Abstract:

Title:

A61K A61K A61K Avenue, 2 Grafton, Inventors:

M Newtonville, MA 02139 (US); 200 Technology Square, 4th Floor, Cambridge, MA 02139 (US).

Inventors: BASTOS, Cecilia, M; 1 Bigelow Way, South Grafton, MA 01560 (US). MUNOZ, Benito; 377 Lowell Avenue, Newtonville, MA 02460 (US). TAFT, Bradley; 22 Bartlett Street, Maiden, MA 02148 (US).

W 1 O | P C T

(10) International Publication Number

WO 2016/105477 A1

62/102,208 12 January 2015 (12.01.2015) US

(22) International Filing Date:

(26) Publication Language:

International Application Number:

PCT/US2015/000202

English

Agents: KAVANAUGH, Theresa, C. et al; Goodwin Procter LLP, Exchange Place, Boston, MA 02109 (US).


Published:

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

(51) International Patent Classification:

C07D 277/56 (2006.01) A61K 31/4245 (2006.01)
C07D 417/12 (2006.01) A61K 31/425 (2006.01)
A61K 31/341 (2006.01) A61K 31/433 (2006.01)
A61K 31/4155 (2006.01) A61P 11/00 (2006.01)
A61K 31/4178 (2006.01) A61P 37/00 (2006.01)
A61K 31/4192 (2006.01)

(21) International Application Number:

(30) Priority Data:


(72) Inventors: BASTOS, Cecilia, M; 1 Bigelow Way, South Grafton, MA 01560 (US). MUNOZ, Benito; 377 Lowell Avenue, Newtonville, MA 02460 (US). TAFT, Bradley; 22 Bartlett Street, Maiden, MA 02148 (US).

(54) Title: DERIVATIVES OF 5-PHENYL- OR 5-HETEROARYLTHIAZOL-2-CARBOXYLIC AMIDE USEFUL FOR THE TREATMENT OF INTER ALIA CYSTIC FIBROSIS

(57) Abstract: The present disclosure is based, in part, on the discovery that disclosed compounds such as those having Formula (IIa), (III), or (IV) can increase cystic fibrosis transmembrane conductance regulator (CFTR) activity as measured in human bronchial epithelial (hBE) cells.
CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. provisional application serial numbers 62/102,208, filed January 12, 2015, and 62/096,416, filed December 23, 2014, 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 (Wiseman et al.). 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)).

percent of patients have a deletion of phenylalanine (Phe) 508 (AF508) 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 AF508 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+, HC0₃⁻) 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, AF508 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. 201 1 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 can increase cystic fibrosis transmembrane conductance regulator (CFTR) activity as measured in human bronchial epithelial (hBE) cells.
For example, disclosed herein are compounds having the Formula (III) or (IV):

![Formula III](image)

![Formula IV](image)

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

- $X_3$ is selected from the group consisting of $O$, $S$, and $NR_{hh}$;
- $pp$ is 1, 2, or 3;
- $R_{ii}$ is independently selected for each occurrence from the group consisting of hydrogen, halogen, $C_{1-4}$ alkyl (optionally substituted by one, two or three halogens);
- $Li$ is selected from the group consisting of $C_{1-6}$ alkyne, $C_{3-6}$ cycloalkylene, $C_{3-6}$ cycloalkylene-$C_4$ alkyne, $C_{1-3}$ alkyne-$NR_{hh}$-$S(0)_w$-$C_{1-3}$ alkyne-$S(0)_w$-$NR_{hh}$-$C_3$.
- $6$-cycloalkylene-$C_0$-$2$ alkyne-$S(0)_w$-$NR_{hh}$, and $C_{3-6}$ cycloalkylene-$C_0$-$2$ alkyne $NR_{hh}$-$S(0)_w$.

wherein $Li$ may be optionally substituted by one, two or three substituents selected from the group consisting of halogen, hydroxy, $C_{1-3}$ 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, $C_i^a$ alkoxy, 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 the heterocycle and the
heteroaryl may be optionally substituted by one or two substituents each selected independently from $R_{gg}$:

$$R_{gg}$$ is selected for each occurrence from group consisting of halogen, hydroxyl, $\text{C}_i\text{C}_i\text{alkyl}$, $\text{C}_i\text{alkoxy}$, $\text{C}_2\text{alkenyl}$, $\text{C}_3\text{cycloalkyl}$, -$\text{NR}R''$, -$\text{NR}'\text{S}(0)-\text{Ci}_3\text{alkyl}$, $\text{S}(0)-\text{w}^-$

5 $\text{NR}R''$, and -$\text{S}(0)-\text{Ci}_3\text{alkyl}$, where $w$ is 0, 1, or 2, wherein $\text{C}_i\text{alkyl}$, $\text{C}_i\text{alkoxy}$, $\text{C}_2\text{alkenyl}$ and $\text{C}_3\text{cycloalkyl}$ may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxyl, -$\text{NR}R''$, -$\text{NR}'\text{S}(0)-\text{Ci}_3\text{alkyl}$, $\text{S}(0)-\text{w}^-\text{NR}R''$, and -$\text{S}(0)-\text{C}_j\text{alkyl}$;

$$R_{gg}$$ is selected for each occurrence from group consisting of halogen, hydroxyl, $\text{C}_i\text{alkyl}$, $\text{C}_i\text{alkoxy}$, $\text{C}_2\text{alkenyl}$, $\text{C}_3\text{cycloalkyl}$, -$\text{NR}R''$, -$\text{NR}'\text{S}(0)-\text{Ci}_3\text{alkyl}$, $\text{S}(0)-\text{w}^-\text{NR}R''$, and -$\text{S}(0)-\text{C}_j\text{alkyl}$, where $w$ is 0, 1, or 2, wherein $\text{C}_i\text{alkyl}$, $\text{C}_i\text{alkoxy}$, $\text{C}_2\text{alkenyl}$ and $\text{C}_3\text{cycloalkyl}$ may each be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, $\text{C}_i\text{alkyl}$, $\text{C}_i\text{alkoxy}$, hydroxyl, $\text{C}(0)\text{OH}$, -$\text{C}(0)\text{OC}_i\text{alkyl}$, -$\text{O}\text{C}_3\text{cycloalkyl}$, -$\text{O}$-$\text{heterocycle}$, -$\text{O}$-$\text{heteroaryl}$, -$\text{O}$-$\text{phenyl}$, -$\text{NR}R''$, -$\text{NR}'\text{S}(0)-\text{Ci}_3\text{alkyl}$, $\text{S}(0)-\text{w}^-\text{NR}R''$, and -$\text{S}(0)-\text{C}_j\text{alkyl}$; $w$ is 0, 1 or 2; and

$$R_{nb}$$ is selected for each occurrence from the group consisting of $\text{H}$, $\text{C}_i\text{alkyl}$ and $\text{C}_3\text{cycloalkyl}$.

[0008] Also contemplated herein are pharmaceutical compositions that include a disclosed compound such as those compounds having Formula (III) or (IV) and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the compositions can include at least one additional CFTR modulator as described anywhere herein or at least two additional CFTR modulators, each independently as described anywhere herein.

[0009] 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 (III) or (IV).

[0010] In certain of these embodiments, the activity of one or more (e.g., one or two) mutant CFTRs (e.g., AF508, 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+I0A, 3659delC, G85E, D1152H, R560T, R347P, 2184insA, A455E, R334W, Q493X, and 2184delA CFTR) is enhanced (e.g., increased). In certain embodiments, AF508 CFTR activity is enhanced (e.g., increased). In other embodiments, the activities of two mutant CFTRs (e.g., AF508 and G551D; AF508 and A455E; or G542X; A508F) are enhanced (e.g., increased).

[0011] 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-fibrinolysis, 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/hyperinsulémia, Diabetes mellitus, Laron dwarfism, myeloperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type I, 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.

[0012] 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.
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-983, VX-152, VX-440, GLPG2222 and GLPG2665) or 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., VX-809, VX-661, VX-983, VX-152, VX-440, GLPG2222 and GLPG2665) and the other is a CFTR potentiator (e.g., ivacaftor and genistein).

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

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.

As discussed above, the present disclosure is directed in part to compounds as described herein, or a pharmaceutically acceptable salt, prodrug or solvate thereof, and pharmaceutical compositions, methods of increasing CFTR activity and methods of treating cystic fibrosis.

For example, disclosed herein are compounds having the Formula (III) or (IV):
and pharmaceutically acceptable salts, stereoisomers, and prodrugs thereof, wherein:

\[ X_3 \] is selected from the group consisting of O, S, and NR\( _h \);

pp is 1, 2, or 3;

R\( _{ii} \) is independently selected for each occurrence from the group consisting of hydrogen, halogen, C\(_1\)-\(_4\) alkyl (optionally substituted by one, two or three halogens);

L\( _i \) is selected from the group consisting of C\(_{6}\) alkyne, C\(_{3}\)-\(_{6}\) cycloalkylene, C\(_{3}\)-\(_{6}\) cycloalkylene-C\(_{4}\) alkyne, C\(_{1}\)-\(_{3}\) alkyne-NR\( _h \)\( _h \)S(0)\( _w \), C\(_{1}\)-\(_{3}\) alkyne-S(0)\( _w \)-NR\( _h \)\( _h \), C\(_{3}\)-\(_{6}\) cycloalkylene-C\(_{2}\) alkyne-S(0)\( _w \)-NR\( _h \)\( _h \), and C\(_{3}\)-\(_{6}\) cycloalkylene- C\(_{0}\)-\(_{2}\) alkyne\( _w \)NR\( _h \)\( _h \)S(0)\( _w \), wherein L\( _i \) may be optionally substituted by one, two or three substituents selected from the group consisting of halogen, hydroxyl, Ci\(_{-3}\) alkyl (optionally substituted by one, two or three substituents each selected independently from R\(_{ii} \));

R\( _{44} \) is selected from the group consisting of H, halogen, hydroxyl, Ci\(_{-3}\) alkoxy, 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 the heterocycle and the heteroaryl may be optionally substituted by one or two substituents each selected independently from R\(_{gg} \);

R\( _{nr} \) is selected for each occurrence from group consisting of halogen, hydroxyl, Ci\(_{-4}\) alkyl, C\(_{1}\)-\(_{4}\) alkoxy, C\(_{2}\)-\(_{4}\) alkenyl, C\(_{3}\)-\(_{6}\) cycloalkyl, -NR\( ^R \), -NR\( ^R \)S(0)\( _w \)-Ci\(_{-3}\) alkyl, S(0)\( _w \)-
NR'R'', and -S(0) _w_Ci, alkyl, where w is 0, 1, or 2, wherein Ci, alkyl, Ci, alkoxy, C, alkenyl and C, cycloalkyl may be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, hydroxy, -NR'R'', -NR'-S(0) _w_Ci, alkyl, S(0) _w-NR'R'', and -S(0) _w-C, alkyl;

- 8 -

R _gg is selected for each occurrence from group consisting of halogen, hydroxy, C, alkyl, Ci, alkoxy, C, alkenyl, C, cycloalkyl, -NR'R'', -NR'-S(0) _w_Ci, alkyl, S(0) _w-NR'R'', and -S(0) _w-C, alkyl, where w is 0, 1, or 2, wherein Ci, alkyl, Ci, alkoxy, C, alkenyl and C, cycloalkyl may each be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, C, alkyl, C, alkoxy, hydroxy, C(0)OH, -C(0)OCi, alkyl, -0-C, cycloalkyl, -O-heterocycle, -O-heteroaryl, -O-phenyl, -NR'R'', -NR'-S(0) _w-C, alkyl, S(0) _w-NR'R'', and -S(0) _w-C, alkyl;

R _hh is selected for each occurrence from the group consisting of H, Ci, alkyl and C, cycloalkyl.

[0018] In an exemplary embodiment, Li is Ci, alkylene or C, cycloalkylene.

[0019] For example, provided herein is a disclosed compound with the formula:

\[
\begin{align*}
\text{(R , pp) } & \quad \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \\
\text{R & } & \text{R} _{44}
\end{align*}
\]

; wherein qq is 0 or 1.

and pharmaceutically acceptable salts thereof (where R, R, and pp are provided herein).

[0020] For example, a disclosed compound may include those having the structures:
acceptable salts thereof.

[0021] In certain embodiments, R_{44} as provided above, may be selected from the group consisting of: pyrrolidinyl, piperidinyl, tetrahydropyranyl, and tetrahydrofuranyl. In other embodiments, R_{44} is selected from the group consisting of:

wherein X independently for each occurrence is selected from the group consisting of O, S, NR_{5h}, C, C(R_{6h}), and C(R=9)(R_{99}); X_{2} independently for each occurrence is selected from the group consisting of O, S and NR_{5h}; R' is H or C_{1-4} alkyl, each R_{66}, R_{77}, R_{88} and R_{99} is independently selected for each occurrence from H and R_{58}, and n is 0, 1, 2, or 3.

[0022] Each of R_{66}, R_{77}, R_{88} and R_{99}, in certain embodiments, is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxyl, C_{1-4} alkyl, C_{3-6}...
cycloalkyl, and heterocycle, wherein Ci-6 alkyl, C3-6 cycloalkyl, and heterocycle are optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, Ci-6 alkyl, C3ealkoxy (optionally substituted by C3-6 cycloalkyl, heterocycle, -Ci-2 alkyl-heterocycle and Ci-2 alkyl- C3-6 cycloalkyl), -S(0)w-Ci-3 alkyl (w is 0, 1, or 2) and -NR'S(0)wCi-6 alkyl; and R' is independently selected for each occurrence from H and Ci-4 alkyl. As provided herein, pp may be 0, 1 or 2, and/or R11 is selected from H, F, or methyl.

[0023] Also disclosed herein are compounds such as those having the Formula (IIia):

\begin{equation}
\text{(IIia)}
\end{equation}

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

- \( R_1 \) is selected from the group consisting of:

\begin{equation}
R_1 = \begin{cases}
C \quad & k = 1 \\
C \quad & k = 2 \\
C \quad & k = 3 \\
C \quad & k = 4 \\
C \quad & k = 5
\end{cases}
\end{equation}

and

- \( R_2 \) is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl:

\begin{equation}
R_2 = \begin{cases}
R_{61} & \text{if } m = 1 \\
R_{62} & \text{if } m = 2 \\
R_{63} & \text{if } m = 3 \\
R_{64} & \text{if } m = 4
\end{cases}
\end{equation}

- \( R_{3a} \) is selected from the group consisting of hydrogen, optionally substituted Ci-C10 alkyl, optionally substituted C2-C10 alkenyl, optionally substituted C2-C10 alkynyl, optionally substituted C3-C12 cycloalkyl, optionally substituted C3-C12 cycloalkenyl, optionally substituted aryl, halo, ORc, NRjRd, C(0)ORc, NO2, CN, C(0)Rc, C(0)C(0)Rc, 0(0) NRdC(0)Rc,
NRdS(0) n Rc, N(Rd)(COORc), NRdC(0)C(0)Re, NRdC(0)NRdRd, N½s(0)n, N½¾,
NRoS(0)nRc, S(0) n Rc, S(0) n N Rd Rd, OC(0)ORc, (C=NRd)Rc, optionally substituted heterocyclic
and optionally substituted heteroaryl;

R4a is selected from the group consisting of hydrogen, optionally substituted Ci-Ci0
alkyl, optionally substituted C2-Ci0 alkenyl, optionally substituted C2-Ci0 alkynyl, optionally
substituted C3-Ci2 cycloalkyl, optionally substituted C3-Ci2 cycloalkenyl, optionally substituted
aryl, halo, ORc, S(0) n Rc, N½¾, C(0)ORc, N0 2, CN, C(0)Rc, C(0)C(0)Re, C(0)NRdRd,
NRdC(0)Re, NRdS(0)Re, N(Rd)(COORc), NRdC(0)C(0)Re, NRdC(0)NRdRd, NRdS(0)nRdRd,
NRdS(0) n Re, S(0) n NRdRo, OC(0)ORc, (C=NRd)Rc, optionally substituted heterocyclic and
optionally substituted heteroaryl;

R4b is selected from the group consisting of hydrogen, optionally substituted Ci-Ci0
alkyl, optionally substituted C2-Ci0 alkenyl, optionally substituted C2-Ci0 alkynyl, optionally
substituted C3-Ci2 cycloalkyl, optionally substituted C3-Ci2 cycloalkenyl, optionally substituted
aryl, optionally substituted heterocyclic and optionally substituted heteroaryl;

R4a is selected from the group consisting of hydrogen, optionally substituted Ci-Ci0
alkyl, optionally substituted C2-Ci0 alkenyl, optionally substituted C2-Ci0 alkynyl, optionally
substituted C3-Ci2 cycloalkyl, optionally substituted C3-Ci2 cycloalkenyl, optionally substituted
heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, C(0)ORc, C(0)Rc,
C(0)C(0)Re and S(0) n Rc;

or alternatively, R4a and the nitrogen atom to which it is attached is taken together with
an adjacent C(R4b1)(R7j) or C(R4b2)(R7b2) to form an optionally substituted, 4- to 12-membered
heterocyclic ring containing one or more ring nitrogen atoms, wherein said heterocyclic ring
optionally contains one or more ring heteroatoms selected from oxygen and sulfur;

each R4a1 and R4b2 is independently selected from the group consisting of hydrogen,

optionally substituted Cj-Ci0 alkyl, optionally substituted C2-Ci0 alkenyl, optionally substituted
C2-Ci0 alkynyl, optionally substituted C3-Ci2 cycloalkyl, optionally substituted C3-Ci2
cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally
substituted heteroaryl, halo, ORc, NRdRdRd, C(0)ORc, N0 2, CN, C(0)Re, C(0)C(0)Re,
C(0)NRdRd, NRdC(0)Re, NRdS(0)Re, N(Rd-i)(COORc), NRdC(0)C(0)Re, NRdC(0)NRdRd,
NRdS(0)nRdRd, NRdS(0) n Re, S(0) n Re, S(0) n NRdRdj, OC(0)ORc and (C=NRd)Rc; or
alternatively, two geminal R4b1 groups or two geminal R4b2 groups and the carbon to which they
are attached are taken together to form a C(O) group, or yet alternatively, two geminal Rbi
groups or two geminal R_b2 groups are taken together with the carbon atom to which they are
attached to form a spiro C3-C12 cycloalkyl, a spiro C3-C1_2 cycloalkenyl, a spiro heterocyclic, a
spiro aryl or spiro heteroaryl, each optionally substituted;

Y is selected from the group consisting of S(0)_n_, NR_d, N R_d S(0) m, NR_d S(0) n N R_d.

NR_d C(O), NR_d (0) 0, NR_d C (0) C (0), NR_d C (0) NR_d, S(0) n NR_d, and O;

each R is independently selected from the group consisting of hydrogen, optionally
substituted C_1-C_10 alkyl, optionally substituted C_2-C_10 alkenyl, optionally substituted C_2-C_1_0
alkynyl, optionally substituted C_3-C_12 cycloalkyl, optionally substituted C_3-C_12 cycloalkenyl,
optionally substituted heterocyclic, optionally substituted aryl and optionally substituted
heteroaryl;

each ³⁄₄ is independently selected from the group consisting of hydrogen, optionally
substituted C_1-C_10 alkyl, optionally substituted C_2-C_10 alkenyl, optionally substituted C_2-C_1_0
alkynyl, optionally substituted C_1-C_10 alkoxy, optionally substituted C_3-C_12 cycloalkyl,
optionally substituted C_3-C_12 cycloalkenyl, optionally substituted heterocyclic, optionally
substituted aryl and optionally substituted heteroaryl; or two geminal R_d groups are taken
together with the nitrogen atom to which they are attached to form an optionally substituted
heterocyclic or an optionally substituted heteroaryl;

k is 0 or 1;

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

each n is independently 0, 1 or 2.

[0024] In some embodiments, m is 0, 1 or 2 (e.g., m is 1). In some embodiments, k is 0. In
some embodiments, m is 0, 1 or 2, and k is 0. In other embodiments, m is 1, and k is 0.

[0025] In some embodiments, R_d is hydrogen.

[0026] In some embodiments, R_a is hydrogen or C_1-C_4 alkyl (optionally substituted by 1, 2
or 3 halogens).

[0027] In some embodiments, each of R_b1 and R_b2 is independently selected from hydrogen,
hydroxyl, d’alkoxy (optionally substituted by one, two or three substituents independently
selected from halogen and hydroxyl) and C_1-C_4 alkyl (optionally substituted by one, two or
three substituents independently selected from halogen, hydroxyl, and C\textsubscript{i}-C\textsubscript{4} alkoxy). In certain embodiments, \( R_1 \), and \( R_2 \) for each occurrence are hydrogen.

**[0028]** In some embodiments, \( R_2 \) is selected from the group consisting of phenyl and a 5-6 membered heteroaryl having one or two heteroatoms each selected from N, S, and O, wherein \( R_2 \) is optionally substituted by one or two substituents each independently selected from the group consisting of halogen and C\textsubscript{1}-C\textsubscript{4} alkyl (optionally substituted by one, two or three halogens).

**[0029]** In certain embodiments, \( R_2 \) is phenyl. In other embodiments, \( R_2 \) is phenyl is substituted with one or two \( R_5 \), wherein each \( R_5 \) is independently selected from the group consisting of optionally substituted C\textsubscript{1}-C\textsubscript{6} alkyl, optionally substituted C\textsubscript{2}-C\textsubscript{10} alkenyl, optionally substituted C\textsubscript{2}-C\textsubscript{10} alkynyl, and halo.

**[0030]** In other embodiments, \( R_2 \) is selected from the group consisting of optionally substituted thienyl, optionally substituted furanyl and optionally substituted pyridinyl.

**[0031]** In some embodiments, \( R_{6a} \) is selected from the group consisting of optionally substituted C\textsubscript{i}-C\textsubscript{6} alkyl, optionally substituted C\textsubscript{3}-C\textsubscript{7} cycloalkyl, phenyl, OR\(_c\), C(0)OR\(_c\), C(0)R\(_c\), optionally substituted heterocycle and optionally substituted heteroaryl, wherein \( R_e \) is selected independently for each occurrence, from the group consisting of H and C\textsubscript{i}-C\textsubscript{6} alky.

**[0032]** In certain embodiments \( R_{6a} \) is a heterocycle, or a 5-6 membered monocyclic or a 8-10 membered bicyclic heteroaryl having one, two or three heteroatoms selected from N, S or O, wherein the heterocycle or heteroaryl is optionally substituted by one, two or three substituents independently selected for each occurrence from the group consisting of halogen, C\textsubscript{i}-alkyl (optionally substituted by one, two or three substituents each independently selected from halogen, hydroxyl, and hydroxyl), C\textsubscript{i}alkoxy (optionally substituted by one, two or three halogens), hydroxyl, and NR\(_d\)R\(_d\) wherein \( R_d \) is independently for each occurrence selected from H and C\(_i\). 4 alkyl, or the two \( R_{6d} \) taken together with the N to which they are attached form a heterocyclic ring. For example, \( R_{6a} \) can be selected from the group consisting of tetrahydropyranyl, thiadiazolyl, tetrahydro furanyl, and morpholinyl. As another example, \( R_{6a} \) can be a monocyclic heteroaryl containing one, two or three ring nitrogen atoms. As a further example, \( R_{6a} \) can be
selected from the group consisting of furanyl, pyridinyl, pyrazinyl, pyrazolyl, imidazolyl, isoxazolyl, triazolyl, thiazolyl, oxadiazolyl, thia Diazolyl, thienyl, piperazinyl, and benzimidazolyl, each optionally substituted.

[0033] In certain embodiments, $R_4$ is selected from the group consisting of:

wherein each $X$ is independently O, S or NR$_g$;

each $R_g$ is independently selected from the group consisting of hydrogen, C1-C4 alkyl, C3-C6 cyclo alkyl; and

each $R_6, R_7$ and $R_8$ is independently selected for each occurrence from the group consisting of hydrogen, C1-C6 alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_{16}$ alkynyl, C3-C7 cycloalkenyI, phenyl, heterocycle, heteroaryl, halo, hydroxyl, carboxyl, OR$_c$, NR$_dR_d$, C(0)OR$_c$, CN, C(0)Re, wherein the C$_i$-$alkyl, C$_2$-$C$_6$ alkenyl, C$_2$-$Cl$_6$ alkynyl, C3-C7 cycloalkenyl, C3-C7 cycloalkenyl, phenyl, heterocycle, and heteroaryl of $R_6$, $R_7$ and $R_8$ may each be optionally substituted by one, two or three substituents selected from halo, hydroxyl, C$_1$-$alkyl and C$_i$-$alkoxy;

$R_c$ is C$_i$-$alkyl; and
Rd is independently for each occurrence selected from the group consisting of H and C₁₄ alkyl, or the two RdS taken together with the N to which they are attached form a heterocyclic ring.

[0034] In certain embodiments, Rd is an optionally substituted C₃-C₇ cycloalkyl (e.g., optionally substituted cyclopropyl or an optionally substituted cyclobutyl).

[0035] In certain of these embodiments, Rd is substituted with a substituent having the formula:

\[
\begin{array}{c}
\text{R}_n \\
\text{R}_n \\
\text{R}_9
\end{array}
\]

wherein each Rh is independently selected for each occurrence from the group consisting of hydrogen, halo, hydroxyl, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, or two geminal Rh groups are independently taken together with the carbon atom to which they are attached to form an optionally substituted carbocyclic or heterocycle;

Rd is selected from the group consisting of hydrogen, halo, CN, hydroxyl, methyl (optionally substituted by one, two or three substituents selected from halogen and hydroxyl), C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₁₄ alkoxy, NRdRj, C(0)ORc, N₂O, CN, C(0)Re, C(0)C(0)Re, C(0)NRdRd, NRdC(0)Re, NRdS(0)Re, NRd(COORc), NRdC(0)C(0)Re, N R₄C(0)NRdRd, NRdS(O)R₄NRdRd₄, NRdS(0)₄Re, s(0)₄Re, s(0)₄NRdRd, o C(0)ORc, (C=NRd)Re;

Rc is independently selected for each occurrence from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, heterocycle, and heteroaryl;

Rd is independently selected for each occurrence from H and C₁₄ alkyl, or the two RJS taken together with the N to which they are attached form a heterocyclic ring; and p is 0, 1, or 2.

[0036] For example, Rd can be selected from the group consisting of:
wherein

\[ \text{each } R_i \text{ is independently selected from the group consisting of hydrogen, optionally substituted } \\ C_1-C_6 \text{ alkyl, optionally substituted } C_2-C_6 \text{ alkenyl, optionally substituted } C_2-C_6 \text{ alkynyl, optionally substituted } C_3-C_6 \text{ cycloalkyl, optionally substituted } C_3-C_6 \text{ cycloalkenyl, optionally substituted aryl, halo, } O \text{Re, NR}_{<}j \text{Rd, C}(0)ORc, NO_2, CN, C(0)Re, C(0)C(0)Re, C(0)NRdR<, NRdC(0)Re, NRdS(0)_{<}N_{<}RdRe, NRd(COO)Re, NRdC(0)C(0)Re, NRdC(O)NRdRd, NRdS(0)_{<}N_{<}RdRd, NRdS(0)_{<}N_{<}RdRd, ORc, C=NR_{<}d \text{Re, optionally substituted heterocyclic and optionally substituted heteroaryl; alternatively, two geminal } R_i \text{ groups are taken together with the carbon atom to which they are attached to form a spiro } C_3-C_7 \]

\[ \text{cycloalkyl, a spiro } C_3-C_7 \text{ cycloalkenyl, a spiro heterocyclic, a spiro aryl or spiro heteroaryl, each optionally substituted; or yet alternatively, two vicinal } R_i \text{ groups are taken together with the carbon atoms to which they are attached to form a fused, optionally substituted cyclic group selected from the group consisting of } C_4-C_8 \text{ cycloalkyl, } C_4-C_8 \text{ cycloalkenyl, 4- to 8-membered heterocyclic, aryl and heteroaryl, each optionally substituted; or further alternatively, two } R_i \text{ groups attached to non-adjacent carbon atoms are taken together with the carbon atoms to which they are attached to form a bridged cyclic group selected from the group consisting of } C_3-C_8 \text{ cycloalkyl, } C_3-C_8 \text{ cycloalkenyl, and 4- to 8-membered heterocyclic, each optionally substituted; } \]

\[ \text{each } R_h \text{ is independently selected from the group consisting of hydrogen, halo, optionally substituted } C_1-C_{10} \text{ alkyl, and optionally substituted } C_3-C_6 \text{ cycloalkyl, or two geminal } R_h \text{ groups are independently taken together with the carbon atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl; } \]
R.9 is selected from the group consisting of hydrogen, optionally substituted C1-C10 alkyl, optionally substituted C2-C10 alkenyl, optionally substituted C2-C10 alkynyl, optionally substituted C3-C12 cycloalkyl, optionally substituted C3-C12 cycloalkenyl, optionally substituted ary1, halo, ORc, N3¾, C(0)ORc, NO2, CN, C(0)Rc, C(0)C(0)Rc, C(0)NRdRd, N3¾O(0)¾.

In some embodiments, Y is S, S(0) ½ or S(0) ½ NRd.<

In some embodiments, R4b is heterocycle or a 5-6 membered monocyclic or a 8-10 membered bicyclic heteroaryl having one, two or three heteroatoms selected from N, S or O, wherein the heterocycle or heteroaryl are optionally substituted by one, two or three substituents independently selected for each occurrence from the group consisting of halogen, Cl3alkyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), Qalkoxy (optionally substituted by one, two or three halogens), hydroxyl, and NRdRd wherein Rd is independently for each occurrence selected from H and C1.3alkyl, or the two Rd taken together with the N to which they are attached form a heterocyclic ring). For example, R.9 can be selected from the group consisting of furanyl, pyridinyl, pyrazinyl, pyrazolyl, imidazolyl, isoxazolyl, triazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, thienyl, piperazinyl, and benzimidazolyl, each optionally substituted.

Exemplary compounds are shown below in Table 1:

### Table 1

<table>
<thead>
<tr>
<th>#</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Also contemplated herein are pharmaceutical compositions that include a disclosed compound such as those compounds having Formula (IIa), (III), or (IV) and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the compositions can

<table>
<thead>
<tr>
<th></th>
<th><img src="image1" alt="Chemical Structure" /></th>
<th><img src="image2" alt="Chemical Structure" /></th>
<th><img src="image3" alt="Chemical Structure" /></th>
<th><img src="image4" alt="Chemical Structure" /></th>
<th><img src="image5" alt="Chemical Structure" /></th>
<th><img src="image6" alt="Chemical Structure" /></th>
<th><img src="image7" alt="Chemical Structure" /></th>
<th><img src="image8" alt="Chemical Structure" /></th>
<th><img src="image9" alt="Chemical Structure" /></th>
<th><img src="image10" alt="Chemical Structure" /></th>
<th><img src="image11" alt="Chemical Structure" /></th>
<th><img src="image12" alt="Chemical Structure" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td><img src="image9" alt="Chemical Structure" /></td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td><img src="image11" alt="Chemical Structure" /></td>
<td><img src="image12" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>
include at least one additional CFTR modulator as described anywhere herein or at least two additional CFTR modulators, each independently as described anywhere herein.

[0041] It is to be understood that the specific embodiments described herein can be taken in combination with other specific embodiments delineated herein. For example, as discussed above, in some embodiments, R\textsubscript{2a} is fluoro, and in some embodiments described above, A is an optionally substituted imidazolyl or pyrazolyl. The disclosure thus contemplates for example, a compound of Formula (III), (III), or (IV), wherein R\textsubscript{2a} is fluoro and A is an optionally substituted imidazolyl or pyrazolyl.

[0042] The features and other details of the disclosure will now be more particularly described. Before further description of the present invention, 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.

[0043] It will be appreciated that the description of the present invention herein should be construed in congruity with the laws and principals of chemical bonding.

[0044] 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\textsubscript{i-j} 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\textsubscript{i-j} alkyl, C\textsuperscript{a}alkyl, and C\textsubscript{g}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.

[0045] 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\textsubscript{2-6}alkenyl, and C\textsuperscript{a}alkenyl,
respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

[0046] 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.

[0047] The term "cycloalkyl," 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.

[0048] The term "cycloalkenyl," 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.

[0049] The term "cycloalkynyl," 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.

[0050] "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.

[0051] 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\textsubscript{i}-alkoxy, and C\textsubscript{2}-alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isoproxy, etc.

[0052] 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, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piprazine, oxetane, azetidine, tetrahydrofuran or dihydrofuran, etc.

[0053] Cycloalkyl, cycloalkenyl, and 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.

[0054] 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, tetrahyronaphthyl, 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, naphthyl and substituted naphthyl.

[0055] 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. Heteroaryl groups 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, indoliziny1, phthalazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzo thiophenyl, benzotriazolyl, benzo thiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinoliny1, tetrahydroquinolyl, dihydroisquinolyl, tetrahydroisoquinolyl, benzofuranyl, furazanyl, pyr rolepyrimidinyl, 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.

[0056] 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, -Ci-Ci alkyl, -C2-C12 alkenyl, -C2-Ci2 alkynyl, -C3-C12 cycloalkyl, -C3-Ci2 cycloalkenyl, C3-C12 cycloalkynyl, heterocyclic, -F, -Cl, -Br, -I, -OH, -N02, -N3, -CN, -NH2, oxo, thioxo, -NHRX, NR2X ary1, -arylalkyl, -heteroarylalkyl, -heterocyclic, -F, -Cl, -Br, -I, -OH, -N02, -N3, -CN, -NH2, oxo, thioxo, -NHRX, NR2X dialkylamino, -diarylamino, -diheteroarylamino, -ORX, -C(0)Ry, -C(0)C(0)Ry, -OC02Ry, -OC(0)Ry, OC(0)C(0)Ry, -NHC(0)Ry, -NHC02Ry, -HNC(0)C(0)Ry, -HNC(0)C(0)Ry, -HNC(0)C(0)Ry, -HNC(0)C(0)Ry.

[0057] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.
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.

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

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, and "O" is the symbol for oxygen. "Me" is an abbreviation for methyl.

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 disclosed 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.

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.
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."

Individual enantiomers and diastereomers of disclosed compounds 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.
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.

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.

The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and both solvated and unsolvated forms are contemplated herein. In one embodiment, a disclosed compound may be amorphous or a single polymorph. In another embodiment, a disclosed compound is a mixture of polymorphs. In another embodiment, a disclosed compound is in a crystalline form.

Isotopically labeled compounds are also contemplated herein, 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 disclosed compounds 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, $^{7}$Li, $^{32}$P, $^{35}$S, $^{18}$F, and $^{36}$Cl, respectively. For example, a disclosed compound may have one or more H atom replaced with deuterium.

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 preferred 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 preferred in some circumstances. Isotopically labeled compounds 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.

[0070] In some embodiments one or more of the nitrogen atoms of a disclosed compound if present are oxidized to N-oxide.

[0071] Representative synthetic routes for the preparation of the compounds disclosed herein are provided throughout the Examples section. As will be understood by the skilled artisan, diastereomers can be separated from the reaction mixture using column chromatography.


[0073] As discussed above, contemplated herein in an embodiment is a method of increasing CFTR activity in a subject comprising administering an effective amount of a disclosed compound. Also contemplated herein is 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.

[0074] "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.

[0075] 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 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.

[0076] 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.

[0077] 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, \text{HCO}_3^-\text{transport}). In certain of these embodiments, the activity of one or more (e.g., one or two) mutant CFTRs (e.g., AF508, S549N, G542X, G551D, R117H, N1303K, W1282X, R553X, 621+1G>T, 1717-1OA, 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., AF508 / AF508 and R117H / R117H) and compound heterozygote mutations (e.g., AF508 / G551D; AF508 / A455E; AF508 / G542X; A508F / W1204X; R553X / W1316X; W1282X/N1303K, 591Δ18 / E831X, F508del/R1 17H/N1303K/3849+10kbOT; Δ303K/384; and DF508/G178R).

[0078] In certain embodiments, the mutation is a Class I mutation, e.g., a G542X; a Class II / I mutation, e.g., a AF508 / 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 AF508 / 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 AF508 / A455E compound heterozygous mutation. Of the more than 1000 known mutations of the
CFTR gene, AF508 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, AF508 CFTR activity is enhanced (e.g., increased). In certain embodiments, AF508 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).

[0079] As discussed above, a method of treating cystic fibrosis is also provided comprising administering a disclosed compound. Methods of treating other conditions associated with CFTR activity, including conditions associated with deficient CFTR activity are in an embodiment, contemplated herein.

[0080] 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 disclosed compound e.g., of Formula (IIa), (III), or (IV) 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, Αβ-lipoproteinemia, lysosomal storage disease, type I chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type I hereditary angioedema, coagulation-fibrinolysis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, and Sjogren's syndrome.

[0081] 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), 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-[(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), GLPG 2665, 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, and compounds described in, e.g., WO2014/045283; WO20 14/08 1821, WO20 14/08 1820, WO2014/152213; WO20 14/1 60440, WO2014/160478, US2014027933; WO20 14/0228376, WO20 13/038390, WO20 1 1/1 13894, WO201 3/038386; and WO2014/1 80562, 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-(IH-imidazol-1-yl) phenyl)-1-(4-carbamoyl-2-methylphenyl)-1'H-pyrrol-2-yl) propanoic acid), CTX-4430, N 1861, N 1785, and N 91115.

[0082] 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, GLPG2222 and GLPG2665) or potentiator (e.g., ivacaftor, genistein and GLPG 1837). 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-983, VX-152,
and VX-440) 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 or GLPG2665) 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).

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, GLPG2665, 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 or GLPG2665, 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., AF508 / AF508 or R117H / R117H) and/or one or more compound heterozygote mutations (e.g., AF508 / G55 ID; AF508 / A455E; AF508 / G542X; A508F / W1204X; R553X / W1316X; W1282X/N1303K; F508del/R1 17H; N1303K/ 3849+1 OkbOT; AF508/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 AF508 / G542X compound heterozygous mutation. In other embodiments, the subject's CFTR genotype includes a Class III mutation, e.g., a G55 ID Class III mutation, e.g., a AF508 / G55 ID 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 AF508 / A455E compound heterozygous
mutation. In certain embodiments, AF508 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.

<table>
<thead>
<tr>
<th>Class</th>
<th>Effect on CFTR protein</th>
<th>Example of mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Shortened protein</td>
<td>W1282X Instead of inserting the amino acid tryptophan (W), the protein sequence is prematurely stopped (indicated by an X).</td>
</tr>
<tr>
<td>II</td>
<td>Protein fails to reach cell membrane</td>
<td>ΔF508 A phenylalanine amino acid (F) is deleted</td>
</tr>
<tr>
<td>III</td>
<td>Channel cannot be regulated properly</td>
<td>G551D A “missense” mutation: instead of a glycine amino acid (G), aspartate (D) is added</td>
</tr>
<tr>
<td>IV</td>
<td>Reduced chloride conductance</td>
<td>R117H Missense</td>
</tr>
<tr>
<td>V</td>
<td>Reduced due to incorrect splicing of gene</td>
<td>3120+1G&gt;A Splice-site mutation in gene intron 16</td>
</tr>
<tr>
<td>VI</td>
<td>Reduced due to protein instability</td>
<td>N287Y a A -&gt;T at 991</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Description</th>
<th>Possible Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A508F / A508F</td>
<td>homozygote</td>
<td>Severe lung disease, pancreatic insufficient</td>
</tr>
<tr>
<td>R117H / R117H</td>
<td>homozygote</td>
<td>Congenital bilateral absence of the vas deferens, No lung or pancreas disease,</td>
</tr>
<tr>
<td>WT / A508F</td>
<td>heterozygote</td>
<td>Unaffected</td>
</tr>
<tr>
<td>WT / 3120+1 G&gt;A</td>
<td>heterozygote</td>
<td>Unaffected</td>
</tr>
<tr>
<td>Compound Heterozygote</td>
<td>No Lung Disease, Pancreatic Insufficient</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------------</td>
<td></td>
</tr>
<tr>
<td>A508F / W1204X</td>
<td>compound heterozygote</td>
<td></td>
</tr>
<tr>
<td>R553X and W1316X</td>
<td>compound heterozygote</td>
<td></td>
</tr>
<tr>
<td>591 Δ18 / E831X</td>
<td>compound heterozygote</td>
<td></td>
</tr>
</tbody>
</table>

[0084] For example, provided herein is a method of treating a patient having one or more of the following mutations in the CFTR gene: \textit{G1244E, G1349D, G178R, G551S, S125IN, 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 AF508 mutation and a second mutation that results in a gating effect in the CFTR protein (e.g., a patient that is heterozygous for AF508 and G551D mutation), a patient with one copy of the AF508 mutation and a second mutation that results in residual CFTR activity, or a patient with one copy of the AF508 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., AF508 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.

[0085] 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 AF508 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.
[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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,l'-methylene-Z>ω-(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.

In an embodiment, methods provided herein may include administering prodrugs of the compounds described herein, for example, prodrugs of a compound of Formula (IIa), (III), or (IV), or a pharmaceutical composition thereof or method of use of the prodrug.

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 disclosed compound 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 (C1-8)alkyl, (C2-12)alkylcarbonyloxymethyl, 1-(alkylcarbonyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkylcarbonyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxy carbonyloxymethyl 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-(Ci-2)alkylamino(C$_2$,$_3$)alkyl (such as β-dimethylaminoethyl), carbamoyl-(Ci-2)alkyl, N,N-di(Ci-2)alkylcarbamoyl-(Ci-2)alkyl and piperidino-, pyrrolidino- or morpholino-alkylcarbonyl.

[0092] Similarly, if a disclosed compound 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 (Ci-6)alkylcarbonyloxymethyl, 1-((Ci-6)alkylcarbonyloxy)ethyl, 1-methyl-1-(Ci-6)alkylcarbonyloxyethyl (Ci-6)alkylcarbonyloxymethyl, N-(Ci-6)alkylcarbonyloxymethyl, succinoyl, (Ci-6)alkylcarbonyl, a-amino(Ci-4)alkylcarbonyl, arylalkylcarbonyl and a-aminoarylalkylcarbonyl, or a-aminoarylalkylcarbonyl-a-aminoarylalkylcarbonyl, where each a-aminoarylalkylcarbonyl group is independently selected from the naturally occurring L-amino acids, P(0)(OH)$_2$, -P(0)(0 (Ci-6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0093] If a disclosed compound 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 Simplicio, et al., Molecules 2008, 13, 519 and references therein.

[0094] Also contemplated in certain embodiments is the use of clathrates of the compounds described herein, pharmaceutical compositions comprising the clathrates, and methods of use of the clathrates. Clathrates of a disclosed compound, e.g., Formula (IIa), (III), or (IV), or a pharmaceutical composition thereof are contemplated.

[0095] As discussed above, the disclosure also contemplates 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 therof, 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 preferred for treatment of a systemic disorder and oral administration may be preferred 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, pharmaceutical ly-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).

[0096] Disclosed compositions may 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.

[0097] 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 preferred liquid carriers, particularly for injectable solutions.

[0098] 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: 97-1 19, 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.

[0099] 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%, preferably 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

[0100] 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.

[0101] 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.

[0102] 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.

[0103] 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.

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°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.

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

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 invention, "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.

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.

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, and defective protein trafficking or protein degradation. For example, the disclosure in some embodiments contemplates administering a disclosed compound 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. For example, a disclosed compound may correct 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 AF508 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, a-galactosidase A, cysteine transporter, acid ceramidase, acid a-L-fucosidase, protective protein, cathepsin A, acid β-glucosidase, acid β-galactosidase, iduronate 2-sulfatase, a-L-iduronidase, galactocerebrosidase, acid a-L-mannosidase, acid β-L-mannosidase, arylsulfatase B, arylsulfatase A, N-acetylgalactosamine-6-sulfate sulfatase, acid β-L-galactosidase, N-acetylgalactosamine-1-phosphotransferase, acid sphingomyelinase, NPC-1, acid cc-glucosidase, β-hexosamidine B, heparin N-sulfatase, a-N-acetylglucosaminidase, a-glucosaminide N-acetyltransferase, N-acetylgalactosamine-6-sulfate sulfatase, a-N-acetylgalactosaminidase, a-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 compounds of e.g., Formula (IIia), (IIi), or (IV) may be used to restore proteostasis (e.g., correct folding and/or alter trafficking) of the proteins described above.

[0109] 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, tauopathies (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, lysoyzme 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 Paugt 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 pallidolusysian 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 Αβ 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.

[0110] 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, Galactosialidosis, Gaucher’s disease (including Types 1, 2 and 3), GmI 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] In yet additional embodiments, a disclosed method 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, a contemplated method 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.

Additional conditions associated with a dysfunction of proteostasis include hemoglobinopathies, inflammatory diseases, intermediate filament diseases, drug-induced lung damage and hearing loss. For example, provided herein are 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). In another embodiment, methods for treating hearing loss, such as noise-induced hearing loss, aminoglycoside-induced hearing loss, and cisplatin-induced hearing loss comprising administering a disclosed compound are provided.

Additional conditions include those associated with a defect in protein trafficking and that can be treated include: PGP mutations, hERG trafficking mutations, nephronogenic diabetes insipidus mutations in the arginine-vasopressin receptor 2, persistent hyperinsulinemic hypoglycemia of infancy (PHH1) mutations in the sulfonlyurea receptor 1, and alAT.

The invention is illustrated by the following examples which are not meant to be limiting in any way.

EXEMPLIFICATION

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 invention.

**Example 1: 5-phenyl-N-((tetrahydrofuran-2-yl)methyl)thiazole-2-carboxamide**

![Chemical structure](image)

[0119] HOBt (0.11 g, 0.8 mmol) and EDC·HCl (0.20 g, 1.1 mmol) were added to a solution of 5-phenylthiazole-2-carboxylic acid (0.15 g, 0.73 mmol) in THF (5 mL) followed by the addition of (tetrahydro-furan-2-yl)-methylamine (0.15 g, 1.4 mmol) and stirred at room temperature for 12 h. Volatiles were removed under vacuum and crude was dissolved in DCM. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford crude product. The crude was purified by combiflash chromatography using EtOAc in hexane to obtain the product (90 mg, 43%) as off white solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.97 (s, 1H), 7.60-7.59 (m, 2H), 7.53 (brs, 1H), 7.44-7.38 (m, 3H), 4.09-4.06 (m, 1H), 3.94-3.88 (m, 1H), 3.80-3.75 (m, 1H), 3.74-3.68 (m, 1H), 3.45-3.38 (m, 1H), 2.03-1.98 (m, 1H), 1.95-1.89 (m, 2H), 1.64-1.58 (m, 1H); LC-MS: [M+H]$^+$ 289.1; HPLC Purity: 99.85% at 254 nm and 99.85% at 220 nm.

**Example 2: N-(2-methoxyethyl)-5-phenylthiazole-2-carboxamide**

![Chemical structure](image)

[0120] The product was prepared using the procedure described in example 1. The crude was purified by combiflash chromatography using EtOAc in hexane to obtain the product (30 mg, 16%) as white solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.98 (s, 1H), 7.60-7.58 (m, 2H), 7.53 (br, 1H), 7.49-7.38 (m, 3H), 3.67-3.62 (m, 2H), 3.59-3.55 (m, 2H), 3.39 (s, 3H); LC-MS: [M+H]$^+$ 263.0; HPLC Purity: 99.62% at 254 nm and 99.68% at 220 nm.

**Example 3: N-(2-morpholinoethyl)-5-phenylthiazole-2-carboxamide**

![Chemical structure](image)
[0121] The product was prepared using the procedure described in example 1. The crude was purified by preparative HPLC obtain the product (85 mg, 37%) as off white solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.99 (s, 1H), 7.62 (bs, 1H), 7.60-7.58 (m, 2H), 7.45-7.35 (m, 3H), 3.75-3.72 (m, 4H), 3.59-3.54 (m, 2H), 2.61-2.58 (m, 2H), 2.58-2.48 (m, 4H); LC-MS: [M+H]$^+$ 317.8; HPLC Purity: 97.36% at 254 nm and 97.87% at 220 nm.

Example 4: N-(3-(1H-imidazol-1-yl)propyl)-5-phenylthiazole-2-carboxamide

[0122] The product was prepared using the procedure described in example 1. The crude was purified by preparative HPLC obtain the product (92 mg, 40%) as white solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.98 (s, 1H), 7.60-7.58 (d, $J = 6.8$ Hz, 2H), 7.52 (s, 1H), 7.45-7.36 (m, 3H), 7.34-7.30 (m, 1H), 7.07 (s, 1H), 6.97 (s, 1H), 4.07-4.04 (t, $J = 7.0$ Hz, 2H), 3.51-3.46 (m, 2H), 2.17-2.10 (m, 2H); LC-MS: [M+H]$^+$ 312.9; HPLC Purity: 99.89% at 254 nm and 99.74% at 220 nm.

Example 5: N-(3-(1-methyl-1H-pyrazol-5-yl)propyl)-5-phenylthiazole-2-carboxamide

[0123] The product was prepared using the procedure described in example 1. The crude was purified by column chromatography using flash silica gel eluted with 50% EtOAc in hexane to afford (0.15 g, 36.27%) as off white solid; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.97 (s, 1H), 7.60-7.58 (m, 2H), 7.45-7.37 (m, 4H), 7.30 (br, 1H), 6.06 (s, 1H), 3.79 (s, 3H), 3.58-3.53
Example 6: N-(2-(5-(hydroxymethyl)-1,3,4-thiadiazol-2-yl)ethyl)-5-phenylthiazole-2-carboxamide

[0124] Step 1: ethyl 2-(2-(3-((tert-butoxycarbonyl)amino)propanoyl)hydrazinyl)-2-oxoacetate: Et$_3$N (4.98 g, 49.261 mmol) was added to an ice-cooled solution of tert-butyl (3-hydrazinyl-3-oxopropyl)carbamate (5.0 g, 24.63 mmol) in DCM (100 mL) followed by ethyl oxalyl chloride (4.01 g, 29.55 mmol) and the resulting reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was diluted with water (50 mL). Organic layer separated off and the aq. layer was further extracted with DCM (50 mL x 2). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the product (7 g, crude) as yellowish sticky mass which was used as such in next step without further purification. As per IH-NMR, triethyl amine present as an impurity in the compound. LC-MS: [M+H]$^+$ = 303.9.

[0125] Step 2: ethyl 5-(2-((tert-butoxycarbonyl)amino)ethyl)-1,3,4-thiadiazole-2-carboxylate: Lawesson’s reagent (9.34 g, 23.10 mmol) was added to a solution of ethyl 2-(2-(3-((tert-butoxycarbonyl)amino)propanoyl)hydrazinyl)-2-oxoacetate (7 g, crude) in 1,4-dioxane...
(150 mL) and the reaction mixture was refluxed for 2h. Then the reaction mixture was cooled, neutralized with saturated sodium carbonate solution and extracted with EtOAc (100 mL x 3). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. The crude compound thus obtained was purified by silica gel of (100-200 mesh) column chromatography using 20% EtOAc in Hexane as eluent to obtain the product (2.5 g, 33.61% after two steps) as yellow viscous mass. 

\[ \text{[0126] Step 3: ethyl 5-(2-aminoethyl)-1,3,4-thiadiazole-2-carboxylate hydrochloride:} \]

4M HCl in 1,4-dioxane (3 mL) was added to an ice-cooled solution of ethyl 5-(2-(tert-butoxycarbonyl)amino)ethyl)-1,3,4-thiadiazole-2-carboxylate (0.200 g, 0.66 mmol) in dioxane (5 mL) and the resulting reaction mixture was stirred at room temperature for 2 h. Volatiles were removed under reduced pressure to obtain the product (0.150 g, crude) as yellowish solid which was used as such for coupling. LC-MS: [M+H]+ = 202.2.

\[ \text{[0127] Step 4: ethyl 5-(2-(5-phenylthiazole-2-carboxamido)ethyl)-1,3,4-thiadiazole-2-carboxylate:} \]

HATU (0.278 g, 0.73 mmol) and DIPEA (0.188 g, 1.46 mmol) were added sequentially to a solution of 5-phenylthiazole-2-carboxylic acid (0.100 g, 0.48 mmol) in THF (10 mL) and the reaction mixture was stirred for 10 min. Ethyl 5-(2-aminoethyl)-1,3,4-thiadiazole-2-carboxylate hydrochloride (0.147 g, crude) was then added and the reaction mixture was stirred at room temperature for 12 h. Volatiles were removed under vacuum and the crude compound was dissolved in DCM. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. The crude compound was purified by silica gel (100-200 mesh) column chromatography using 20% EtOAc in Hexane as eluent to obtain the product (0.150 g, 63%) as off white solid. 1H NMR (400 MHz, DMSO): δ 9.13 (t, J = 5.9 Hz, 1H), 8.42 (s, 1H), 7.77 (d, J = 8.5 Hz 2H), 7.50-7.49 (m, 2H), 7.48-7.44 (m, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.71 (q, J = 6.3 Hz, 2H), 3.49 (t, J = 6.5 Hz, 2H), 1.32 (t, J = 7.12 Hz, 3H); LC-MS: [M+H]+ = 388.8.

\[ \text{[0128] Step 5: N-il-iS-il-hydroxymethyO-1^-thiadiazol^-yOethyO-S-phenylthiazole-2-carboxamide:} \]

sodium borohydride (0.063 g, 1.67 mmol) was added in portions to an ice-
cooled solution of ethyl 5-(2-(5-phenylthiazole-2-carboxamido)ethyl)-1,3,4-thiadiazole-2-carboxylate (0.130 g, 0.33 mmol) in ethanol (20 mL) and the reaction mixture was stirred for 2 h at room temperature. Volatiles were removed under reduced pressure and the reaction mixture was diluted with cold water. The aq. layer was extracted with EtOAc (30 mL x 3).

Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. The crude compound thus obtained was purified by silica gel (100-200 mesh) column chromatography using 70% EtOAc in Hexane as eluent to obtain the product (0.050 g, 43.47%) as white solid. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 9.09 (t, \(J = 5.8\) Hz, 1H), 8.42 (s, 1H), 7.77 (dd, 2H), 7.50-7.46 (m, 2H), 7.43-7.41 (m, 1H), 6.13 (t, \(J = 5.9\) Hz, 1H), 4.79 (d, \(J = 5.9\) Hz, 2H), 3.67 (q, \(J = 6.5\) Hz, 2H), 3.39-3.35 (m, 2H); LC-MS: [M+H\(^+\)] = 347.0; HPLC purity: 99.27% at 220 nm and 99.85% at 254 nm.

Example 7: N-(2-(5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl)ethyl)-5-phenylthiazole-2-carboxamide

**Step 1:** 3-(1,3-dioxoisindolin-2-yl)-N’-(2-methoxyacetyl)propanehydrazide:

EDC⋅HCl (2.8 g, 15.0 mmol) was added to a solution of 3-(1,3-dioxoisindolin-2-yl)propanoic acid (2.2 g, 10.0 mmol) in THF (30 mL) followed by HOBt (1.84 g, 12.0 mmol) and the reaction mixture was stirred for 20 min at room temperature. 2-methoxyacetohydrazide (1.05 g, 10.0 mmol) was added to the reaction mixture followed by DIPEA (6.4 g, 50.0 mmol) and the reaction mixture was stirred at room temperature for 16 h. Volatiles were removed under reduced pressure and the reaction mixture was diluted with water (30 mL). The aq. layer was
extracted with DCM (3 x 25 mL), combined organic layer was washed with aqueous NaHCO$_3$ solution (50 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to obtain the product (2.0 g, 65%) as white solid. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 9.91 (s, 1H), 9.72 (s, 1H), 7.88-7.82 (m, 4H), 3.88 (s, 2H), 3.78 (t, $J = 7.6$ Hz, 2H), 3.30 (s, 3H), 2.25 (t, $J = 7.6$ Hz, 2H); LC-MS: [M+H]$^+$ = 306.3 m/z.

[0130] Step 2: 2-(2-(5-(methoxymethyl)-1,3,4-oxadiazol-2-y)ethyl)isoindoline-1,3-dione: T$_3$P (10 mL, 15.7 mmol) was added to a solution of 3-(1,3-dioxoisindolin-2-yl)-N'-(2-methoxyacetyl)propanehydrazide (2.0 g, 6.55 mmol) in 1,4-dioxane (60 mL) and the reaction mixture was heated to 100 °C for 18 h. Volatiles were removed under reduced pressure and the crude reaction mixture was diluted with aqueous NaHCO$_3$ solution (50 mL). The aq. layer was extracted with EtOAc (2 x 50 mL). Combined organic layer was washed with water (50 mL), brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the product (1.4 g, 74%) as off-white solid which was used as such without further purification. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.89-7.83 (m, 4H), 4.57 (s, 2H), 3.94 (t, $J = 7.6$ Hz, 2H), 3.28 (s, 3H), 3.22 (t, $J = 7.6$ Hz, 2H); LC-MS: [M+H]$^+$ = 288.2 m/z.

[0131] Step 3: 2-(2-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)ethyl)isoindoline-1,3-dione: hydrazine hydrate (0.4 mL) was added to a solution of 2-(2-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)ethyl)isoindoline-1,3-dione (0.75 g, 2.6 mmol) in ethanol (10 mL) and the reaction mixture was stirred at room temperature for 16 h. Then the reaction mixture was filtered and concentrated under reduced pressure to obtain the product (0.32 g, crude) which was used as such in next step without further purification. LC-MS: [M+H]$^+$ = 157.9 m/z.

[0132] Step 4: N-(2-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)ethyl)-5-phenylthiazole-2-carboxamide: A solution of 2-(2-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)ethyl)isoindoline-1,3-dione (0.314 g, crude) and ethyl 5-phenylthiazole-2-carboxylate (0.29 g, 1.2 mmol) in DMF (5 mL) was heated to 65 °C for 16 h. After completion, the reaction mixture was diluted with water (25 mL) and extracted with DCM (2 x 25 mL). Combined organic layer was washed with water (30 mL) followed by brine (30 mL) and dried over sodium sulfate. Solvent was removed under reduced pressure to afford crude product. The crude compound was purified by
combiflash to obtain the product (0.14 g) as off-white solid. LC-MS: [M+H]+ = 345.1 m/z. As per 1H-NMR, compound is impure and used as such in next step without further purification.

[0133] Step 5: N-i2-i5-i-hydroxymethyl)-l,3,4-oxadiazol-2-yl)ethyl)-5-phenylthiazole-2-carboxamide: BBr₃ (0.15 ml, 1.56 mmol) was added to a -78 °C solution of N-(2-(5-(methoxymethyl)-l,3,4-oxadiazol-2-yl)ethyl)-5-phenylthiazole-2-carboxamide (0.140 g, crude) in DCM (6 mL) and the reaction mixture was stirred at room temperature for 5 h. Then the reaction mixture was poured onto ice, stirred for 10 min. The aq. layer was basified with saturated sodium bicarbonate solution and extracted with DCM (2 x 20 mL). Combined organic layer was washed with water, dried over sodium sulfate and concentrated under reduced pressure to afford crude product. The crude compound thus obtained was purified by crystallization to obtain the product (35 mg, 4.3% over three steps) as white crystal. ¹H NMR (400 MHz, DMSO-de): δ 9.07 (t, J = 6.0 Hz, 1H), 8.42 (s, 1H), 7.77 (d, J = 7.2 Hz, 2H), 7.48 (m, 2H), 7.42 (m, 2H), 5.86 (t, J = 6.0 Hz, 1H), 4.59 (d, J = 6.0 Hz, 2H), 3.66 (q, J = 6.7 Hz, 2H), 3.14 (t, J = 7.2 Hz, 2H); LC-MS: [M+H]+ = 331.1 m/z; HPLC purity 98.02% at 314 nm, 97.60 % at 254 nm.

Examples 8 and 9: N-(2-(4-(hydroxymethyl)-5-methyl-lH-1,2,3-triazol-l-yl)ethyl)-5-phenylthiazole-2-carboxamide and N-(2-(5-(hydroxymethyl)-4-methyl-lH-1,2,3-triazol-l-yl)ethyl)-5-phenylthiazole-2-carboxamide

[0134] Step 1: N-(2-(4-(hydroxymethyl)-5-methyl-lH-1,2,3-triazol-l-yl)ethyl)-5-phenylthiazole-2-carboxamide and N-(2-(5-(hydroxymethyl)-4-methyl-lH-1,2,3-triazol-l-yl)ethyl)-5-phenylthiazole-2-carboxamide
yl)ethyl)-5-phenylthiazole-2-carboxamide: a solution of 2-(2-azidoethyl)isoindoline-1,3-dione (5.0 g, 23.0 mmol) and 2-butyn-1-ol (2.0 mL, 26.7 mmol) in toluene (50 mL) was heated to 110 °C in a sealed tube and for 48 h. After completion, volatiles were removed under reduced pressure and crude reaction mixture was washed with ether (100 mL). Residue was dried to obtain (4.5 g, 68%) as a mixture of two regioisomers which were used as such in the next step without further purification. \(^1\)H NMR (400 MHz, DMSO-\(d_6\): \(\delta\) 7.86-7.82 (m, 8H), 5.36 (t, \(J = 5.2\) Hz, 1H), 5.00 (t, \(J = 5.2\) Hz, 1H), 4.59 (t, \(J = 5.6\) Hz, 2H), 4.56 (t, \(J = 5.2\) Hz, 2H), 4.53 (d, \(J = 5.6\) Hz, 2H), 4.40 (d, \(J = 5.6\) Hz, 2H), 4.02 (t, \(J = 6.0\) Hz, 2H), 3.95 (t, \(J = 6.0\) Hz, 2H), 2.30 (s, 3H), 2.15 (s, 3H); LC-MS: [M+H]^+ = 287.1 m/z.

[0135] Step 2: (1-(2-aminoethyl)-4-methyl-1H-1,2,3-triazol-5-yl)methanol and (1-(2-aminoethyl)-5-methyl-1H-1,2,3-triazol-4-yl)methanol: hydrazine hydrate (0.200 mL, 4.0 mmol) was added to a solution of N-(2-(4-(hydroxymethyl)-5-methyl-1H-1,2,3-triazol-1-yl)ethyl)-5-phenylthiazole-2-carboxamide and N-(2-(5-(hydroxymethyl)-4-methyl-1H-1,2,3-triazol-1-yl)ethyl)-5-phenylthiazole-2-carboxamide (0.575 g, 2.0 mmol) in ethanol (10 mL) and the mixture was heated to 60 °C for 2 h. After completion, the mixture was filtered and filtrate was concentrated under reduced pressure to obtain the product as a mixture of isomers (0.305 g, crude) which was used as such in next step without purification. LC-MS: (M+H)^+ = 157.2.

[0136] Step 3: N-(2-(4-(hydroxymethyl)-4-methyl-1H-1,2,3-triazol-1-yl)ethyl)-5-phenylthiazole-2-carboxamide and N-(2-(5-(hydroxymethyl)-4-methyl-1H-1,2,3-triazol-1-yl)ethyl)-5-phenylthiazole-2-carboxamide: HATU (0.685 g, 1.8 mmol) and DIPEA (0.58 g, 4.5 mmol) were added sequentially to a solution of 5-phenylthiazole-2-carboxylic acid (0.305 g, 1.5 mmol) in DMF (5 mL). After 10 min stirring, to the resulting reaction mixture was added (l-(2-aminoethyl)-4-methyl-1H-1,2,3-triazol-5-yl)methanol and (l-(2-aminoethyl)-5-methyl-1H-1,2,3-triazol-4-yl)methanol (0.235 g, crude) and the reaction mixture was stirred at room temperature for 12 h. Reaction mixture was diluted with water (15 mL), extracted with dichloromethane (3 x 25 mL) and washed with brine (2 x 50 mL). Combined organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure to obtain 0.9 g of crude material which was purified by prep HPLC to obtain target compounds. Yield: 25% over two steps.
N-(2-(5-(hydroxymethyl)-4-methyl-1H-1,3,5-tetrazol-1-yl)ethyl)-5-phenylthiazole-2-carboxamide: 0.09 g; white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.98 (t, J = 5.6 Hz, IH), 8.41 (s, IH), 7.77 (d, J = 7.2 Hz, 2H), 7.50-7.40 (m, 3H), 5.32 (t, J = 5.2 Hz, IH), 4.54-4.51 (m, 4H), 3.73-3.69 (m, 2H), 2.20 (s, 3H); LC-MS: [M+H]⁺ = 344.0 m/z;

HPLC purity 99.68% at 220 nm, 99.63% at 254 nm.

N-(2-(4-(hydroxymethyl)-5-methyl-1H-1,2,3-triazol-1-yl)ethyl)-5-phenylthiazole-2-carboxamide: 0.085 g; white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.03 (t, J = 5.6 Hz, IH), 8.42 (s, IH), 7.78 (d, J = 7.2 Hz, 2H), 7.50-7.40 (m, 3H), 5.00 (t, J = 5.6 Hz, IH), 4.47-4.43 (m, 4H), 3.68-3.64 (m, 2H), 2.28 (s, 3H); LC-MS: [M+H]⁺ = 344.0 m/z;

HPLC purity 99.75% at 220 nm, 99.62% at 254 nm.

Example 10: N-cis-3-(5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl-5-phenylthiazole-2-carboxamide
Step 1: ethyl 3-oxocyclobutane-1-carboxylate: triethyl orthoacetate (21.31 g, 0.131 mol) was added to a solution of 3-oxocyclobutane-1-carboxylic acid (5.0 g, 0.043 mol) in toluene (100 mL) and the reaction mixture was refluxed for 6 h. The reaction mixture was quenched with a 1N HCl solution and the layers were separated off. The organic layer was washed with saturated NaHCO₃ solution (2 x 50 mL), brine (2 x 50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the product (5.3 g, 85%) as a yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ 4.23-4.17 (q, J = 7.0 Hz, 2H), 3.44-3.37 (m, 2H), 3.32-3.16 (m, 3H), 1.30-1.26 (t, J = 7.0 Hz, 3H).

Step 2: ethyl cis-3-hydroxyccyclobutane-1-carboxylate: sodium borohydride (1.55 g, 0.041 mol) was added to an iced cold solution of ethyl 3-oxocyclobutane-1-carboxylate (5.3 g, 0.037 mol) in methanol (75 mL) and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with acetone (10 mL) and volatiles were removed under reduced pressure. The crude reaction mixture was suspended in NaHCO₃ solution (30 mL) and extracted with DCM (100 mL). The organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the product (3.2 g, 59%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 4.20-4.09 (overlapped q and m, 3H), 3.68 (d, J = 2.3 Hz, 1H), 2.62-2.54 (m, 3H), 2.20-2.10 (m, 2H), 1.26-1.22 (t, J = 7.0 Hz, 3H); LC-MS: [M+H]+ 145.1.

Step 3: ethyl cis-3-((methylsulfonyl)oxy)cyclobutane-1-carboxylate: Et₃N (8.96 mL, 0.0666 mol) was added to a solution of ethyl cis-3-hydroxyccyclobutane-1-carboxylate (3.2 g, 0.0222 mol) in DCM (100 mL) followed by MsCl (3.03 g, 0.0266 mol) drop wise and the resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured onto ice cold water (50 mL) and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the crude product (5.1 g) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 4.95-4.88 (m, 1H), 4.17-4.12 (q, J = 7.1 Hz, 2H), 3.71 (d, 1H), 2.98 (s, 3H), 2.74-2.66 (m, 3H), 2.60-2.59 (m, 2H), 1.27-1.25 (t, J = 7.1 Hz, 3H); LC-MS: [M+H]+ 223.0.

Step 4: ethyl fra«$-3-azidocyclobutane-1-carboxylate: a mixture of sodium azide (2.98 g, 0.044 mol) and ethyl cis-3-((methylsulfonyl)oxy)cyclobutane-1-carboxylate (5.1 g,
0.022 mol) in DMF (25 mL) was heated to 90°C for 16 h. The reaction mixture was poured onto water (70 mL) and extracted with ethyl acetate (2 x 100 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude product which was chromatographed on 230-400 mesh silica gel using 10% EtOAc in hexane as eluent to afford the product (3.8 g, 100% over two steps) as colorless liquid. \( \text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 4.18-4.10 (m, 3H), 3.11-3.04 (m, 1H), 2.60-2.53 (m, 2H), 2.36-2.29 (m, 2H), 1.27-1.22 (t, \( J = 7.1 \) Hz, 3H); LC-MS: [M+H]\(^+\) 171.1.

[0143] Step 5a/b: ethyl trans-3-aminocyclobutane-l-carboxylate hydrochloride: a mixture of ethyl trans-3-azidocyclobutane-l-carboxylate (3.8 g, 0.0221 mol) and 10% Pd/C (1.0 g) in ethanol (50 mL) was hydrogenated (50 psi) for 4 h at room temperature. The reaction mixture was filtered through a celite bed and the filtrate was concentrated under reduced pressure to obtain the crude compound. The crude compound was treated with 4 M HCl in dioxane to afford HCl salt (3.8 g, 95%) as colorless viscous oil.

[0144] Step 6: ethyl trans-3-(5-phenylthiazole-2-carboxamido)cyclobutane-l-carboxylate: Et,N (0.15 mL, 0.0011 mol) and HATU (0.255 g, 0.00066 mol) were added sequentially to a suspension of ethyl trans-3-aminocyclobutane-l-carboxylate hydrochloride (0.100 g, 0.00055 mol) and 5-phenylthiazole-2-carboxylic acid (0.125 g, 0.000612 mol) in THF (10 mL) and the reaction mixture was stirred for 12 h at room temperature. Volatiles were removed under reduced pressure and the crude reaction mixture was diluted with water (10 mL). The aq. phase was extracted with ethyl acetate (2 x 25 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude compound which was further purified by (230-400 mesh) silica gel column chromatography using 25% EtOAc in hexane to afford the product (0.130 g, 70%) as off white solid. \(^{1}\text{H} \) NMR (400 MHz, DMSO-d\(_6\)): \( \delta \) 7.97 (s, 1H), 7.60-7.57 (m, 2H), 7.45-7.36 (m, 4H), 4.76-4.74 (m, 1H), 4.18 (q, \( J = 7.0 \) Hz, 2H), 3.11-3.10 (m, 1H), 2.78-2.72 (m, 2H), 2.43-2.35 (m, 2H), 1.28 (t, \( J = 7.0 \) Hz, 3H); LC-MS: [M+H]\(^+\) 330.9 m/z.

[0145] Step 7: trans-3-(5-phenylthiazole-2-carboxamido)cyclobutane-l-carboxylic acid: lithium hydroxide monohydrate (0.153 g, 0.0036 mol) was added to a solution of ethyl trans-3-(5-phenylthiazole-2-carboxamido)cyclobutane-l-carboxylate (1.1 g, 0.0033 mol) in
THF : water (45 mL, 2:1) and the resultant reaction mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated under vacuum and partitioned between ethyl acetate (30 mL) and water (10 mL). Separated aqueous layer was acidified with saturated citric acid solution (15 mL), precipitate thus formed was filtered, washed with water and dried to afford the product (0.315 g, 98%) as white solid. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 12.21 (s, 1H), 9.25 (d, $J = 8.1$ Hz, 1H), 8.42 (s, 1H), 7.77 (d, $J = 7.3$ Hz, 2H), 7.50-7.40 (m, 3H), 4.60-4.54 (m, 1H), 2.96-2.91 (m, 1H), 2.50-2.39 (m, 4H); LC-MS: [M+H]$^+$ 303.1 m/z.

[0146] **Step 8: tert-butyl 2-trans-3-(5-phenylthiazole-2-carboxamido)cyclobutane-1-carboxyl)hydrazine-1-carboxylate:** HATU (1.49 g, 0.0039 mol) was added to a solution of trans-3-(5-phenylthiazole-2-carboxamido)cyclobutane-1-carboxylic acid (0.990 g, 0.0032 mol) in THF (90 mL) and stirred at room temperature for 15 min. To the resulting reaction mixture was added N-Boc-hydrazine (0.518 g, 0.0039 mol) followed by Et$_3$N (0.88 mL, 0.00654 mol) and stirring continued for 2 h at room temperature. The reaction mixture was poured onto water (80 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude compound. The crude compound was further purified by silica gel (230-400 mesh) column chromatography using EtOAc as eluent to afford the product (1.8 g, crude) as white solid with polar impurity. LC-MS: [M+H]$^+$ 417.2 m/z.

[0147] **Step 9: N-trans-3-(hydrazinecarbonyl)cyclobutyl)-5-phenylthiazole-2-carboxamide hydrochloride:** 4 M HCl in dioxane solution (12 mL) was added to a solution of tert-butyl 2-trans-3-(5-phenylthiazole-2-carboxamido)cyclobutane-1-carboxyl)hydrazine-1-carboxylate (0.800 g, 0.00192 mol) in 1,4-dioxane (5 mL) and the reaction mixture was stirred at room temperature for 6 h. Volatiles were removed under reduced pressure and the reaction mixture was diluted with diethyl ether (100 mL) to afford the product (0.650 g, crude) as off white solid. LC-MS: [M+H]$^+$ 317.2 m/z.

[0148] **Step 10: N-trans-3-(2-(2-((tert-butylidimethylsilyl)oxy)acetyl)hydrazine-1-carbonyl)cyclobutyl)-5-phenylthiazole-2-carboxamide:** HATU (0.256 g, 0.00067 mol) was added to a solution of N-trans-3-(hydrazinecarbonyl)cyclobutyl)-5-phenylthiazole-2-carboxamide hydrochloride (0.161 g, 0.00085 mol) in THF (20 mL) and stirred at room
temperature for 15 minutes. Then added 2-((tert-butyldimethylsilyl)oxy)acetic acid (0.200 g, 0.00056 mol) and Et₃N (0.301 mL, 0.00224 mol) were added and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the product (0.070 g, 21%).

Concentrated under reduced pressure obtained crude product. The crude compound was purified by column chromatography on 230-400 mesh silica gel using 90% EtOAc in hexane afforded the product (0.103 g, crude) as off white solid. LC-MS: [M+H]+ 489.1 m/z.

**Step 11: N-trans-3-(5-(((tert-butyldimethylsilyl)oxy)methyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-5-phenylthiazole-2-carboxamide:** Iodine (0.206 g, 0.0008 mol) was added to a solution of PPh₃ (0.212 g, 0.00081 mol) in DCM (30 mL) at room temperature and the reaction mixture was stirred for 15 min. The resulting reaction mixture was cooled in an ice bath and to the reaction mixture was triethyl amine (0.27 mL, 0.00204 mol) followed by N-trans-3-(2-(((tert-butyldimethylsilyl)oxy)acetyl)hydrazine-1-carbonyl)cyclobutyl)-5-phenylthiazole-2-carboxamide (0.200 g, 0.00046 mol). The reaction mixture was stirred at room temperature for 3 h. Volatiles were removed under reduced pressure; the crude compound was diluted with ethyl acetate and filtered. The filtrate was concentrated under reduced pressure to afford crude product. The crude compound was purified by (230-400 mesh) silica gel column chromatography using 60% EtOAc in hexane as eluent to obtain the product (0.110 g, 21% over four steps) as off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.41 (d, J = 8.0 Hz, 1H), 8.44 (s, 1H), 7.79-7.77 (m, 2H), 7.50-7.47 (m, 2H), 7.43-7.41 (m, 1H), 4.87 (s, 2H), 4.73-4.67 (m, 1H), 3.73-3.69 (m, 1H), 2.80-2.72 (m, 2H), 2.60-2.54 (m, 2H), 0.88 (s, 9H), 0.10 (s, 6H); LC-MS: [M+H]+ 471.3 m/z.

**Step 12: N-trans-3-(5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-5-phenylthiazole-2-carboxamide:** Tetra butyl ammonium fluoride (0.46 mL, 0.00046 mol, 1 M in THF solution) was added to a cold solution of N-trans-3-(5-(((tert-butyldimethylsilyl)oxy)methyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-5-phenylthiazole-2-carboxamide (0.110 g, 0.00023 mol) in THF (5 mL) and the reaction mixture was stirred for 1 h. Volatiles were removed under reduced pressure; the crude reaction mixture was suspended in water (10 mL) and extracted with ethyl acetate (15 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the product (0.070 g, 21%).
84%) as off white solid. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 9.41 (d, $J = 8$ Hz, 1H), 8.45 (s, 1H), 7.80-7.77 (m, 2H), 7.50-7.42 (m, 3H), 5.89-5.86 (m, 1H), 4.72-4.67 (m, 1H), 4.63 (d, $J = 4$ Hz, 2H), 3.72-3.67 (m, 1H), 2.79-2.71 (m, 2H), 2.61-2.56 (m, 2H); LC-MS: [M+H]$^+$ 356.8 m/z; HPLC purity: 99.39% at 220 nm and 98.86% at 254 nm.

Example 11: N-trans-3-(5-((R)-l-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-5-phenylthiazole-2-carboxamide

[0151] **Step la:** methyl (2R)-2-[(tert-butyldimethylsilyl)oxy]propanoate: into a 250-mL round-bottom flask, was placed a solution of methyl (2R)-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 (3x100 mL) and the organic layers combined. The resulting mixture was
washed with brine (3x50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 7 g (67%) of methyl (2R)-2-[(tert-butyldimethylsilyl)oxy]propanoate as colorless oil.

[0152] Step 1b: (2R)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazide: into a 250-mL round-bottom flask, was placed a solution of methyl (2R)-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 (3x100 mL) and the organic layers combined. The resulting mixture was washed with brine (2x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 6.5 g (93%) of (2R)-2-[(tert-butyldimethylsilyl)oxy]propanehydrazide as colorless oil. LC-MS (ES, m/z): [M+I] + = 219.

[0153] Step 1: methyl (trans-3-(1,3-dioxo-2,3-dihydro-IH-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-IH-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. This resulted in 7.2 g (45%) of methyl trans-3-(1,3-dioxo-2,3-dihydro-IH-isoindol-2-yl)cyclobutane-1 -carboxylate as a white solid. LC-MS (ES, m/z): [M+I] + = 260. 1H NMR (400MHz, CDCb): 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, 2H), 3.20-3.12 (m, 2H), 2.66-2.60 (m, 2H).

[0154] Step 2: trans-3-(1,3-dioxo-2,3-dihydro-IH-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-IH-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. This resulted in 6.2 g (91%) of trans-3-(1,3-dioxo-2,3-dihydro-1H-isindol-2-yl)cyclobutane-1-carboxylic acid as a white solid. LC-MS (ES, m/z): [M-1]⁻ = 244.

[0155] Step 3: (2R)-2-[(tert-butyldimethylsilyloxy)-N-[trans-3-(1,3-dioxo-2,3-dihydro-1H-isindoI-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-isindol-2-yl)cyclobutane-1-carboxylic acid (6.2 g, 25.28 mmol, 1.00 equiv), (2R)-2-[(tert-butyldimethylsilyloxy)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 (3x50 mL) and the organic layers combined. The resulting mixture was washed with brine (2x50 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). This resulted in 7 g (62%) of (2R)-2-[(tert-butyldimethylsilyloxy)-N-[trans-3-(1,3-dioxo-2,3-dihydro-1H-isindol-2-yl)cyclobutyl]carbonyl]propanehydrazide as colorless oil. LC-MS (ES, m/z): [M+1]⁺ = 446.

[0156] Step 4: 2-[trans-3-[5-[(IR)-1-[(tert-butyldimethylsilyloxy)ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-2,3-dihydro-1H-isindole-1,3-dione: into a 250-mL round-bottom flask, was placed a solution of (2R)-2-[(tert-butyldimethylsilyloxy)-N-[trans-3-(1,3-dioxo-2,3-dihydro-1H-isindol-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 (2x50 mL) and the organic layers combined. The resulting mixture was washed with brine (2x50 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, H2O/CH3CN= 100:1 increasing to H2O/CH3CN=1:100 within 30 min; Detector, UV 254 nm. This resulted in 3.28 g (49%) of 2-[trans-3-[(IR)-1-[(tert-butyl(dimethyl)silyl)oxyl]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-2,3-dihydro-IH-isodole-1,3-dione as colorless oil. LC-MS (ES, m/z): [M+1]+ = 485. 

1H NMR (400MHz, CDCl3): 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).

[0157] Step 5: trans-3-[5-[(IR)-1-[(tert-butyl(dimethyl)silyl)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-[(IR)-1-[(tert-butyl(dimethyl)silyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-2,3-dihydro-IH-isodole-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 out. The resulting mixture was concentrated under vacuum. This resulted in 760 mg (crude) of trans-3-[5-[(IR)-1-[(tert-butyl(dimethyl)silyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutan-1-amine as colorless oil. LC-MS (ES, m/z): [M+1]+ = 298.

[0158] Step 6: N-[trans-3-[5-[(IR)-1-[(tert-butyl(dimethyl)silyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,3-thiazole-2-carboxamide: into a 100-mL round-bottom flask, was placed a solution of lithio 5-phenyl-l,3-thiazole-2-carboxylate (332 mg, 1.57 mmol, 1.20 equiv), (lr,3r)-3-[5-[(IR)-1-[(tert-butyl(dimethyl)silyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutan-1-amine (390 mg, 1.31 mmol, 1.00 equiv) and HATU (750 mg, 1.97 mmol, 1.50 equiv) in THF (50 mL). This was followed by the addition of DIEA (508 mg, 3.93 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 (2x30 mL), dried and concentrated under vacuum. This resulted in 300 mg (47%) of 5-phenyl-N-[trans-3-[5-[(IR)-1-[(tert-butyl(dimethyl)silyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,3-thiazole-2-carboxamide as a light yellow crude solid. LC-MS (ES, m/z): [M+1]+ = 485.
Step 7: 5-phenyl-N-[trans-3-[5-[(L,R)-l-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,3-thiazole-2-carboxamide: into a 50-mL round-bottom flask, was placed a solution of 5-phenyl-N-[lR,3r]-3-[5-[(L,R)-l-[(tert-butyldimethylsilyl)oxy]ethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,3-thiazole-2-carboxamide (300 mg, 0.62 mmol, 1.00 equiv) in THF (2 mL). To the solution was added TBAF (1 mol/L in tetrahydrofuran, 1 mL). The resulting solution was stirred for 3 hours at room temperature. The resulting solution was diluted with 20 mL of water. The resulting solution was extracted with ethyl acetate (3x30 mL) and the organic layers combined. The resulting mixture was washed with brine (2x10 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, H₂O/CH₃CN=100:1 increasing to H₂O/CH₃CN=1:100 within 30 min; Detector, UV 254 nm. This resulted in 115.6 mg (50%) of 5-phenyl-N-[trans-3-[5-[(L,R)-l-hydroxyethyl]-1,3,4-oxadiazol-2-yl]cyclobutyl]-1,3-thiazole-2-carboxamide as a white solid. LC-MS (ES, m/z): [M+H]⁺ = 371. ¹H NMR (400MHz, DMSO-d₆): 4.94-9.40 (d, J = 8.0 Hz, 1H), 8.43 (s, 1H), 7.80-7.78 (m, 2H), 7.51-7.42 (m, 3H), 5.96-5.94 (d, J = 6.0 Hz, 1H), 4.95-4.90 (m, 1H), 4.75-4.65 (m, 1H), 3.73-3.67 (m, 1H), 2.80-2.72 (m, 2H), 2.63-2.57 (m, 2H), 1.50-1.48 (d, J = 6.4 Hz, 3H).

Example 12: N-trans-3-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)cyclobutyl)-5-phenylthiazole-2-carboxamide
Step 1: tert-butyl (3-oxocyclobutyl)carbamate: DPPA (4.0 g, 1.1 eq.) is 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 is stirred at -5-0 °C for 16 h. The reaction mixture is washed with NaHCO₃ (2*9 mL), water (1*9 mL) and NaCl aq. (1*4.5 mL) at 0-10 °C. The organic phase is dried over Na₂SO₄, filtered and t-BuOH (7.5 mL) is added to the filtrate. The reaction mixture is then heated at 90-100 °C for 16 h. The mixture is concentrated under vacuum at 60-70 °C and then suspended in TBME (4.5 mL), filtered and the solid is dried over air to give 1.15 g (purity: 98.5%, yield: 47.2%) of product as a white solid.

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) is added dropwise to a cold (below -70 °C) solution of NaBH₄ (20.4 mg, 0.5 eq.) in a solution of 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 is stirred at-60—50 °C for 3 h, water (2 mL) is 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*1 mL) and the combined organic layers are washed with brine (1 mL). The organic layer is concentrated under vacuum at 35-40 °C, the solid is dissolved in toluene (1 mL, 80-90 °C) and then is gradually cooled to 25-30 °C for 2.5 h. The mixture is stirred for 2 h at 25-30 °C,
filtered, and the solid is dried in the air to give the product (177 mg with ratio of cis:trans (96.4:3.6), yield: 87.6%) as an off-white solid.

[0162] Step 3: tert-butyl (trans-3-azidocyclobutyl)carbamate: a solution of PPh₃ (315 mg) and DIAD (243 mg) in THF (3 mL) is stirred for 20 min at 0-10 °C. Then 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) is added dropwise, the mixture is then warmed to 25-30 °C and it is stirred for 2 h. Brine (3 mL) is added to the reaction mixture, extracted with ethyl acetate (3 mL) and is then concentrated under vacuum to give the crude oil. The mixture is purified by SiO₂ column chromatography and is eluted with ethyl acetate/petroleum ether (0%-10%) gradually. The product is suspended in n-heptane (0.3 mL) and stirred for 0.5 h at 20-25 °C, the mixture is filtered and the solid is dried in air to give the product in 85% yield and ratio of cis/trans= 4:96 checked by ¹H NMR.

[0163] 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-l-ol (326 mg, 5.0 eq.) in DMF (1.2 mL) is heated at 90-95 °C for 20 h. The mixture is concentrated under vacuum at 65 °C to give 1:1 mixture of 4 and 5 regioisomers (353 mg). The mixture is 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.

[0164] Step 5: (l-(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.) is added slowly (5 portions) to a solution of HCl/dioxane (3.5 mol/L, 2 mL) at 20-30 °C, and then is stirred for 18 h at 20-30 °C. The reaction mixture is concentrated under vacuum at 55 °C to give the product (93.4 mg, assay 67% based on free base, Y: 100%) as a solid.

[0165] Step 6: of 5-phenyl-N-trans-3-[5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,3-thiazole-2-carboxamide as a white solid: DIEA (386 mg, 2.99 mmol, 3.00 equiv) was added dropwise to a cold solution 0°C of lithio 5-phenyl-1,3-thiazole-2-carboxylate (180 mg, 0.85 mmol, 1.00 equiv), [l-[trans-3-aminocyclobutyl]-1H-1,2,3-triazol-5-yl]methanol
hydrochloride (204 mg, 1.00 mmol, 1.00 equiv) and HATU (567 mg, 1.49 mmol, 1.50 equiv) in DMF (5 mL). The resulting solution was stirred for 1 hour at room temperature. The reaction was then quenched by the addition of 50 mL of water/ice. The resulting solution was extracted with ethyl acetate (3x80 mL) and the organic layers combined. The resulting mixture was washed with brine (3x30 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude mixture was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, H₂O/CH₃CN=100:1 increasing to H₂O/CH₃CN=l:100 within 35 min; Detector, UV 254 nm. This resulted in 115 mg (38%) of 5-phenyl-N-trans-3-[5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]cyclobutyl]-1,3-thiazole-2-carboxamide as a white solid. LC-MS (ES, m/z): [M+H]⁺ = 356. ¹H NMR (400MHz, DMSO-d₆): δ 9.47-9.45 (d, J = 8.0 Hz, 1H), 8.45 (s, 1H), 7.81-7.79 (d, J = 7.6 Hz, 2H), 7.65 (s, 1H), 7.52-7.42 (m, 3H), 5.43 (s, 1H), 5.26-5.19 (m, 1H), 4.85-4.76 (m, 1H), 4.56 (s, 2H), 2.90-2.81 (m, 4H).

**Example 13: CFTR activity assays**

*Ussing measurements*

As discussed above, Ussing measurements are used to measure CFTR activity. In this method, primary lung epithelial cells (hBEs) homozygous for the Cystic Fibrosis-causing AF508 mutation are differentiated for a minimum of 4 weeks in an air-liquid interface on SnapWell filter plates prior to the Ussing measurements. Cells are apically mucus-washed for 30 minutes prior to treatment with compounds. The basolateral media is removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO stocks. Treated cells are incubated at 37°C and 5% CO₂ for 24 hours. At the end of the treatment period, the cells on filters are transferred to the Ussing chamber and equilibrated for 30 minutes. The short-circuit current is measured in voltage clamp-mode (Vₜₐₜₐ = 0 mV), and the entire assay is conducted at a temperature of 36°C -36.5°C. Once the voltages stabilized, the chambers are clamped, and data is recorded by pulse readings every 5 seconds. Following baseline current stabilization, the following additions can be applied and the changes in current and resistance of the cells can be monitored:

1. Benzamil to the apical chamber to inhibit ENaC sodium channel.
2. Forskolin to both chambers to activate AF508-CFTR by phosphorylation.
3. Genistein to both chambers to potentiate AF508-CFTR channel opening.

4. CFTRinh-172 to the apical chamber to inhibit AF508-CFTR Cl- conductance.

[0167] The inhibitable current (that current that is blocked by CFTRinh-172) is measured as the specific activity of the AF508-CFTR channel, and increases in response to compound in this activity over that observed in vehicle-treated samples are identified as the correction of AF508-CFTR function imparted by the compound tested.

ii. hBE Equivalent Current (Ieq) Assay

[0168] Primary lung epithelial cells homozygous for the Cystic Fibrosis-causing AF508 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% CO₂ 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 CO₂-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 (Vₜ) and conductance (Gₓ) 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 Vₜ and Gₓ values were measured for approximately 20 minutes.
2. Benzamil was added to block ENaC for 15 minutes.
3. Forskolin plus VX-770 were added to maximally activate AF508-CFTR for 27 minutes.
4. Bumetanide was added to inhibit the NaK₂Cl cotransporter and shut-off secretion of chloride.

[0169] 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. The results are shown below in Table 2. (** 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

<table>
<thead>
<tr>
<th>#</th>
<th>Structure</th>
<th>Ieq</th>
<th>Ussing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure 6" /></td>
<td>**</td>
<td>##</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Structure 7" /></td>
<td>**</td>
<td>##</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Structure 8" /></td>
<td>**</td>
<td>##</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Structure 9" /></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><img src="image10" alt="Structure 10" /></td>
<td></td>
<td>##</td>
</tr>
</tbody>
</table>
As discussed above, Ussing measurements can be used to measure CFTR activity. In this method, primary lung epithelial cells (hBEs) with a Cystic fibrosis causing class I mutation are differentiated for a minimum of 4 weeks in an air-liquid interface on SnapWell™ filter plates prior to the Ussing measurements. Cells are apically mucus-washed for 30 minutes prior to treatment with compounds. The basolateral media is removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO or aqueous stocks. Treated cells are incubated at 37 °C and 5% CO₂ for 24 hours. At the end of the treatment period, the cells on filters are transferred to the Ussing chamber and equilibrated for 30 minutes. The short-circuit current is measured in voltage clamp-mode ($V_{hold} = 0$ mV), and the entire assay is conducted at a temperature of 36°C -36.5 °C. Once the voltages stabilize, the chambers are clamped, and data are recorded by pulse readings every 5 seconds. Following baseline current stabilization, the following additions are applied and the changes in current and resistance of the cells are monitored:

1. Benzamil to the apical chamber to inhibit ENaC sodium channel.
2. Forskolin to both chambers to activate AF508-CFTR by phosphorylation.
3. Ivacaftor or Genistein to the apical chamber to potentiate AF508-CFTR channel opening.
4. CFTRinh-172 to the apical chamber to inhibit AF508-CFTR Cl- conductance.
The forskolin-insensitive current and inhibitable current (that potentiated current that is blocked by CFTRinh-172) are measured as the specific activity of the AF508-CFTR channel, and increase in response to compound in this activity over that observed in vehicle-treated samples are identified as the correction of AF508-CFTR function imparted by the compound tested.

Example 15

Ussing measurements

As discussed above, Ussing measurements can be used to measure CFTR activity. In this method, primary lung epithelial cells (hBEs) with a Cystic Fibrosis-causing class III mutation are differentiated for a minimum of 4 weeks in an air-liquid interface on SnapWell™ filter plates prior to the Ussing measurements. Cells are apically mucus-washed for 30 minutes prior to treatment with compounds. The basolateral media is removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO stocks. Treated cells are incubated at 37 °C and 5% C0₂ for 24 hours. At the end of the treatment period, the cells on filters are transferred to the Ussing chamber and equilibrated for 30 minutes. The short-circuit current is measured in voltage clamp-mode \( V_{\text{hoi}} = 0 \) mV, and the entire assay is conducted at a temperature of 36 °C -36.5 °C. Once the voltages stabilize, the chambers are clamped, and data is recorded by pulse readings every 5 seconds. Following baseline current stabilization, the following additions are applied and the changes in current and resistance of the cells is monitored:

1. Benzamil to the apical chamber to inhibit ENaC sodium channel.
2. Forskolin to both chambers to activate AF508-CFTR by phosphorylation.
3. VX-770 or Genistein to the apical chamber to potentiate AF508-CFTR channel opening.
4. CFTRinh-1 72 to the apical chamber to inhibit AF508-CFTR Cl- conductance.

The forskolin-sensitive current and inhibitable current (that potentiated current that is blocked by CFTRinh-172) are measured as the specific activity of the AF508-CFTR channel, and increase in response to compound in this activity over that observed in vehicle-treated
samples are identified as the correction of AF508-CFTR function imparted by the compound tested.

[0176] Example 16

i. Ussing measurements

[0177] As discussed above, Ussing measurements can be used to measure CFTR activity. In this method, primary lung epithelial cells (hBEs) with a Cystic Fibrosis-causing class V mutation are differentiated for a minimum of 4 weeks in an air-liquid interface on SnapWell™ filter plates prior to the Ussing measurements. Cells are apically mucus-washed for 30 minutes prior to treatment with compounds. The basolateral media is removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO stocks. Treated cells are incubated at 37 °C and 5% CO₂ for 24 hours. At the end of the treatment period, the cells on filters are transferred to the Ussing chamber and equilibrated for 30 minutes. The short-circuit current is measured in voltage clamp-mode (V\text{hold} = 0 \text{ mV}), and the entire assay is conducted at a temperature of 36 °C -36.5 °C. Once the voltages stabilize, the chambers are clamped, and data is recorded by pulse readings every 5 seconds. Following baseline current stabilization, the following additions are applied and the changes in current and resistance of the cells is monitored:

1. Benzamil to the apical chamber to inhibit ENaC sodium channel.

2. Forskolin to both chambers to activate AF508-CFTR by phosphorylation.

3. VX-770 or Genistiein to the apical chamber to potentiate AF508-CFTR channel opening.

4. CFTRinh-172 to the apical chamber to inhibit AF508-CFTR Cl- conductance.

[0178] The forskolin-sensitive current and inhibitable current (that potentiated current that is blocked by CFTRinh-1 72) are measured as the specific activity of the AF508-CFTR channel, and increases in response to compound in this activity over that observed in vehicle-treated samples are identified as the correction of AF508-CFTR function imparted by the compound tested.
**ii. hBE Equivalent Current (Ieq) Assay**

[0179] Primary lung epithelial cells homozygous for the Cystic Fibrosis-causing AF508 mutation are 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 are apically mucus-washed for 30 minutes 24h prior to treatment with compounds. The basolateral media is removed and replaced with media containing the compound of interest diluted to its final concentration from DMSO stocks. Treated cells are incubated at 37 °C and 5% CO₂ for 24 hours. At the end of the treatment period, the media is changed to the Ieq experimental solution for 30 minutes before the experiment and plates are maintained in a CO₂-free incubator during this period. The plates containing the cells are then placed in pre-warmed heating blocks at 36 °C±0.5 for 15 minutes before measurements are taken. The transepithelial voltage (Vₜ) and conductance (Gₜ) are measured using a custom 24 channel current clamp (TECC-24) with 24 well electrode manifold. The Ieq assay measurements are made following additions with standardized time periods:

1. The baseline Vₜ and Gₜ values are measured for approximately 20 minutes.

2. Benzamil is added to block ENaC for 15 minutes.

3. Forskolin plus VX-770 (ivacaftor) are added to maximally activate AF508-CFTR for 27 minutes.

4. Bumetanide is added to inhibit the NaK₂Cl cotransporter and shut-off secretion of chloride.

[0180] The activity data captured is the area under the curve (AUC) for the traces of the equivalent chloride current. The AUC is collected from the time of the forskolin/VX-770 addition until the inhibition by bumetanide addition. Correction in response to compound treatment is scored as the increase in the AUC for compound-treated samples over that of vehicle-treated samples.

[0181] While this invention has been particularly shown and described with references to preferred 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 invention encompassed by the appended claims.

INCORPORATION BY REFERENCE

[0182] 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

[0183] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[0184] 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 invention.
What is claimed is:

1. A compound represented by formula III or IV:

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

- $X_3$ 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$_i$-alkyl (optionally substituted by one, two or three halogens);
- $L_i$ is selected from the group consisting of C$_i$-alkylene, C$_3$-6cycloalkylene, C$_3$-6cycloalkylene-C$_i$-alkylene, C$_3$-alkylene-NRhh-S(0)$_w$, C$_3$-3alkylene-S(0)$_w$NRhh, C$_3$-3alkylene-C$_i$-3alkylene-S(0)$_w$NRhh, and C$_3$-6cycloalkylene- C$_0$-2alkylene NRhh-S(0)$_w$; wherein $L_i$ may be optionally substituted by one, two or three substituents selected from the group consisting of halogen, hydroxyl, C$_i$-alkyl (optionally substituted by one, two or three substituents each selected independently from $R_{gg}$);

- $R_{44}$ is selected from the group consisting of H, halogen, hydroxyl, C$_i$-alkoxy, 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 the heterocycle and the heteroaryl may be optionally substituted by one or two substituents each selected independently from $R_{gg}$;
**R** is selected for each occurrence from group consisting of halogen, hydroxyl, C\textsubscript{i}\textsubscript{4} alkyl, C\textsubscript{2,4} alkoxy, C\textsubscript{5,6} cycloalkyl, -NR'R'', -NR'S(0)\textsubscript{w}-Ci\textsubscript{3+3} alkyl, S(0)\textsubscript{w}-NR'R'', and -S(0)\textsubscript{w}-Ci\textsubscript{3} alkyl, where w is 0, 1, or 2, wherein C\textsubscript{i} alkyl, C\textsubscript{4} alkoxy, C\textsubscript{2,4} alkenyl and C\textsubscript{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(0)\textsubscript{w}-Ci\textsubscript{3} alkyl, S(0)\textsubscript{w}-NR'R'', and -S(0)\textsubscript{w}-Ci\textsubscript{3} alkyl;

**R\textsubscript{g}** is selected for each occurrence from group consisting of halogen, hydroxyl, C\textsubscript{1,6} alkyl, C\textsubscript{1,6} alkoxy, C\textsubscript{2,6} alkenyl, C\textsubscript{3,6} cycloalkyl, -NR'R'', -NR'S(0)\textsubscript{w}-C\textsubscript{1,3} alkyl, S(0)\textsubscript{w}-NR'R'', and -S(0)\textsubscript{w}-Ci\textsubscript{3} alkyl, where w is 0, 1, or 2, wherein C\textsubscript{1,6} alkyl, C\textsubscript{1,6} alkoxy, C\textsubscript{2,6} alkenyl and C\textsubscript{3,6} cycloalkyl may each be optionally substituted by one, two or three substituents each independently selected from the group consisting of halogen, C\textsubscript{1,6} alkyl, C\textsubscript{1,6} alkoxy, hydroxyl, C(0)OH, -C(0)OCi\textsubscript{6} alkyl, -0-C\textsubscript{3,6} cycloalkyl, -O-heterocycle, -O-heteroaryl, -O-phenyl, -NR'R'', -NR'S(0)\textsubscript{w}-Ci\textsubscript{3} alkyl, S(0)\textsubscript{w}-NR'R'', and -S(0)\textsubscript{w}-Ci\textsubscript{3} alkyl; w is 0, 1 or 2; and

**R\textsubscript{h}** is selected for each occurrence from the group consisting of H, C\textsubscript{1,6} alkyl and C\textsubscript{3,6} cycloalkyl.

2. The compound of claim 1, wherein Li is C\textsubscript{i} alkenylene or C\textsubscript{3} cycloalkylene.

3. The compound of claim 1 or 2, represented by:

![Chemical Structure](image)

wherein qq is 0 or 1.

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

![Chemical Structure](image)

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

\[ \text{wherein } X \text{ independently for each occurrence is selected from the group consisting of } O, S, NR_{bb}, C, \text{ and } C(R_{88}) \text{ and } C(R_{88})_{(R99)} \text{; } X_2 \text{ independently for each occurrence is selected from the group consisting of } O, S \text{ and } NR_{bb}; R'' \text{ is } H \text{ or } C_4\text{-alkyl, each } 3_4 \text{ of } R_{77}, R_{88} \text{ and } R_{99} \text{ is independently selected for each occurrence from } H \text{ and } R_{86}, \text{ and } n \text{ is } 0, 1, 2, \text{ or } 3. \]

7. The compound of claim 6, where each R_{66}, R_{77}, R_{88} \text{ and } R_{99} \text{ is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxyl, } C_6\text{-alkyl, } C_3\text{-6 cycloalkyl}, \text{ and heterocycle, wherein } C_6\text{-alkyl, } C_3\text{-6 cycloalkyl, and heterocycle are optionally substituted by one, two or three substituents each independently selected from the group consisting of hydroxyl, } C_6\text{-alkyl, } C_6\text{-alkoxy (optionally substituted by } C_3\text{-6 cycloalkyl, heterocycle, } -C_1\text{-alkyl-heterocycle and } C_1\text{-alkyl- } C_3\text{-6 cycloalkyl}), \text{ and } -S(0)_w -C_3\text{ alkyl (w is } 0, 1, \text{ or } 2) \text{ and } -NR'S(0)^w -C_4\text{ alkyl}. \]

\[ \text{R'} \text{ is independently selected for each occurrence from } H \text{ and } C_4\text{ alkyl.} \]
8. The compound of any one of claims 1-7, wherein \( p = 0, 1 \) or 2, and \( R_{11} \) is selected from \( H, \) 
\( F, \) or methyl.

9. A compound having the Formula (IIa):

\[
\text{\includegraphics[width=0.5\textwidth]{formula.png}}
\]

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

- \( R_1 \) is selected from the group consisting of:

\[
\text{\includegraphics[width=0.5\textwidth]{substitutions.png}}
\]

- \( R_2 \) is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl;

- \( R_{3a} \) is selected from the group consisting of hydrogen, optionally substituted \( C_1-C_{10} \) alkyl, optionally substituted \( C_2-Cl_0 \) alkenyl, optionally substituted \( C_2-Cio \) alkynyl, optionally substituted \( C_3-Ci2 \) cycloalkyl, optionally substituted \( C_3-Ci2 \) cycloalkenyl, optionally substituted aryl, halo, \( \text{OR}_c, \) \( \text{NR}_d \text{R}_d, \) \( 0(0)^n, \) \( \text{NO}_2, \) \( \text{CN}, \) \( \text{C}(0)\text{R}_c, \) \( \text{C}(0)\text{C}(0)\text{R}_c, \) \( \text{C}(0)\text{NR}_d \text{R}_d, \) \( \text{NR}_d \text{C}(0)\text{R}_c, \) \( \text{NR}_d S(0)_n \text{R}_c, \) \( \text{N} \text{RdC}(0)_c \text{Rc}, \) \( \text{NRdC}(0)\text{NRdRd}, \) \( \text{NRdS}(0)_n \text{NRdRd}, \) \( \text{NRdS}(0)_n \text{R}_c, \) \( \text{S}(0)_n \text{R}_c, \) \( \text{S}(0)_n \text{NR}_d \text{R}_d, \) \( \text{OC}(0)\text{OR}_c (\text{C} = \text{NR}_d) \text{R}_c, \) optionally substituted heterocyclic and optionally substituted heteroaryl;

- \( R_{4a} \) is selected from the group consisting of hydrogen, optionally substituted \( C_1-C_{10} \) alkyl, optionally substituted \( C_2-Cl_0 \) alkenyl, optionally substituted \( C_2-Cio \) alkynyl, optionally substituted \( C_3-Ci2 \) cycloalkyl, optionally substituted \( C_3-Ci2 \) cycloalkenyl, optionally substituted
aryl, halo, ORc, S(0)Rc, NRdRd, C(0)ORc, NO2, CN, C(0)Rc, C(0)C(0)Rc, C(0)NRdRd, NRdC(0)Rc, NRdS(0)Rc, N(Rd)(COORc), NRdC(0)C(0)Rc, NRdC(0)NRdRd, NRdS(0)nRdRd, NRdS(0)nRd, and O;

Optionally substituted aryl, alkyl, heterocyclic, optionally substituted ary1, optionally substituted alkynyl, optionally substituted heteroaryl, optionally substituted cycloalkenyl, optionally substituted heteroaryl; optionally substituted nitrogen atoms, wherein said heterocyclic ring optionally contains one or more ring heteroatoms selected from oxygen and sulfur;

Rb1 is selected from the group consisting of hydrogen, optionally substituted C1-C10 alkyl, optionally substituted C2-C10 alkenyl, optionally substituted C2-Cio alkynyl, optionally substituted C3-C12 cycloalkyl, optionally substituted C3-C12 cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, C(0)ORc, C(0)Rc, C(O)(C)(O)Rc and S(O)nRc;

or alternatively, Rb1 and the nitrogen atom to which it is attached is taken together with an adjacent C(Rb1)(Rb1) or C(Rb1)(Rb2) to form an optionally substituted, 4- to 12-membered heterocyclic ring containing one or more ring nitrogen atoms, wherein said heterocyclic ring optionally contains one or more ring heteroatoms selected from oxygen and sulfur;

each Rb1 and Rb2 is independently selected from the group consisting of hydrogen, optionally substituted C1-C10 alkyl, optionally substituted C2-C10 alkenyl, optionally substituted C2-Cio alkynyl, optionally substituted C3-C12 cycloalkyl, optionally substituted C3-C12 cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, ORc, N34%, C(0)ORc, NO2, CN, C(0)Rc, C(0)C(0)Rc, C(0)NRdRd, NRdC(0)Rc, NRdS(0)nRc, N(Rd)(COORc), NRdC(0)C(0)Rc, NRdC(0)NRdRd, NRdS(0)nNRdRd, NRdS(0)nRd, S(0)nRc, S(0)nRd, ORc, and (C=NRd)Rc; or

Alternatively, two geminal Rb1 groups or two geminal Rb2 groups and the carbon to which they are attached are taken together to form a (C) group, or yet alternatively, two geminal Rb1 groups or two geminal Rb2 groups are taken together with the carbon atom to which they are attached to form a spiro C3-C12 cycloalkyl, a spiro C3-C12 cycloalkenyl, a spiro heterocyclic, a spiro aryl or spiro heteroaryl, each optionally substituted;

Y is selected from the group consisting of S(0)n, NRd, NRdS(0)n, NRdS(0)n, NRd, NRdC(0), NRdC(0), NRdC(0)NRd, S(0)nNRd, and O;
each Rcis independently selected from the group consisting of hydrogen, optionally substituted C\textsubscript{1}-C\textsubscript{10} alkyl, optionally substituted C\textsubscript{2}-C\textsubscript{10} alkenyl, optionally substituted C\textsubscript{2}-C\textsubscript{10} alkynyl, optionally substituted C\textsubscript{3}-C\textsubscript{6} cycloalkyl, optionally substituted C\textsubscript{3}-C\textsubscript{6} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;

- each R\textsubscript{d} is independently selected from the group consisting of hydrogen, optionally substituted C\textsubscript{1}-C\textsubscript{10} alkyl, optionally substituted C\textsubscript{2}-C\textsubscript{10} alkenyl, optionally substituted C\textsubscript{2}-C\textsubscript{10} alkynyl, optionally substituted C\textsubscript{3}-C\textsubscript{6} cycloalkyl, optionally substituted C\textsubscript{3}-C\textsubscript{6} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two geminal R\textsubscript{d} groups are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl;

- k is 0 or 1;
- m is 0, 1, 2, 3, 4, or 5;
- each n is independently 0, 1 or 2.

- 10. The compound of claim 9, wherein m is 0, 1 or 2.
- 11. The compound of claim 9 or 10, wherein k is 0.
- 12. The compound of any one of claims 9-11, wherein m is 1.
- 13. The compound of any one claims 9-12, wherein R\textsubscript{3a} is hydrogen.
- 14. The compound of any one of claims 9-13, wherein R\textsubscript{a} is hydrogen or C\textsubscript{1}-C\textsubscript{4} alkyl (optionally substituted by 1, 2 or 3 halogens).
- 15. The compound of any one claims 9-14, wherein each of R\textsubscript{b} and R\textsubscript{t} is independently selected from of hydrogen, hydroxyl, C\textsubscript{1,4}alkoxy (optionally substituted by one, two or three substituents independently selected from halogen and hydroxyl) and C\textsubscript{1,4}alkoxy.
- 16. The compound of claim 15, wherein each of R\textsubscript{b} and R\textsubscript{b2} is hydrogen.
- 17. The compound of any one of claims 9-16, wherein R\textsubscript{2} is selected from the group consisting of phenyl and a 5-6 membered heteroaryl having one or two heteroatoms each selected from N, S, and O, wherein R\textsubscript{2} is optionally substituted by one or two substituents each independently...
selected from the group consisting of halogen, and C1-C4 alkyl (optionally substituted by one, two or three halogens.

18. The compound of any one of claims 9-17, wherein $R_2$ is phenyl.

19. The compound of any one of claims 9-18, wherein $R_2$ is phenyl is substituted with one or two $R_s$ wherein each $R_s$ is independently selected from the group consisting of optionally substituted C1-C10 alkyl, optionally substituted C2-C10 alkenyl, optionally substituted C2-C10 alkynyl, and halo.

20. The compound of any one of claims 9-17, wherein $R_2$ is selected from the group consisting of: optionally substituted thienyl, optionally substituted furanyl and optionally substituted pyridinyl.

21. The compound of any one of claims 9-20, wherein $R_{4b}$ is selected from the group consisting of optionally substituted C1-C6 alkyl, optionally substituted C3-C7 cycloalkyl, phenyl, OR, C(0)OR, C(0)RC, optionally substituted heterocycle and optionally substituted heteroaryl, wherein $R_c$ is selected, independently for each occurrence, from the group consisting of H and C1-C6 alkyl.

22. The compound of any one of claims 9-20, wherein $R_a$ is a heterocycle, or a 5-6 membered monocyclic or a 8-10 membered bicyclic heteroaryl having one, two or three heteroatoms selected from N, S or O, wherein the heterocycle or heteroaryl are optionally substituted by one, two or three substituents independently selected for each occurrence from the group consisting of halogen, C1-C6 alkyl (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), C1-C6 alkoxy (optionally substituted by one, two or three halogens), hydroxyl, and NRaR$_d$ wherein $R_d$ is independently for each occurrence selected from H and C1-C6 alkyl, or the two $R_d$s taken together with the N to which they are attached form a heterocyclic ring.

23. The compound of claim 22, wherein $R_{4a}$ is selected from the group consisting of tetrahydropyranyl, thiadiazolyl, tetrahydrofuranyl, and morpholinyl.

24. The compound of any one of claims 9-20, wherein $R_{4a}$ is monocyclic heteroaryl containing one, two or three ring nitrogen atoms.

25. The compound of any one of claims 9-20, wherein $R_{4a}$ is selected from the group consisting of furanyl, pyridinyl, pyrazinyl, pyrazolyl, imidazolyl, isoxazolyl, triazolyl,
thiazolyl, oxadiazolyl, thiadiazolyl, thienyl, piperazinyl, and benzimidazolyl, each optionally substituted.

26. The compound of claim 20, wherein \( R_a \) is selected from the group consisting of:

\[
\begin{align*}
\text{thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl, thiazolyl, oxadiazolyl, thienyl, piperazinyl.}
\end{align*}
\]

wherein each \( X \) is independently \( O, S \) or \( NR_g \);

each \( R_g \) is independently selected from the group consisting of hydrogen, \( C_1-C_4 \) alkyl, \( C_3-C_6 \) cycloalkyl, and

wherein each \( R_6, R_7 \) and \( R_8 \) is independently selected for each occurrence from the group consisting of hydrogen, \( C_1-C_6 \) alkyl, \( C_2-C_6 \) alkenyl, \( C_2-C_6 \) alkynyl, \( C_3-C_7 \) cycloalkyl, \( C_3-C_7 \) cycloalkenyl, phenyl, heterocycle, heteroaryl, halo, hydroxyl, carboxyl, \( \text{OR}_c, \text{NR}_d \text{R}_d \), \( \text{C}(0)\text{OR}_c \), \( \text{CN}, \text{C}(0)\text{R}_c \), wherein the \( C_i \text{alkyl}, C_2-C_6 \text{ alkenyl}, C_2-C_6 \text{ alkynyl}, C_3-C_7 \text{ cycloalkyl}, C_3-C_7 \text{ cycloalkenyl}, \) phenyl, heterocycle, and heteroaryl of \( R_6 \) \( R_7 \) and \( R_8 \) may each be optionally substituted by one, two or three substituents selected from halo, hydroxyl, \( C_1- \) ealkyl and \( C_1- \) ealkoxy;

\( R_c \) is \( C^1 \text{alkyl} \); and

\( R_d \) is independently for each occurrence selected from the group consisting of \( H \) and \( C_1- \) alkyl, or the two \( R_d \) taken together with the \( N \) to which they are attached form a heterocyclic ring.

27. The compound of claim 26, wherein \( R_{4a} \) is an optionally substituted \( C_3-C_7 \) cycloalkyl.

28. The compound of any one of claims 9-12, wherein \( R_{4a} \) is an optionally substituted cyclopropyl or an optionally substituted cyclobutyl.
29. The compound of claim 27 or 28, wherein $R_{4a}$ is a $C_3$-$C_7$ cycloalkyl substituted with a substituent having the formula:

$$
\begin{array}{c}
\text{R}_h \\
\text{R}_h \\
\text{R}_9 \\
\end{array}
$$

wherein:

- each $R_h$ is independently selected from the group consisting of hydrogen, halo, optionally substituted $C_1$-$C_{10}$ alkyl, and optionally substituted $C_3$-$C_6$ cycloalkyl, or two geminal $R_h$ groups are independently taken together with the carbon atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl;
- $R_9$ is selected from the group consisting of hydrogen, optionally substituted $C_1$-$C_{10}$ alkyl, optionally substituted $C_2$-$C_{10}$ alkenyl, optionally substituted $C_2$-$C_{10}$ alkynyl, optionally substituted $C_3$-$C_{12}$ cycloalkenyl, optionally substituted aryl, halo, OR, NR, NRC(O)R, NO$_2$, CN, C(0)OR, C(0)C(0)R, C(0)NRdRd, NRC(0)R, NRdOR, NRd(NH)Rd, O,NRC(0)R, (C=NRd)R, or optionally substituted heteroaryl;
- $p$ is 0, 1, or 2;
- and wherein the $C_3$-$C_7$ cycloalkyl is optionally further substituted.

30. The compound of any one of claims 27 to 29, wherein $R_{4a}$ is selected from the group consisting of:

$$
\begin{array}{c}
\text{R}_9 \\
\text{R}_9 \\
\text{R}_9 \\
\end{array}
$$

and

$$
\begin{array}{c}
\text{R}_9 \\
\text{R}_9 \\
\end{array}
$$

wherein each $R_i$ is independently selected from the group consisting of hydrogen, optionally substituted $C_1$-$C_{10}$ alkyl, optionally substituted $C_2$-$C_{10}$ alkenyl, optionally substituted $C_2$-$C_{10}$ alkynyl, optionally substituted $C_3$-$C_{12}$ cycloalkenyl, optionally substituted aryl, halo, OR, NR, NRC(O)R, NO$_2$, CN, C(0)OR, C(0)C(0)R, C(0)NRdRd, NRC(0)R, NRdOR, NRd(NH)Rd, O,NRC(0)R, (C=NRd)R, or optionally substituted heteroaryl.
alkynyl, optionally substituted C3-C12 cycloalkenyl, optionally substituted C2=C6 cycloalkyl, optionally substituted aryl, halo, ORc, NRjRd, C(0)O Rc, NO2, CN, C(0)Rc, C(0)(C(0))Rc, C(0)NR dRd, NRc(C(0))Rc, NRcS(0)nRc, NRc(COO) c, NRdC(0)(C(0))Rc, NRDd(C0)NRdRd, NRcS(0)nNRdRc, S(0)nRc, S(0)nRc, S(0)nNRdRd, OC(0)ORc, (C=NRd)Rc, optionally substituted heterocyclic and optionally substituted heteroaryl; alternatively, two geminal Rio groups are taken together with the carbon atom to which they are attached to form a spiro C3-C12 cycloalkyl, a spiro C3-C12 cycloalkenyl, a spiro heterocyclic, a spiro aryl or spiro heteroaryl, each optionally substituted; or yet alternatively, two vicinal Rio groups are taken together with the carbon atoms to which they are attached to form a fused, optionally substituted cyclic group selected from the group consisting of C4-C8 cycloalkyl, C4-C8 cycloalkenyl, 4- to 8-membered heterocyclic, aryl and heteroaryl, each optionally substituted; or further alternatively, two Rio groups attached to non-adjacent carbon atoms are taken together with the carbon atoms to which they are attached to form a bridged cyclic group selected from the group consisting of C4-C8 cycloalkyl, C4-C8 cycloalkenyl, and 4- to 8-membered heterocyclic, each optionally substituted;

each Ri is independently selected from the group consisting of hydrogen, halo, optionally substituted CpC6 alkyl, and optionally substituted C3-C6 cycloalkyl, or two geminal Ri groups are independently taken together with the carbon atom to which they are attached to form an optionally substituted heterocyclic or an optionally substituted heteroaryl;

5 R9 is selected from the group consisting of hydrogen, optionally substituted C1-C10 alkyl, optionally substituted C2-C10 alkenyl, optionally substituted C2-C10 alkynyl, optionally substituted C3-C12 cycloalkyl, optionally substituted ary1, halo, ORc, NRdRd, C(0)ORc, NO2, CN, C(0)Rc, C(0)(C(0))Rc, C(0)NRjRd, NRdC(0)Rc, NRdS(0)nRc, NRd(COO) c, NRdC(0)(C(0))Rc, NRd(C0)NRdRd, NRdS(0)nRc, 10 S(0)nRc, SiOinNRdRd, OC(0)ORc, (C=NRd)Rc, optionally substituted heterocyclic and optionally substituted heteroaryl;

p is 0, 1, or 2.

31. The compound of any one of claims 9-30, wherein Y is S, S(0) 2 or S(0)2NR d.
32. The compound of any one of claims 9-20 wherein R4b is heterocycle or a 5-6 membered monocyclic or a 8-10 membered bicyclic heteroaryl having one, two or three heteroatoms selected from N, S or O, wherein the heterocycle or heteroaryl are optionally substituted by
one, two or three substituents independently selected for each occurrence from the group consisting of halogen, \( \text{C}_1^6 \text{alkyl} \) (optionally substituted by one, two or three substituents each independently selected from halogen and hydroxyl), \( \text{C}_1^6 \text{alkoxy} \) (optionally substituted by one, two or three halogens), hydroxyl, and \( \text{NRdRd} \) wherein \( \frac{3}{4} \) is independently for each occurrence selected from \( \text{H} \) and \( \text{C}_1^4 \text{alkyl} \), or the two \( \text{R}_{4b} \) taken together with the \( \text{N} \) to which they are attached form a heterocyclic ring.

33. The compound of any one of claims 9-20, wherein \( \text{R}_{4b} \) is selected from the group consisting of furanyl, pyridinyl, pyrazinyl, pyrazolyl, imidazolyl, isoxazolyl, triazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, thienyl, piperazinyl, and benzimidazolyl, each optionally substituted.

34. A compound selected from the group consisting of:
and pharmaceutically acceptable salts thereof.

35. A pharmaceutical composition comprising a compound of any one of claims 1-34 and a pharmaceutically acceptable carrier or excipient.

36. The pharmaceutical composition of claim 35, wherein the composition further comprises at least one additional CFTR modulator.

37. The pharmaceutical composition of claim 35, wherein the composition further comprises at least two additional CFTR modulators.

38. A method of enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof comprising administering to said subject an effective amount of a compound of any one of claims 1-34, or a pharmaceutical composition of any one claims 35-36.

39. The method of claim 38, wherein the activity of a mutant CFTR is enhanced.

41. The method of claim 40 wherein AF508 CFTR activity is enhanced.

42. The method of any one of claims 38-41, wherein the subject is suffering from a disease associated with decreased CFTR activity.

43. The method of claim 42, wherein the disease is selected from the group consisting of cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, A-β-lipoproteinemia, lysosomal storage disease, type I chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type I hereditary angioedema, coagulation-fibrinolysis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, Sjogren's syndrome, familial hypercholesterolemia, I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhoff/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myeloperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type I, 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 Strausssler-Scheinker syndrome.

44. The method of claim 43 wherein the disease is cystic fibrosis.

45. The method of claim 44, wherein the subject is a human patient.

46. The method of claim 45, further comprising administering an additional CFTR modulator.

47. The method of claim 46, wherein at least two additional CFTR modulators are administered.
48. The method of claim 46 or 47, wherein at least one CFTR modulator is a CFTR corrector or potentiator.

49. The method of claim 48, wherein the CFTR corrector is selected from the group consisting of VX-809, VX-661, VX-152, VX-440, GLPG-2222, GLPG2665, and VX-983 and the CFTR potentiator is selected from the group consisting of GLPG-1 837, ivacaftor and genistein.

50. The method of claim 49, wherein one of the at least two additional therapeutic agents is a CFTR corrector and the other is a CFTR potentiator.

51. A method of identifying a candidate agent that increases CFTR activity, comprising:
   a) contacting a cell that expresses a CFTR protein with the candidate agent and a compound of any one of claims 1 to 34;
   b) measuring the CFTR activity in the cell in the presence of the candidate agent and the compound of any one of claims 1 to 34; and
   c) 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.

52. The method of claim 51, wherein the cell expresses a mutant CFTR protein.

53. The method of any one of claims 51 and 52, wherein CFTR activity is measured by measuring chloride channel activity of the CFTR, and/or other ion transport activity.

54. The method of claim 53, wherein the method is high-throughput.

55. The method of any one of claims 50-54, wherein the candidate agent is a CFTR corrector or a CFTR potentiator.

56. A method of treating cystic fibrosis in a patient in need thereof, comprising administering an effective amount of compound of any one of claims 1-34 or a pharmaceutical composition of any one of claims 35-37.
INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/002020

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D277/56 C07D417/12 A61K31/341 A61K31/4155 A61K31/4178
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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>wo 2007078113 AI (SK CORP [KR]; CHO JEONG woo [KR]; CHOI SANG RAK [KR]; HWANG SUN GWAN [ ] 12 July 2007 (2007-07-12) page 1, line 5 - line 8 page 4, line 5 - line 14 tables 1-31</td>
<td>1-56</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

K: 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

“A” document member of the same patent family

Date of the actual completion of the international search
15 March 2016

Date of mailing of the international search report
22/03/2016

Name and mailing address of the ISA/Authorized officer
European Patent Office, P.O. 5818 Patentlaan 2 NL - 2380 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Hoepfner, Wolfgang

Form PCT/ISA210 (second sheet) (April 2000)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 2007078113 A1</td>
<td>12-07-2007</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>WO 2011008931 A2</td>
<td>20-01-2011</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>