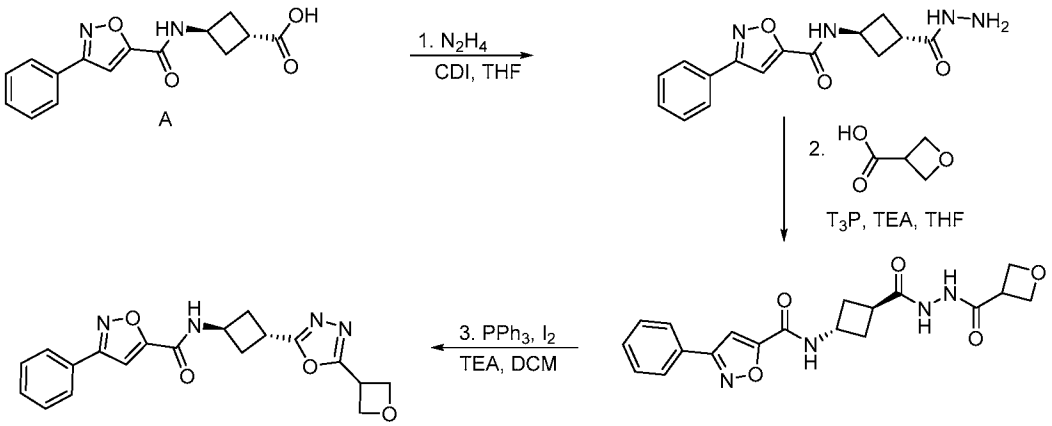
[0160] Step 1: 3-phenyl-*N*-[*trans*-3-(hydrazinecarbonyl)cyclobutyl]isoxazole-5-carboxamide: a solution of *trans*-3-(3-phenylisoxazole-5-amido)cyclobutane-1-carboxylic acid (1.706 g, 5.96 mmol, 1.00 eq.) and CDI (1.933 g, 11.92 mmol, 2.00 eq.) in tetrahydrofuran (30 mL) was stirred for 0.5 hour at room temperature. Hydrazine hydrate (1.118 g, 22.33 mmol, 3.75 eq.) was added to the reaction mixture and stirred for 2 hours at room temperature. The product was precipitated by the addition of water and collected by filtration to give 780 mg (44%) of 3-phenyl-*N*-[*trans*-3-(hydrazinecarbonyl)cyclobutyl]isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+$ = 301.2.

[0161] Step 2: 3-phenyl-*N*-[*trans*-3-[[(1-methylazetidin-3-yl)formohydrazido]carbonyl]cyclobutyl]-isoxazole-5-carboxamide: 1-methylazetidine-3-carboxylic acid (172.5 mg, 1.50 mmol, 1.50 eq.), HATU (570 mg, 1.50 mmol, 1.50 eq.) and DIEA (387 mg, 2.99 mmol, 3.00 eq.) were added to a solution of 3-phenyl-*N*-[trans-3-(hydrazinecarbonyl)cyclobutyl]-isoxazole-5-carboxamide (300 mg, 1.00 mmol, 1.00 eq.) in DMF (10 mL) and then stirred for 2 hours at room temperature. The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, $MeCN/H_2O$ = 5:95 increasing to $MeCN/H_2O$ = 95:5 within 30 min; Detector, UV 254 nm to give 200 mg (50%) of 3-phenyl-*N*-[*trans*-3-[[(1-methylazetidin-3-yl)formohydrazido]carbonyl]cyclobutyl]-isoxazole-5-carboxamide as an off-white solid; LC-MS (ES, *m/z*): $[M+H]^+$ = 398.0.

[0162] Step 3: 3-phenyl-*N*-[*trans*-3-[5-(1-methylazetidin-3-yl)-1,3,4-oxadiazol-2-yl]cyclobutyl]-isoxazole-5-carboxamide: I_2 (232 mg) and TEA (276 mg, 2.73 mmol, 5.99 eq.) were added to a cold (0 °C) solution of PPh_3 (239 mg, 0.91 mmol, 2.00 eq.) in DCM (20 mL). To the mixture was added 3-phenyl-*N*-[*trans*-3-[[(1-methylazetidin-3-

yl)formohydrazido]carbonyl]cyclobutyl]-isoxazole-5-carboxamide (181 mg, 0.46 mmol, 1.00 eq.) at 0 °C. The resulting solution was stirred for 3 hours at room temperature, diluted with 50 mL of DCM, washed with $NaHSO_3$ aqueous (2x50 mL) and concentrated under vacuum. The residue was applied onto a Prep-TLC with ethyl acetate/petroleum ether (1:1). The resulting crude product was purified by Prep-HPLC with the following conditions (HPLC-10): Column: XBridge C18 OBD Prep Column 100Å, 10 μm, 19 mm X 250 mm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 20% B to 30% B in 10 min; 254&220 nm to give 50 mg (29%) of 3-phenyl-*N*-[*trans*-3-[5-(1-methylazetidin-3-yl)-1,3,4-oxadiazol-2-yl]cyclobutyl]-isoxazole-5-carboxamide as a yellow solid; LC-MS (ES, *m/z*): $[M\text{-}TFA+H]^+$ = 380.1; ^1H NMR (300 MHz, DMSO-d_6, *ppm*): δ 10.19-10.12 (m, 1H), 9.49-9.47 (d, *J* = 7.5 Hz, 1H), 7.95-7.92 (m, 2H), 7.66-7.64 (d, *J* = 8.1 Hz, 1H), 7.56-7.54 (t, *J* = 3.3 Hz, 3H), 4.75-4.62 (m, 6H), 3.78-3.69 (m, 1H), 2.94 (s, 3H), 2.44-2.72 (m, 4H); HPLC purity: 97.1% at 254 nm.

Example 22: *N-trans*-3-(5-(oxetan-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



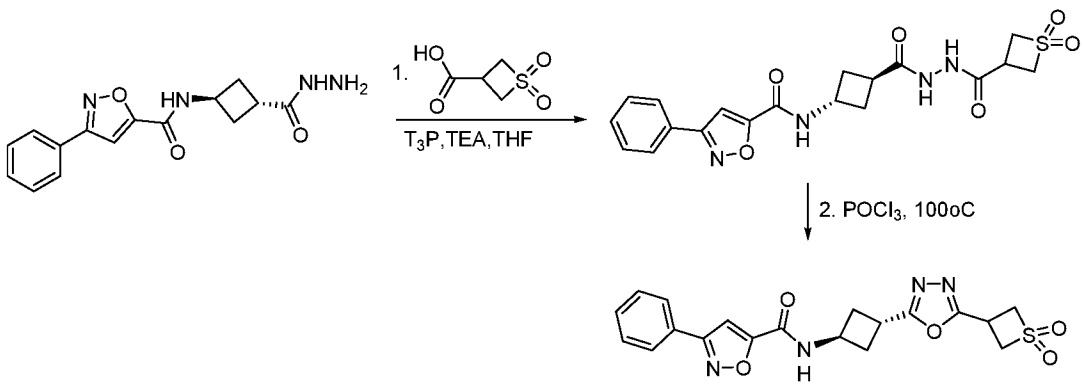
[0163] Step 1: 3-phenyl-*N*-[*trans*-3-(hydrazinecarbonyl)cyclobutyl]isoxazole-5-carboxamide: CDI (2.26 g, 13.94 mmol, 2.00 eq.) was added to a solution of *N-trans*-3-(3-phenylisoxazole-5-amido)cyclobutane-1-carboxylic acid (prepared according to procedure shown in example 13, 2 g, 6.99 mmol 1.00 eq.) in THF (3mL) and the solution was stirred for 1 hour at room temperature, followed by the addition of hydrazine hydrate (1.33 g, 21.25 mmol, 3.00 eq., 80%). The resulting solution was stirred for additional 1 hour at room temperature and then quenched with water. After removing the solids by filtration, the resulting mixture

was concentrated under vacuum and the residue was washed with 10 mL of methanol to give 960 mg (46%) of 3-phenyl-*N*-[*trans*-3-(hydrazinecarbonyl)cyclobutyl]isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+ = 301.1$.

[0164] Step 2: 3-phenyl-*N*-[*trans*-3-[(oxetan-3-ylformohydrazido)carbonyl]cyclobutyl]isoxazole-5-carboxamide: oxetane-3-carboxylic acid (170 mg, 1.67 mmol, 1.00 eq.), T_3P (5.3 g, 8.33 mmol, 5.00 eq., 50%) and TEA (838 mg, 8.3 mmol, 5.00 eq.) were added to a solution of 3-phenyl-*N*-[*trans*-3-(hydrazinecarbonyl)cyclobutyl]isoxazole-5-carboxamide (500 mg, 1.66 mmol, 1.00 eq.) in THF (50mL). The resulting solution was stirred for 20 min at room temperature, then quenched by the addition of 200mL of water. The resulting solution was extracted with dichloromethane (3x200mL) and the organic layers combined. The resulting mixture was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue solid was washed with 2mL of methanol to afford 420 mg (66%) of 3-phenyl-*N*-[*trans*-3-[(oxetan-3-ylformohydrazido)carbonyl]cyclobutyl]isoxazole-5-carboxamide as an off-white solid; LC-MS (ES, *m/z*): $[M+H]^+ = 385.0$.

[0165] Step 3: 3-phenyl-*N*-[*trans*-3-[5-(oxetan-3-yl)-1,3,4-oxadiazol-2-yl]cyclobutyl]isoxazole-5-carboxamide: I_2 (579 mg, 2.28 mmol, 2.50 eq.), TEA (598 mg, 5.91 mmol, 6.50 eq.) and 3-phenyl-*N*-[*trans*-3-[(oxetan-3-ylformohydrazido)carbonyl]cyclobutyl]isoxazole-5-carboxamide (350 mg, 0.91 mmol, 1.00 eq.) were added to a cold solution of PPh_3 (597 mg, 2.28 mmol, 2.50 eq.) in dichloromethane (30mL) at 0 °C. The resulting solution was stirred for 1 hour at room temperature, then quenched by the addition of water. The resulting solution was extracted with ethyl acetate and the organic layers combined. The resulting mixture was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (10:1) to afford 100.4 mg (30%) of 3-phenyl-*N*-[*trans*-3-[5-(oxetan-3-yl)-1,3,4-oxadiazol-2-yl]cyclobutyl]isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+ = 367.1$; ^1H NMR (300MHz, DMSO-d_6, *ppm*): δ 9.46-9.44 (d, 1H, $J = 7.5$ Hz), 7.95-7.92 (m, 2H), 7.66 (s, 1H), 7.56-7.54 (m, 3H), 4.95-4.90 (m, 2H), 4.83-4.79 (m, 2H) , 4.75-4.51 (m, 2H), 3.78-3.71 (m, 1H) , 2.70-2.65 (m, 4H); HPLC purity: 96.5% at 254 nm.

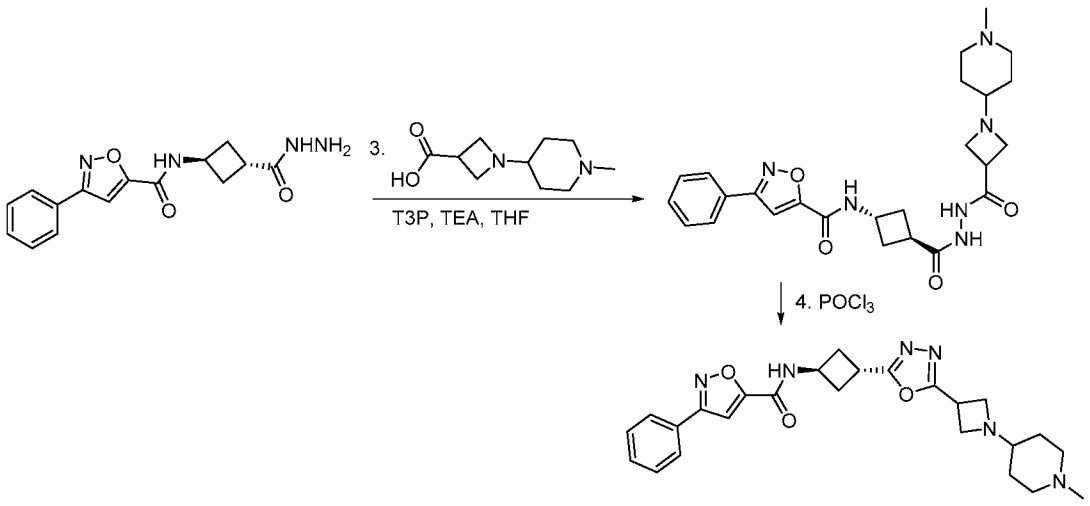
Example 23: *N*-(*trans*-3-(5-(1,1-dioxidothietan-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0166] Step 1: *N*-(*trans*-3-(2-(1,1-dioxidothietane-3-carbonyl)hydrazine-1-carbonyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide: a solution of thietane-3-carboxylic acid 1,1-dioxide (500 mg, 3.4 mmol, 1.00 eq.), 3-phenyl-*N*-[*trans*-3-(hydrazinecarbonyl)cyclobutyl]-isoxazole-5-carboxamide (1.0 g, 3.4 mmol, 1.00 eq.), T_3P (10 mL) and TEA (4 mL) in tetrahydrofuran (20 mL) was stirred for 1 hour at room temperature. The reaction was then quenched by the addition of water and the solids were collected by filtration to afford 30 mg (42%) of *N*-(*trans*-3-(2-(1,1-dioxidothietane-3-carbonyl)hydrazine-1-carbonyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide as a light yellow solid. LC-MS (ES, *m/z*): $[M+H]^+ = 433.1$.

[0167] Step 2: *N*-(*trans*-3-(5-(1,1-dioxidothietan-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide: a solution of *N*-(*trans*-3-(2-(1,1-dioxidothietane-3-carbonyl)hydrazine-1-carbonyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide (400 mg, 0.92 mmol, 1.00 eq.) in $POCl_3$ (8 mL) was stirred for 3 hours at 100 °C in an oil bath. The reaction was then quenched by the addition of sodium bicarbonate aqueous/ice, extracted with ethyl acetate and the organic layers combined. The resulting mixture was washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum to give 105.8 mg (28%) of *N*-(*trans*-3-(5-(1,1-dioxidothietan-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+ = 415.2$; ^1H NMR (DMSO-d_6, 400 MHz): δ 9.46-9.42 (m, 1H), 7.95-7.91 (m, 2H), 7.66-7.65 (m, 1H), 7.55-7.54 (m, 3H), 4.75-4.57 (m, 5H), 4.23-4.14 (m, 1H), 3.73-3.52 (m, 1H), 2.70-2.66 (m, 4H); HPLC purity: 99.2% at 254 nm.

Example 24 and 25: ***N-cis*****-(3-(5-(1-(1-methylpiperidin-4-yl)azetidin-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide and** ***N-trans*****-(3-(5-(1-(1-methylpiperidin-4-yl)azetidin-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide**



[0168] **Step 1: benzyl 1-(1-methylpiperidin-4-yl)azetidine-3-carboxylate**: a solution of trifluoroacetic acid benzyl azetidine-3-carboxylate (1.3 g, 4.26 mmol, 1.00 eq.), 1-methylpiperidin-4-one (482 mg, 4.26 mmol, 1.10 eq.) and acetic acid (255 mg, 4.25 mmol, 1.00 eq.) in DCE (20 mL) was stirred for 30 min, followed by the addition of $NaBH(OAc)_3$ (1.44 g, 6.79 mmol, 1.60 eq.). The resulting solution was stirred for 16 hours at room temperature. The reaction was then quenched by the addition of water, extracted with dichloromethane and the organic layers combined. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with DCM/MeOH (10:1) to give 830 mg (68%) of benzyl 1-(1-methylpiperidin-4-yl)azetidine-3-carboxylate as yellow oil; LC-MS (ES, *m/z*): $[M+H]^+ = 289.2$.

[0169] **Step 2: 1-(1-methylpiperidin-4-yl)azetidine-3-carboxylic acid**: Palladium on carbon (100 mg) was added to a solution of benzyl 1-(1-methylpiperidin-4-yl)azetidine-3-carboxylate (830 mg, 2.88 mmol, 1.00 eq.) in methanol (20 mL), the solution was degassed and back filled with hydrogen. The resulting solution was stirred for 2 hours at room temperature, and the solids were filtered out. The resulting mixture was concentrated under vacuum to give 570 mg (crude) of 1-(1-methylpiperidin-4-yl)azetidine-3-carboxylic acid as light yellow oil; LC-MS (ES, *m/z*): $[M+H]^+ = 199.1$.

[0170] **Step 3: 3-phenyl-*N*-[*trans*-3-([[1-(1-methylpiperidin-4-yl)azetidin-3-yl]formohydrazido]carbonyl)cyclobutyl]-isoxazole-5-carboxamide**: a solution of 3-phenyl-*N*-[*trans*-3-(hydrazinecarbonyl)cyclobutyl]-isoxazole-5-carboxamide (409 mg, 1.36 mmol, 1.00 eq.), 1-(1-methylpiperidin-4-yl)azetidine-3-carboxylic acid (270 mg, 1.36 mmol, 1.00 eq.), T_3P (4.3 g, 6.76 mmol, 5.00 eq., 50%) and TEA (688 mg, 6.80 mmol, 5.00 eq.) in tetrahydrofuran (10 mL) was stirred for 30 min at room temperature. The reaction was then quenched by the addition of water, extracted with ethyl acetate and the aqueous layers combined and concentrated under vacuum. The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, methanol/H_2O = 5:95 increasing to methanol/H_2O = 95:5 within 30 min; Detector, UV 254 nm to give 220 mg (34%) of 3-phenyl-*N*-[*trans*-3-([[1-(1-methylpiperidin-4-yl)azetidin-3-yl]formohydrazido]carbonyl)cyclobutyl]-isoxazole-5-carboxamide as a light yellow solid; LC-MS (ES, *m/z*): $[M+H]^+$ = 481.2.

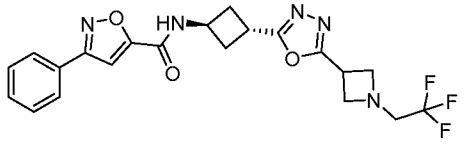
[0171] **Step 4**: a solution of 3-phenyl-*N*-[*trans*-3-([[1-(1-methylpiperidin-4-yl)azetidin-3-yl]formohydrazido]carbonyl)cyclobutyl]-isoxazole-5-carboxamide (160 mg, 0.33 mmol, 1.00 eq.) in $POCl_3$ (8 mL) was stirred for 1 hour at 100 °C. The reaction was then quenched by the addition of water/ice, the pH value of the solution was adjusted to 8 with sodium bicarbonate aqueous. The resulting solution was extracted with dichloromethane and the organic layers combined, washed with brine, dried and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (HPLC-10): Column, XBridge Shield RP18 OBD Column, 5um, 19*150mm; mobile phase, water (0.05% NH_4HCO_3) and ACN (27.0% ACN up to 37.0% in 8 min); Detector, UV 254/220 nm to give 19.6 mg (13%) of front peak as a white solid and 4.2 mg (3%) of second peak as an off-white solid.

[0172] **Front Peak:** LC-MS (ES, *m/z*): $[M+H]^+$ = 463.2; ^1H NMR (300MHz, DMSO-d_6, *ppm*): δ 9.45-9.43 (d, 1H, *J* = 7.5Hz), 7.95-7.92 (m, 2H), 7.66 (s, 1H), 7.56-7.53 (m, 3H), 4.67-4.64 (m, 1H), 3.85-3.80 (m, 1H), 3.73-3.69(m, 1H), 3.60-3.55 (m, 2H), 3.29-3.24 (m, 3H), 2.68-2.62 (m, 5H), 2.12 (s, 3H), 2.04-1.98 (m, 1H), 1.91-1.84 (m, 2H), 1.62-1.58 (m, 2H), 1.21-1.11 (m, 2H); HPLC purity: 97.8% at 254 nm.

[0173] **Second Peak:** LC-MS (ES, *m/z*): $[M+H]^+$ = 463.2; ^1H NMR (300MHz, DMSO-d_6, *ppm*): δ 9.47-9.44 (d, 1H, *J* = 7.8Hz), 7.95-7.92 (m, 2H), 7.66 (s, 1H), 7.56-7.54 (m, 3H), 4.72-

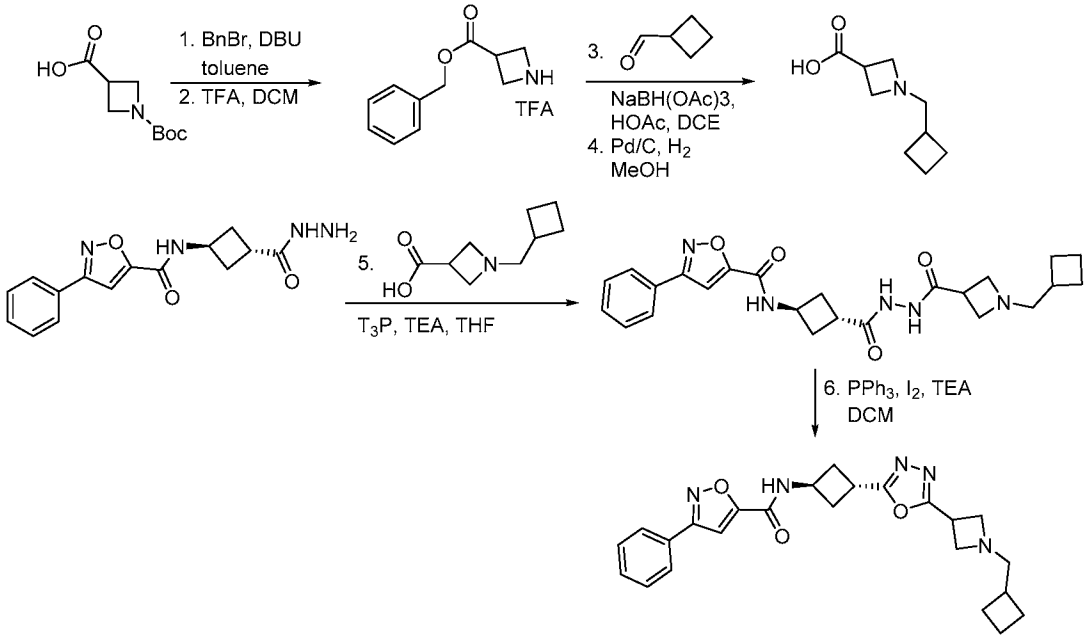
4.64 (m, 1H), 3.77-3.74 (m, 1H), 3.62 (s, 2H), 3.29 (s, 3H), 2.71-2.66 (m, 6H), 2.40-2.30 (m, 1H), 2.12 (s, 3H), 1.89-1.75 (m, 4H), 1.29-1.25 (m, 2H); HPLC purity: 95.1% at 254 nm.

Example 26: 3-phenyl-*N*-(*trans*-3-(5-(1-(2,2,2-trifluoroethyl)azetidin-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)isoxazole-5-carboxamide



[0174] The title compound was prepared using a similar method as shown in example 20.

Example 27: *N*-(*trans*-3-(5-(1-(cyclobutylmethyl)azetidin-3-yl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0175] **Step 1: 3-benzyl 1-tert-butyl azetidine-1,3-dicarboxylate**: a solution of 1-[(tert-butoxy)carbonyl]azetidine-3-carboxylic acid (5 g, 24.85 mmol, 1.00 eq.), BnBr (4.65 g, 27.19 mmol, 1.10 eq.) and DBU (5.67 g, 37.24 mmol, 1.50 eq.) in toluene (80mL) was stirred for 4 hours at room temperature. The reaction was then quenched by the addition of water, extracted with ethyl acetate and the organic layers combined. The resulting mixture was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:6) to give 5.4 g (75%) of

3-benzyl 1-tert-butyl azetidine-1,3-dicarboxylate as colorless oil; LC-MS (ES, *m/z*): [M+H-Boc]$^+$ = 192.0.

[0176] Step 2: 2,2,2-trifluoroacetic acid benzyl azetidine-3-carboxylate: a solution of 3-benzyl 1-tert-butyl azetidine-1,3-dicarboxylate (5.4 g, 18.53 mmol, 1.00 eq.)) and trifluoroacetic acid (7 mL).in dichloromethane (50mL) was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum to give 7 g (crude) of 2,2,2-trifluoroacetic acid benzyl azetidine-3-carboxylate as light yellow oil; LC-MS (ES, *m/z*): [M+H-TFA]$^+$ = 191.8.

[0177] Step 3: benzyl 1-(cyclobutylmethyl)azetidine-3-carboxylate: a solution of 2,2,2-trifluoroacetic acid cyclohexylmethyl azetidine-3-carboxylate (1.3 g, 4.18 mmol, 1.00 eq.), cyclobutanecarboxaldehyde (358 mg, 4.26 mmol, 1.00 eq.) and acetic acid (255 mg, 4.25 mmol, 1.00 eq.) in DCE (20mL) was stirred for 30 min, and then $NaBH(OAc)_3$ (1.44 g, 6.79 mmol, 1.60 eq.) was added. The resulting solution was stirred for 2 hours at room temperature. The reaction was then quenched by the addition of water, extracted with dichloromethane and the organic layers combined. The resulting mixture was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1) to give 650 mg (59%) of benzyl 1-(cyclobutylmethyl)azetidine-3-carboxylate as colorless oil; LC-MS (ES, *m/z*): [M+H]$^+$ = 260.1.

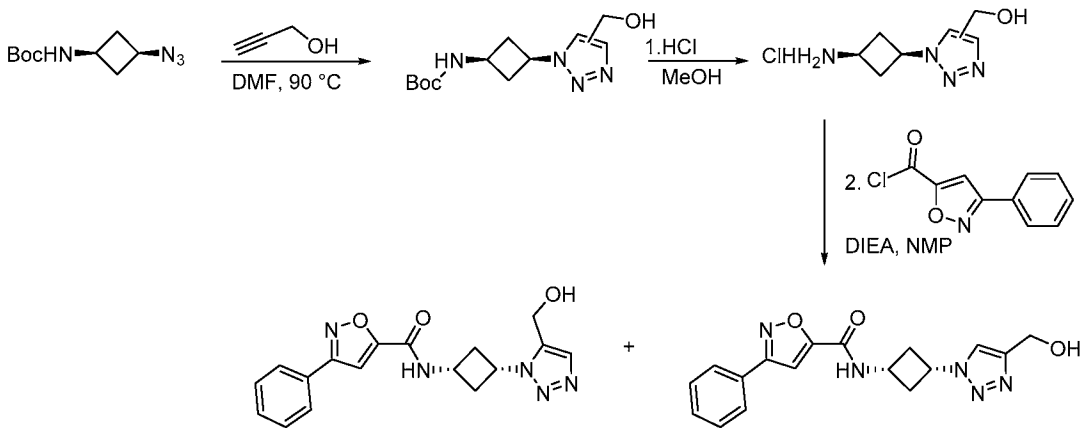
[0178] Step 4: 1-(cyclobutylmethyl)azetidine-3-carboxylic acid: to a solution of benzyl 1-(cyclobutylmethyl)azetidine-3-carboxylate (650 mg, 2.51 mmol, 1.00 eq.) in methanol (10mL) was added Palladium on carbon (65 mg) and the solution was degassed and back filled with hydrogen. The resulting solution was stirred for 2 hours at room temperature. The solids were filtered out and concentrated under vacuum to afford 425 mg (99%) of 1-(cyclobutylmethyl)azetidine-3-carboxylic acid as a white solid; LC-MS (ES, *m/z*): [M+H]$^+$ = 170.1.

[0179] Step 5: 3-phenyl-*N*-[*trans*-3-([[1-(cyclobutylmethyl)azetidin-3-yl]formohydrazido]carbonyl)cyclobutyl]-isoxazole-5-carboxamide: a solution of 3-phenyl-*N*-[(*trans*-3-(hydrazinecarbonyl)cyclobutyl]-isoxazole-5-carboxamide (300 mg, 1.00 mmol, 1.00 eq.), 1-(cyclobutylmethyl)azetidine-3-carboxylic acid (200 mg, 1.20 mmol, 1.20 eq.), T_3P (3.18 g, 5.00 mmol, 5.00 eq., 50%) and TEA (505 mg, 4.99 mmol, 5.00 eq.) in tetrahydrofuran (10mL) was stirred for 30 min at room temperature. The reaction was then quenched by the

addition of water, extracted with ethyl acetate and the aqueous layers combined and concentrated under vacuum. The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, MeCN/H_2O = 5:95 increasing to MeCN/H_2O = 95:5 within 30 min; Detector, UV 254 nm to afford 210 mg (47%) of 3-phenyl-*N*-[*trans*-3-([[1-(cyclobutylmethyl)azetidin-3-yl]formohydrazido]carbonyl)cyclobutyl]-isoxazole-5-carboxamide as a light yellow solid; LC-MS (ES, *m/z*): $[M+H]^+$ = 452.1.

[0180] Step 6: 3-phenyl-*N*-[*trans*-3-[5-[1-(cyclobutylmethyl)azetidin-3-yl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-isoxazole-5-carboxamide: I_2 (401 mg, 1.58 mmol, 2.50 eq.), TEA (415 mg, 4.10 mmol, 6.50 eq.) and 3-phenyl-*N*-[*trans*-3-([[1-(cyclobutylmethyl)azetidin-3-yl]formohydrazido]carbonyl)cyclobutyl]-isoxazole-5-carboxamide (285 mg, 0.63 mmol, 1.00 eq.) were added to a solution of Ph_3P (414 mg, 1.58 mmol, 2.50 eq.) in dichloromethane (20mL) under N_2. The reaction mixture was stirred for 1 hour at room temperature, quenched with water and then extracted with ethyl acetate and the organic layers combined. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with DCM/MeOH (25:1). The resulting crude product was purified by Prep-HPLC with the following conditions (HPLC-10): Column, X Bridge Prep C18 OBD Column, 19*150mm, 5um; mobile phase, water (0.05% NH_4HCO_3) and ACN (30% ACN up to 80% within 8 min); Detector, UV 254 nm to give 125.6 mg (46%) of 3-phenyl-*N*-[*trans*-3-[5-[1-(cyclobutylmethyl)azetidin-3-yl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+$ = 434.3; ^1H NMR (400MHz, DMSO-d_6, *ppm*): δ 9.45-9.43 (d, 1H, *J* = 7.6 Hz), 7.95-7.93 (m, 2H), 7.65 (s, 1H), 7.55-7.54 (m, 2H), 4.71-4.63 (m, 1H), 3.88-3.81 (m, 1H), 3.74-3.67 (m, 1H), 3.59-3.55 (t, 2H, *J* = 7.2 Hz), 3.31 (s, 1H), 3.29-3.26 (d, 1H, *J* = 6.8 Hz), 2.70-2.63 (m, 4H), 2.45-2.43 (m, 2H), 2.32-2.24 (m, 1H), 1.99-1.95 (m, 2H), 1.88-1.73 (m, 2H), 1.67-1.59 (m, 2H); HPLC purity: 99.3% at 254 nm.

Examples 28 and 29: *N*-(*cis*-3-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide and *N*-(*cis*-3-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide.



[0181] **Step 1: 1-[*cis*-3-aminocyclobutyl]-1H-1,2,3-triazol-5-yl]methanol hydrochloride**: a solution of tert-butyl *N*-[*cis*-3-[4/5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]carbamate (prepared using a procedure similar to example 36; 400 mg, 1.49 mmol, 1.00 eq.) in hydrogen chloride/MeOH (5 mL) was stirred for 18 hours at room temperature. The resulting mixture was concentrated under vacuum and diluted with 3 mL of dioxane. The solids were collected by filtration and dried in an oven under reduced pressure to give 301 mg (crude) of 1-[*cis*-3-aminocyclobutyl]-1H-1,2,3-triazol-5-yl]methanol hydrochloride as a white solid; LC-MS (ES, *m/z*): $[M+1]^+ = 167.1$.

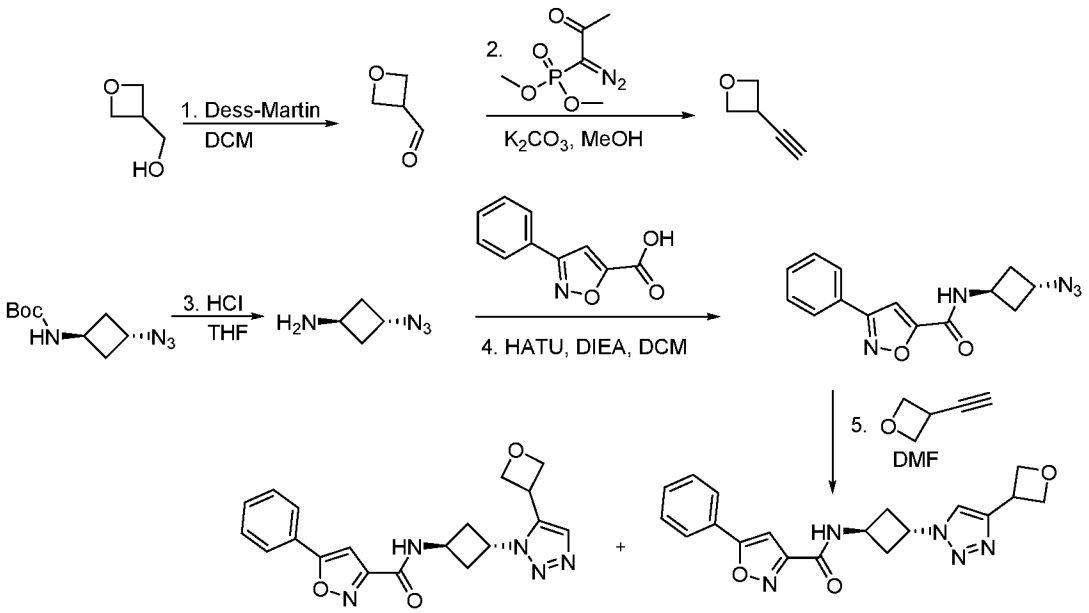
[0182] **Step 2**: **3-phenyl-*N*-[*cis*-3-[4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide and 3-phenyl-*N*-[*cis*-3-[5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide**: DIEA (787 mg, 6.09 mmol, 3.00 eq.) was added dropwise to a cold solution (10 °C) of [1-[*cis*-3-aminocyclobutyl]-1H-1,2,3-triazol-4/5-yl]methanol hydrochloride (410 mg, 2.00 mmol, 1.00 eq.) in NMP (4 mL) and stirred for 30 min at 25°C, followed by the addition of a solution of 3-phenylisoxazole-5-carbonyl chloride (310 mg, 1.64 mmol, 1.00 eq.) in NMP (1 mL) dropwise with stirring at 0 to 10 °C. The reaction was stirred for 30min and then quenched by the addition of 0.5 mL of methanol. The mixture was stirred at 25 °C for 30 min then 40 mL of water was added. The crude solid was collected by filtration and purified by prep-HPLC: Column: XBridge BEH130 Prep C18 OBD Column 19*150 mm, 5um, 13nm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 22% B to 47% B in 8 min; 254 nm to give 152 mg (22%) of 3-phenyl-*N*-[*cis*-3-[5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide as a white solid and 143.15 mg (28%) of 3-phenyl-*N*-

[*cis*-3-[4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide as a white solid.

[0183] 3-phenyl-*N*-[*cis*-3-[5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide: LC-MS (ES, *m/z*): $[M+1]^+ = 340.0$; ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 9.48-9.45 (d, J = 7.5 Hz, 1H), 7.94-7.91 (m, 2H), 7.66-7.62 (m, 2H), 7.56-7.54 (m, 3H), 5.46-5.42 (m, 1H), 4.89-4.80 (m, 1H), 4.58-4.57 (d, J = 5.4 Hz, 2H), 4.45-4.35 (m, 1H), 2.92-2.80 (m, 4H); HPLC purity: 99.2% at 254 nm.

[0184] 3-phenyl-*N*-[*cis*-3-[4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide: LC-MS (ES, *m/z*): $[M+1]^+ = 340.0$; ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 9.41-9.39 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H), 7.96-7.93 (m, 2H), 7.67 (s, 1H), 7.56-7.54 (m, 3H), 5.23-5.19 (t, J = 5.6 Hz, 1H), 4.98-4.92 (m, 1H), 4.55-4.53 (d, J = 5.4 Hz, 2H), 4.45-4.37 (m, 1H), 2.98-2.90 (m, 2H), 2.75-2.65 (m, 2H); HPLC purity: 99.3% at 254 nm.

Examples 30 and 31: *N*-(*trans*-3-(5-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-5-phenylisoxazole-3-carboxamide and *N*-(*trans*-3-(4-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-5-phenylisoxazole-3-carboxamide



[0185] Step 1: oxetane-3-carbaldehyde: a solution of oxetan-3-ylmethanol (2 g, 22.70 mmol, 1.00 eq.) in dichloromethane (20 mL) and 1,1,1-triacetoxy-1,1-dihydro-1,2-

benziodoxol-3(1H)-one (11.7 g, 27.59 mmol, 1.00 eq.) was stirred for 2 hours at 25 °C. The solids were filtered out and the mixture was concentrated under vacuum to give 2.1 g (crude) of oxetane-3-carbaldehyde as yellow oil.

[0186] **Step 2: 3-**ethynyloxetane: a solution of oxetane-3-carbaldehyde (2.1 g, 24.39 mmol, 1.00 eq.), potassium carbonate (6.6 g, 47.75 mmol, 2.00 eq.) and dimethyl (1-diazo-2-oxopropyl)phosphonate (7 g, 36.44 mmol, 1.50 eq.) in methanol (30 mL) was stirred for 3 hours at 25 °C. The resulting solution was diluted with 150 mL of water, extracted with ethyl acetate (2x100 mL) and the organic layers combined. The resulting mixture was washed with brine (2x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give 820 mg (41%) of 3-ethynyloxetane as colorless oil.

[0187] **Step 3: *trans*-3-azidocyclobutan-1-amine**: a solution of tert-butyl *N*-[*trans*-3-azidocyclobutyl]carbamate (1 g, 4.71 mmol, 1.00 eq.) in tetrahydrofuran (20 mL)/conc. HCl aqueous (5 mL) was stirred for 2 hours at 25°C. The resulting mixture was concentrated under vacuum to give 800 mg (crude) of *cis*-3-azidocyclobutan-1-amine as yellow oil.

[0188] **Step 4: 3-phenyl-*N*-[*trans*-3-azidocyclobutyl]-isoxazole-5-carboxamide**: HATU (1.37 g, 3.60 mmol, 1.50 eq.), DIEA (928 mg, 7.18 mmol, 3.00 eq.) and 3-phenyl-isoxazole-5-carboxylic acid (453 mg, 2.39 mmol, 1.00 eq.) were added to a solution of *trans*-3-azidocyclobutan-1-amine (800 mg, 7.13 mmol, 1.00 eq.) in dichloromethane (15 mL) and the mixture was stirred for 2 hours at 25 °C. The resulting solution was diluted with 150 mL of H_2O, extracted with ethyl acetate (2 x100 mL) and the organic layers combined. The organic layer was washed with brine (2x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with petroleum ether:ethyl acetate (10:1) to afford 390 mg (19%) of 3-phenyl-*N*-[*trans*-3-azidocyclobutyl]-isoxazole-5-carboxamide as a yellow solid; LC-MS (ES, *m/z*): $[M+H]^+ = 284.1$.

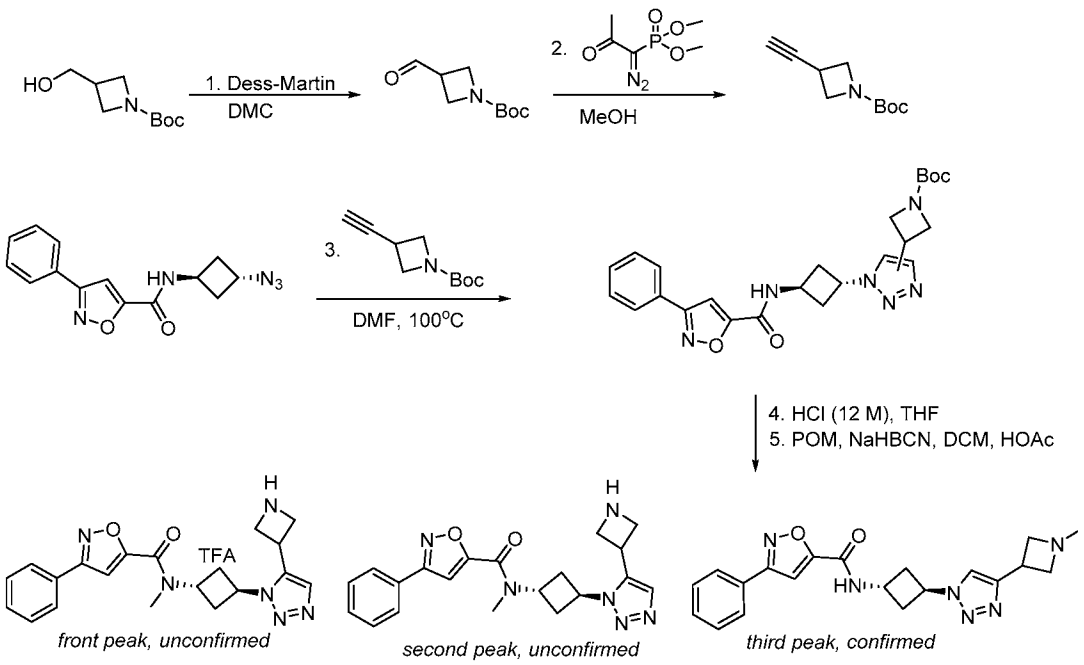
[0189] **Step 5**: **5-phenyl-*N*-[*trans*-3-[4-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-3-carboxamide** and **5-phenyl-*N*-[*trans*-3-[5-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-3-carboxamide:** a solution of 3-phenyl-*N*-[(*trans*-3-azidocyclobutyl]isoxazole-5-carboxamide (283 mg, 1.00 mmol, 1.00 eq.) and 3-ethynyloxetane (410 mg, 4.99 mmol, 5.00 eq.) in DMF (10 mL) was stirred for 16 hours at 100 °C. The resulting solution was diluted with 100 mL of H_2O, extracted with ethyl acetate (2x100 mL) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated

under vacuum. The crude product was purified by Prep-TLC (petroleum ether:ethyl acetate = 1:5). The resulting isomers was separated by Chiral-Prep-HPLC with the following conditions (Prep-HPLC-032): Column, Phenomenex Lux 5u Cellulose-4 AXIA Packed, 250*21.2 mm, 5um; mobile phase, Hex and ethanol (hold 50.0% ethanol in 20 min); Detector, UV 254/220 nm to afford 16.8 mg (5%) of 5-phenyl-*N*-[*trans*-3-[5-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-3-carboxamide as a white solid and 29.1 mg (8%) of 3-phenyl-*N*-[*trans*-3-[4-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide as a white solid.

[0190] 5-phenyl-*N*-[*trans*-3-[5-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-3-carboxamide: LC-MS (ES, *m/z*): $[M+H]^+ = 366.1$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.51-9.49 (d, $J = 7.2$ Hz, 1H), 7.96-7.94 (m, 3H), 7.68 (s, 1H), 7.57-7.56 (m, 3H), 4.97-4.93 (m, 3H), 4.75-4.70 (m, 1H), 4.66-4.62 (m, 2H), 4.48-4.42 (m, 1H), 2.86-2.74 (m, 4H); HPLC purity: 99.5% at 254 nm.

[0191] 5-phenyl-*N*-[*trans*-3-[4-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-3-carboxamide: LC-MS (ES, *m/z*): $[M+H]^+ = 366.1$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.52-9.50 (d, $J = 6.9$ Hz, 1H), 8.33 (s, 1H), 7.96-7.93 (m, 2H), 7.68 (s, 1H), 7.56-7.54 (m, 3H), 5.34-5.24 (m, 1H), 4.92-4.88 (m, 2H), 4.76-4.65 (m, 3H), 4.42-4.32 (m, 1H), 2.91-2.75 (m, 4H); HPLC purity: 98% at 254 nm.

Example 32 and 33: *N*-(*trans*-3-(4-(1-methylazetidin-3-yl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide and *N*-(*trans*-3-(5-(1-methylazetidin-3-yl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0192] **Step 1: tert-butyl 3-formylazetidine-1-carboxylate**: a solution of tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (3.74 g, 19.97 mmol, 1.00 equip), and Dess-Martin reagent (12.72 g, 30.00 mmol, 1.50 eq.) in dichloromethane (100 mL) was stirred for 2 hours at room temperature. The solids were filtered out, the resulting mixture was concentrated under vacuum to give 3.8 g (crude) of tert-butyl 3-formylazetidine-1-carboxylate as a white solid.

[0193] **Step 2: tert-butyl 3-ethynylazetidine-1-carboxylate**: a solution of tert-butyl 3-formylazetidine-1-carboxylate (3.7 g, 19.98 mmol, 1.00 eq.), potassium carbonate (8.28 g, 59.91 mmol, 3.00 eq.) and dimethyl (1-diazo-2-oxopropyl)phosphonate (5.76 g, 29.98 mmol, 1.50 eq.) in methanol (50 mL) was stirred for 3 hours at room temperature. The resulting solution was diluted with 200 mL of ether, washed with saturated sodium bicarbonate aqueous (2 x 200 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to give 3.282 g (crude) of tert-butyl 3-ethynylazetidine-1-carboxylate as yellow oil.

[0194] **Step 3: tert-butyl 3-[1-[*trans*-3-(3-phenylisoxazole-5-amido)cyclobutyl]-1H-1,2,3-triazol-4/5-yl]azetidine-1-carboxylate**: a solution of 3-phenyl-*N*-[*trans*-3-azidocyclobutyl]isoxazole-5-carboxamide (327 mg, 1.15 mmol, 1.00 eq.) and tert-butyl 3-ethynylazetidine-1-carboxylate (627 mg, 3.46 mmol, 3.00 eq.) in DMF (4 mL) was placed in a microwave reactor for 6 hours at 140 °C. The resulting mixture was concentrated under vacuum and the residue was applied onto a silica gel column with ethyl acetate/petroleum ether

(1:1) to give 553 mg (crude) mixture of tert-butyl 3-[1-[*trans*-3-(3-phenylisoxazole-5-amido)cyclobutyl]-1H-1,2,3-triazol-5-yl]azetidine-1-carboxylate and tert-butyl 3-[1-[*trans*-3-(3-phenylisoxazole-5-amido)cyclobutyl]-1H-1,2,3-triazol-4-yl]azetidine-1-carboxylate as a yellow solid; LC-MS (ES, *m/z*): $[M+H]^+ = 465.3$.

[0195] Step 4: 3-phenyl-*N*-[*trans*-3-[4/5-(azetidin-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide hydrochloride: a solution of the mixture of tert-butyl 3-[1-*trans*-3-(3-phenylisoxazole-5-amido)cyclobutyl]-1H-1,2,3-triazol-4/5-yl]azetidine-1-carboxylate (553 mg, 1.19 mmol, 1.00 eq.) in tetrahydrofuran (10 mL)/hydrogen chloride aqueous (6N, 6 mL) was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum to give 551 mg (crude) of a mixture of 3-phenyl-*N*-[*trans*-3-[4/5-(azetidin-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide hydrochloride as a brown solid; LC-MS (ES, *m/z*): $[M-HCl+H]^+ = 365.3$.

[0196] Step 5: ***N*-(*trans*-3-(4-(1-methylazetidin-3-yl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide** and ***N*-(*trans*-3-(5-(1-methylazetidin-3-yl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide:** a solution of the mixture of 3-phenyl-*N*-[*trans*-3-[4/5-(azetidin-3-yl)-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide hydrochloride, POM (302 mg, 6.86 mmol, 4.99 eq.) and acetic acid (165 mg, 2.75 mmol, 2.00 eq.) in DCM (20 mL) was stirred for 30 min at room temperature. NaBHCN (346 mg, 5.49 mmol, 4.00 eq.) was added to the reaction mixture and it was stirred for 3 hours at room temperature. The mixture was concentrated under vacuum and the crude product was purified by Prep-HPLC with the following conditions (HPLC-10): Column, XBridge C18 OBD Prep Column, 19 mm X 250 mm; mobile phase, water (10 mmol/L NH_4HCO_3) and ACN (40.0% ACN up to 90.0% in 8 min); Detector, UV 254/220 nm. This resulted in 50 mg crude first peak, 20 mg (4%) of second peak as a white solid and 75 mg (15%) of third peak) as a white solid. Then the crude first peak was purified by Prep-HPLC with the following conditions (HPLC-10): Column, XBridge C18 OBD Prep Column, 19 mm X 250 mm; mobile phase, water (0.05% TFA) and ACN (20.0% ACN up to 50.0% in 10 min); Detector, UV 254/220 nm to give 30 mg of product as a yellow oil.

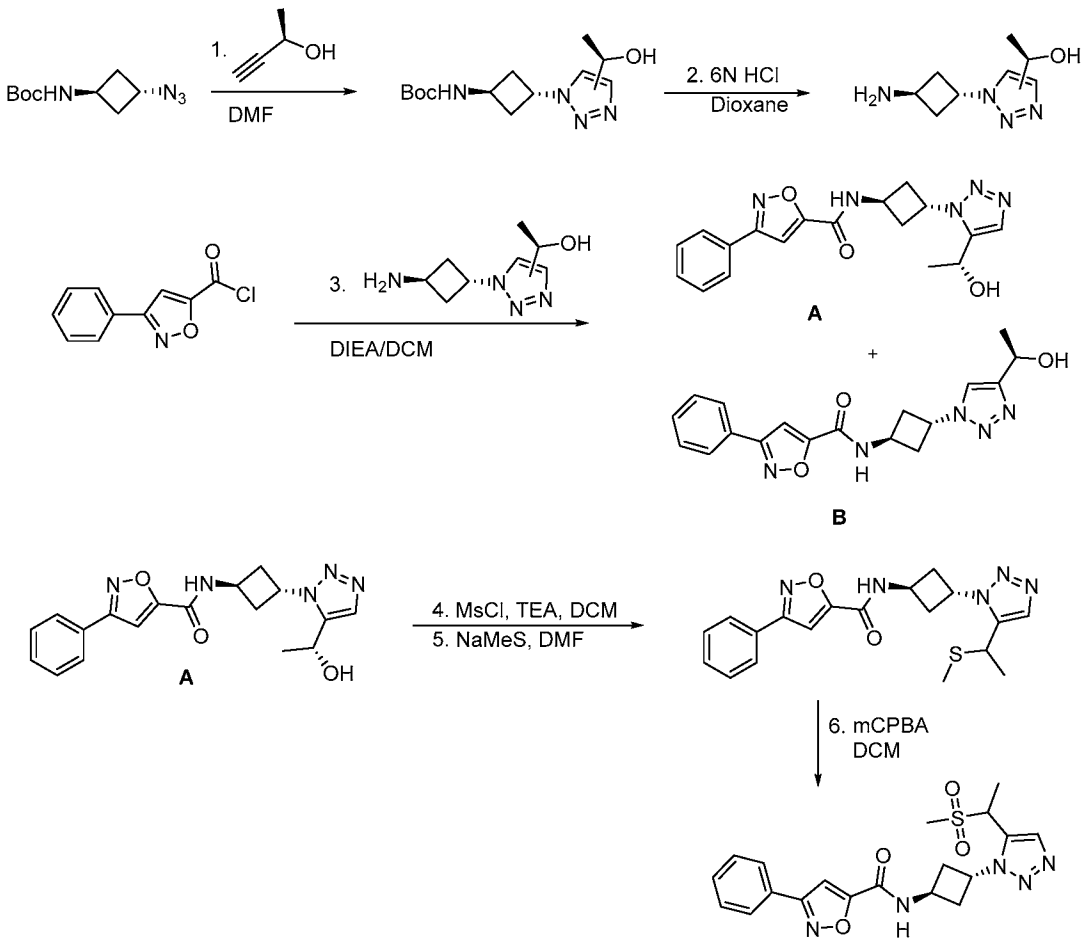
[0197] First peak (putative structure):

[0198] Second peak (putative structure): LC-MS (ES, *m/z*): $[M+H]^+ = 379.2$; ^1H NMR (400 MHz, CD_3OD, *ppm*): 8.05(s, 1H), 7.89-7.88 (d, $J = 2.8$ Hz, 2H), 7.52-7.51 (m, 3H), 7.43

(s, 1H), 5.11 (br, 1H), 4.90-4.88 (m, 1H), 4.74-7.54 (m, 1H), 4.54-4.46 (m, 2H), 4.36-4.25 (m, 2H), 3.10-2.91 (m, 5H), 2.89-2.88 (m, 2H); HPLC purity: 99.4% at 254 nm.

[0199] Third peak: *N*-(*trans*-3-(4-(1-methylazetidin-3-yl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide: LC-MS $[M+H]^+ = 379.3$; ^1H NMR (400MHz, DMSO-d_6, *ppm*): δ 9.53-9.51 (d, $J = 6.8$ Hz, 1H), 8.23 (s, 1H), 7.96-7.74 (m, 2H), 7.69 (s, 1H), 7.56-7.54 (m, 3H), 5.28-5.24 (m, 1H), 4.72-4.67 (m, 1H), 3.64-3.56 (m, 3H), 3.12-3.09 (m, 2H), 2.88-2.75 (m, 4H), 2.08 (s, 3H); HPLC purity; 98.7% at 254 nm.

Examples 34: ***N*-(*trans*-3-(5-(1-(methylsulfonyl)ethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide**



Preparation of intermediates A and B:

[0200] Step 1: *N*-[*trans*-3-[4/5-[(1*R*)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]carbamate: a solution of tert-butyl *N*-[*trans*-3-azidocyclobutyl]carbamate (2 g,

9.42 mmol, 1.00 eq.) and (2R)-but-3-yn-2-ol (3.3 g, 47.08 mmol, 5.00 eq.) in DMF (5 mL) was stirred for overnight at 100 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (3:1) to give 2.1 g (79%) of a mixture of tert-butyl *N*-[*trans*-3-[4/5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]carbamate as a light yellow solid; LC-MS (ES, *m/z*): $[M+H]^+$ = 283.2.

[0201] Step 2: (1*R*)-1-[1-[*trans*-3-aminocyclobutyl]-1H-1,2,3-triazol-4/5-yl]ethanol: a solution of the mixture of tert-butyl *N*-[*trans*-3-[4/5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]carbamate in dioxane (10 mL)/ hydrogen chloride aqueous (6N, 3 mL) was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum to give 1.45 g (crude) of a mixture of (1*R*)-1-[1-[*trans*-3-aminocyclobutyl]-1H-1,2,3-triazol-4/5-yl]ethanol as a light yellow solid; LC-MS-PH (ES, *m/z*): $[M+H]^+$ = 183.1.

[0202] Step 3: *N*-(*trans*-3-(5-((*R*)-1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide (A) and *N*-(*trans*-3-(4-((R)-1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide (B): DIEA (2.55 g, 3.00 eq.) and 3-phenylisoxazole-5-carbonyl chloride (1.77 g, 8.53 mmol, 1.30 eq.) were added dropwise to a cold (0 °C) solution of a mixture of (1*R*)-1-[1-[*trans*-3-aminocyclobutyl]-1H-1,2,3-triazol-4/5-yl]ethanol in dichloromethane (20 mL) and the mixture was stirred for 2 hours at 0 °C. The resulting mixture was washed with hydrogen chloride aqueous (2N) (1x50 mL) and potassium carbonate (5%) (1x100 mL), concentrated under vacuum, and the crude product was purified by prep-HPLC to give 0.236 g (10%) of *N*-(*trans*-3-(5-((*R*)-1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide and 0.333 g (14%) of *N*-(*trans*-3-(4-((*R*)-1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+$ = 354.2.

Preparation of *N*-(*trans*-3-(5-(1-(methylsulfonyl)ethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide:

[0203] Step 4: *N*-(*trans*-3-(5-((*R*)-1-chloroethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide: MsCl (81.3 mg, 2.00 eq.) was added dropwise to a 0 °C solution of 3-phenyl-*N*-[(*trans*-3-[5-[(1*R*)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide (126 mg, 0.36 mmol, 1.00 eq.) and TEA (108 mg, 3.00 eq.) in dichloromethane (20 mL) and the solution was stirred for 5 hours at room temperature.

The mixture was diluted with 30 ml of dichloromethane, washed with $CuSO_4$ aqueous (2x30 mL) and concentrated under vacuum to give 151 mg (crude) of *N*-(*trans*-3-(5-((*R*)-1-chloroethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide as a brown oil; LC-MS (ES, *m/z*): $[M+H]^+ = 372.1$.

[0204] **Step 5:** a solution of *N*-(*trans*-3-(5-((*R*)-1-chloroethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide (151 mg, 0.41 mmol, 1.00 eq.) and NaSMe (50 mg, 2.00 eq.) in DMF (5 mL) was stirred for 5 hours at 100 °C in an oil bath. The reaction was then quenched by the addition of 20 mL of water, extracted with ethyl acetate (3x20 mL) and the organic layers combined. The resulting mixture was washed with brine (2x10 mL) and concentrated under vacuum to give 189 mg (crude) of 3-phenyl-*N*-[*trans*-3-[5-[1-(methylsulfanyl)ethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-isoxazole-5-carboxamide as brown oil; LC-MS (ES, *m/z*): $[M+H]^+ = 384.4$.

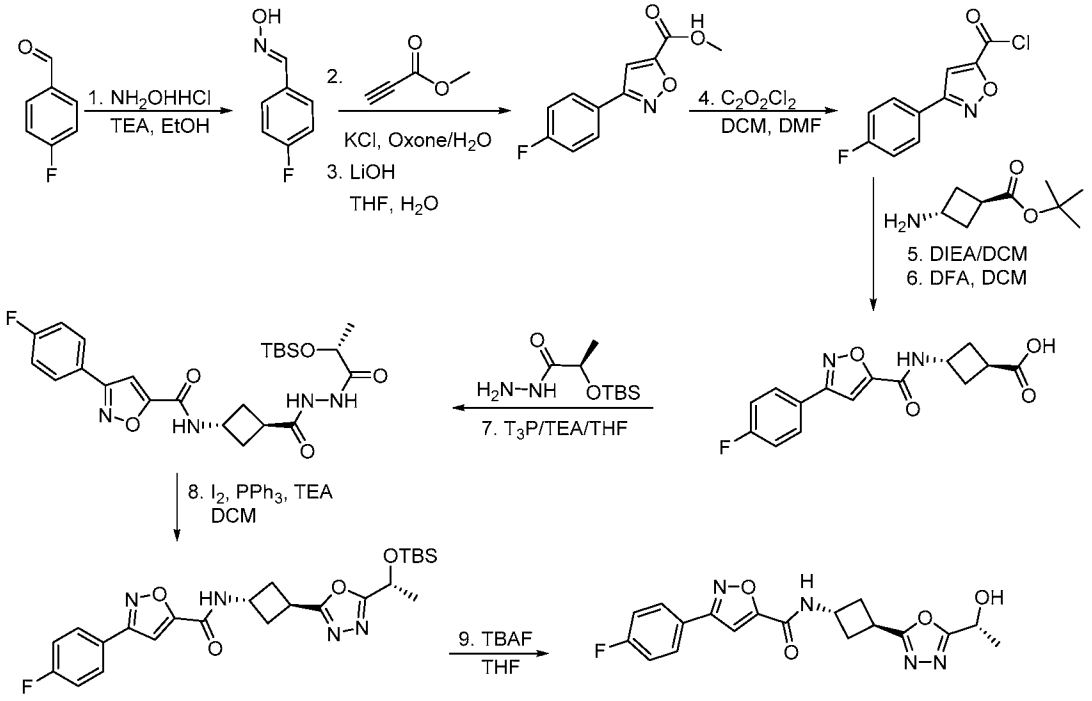
[0205] **Step 6:** mCPBA (338 mg, 1.96 mmol, 4.00 eq.) was added in several batches to a 0 °C solution of 3-phenyl-*N*-[*trans*-3-[5-[1-(methylsulfanyl)ethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]isoxazole-5-carboxamide (189 mg, 0.49 mmol, 1.00 eq.) in dichloromethane (10 mL) and the mixture was stirred for 5 hours at room temperature. The reaction mixture was diluted with 50 mL of dichloromethane, washed with $Na_2S_2O_3$ aqueous (1x50 mL) and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Water): Column, Xbridge Prep C18, 5 um,19*150 mm; mobile phase, water with 0.08% NH_4HCO_3 and CH_3CN (30% CH_3CN up to 70% CH_3CN in 10 min, up to 95% in 2 min and down to 30% in 2 min); Detector, UV 254 nm and 220 nm to give 23.3 mg (11%) of 3-phenyl-*N*-[*trans*-3-[5-[1-methanesulfonylethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+ = 416.2$; ^1H NMR (DMSO-d_6, 400 MHz): δ 9.52-9.49 (d, $J = 12.0$ Hz, 1H), 7.95-7.93 (m, 3H), 7.69 (s, 1H), 7.56-7.54 (m, 3H), 5.36-5.29 (m, 1H), 4.93-4.87 (m, 1H), 4.85-4.76 (m, 1H), 3.01 (s, 3H), 2.92-2.78 (m, 4H), 1.69-1.67 (d, $J = 7.2$ Hz, 3H); HPLC purity: 99.2% at 254 nm.

Example 35: *N*-(*trans*-3-(4-(1-(methylsulfonyl)ethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide

[0206] The title compound was prepared by a similar procedure as shown in example 34 using intermediate B as the starting material. The crude product was purified by Prep-HPLC with the following conditions (Water): Column, Xbridge Prep C18, 5 um,19*150 mm; mobile

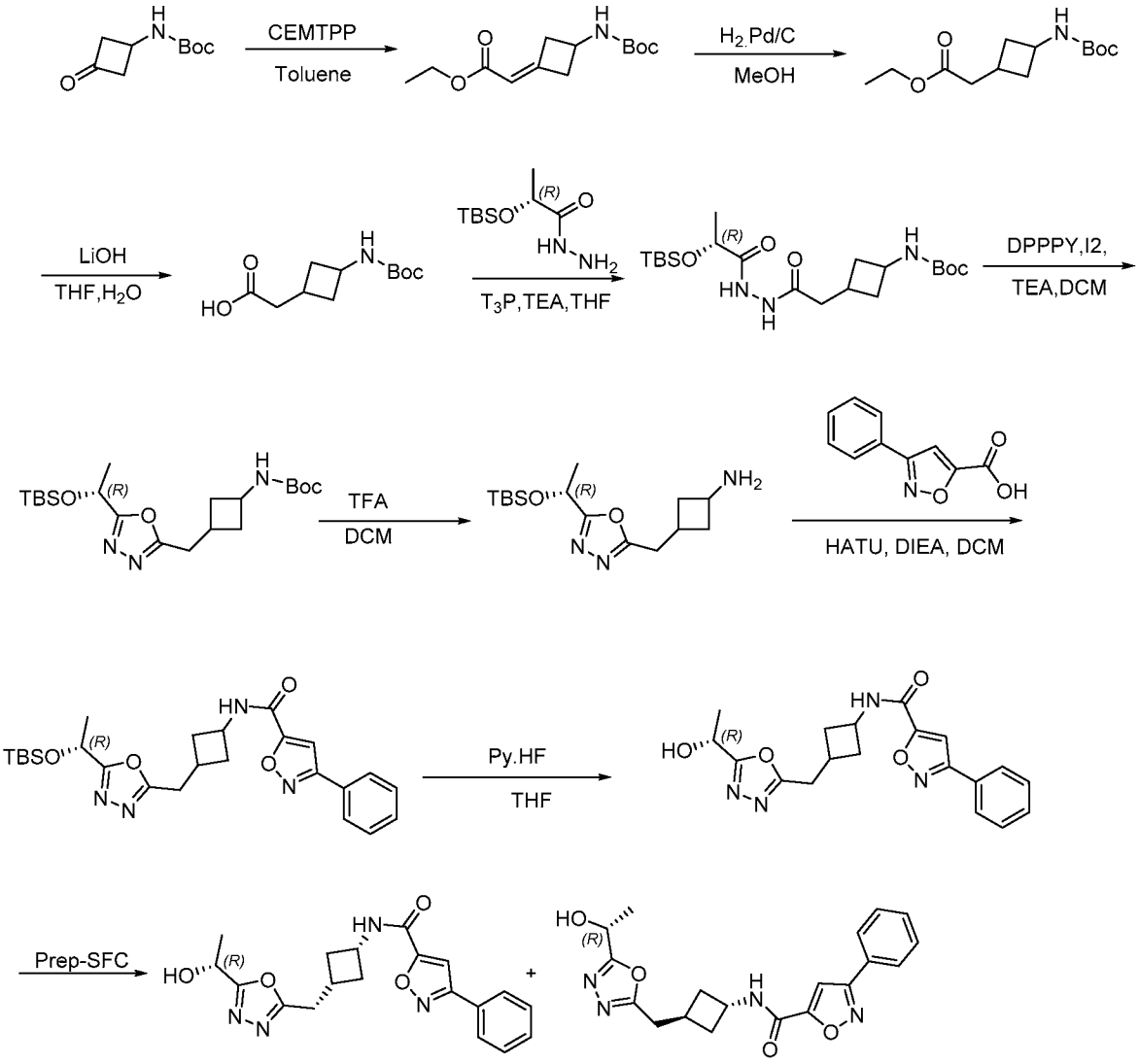
phase, water with 0.08% NH_4HCO_3 and CH_3CN (30% CH_3CN up to 75% CH_3CN in 10 min, up to 95% in 2 min and down to 30% in 2 min); Detector, UV 254 nm and 220 nm to give 54.5 mg (17.6%) of 3-phenyl-*N*-[*trans*-3-[5-[1-methanesulfonylethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-isoxazole-5-carboxamide as a white solid; LC-MS (ES, *m/z*): $[M+H]^+ = 416.2$; ^1H NMR (DMSO-d_6, 400 MHz): δ 9.54-9.52 (d, *J* = 7.2 Hz, 1H), 8.43 (s, 1H), 7.96-7.94 (m, 2H), 7.68 (s, 1H), 7.56-7.54 (m, 3H), 5.37-5.29 (m, 1H), 4.72-4.68 (m, 2H), 2.95 (s, 3H), 2.88-2.81 (m, 4H), 1.68-1.66 (d, *J* = 7.2 Hz, 3H); HPLC purity: 98.4% at 254 nm.

Example 36: 3-(4-fluorophenyl)-*N*-(*trans*-3-(5-((*R*)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)isoxazole-5-carboxamide



[0207] The title compound was prepared using a methodology similar to the one shown in example 13 and purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, H_2O/CH_3CN = 100:1 increasing to H_2O/CH_3CN = 1:100 within 30 min; Detector, UV 254 nm to give 37.7 mg (25%) as a white solid; LC-MS (ES, *m/z*): $[M+1]^+ = 373.0$; ^1H NMR (400MHz, DMSO-d_6): δ9.49-9.47 (d, *J* = 7.6 Hz, 1H), 8.03-7.98 (m, 2H), 7.68 (s, 1H), 7.42-7.37 (m, 2H), 5.97-5.95 (d, *J* = 6 Hz, 1H), 7.96-4.89 (m, 1H), 4.71-4.65 (m, 1H), 3.76-3.72 (m, 1H), 2.73-2.60 (m, 4H), 1.50-1.48 (d, *J* = 6.4 Hz, 3H); HPLC purity: 99.8% at 254 nm.

Examples 37 and 38: N-((1S,3s)-3-((5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide and N-((1R,3r)-3-((5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0208] Step 1: Ethyl 2-(3-((tert-Butoxycarbonyl)amino)cyclobutylidene)acetate. To a 250-mL round-bottom flask was placed a solution of tert-butyl N-(3-oxocyclobutyl)carbamate (13 g, 70.19 mmol, 1.00 equiv) in toluene (100 mL), then (carbethoxymethylene)triphenylphosphorane (CEMTPP) (25.7 g, 73.77 mmol, 1.05 equiv) was added. The resulting solution was stirred for 2 h at 100°C. The resulting mixture was concentrated under vacuum then the residue was applied onto a silica gel column and eluted

with EtOAc/petroleum ether (1:5) affording 16.7 g (93%) of ethyl 2-(3-[[(tert-butoxy)carbonyl]amino]cyclobutylidene) acetate as a white solid. LCMS (ES, *m/z*): $[M+H]^+$ = 256.2.

[0209] Step 2: Ethyl 2-(3-((tert-Butoxycarbonyl)amino)cyclobutyl)acetate. To a 250-mL round-bottom flask, was placed a solution of ethyl 2-(3-[[(tert-butoxy)carbonyl]amino]cyclobutylidene)acetate (16.7 g, 65.41 mmol, 1.00 equiv, as prepared above) in MeOH (100 mL), then Pd on carbon (1 g) was added. The solution was degassed and back filled with hydrogen. The resulting solution was stirred for 3 h at RT. The solids were removed by filtration, then the resulting solution was concentrated under reduced pressure affording 15.5 g (92%) of ethyl 2-(3-[[(tert-butoxy)carbonyl]amino]cyclobutyl) acetate as colorless oil. LCMS (ES, *m/z*): $[M+H]^+$ = 258.2.

[0210] Step 3: 2-(3-[[(tert-Butoxy)carbonyl]amino]cyclobutyl)acetic acid. To a 500-mL round-bottom flask was placed a solution of ethyl 2-(3-[[(tert-butoxy)carbonyl]amino]cyclobutyl)acetate (15.5 g, 60.23 mmol, 1.00 equiv) in THF/H_2O (150/50 mL) and LiOH (2.16 g, 90.20 mmol, 1.50 equiv). The resulting solution was stirred for 3 h at rt, then the resulting mixture was concentrated under reduced pressure. The resulting solution was diluted with 200 mL of aq.$NaHSO_4$, extracted with 3x150 mL of EtOAc, and then the organic extracts were combined. The solution was washed with 2x100 mL of brine, dried, and concentrated under reduced pressure, affording 13.8 g (crude) of 2-(3-[[(tert-butoxy)carbonyl]amino]cyclobutyl)acetic acid as colorless oil. LCMS (ES, *m/z*): $[M+H]^+$ = 230.1.

[0211] Step 4: tert-Butyl N-(3-[2-[(2R)-2-[(tert-Butyldimethylsilyl)oxy] propanehydrazido]-2-oxoethyl]cyclobutyl)carbamate. To a 500-mL round-bottom flask was placed a solution of 2-(3-[[(tert-butoxy)carbonyl]amino]cyclobutyl)acetic acid (13 g, 56.70 mmol, 1.00 equiv) in THF (250 mL). To this solution were added (2R)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazide (18.6 g, 85.18 mmol, 1.50 equiv), TEA (28.9 g, 285.60 mmol, 5.00 equiv) and T_3P (72 g, 113.21 mmol, 2.00 equiv). The reaction was stirred for 2 h at RT, then diluted with 400 mL of H_2O and extracted with EtOAc (3x300 mL). The organic extracts were combined, washed with brine (2x300 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column with petroleum ether/EtOAc (2:1) affording 14.5 g (60%) of tert-butyl N-(3-[2-[(2R)-2-[(tert-

butyldimethylsilyl)oxy]propanehydrazido]-2-oxoethyl]cyclobutyl)carbamate as yellow oil. LCMS (ES, *m/z*): $[M+H]^+$ = 430.3.

[0212] Step 5: tert-butyl N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]carbamate. To a 250-mL 3-necked round-bottom flask purged and maintained with nitrogen was placed a solution of PPh_3 (2.84 g, 10.83 mmol, 2.00 equiv) in DCM (100 mL). To this solution were added I_2 (2.75 g, 10.83 mmol, 2.00 equiv), TEA (3.7 g, 36.56 mmol, 5.00 equiv) and tert-butyl N-[3-([N-[(2R)-2-[(tert-butyldimethylsilyl)oxy]propanoyl]hydrazinecarbonyl]methyl)cyclobutyl]carbamate (3.1 g, 7.22 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at RT, then diluted with 150 mL of H_2O and extracted with EtOAc (2x150 mL). The organic extracts were combined, washed with brine (2x100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with petroleum ether/EtOAc (5:1) affording 2 g (67%) of tert-butyl N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]carbamate as yellow oil. LCMS (ES, *m/z*): $[M+H]^+$ = 412.3. ^1H NMR (400 MHz, CDCl3): δ 5.11-5.02 (m, 1H), 4.15-4.08 (m, 1H), 3.02-2.92 (m, 2H), 2.59-2.52 (m, 1H), 2.26-2.19 (m, 1H), 2.14-2.08 (m, 1H), 1.70-1.62 (m, 2H), 1.58-1.56 (d, *J* = 7.6 Hz, 2H), 1.43 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H).

[0213] Step 6: 3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutan-1-amine. To a 100-mL round-bottom flask was placed a solution of tert-butyl N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]carbamate (2 g, 4.86 mmol, 1.00 equiv) in DCM (50 mL), then TFA (3 mL, 8.00 equiv) was added. The resulting solution was stirred for 2 h at RT then concentrated under reduced pressure affording 2.5 g (crude) of 3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutan-1-amine as yellow crude oil. LCMS (ES, *m/z*): $[M+H]^+$ = 312.2.

[0214] Step 7: N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide. To a 100-mL round-bottom flask was placed a solution of 3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutan-1-amine (1 g, crude) in DCM (50 mL), then 3-phenyl-1,2-oxazole-5-carboxylic acid (468 mg, 2.47 mmol, 1.00 equiv), HATU (1.28 g, 3.37 mmol, 1.20

equiv) and DIEA (1.1 mL, 2.80 equiv) were added. The resulting solution was stirred for 2 h at RT, washed with water (3x 50 mL), and then concentrated under reduced pressure affording 680 mg (crude) of N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide as yellow oil. LCMS (ES, *m/z*): $[M+H]^+ = 483.2$.

[0215] **Step 8:** N-[3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide. To a 100-mL 3-necked round-bottom flask was placed a solution of N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide (1 g, 2.07 mmol, 1.00 equiv) in THF (20 mL), then Py.HF (2.5 mL, 8.00 equiv) was added. The resulting solution was stirred for 2 h at 0°C then quenched by the addition of 100 mL of brine. The resulting mixture was extracted with EtOAc (3x100 mL), then the organic extracts were combined, washed with $NaHCO_3$ (2x100 mL), brine (2x 100mL), and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with petroleum ether/EtOAc (1:3) affording 460 mg of N-[3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide as light yellow oil. LCMS (ES, *m/z*): $[M+H]^+ = 369.2$.

[0216] N-[3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide (520 mg, 1.41 mmol, 1.00 equiv) was purified by Prep-SFC with the following conditions: Column: Phenomenex Lux 5u Cellulose-4, 250*50 mm; Mobile Phase A:CO_2 :50, Mobile Phase B: MeOH-Preparative:50; Flow rate: 150 mL/min; 220 nm; RT1:6.38; RT2:7.33 affording 98.6 mg (19%) of 3-phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 78.7 mg (15%) of 3-phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0217] **3-Phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide:** LCMS (ES, *m/z*): $[M+H]^+ = 369.0$. ^1H NMR (300 MHz, DMSO-d_6): δ 9.23-9.20 (d, $J = 7.8$ Hz, 1H), 7.94-7.91 (m, 2H), 7.62 (s, 1H), 7.55-7.53 (m, 3H), 5.92 (s, 1H), 4.92-4.85 (q, $J = 6.6$ Hz, 1H), 4.35-4.27 (m, 1H), 2.99-2.97 (d, $J = 6.6$ Hz, 2H), 2.45-2.35 (m, 3H), 1.98-1.92 (m, 2H), 1.47-1.44 (d, $J = 6.6$ Hz, 3H). Purity (HPLC, 254 nm): 99.0%.

[0218] 3-Phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 369.0. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23-9.20 (d, *J* = 8.4 Hz, 1H), 7.94-7.91 (m, 2H), 7.62 (s, 1H), 7.55-7.53 (m, 3H), 5.92 (s, 1H), 4.92-4.85 (q, *J* = 6.6 Hz, 1H), 4.35-4.28 (m, 1H), 2.99-2.97 (d, *J* = 6.6 Hz, 2H), 2.45-2.35 (m, 3H), 1.98-1.92 (m, 2H), 1.47-1.44 (d, *J* = 6.6 Hz, 3H). Purity (HPLC, 254 nm): 98.3%.

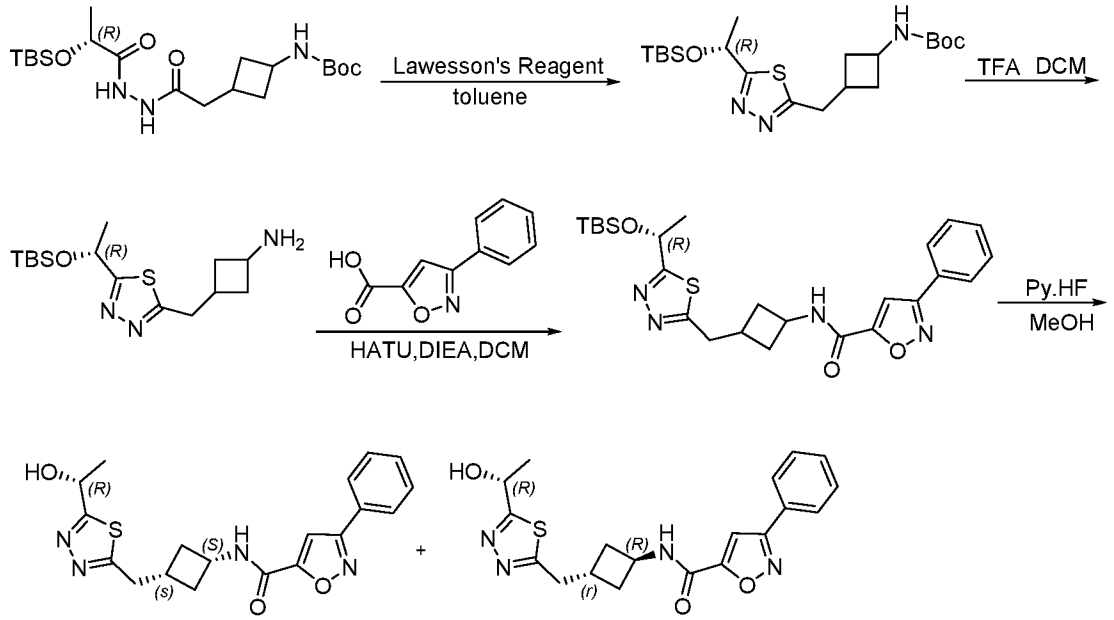
Example 39 and 40: 3-(4-Fluorophenyl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-(4-Fluorophenyl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide

[0219] The title compounds were prepared using a methodology similar to the one shown in Example 37. The mixture was separated by Chiral-Prep-HPLC with the following conditions: Column: Repaired IA, 21.2*150 mm, 5 um; Mobile Phase A:Hex-HPLC, Mobile Phase B: EtOH-HPLC; Flow rate: 20 mL/min; Gradient: 50 B to 50 B in 11.5 min; 254/220 nm; RT1:7.21; RT2:8.75. This resulted in 95 mg (34%) of 3-(4-fluorophenyl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 79.6 mg (28%) of 3-(4-fluorophenyl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0220] 3-(4-fluorophenyl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 386.9. 1H NMR (300 MHz, DMSO-d_6): δ 9.23-9.20 (d, *J* = 7.8 Hz, 1H), 8.02-7.97 (m, 2H), 7.63 (s, 1H), 7.42-7.36 (m, 2H), 5.92-5.90 (d, *J* = 5.4 Hz 1H), 4.91-4.87 (m, 1H), 4.35-4.28 (m, 1H), 2.99-2.97 (d, *J* = 6.9 Hz, 2H), 2.45-2.40 (m, 3H), 1.97-1.92 (m, 2H), 1.47-1.44 (d, *J* = 6.9 Hz, 3H). Purity (HPLC, 254 nm): 99.3%.

[0221] 3-(4-fluorophenyl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 386. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.31-9.29 (d, *J* = 7.2 Hz, 1H), 8.01-7.96 (m, 2H), 7.64 (s, 1H), 7.41-7.35 (m, 2H), 5.92-5.90 (d, *J* = 5.7 Hz 1H), 4.93-4.84 (m, 1H), 4.58-4.51 (q, *J* = 7.5 Hz, 1H), 3.10-3.07 (d, *J* = 7.8 Hz, 2H), 2.70-2.64 (s, 1H), 2.38-2.29 (m, 2H), 2.18-2.09 (m, 2H), 1.46-1.44 (d, *J* = 6.6 Hz, 3H). Purity (HPLC, 254 nm): 98.0%.

Examples 41 and 42: 3-Phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide



[0222] Step 1: tert-Butyl N-[3-([5-[(1R)-1-[(tert-Butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]carbamate. To a 250-mL round-bottom flask was placed a solution of tert-butyl N-(3-[2-[(2R)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazido]-2-oxoethyl]cyclobutyl)carbamate (6 g, 13.97 mmol, 1.00 equiv) in toluene (100 mL) then Lawesson's reagent (8.5 g, 21.02 mmol, 1.50 equiv) was added. The resulting solution was stirred for 1.5 h at 80°C then concentrated under reduced pressure. The resulting solution was diluted with 200 mL of H_2O and then extracted with EtOAc (3x200 mL). The organic extracts were combined, washed with brine (2x200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Flash-Prep-HPLC (CombiFlash-1: Column, C18; mobile phase, X:H_2O (0.5% NH_4HCO_3), Y:CAN, X/Y=80/20 increasing to X/Y = 5/95 within 40 min; Detector, UV 254 nm) affording 2.2 g (37%) of tert-butyl N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]carbamate as yellow oil. LCMS (ES, *m/z*): $[M+H-BOC]^+$ = 328.0.

[0223] Step 2: 3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutan-1-amine. To a 50-mL round-bottom flask was placed a solution of tert-butyl N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-

yl]methyl)cyclobutyl]carbamate (2.2 g, 5.14 mmol, 1.00 equiv) in DCM (20 mL) and TFA (4 mL). The resulting solution was stirred for 1 h at RT then concentrated under reduced pressure affording 3 g (crude) of 3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutan-1-amine as yellow oil.

[0224] Step 3: N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide. To a 50-mL round-bottom flask was placed a solution of 3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutan-1-amine (500 mg, 1.53 mmol, 1.00 equiv) in DCM (20 mL), then HATU (753 mg, 1.98 mmol, 1.30 equiv), 3-phenyl-1,2-oxazole-5-carboxylic acid (317 mg, 1.68 mmol, 1.10 equiv) and DIEA (589 mg, 4.56 mmol, 3.00 equiv) were added. The resulting mixture was stirred for 2 h at RT then diluted with 100 mL of H_2O and extracted with EtOAc (2x50 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:5) affording 320 mg (42%) of N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide as yellow oil. LCMS (ES, *m/z*): $[M+H]^+ = 499.1$.

[0225] Step 4: 3-Phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 10-mL round-bottom flask was placed a solution of N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-3-phenyl-1,2-oxazole-5-carboxamide (320 mg, 0.64 mmol, 1.00 equiv) in MeOH (3 mL), then Py.HF (1 mL) was added. The resulting solution was stirred for 2 h at rt, diluted with 50 mL of H_2O, and extracted with EtOAc (2x50 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:1). The resulting isomers were separated by Chiral-Prep-HPLC (Prep-HPLC-004: Column, Phenomenex Lux 5u Cellulose-4AXIA Packed, 250*21.2mm,5um; mobile phase, Hex and IPA (hold 50.0% IPA in 18 min); Detector, UV 254/220 nm) affording 88.7 mg (36%) of 3-phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-

5-carboxamide as a white solid and 57.8 mg (23%) of 3-phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0226] 3-Phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+ = 385.0$. ^1H NMR (300 MHz, DMSO-d_6) δ 9.23-9.20 (d, $J = 7.5$ Hz, 1H), 7.94-7.91 (m, 2H), 7.62 (s, 1H), 7.55-7.53 (m, 3H), 6.26-6.24 (d, $J = 5.1$ Hz, 1H), 5.09-5.03 (m, 1H), 4.35-4.28 (m, 1H), 3.19-3.16 (d, $J = 7.2$ Hz, 2H), 2.43-2.34 (m, 3H), 1.98-1.92 (m, 2H), 1.49-1.47 (d, $J = 6.3$ Hz, 3H).). Purity (HPLC, 254 nm): 97.9%.

[0227] 3-Phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+ = 385$. ^1H NMR (300 MHz, DMSO-d_6): δ 9.31-9.29 (d, $J = 7.2$ Hz, 1H), 7.94-7.91 (m, 2H), 7.64 (s, 1H), 7.55-7.53 (m, 3H), 6.25-6.24 (d, $J = 5.1$ Hz, 1H), 5.09-5.01 (m, 1H), 4.60-4.52 (m, 1H), 3.29-3.26 (m, 2H), 2.66-2.62 (m, 1H), 2.37-2.27 (m, 2H), 2.18-2.12 (m, 2H), 1.49-1.47 (d, $J = 6.6$ Hz, 3H). Purity (HPLC, 254 nm): 98.4%.

Examples 43 and 44: 3-(4-Fluorophenyl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-(4-Fluorophenyl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide

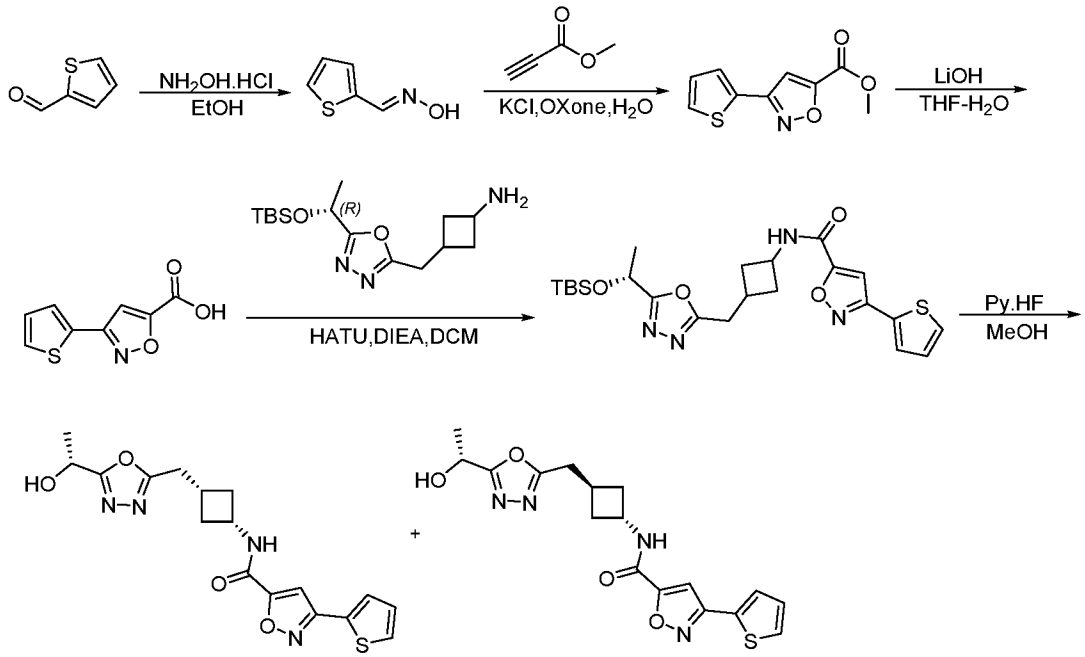
[0228] The title compounds were prepared using a methodology similar to the one shown in Example 41. The resulting isomers were separated by Prep-SFC (Prep SFC100: Column, Phenomenex Lux 5u Cellulose-4AXIA Packed, 250*21.2mm,5um; mobile phase, CO2(60%), ETOH(0.2%DEA)--(40%); Detector, uv 220 nm) affording 125 mg (22%) of 3-(4-fluorophenyl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 110.8 mg (20%) of 3-(4-fluorophenyl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0229] 3-(4-Fluorophenyl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+ = 403$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.24-9.22 (d, $J = 8.0$ Hz, 1H), 8.01-7.98 (m, 2H), 7.63 (s, 1H),

7.41-7.37 (m, 2H), 6.25 (s, 1H), 5.05-5.04 (m, 1H), 4.34-4.28 (m, 1H), 3.18-3.16 (d, J = 6.8 Hz, 2H), 2.45-2.36 (m, 3H), 1.94-1.92 (m, 2H), 1.48-1.47 (d, J = 6.4 Hz, 3H). Purity (HPLC, 254 nm): 99.4%.

[0230] **3-(4-Fluorophenyl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-thiadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide**: LCMS (ES, *m/z*): $[M+H]^+$ = 403.0. ^1H NMR (300 MHz, DMSO-d_6) δ 9.32-9.29 (d, J = 7.5 Hz, 1H), 8.02-7.97 (m, 2H), 7.65 (s, 1H), 7.42-7.36 (m, 2H), 6.25-6.24 (d, J = 5.1 Hz, 1H), 5.09-5.01 (m, 1H), 4.62-4.50 (m, 1H), 3.29-3.26 (d, J = 8.1 Hz, 2H), 2.69-2.60 (m, 1H), 2.37-2.27 (m, 2H), 2.19-2.10 (m, 2H), 1.49-1.47 (d, J = 6.6 Hz, 3H). Purity (HPLC, 254 nm): 96.3%.

Examples 45 and 46: N-[(1s,3s)-3-([5-[(1R)-1-Hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide and N-[(1r,3r)-3-([5-[(1R)-1-Hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide



[0231] **Step 1: N-(thiophen-2-ylmethylidene)hydroxylamine.** To a 100-mL round-bottom flask was placed a solution of thiophene-2-carbaldehyde (5 g, 44.58 mmol, 1.00 equiv) in EtOH (50 mL) then $NH_2OH.HCl$ (3.7 g, 1.20 equiv) was added. The resulting solution was stirred for 2 h at RT then the reaction was extracted with EtOAc. The organic extracts were

combined, dried, and concentrated under reduced pressure affording 4.5 g (79%) of N-(thiophen-2-ylmethylidene)hydroxylamine as yellow oil. LCMS (ES, *m/z*): $[M+H]^+$ = 128.0.

[0232] Step 2: Methyl 3-(Thiophen-2-yl)-1,2-oxazole-5-carboxylate. To a 100-mL round-bottom flask was placed a solution of N-(thiophen-2-ylmethylidene)hydroxylamine (4.5 g, 35.39 mmol, 1.00 equiv) in H_2O (50 mL), then methyl prop-2-ynoate (8 mL, 2.50 equiv), KCl (2.6 g, 1.00 equiv) and Oxone (14.4 g, 1.50 equiv) were added. The resulting solution was stirred for 2 h at RT then the reaction was extracted with EtOAc (3x100 mL). The organic extracts were combined, dried, and concentrated under reduced pressure affording 5.4 g (73%) of methyl 3-(thiophen-2-yl)-1,2-oxazole-5-carboxylate as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+$ = 210.0.

[0233] Step 3: 3-(thiophen-2-yl)-1,2-oxazole-5-carboxylic acid. To a 250-mL round-bottom flask was placed a solution of methyl 3-(thiophen-2-yl)-1,2-oxazole-5-carboxylate (5.4 g, 25.81 mmol, 1.00 equiv) in THF and H_2O (30 mL/10 mL), then LiOH (1.33 g, 55.53 mmol, 2.00 equiv) was added. The resulting solution was stirred for 1 h at RT. After concentrating under reduced pressure, the residue was diluted with 100 mL of H_2O then the resulting solution was washed with EtOAc (2x 30mL). The pH value of the aqueous layer was adjusted to 3 with HCl, then the solution was extracted with EtOAc (3x 100 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 3.2 g (64%) of 3-(thiophen-2-yl)-1,2-oxazole-5-carboxylic acid as a white solid. LCMS (ES, *m/z*): $[M+H]^+$ = 196.1.

[0234] Step 4: N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide. To a 100-mL 3-necked round-bottom flask was placed a solution of 3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutan-1-amine (1.25 g, 4.02 mmol, 1.00 equiv) in DCM (30 mL) then 3-(thiophen-2-yl)-1,2-oxazole-5-carboxylic acid (800 mg, 4.10 mmol, 1.02 equiv), HATU (2.3 g, 6.05 mmol, 1.50 equiv) and DIEA (3.1 g, 24.01 mmol, 6.00 equiv) were added. The resulting solution was stirred for 3 h at RT then washed with brine (2x60 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:8 affording 2.3 g (crude) of N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-

oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide as yellow oil. LCMS (ES, *m/z*): $[M+H]^+$ = 489.2.

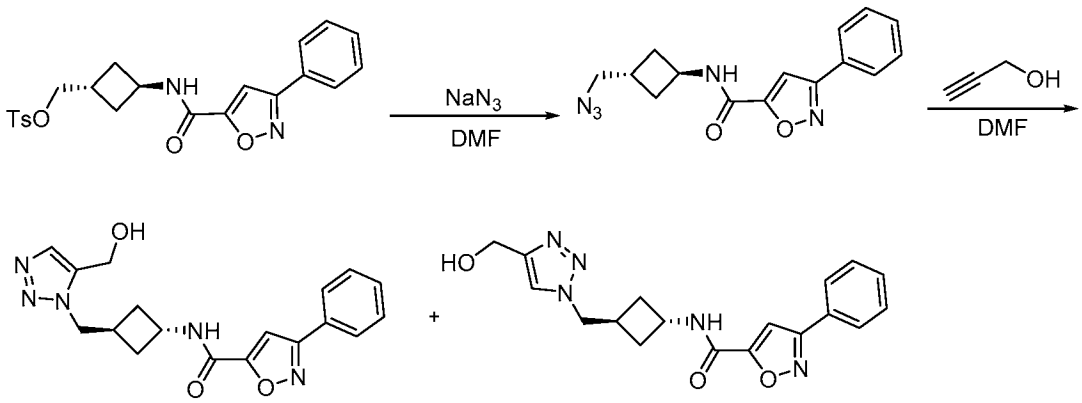
[0235] Step 5: N-[(1s,3s)-3-([5-[(1R)-1-Hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide and N-[(1r,3r)-3-([5-[(1R)-1-Hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide. To a 100-mL 3-necked round-bottom flask was placed a solution of N-[3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide (1.1 g, 2.25 mmol, 1.00 equiv) in MeOH (50 mL) then Py.HF (6 mL) was added. The resulting solution was stirred for 1 h at RT then concentrated under reduced pressure. The residue was dissolved in EtOAc (60 mL), washed with $NaHCO_3$ solution (2x50 mL) and brine (2x50 mL), then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:3) affording 150 mg of a mixture of the title compounds. The mixture was separated by Chiral-Prep-HPLC (Column: Phenomenex Lux 5u Cellulose-4,AXIA Packed, 250*21.2mm, 5um; Mobile Phase A:Hex, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 30 B to 30 B in 27 min; 254/220 nm; RT1:19.83; RT2:23.28) affording 52.6 mg of N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide as a white solid and 51.3 mg of N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide as a white solid.

[0236] N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide: LC-MS (ES, *m/z*): $[M+H]^+$ = 375.0. ^1H NMR (300 MHz, DMSO-d_6): δ 9.24-9.20 (d, *J* = 7.5 Hz, 1H), 7.80-7.78 (m, 2H), 7.59 (s, 1H), 7.26-7.23 (m, 1H), 5.92-5.90 (d, *J* = 5.7 Hz, 1H), 4.93-4.84 (m, 1H), 4.35-4.27 (m, 1H), 2.99-2.96 (d, *J* = 6.6 Hz, 2H), 2.47-2.37 (m, 3H), 1.97-1.91 (m, 2H), 1.46-1.44 (d, *J* = 6.6 Hz, 3H). Purity (HPLC, 254 nm): 95.9%.

[0237] N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-3-(thiophen-2-yl)-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 375.0. ^1H NMR (300 MHz, DMSO-d_6): δ 9.32-9.30 (d, *J* = 7.2 Hz, 1H), 7.80-7.78 (d, *J* = 4.5 Hz, 2H), 7.60 (s, 1H), 7.26-7.23 (m, 1H), 5.93-5.91(d, *J* = 5.4 Hz, 1H), 4.93-4.85 (m, 1H), 4.58-4.51 (m,

1H), 3.10-3.08 (d, J = 7.8 Hz, 2H), 2.72-2.65 (m, 1H), 2.83-2.29 (m, 2H), 2.18-2.11 (m, 2H), 1.47-1.44 (d, J = 6.9 Hz, 3H). Purity (HPLC, 254 nm): 99.7%.

Examples 47 and 48: N-((1r,3r)-3-((5-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide and N-((1r,3r)-3-((4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide



[0238] Step 1: N-((1r,3r)-3-(Azidomethyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide. To a 50-mL round-bottom flask was placed a solution of ((1r,3r)-3-(3-phenylisoxazole-5-carboxamido)cyclobutyl)methyl 4-methylbenzenesulfonate (1.5 g, 3.52 mmol, 1.00 equiv) in DMF (15 mL) then NaN_3 (390 mg, 6.00 mmol, 1.50 equiv) was added. The resulting solution was stirred for 5 h at 80°C, quenched by the addition of 20 mL of ice/water, and extracted with DCM (2x30 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:20) affording 0.9 g (86%) of N-((1r,3r)-3-(azidomethyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide as a white solid. LCMS: (ES, m/z): $[M+H]^+$ = 298.1.

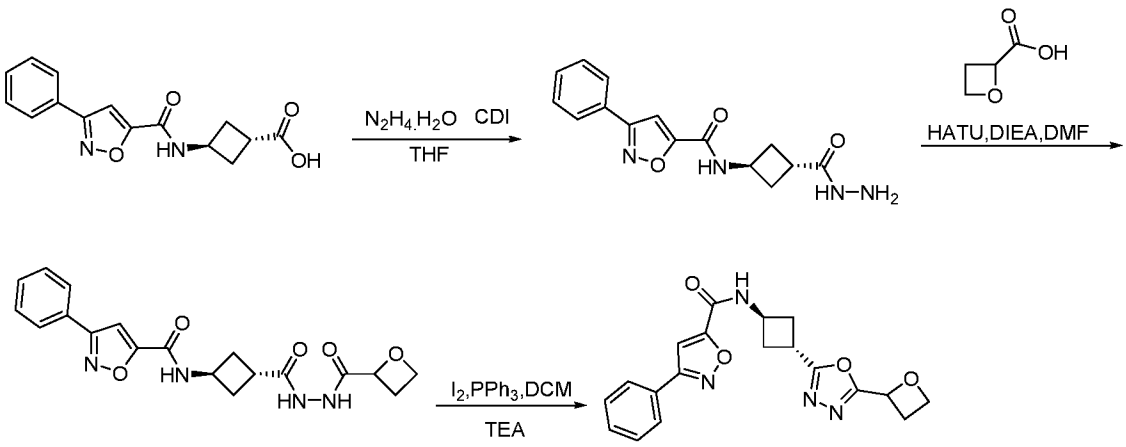
[0239] Step 2: N-((1r,3r)-3-((5-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide and N-((1r,3r)-3-((4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide. To a 25-mL round-bottom flask was placed a solution of N-((1r,3r)-3-(azidomethyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide (700 mg, 2.35 mmol, 1.00 equiv) in DMF (5 mL) then prop-2-yn-1-ol (660 mg, 11.77 mmol, 5.00 equiv) was added. The resulting solution was stirred for 24 h at 80°C, then the solvent was removed under reduced

pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:5). The resulting mixture was separated by Prep-SFC (Column: Lux 5u Celluloes-3,AXIA Packed, 250*21.2mm;Mobile Phase A:CO_2 :70, Mobile Phase B: MeOH:30; Flow rate: 40 mL/min; 220 nm; RT1:4.47; RT2:5.32) affording 120 mg (27%) of N-((1r,3r)-3-((5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide as a white solid and 119.8 mg (27%) of N-((1r,3r)-3-((4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide as a white solid.

[0240] N-((1r,3r)-3-((5-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+ = 354.1$. ^1H NMR (300 MHz, DMSO-d_6): δ 9.29-9.27 (d, $J = 7.2$ Hz, 1H), 8.00 (s, 1H), 7.93-7.90 (m, 2H), 7.63 (s, 1H), 7.55-7.52 (m, 3H), 5.17-5.13 (t, $J = 5.7$ Hz, 1H), 4.60-4.49 (m, 5H), 2.74-2.70 (m, 1H), 2.31-2.12 (m, 4H). Purity (HPLC, 254 nm): 98.8%.

[0241] N-((1r,3r)-3-((4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)cyclobutyl)-3-phenylisoxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+ = 354$. ^1H NMR (300 MHz, DMSO-d_6): δ 9.30-9.27 (d, $J = 7.5$ Hz, 1H), 7.93-7.90 (m, 2H), 7.63-7.60 (m, 2H), 7.57-7.52 (m, 5H), 5.51-5.47 (t, $J = 5.7$ Hz, 1H), 4.66-4.60 (m, 3H), 4.53-4.47(m, 2H), 2.86-2.78 (m, 1H), 2.30-2.15 (m, 4H). Purity (HPLC, 254 nm): 96.9%.

Example 49: 3-Phenyl-N-[(1r,3r)-3-[5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide



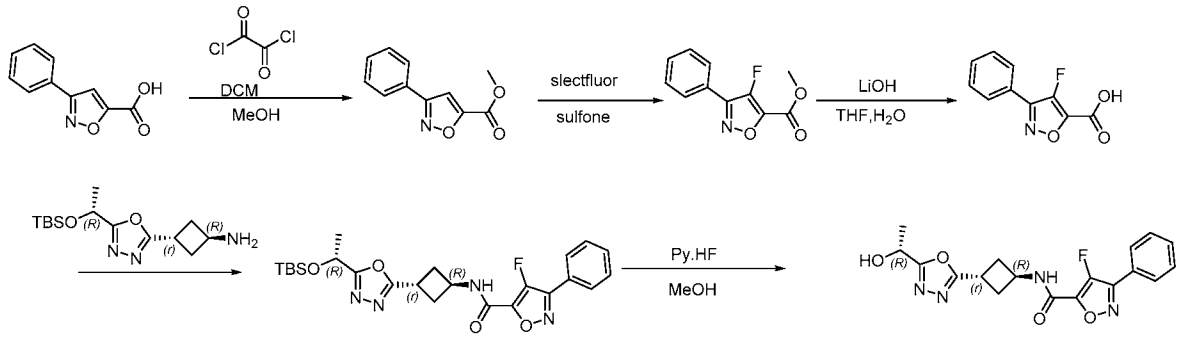
[0242] Step 1: 3-Phenyl-N-[(1r,3r)-3-(hydrazinecarbonyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 100-mL round-bottom flask was placed a solution of (1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylic acid (2.87 g, 10.03 mmol, 1.00 equiv) in THF (50 mL), then CDI (3.24 g, 20.00 mmol, 2.00 equiv) was added. The resulting solution was stirred for 1 h at 25°C and then $N_2H_4.H_2O$ (2.1 g, 30.00 mmol, 3.00 equiv) was added. The resulting solution was stirred for 16 h at RT then diluted with 300 mL of H_2O. The solids were collected by filtration and dried in an oven under reduced pressure affording 487 mg (16%) of 3-phenyl-N-[(1r,3r)-3-(hydrazinecarbonyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a light yellow solid. LCMS (ES, *m/z*): $[M+H]^+ = 301.1$.

[0243] Step 2: 3-Phenyl-N-[(1r,3r)-3-[(oxetan-2-ylformohydrazido)carbonyl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 25-mL round-bottom flask was placed a solution of 3-phenyl-N-[(1r,3r)-3-(hydrazinecarbonyl)cyclobutyl]-1,2-oxazole-5-carboxamide (280 mg, 0.93 mmol, 1.00 equiv) in DMF (5 mL) then HATU (570 mg, 1.50 mmol, 1.50 equiv), DIEA (361 mg, 2.79 mmol, 3.00 equiv) and oxetane-2-carboxylic acid (143 mg, 1.40 mmol, 1.50 equiv) were added. The resulting solution was stirred for 2 h at RT then diluted with 50 mL of H_2O and extracted with EtOAc (2x50 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Prep-TLC (petroleum ether/ethyl acetate=1:2) affording 220 mg (61%) of 3-phenyl-N-[(1r,3r)-3-[(oxetan-2-ylformohydrazido)carbonyl]cyclobutyl]-1,2-oxazole-5-carboxamide as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+ = 385.1$.

[0244] Step 3: 3-Phenyl-N-[(1r,3r)-3-[5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 100-mL 3-necked round-bottom flask was placed a solution of PPh_3 (299 mg, 1.14 mmol, 2.00 equiv) in DCM (20 mL), then I_2 (290 mg, 1.14 mmol, 2.00 equiv) and TEA (230 mg, 2.27 mmol, 4.00 equiv) were added. The resulting solution was stirred for 10 min at RT then 3-phenyl-N-[(1r,3r)-3-[(oxetan-2-ylformohydrazido)carbonyl]cyclobutyl]-1,2-oxazole-5-carboxamide (220 mg, 0.57 mmol, 1.00 equiv) was added and stirred for 1 h at rt. The reaction was diluted with 100 mL of H_2O and extracted with EtOAc (2x100 mL). The organic extracts were combined, washed with brine (2x100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (2:1)

affording 174.8 mg (83%) of 3-phenyl-N-[(1r,3r)-3-[5-(oxetan-2-yl)-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as an off-white solid. LCMS (ES, *m/z*): $[M+H]^+$ = 367.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (d, *J* = 7.2 Hz, 1H), 7.93-7.91 (m, 2H), 7.65 (s, 1H), 7.54-7.52 (m, 3H), 5.88-5.84 (t, *J* = 7.6 Hz, 1H), 4.72-4.62 (m, 3H), 3.81-3.74 (m, 1H), 3.12-2.96 (m, 2H), 2.73-2.66 (m, 4H). Purity (HPLC, 254 nm): 99.5%.

Example 50: 4-Fluoro-3-phenyl-N-[(1r,3r)-3-[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide



[0245] Step 1: Methyl 3-Phenyl-1,2-oxazole-5-carboxylate. To a 50-mL round-bottom flask was placed a solution of 3-phenyl-1,2-oxazole-5-carboxylic acid (1.89 g, 9.99 mmol, 1.00 equiv) in DCM (20 mL) then oxalyl chloride (1.9 g, 14.97 mmol, 1.50 equiv) and a drop of DMF were added. The resulting solution was stirred for 1 h at RT then MeOH (5 mL) was added. The reaction was stirred for 1 h at RT then concentrated under reduced pressure affording 1.9 g (94%) of methyl 3-phenyl-1,2-oxazole-5-carboxylate as a yellow solid.

[0246] Step 2: Methyl 4-Fluoro-3-phenyl-1, 2-oxazole-5-carboxylate. To a 25-mL round-bottom flask was placed a solution of methyl 3-phenyl-1,2-oxazole-5-carboxylate (1 g, 4.92 mmol, 1.00 equiv) in sulfone (10 mL) then Selectfluor (3.54 g, 10.00 mmol, 2.00 equiv) was added. The resulting solution was stirred for 16 h at 120°C, diluted with 100 mL of H_2O, and extracted with EtOAc (2x100 mL). The organic extracts were combined, washed with brine (2x100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Prep-TLC (petroleum ether/ethyl acetate=10:1) affording 250 mg (25%) of methyl 4-fluoro-3-phenyl-1,2-oxazole-5-carboxylate as a white solid. LCMS (ES, *m/z*): $[M+H]^+$ = 222.0.

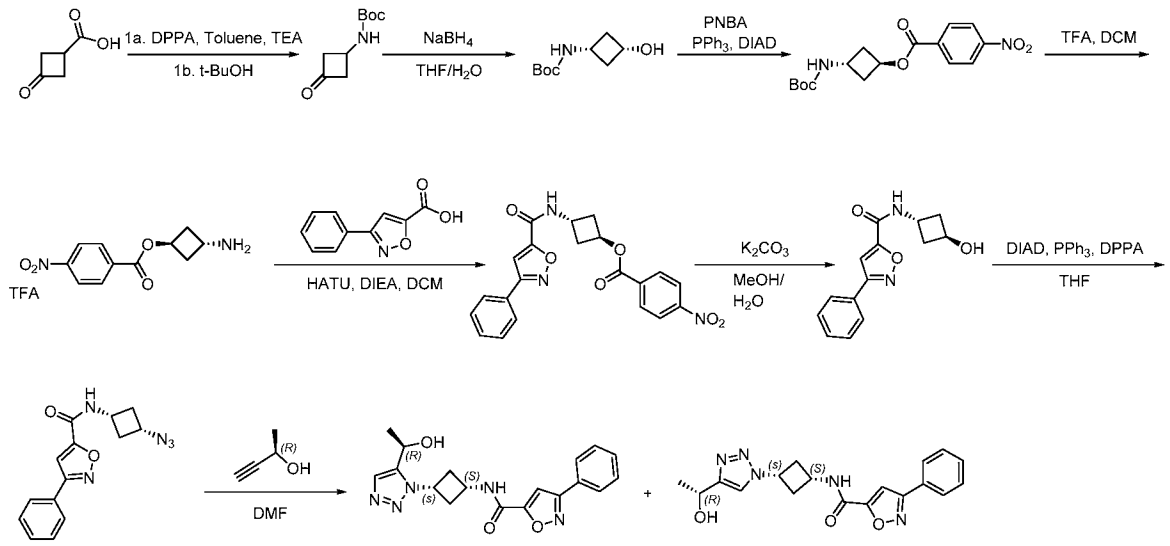
[0247] Step 3: 4-Fluoro-3-phenyl-1,2-oxazole-5-carboxylic acid. To a 25-mL round-bottom flask was placed a solution of methyl 4-fluoro-3-phenyl-1,2-oxazole-5-carboxylate (250 mg, 1.13 mmol, 1.00 equiv) in THF/H_2O (10/3 mL) then LiOH (82 mg, 3.42 mmol, 3.00 equiv) was added. The resulting solution was stirred for 2 h at RT and then diluted with 50 mL of H_2O. The pH of the solution was adjusted to 4-5 using concentrated 12M HCl, then extracted with EtOAc (2x50 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 210 mg (90%) of 4-fluoro-3-phenyl-1,2-oxazole-5-carboxylic acid as a white solid.

[0248] Step 3: 4-Fluoro-3-phenyl-N-[(1r,3r)-3-[5-[(1S)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 50-mL round-bottom flask was placed a solution of 4-fluoro-3-phenyl-1,2-oxazole-5-carboxylic acid (210 mg, 1.01 mmol, 1.00 equiv) in DCM (10 mL), then HATU (570 mg, 1.50 mmol, 1.50 equiv), (1r,3r)-3-5-[(1S)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-ylcyclobutan-1-amine (300 mg, 1.01 mmol, 1.00 equiv) and DIEA (387 mg, 2.99 mmol, 3.00 equiv) were added. The resulting solution was stirred for 1 h at RT, diluted with 100 mL of H_2O, and extracted with EtOAc (2x100 mL). The organic extracts were combined, washed with brine (2x100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:5) affording 360 mg (73%) of 4-fluoro-3-phenyl-N-[(1r,3r)-3-[5-[(1S)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, *m/z*): $[M+H]^+ = 487.3$.

[0249] Step 4: 4-Fluoro-3-phenyl-N-[(1r,3r)-3-[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 25-mL round-bottom flask was placed a solution of 4-fluoro-3-phenyl-N-[(1r,3r)-3-[5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide (360 mg, 0.74 mmol, 1.00 equiv) in methanol (6 mL) then Py.HF (2 mL) was added. The resulting solution was stirred for 1 h at RT then diluted with 50 mL of H_2O, and extracted with EtOAc (2x50 mL). The organic extracts were combined, washed with brine (3x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Bridge C18 OBD Prep Column, 19 mm X 250 mm; mobile phase, Water (0.5% NH_4HCO_3) and ACN (30.0% ACN up to 50.0% in 8 min);

Detector, UV 254/220 nm) affording 133.3 mg (48%) of 4-fluoro-3-phenyl-N-[(1r,3r)-3-[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, *m/z*): $[M+H]^+ = 372.9$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49-9.47 (d, J = 7.2 Hz, 1H), 7.99-7.94 (m, 1H), 7.65-7.60 (m, 1H), 7.52 (s, 1H), 7.48-7.37 (m, 2H), 5.96-5.95 (d, J = 6.4 Hz, 1H), 4.95-4.89 (m, 1H), 4.70-4.64 (m, 1H), 3.78-3.72 (m, 1H), 2.72-2.63 (m, 4H), 1.49-1.48 (d, J = 6.8 Hz, 3H). Purity (HPLC, 254 nm): 99.7%.

Examples 51 and 52: 3-Phenyl-N-[(1s,3s)-3-[5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1s,3s)-3-[4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide



[0250] Step 1: tert-Butyl N-(3-Oxocyclobutyl)carbamate. To a 1000-mL 3-necked round-bottom flask was placed a solution of 3-oxocyclobutane-1-carboxylic acid (20 g, 175.29 mmol, 1.00 equiv) in toluene (400 mL), then TEA (19.5 g, 192.71 mmol, 1.10 equiv) and DPPA (53 g, 192.73 mmol, 1.10 equiv) were added. The resulting solution was stirred overnight at 0°C, then washed with saturated sodium bicarbonate aqueous (2x120 mL), H_2O (1x120 mL), and brine (1x60 mL) at 0~10°C. The solution was dried over anhydrous Na_2SO_4 and filtered. To this solution was added t-BuOH (100 mL) and then the reaction was stirred for 16 h at 100°C. The solvent was removed under reduced pressure then the residue was washed with TBME (60mL) affording 8.3 g (26%) of tert-butyl N-(3-oxocyclobutyl)carbamate as a light white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (brs, 1H), 4.29 (brs, 1H), 3.48-3.36 (m, 2H), 3.13-3.01 (m, 2H), 1.48 (s, 9H).

[0251] Step 2: tert-Butyl N-[(1s,3s)-3-Hydroxycyclobutyl]carbamate. To a 250-mL round-bottom flask was placed a solution of tert-butyl N-(3-oxocyclobutyl)carbamate (8.3 g, 44.81 mmol, 1.00 equiv) in THF/H_2O=9:1 (100 mL) then $NaBH_4$ (830 mg, 22.54 mmol, 0.50 equiv) was added in portions at -70°C. The resulting solution was stirred for 1 h at -50°C then the reaction was quenched by the addition of water. The mixture was extracted with EtOAc, the organic extracts were combined and the solvent was removed under reduced pressure. The residue was dissolved in 20 mL of toluene at 80°C, then the solution was cooled to RT and stirred for 1 h. The solids were collected by filtration affording 7.56 g (90%) of tert-butyl N-[(1s,3s)-3-hydroxycyclobutyl]carbamate as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (brs, 1H), 4.08-4.01 (m, 1H), 3.69-3.66 (m, 1H), 2.82-2.76 (m, 2H), 2.00 (brs, 1H), 1.88-1.75 (m, 2H), 1.46 (s, 9H).

[0252] Step 3: (1r,3r)-3-[[(tert-Butoxy)carbonyl]amino]cyclobutyl-4-nitrobenzoate. To a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of tert-butyl N-[(1s,3s)-3-hydroxycyclobutyl]carbamate (7.56 g, 40.38 mmol, 1.00 equiv) in THF (100 mL), then PPh_3 (15.89 g, 60.58 mmol, 1.50 equiv) and PNBA (7.43 g, 1.10 equiv) were added. This was followed by the addition of DIAD (12.25 g, 60.58 mmol, 1.50 equiv) dropwise with stirring at 0°C. The resulting solution was stirred overnight at RT, then the reaction was quenched by the addition of water and extracted with EtOAc. The organic extracts were combined and then concentrated under reduced pressure. The residue was dissolved in 10 mL of EtOH and stirred for 2 h at RT. The solids were collected by filtration affording 10.8 g (80%) of (1r,3r)-3-[[(tert-butoxy)carbonyl]amino]cyclobutyl 4-nitrobenzoate as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28-8.17 (m, 4H), 5.36-5.32 (m, 1H), 4.77 (brs, 1H), 4.36 (brs, 1H), 2.65-2.56 (m, 2H), 2.47-2.38 (m, 2H), 1.43 (s, 9H).

[0253] Step 4: (1r,3r)-3-Aminocyclobutyl 4-nitrobenzoate trifluoroacetic acid salt. To a 100-mL round-bottom flask was placed a solution of (1r,3r)-3-[[(tert-butoxy)carbonyl]amino]cyclobutyl 4-nitrobenzoate (10.8 g, 32.11 mmol, 1.00 equiv) in DCM (25 mL) and TFA (7 mL). The resulting solution was stirred overnight at RT, then the solvent was removed under reduced pressure affording 10.3 g (92%) of (1r,3r)-3-aminocyclobutyl 4-nitrobenzoate trifluoroacetic acid salt as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.28-8.25 (m, 4H), 5.52-5.44 (m, 1H), 4.09-4.00 (m, 1H), 2.85-2.62 (m, 4H).

[0254] Step 5: (1r,3r)-3-(3-Phenyl-1,2-oxazole-5-amido)cyclobutyl 4-nitrobenzoate. To a 250-mL round-bottom flask was placed a solution of (1r,3r)-3-aminocyclobutyl 4-nitrobenzoate trifluoroacetic acid salt (4 g, 11.42 mmol, 1.00 equiv), DIEA (7.4 g, 57.26 mmol, 5.00 equiv) and 3-phenyl-1,2-oxazole-5-carboxylic acid (2.6 g, 13.74 mmol, 1.20 equiv) in DCM (100 mL). To this solution was added HATU (6.5 g, 17.09 mmol, 1.50 equiv), then the reaction was stirred for 30 min at RT. The reaction was quenched with H_2O and extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:5) affording 4.57 g (98%) of (1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl 4-nitrobenzoate as a white solid. LCMS (ES, *m/z*): $[M+H]^+ = 408.1$.

[0255] Step 6: 3-Phenyl-N-[(1r,3r)-3-hydroxycyclobutyl]-1,2-oxazole-5-carboxamide. To a 100-mL round-bottom flask was placed a solution of (1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl 4-nitrobenzoate (4.4 g, 10.80 mmol, 1.00 equiv) in MeOH/H_2O=2:1 (30 mL), then K_2CO_3 (4.4 g, 31.83 mmol, 3.00 equiv) was added. The resulting mixture was stirred overnight at 40°C. The reaction was quenched with H_2O and then extracted with EtOAc. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure affording 2.2 g (79%) of 3-phenyl-N-[(1r,3r)-3-hydroxycyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, *m/z*): $[M+H]^+ = 259.1$.

[0256] Step 7: 3-Phenyl-N-[(1s,3s)-3-azidocyclobutyl]-1,2-oxazole-5-carboxamide. To a 100-mL round-bottom flask was placed a solution of 3-phenyl-N-[(1r,3r)-3-hydroxycyclobutyl]-1,2-oxazole-5-carboxamide (2.2 g, 8.52 mmol, 1.00 equiv), DPPA (2.8 g, 10.17 mmol, 1.20 equiv) and PPh_3 (3.3 g, 12.58 mmol, 1.50 equiv) in THF (40 mL), then DIAD (2.6 g, 12.86 mmol, 1.50 equiv) was added dropwise. The reaction was stirred for 1 h at 30°C, quenched by the addition of brine, and extracted with EtOAc. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:10) affording 860 mg (36%) of 3-phenyl-N-[(1s,3s)-3-azidocyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0257] Step 8: 3-Phenyl-N-[(1s,3s)-3-[5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1s,3s)-3-[4-[(1R)-1-

hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 10-mL sealed tube was placed a solution of 3-phenyl-N-[(1s,3s)-3-azidocyclobutyl]-1,2-oxazole-5-carboxamide (550 mg, 1.94 mmol, 1.00 equiv) in DMF (2.5 mL), then (2R)-but-3-yn-2-ol (680 mg, 9.70 mmol, 5.00 equiv) was added. The resulting solution was stirred overnight at 100°C. After removing the solvent under reduced pressure, the residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:3). The resulting mixture was separated by Prep-SFC (Prep SFC80-1: Column, Chiralpak AD-H, 2*25cm; mobile phase, CO_2 (50%) and ethanol (50%); Detector, UV 220 nm) affording 170.0 mg (25%) of 3-phenyl-N-[(1s,3s)-3-[5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 222 mg (32%) of 3-phenyl-N-[(1s,3s)-3-[4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0258] 3-Phenyl-N-[(1s,3s)-3-[5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$=354. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.50-9.47 (d, J = 7.2 Hz, 1H), 7.94-7.90 (m, 2H), 7.66 (s, 1H), 7.61 (s, 1H), 7.56-7.54 (m, 3H), 5.52-5.50 (d, J = 6.0 Hz, 1H), 4.95-4.85 (m, 2H), 4.45-4.31 (m, 1H), 2.94-2.80 (m, 4H), 1.45-1.43 (d, J = 6.6 Hz, 3H). Purity (HPLC, 254 nm): 99.4%.

[0259] 3-Phenyl-N-[(1s,3s)-3-[4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 354. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.41-9.39 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H), 7.96-7.93 (m, 2H), 7.68 (s, 1H), 7.56-7.54 (m, 3H), 5.30-5.28 (d, J = 4.8 Hz, 1H), 5.00-4.80 (m, 2H), 4.48-4.35 (m, 1H), 2.98-2.89 (m, 2H), 2.74-2.64 (m, 2H), 1.43-1.41 (d, J = 6.6 Hz, 3H).

Examples 53 and 54: 3-Phenyl-N-[(1s,3s)-3-[5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1s,3s)-3-[4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide

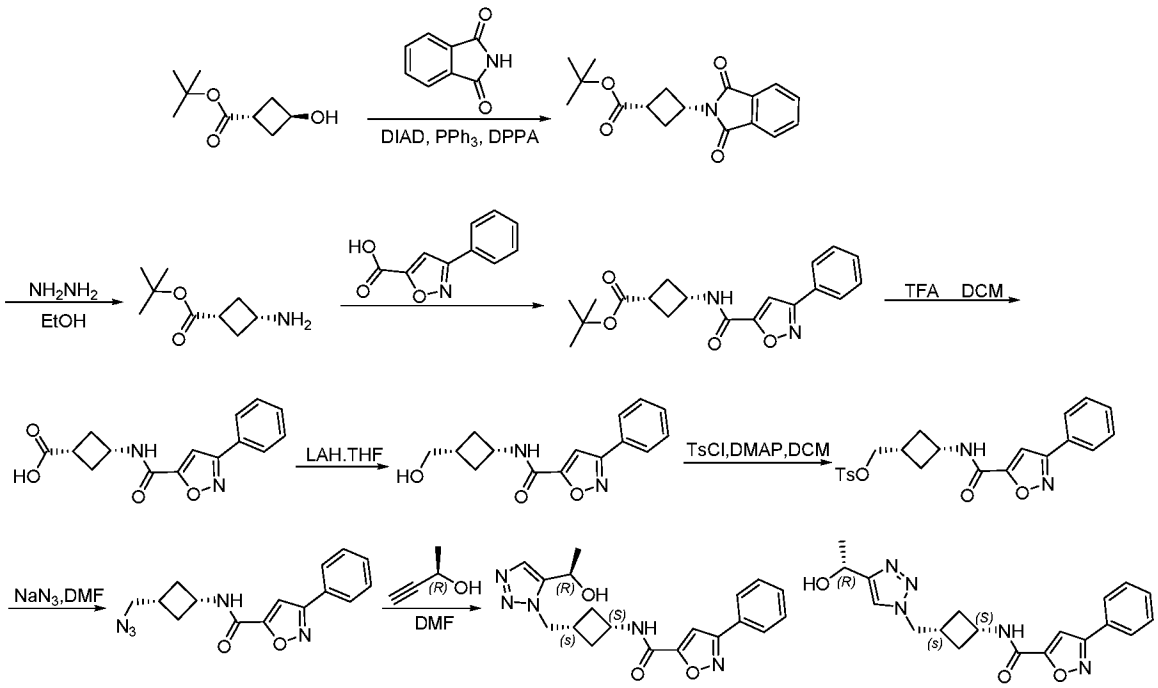
[0260] Step 1: 3-Phenyl-N-[(1s,3s)-3-[5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1s,3s)-3-[4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 10-mL sealed tube, was placed a solution of 3-phenyl-N-[(1s,3s)-3-azidocyclobutyl]-1,2-oxazole-5-carboxamide (500 mg, 1.77 mmol, 1.00 equiv) in DMF (2.5 mL), then (2S)-but-3-yn-2-ol (618 mg, 8.82 mmol, 5.00 equiv) was added. The reaction was stirred overnight at 100°C then concentrated under reduced pressure. The residue was applied onto a silica gel column with

EtOAc/petroleum ether (1:3). The resulting mixture was separated by Prep-SFC (Prep SFC80-1: Column, Chiralpak AD-H, 2*25cm; mobile phase, CO2(55%) and methanol(45%); Detector, UV 220nm) affording 106.1 mg (17%) of 3-phenyl-N-[(1s,3s)-3-[5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 192.2 mg (31%) of 3-phenyl-N-[(1s,3s)-3-[4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0261] 3-Phenyl-N-[(1s,3s)-3-[5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+ = 354$. ^1H NMR (300 MHz, DMSO-d_6) δ 9.50-9.47 (d, $J = 7.5$ Hz, 1H), 7.94-7.90 (m, 2H), 7.66 (s, 1H), 7.61 (s, 1H), 7.56-7.54 (m, 3H), 5.52-5.50 (d, $J = 6.0$ Hz, 1H), 4.95-4.85 (m, 2H), 4.45-4.31 (m, 1H), 2.94-2.80 (m, 4H), 1.45-1.43 (d, $J = 6.3$ Hz, 3H). Purity (HPLC, 254 nm): 96.0%.

[0262] 3-Phenyl-N-[(1s,3s)-3-[4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+ = 354$. ^1H NMR (300 MHz, DMSO-d_6) δ 9.41-9.39 (d, $J = 8.1$ Hz, 1H), 8.13 (s, 1H), 7.96-7.93 (m, 2H), 7.68 (s, 1H), 7.56-7.54 (m, 3H), 5.30-5.28 (d, $J = 4.5$ Hz, 1H), 5.00-4.92 (m, 1H), 4.88-4.80 (m, 1H), 4.48-4.35 (m, 1H), 2.98-2.89 (m, 2H), 2.74-2.50 (m, 2H), 1.43-1.41 (d, $J = 6.6$ Hz, 3H). Purity (HPLC, 254 nm): 97.7%.

Examples 55 and 56: 3-Phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1s,3s)-3-([4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide



[0263] Step 1: tert-Butyl (1s,3s)-3-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylate. To a 250-mL 3-necked round-bottom flask was placed a solution of tert-butyl (1r,3r)-3-hydroxycyclobutane-1-carboxylate (1.1 g, 5.87 mmol, 1.00 equiv), 2,3-dihydro-1H-isoindole-1,3-dione (1.04 g, 7.07 mmol, 1.19 equiv), and PPh_3 (2.5 g) in THF (60 mL). This was followed by the addition of DIAD (300 mg) dropwise with stirring at 0°C. The resulting solution was stirred for 1 h at RT then the reaction was quenched by the addition of 50 mL of water. The resulting solution was extracted with EtOAc (3x50 mL) and the organic layers combined. The resulting mixture was washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:40) affording 810 mg of tert-butyl (1s,3s)-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylate as a white solid. LCMS (ES, *m/z*): $[M+H]^+$ = 302.2.

[0264] Step 2: tert-Butyl (1s,3s)-3-Aminocyclobutane-1-carboxylate. To a 2000-mL round-bottom flask was placed a solution of tert-butyl (1s,3s)-3-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)cyclobutane-1-carboxylate (810 mg, 2.64 mmol, 1.00 equiv) in EtOH (50 mL) and then $N_2H_4.H_2O$ (400 mg, 3.00 equiv) was added. The resulting solution was stirred for 4 h at RT, then the solids were removed by filtration. The filtrate was concentrated under reduced

pressure affording 500 mg of crude tert-butyl (1s,3s)-3-aminocyclobutane-1-carboxylate as light yellow oil. LCMS $[M+H]^+ = 172.1$

[0265] Step 3: tert-Butyl (1s,3s)-3-(3-Phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylate. To a 100-mL round-bottom flask was placed a solution of tert-butyl (1s,3s)-3-aminocyclobutane-1-carboxylate (1.7 g, 9.93 mmol, 1.00 equiv) in DCM (50 mL), then 3-phenyl-1,2-oxazole-5-carboxylic acid (1.9 g, 10.04 mmol, 1.00 equiv), HATU (5.7 g, 14.99 mmol, 1.50 equiv) and DIEA (3.9 g, 30.18 mmol, 3.00 equiv) were added. The resulting solution was stirred for 1 h at RT, then quenched by the addition of water and extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:7) affording 2 g (59%) of tert-butyl (1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylate as a white solid. LCMS (ES, *m/z*): $[M+H]^+ = 343.2$.

[0266] Step 4: (1s,3s)-3-(3-Phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylic acid. To a 25-mL round-bottom flask was placed a solution of tert-butyl (1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylate (830 mg, 2.42 mmol, 1.00 equiv) in DCM (10 mL) and TFA (3 mL). The resulting solution was stirred for 2 h at rt, then the reaction was concentrated under reduced pressure affording 680 mg (98%) of (1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylic acid as a light yellow solid.

[0267] Step 5: 3-Phenyl-N-[(1s,3s)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 100-mL 3-necked round-bottom flask was placed a solution of (1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylic acid (1.2 g, 4.19 mmol, 1.00 equiv) in THF (50 mL) followed by the addition of $LiAlH_4$ (319 mg, 8.41 mmol, 2.00 equiv) in portions at 0^oC over 5 min. The resulting solution was stirred for 2 h at RT, then quenched by the addition of 100 mL of 2N HCl, and extracted with EtOAc (2x100 mL). The organic extracts were combined, washed with brine (2x100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 860 mg (75%) of 3-phenyl-N-[(1s,3s)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a light yellow solid. LCMS (ES, *m/z*): $[M+H]^+ = 273.1$.

[0268] Step 6: [(1s,3s)-3-(3-Phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate. To a 50-mL round-bottom flask was placed a solution of 3-

phenyl-N-[(1s,3s)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide (860 mg, 3.16 mmol, 1.00 equiv) in DCM (20 mL) then DMAP (781 mg, 6.39 mmol, 2.00 equiv) and TsCl (779 mg, 4.09 mmol, 1.30 equiv) were added. The resulting solution was stirred for 16 h at RT, diluted with 100 mL of H_2O, and extracted with EtOAc (2x100 mL). The organic extracts were combined, washed with brine (2x100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 1.1 g (82%) of [(1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+ = 427.2$.

[0269] Step 7: 3-Phenyl-N-[(1s,3s)-3-(azidomethyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 25-mL round-bottom flask was placed a solution of [(1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (1.1 g, 2.58 mmol, 1.00 equiv) in DMF (10 mL), then NaN_3 (254 mg, 3.91 mmol, 1.50 equiv) was added. The resulting solution was stirred for 1 h at 80°C, diluted with 100 mL of H_2O, and extracted with EtOAc (2x100 mL). The organic extracts were combined, washed with brine (5x100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 750 mg (98%) of 3-phenyl-N-[(1s,3s)-3-(azidomethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a yellow solid.

[0270] Step 8: 3-Phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1s,3s)-3-([4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 25-mL round-bottom flask was placed a solution of 3-phenyl-N-[(1s,3s)-3-(azidomethyl)cyclobutyl]-1,2-oxazole-5-carboxamide (350 mg, 1.18 mmol, 1.00 equiv) in DMF (5 mL), then (2R)-but-3-yn-2-ol (420 mg, 5.99 mmol, 5.00 equiv) was added. The resulting solution was stirred for 16 h at 80°C, then diluted with 50 mL of H_2O, and extracted with EtOAc (3x50 mL). The organic extracts were combined, washed with brine (3x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (5:1). The pure isomers were separated by Chiral-Prep-HPLC (Prep-HPLC-009: Column, Chiralpak IB, 2*25cm, 5um; mobile phase, Hex and ethanol (hold 15.0% ethanol in 29 min); Detector, UV 254/220 nm) affording 29.4 mg (7%) of 3-phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a light yellow solid and

31.6 mg (7%) of 3-phenyl-N-[(1s,3s)-3-([4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0271] 3-Phenyl-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 368.1. ^1H NMR (300 MHz, DMSO-d_6) δ 9.25-9.22 (d, *J* = 7.8 Hz, 1H), 7.94-7.91 (m, 2H), 7.63-7.60 (d, *J* = 6.9 Hz, 2H), 7.55-7.53 (m, 3H), 5.53-7.51 (d, *J* = 6.0 Hz, 1H), 4.93-4.85 (m, 1H), 4.43-4.40 (d, *J* = 7.2 Hz, 2H), 4.35-4.27 (m, 1H), 2.64-2.55 (m, 1H), 2.39-2.30 (m, 2H), 2.03-1.94 (m, 2H), 1.48-1.46 (d, *J* = 6.3 Hz, 3H). Purity (HPLC, 254 nm): 95.2%.

[0272] 3-Phenyl-N-[(1s,3s)-3-([4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 368.1. ^1H NMR (300 MHz, DMSO-d_6) δ 9.22-9.19 (d, *J* = 7.8 Hz, 1H), 7.90-7.76 (m, 2H), 7.84 (s, 1H), 7.59 (s, 1H), 7.55-7.46 (m, 3H), 5.19-5.18 (d, *J* = 4.5 Hz, 1H), 4.80-4.76 (m, 1H), 4.35-4.24 (m, 3H), 2.60-2.50 (m, 1H), 2.33-2.25 (m, 2H), 1.95-1.88 (m, 2H), 1.37-1.35 (d, *J* = 6.3 Hz, 3H). Purity (HPLC, 254 nm): 95.0%.

Examples 57 and 58: 3-Phenyl-N-[(1s,3s)-3-([5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1s,3s)-3-([4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide.

[0273] Into a 25-mL round-bottom flask, was placed a solution of 3-phenyl-N-[(1s,3s)-3-(azidomethyl)cyclobutyl]-1,2-oxazole-5-carboxamide (270 mg, 0.91 mmol, 1.00 equiv) in toluene (5 mL), then (2S)-but-3-yn-2-ol (315 mg, 4.49 mmol, 5.00 equiv) was added. The resulting solution was stirred for 16 h at 100°C and then concentrated under reduced pressure. The crude product was purified by Prep-TLC (petroleum ether/EtOAc=1:5). The resulting mixture was separated by Chiral-Prep-HPLC (2#-Gilson Gx 281(HPLC-09): Column: Chiralpak IB, 2*25cm, 5um; Mobile Phase A: hexane, Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient: 30 B to 30 B in 15 min; 254/220 nm; RT1:7.642; RT2:10.588) affording 32.8 mg (10%) of 3-phenyl-N-[(1s,3s)-3-([5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 68.5 mg (21%) of 3-phenyl-N-[(1s,3s)-3-([4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0274] 3-Phenyl-N-[(1s,3s)-3-([5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 368.2. ^1H NMR (400 MHz, DMSO-d_6) δ 9.24-9.22 (d, *J* = 7.6 Hz, 1H), 7.94-7.92 (m, 2H), 7.62-7.60 (d, *J* = 8.4 Hz, 1H), 7.55-7.53 (m, 3H), 5.52-5.50 (d, *J* = 6.0 Hz, 1H), 4.95-4.83 (m, 1H), 4.43-4.40 (m, 2H), 4.35-4.31 (m, 3H), 2.54-2.52 (m, 1H), 2.36-2.33 (m, 2H), 2.05-1.98 (m, 2H), 1.48-1.46 (d, *J* = 6.4 Hz, 3H). Purity (HPLC, 254 nm): 93.1%.

[0275] 3-Phenyl-N-[(1s,3s)-3-([4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 368.2. ^1H NMR (400 MHz, DMSO-d_6) δ 9.24-9.22 (d, *J* = 7.6 Hz, 1H), 7.94-7.92 (m, 2H), 7.87 (s, 1H), 7.62 (s, 1H), 7.55-7.53 (m, 3H), 5.22-5.21 (d, *J* = 4.8 Hz, 1H), 4.85-4.79 (m, 1H), 4.38-4.37 (d, *J* = 7.2 Hz, 2H), 4.34-4.28 (m, 1H), 2.54-2.46 (m, 1H), 2.39-2.32 (m, 2H), 2.01-1.93 (m, 2H), 1.41-1.39 (d, *J* = 6.4 Hz, 3H). Purity (HPLC, 254 nm): 98.6%.

Examples 59 and 60: 3-Phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1r,3r)-3-([4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide

[0276] Step 1: 3-Phenyl-N-[(1r,3r)-3-(azidomethyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 25-mL round-bottom flask was placed a solution of [(1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (920 mg, 2.16 mmol, 1.00 equiv) in DMF (10 mL), then NaN_3 (169 mg, 2.60 mmol, 1.20 equiv) was added. The resulting solution was stirred for 2 h at 80°C, then diluted with 100 mL of H_2O, and extracted with EtOAc (2x50 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 600 mg (94%) of 3-phenyl-N-[(1r,3r)-3-(azidomethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a light yellow solid.

[0277] Step 2: 3-Phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-phenyl-N-[(1r,3r)-3-([4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 5-mL round-bottom flask was placed a solution of 3-phenyl-N-[(1r,3r)-3-(azidomethyl)cyclobutyl]-1,2-oxazole-5-carboxamide (300 mg, 1.01 mmol, 1.00 equiv) in DMF (5 mL), then (2R)-but-3-yn-2-ol (210 mg, 3.00 mmol, 3.00 equiv) was added. The resulting solution was stirred for 16 h at 100°C, then diluted with 50 mL of H_2O, and extracted

with EtOAc (2x50 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Prep-TLC (petroleum ether/ethyl acetate=1:5). The resulting mixture was separated by Chiral-Prep-HPLC (Prep-HPLC-004: Column, Chiralpak IA, 2*25cm, 5um; mobile phase, Hex and IPA (hold 30.0% IPA in 15 min); Detector, UV 254/220 nm) affording 103.5 mg (28%) of 3-phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 127.1 mg (38%) of 3-phenyl-N-[(1r,3r)-3-([4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a light yellow solid.

[0278] 3-Phenyl-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 368.2. ^1H NMR (400 MHz, DMSO-d_6) δ 9.29-9.27 (d, *J* = 7.2 Hz, 1H), 7.92-7.90 (m, 2H), 7.62-7.59 (m, 2H), 7.53-7.52 (m, 3H), 5.53-5.52 (d, *J* = 6.0 Hz, 1H), 4.92-4.89 (m, 1H), 4.62-4.58 (m, 1H), 4.56-4.48 (m, 2H), 2.85-2.81 (m, 1H), 2.27-2.17 (m, 4H), 1.46-1.44 (d, *J* = 6.4 Hz, 3H). Purity (HPLC, 254 nm): 95.0%.

[0279] 3-Phenyl-N-[(1r,3r)-3-([4-[(1R)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 368.2. ^1H NMR (400 MHz, DMSO-d_6) δ 9.27-9.25 (d, *J* = 7.2 Hz, 1H), 7.94 (s, 1H), 7.93-7.89 (m, 2H), 7.62 (s, 1H), 7.53-7.51 (m, 3H), 5.21-5.20 (d, *J* = 4.8 Hz, 1H), 4.83-4.80 (m, 1H), 4.59-4.51 (m, 1H), 4.48-4.46 (d, *J* = 7.6 Hz, 2H), 2.74-2.66 (m, 1H), 2.28-2.21 (m, 2H), 2.17-2.11 (m, 2H), 1.39-1.37 (d, *J* = 6.8 Hz, 3H). Purity (HPLC, 254 nm): 96.9%.

Examples 61 and 62: 3-Phenyl-N-[(1r,3r)-3-([5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1r,3r)-3-([4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide

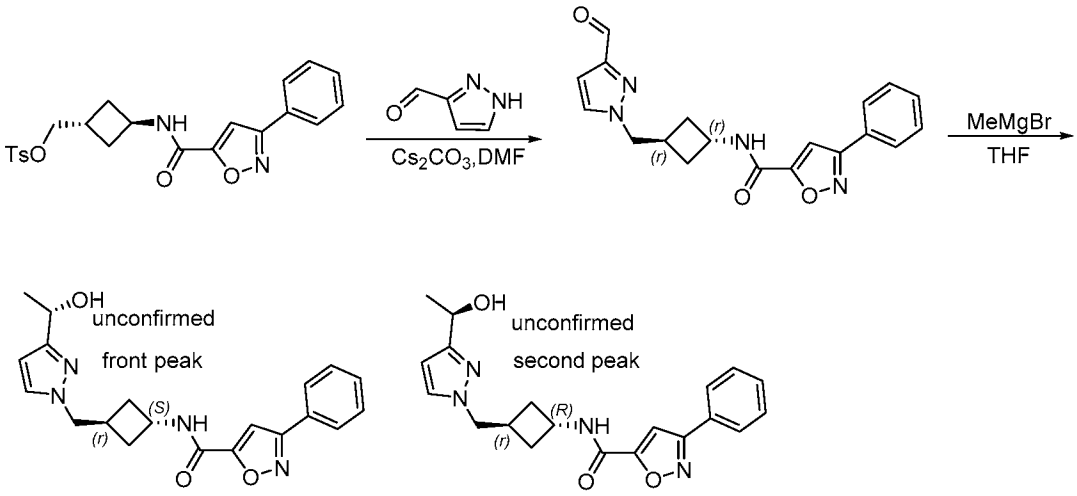
[0280] To a 25-mL round-bottom flask was placed a solution of 3-phenyl-N-[(1r,3r)-3-(azidomethyl)cyclobutyl]-1,2-oxazole-5-carboxamide (210 mg, 0.71 mmol, 1.00 equiv) in toluene (5 mL), then (2S)-but-3-yn-2-ol (245 mg, 3.50 mmol, 5.00 equiv)was added. The resulting solution was stirred for 16 h at 100°C, then concentrated under reduced pressure. The crude product was purified by Prep-TLC (petroleum ether/EtOAc=1:5). The resulting mixture was separated by Chiral-Prep-HPLC (Prep-HPLC-004: Column, Chiralpak IC, 2*25cm, 5um; mobile phase, Hex and ethanol (hold 50.0% ethanol in 15 min); Detector, UV 254/220 nm)

affording 44.2 mg (17%) of 3-phenyl-N-[(1r,3r)-3-([5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 78.5 mg (30%) of 3-phenyl-N-[(1r,3r)-3-([4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0281] 3-Phenyl-N-[(1r,3r)-3-([5-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 368.2. ^1H NMR (400 MHz, DMSO-d_6) δ 9.31-9.29 (d, *J* = 7.2 Hz, 1H), 7.94-7.91 (m, 2H), 7.64-7.60 (m, 2H), 7.55-7.52 (m, 3H), 5.55-5.53 (d, *J* = 6.0 Hz, 1H), 4.95-4.89 (m, 1H), 4.64-4.47 (m, 3H), 2.88-2.82 (m, 1H), 2.30-2.19 (m, 4H), 1.48-1.46 (d, *J* = 6.4 Hz, 3H). Purity (HPLC, 254 nm): 97.5%.

[0282] 3-Phenyl-N-[(1r,3r)-3-([4-[(1S)-1-hydroxyethyl]-1H-1,2,3-triazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 368.2. ^1H NMR (400 MHz, DMSO-d_6) δ 9.30-9.28 (d, *J* = 7.6 Hz, 1H), 7.96 (s, 1H), 7.94-7.91 (m, 2H), 7.64 (s, 1H), 7.55-7.53 (m, 3H), 5.23-5.21 (d, *J* = 4.8 Hz, 1H), 4.85-4.79 (m, 1H), 4.58-4.53 (m, 1H), 4.50-4.48 (d, *J* = 7.6 Hz, 2H), 2.75-2.71 (m, 1H), 2.30-2.23 (m, 2H), 2.18-2.12 (m, 2H), 1.41-1.39 (d, *J* = 6.4 Hz, 3H). Purity (HPLC, 254 nm): 99.2%.

Examples 63 and 64: 3-Phenyl-N-[(1r,3r)-3-([3-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-Phenyl-N-[(1r,3r)-3-([3-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide



[0283] Step 1: 3-Phenyl-N-[(1r,3r)-3-[(3-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 50-mL round-bottom flask was placed a solution of [(1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (1.28 g, 3.00 mmol, 1.00 equiv) in DMF (20 mL), then Cs_2CO_3 (1.95 g, 5.98 mmol, 2.00 equiv) and 1H-pyrazole-3-carbaldehyde (432 mg, 4.50 mmol, 1.50 equiv) were added. The resulting solution was stirred for 3 h at 100°C, then the solids were removed by filtration. The filtrate was purified by Flash-Prep-HPLC (CombiFlash-1: Column, C18; mobile phase, X: H_2O (0.5% NH_4HCO_3), Y: CAN, X/Y=90/10 increasing to X/Y=5/95 within 40 min; Detector, UV 254 nm) affording 450 mg (43%) of 3-phenyl-N-[(1r,3r)-3-[(3-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+$ = 351.2.

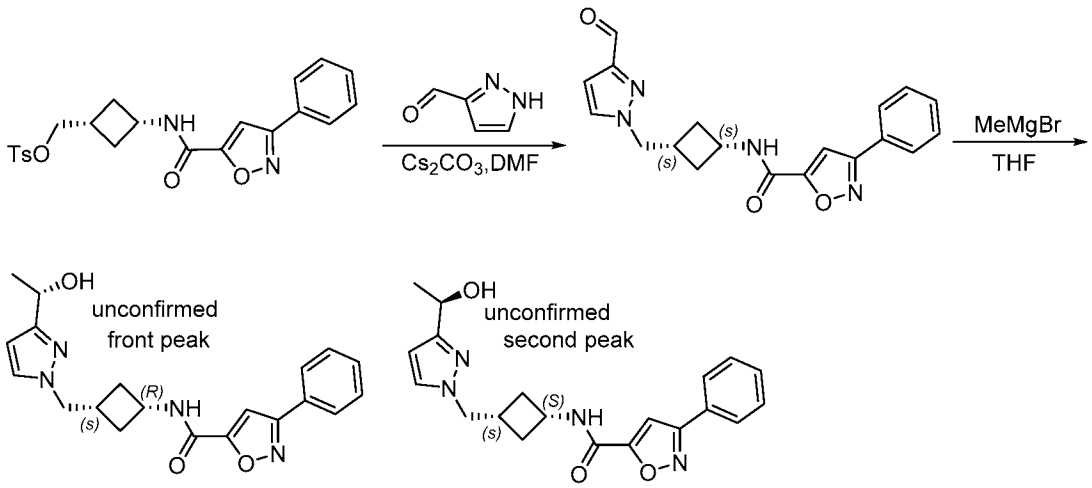
[0284] Step 2: 3-Phenyl-N-[(1r,3r)-3-([3-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) and 3-phenyl-N-[(1r,3r)-3-([3-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak). To a 50-mL 3-necked round-bottom flask was placed a solution of 3-phenyl-N-[(1r,3r)-3-[(3-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide (450 mg, 1.28 mmol, 1.00 equiv) in THF (20 mL). The solution was cooled to 0°C, then MeMgBr (1.3 mL, 3.00 equiv, 3 mol/L) was added dropwise with stirring at 0°C over 10 min. The reaction was stirred for 2 h at RT, then quenched by the addition of 10 mL of 2N HCl and 50 mL of H_2O, and extracted with EtOAc (3x50 mL). The organic extracts were combined, washed with brine (3x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (2:1). The resulting mixture was separated by Chiral-Prep-HPLC (Prep-HPLC-004: Column, Chiralpak IC, 2*25cm, 5um; mobile phase, Hex and ethanol (hold 50.0% ethanol in 13 min); Detector, UV 254/220 nm) affording 126.1 mg (27%) of 3-phenyl-N-[(1r,3r)-3-([3-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) as a light yellow solid and 136.9 mg (29%) of 3-phenyl-N-[(1r,3r)-3-([3-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak) as a white solid.

[0285] 3-Phenyl-N-[(1r,3r)-3-([3-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 367.0. ^1H NMR (300 MHz, DMSO-d_6) δ 9.28-9.25 (d, *J* = 7.2 Hz, 1H), 7.94-7.91 (m, 2H), 7.65-7.63 (m,

2H), 7.55-7.53 (m, 3H), 6.15-6.14 (d, J = 1.8 Hz, 1H), 4.95-4.93 (d, J = 4.8 Hz, 1H), 4.72-4.64 (m, 1H), 4.58-4.45 (m, 1H), 4.19-4.16 (d, J = 7.8 Hz, 2H), 2.72-2.64 (m, 1H), 2.27-2.12 (m, 4H), 1.34-1.32 (d, J = 6.3 Hz, 3H). Purity (HPLC, 254 nm): 98.9%.

[0286] 3-Phenyl-N-[(1r,3r)-3-([3-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 367.0. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.28-9.25 (d, J = 7.5 Hz, 1H), 7.94-7.91 (m, 2H), 7.65-7.63 (m, 2H), 7.55-7.53 (m, 3H), 6.15-6.14 (d, J = 2.1 Hz, 1H), 4.95-4.93 (d, J = 5.1 Hz, 1H), 4.72-4.63 (m, 1H), 4.55-4.48 (m, 1H), 4.19-4.16 (d, J = 7.5 Hz, 2H), 2.69-2.64 (m, 1H), 2.27-2.11 (m, 4H), 1.34-1.32 (d, J = 6.3 Hz, 3H). Purity (HPLC, 254 nm): 98.3%.

Examples 65 and 66: 3-Phenyl-N-[(1s,3s)-3-([3-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) and 3-Phenyl-N-[(1s,3s)-3-([3-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak)



[0287] Step 1: 3-Phenyl-N-[(1s,3s)-3-[(3-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 50-mL round-bottom flask was placed a solution of [(1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (1.3 g, 3.05 mmol, 1.00 equiv) in DMF (15 mL), then Cs_2CO_3 (1.96 g, 6.02 mmol, 2.00 equiv) and 1H-pyrazole-3-carbaldehyde (432 mg, 4.50 mmol, 1.50 equiv) were added. The resulting solution was stirred for 3 h at 100°C, then the solids were removed by filtration. The filtrate was purified by Flash-Prep-HPLC (CombiFlash-1: Column, C18; mobile phase, X: H_2O (0.5% NH_4HCO_3), Y: ACN, X/Y=90/10 increasing to X/ACN=5/95 within 40 min; Detector, UV 254

nm) affording 430 mg (40%) of 3-phenyl-N-[(1s,3s)-3-[(3-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+$ = 351.2.

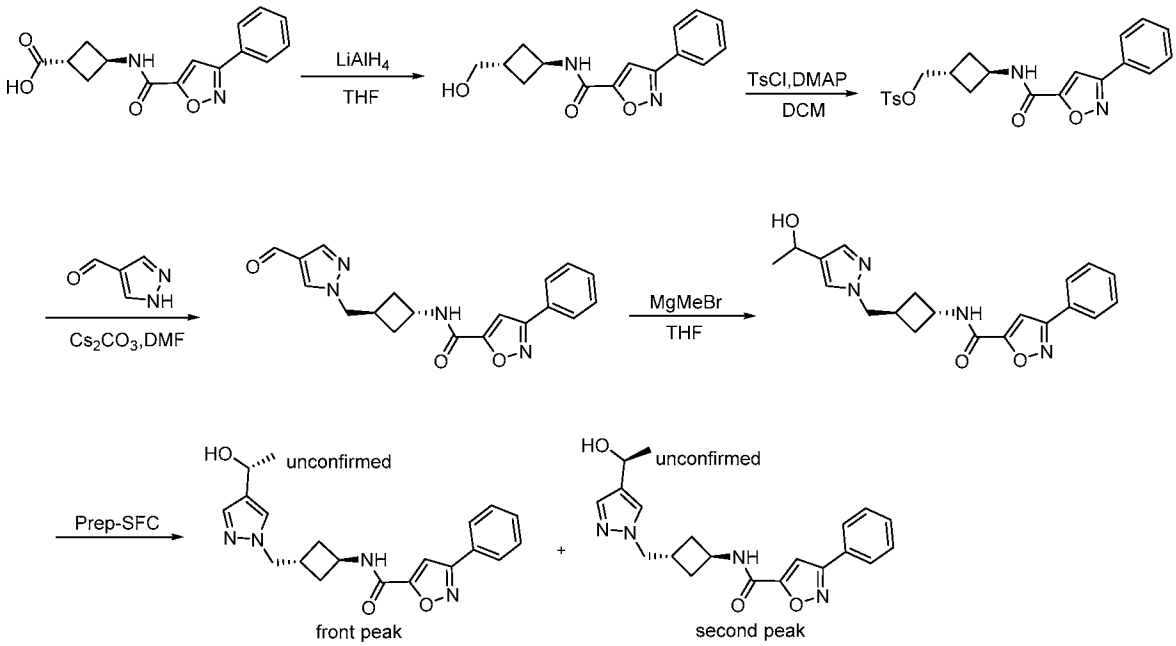
[0288] Step 2: 3-Phenyl-N-[(1s,3s)-3-([3-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) and 3-phenyl-N-[(1s,3s)-3-([3-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak). To a 100-mL 3-necked round-bottom flask was placed a solution of 3-phenyl-N-[(1s,3s)-3-[(3-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide (430 mg, 1.23 mmol, 1.00 equiv) in THF (30 mL), then the solution was cooled to 0°C and MeMgBr (1.2 mL, 3 mol/L, 3.00 equiv) was added dropwise with stirring at 0°C over 5 min. The reaction was stirred for 3 h at RT, then quenched by the addition of 2N HCl (10 mL) and 50 mL of H_2O, and extracted with EtOAc (3x50 mL). The organic extracts were combined, washed with brine (3x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (2:1). The pure isomers were separated by Chiral-Prep-HPLC (Prep-HPLC-009: Column, Phenomenex Lux 5u Cellulose-3, 5*25cm, 5um; mobile phase, Hex and IPA (hold 50.0% IPA-in 17 min); Detector, UV 220/254 nm) affording 89.5 mg (20%) of 3-phenyl-N-[(1s,3s)-3-([3-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) as a white solid and 65.5 mg (15%) of 3-phenyl-N-[(1s,3s)-3-([3-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak) as a white solid.

[0289] 3-Phenyl-N-[(1s,3s)-3-([3-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak): LCMS (ES, *m/z*): $[M+H]^+$ = 367.1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21-9.18 (d, *J* = 7.5 Hz, 1H), 7.94-7.92 (m, 2H), 7.62 (s, 1H), 7.55-7.53 (m, 4H), 6.15 (d, *J* = 2.1 Hz, 1H), 4.94-4.92 (d, *J* = 4.8 Hz, 1H), 4.71-4.63 (m, 1H), 4.34-4.26 (m, 1H), 4.09-4.06 (d, *J* = 6.9 Hz, 2H), 2.48-2.29 (m, 3H), 1.98-1.89 (m, 2H), 1.34-1.32 (d, *J* = 6.3 Hz, 3H). Purity (HPLC, 254 nm): 98.2%.

[0290] 3-Phenyl-N-[(1s,3s)-3-([3-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak): LCMS (ES, *m/z*): $[M+H]^+$ = 367.2. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21-9.18 (d, *J* = 7.5 Hz, 1H), 7.93-7.90 (m, 2H), 7.61 (s, 1H), 7.54-7.52 (m, 4H), 6.14 (d, *J* = 2.1 Hz, 1H), 4.94-4.93 (d, *J* = 4.8 Hz, 1H), 4.70-

4.62 (m, 1H), 4.35-4.22 (m, 1H), 4.08-4.05 (d, J = 6.9 Hz, 2H), 2.46-2.28 (m, 3H), 1.97-1.88 (m, 2H), 1.33-1.31 (d, J = 6.6 Hz, 3H). Purity (HPLC, 254 nm): 97.9%.

Examples 67 and 68: 3-Phenyl-N-[(1r,3r)-3-([4-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) and 3-Phenyl-N-[(1r,3r)-3-([4-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak)



[0291] Step 1: 3-Phenyl-N-[(1r,3r)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 250-mL 3-necked round-bottom flask was placed a solution of (1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylic acid (2 g, 6.99 mmol, 1.00 equiv) in THF (40 mL), then the solution was cooled to 0°C and $LiAlH_4$ (800 mg, 21.08 mmol, 3.00 equiv) was added. The resulting solution was stirred for 2 h at 5°C, then quenched by the addition of $Na_2SO_4.10H_2O$. The solids were removed by filtration, then the filtrate was concentrated under reduced pressure affording 850 mg (45%) of 3-phenyl-N-[(1r,3r)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a yellow oil. LCMS (ES, *m/z*): $[M+H]^+$ = 273.1.

[0292] Step 2: [(1r,3r)-3-(3-Phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate. To a 50-mL round-bottom flask was placed a solution of 3-

phenyl-N-[(1r,3r)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide (850 mg, 3.12 mmol, 1.00 equiv) and DMAP (762 mg, 6.24 mmol, 1.20 equiv) in DCM (20 mL). To this solution was added TsCl (712 mg, 3.73 mmol, 1.20 equiv) then the mixture was stirred for 24 h at RT. The reaction was diluted with 50 mL of water/ice and extracted with DCM. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 980 mg (crude) of [(1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate as a light yellow solid. LCMS (ES, *m/z*): $[M+H]^+ = 427.1$.

[0293] Step 3: 3-Phenyl-N-[(1r,3r)-3-[(4-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 50-mL round-bottom flask was placed a solution of [(1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (980 mg, 2.30 mmol, 1.00 equiv) in DMF (20 mL), then 1H-pyrazole-4-carbaldehyde (331 mg, 3.44 mmol, 1.50 equiv) and Cs_2CO_3 (1.1 g, 3.37 mmol, 1.50 equiv) were added. The resulting solution was stirred for 3 h at 70°C, diluted with 50 mL of H_2O, filtered, and then extracted with EtOAc. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:3) affording 400 mg (50%) of 3-phenyl-N-[(1r,3r)-3-[(4-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, *m/z*): $[M+H]^+ = 351.1$.

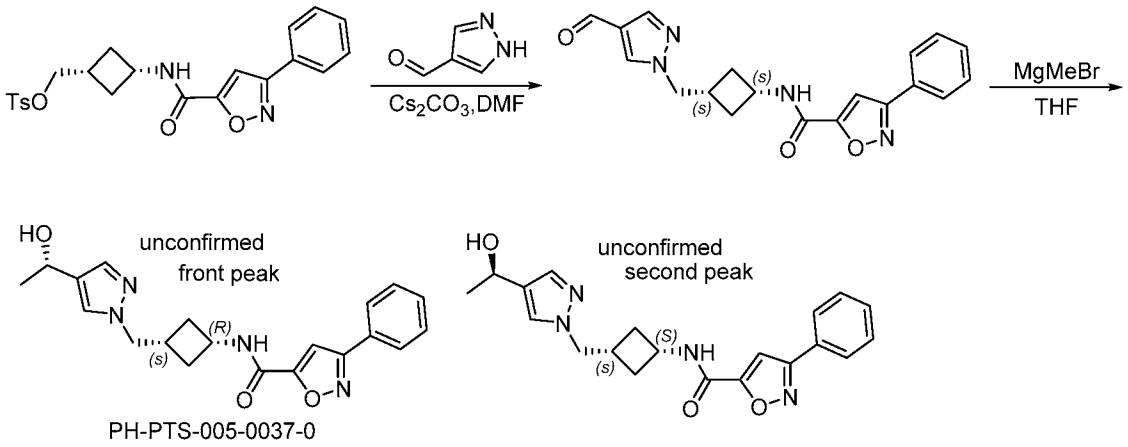
[0294] Step 4: 3-Phenyl-N-[(1r,3r)-3-[[4-(1-hydroxyethyl)-1H-pyrazol-1-yl]methyl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 150-mL round-bottom flask was placed a solution of 3-phenyl-N-[(1r,3r)-3-[(4-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide (600 mg, 1.71 mmol, 1.00 equiv) in THF (20 mL) then the solution was cooled to 5°C. To this solution was added MeMgBr (1M in hexane, 1.79 mL, 1.79 mmol, 4.00 equiv) at 5°C under nitrogen. The resulting solution was stirred for 3 h at 5°C. The pH value of the solution was adjusted to 3 with 1M HCl, then the resulting solution was extracted with EtOAc. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:3) affording 440 mg (70%) of 3-phenyl-N-[(1r,3r)-3-[[4-(1-hydroxyethyl)-1H-pyrazol-1-yl]methyl]cyclobutyl]-1,2-oxazole-5-carboxamide as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+ = 367.2$.

[0295] Step 5: 3-Phenyl-N-[(1r,3r)-3-([4-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) and 3-phenyl-N-[(1r,3r)-3-([4-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak). The crude N-(3-[[4-(1-hydroxyethyl)-1H-pyrazol-1-yl]methyl]cyclobutyl)-3-phenyl-1,2-oxazole-5-carboxamide (440 mg, 1.20 mmol, 1.00 equiv) was separated by Prep-SFC (Column: Phenomenex Lux 5u Cellulose-4£¬AXIA Packed, 250*21.2mm, 5um; Mobile Phase A: CO2: 60, Mobile Phase B: Hex: 40; Flow rate: 40 mL/min; 220 nm; RT1:5.12; RT2:6.06) affording 141.7 mg (32%) of 3-phenyl-N-[(1r,3r)-3-([4-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) as a white solid and 146.5 mg (33%) of 3-phenyl-N-[(1r,3r)-3-([4-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak) as a red solid.

[0296] 3-Phenyl-N-[(1r,3r)-3-([4-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak): LCMS (ES, *m/z*): $[M+H-H_2O]^+$ = 349.1. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.26-9.23 (d, *J* = 7.5 Hz, 1H), 7.93-7.90 (m, 2H), 7.62-7.60 (m, 2H), 7.54-7.52 (m, 3H), 7.32 (s, 1H), 4.85-4.83 (d, *J* = 4.8 Hz, 1H), 4.71-4.63 (m, 1H), 4.55-4.47 (m, 1H), 4.20-4.17 (d, *J* = 7.8 Hz, 2H), 2.68-2.64 (m, 1H), 2.27-2.10 (m, 4H), 1.33-1.31 (d, *J* = 6.3 Hz, 3H). Purity (HPLC, 254 nm): 98.2%.

[0297] 3-Phenyl-N-[(1r,3r)-3-([4-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak): LCMS (ES, *m/z*): $[M+H-H_2O]^+$ = 349.1. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.26-9.24 (d, *J* = 7.2 Hz, 1H), 7.93-7.90 (m, 2H), 7.64-7.60 (m, 2H), 7.54-7.52 (m, 3H), 7.32 (s, 1H), 4.85-4.84 (d, *J* = 4.8 Hz, 1H), 4.71-4.63 (m, 1H), 4.58-4.45 (m, 1H), 4.20-4.17 (d, *J* = 7.8 Hz, 2H), 2.68-2.64 (m, 1H), 2.27-2.10 (m, 4H), 1.33-1.31 (d, *J* = 6.3 Hz, 3H). Purity (HPLC, 254 nm): 97.0%.

Examples 69 and 70: 3-Phenyl-N-[(1s,3s)-3-([4-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) and 3-phenyl-N-[(1s,3s)-3-([4-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak)



PH-PTS-005-0037-0

[0298] Step 1: 3-Phenyl-N-[(1s,3s)-3-[(4-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide. To a 50-mL round-bottom flask was placed a solution of [(1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (1 g, 2.34 mmol, 1.00 equiv) in DMF (15 mL) then Cs_2CO_3 (1.5 g, 4.60 mmol, 2.00 equiv) and 1H-pyrazole-4-carbaldehyde (338 mg, 3.52 mmol, 1.50 equiv) were added. The resulting solution was stirred for 3 h at 100°C then the solids were removed by filtration. The crude product was purified by Flash-Prep-HPLC (CombiFlash-1: Column, C18 silica gel; mobile phase, X: H_2O (0.5% NH_4HCO_3), Y: ACN, X/Y=90/10 increasing to X/Y=5/95 within 40 min; Detector, UV 254 nm) affording 460 mg (56%) of 3-phenyl-N-[(1s,3s)-3-[(4-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+$ = 351.1.

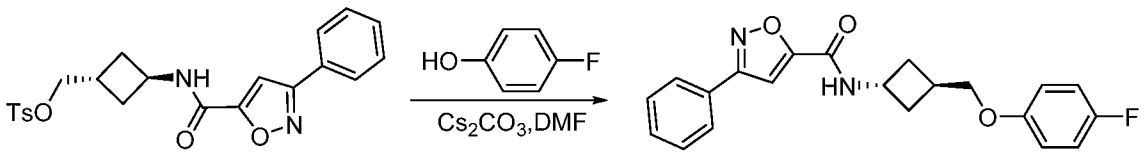
[0299] Step 2: 3-Phenyl-N-[(1s,3s)-3-([4-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak) and 3-phenyl-N-[(1s,3s)-3-([4-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak). To a 100-mL 3-necked round-bottom flask was placed a solution of 3-phenyl-N-[(1s,3s)-3-[(4-formyl-1H-pyrazol-1-yl)methyl]cyclobutyl]-1,2-oxazole-5-carboxamide (460 mg, 1.31 mmol, 1.00 equiv) in THF (30 mL) then the solution was cooled to 0°C. To this solution was added MeMgBr (1.3 mL, 3.00 equiv) dropwise with stirring at 0°C over 10 min. The resulting solution was stirred for 3 h at RT, quenched with 2N HCl (10 mL) and 50 mL of H_2O, and extracted with EtOAc (3x50 mL). The organic extracts were combined, washed with brine (3x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (2:1). The

product was purified by Chiral-Prep-HPLC (Prep-HPLC-004: Column, Chiralpak IB, 2*25cm, 5um; mobile phase, Hex and ethanol (hold 10.0% ethanol in 41 min); Detector, uv 254/220 nm) affording 132.3 mg (28%) of 3-phenyl-N-[(1s,3s)-3-([4-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide front peak) as an off-white solid and 139.4 mg (29%) of 3-phenyl-N-[(1s,3s)-3-([4-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak) as an off-white solid.

[0300] 3-Phenyl-N-[(1s,3s)-3-([4-[(1R)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (front peak): LCMS (ES, *m/z*): $[M+H]^+$ = 367.1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21-9.18 (d, *J* = 7.5 Hz, 1H), 7.94-7.91 (m, 2H), 7.62 (s, 1H), 7.55-7.51 (m, 3H), 7.48 (s, 1H), 7.32 (s, 1H), 4.85 (brs, 1H), 4.70-4.64 (q, *J* = 6.6 Hz, 1H), 4.36-4.23 (m, 1H), 4.10-4.07 (d, *J* = 6.9 Hz, 2H), 2.46-2.29 (m, 3H), 1.99-1.89 (m, 2H), 1.33-1.31 (d, *J* = 6.3 Hz, 3H). Purity (HPLC, 254 nm): 96.4%.

[0301] 3-Phenyl-N-[(1s,3s)-3-([4-[(1S)-1-hydroxyethyl]-1H-pyrazol-1-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide (second peak): LCMS (ES, *m/z*): $[M+H]^+$ = 367.1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21-9.18 (d, *J* = 7.5 Hz, 1H), 7.92-7.87 (m, 2H), 7.68 (s, 1H), 7.61-7.48 (m, 4H), 7.31 (s, 1H), 4.85 (brs, 1H), 4.73-4.65 (m, 1H), 4.36-4.28 (m, 1H), 4.09-4.07 (d, *J* = 6.6 Hz, 2H), 2.43-2.32 (m, 3H), 1.95-1.85 (m, 2H), 1.32-1.31 (d, *J* = 5.1 Hz, 3H). Purity (HPLC, 254 nm): 96.0%.

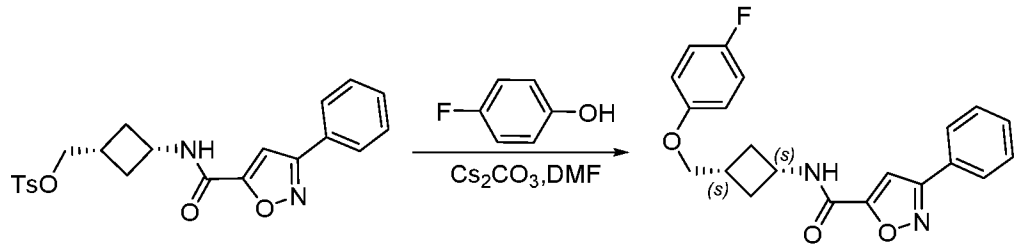
Example 71: 3-Phenyl-N-[(1r,3r)-3-(4-fluorophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide.



[0302] To a 50-mL round-bottom flask was placed a solution of [(1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (550 mg, 1.29 mmol, 1.00 equiv) in DMF (10 mL), then 4-fluorophenol (217 mg, 1.94 mmol, 1.50 equiv) and Cs_2CO_3 (631 mg, 1.93 mmol, 1.50 equiv) were added. The resulting solution was stirred for 3 h at 70°C, then diluted with H_2O, and extracted with EtOAc. The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was

applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:4). The resulting crude product was further purified by Prep-HPLC (Waters: Column, X Bridge Shield RP18 OBD Column, 5 um, 19*150 mm; mobile phase, water with 0.03%TFA and CH_3CN (10.0% CH_3CN up to 30 % CH_3CN in 8 min, up to 100% in 4 min and down to 10% in 3 min); Detector, uv 254 nm and 220 nm) affording 152.3 mg (53%) of 3-phenyl-N-[(1r,3r)-3-(4-fluorophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, *m/z*): $[M+H]^+$ = 367.1. ^1H NMR (300 MHz, DMSO-d_6): δ 9.31-9.29 (d, J = 7.2 Hz, 1H), 7.92-7.91 (m, 2H), 7.63 (s, 1H), 7.55-7.54 (m, 3H), 7.15-7.09 (m, 2H), 6.99-6.95 (m, 2H), 4.61-4.53 (m, 1H), 4.05-4.03 (d, J = 6.9 Hz, 2H), 2.69-2.63 (m, 1H), 2.38-2.29 (m, 2H), 2.23-2.17 (m, 2H). Purity (HPLC, 254 nm): 97.4%.

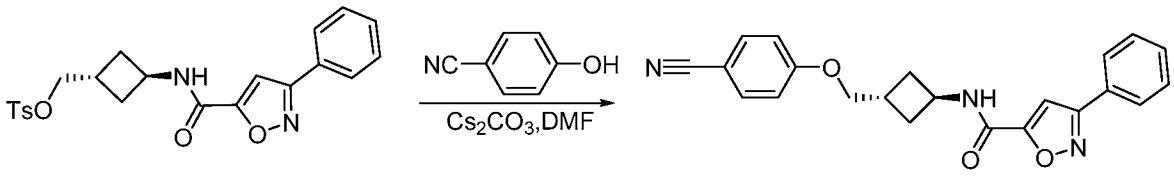
Example 72: 3-phenyl-N-[(1s,3s)-3-(4-fluorophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide



[0303] To a 25-mL round-bottom flask was placed a solution of [(1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (213 mg, 0.50 mmol, 1.00 equiv) in DMF (5 mL), then Cs_2CO_3 (326 mg, 1.00 mmol, 2.00 equiv) and 4-fluorophenol (84 mg, 0.75 mmol, 1.50 equiv) were added. The resulting solution was stirred for 3 h at 100°C, then diluted with 50 mL of H_2O, and extracted with EtOAc (2x50 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Prep-TLC (petroleum ether/ethyl acetate=1:2) affording 56.9 mg (31%) of 3-phenyl-N-[(1s,3s)-3-(4-fluorophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, *m/z*): $[M+H]^+$ = 367.1. ^1H NMR (300 MHz, DMSO-d_6) δ 9.23-9.21 (d, J = 7.5 Hz, 1H), 7.94-7.90 (m, 2H), 7.62 (s, 1H), 7.55-7.48 (m, 3H), 7.14-7.07 (m, 2H), 6.97-6.93 (m, 2H), 4.40-4.32

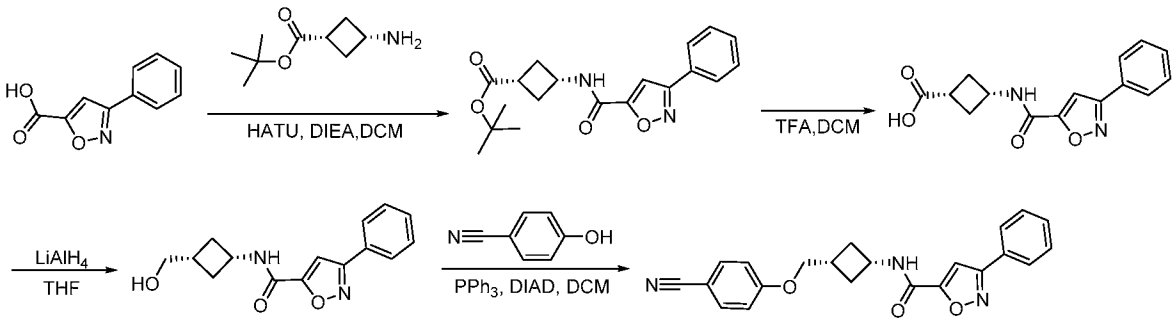
(m, 1H), 3.94-3.92 (d, J = 5.1 Hz, 2H), 2.43-2.39 (m, 3H), 2.00-1.94 (m, 2H). Purity (HPLC, 254 nm): 99.5%.

Example 73: 3-phenyl-N-[(1r,3r)-3-(4-cyanophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide



[0304] To a 50-mL round-bottom flask was placed a solution of [(1r,3r)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutyl]methyl 4-methylbenzene-1-sulfonate (560 mg, 1.31 mmol, 1.00 equiv) in DMF (10 mL), then 4-hydroxybenzonitrile (235 mg, 1.97 mmol, 1.50 equiv) and Cs_2CO_3 (643 mg, 1.97 mmol, 1.50 equiv) were added. The resulting solution was stirred for 2 h at 110°C, then diluted by the addition of water, and extracted with EtOAc. The organic extracts were combined, was washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. This residue was purified by Prep-HPLC (Waters: Column, X Bridge Prep C18 5um, 19*150 mm; mobile phase, water with 0.03% TFA and CH_3CN (10.0% CH_3CN up to 30% CH_3CN in 6 min, up to 100% in 5 min and down to 10% in 2 min); Detector, uv 254 nm and 220 nm) affording 129.9 mg (87%) of 3-phenyl-N-[(1r,3r)-3-(4-cyanophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, m/z): $[M+H]^+$ = 374.1. ^1H NMR (300 MHz, DMSO-d_6): δ 9.32-9.30 (d, J = 7.5 Hz, 1H), 7.94-7.91(m, 2H), 7.78-7.76 (d, J = 8.7 Hz, 2H), 7.63 (s, 1H), 7.55-7.54 (m, 3H), 7.15-7.12 (m, J = 8.7 Hz, 2H), 4.63-4.55 (m, 1H), 4.19-4.17 (d, J = 6.9 Hz, 2H), 2.72-2.66 (m, 1H) , 2.40-2.30 (m, 2H), 2.24-2.18 (m, 2H). Purity (HPLC, 254 nm): 97.3%.

Example 74: 3-Phenyl-N-[(1s,3s)-3-(4-cyanophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide



[0305] Step 1: tert-Butyl (1s,3s)-3-(3-Phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylate. To a 100-mL round-bottom flask was placed a solution of tert-butyl (1s,3s)-3-aminocyclobutane-1-carboxylate (1.7 g, 9.93 mmol, 1.00 equiv) in DCM (50 mL), then 3-phenyl-1,2-oxazole-5-carboxylic acid (1.9 g, 10.04 mmol, 1.00 equiv), HATU (5.7 g, 14.99 mmol, 1.50 equiv) and DIEA (3.9 g, 30.18 mmol, 3.00 equiv) were added. The resulting solution was stirred for 1 h at RT, then quenched by the addition of water, and extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:7) affording 2 g (59%) of tert-butyl (1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylate as a white solid. LCMS (ES, *m/z*): $[M+Na]^+ = 365.1$.

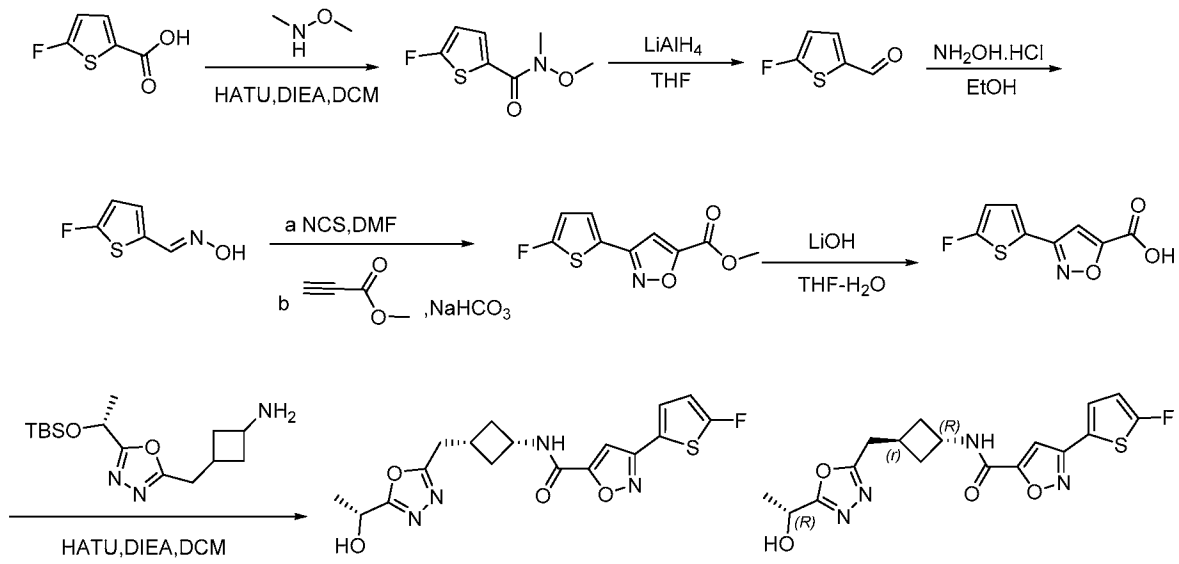
[0306] Step 2: (1s,3s)-3-(3-Phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylic acid. To a 100-mL round-bottom flask was placed a solution of tert-butyl (1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylate (2 g, 5.84 mmol, 1.00 equiv) in DCM (20 mL) and TFA (7 mL). The resulting solution was stirred for 4 h at RT, then the solvent was removed under reduced pressure affording 1.8 g (crude) of (1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylic acid as an off-white solid. LCMS (ES, *m/z*): $[M+H]^+ = 286.8$.

[0307] Step 3: 3-Phenyl-N-[(1s,3s)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 100-mL round-bottom flask was placed a solution of (1s,3s)-3-(3-phenyl-1,2-oxazole-5-amido)cyclobutane-1-carboxylic acid (1 g, 2.79 mmol, 1.00 equiv, 80%) in THF (25 mL), then the solution was cooled to 0°C. To this solution was added $LiAlH_4$ (425 mg, 11.18 mmol, 4.00 equiv) in portions at 0°C, then the resulting solution was stirred for 1 h at 10°C. The reaction was quenched by the addition of $Na_2SO_4.10H_2O$, then the solids were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue

was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:2) affording 420 mg (55%) of 3-phenyl-N-[(1s,3s)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, *m/z*): $[M+H]^+ = 273.1$.

[0308] Step 4: 3-Phenyl-N-[(1s,3s)-3-(4-cyanophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-phenyl-N-[(1s,3s)-3-(hydroxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide (420 mg, 1.31 mmol, 1.00 equiv, 85%), 4-hydroxybenzonitrile (320 mg, 2.69 mmol, 2.00 equiv) and PPh_3 (1.08 g, 4.12 mmol, 3.00 equiv) in THF (10 mL). This was followed by the addition of DIAD (840 mg, 4.15 mmol, 3.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred for 2 h at RT. The reaction was quenched by the addition of water, then extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Flash-Prep-HPLC (IntelFlash-1: Column, C18; mobile phase, MeCN/H_2O=5:95 increasing to MeCN/H_2O=50:50 within 20 min; Detector, UV 254 nm) affording 148.5 mg (30%) of 3-phenyl-N-[(1s,3s)-3-(4-cyanophenoxymethyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid. LCMS (ES, *m/z*): $[M+H]^+ = 374.2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25-9.24 (d, J = 7.6 Hz, 1H), 7.94-7.92 (m, 2H), 7.79-7.76 (m, 2H), 7.64 (s, 1H), 7.55-7.53 (m, 3H), 7.16-7.12 (m, 2H), 4.43-4.35 (p, J = 8.0 Hz, 1H), 4.08-4.06 (d, J = 6.0 Hz, 2H), 2.45-2.40 (m, 3H), 2.02-1.97 (m, 2H). Purity (HPLC, 254 nm): 98.2%.

Example 75 and 76: 3-(5-Fluorothiophen-2-yl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-(5-Fluorothiophen-2-yl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide



[0309] **Step 1: 5-Fluoro-N-methoxy-N-methylthiophene-2-carboxamide.** To a 100-mL round-bottom flask was placed a solution of 5-fluorothiophene-2-carboxylic acid (1 g, 6.84 mmol, 1.00 equiv) in DCM (50 mL), then methoxy(methyl)amine hydrochloride (730 mg, 7.53 mmol, 1.10 equiv), HATU (3.9 g, 10.26 mmol, 1.50 equiv), and DIEA (2.82 mL, 3.00 equiv) were added. The reaction was stirred for 3 h at room temperature, diluted with H_2O, and extracted with DCM (2x100 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with EtOAc/petroleum ether (1:4) affording 1.14 g (88%) of 5-fluoro-N-methoxy-N-methylthiophene-2-carboxamide as a yellow liquid. LCMS (ES, *m/z*): $[M+H]^+ = 190.0$.

[0310] **Step 2: (E)-N-[(5-Fluorothiophen-2-yl)methylidene]hydroxylamine.** To a 50-mL round-bottom flask was placed a solution of 5-fluoro-N-methoxy-N-methylthiophene-2-carboxamide (1.14 g, 6.03 mmol, 1.00 equiv) in THF (20 mL), then $LiAlH_4$ (342 mg, 9.01 mmol, 1.20 equiv) was added. The action was stirred for 1 h at room temperature, then quenched by the addition of 20 mL of H_2O/ice, and extracted with EtOAc (2x20 mL). The organic extracts were dried and used directly in the next step.

[0311] To a 250-mL round-bottom flask was placed a solution of 5-fluorothiophene-2-carbaldehyde (780 mg, 5.99 mmol, 1.00 equiv) in EtOH/EtOAc (120 mL), then $NH_2OH.HCl$ (0.5 g, 1.20 equiv) was added. The resulting solution was stirred for 3 h at room temperature

then the solvent was removed under reduced pressure. The residue was dissolved in H_2O (50 mL), then the resulting solution was extracted with EtOAc (3x100 mL). The organic extracts were combined, washed with brine (2x100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 650 mg (75%) of (E)-N-[(5-fluorothiophen-2-yl)methylidene]hydroxylamine as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+ = 146.0$.

[0312] Step 3: Methyl 3-(5-Fluorothiophen-2-yl)-1,2-oxazole-5-carboxylate. To a 25-mL round-bottom flask was placed a solution of (E)-N-[(5-fluorothiophen-2-yl)methylidene]hydroxylamine (300 mg, 2.07 mmol, 1.00 equiv) DMF (5 mL), then NCS (414 mg, 3.11 mmol, 1.50 equiv) was added in small portions. The resulting solution was stirred for 1 h at room temperature, then methyl prop-2-ynoate (0.27 mL, 2.00 equiv) was added followed by Na_2CO_3 (260 mg, 3.09 mmol, 1.50 equiv) in small portions. The reaction was stirred for 2 h at room temperature, diluted with 50 mL of H_2O, and extracted with EtOAc (3x100 mL). The organic extracts were combined, washed with brine (2x50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by prep TLC (ethyl acetate / petroleum ether = 1/3) affording 200 mg (43%) of methyl 3-(5-fluorothiophen-2-yl)-1,2-oxazole-5-carboxylate as a yellow solid.

[0313] Step 4: 3-(5-fluorothiophen-2-yl)-1,2-oxazole-5-carboxylic acid. To a 50-mL round-bottom flask was placed a solution of methyl 3-(5-fluorothiophen-2-yl)-1,2-oxazole-5-carboxylate (254 mg, 1.12 mmol, 1.00 equiv) in THF-H_2O (3:1, 10 mL), then LiOH (52 mg, 2.17 mmol, 2.00 equiv) was added. The reaction was stirred for 1 h at room temperature, diluted with H_2O (20 mL), and washed with ethyl acetate (2x50 mL). The pH of the aqueous layer was adjusted to 3 with1M HCl, then the resulting solution was extracted with EtOAc (3x50 mL). The organic extracts were combined, was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure affording 170 mg (71%) of 3-(5-fluorothiophen-2-yl)-1,2-oxazole-5-carboxylic acid as a yellow solid. LCMS (ES, *m/z*): $[M+H]^+ = 214.1$.

[0314] Step 5: 3-(5-Fluorothiophen-2-yl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide and 3-(5-Fluorothiophen-2-yl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide. To a 50-mL round-bottom flask was placed a solution of 3-(5-fluorothiophen-2-yl)-1,2-oxazole-5-carboxylic acid (170 mg, 0.80 mmol, 1.00 equiv) in DCM

(20 mL), then 3-([5-[(1R)-1-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutan-1-amine (273 mg, 0.88 mmol, 1.10 equiv), HATU (455 mg, 1.20 mmol, 1.50 equiv), and DIEA (0.33 mL, 3.00 equiv) were added. The reaction was stirred for 3 h at room temperature, diluted with H_2O, and extracted with DCM. The organic extracts were combined, washed with brine (2 x30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/petroleum ether = 1/4), then the resulting pure isomers were separated by Chiral-Prep-HPLC (Prep-HPLC-032: Column, Lux 5u Cellulose-4,AXIA Packed, 250*21.2mm; mobile phase, Hex and IPA (hold 30.0% IPA in 21 min); Detector, UV 254/220 nm) affording 37.2 mg (19%) of 3-(5-fluorothiophen-2-yl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid and 9.4 mg (5%) of 3-(5-fluorothiophen-2-yl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide as a white solid.

[0315] 3-(5-Fluorothiophen-2-yl)-N-[(1s,3s)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 393.1. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23-9.20 (d, *J* = 7.8 Hz, 1H), 7.61 (s, 1H), 7.57-7.55 (t, *J* = 3.9 Hz, 2H), 6.94-6.92 (m, 1H), 5.91-5.89 (d, *J* = 5.7 Hz, 1H), 4.92-4.83 (m, 1H), 4.33-4.23 (m, 1H), 2.97-2.95 (d, *J* = 6.3 Hz, 2H), 2.46-2.33 (m, 3H), 1.96-1.90 (m, 2H), 1.45-1.43 (d, *J* = 6.6 Hz, 3H). Purity (HPLC, 254 nm): 98.8%.

[0316] 3-(5-Fluorothiophen-2-yl)-N-[(1r,3r)-3-([5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]methyl)cyclobutyl]-1,2-oxazole-5-carboxamide: LCMS (ES, *m/z*): $[M+H]^+$ = 393.1. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.33-9.31 (d, *J* = 7.2 Hz, 1H), 7.62 (s, 1H), 7.57-7.54 (t, *J* = 4.2 Hz, 1H), 6.94-6.92 (m, 1H), 5.92-5.90 (d, *J* = 5.7 Hz, 1H), 4.92-4.84 (m, 1H), 4.57-4.49 (m, 1H), 3.09-3.06 (d, *J* = 7.8 Hz, 2H), 2.72-2.64 (m, 1H), 2.37-2.27 (m, 2H), 2.17-2.12 (m, 2H), 1.46-1.43 (d, *J* = 6.6 Hz, 3H). Purity (HPLC, 254 nm): 99.3%.

Example 77: CFTR activity assays

i. Ussing measurements

[0317] As discussed above, Ussing measurements can be used to measure CFTR activity. In this example, primary lung epithelial cells (hBEs) homozygous for the Cystic Fibrosis-causing ΔF508 mutation were differentiated for a minimum of 4 weeks in an air-liquid interface on SnapWell filter plates prior to the Ussing measurements. Cells were apically

mucus-washed for 30 minutes prior to treatment with compounds. The basolateral media was removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO stocks. Treated cells were incubated at 37°C and 5% CO_2 for 24 hours. At the end of the treatment period, the cells on filters were transferred to the Ussing chamber and equilibrated for 30 minutes. The short-circuit current was measured in voltage clamp-mode (V_{hold} = 0 mV), and the entire assay was conducted at a temperature of 36°C - 36.5°C. Once the voltages stabilized, the chambers were clamped, and data was recorded by pulse readings every 5 seconds. Following baseline current stabilization, the following additions were applied and the changes in current and resistance of the cells was monitored:

1. Benzamil to the apical chamber to inhibit ENaC sodium channel.
2. Forskolin to both chambers to activate ΔF508-CFTR by phosphorylation.
3. Genistein or VX-770 (ivacaftor) to both chambers to potentiate ΔF508-CFTR channel opening.
4. CFTRinh-172 to the apical chamber to inhibit ΔF508-CFTR Cl- conductance.

[0318] The inhibitable current (that current that is blocked by CFTRinh-172) is measured as the specific activity of the ΔF508-CFTR channel, and increases in response to compound in this activity over that observed in vehicle-treated samples are identified as the correction of ΔF508-CFTR function imparted by the compound tested.

ii. hBE Equivalent Current (Ieq) Assay

[0319] Primary lung epithelial cells homozygous for the Cystic Fibrosis-causing ΔF508 mutation were differentiated for a minimum of 4 weeks in an air-liquid interface on Costar 24 well HTS filter plates prior to the equivalent current (Ieq) measurements. Cells were apically mucus-washed for 30 minutes 24h prior to treatment with compounds. The basolateral media was removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO stocks. Treated cells were incubated at 37°C and 5% CO_2 for 24 hours. At the end of the treatment period, the media was changed to the Ieq experimental solution for 30 minutes before the experiment and plates are maintained in a CO_2-free incubator during this period. The plates containing the cells were then placed in pre-warmed heating blocks at 36°C±0.5 for 15 minutes before measurements are taken. The transepithelial voltage (V_T) and conductance (G_T) were measured using a custom 24 channel current clamp (TECC-

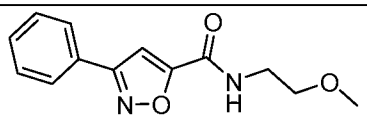
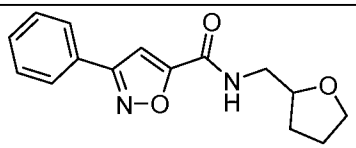
24) with 24 well electrode manifold. The Ieq assay measurements were made following additions with standardized time periods:

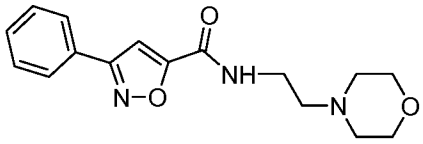
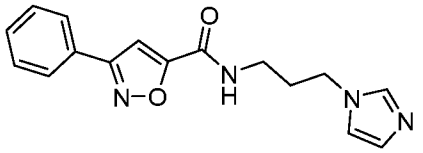
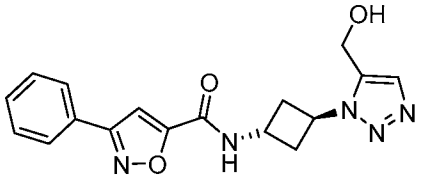
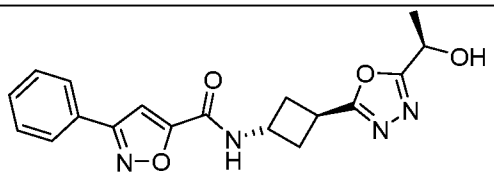
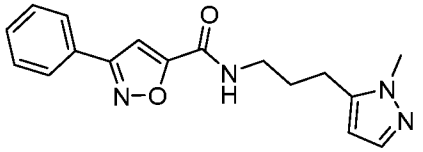
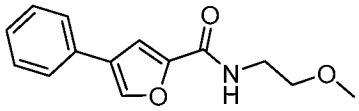
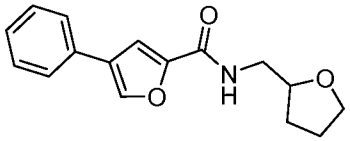
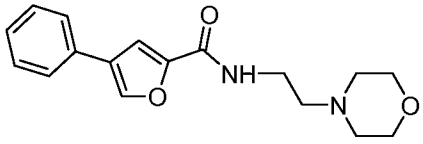
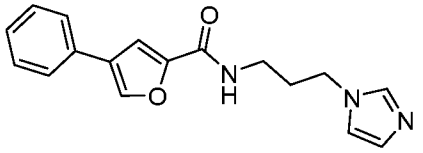
1. The baseline V_T and G_T values were measured for approximately 20 minutes.
2. Benzamil was added to block ENaC for 15 minutes.
3. Forskolin plus VX-770 (ivacaftor) were added to maximally activate ΔF508-CFTR for 27 minutes.
4. Bumetanide was added to inhibit the NaK_2Cl cotransporter and shut-off secretion of chloride.

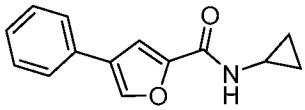
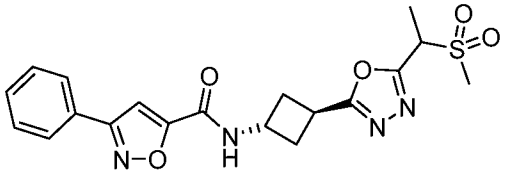
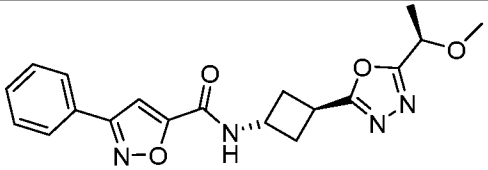
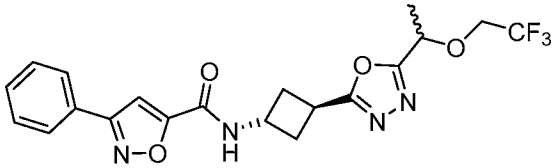
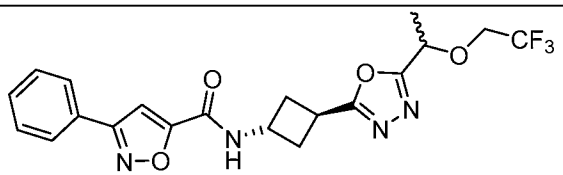
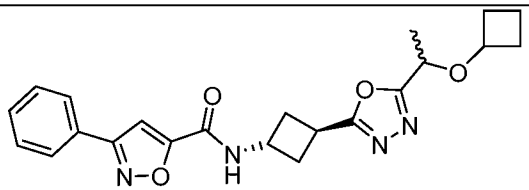
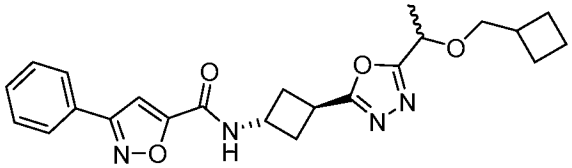
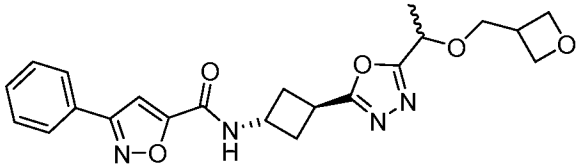
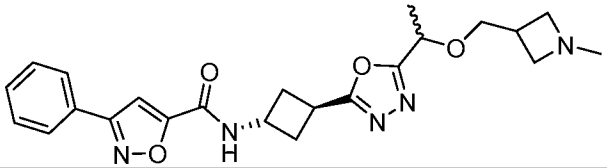
[0320] The activity data captured was the area under the curve (AUC) for the traces of the equivalent chloride current. The AUC was collected from the time of the forskolin/VX-770 addition until the inhibition by bumetanide addition. Correction in response to compound treatment was scored as the increase in the AUC for compound-treated samples over that of vehicle-treated samples.

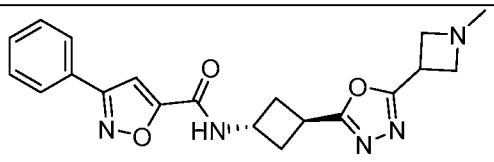
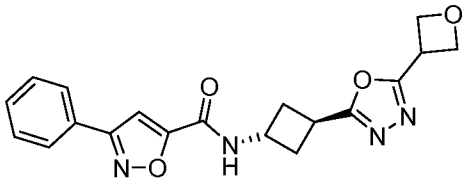
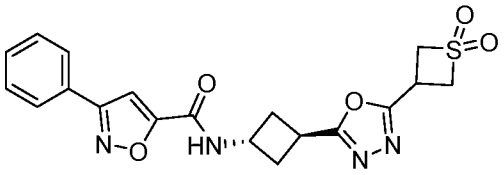
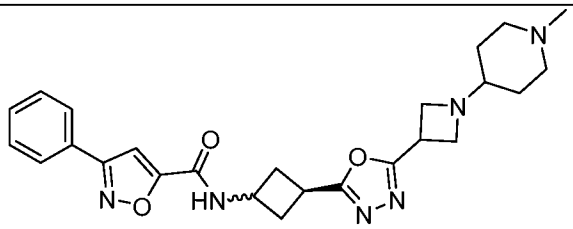
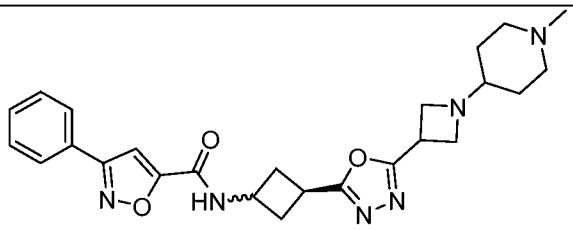
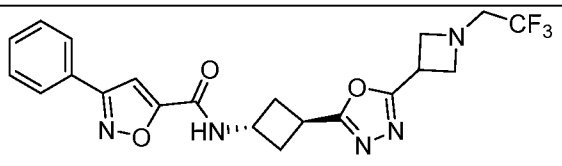
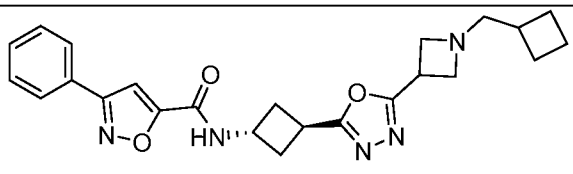
[0321] The results are shown below in Table 2. ++ indicates activity ≥25% run at 10 uM of VX-809 at 1 uM, + indicates activity 10 to < 25% run at 10 uM of VX-809 at 1 uM, ** indicates activity ≥200% of VX-809 (1 uM) with compound at 10 uM and VX-809 at 1 uM; * indicates activity 100-200% of VX-809(1 uM) with compound at 10 uM and VX-809 at 1 uM. ## indicates activity ≥200% of VX-809 (3 uM) with compound at 10 uM and VX-809 at 3 uM; # indicates activity 100-200% of VX-809(3 uM) with compound at 10 uM and VX-809 at 3 uM.

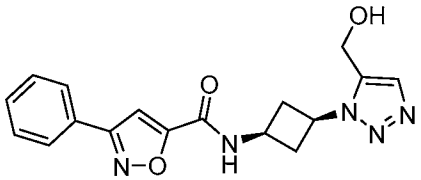
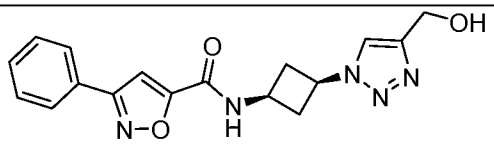
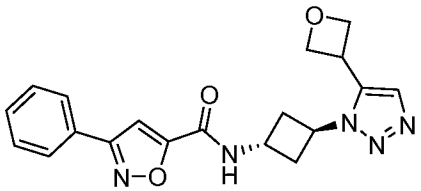
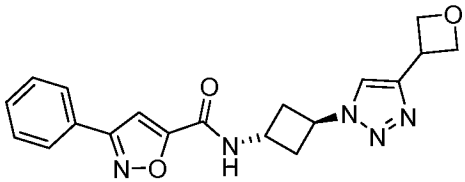
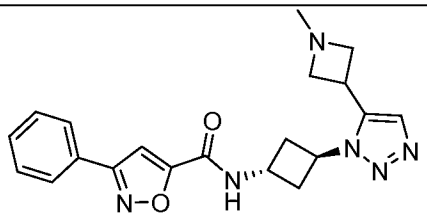
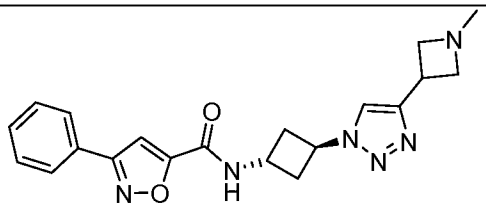
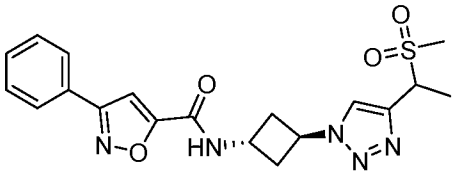
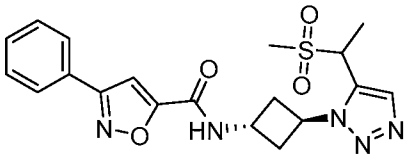
Table 2

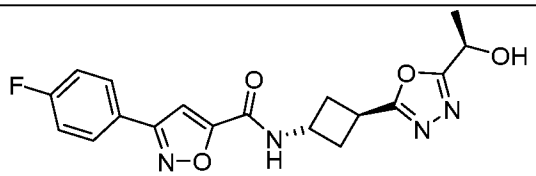
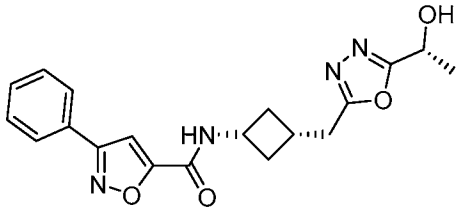
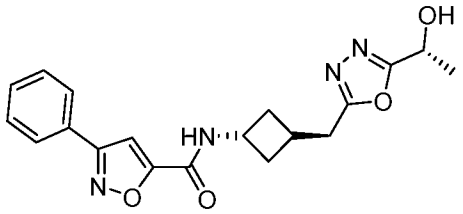
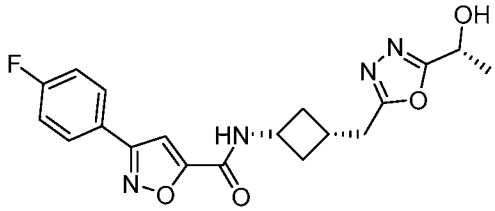
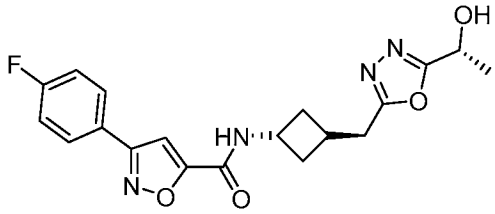
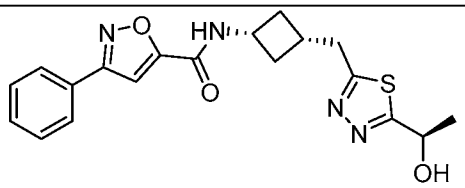
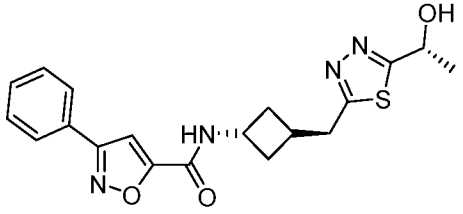
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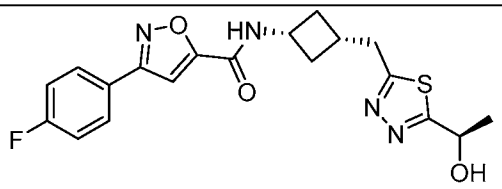
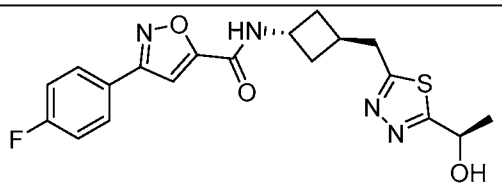
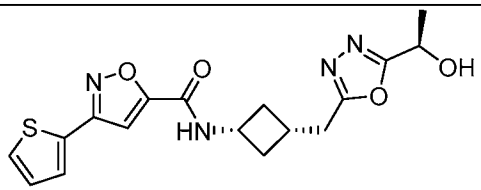
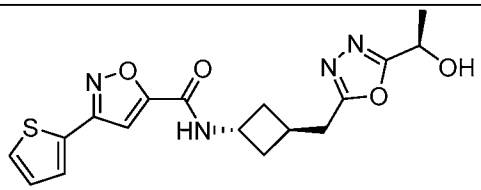
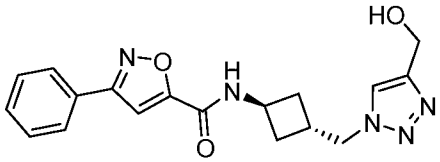
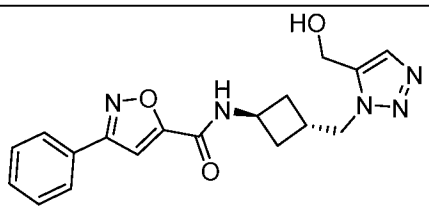
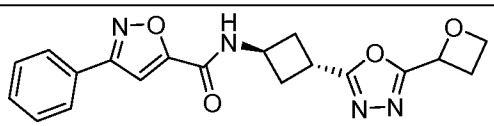
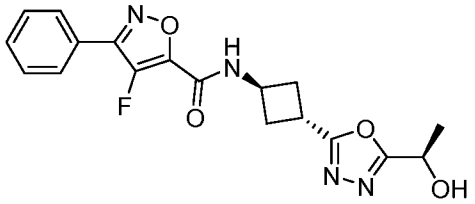
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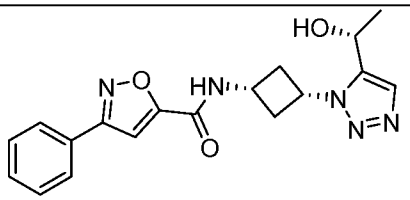
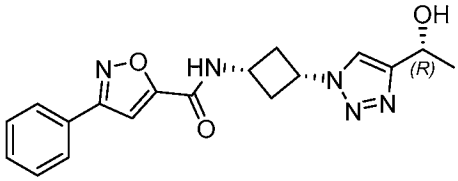
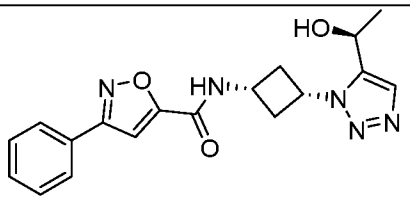
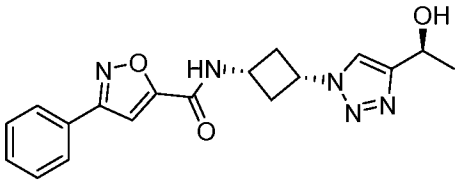
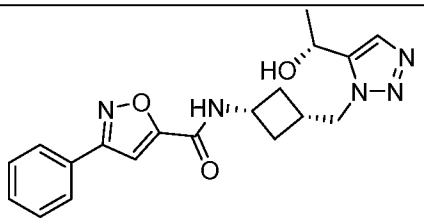
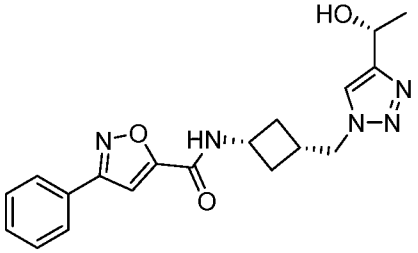
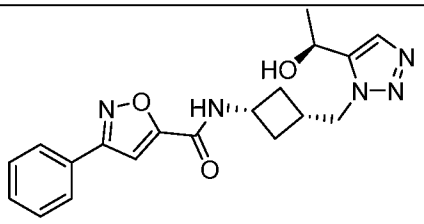
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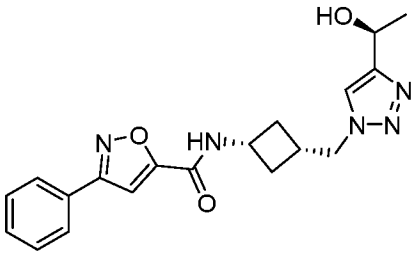
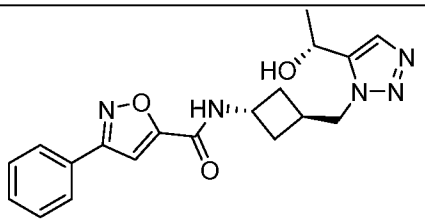
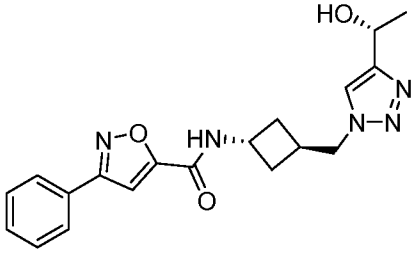
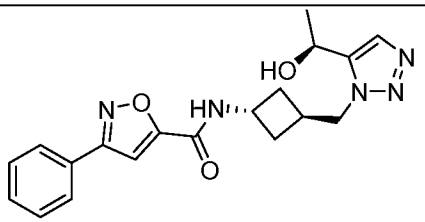
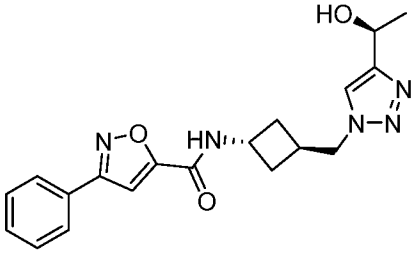
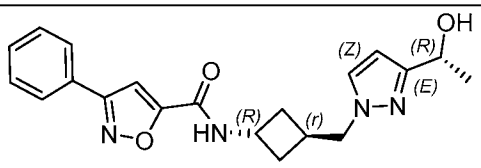
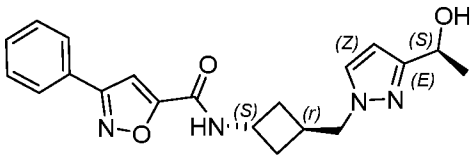
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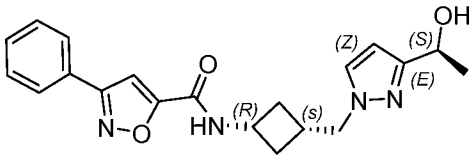
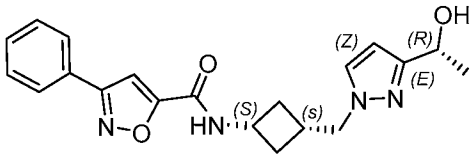
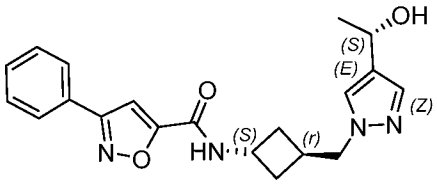
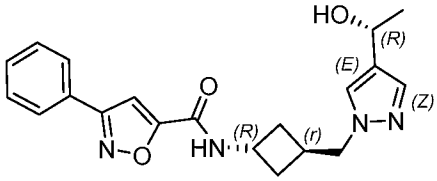
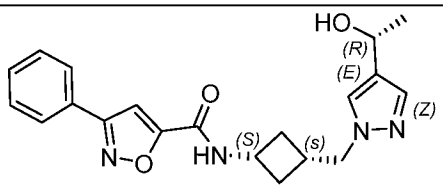
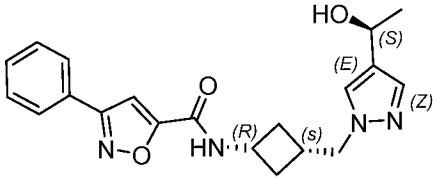
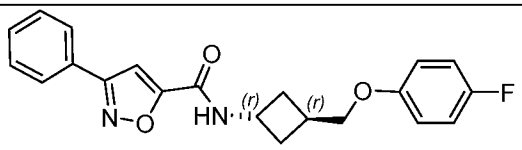
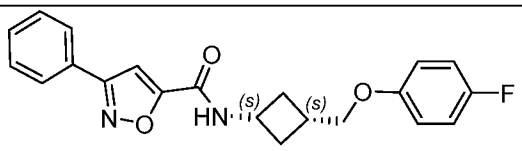
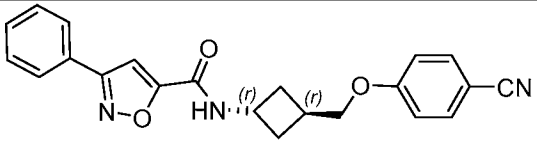
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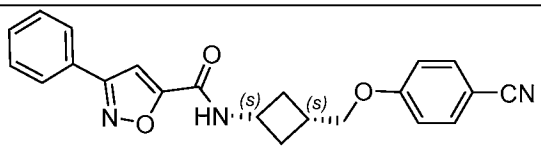
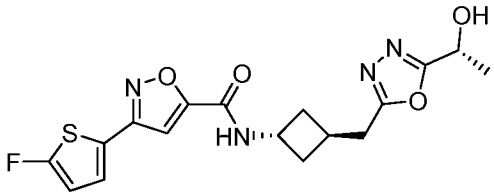
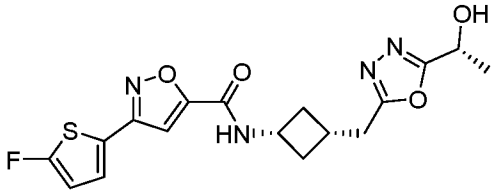
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Example 78

i. Ussing measurements

[0322] As discussed above, Ussing measurements were used to measure CFTR activity. In this method, primary lung epithelial cells (hBEs) with a Cystic fibrosis causing class I mutation were differentiated for a minimum of 4 weeks in an air-liquid interface on SnapWell™ filter plates prior to the Ussing measurements. Cells were apically mucus-washed for 30 minutes prior to treatment with compounds. The basolateral media was removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO or aqueous stocks. Treated cells were incubated at 37°C and 5% CO_2 for 24 hours. At the end of the treatment period, the cells on filters were transferred to the Ussing chamber and equilibrated for 30 minutes. The short-circuit current was measured in voltage clamp-mode (V_{hold} = 0 mV), and the entire assay was conducted at a temperature of 36°C -36.5°C. Once the voltages stabilized, the chambers were clamped, and data were recorded by pulse readings every 5 seconds. Following baseline current stabilization, the following additions were applied and the changes in current and resistance of the cells were monitored:

1. Benzamil to the apical chamber to inhibit ENaC sodium channel.
2. Forskolin to both chambers to activate ΔF508-CFTR by phosphorylation.

3. Ivacaftor or Genistein to the apical chamber to potentiate ΔF508-CFTR channel opening.

4. CFTRinh-172 to the apical chamber to inhibit ΔF508-CFTR Cl- conductance.

[0323] The forskolin-sensitive current and inhibitable current (that potentiated current that was blocked by CFTRinh-172) were measured as the specific activity of the ΔF508-CFTR channel, and increase in response to compound in this activity over that observed in vehicle-treated samples were identified as the correction of ΔF508-CFTR function imparted by the compound tested.

[0324] The results are shown below in Tables 3 and 4. Compound A is 10 uM and VX-809 is 3 uM and ivacaftor is 1 uM.

Table 3. Activity in F508/F508del HBEs (relative to VX-809 and ivacaftor activity)

VX-809 + ivacaftor	100%
Compound A + VX-809 + ivacaftor	242%

Table 4. Activity in G542X/F508del HBEs (relative to VX-809 and ivacaftor activity)

VX-809 + ivacaftor	100%
Compound A + VX-809 + ivacaftor	190%

Example 79

i. Ussing measurements

[0325] As discussed above, Ussing measurements was used to measure CFTR activity. In this method, primary lung epithelial cells (hBEs) with a Cystic Fibrosis-causing class III mutation were differentiated for a minimum of 4 weeks in an air-liquid interface on SnapWell™ filter plates prior to the Ussing measurements. Cells were apically mucus-washed for 30 minutes prior to treatment with compounds. The basolateral media was removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO stocks. Treated cells were incubated at 37°C and 5% CO_2 for 24 hours. At the end of the treatment period, the cells on filters were transferred to the Ussing chamber and

equilibrated for 30 minutes. The short-circuit current was measured in voltage clamp-mode (V_{hold} = 0 mV), and the entire assay was conducted at a temperature of 36°C -36.5°C. Once the voltages stabilized, the chambers were clamped, and data was recorded by pulse readings every 5 seconds. Following baseline current stabilization, the following additions were applied and the changes in current and resistance of the cells was monitored:

1. Benzamil to the apical chamber to inhibit ENaC sodium channel.
2. Forskolin to both chambers to activate ΔF508-CFTR by phosphorylation.
3. Ivacaftor or Genistein to the apical chamber to potentiate ΔF508-CFTR channel opening.
4. CFTRinh-172 to the apical chamber to inhibit ΔF508-CFTR Cl- conductance.

[0326] The forskolin-sensitive current and inhibitable current (that potentiated current that is blocked by CFTRinh-172) were measured as the specific activity of the ΔF508-CFTR channel, and increase in response to compound in this activity over that observed in vehicle-treated samples were identified as the correction of ΔF508-CFTR function imparted by the compound tested.

[0327] The results are shown below in Tables 5 and 6. Compound A is 10 uM and VX-809 is 3 uM and ivacaftor is 1 uM.

Table 5. Activity in R117H/F508del HBEs (relative to ivacaftor activity)

ivacaftor	100%
Compound A + ivacaftor	193%

Table 6. Activity in G551D/F508del HBEs (relative to ivacaftor activity)

ivacaftor	100%
Compound A + ivacaftor	160%

[0328] Table 7 indicates mutation type and activity with compounds/combination with compound A. ## indicates activity at 30uM of 50% to < 100% of the indicated relative activity treatment, #### indicates activity at 30uM of ≥150% of the indicated relative activity treatment, + indicates activity at 10uM of 15% to < 50% of the indicated relative activity

treatment, ++ indicates activity at 10uM of 50% to < 100% of the indicated relative activity treatment, +++ indicates activity at 10uM of 100% to <150% of the indicated relative activity treatment, ++++ indicates activity at 10uM of ≥150% of the indicated relative activity treatment. NB124 is used at 250 ug/ml, ivacaftor is used at 1uM, lumacaftor is used at 3 uM, and VX-661 is used at 3 uM.

Genotype	Relative Activity of 100%	Stand Alone	Combination with ivacaftor	Combination with ivacaftor and lumacaftor	Combination with ivacaftor and VX-661	Combination with NB124
G542X/ G542X	NB124	++				++++
G542X/ F508del	ivacaftor and lumacaftor	+		++++		
F508del/ F508del	ivacaftor and lumacaftor	+		++++		
F508del/ F508del	ivacaftor and VX-661				++++	
G551D/ F508del	ivacaftor	+	++++			
R117H/ F508del	ivacaftor	+++	++++			
3849 + 10kb C>T/ N1303K	ivacaftor	++	+++			

[0329] While this disclosure has been particularly shown and described with references to certain embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the disclosure encompassed by the appended claims.

INCORPORATION BY REFERENCE

[0330] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

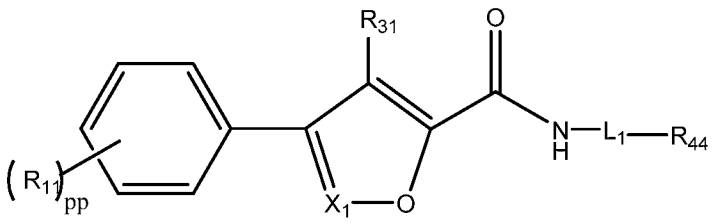
EQUIVALENTS

[0331] While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

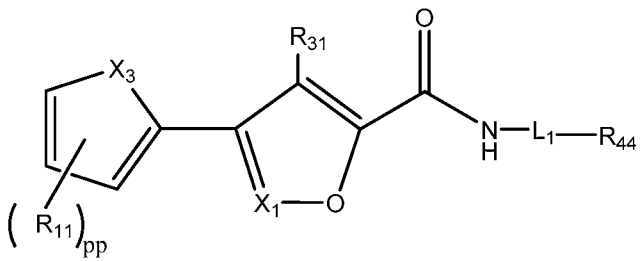
[0332] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

What is claimed is:

1. A method of treating cystic fibrosis in a patient in need thereof, comprising administering a pharmaceutically effective amount of a compound represented by formula I and II:



I



II

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

X_1 is CR_{33} or N;

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;

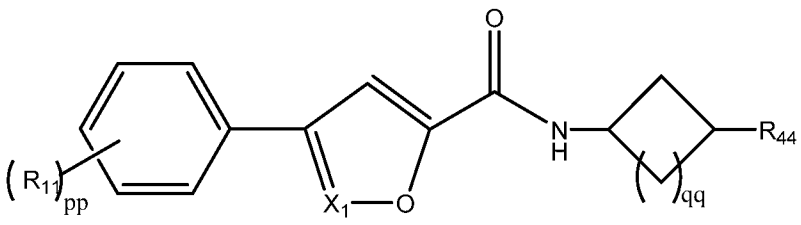
R_{hh} is selected for each occurrence from the group consisting of H, C_{1-6} alkyl and C_{3-6} cycloalkyl; and

optionally administering to said patient a) CFTR potentiator and/or b) a CFTR corrector.

2. The method of claim 1, wherein L_1 is C_{1-3} alkylene or C_{3-5} cycloalkylene.

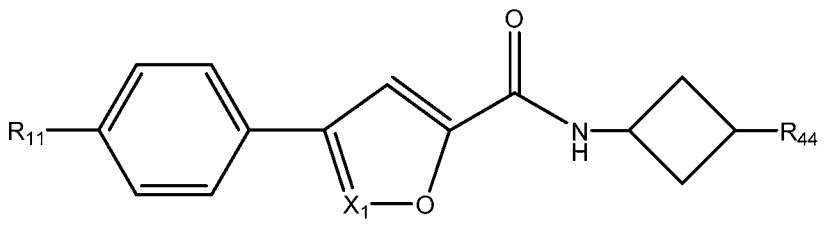
3. The method of claims 1-2, wherein R_{31} is H or F.

4. The method of any one of claims 1-3, represented by:



wherein qq is 0 or 1.

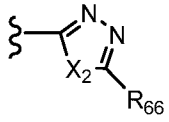
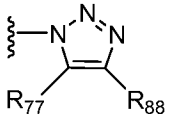
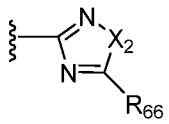
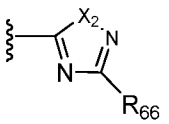
5. The method of any one of claims 1-4, represented by:



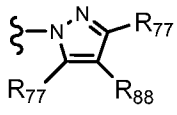
.

6. The method of any one of claims 1-4, wherein R_{44} is selected from the group consisting of: pyrrolidinyl, piperidinyl, tetrahydropyranyl, and tetrahydofuranyl.

7. The compound of any one of claims 1-4, wherein R_{44} is selected from the group consisting of

,



and ;

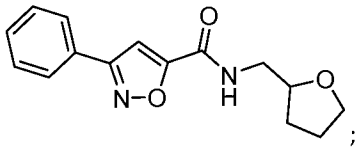
wherein X_2 independently for each occurrence is selected from the group consisting of O, S or NR_{hh}; and each R_{66}, R_{77} and R_{88} is independently selected for each occurrence from R_{gg}.

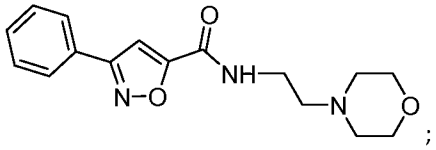
8. The method of claim 7, where each R_{66}, R_{77} and R_{88} is selected from the group consisting of H, halogen, methyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), ethyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), propyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), isopropyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), *n*-butyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), *t*-butyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy), *s*-butyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy) and isobutyl (optionally substituted by one, two or three substituents each selected from halogen, hydroxyl, methoxy and ethoxy).

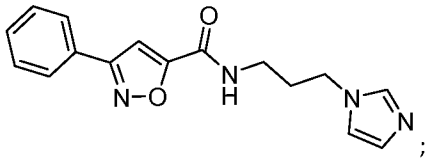
9. The method of any one of claims 1-9, wherein pp is 0, 1 or 2, and R_{11} is selected from H, F, or methyl.

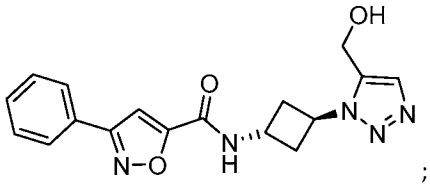
10. A method of treating cystic fibrosis in patients in need thereof, comprising:

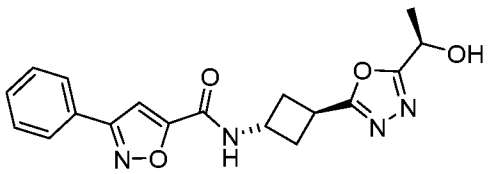
administering to said subject an effective amount of a compound selected from the group consisting of :

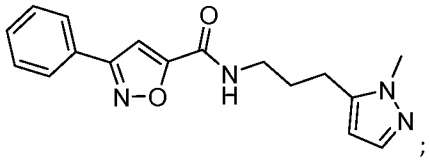

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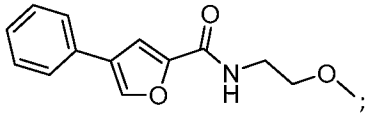

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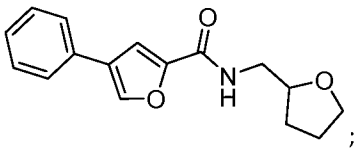

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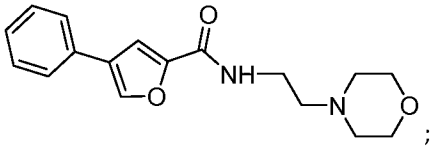

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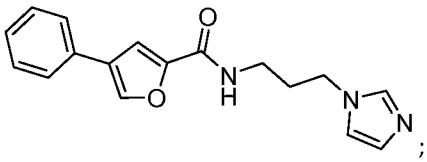

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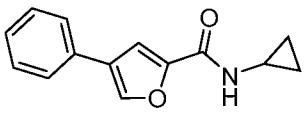

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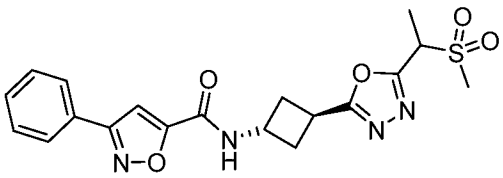

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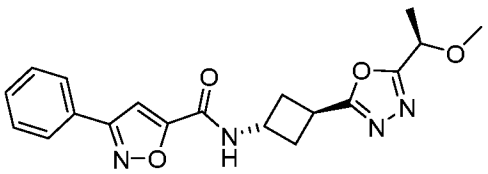

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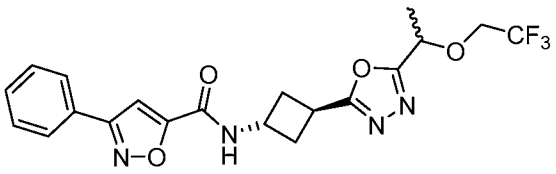

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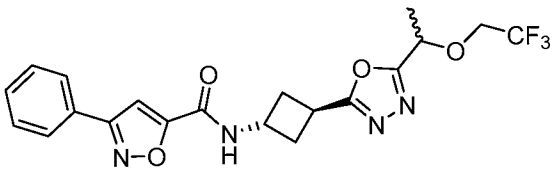

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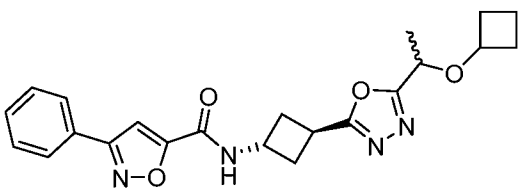

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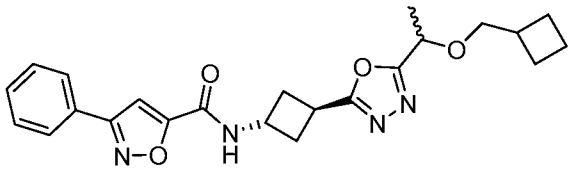

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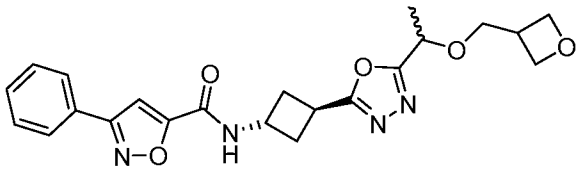

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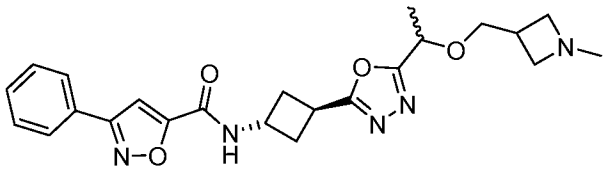

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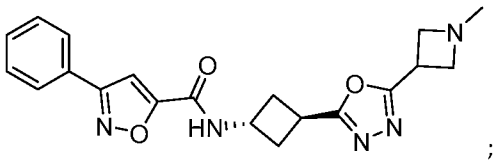

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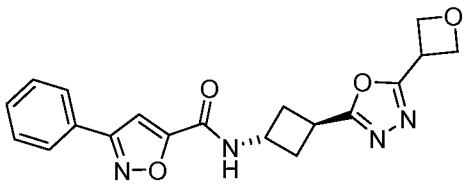

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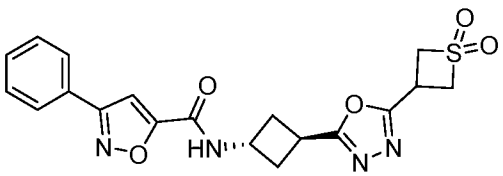

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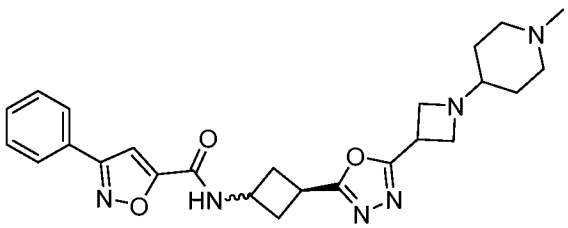

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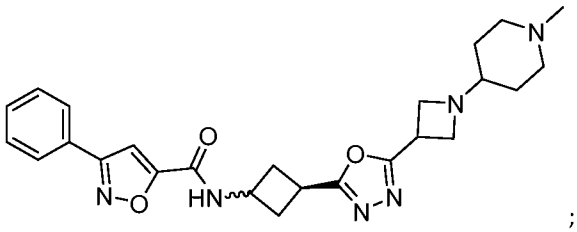

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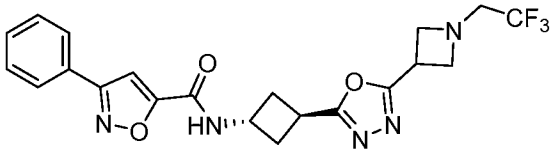

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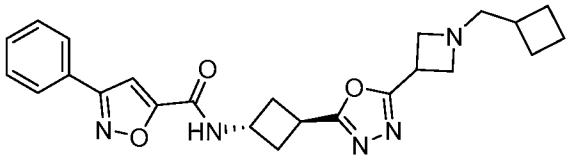

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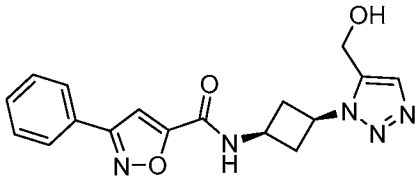

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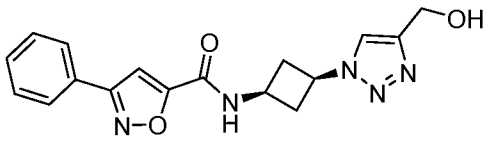

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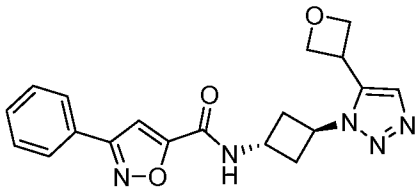

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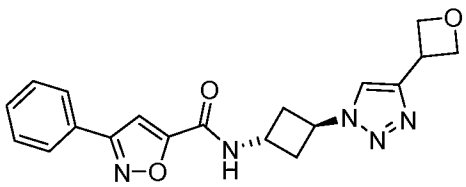

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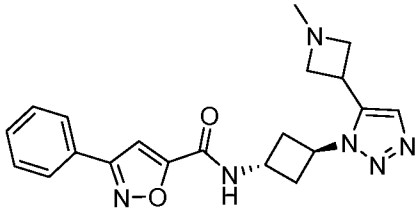

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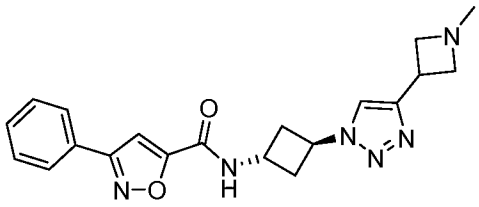

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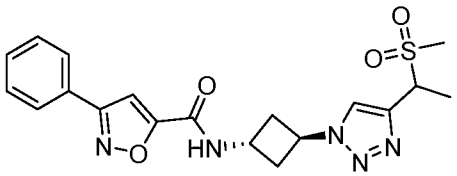

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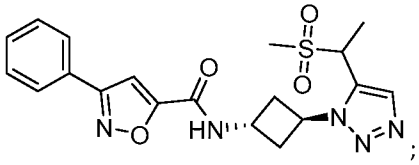

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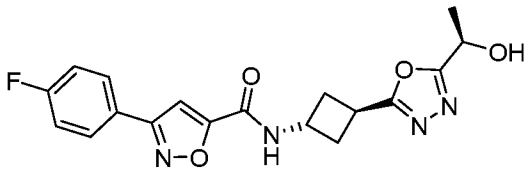

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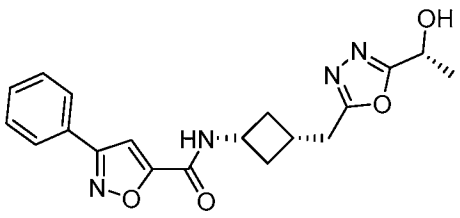

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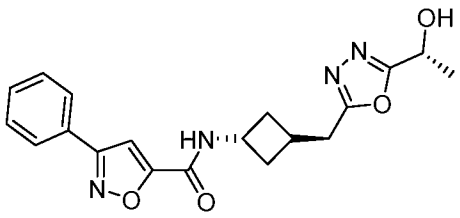

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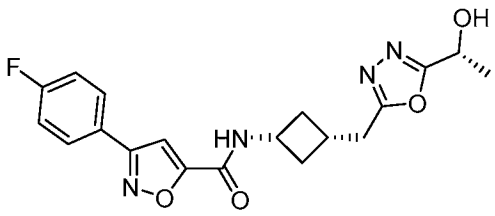

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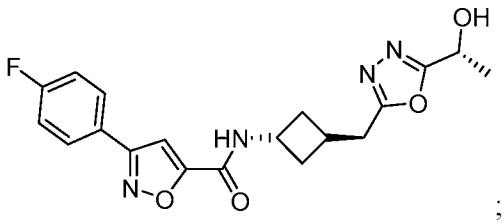

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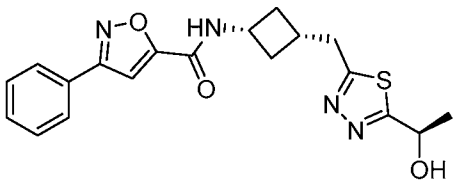

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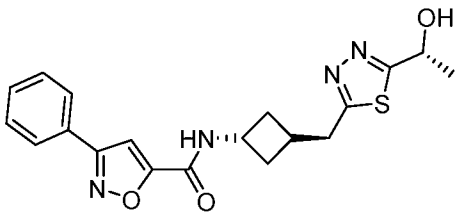

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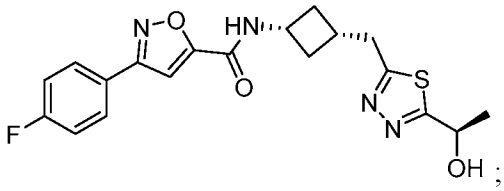

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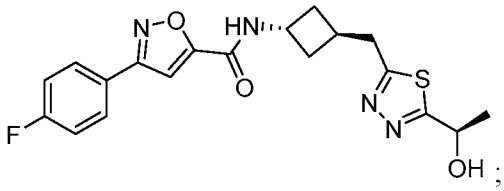

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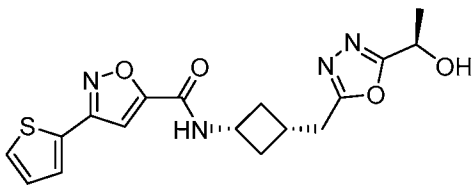

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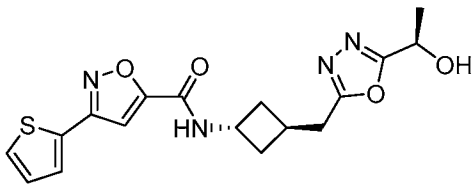

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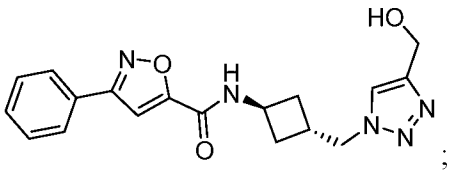

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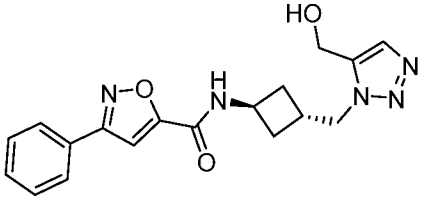

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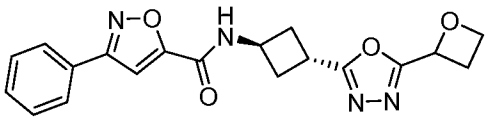

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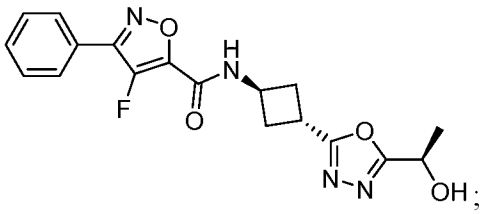

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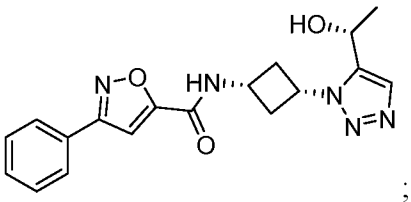

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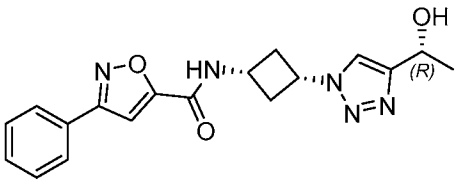

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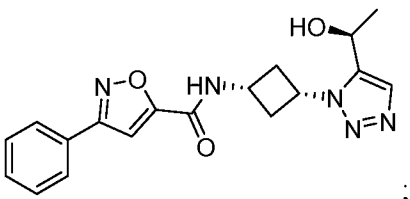

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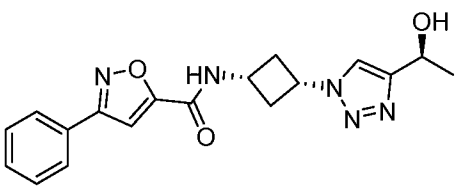

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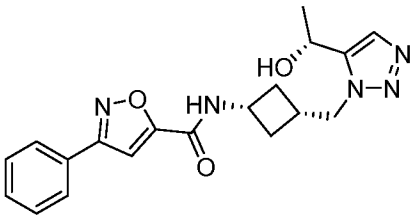

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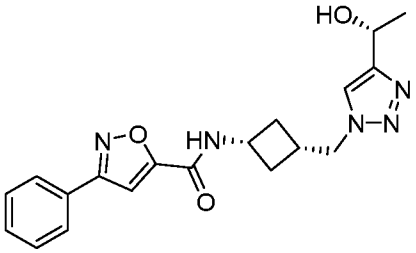

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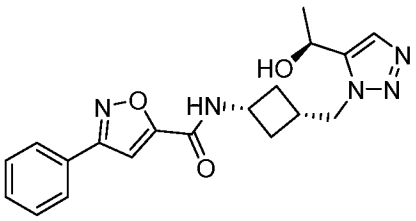

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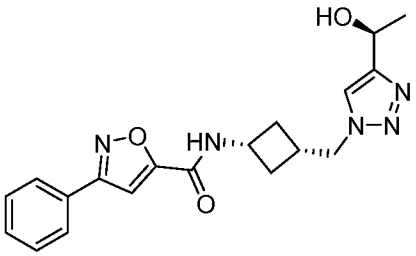

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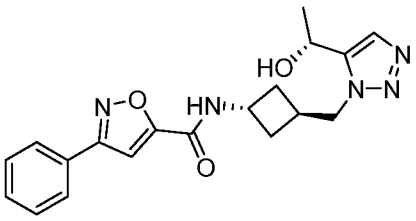

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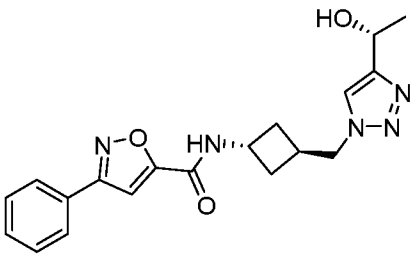

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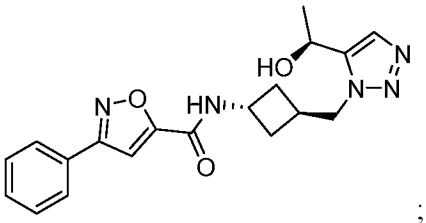

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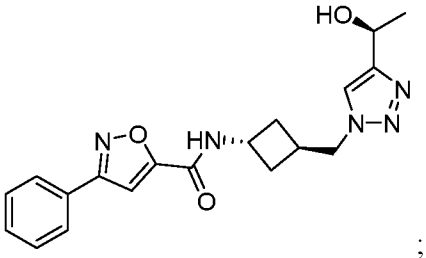

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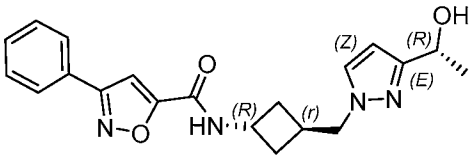

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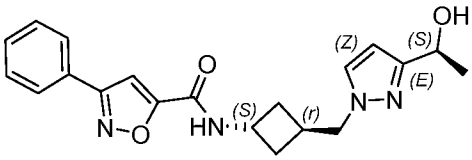

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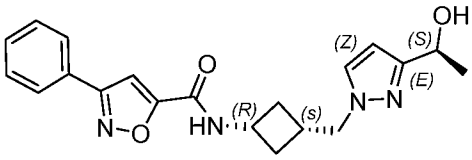

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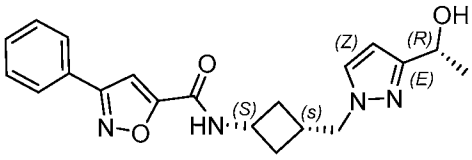

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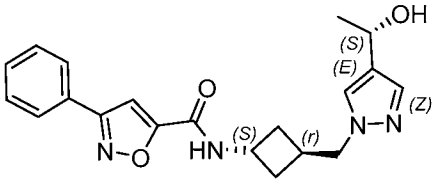

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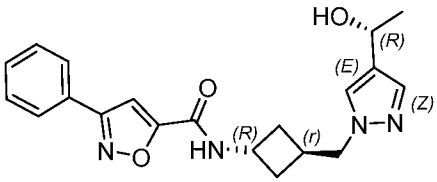

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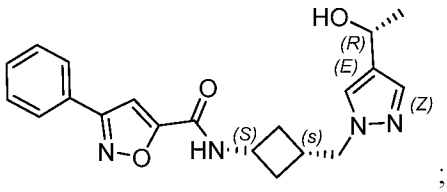

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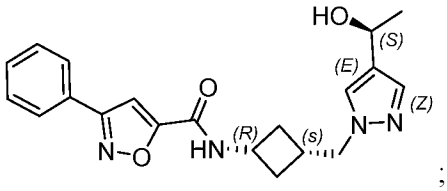

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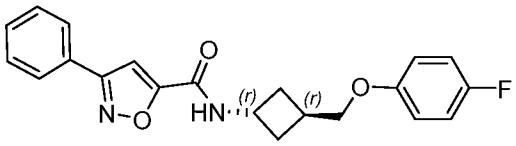

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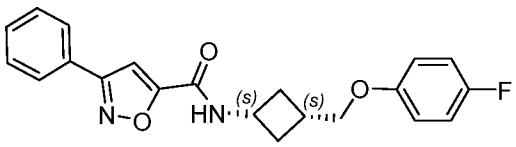

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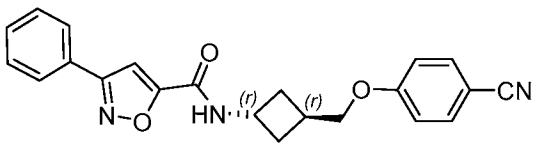

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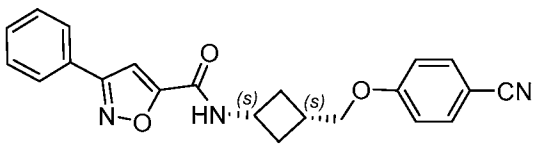

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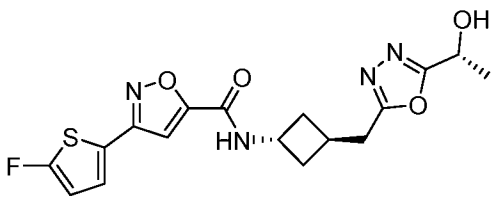

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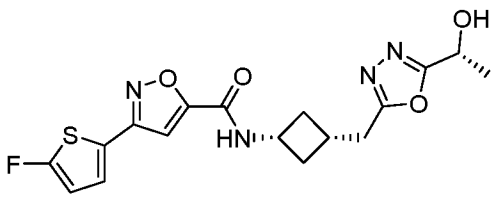

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4 and pharmaceutically acceptable salts thereof; and

5 optionally administering a CFTR potentiator and/or corrector.

11. The method of any one of claims 1- 10, wherein the patient has a ΔF508 mutant gene.

12. The method of any one of claims 1-10, wherein the patient has a homozygote mutation selected from the group consisting of: ΔF508 / ΔF508 or R117H / R117H.

13. The method of any one of claims 1-10, wherein the patient has a heterozygote mutation selected from the group consisting of: ΔF508 / G551D; ΔF508 / A455E; ΔF508 / G542X; Δ508F / W1204X; R553X / W1316X; W1282X/N1303K; F508D/R117H; N1303K/ 3849+10kbC>T; ΔF508/R334W; ΔF508/G178R and 591Δ18 / E831X.

14. The method of any one of claims 1-10, wherein the patient's CFTR genotype includes a Class I, II, III, IV, V or VI mutation.

15. The method of any one of claims 1-10, wherein the patient has one or more mutations in the CFTR gene, wherein the mutations are each selected from the group consisting of: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R , G970R and R117H.

16. The method of any one of claims 1-10, wherein the patient has one copy of a F508del mutation and a second mutation that results in a gating defect in the CFTR protein.

17. The method of claim 16, wherein the patient is heterozygous for F508D and G551D CFTR mutation.

18. The method of any one of claims 1-10, wherein the patient has one copy of a F508del mutation and a second mutation that results in residual CFTR activity.

19. The method of claim 18, wherein the patient has one copy of the F508del mutation and a second mutation that results in residual CFTR protein.

20. The method of any one of claims 1-19, wherein the subject is a human patient.

21. The method of any one of claims 1-20, comprising:

administering to the patient an effective amount of the compound; and

administering ivacaftor.

22. The method of claim 21, further comprising administering one or more of a compound selected from the group consisting of VX-661, VX-152, VX-440, VX-371, and lumacaftor..

23. A method of treating a patient with F508del homozygous CFTR mutation, comprising:

administering to the patient an effective amount of a compound shown in of any one of claims 1 to 10;

administering ivacaftor; and

administering lumacaftor or VX661.

24. A method of treating a patient with a G542X class I CFTR mutation, comprising:

administering to the patient an effective amount of a compound shown in any one of claims 1 to 10; and

optionally administering NB124.

25. A method of treating a patient with a A455E Class V CFTR mutation, comprising:

administering to the patient an effective amount of a compound shown in of any one of claims 1 to 10;

administering ivacaftor; and

administering a CFTR corrector selected from VX-661 and lumacaftor.

26. A method of treating a patient with A455E/F508del CFTR mutation, comprising:

administering to the patient an effective amount of a compound shown in of any one of claims 1 to 10;

administering ivacaftor; and

administering a CFTR corrector selected from VX-661 and lumacaftor.

27. A method of treating a patient with a G551D Class III CFTR mutation, comprising:

administering to the patient an effective amount of a compound shown in of any one of claims 1 to 10;

administering ivacaftor; and

optionally administering a CFTR corrector selected from VX-661 and lumacaftor.

28. A method of treating a patient with G551D/F508del CFTR mutations, comprising:

administering to the patient an effective amount of a compound of shown in of any one of claims 1 to 10;

and optionally administering ivacaftor.

29. A method of treating a patient with 3849 + 10kb C>T/N1303 CFTR mutations, comprising:

administering to the patient an effective amount of a compound of shown in of any one of claims 1 to 10;

and optionally administering ivacaftor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043835

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D405/12 C07D407/12 C07D409/14 C07D413/12
C07D417/12 C07D261/14 C07D307/54 A61K31/42 A61K31/422
A61K31/341 A61P11/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2016/105485 A2 (PROTEOSTASIS THERAPEUTICS INC [US]) 30 June 2016 (2016-06-30) claims 1, 36, 40, 44-48, 59 -----	1-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2016	06/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sáez Díaz, R

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/043835

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016105485 A2	30-06-2016	NONE	