

SILICONE ATOMS CONTAINING IVACAFTOR ANALOGUES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. provisional application number 62/319,439, filed April 7, 2016; the contents of which is hereby incorporated by
5 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-
10 529, 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
15 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
20 proteins that are critical for normal physiology (Balch et al., *Science* **319**, 916-9 (2008); Powers, et al., *Annu Rev Biochem* **78**, 959-91 (2009); Hutt et al., *FEBS Lett* **583**, 2639-46 (2009)).

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

percent of patients have a deletion of phenylalanine (Phe) 508 ($\Delta F508$) 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 $\Delta F508$ mutation is thus associated with defective folding and trafficking, as well as enhanced degradation of the mutant CFTR protein (Qu et al., *J Biol Chem* **272**, 15739-44 (1997)). The loss of a functional CFTR channel at the plasma membrane disrupts ionic homeostasis (Cl^- , Na^+ , HCO_3^-) and airway surface hydration leading to reduced lung function (Riordan et al.). Reduced periciliary liquid volume and increased mucus viscosity impede mucociliary clearance resulting in chronic infection and inflammation, phenotypic hallmarks of CF disease (Boucher, *J Intern Med* 261, 5-16 (2007)).

In addition to respiratory dysfunction, $\Delta F508$ 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, cholestatic liver disease (e.g. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)) (Sloane et al. (2012), PLoS ONE 7(6): e39809.doi:10.1371/journal.pone.0039809; Bombieri et al. (2011), *J Cyst Fibros.* 2011 Jun;10 Suppl 2:S86-102; (Albert et al. (2008), *Clinical Respiratory Medicine*, Third Ed., Mosby Inc.; Levin et al. (2005), *Invest Ophthalmol Vis Sci.*, 46(4):1428-34; Froussard (2007), *Pancreas* 35(1): 94-5), Son et al. (2017) *J Med Chem* 60(6):2401-10.

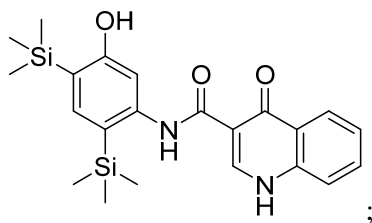
[0005] A potential strategy for improving e.g., a drug's metabolic properties, efficacy, and/or safety profile is silicon modification. At the same time, because the general properties are similar to those of carbon, replacement of carbon by silicon would not be expected to affect e.g., the biochemical potency and/or selectivity of the drug as compared to the original chemical entity that contains only carbon.

[0006] 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

5 **[0007]** This disclosure is directed in part to a compound selected from *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide and a pharmaceutically acceptable salt thereof, wherein at least one carbon atom is replaced by silicon. In some embodiments, the carbon atom(s) replaced by silicon is a non-aromatic carbon. In other
10 embodiments, the carbon atom(s) replaced by silicon is the quaternary carbon atom of one *tert*-butyl moiety or two *tert*-butyl moieties. In certain embodiments, one or more hydrogens are replaced by deuterium.

[0007a] In one aspect of the present disclosure, there is provided a compound represented by:



or a pharmaceutically acceptable salt thereof.

[0007b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

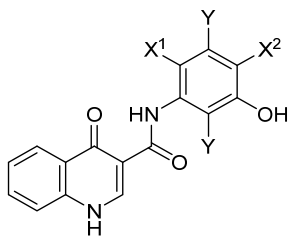
[0007c] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, 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/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myeloperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis

CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, Huntington's disease, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidoluysian, myotonic dystrophy, hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, cholestatic liver disease, and Straussler-Scheinker syndrome, in a subject in need thereof.

[0007d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.

[0007e] In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treating cystic fibrosis in a patient in need thereof.

[0008] For example, disclosed herein are compounds having Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, in which X¹, X² and Y are as defined herein.

[0009] Also contemplated herein are pharmaceutical compositions that include a disclosed compound, e.g., *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide wherein at least one carbon atom is replaced by silicon, and a pharmaceutically acceptable carrier or excipient. Further contemplated herein are pharmaceutical compositions

5 that include a disclosed compound such as those compounds having Formula I and a pharmaceutically acceptable carrier or excipient. In certain embodiments, the compositions can include at least one additional CFTR modulator, for example, may include one, two, three, four, five or more additional CFTR modulators.

[0010] In certain embodiments, a method is provided comprising administering a disclosed compound to a subject (e.g., a human patient) 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/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myeloperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, Huntington's disease, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidolusian, myotonic dystrophy, hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, cholestatic liver disease (e.g. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)), and Straussler-Scheinker syndrome). In certain embodiments, the disease is cystic fibrosis. For example, contemplated herein is a method for treating a patient suffering from cystic fibrosis comprising administering to said patient an effective amount of a disclosed compound.

[0011] In some embodiments, disclosed methods described herein can further include administering at least one additional CFTR modulator e.g., administering at least two, three, four or five additional CFTR modulators. In certain embodiments, at least one additional CFTR modulator is a CFTR corrector (e.g., VX-661 (tezacaftor), VX-152, VX-440, VX-445, VX-659, or VX-983) or, e.g., VX-809 (lumacaftor) or, e.g., GLPG2851, GLPG2665, GLPG2737, or GLPG2222.

DETAILED DESCRIPTION

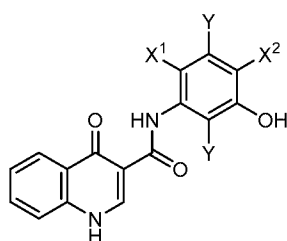
[0012] As used herein, the words “a” and “an” are meant to include one or more unless otherwise specified. For example, the term “an agent” encompasses both a single agent and a combination of two or more agents.

5 **[0013]** As discussed above, the present disclosure is directed in part to compounds as described herein having the Formula I or a pharmaceutically acceptable salt thereof, pharmaceutical compositions, methods of increasing CFTR activity and methods of treating cystic fibrosis. In part, the disclosure relates to novel derivatives of ivacaftor, and pharmaceutically acceptable salts thereof. Ivacaftor, also known as VX-770 and by the
10 chemical name, *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide, acts as a CFTR potentiator.

[0014] For example, provided herein is a compound selected from *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide and a pharmaceutically acceptable salt thereof, wherein at least one carbon atom may be replaced by silicon.

15 **[0015]** In certain embodiments, one carbon atom may be replaced by silicon. In other embodiments, two carbons atoms may be replaced by silicon. For example, the carbon replaced by silicon may be a non-aromatic carbon. In another embodiment, the quaternary carbon atom of one *tert*-butyl moiety may be replaced by silicon. In a further embodiment, the quaternary carbon atoms of two *tert*-butyl moieties may be replaced by silicon. In certain
20 embodiments, one or more hydrogens may be replaced by deuterium. For example, one or more hydrogens of the *tert*-butyl moiety may be replaced by deuterium.

[0016] Also provided herein are compounds having Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from the group consisting of $-\text{Si}(\text{R}^3)_3$, $-\text{C}(\text{CY}_3)_3$, hydrogen, halogen, C_{1-3} alkyl optionally substituted by one or more halogens, C_{3-6} cycloalkyl, and 4-6 membered saturated monocyclic heterocyclyl; wherein C_{3-6} cycloalkyl and 4-6 membered saturated monocyclic heterocyclyl may be optionally substituted by one, two, three or more substituents each independently selected for each occurrence from R^{11} ;

X^2 is selected from the group consisting of $-\text{Si}(\text{R}^3)_3$ and $-\text{C}(\text{CY}_3)_3$;

wherein at least one of X^1 or X^2 is $-\text{Si}(\text{R}^3)_3$;

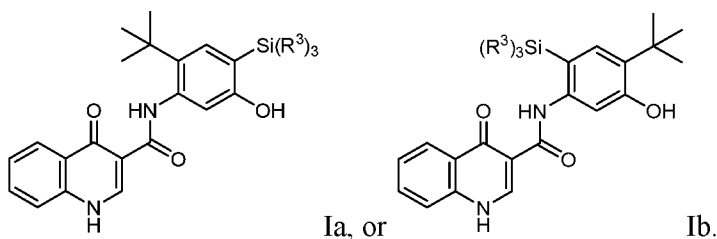
R^3 is independently selected for each occurrence from the group consisting of hydroxyl, C_{1-4} alkyl, C_{1-4} alkoxy, and phenyl, wherein C_{1-4} alkyl, C_{1-4} alkoxy, and phenyl may optionally be substituted by one, two, three or more deuterium atoms; or two R^3 groups together with the silicon to which they are attached form a 4-6 membered saturated cyclosilane;

Y is independently selected for each occurrence from the group consisting of hydrogen and deuterium; and

R^{11} is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxyl, cyano, and C_{1-6} alkyl; wherein C_{1-6} alkyl may be optionally substituted by one or more substituents each independently selected for each occurrence from the group consisting of halogen, hydroxyl, and C_{1-6} alkoxy.

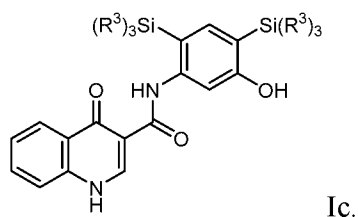
[0017] In some embodiments, one of X^1 or X^2 is $-\text{C}(\text{CH}_3)_3$ and the other one of X^1 or X^2 is $-\text{Si}(\text{R}^3)_3$.

[0018] For example, in certain embodiments the compound may be represented by:



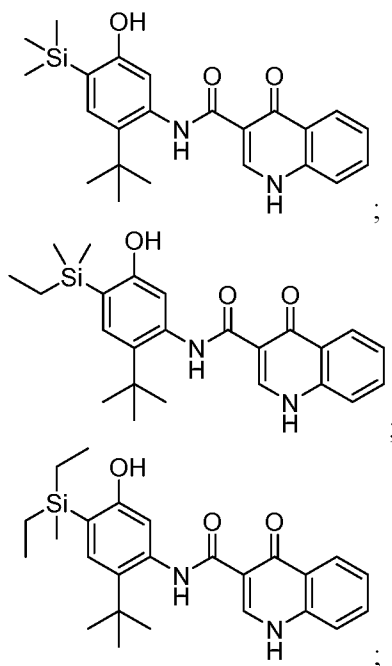
[0019] In other embodiments, both of X^1 and X^2 are $-\text{Si}(\text{R}^3)_3$.

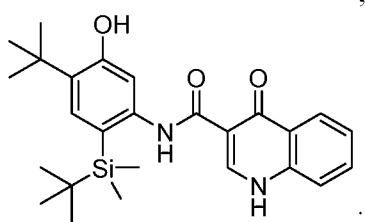
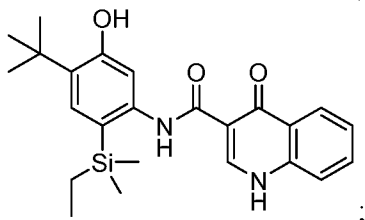
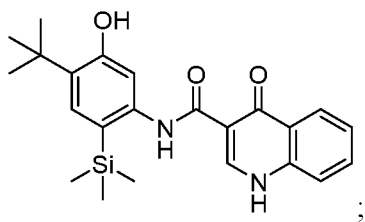
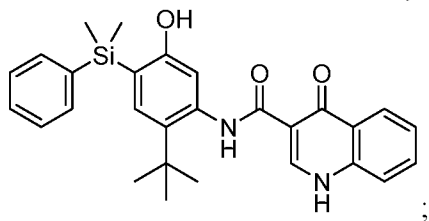
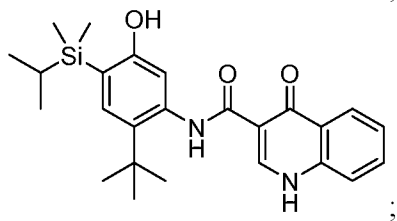
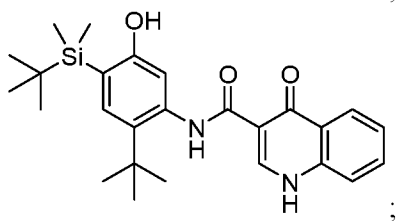
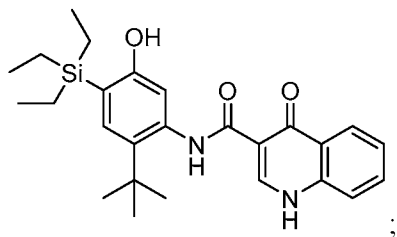
[0020] For example, in certain embodiments the compound may be represented by:

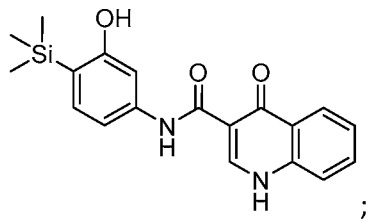
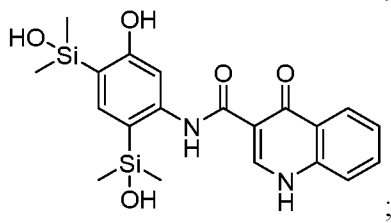
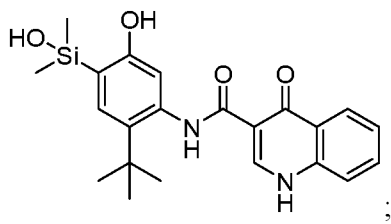
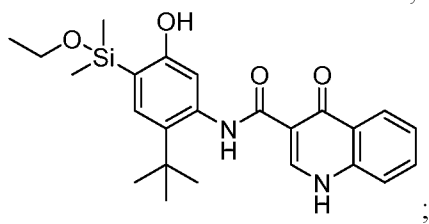
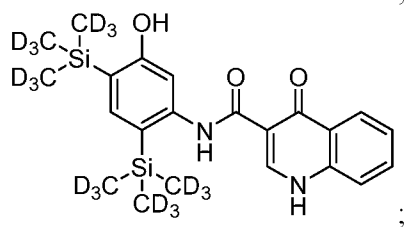
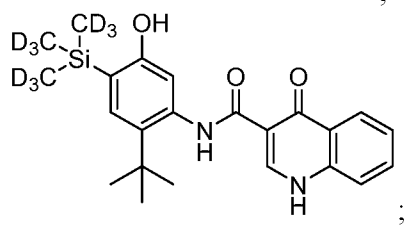
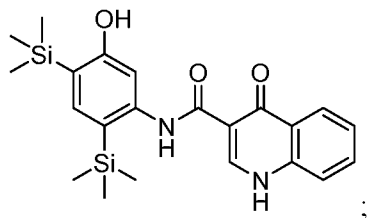


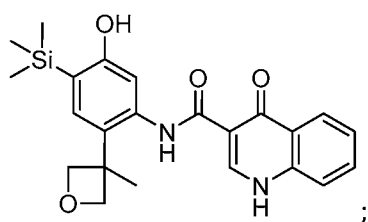
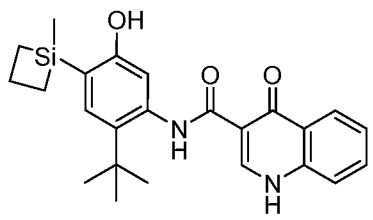
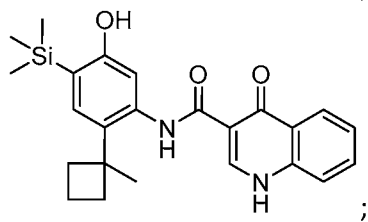
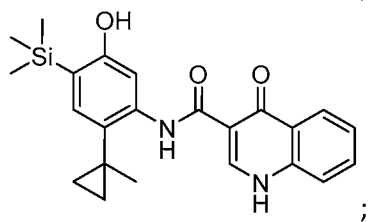
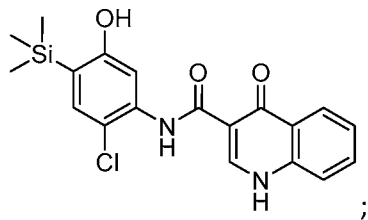
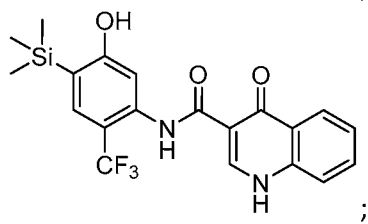
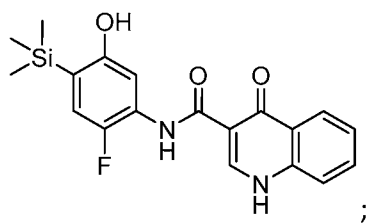
[0021] In some embodiments, R^3 may be independently selected for each occurrence from the group consisting of hydroxyl, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, and phenyl, wherein methyl, ethyl, isopropyl, *tert*-butyl, methoxy, ethoxy, isopropoxy, *tert*-butoxy, and phenyl may optionally be substituted by one, two, three or more deuterium atoms. For example, R^3 may be independently selected for each occurrence from $-\text{CH}_3$ and $-\text{CD}_3$.

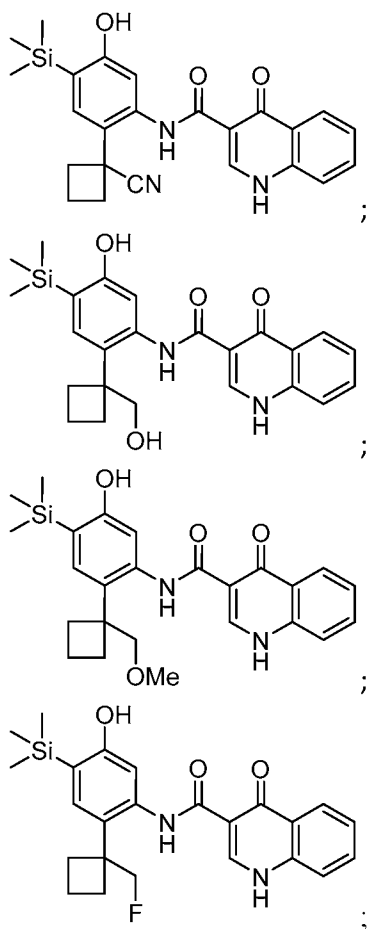
10 [0022] For example, disclosed herein are compounds selected from the group consisting of:











and a pharmaceutically acceptable salt thereof; wherein any atom not designated as deuterium is present at its natural isotopic abundance.

[0023] Also contemplated herein are pharmaceutical compositions that include a disclosed compound, e.g., *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide wherein at least one carbon atom is replaced by silicon, and a pharmaceutically acceptable carrier or excipient. Further contemplated herein are pharmaceutical compositions that include a disclosed compound such as those compounds having Formula I 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.

[0024] The features and other details of the disclosure will now be more particularly described. Before further description of the disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art.

5 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.

[0025] It will be appreciated that the description of the disclosure herein should be construed in congruity with the laws and principals of chemical bonding.

[0026] 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, "C₁-C₁₀ 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 C₁₋₆ alkyl, C₁₋₄ alkyl, and C₁₋₃ alkyl, respectively. Examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *n*-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

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[0027] 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 C₂₋₆ alkenyl, and C₃₋₄ alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

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[0028] 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.

[0029] The term "cycloalkyl," as used herein, refers to saturated cyclic alkyl moieties having 3 or more carbon atoms, for example, 3-10, 3-6, or 4-6 carbons, referred to herein as C₃₋₁₀ cycloalkyl, C₃₋₆ cycloalkyl or C₄₋₆ cycloalkyl, respectively for example. Examples of

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cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl.

[0030] The term "cycloalkenyl," as used herein, refers to cyclic alkenyl moieties having 3 or more carbon atoms.

5 **[0031]** The term "cycloalkynyl," as used herein, refers to cyclic alkynyl moieties having 5 or more carbon atoms.

[0032] "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.

10 **[0033]** 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 C₁₋₆ alkoxy, and C₂₋₆ alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

15 **[0034]** The term "heterocyclic" or "heterocycle" or "heterocyclyl" 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
20 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
25 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, piperazine, oxetane, azetidine, tetrahydrofuran or dihydrofuran, etc.

[0035] 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.

[0036] 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. Contemplated heteroaryl groups 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, quinoliny, isoquinoliny, indolyl, benzimidazolyl, benzofuranyl, cinnoliny, indazolyl, indoliziny, phthalazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, thiazolopyridinyl, oxazolopyridinyl and azaindolyl. The foregoing heteroaryl groups may be C-attached or heteroatom-attached (where such is possible). For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). In some embodiments, the heteroaryl is 4- to 12-membered heteroaryl. In yet other embodiments, the heteroaryl is a mono or bicyclic 4- to 10-membered heteroaryl.

[0037] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

[0038] 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.

[0039] The terms “hydroxy” and “hydroxyl” as used herein refers to the radical -OH.

[0040] As will be understood by the skilled artisan, “H” is the symbol for hydrogen, “D” is the symbol for deuterium, “N” is the symbol for nitrogen, “S” is the symbol for sulfur, “O” is the symbol for oxygen. “Me” is an abbreviation for methyl.

[0041] 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.

[0042] 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 $\equiv$ 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.

[0043] 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”
5 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.”

[0044] Individual enantiomers and diastereoisomers of disclosed compounds can be prepared
10 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
15 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
20 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*
25 *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.

[0045] 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.

[0046] 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.

[0047] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that disclosed compounds include both solvated and unsolvated forms. In one embodiment, a disclosed compound is amorphous or, in another embodiment, 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.

[0048] 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 compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

[0049] For example, a disclosed compound may have one or more H atoms replaced with deuterium. It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide wherein at least one carbon atom is replaced by silicon, or a preparation of a

disclosed compound having Formula I will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this disclosure.

- 5 **[0050]** In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).

[0051] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

- 15 **[0052]** In other embodiments, a disclosed compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[0053] The term "isotopologue" refers to a species in which the chemical structure differs from a specific compound of this disclosure only in the isotopic composition thereof.

- 25 **[0054]** The term "compound," when referring to a compound of this disclosure, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen

atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this disclosure will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues in total will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues in total will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

10 [0055] Certain isotopically labeled disclosed compounds (*e.g.*, those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^3H) and carbon-14 (*i.e.*, ^{14}C) isotopes are suitable for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be suitable in some circumstances. Isotopically labeled compounds 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.

20 [0056] In some embodiments one or more of the nitrogen atoms of a disclosed compound if present are oxidized to N-oxide.

[0057] 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.

25 [0058] 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.

[0059] “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.

[0060] 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.

[0061] 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.

[0062] In some examples, CFTR activity is enhanced after administration of a compound described herein when there is an increase in the CFTR activity as compared to that in the absence of the administration of the compound. CFTR activity encompasses, for example, chloride channel activity of the CFTR, and/or other ion transport activity (for example, HCO_3^- transport). In certain of these embodiments, the activity of one or more (e.g., one or two) mutant CFTRs (e.g., ΔF508 , S549N, G542X, G551D, R117H, N1303K, W1282X, R553X, 621+1G>T, 1717-1G>A, 3849+10kbC>T, 2789+5G>A, 3120+1G>A, I507del, R1162X, 1898+1G>A, 3659delC, G85E, D1152H, R560T, R347P, 2184insA, A455E, R334W, Q493X, and 2184delA CFTR) is enhanced (e.g., increased). Contemplated patients may have a CFTR mutation(s) from one or more classes, such as without limitation, Class I CFTR mutations, Class II CFTR mutations, Class III CFTR mutations, Class IV CFTR mutations, Class V CFTR mutations, and Class VI mutations. Contemplated subject (e.g., human subject) CFTR

genotypes include, without limitation, homozygote mutations (e.g., $\Delta F508$ / $\Delta F508$ and R117H / R117H) and compound heterozygote mutations (e.g., $\Delta F508$ / G551D; $\Delta F508$ / A455E; $\Delta F508$ / G542X; $\Delta 508F$ / W1204X; R553X / W1316X; W1282X/N1303K, 591 Δ 18 / E831X, F508del/R117H/ N1303K/ 3849+10kbC>T; $\Delta 303K$ / 384; and DF508/G178R).

- 5 **[0063]** In certain embodiments, the mutation is a Class I mutation, e.g., a G542X; a Class II/ I mutation, e.g., a $\Delta F508$ / 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 $\Delta F508$ / 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 $\Delta F508$ /
- 10 A455E compound heterozygous mutation. Of the more than 1000 known mutations of the *CFTR* gene, $\Delta F508$ 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, $\Delta F508$ CFTR activity is enhanced (e.g., increased). In certain
- 15 embodiments, $\Delta F508$ 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):
- 20 545-59; Bruscia et al. (2005), *PNAS* 103(8): 2965-2971).

[0064] As discussed above, the disclosure also encompasses a method of treating cystic fibrosis. Methods of treating other conditions associated with CFTR activity, including conditions associated with deficient CFTR activity, comprising administering an effective amount of a disclosed compound, are also provided herein.

- 25 **[0065]** For example, provided herein is a method of treating a condition associated with deficient or decreased CFTR activity comprising administering an effective amount of a disclosed compound 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, 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, cholestatic liver disease (e.g. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)), and Sjogren's syndrome.

[0066] 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 amplifiers, 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 amplifier. Non-limiting examples of CFTR modulators, correctors and amplifiers include VX-152, VX-440, VX-809 (lumacaftor) (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid, VX-661 (1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-[1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(2-hydroxy-1,1-dimethylethyl)-1H-indol-5-yl]-cyclopropanecarboxamide), VX-983, Ataluren (PTC124) (3-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]benzoic acid), FDL169, GLPG2222 (for example, a CFTR corrector), GLPG2851, GLPG2665, GLPG2737; and compounds described in, e.g., WO2014/144860 and 2014/176553, hereby incorporated by reference. Non-limiting examples of modulators include GLPG2451, GLPG1837, GLPG3067, QBW-251, QR-010, NB-124, riociquat, and compounds described in, e.g., WO2014/045283; WO2014/081821, WO2014/081820, WO2014/152213; WO2014/160440, WO2014/160478, US2014027933; WO2014/0228376, WO2013/038390, WO2011/113894, WO2013/038386; and WO2014/180562, of which the disclosed modulators in those publications are

contemplated as an additional therapeutic agent and incorporated by reference. Non-limiting examples of anti-inflammatory agents include N6022 (3-(5-(4-(1H-imidazol-1-yl) phenyl)-1-(4-carbamoyl-2-methylphenyl)-¹H-pyrrol-2-yl) propanoic acid), CTX-4430, N1861, N1785, and N91115.

- 5 **[0067]** In some embodiments, the methods described herein can further include administering an additional therapeutic agent or administering at least two additional CFTR therapeutic agents. These therapeutic agents may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide, e.g., any therapeutic agent known to be useful for co-administration with *N*-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. 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-152, VX-440, VX-661, VX-445, VX-659, VX-983, FDL169, GLPG2851, GLPG2665, GLPG2737, and GLPG2222) or amplifier. In certain of these 15 embodiments, one of the at least two additional therapeutic agents is a CFTR corrector (e.g., VX-809, VX-661 and VX-983) and the other is a CFTR amplifier. In certain of these embodiments, one of the at least two additional therapeutic agents is a CFTR corrector (e.g., 20 GLPG2222) and the other is a CFTR amplifier. 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 amplifier. 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). In other embodiments, the methods described herein can further include administering an epithelial sodium channel (ENaC) inhibitor (e.g., VX-371). In other embodiments, the methods 25 described herein can further include administering gene or RNA therapies, including SHP-636.

[0068] 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, modulator or amplifier (e.g., VX-809, VX-661, VX-983, VX-445, VX-659, GLPG2222, NB124, ataluren);

5 e.g., one of the at least two additional therapeutic agents is GLPG2222, and the other is GLPG1837 or GLPG3067; or one of the at least two additional therapeutic agents is VX-809 or VX-661. Additional agents, e.g. amplifiers, are disclosed in co-pending applications PCT/US14/044100, PCT/US15/020460, PCT/US15/020499, and PCT/US15/036691, each incorporated by reference. For example, an exemplary amplifier is *N*-(3-(5-(hydroxymethyl)-

10 *1H*-1,2,3-triazol-1-yl)propyl)-5-phenylisoxazole-3-carboxamide ("Compound A"). 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

15 includes, without limitation, one or more homozygote mutations (e.g., $\Delta F508$ / $\Delta F508$ or R117H / R117H) and/or one or more compound heterozygote mutations (e.g., $\Delta F508$ / G551D; $\Delta F508$ / A455E; $\Delta F508$ / G542X; $\Delta 508F$ / W1204X; R553X / W1316X; W1282X / N1303K; F508del / R117H; N1303K / 3849+10kbC>T; $\Delta F508$ / R334W; $\Delta F508$ / G178R, and 591 Δ 18 / E831X). In certain embodiments, the subject's CFTR genotype includes a Class I mutation,

20 e.g., a G542X Class I mutation, e.g., a $\Delta F508$ / G542X compound heterozygous mutation. In other embodiments, the subject's CFTR genotype includes a Class III mutation, e.g., a G551D Class III mutation, e.g., a $\Delta F508$ / G551D compound heterozygous mutation. In still other embodiments, the subject's CFTR genotype includes a Class V mutation, e.g., a A455E Class V mutation, e.g., a $\Delta F508$ / A455E compound heterozygous mutation. In certain embodiments,

25 $\Delta F508$ CFTR activity and/or G542X CFTR activity and/or G551D CFTR activity and/or A455E activity is enhanced (e.g., increased). In certain embodiments, the enhancement in activity (e.g., increase in activity) provided by the combination of the disclosed compound and one or two additional therapeutic agents is greater than additive when compared to the enhancement in activity provided by each therapeutic component individually.

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

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

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

[0069] For example, provided herein is a method of treating a patient having one or more of the following mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, G970R, or R117H, G551D, and/or G167R, and/or e.g., a patient with

5 one or two copies of the F508del mutation, or one copy of the ΔF508 mutation and a second mutation that results in a gating effect in the CFTR protein (e.g., a patient that is heterozygous for ΔF508 and G551D mutation), a patient with one copy of the ΔF508 mutation and a second mutation that results in residual CFTR activity, or a patient with one copy of the ΔF508 mutation and a second mutation that results in residual CFTR activity, comprising

10 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 VX-661 or lumacaftor to said patient and an effective amount of a disclosed compound that may act as a potentiator or a

15 disclosed compound that may act as an amplifier. Such administration may result, for example, in increased chloride transport in human bronchial epithelial cells with e.g., one or two copies of mutations, e.g., ΔF508 mutation, as compared to administration of lumacaftor or 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 or as a corrector.

[0070] The phrase “combination therapy,” as used herein, refers to an embodiment where a patient is co-administered a disclosed compound, a CFTR amplifier, 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 an amplifier 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 $\Delta F508$ mutation, that achieves clinical improvement (or better) as compared to the chloride activity level in cells or patients with a G551D mutation receiving a corrector agent alone (e.g., lumacaftor or VX-661). 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.

[0071] 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.

[0072] 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.

[0073] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in a disclosed compounds used in disclosed compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron

salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a
 5 zwitterion, or a base salt.

[0074] In an embodiment, contemplated methods may include for example, administering prodrugs of the compounds described herein, for example, prodrugs of a compound of Formula I, or a pharmaceutical composition thereof.

[0075] The term “prodrug” refers to compounds that are transformed *in vivo* to yield a
 10 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,
 15 255). For example, if a compound of the disclosure or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (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
 20 atoms, alkoxy carbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxy carbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxy carbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxy carbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxy carbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁₋₂)alkylamino-(C₂₋₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁₋₂)alkyl, N,N-di(C₁₋₂)alkyl carbamoyl-(C₁₋₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂₋₃)alkyl.
 25

[0076] Similarly, if a compound of the disclosure contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C₁₋₆)alkylcarbonyloxymethyl, 1-((C₁₋₆)alkylcarbonyloxy)ethyl, 1-methyl-1-((C₁₋

₆)alkylcarbonyloxy)ethyl (C₁₋₆)alkoxycarbonyloxy)methyl, N-(C₁₋₆)alkoxycarbonylaminomethyl, succinoyl, (C₁₋₆)alkylcarbonyl, α -amino(C₁₋₄)alkylcarbonyl, arylalkylcarbonyl and α -aminoalkylcarbonyl, or α -aminoalkylcarbonyl- α -aminoalkylcarbonyl, where each α -aminoalkylcarbonyl group is independently selected from the naturally occurring
5 L-amino acids, P(O)(OH)₂, -P(O)(O(C₁₋₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0077] If a compound of the disclosure incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-alkylcarbonyloxyalkyl derivative, an (oxodioxolenyl)methyl derivative, an N-Mannich base, imine or enamine. In
10 addition, a secondary amine can be metabolically cleaved to generate a bioactive primary amine, or a tertiary amine can be metabolically cleaved to generate a bioactive primary or secondary amine. For examples, see Simpicio, *et al.*, *Molecules* **2008**, *13*, 519 and references therein.

[0078] Also contemplated in certain embodiments is the use of clathrates of the compounds
15 described herein, pharmaceutical compositions comprising the clathrates, and methods of use of the clathrates. Clathrates of a disclosed compound or a pharmaceutical composition thereof are also contemplated herein.

[0079] As discussed above, the disclosure also contemplates administration of
pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and
20 a compound described herein. A disclosed compound, or a pharmaceutically acceptable salt, solvate, clathrate or prodrug thereof, can be administered in pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient. The excipient can be chosen based on the expected route of administration of the composition in therapeutic applications. The route of administration of the composition depends on the condition to be treated. For
25 example, intravenous injection may be suitable for treatment of a systemic disorder and oral administration may be suitable to treat a gastrointestinal disorder. The route of administration and the dosage of the composition to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or

conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. A pharmaceutical composition comprising a disclosed compound or a pharmaceutically acceptable salt, solvate, clathrate or prodrug, can be administered by a variety of routes including, but not limited to, parenteral, oral, pulmonary, ophthalmic, nasal, rectal, vaginal, aural, topical, buccal, transdermal, intravenous, intramuscular, subcutaneous, intradermal, intraocular, intracerebral, intralymphatic, intraarticular, intrathecal and intraperitoneal. The compositions can also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the pharmacologic agent or composition. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like. Pharmaceutical compositions can also include large, slowly metabolized macromolecules such as proteins, polysaccharides such as chitosan, polylactic acids, polyglycolic acids and copolymers (such as latex functionalized SEPHAROSE™, agarose, cellulose, and the like), polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes).

[0080] Disclosed compositions can be administered parenterally such as, for example, by intravenous, intramuscular, intrathecal or subcutaneous injection. Parenteral administration can be accomplished by incorporating a composition into a solution or suspension. Such solutions or suspensions may also include sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents.

Parenteral formulations may also include antibacterial agents such as, for example, benzyl alcohol or methyl parabens, antioxidants such as, for example, ascorbic acid or sodium bisulfite and chelating agents such as EDTA. Buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose may also be added. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

[0081] Additionally, auxiliary substances, such as wetting or emulsifying agents, surfactants, pH buffering substances and the like can be present in compositions. Other components of pharmaceutical compositions are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, and mineral oil. In general, glycols such as propylene glycol or polyethylene glycol are suitable liquid carriers, particularly for injectable solutions.

[0082] Injectable formulations can be prepared either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The preparation also can also be emulsified or encapsulated in liposomes or micro particles such as polylactide, polyglycolide, or copolymer for enhanced adjuvant effect, as discussed above [Langer, *Science* 249: 1527, 1990 and Hanes, *Advanced Drug Delivery Reviews* 28: 97-119, 1997]. The compositions and pharmacologic agents described herein can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient.

[0083] Additional formulations suitable for other modes of administration include oral, intranasal, and pulmonary formulations, suppositories, transdermal applications and ocular delivery. For suppositories, binders and carriers include, for example, polyalkylene glycols or triglycerides; such suppositories can be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10%, or about 1% to about 2%. Oral formulations include excipients, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, and magnesium carbonate. Topical application can result in transdermal or intradermal delivery. Transdermal delivery can be achieved using a skin patch or using transferosomes. [Paul et al., *Eur. J. Immunol.* 25: 3521-24, 1995; Cevc et al., *Biochem. Biophys. Acta* 1368: 201-15, 1998].

[0084] 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.

- 10 **[0085]** 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
- 15 pessaries, tampons, creams, gels, pastes, foams or spray.

- [0086]** 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
- 20 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.

- [0087]** For topical administration, suitable formulations may include biocompatible oil, wax, gel, powder, polymer, or other liquid or solid carriers. Such formulations may be
- 25 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.

[0088] 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
5 water may be added, and pouring the hot mixture into a suppository mold.

[0089] Transdermal administration includes percutaneous absorption of the composition through the skin. Transdermal formulations include patches, ointments, creams, gels, salves and the like.

10 **[0090]** In addition to the usual meaning of administering the formulations described herein to any part, tissue or organ whose primary function is gas exchange with the external environment, for purposes of the present disclosure, “pulmonary” will also mean to include a tissue or cavity that is contingent to the respiratory tract, in particular, the sinuses. For pulmonary administration, an aerosol formulation containing the active agent, a manual pump
15 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.

[0091] 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
20 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.

25 **[0092]** The disclosure also encompasses the treatment of a condition associated with a dysfunction in proteostasis in a subject comprising administering to said subject an effective amount of a disclosed compound that enhances, improves or restores proteostasis of a protein. Proteostasis refers to protein homeostasis. Dysfunction in protein homeostasis is a result of

protein misfolding, protein aggregation, defective protein trafficking or protein degradation. For example, the disclosure contemplates administering a disclosed compound e.g., Formula I that corrects protein misfolding, reduces protein aggregation, corrects or restores protein trafficking and/or affects protein degradation for the treatment of a condition associated with a dysfunction in proteostasis. In some aspects, a disclosed compound e.g., Formula I that corrects protein misfolding and/or corrects or restores protein trafficking is administered. In cystic fibrosis, the mutated or defective enzyme is the cystic fibrosis transmembrane conductance regulator (CFTR). One of the most common mutations of this protein is $\Delta F508$ which is a deletion (Δ) of three nucleotides resulting in a loss of the amino acid phenylalanine (F) at the 508th (508) position on the protein. As described above, mutated cystic fibrosis transmembrane conductance regulator exists in a misfolded state and is characterized by altered trafficking as compared to the wild type CFTR. Additional exemplary proteins of which there can be a dysfunction in proteostasis, for example that can exist in a misfolded state, include, but are not limited to, glucocerebrosidase, hexosamine A, aspartylglucosaminidase, α -galactosidase A, cysteine transporter, acid ceramidase, acid α -L-fucosidase, protective protein, cathepsin A, acid β -glucosidase, acid β -galactosidase, iduronate 2-sulfatase, α -L-iduronidase, galactocerebrosidase, acid α -mannosidase, acid β -mannosidase, arylsulfatase B, arylsulfatase A, *N*-acetylgalactosamine-6-sulfate sulfatase, acid β -galactosidase, *N*-acetylglucosamine-1-phosphotransferase, acid sphingomyelinase, NPC-1, acid α -glucosidase, β -hexosamine B, heparin *N*-sulfatase, α -*N*-acetylglucosaminidase, α -glucosaminide *N*-acetyltransferase, *N*-acetylglucosamine-6-sulfate sulfatase, α -*N*-acetylgalactosaminidase, α -neuramidase, β -glucuronidase, β -hexosamine A and acid lipase, polyglutamine, α -synuclein, TDP-43, superoxide dismutase (SOD), A β peptide, tau protein, transthyretin and insulin. The compounds of Formula I can be used to restore proteostasis (e.g., correct folding and/or alter trafficking) of the proteins described above.

[0093] 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, lysozyme amyloidosis, fibrinogen amyloidosis, dialysis amyloidosis, inclusion body myositis/myopathy, cataracts, medullary thyroid carcinoma, cardiac atrial amyloidosis, pituitary prolactinoma, hereditary lattice corneal dystrophy, cutaneous lichen amyloidosis, corneal lactoferrin amyloidosis, corneal lactoferrin amyloidosis, pulmonary alveolar proteinosis, odontogenic tumor amyloid, seminal vesical amyloid, sickle cell disease, critical illness myopathy, von Hippel-Lindau disease, spinocerebellar ataxia 1, Angelman syndrome, giant axon neuropathy, inclusion body myopathy with Paget disease of bone, frontotemporal dementia (IBMPFD) and prion diseases. Neurodegenerative diseases associated with aggregation of polyglutamine include, but are not limited to, Huntington's disease, dentatorubral and pallidolusian 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 A β 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.

[0094] In a further embodiment, the protein conformation disease is a loss of function disorder. The terms “loss of function disease” and “loss of function disorder” are used interchangeably herein. Loss of function diseases are a group of diseases characterized by inefficient folding of a protein resulting in excessive degradation of the protein. Loss of function diseases include, for example, lysosomal storage diseases. Lysosomal storage diseases are a group of diseases characterized by a specific lysosomal enzyme deficiency which may occur in a variety of tissues, resulting in the build-up of molecules normally degraded by the deficient enzyme. The lysosomal enzyme deficiency can be in a lysosomal hydrolase or a protein involved in the lysosomal trafficking. Lysosomal storage diseases include, but are not limited to, aspartylglucosaminuria, Fabry’s disease, Batten disease, Cystinosis, Farber, Fucosidosis, Galactasidosialidosis, Gaucher’s disease (including Types 1, 2 and 3), Gm1 gangliosidosis, Hunter’s disease, Hurler-Scheie’s disease, Krabbe’s disease, α -Mannosidosis, β -Mannosidosis, Maroteaux-Lamy’s disease, Metachromatic Leukodystrophy, Morquio A syndrome, Morquio B syndrome, Mucopolipidosis II, Mucopolipidosis 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.

[0095] In another embodiment, a 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.

[0096] In yet another embodiment, a treatment of a 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 is contemplated.

[0097] In a further embodiment, a treatment of a 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 is contemplated.

[0098] 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
5 a condition selected from the group consisting of polyendocrinopathy/hyperinsulinemia, diabetes mellitus, Charcot-Marie Tooth syndrome, Pelizaeus-Merzbacher disease, and Gorham's Syndrome.

[0099] Additional conditions associated with a dysfunction of proteostasis include
10 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
15 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.

[0100] Additional conditions include those associated with a defect in protein trafficking and that can be treated according to a disclosed methods include: PGP mutations, hERG
20 trafficking mutations, nephrogenic diabetes insipidus mutations in the arginine-vasopressin receptor 2, persistent hyperinsulinemic hypoglycemia of infancy (PHH1) mutations in the sulfonylurea receptor 1, and $\alpha 1$ AT.

[0101] The disclosure is illustrated by the following examples which are not meant to be limiting in any way.

EXEMPLIFICATION

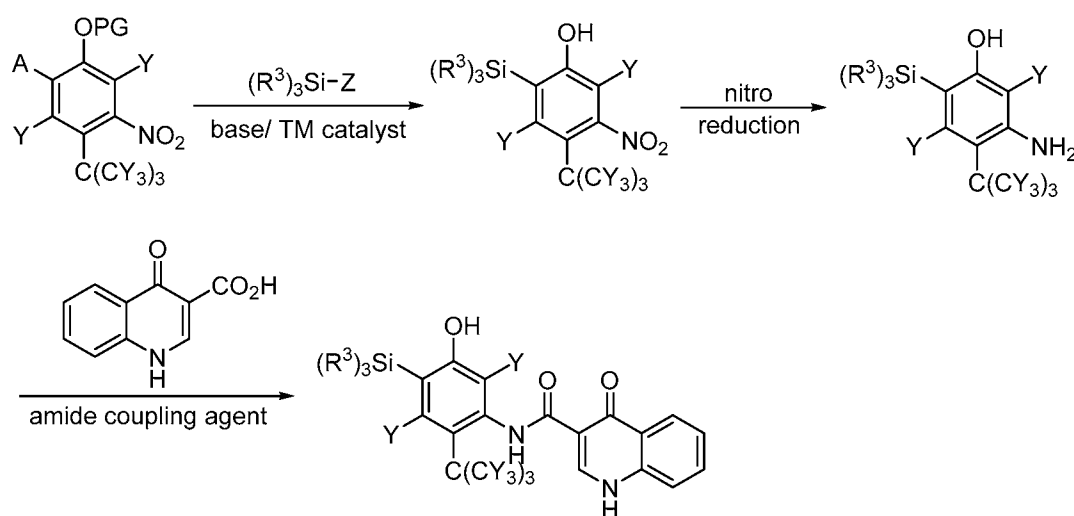
25 [0102] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the

synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials. At least some of the compounds identified as “intermediates” herein are contemplated as compounds of the disclosure.

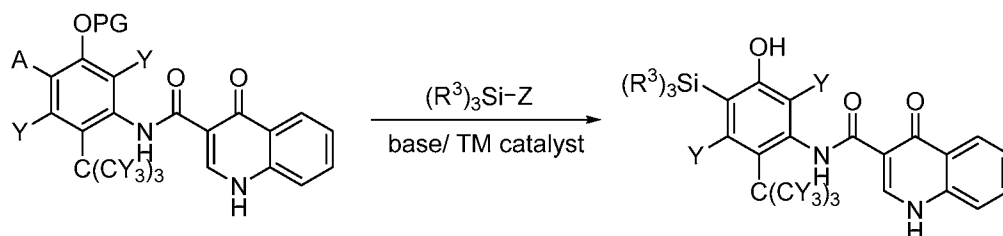
General Procedures:

[0103] General procedures for the preparation of compounds of the invention are outlined in Schemes I-IV. The disclosed compounds may be prepared, for example, through transition metal-catalyzed coupling of a suitably substituted silyl reagent with a suitably functionalized phenol derivative followed by nitro reduction and amide coupling (Scheme I), or through transition metal-catalyzed coupling of a suitably substituted silyl reagent with a suitably functionalized quinolone carboxamide (Schemes II-IV).

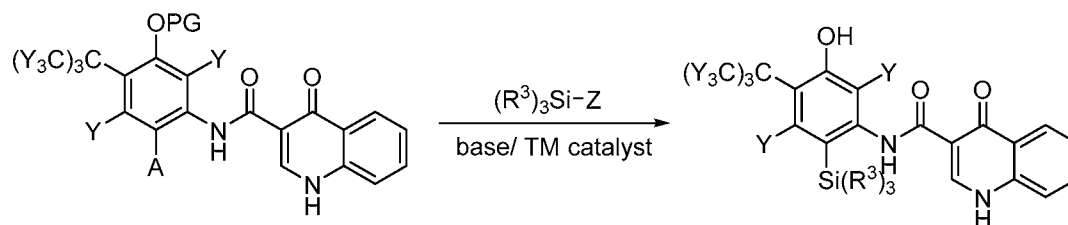
Scheme I:



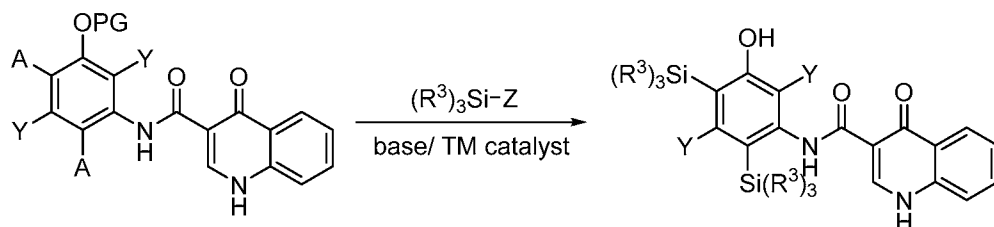
Scheme II:



Scheme III:



5 Scheme IV:



List of Abbreviations

Abbreviation	Name
rt	room temperature
THF	tetrahydrofuran
MeCN	acetonitrile

DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DCM	dichloromethane
MeOH	methanol
EtOAc	ethyl acetate
DMF	<i>N,N</i> -dimethylformamide
DMAP	4-(dimethylamino)pyridine
AcOH	acetic acid
NaOAc	sodium acetate
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate
DIEA	<i>N,N</i> -diisopropylethylamine
TEA	triethylamine
dba	dibenzylideneacetone
cod	cis,cis-1,5-cyclooctadiene
JohnPhos	(2-biphenyl)di-tert-butylphosphine
Ni(OAc) ₂	nickel(II) acetate
NIS	<i>N</i> -iodosuccinimide
atm	atmosphere
NaBH(OAc) ₃	sodium triacetoxymethylborohydride
conc	concentrated

ESI	Electrospray Ionization
pos	positive
neg	negative
Calcd.	Calculated

Example 1: Preparation of N-[2-tert-Butyl-5-hydroxy-4-(trimethylsilyl)phenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 1)

[0104] A. 2-Bromo-4-tert-butylphenyl methyl carbonate. To a 500-mL round-bottom flask was placed a solution of 2-bromo-4-tert-butylphenol (60 g, 263.1 mmol), TEA (53.145 g, 525 mmol), and DMAP (321 mg, 26.31 mmol) in DCM (900 mL) then the solution was cooled to 0°C and methyl chloroformate (29.7 g, 315 mmol) was added dropwise with stirring. The reaction was stirred for 5 h at 0°C, quenched by the addition of 500 mL of water/ice, and extracted with DCM (3x500 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (1:100-2:100) affording 60.6 g of the title compound as a light yellow oil.

[0105] B. 2-Bromo-4-tert-butyl-5-nitrophenyl methyl carbonate. To concentrated sulfuric acid (500 mL) cooled to 0°C was added 2-bromo-4-tert-butylphenyl methyl carbonate (20 g, 69.9 mmol, as prepared in the previous step), in small portions. After completion of addition, KNO₃ (8.474 g, 83.9 mmol) was added in small portions at a rate that maintained the temperature below 0°C. The reaction was stirred for 2 h at rt then poured into 100 mL of water/ice and extracted with DCM (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (1:9) affording 20 g of the title compound as a light yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.80 (s, 1H), 7.31 (s, 1H), 5.32 (s, 1H), 4.00 (s, 3H), 1.48 (s, 9H).

[0106] C. 4-tert-Butyl-5-nitro-2-(trimethylsilyl)phenol. To a 40-mL vial purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-bromo-4-tert-butyl-5-nitrophenyl methyl carbonate (1 g, 3.01 mmol, as prepared in the previous step), hexamethyldisilane (8.8 g, 60 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (155 mg, 0.15 mmol), JohnPhos (134 mg, 0.45 mmol), and $\text{KF}/\text{Al}_2\text{O}_3$ (50%, 1.205 g) in DMPU (10 mL). The reaction was stirred for 6 h at 110°C then cooled to rt and filtered. The filtrate was diluted with 100 mL of water and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. This reaction was repeated an additional 49 times then the combined crude product was purified by column chromatography eluting with EtOAc/petroleum ether (1:20) affording 30 g of 4-tert-butyl-5-nitro-2-(trimethylsilyl)phenol as a yellow solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_{13}\text{H}_{22}\text{NO}_3\text{Si}^+$: 268.1 (M+H); Found: 268.1.

[0107] D. 5-Amino-4-tert-butyl-2-(trimethylsilyl)phenol. To a 500-mL round-bottom flask was placed a solution of 4-tert-butyl-5-nitro-2-(trimethylsilyl)phenol (10 g, 37.5 mmol, as prepared in the previous step) and $\text{Ni}(\text{OAc})_2$ (10 g, 56.8 mmol) in MeOH/THF (80/80 mL) then the solution was cooled to 0°C and NaBH_4 (5 g, 132 mmol) was added in portions. The reaction was stirred for 30 min at rt then the solids were removed by filtration. The filtrate was with 300 mL of saturated aqueous NH_4Cl solution and extracted with EtOAc (3x300 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and then diluted with 150 mL of DMF. The resulting solution was concentrated under reduced pressure to remove the low boiling solvents affording a DMF solution of the title compound, which was used directly in the next step. This reaction was repeated an additional 2 times and the 3 batches were combined. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_{13}\text{H}_{24}\text{NOSi}^+$: 238.2 (M+H); Found: 238.2.

[0108] E. N-[2-tert-Butyl-5-hydroxy-4-(trimethylsilyl)phenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 1-L round-bottom flask, was placed a solution of 5-amino-4-tert-butyl-2-(trimethylsilyl)phenol in DMF (450 mL, as prepared in the previous step), then 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (21 g, 0.11 mol), HATU (50 g, 0.13 mol), and TEA (33 g, 0.33 mol) were added. The reaction was stirred for 48 h at rt then diluted with 300 mL of water and extracted with EtOAc (3x300 mL). The organic extracts were combined,

dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Bridge C18 OBD Prep Column, 19 mm X 250 mm; mobile phase, Water (10 mmol/L NH_4HCO_3) and MeCN (70% MeCN up to 90% in 6 min); Detector, UV 254/220 nm) affording 5.13 g of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_3\text{Si}^+$: 409.2 (M+H); Found: 409.1. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.90 (s, 1H), 11.91 (s, 1H), 9.28 (s, 1H), 8.88 (s, 1H), 8.35-8.32 (m, 1H), 7.82-7.74 (m, 2H), 7.55-7.49 (m, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 1.39 (s, 9H), 0.25 (s, 9H). HPLC purity (254 nm): 96.2%.

Example 2: Preparation of N-[2-tert-Butyl-4-(ethyldimethylsilyl)-5-hydroxyphenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 2)

[0109] A. 4-Oxo-1,4-dihydroquinoline-3-carbonyl chloride. To a 500-mL round-bottom flask was placed a solution of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6 g, 31.72 mmol) in DCM (250 mL), TEA (6.4 g, 63.25 mmol) then the solution was cooled to 0°C and thionyl chloride (7.49 g) was added dropwise with stirring. The reaction was stirred for 2 h at 50°C then concentrated under reduced pressure affording 5.5 g of the title compound as a white solid.

[0110] B. 3-Amino-4-tert-butylphenyl methyl carbonate. To a 500-mL round-bottom flask was placed a solution of 2-bromo-4-tert-butyl-5-nitrophenyl methyl carbonate (10 g, 30.11 mmol, as prepared in Example 1, Step B) in MeOH (300 mL) then Pd on carbon (1 g) was added. The resulting solution was degassed and back-filled with H_2 (5 atm) and stirred for 16 h at rt. The H_2 was purged then the solids were removed by filtration. The filtrate was concentrated under reduced pressure affording 6.3 g of the title compound as a brown solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_{12}\text{H}_{18}\text{NO}_3^+$: 224.1 (M+H); Found: 224.1.

[0111] C. 5-Amino-4-tert-butyl-2-iodophenyl methyl carbonate. To a 100-mL round-bottom flask was placed a solution of 3-amino-4-tert-butylphenyl methyl carbonate (6.3 g, 28.22 mmol, as prepared in the previous step) and NIS (4.5 g, 20.00 mmol) in DMF (40 mL). The reaction was stirred for 1.5 h at rt, quenched by the addition of 50 mL of water, and extracted with EtOAc (3x50 mL). The organic extracts were combined and concentrated under reduced pressure. The residue was purified by column chromatography eluting with

EtOAc/petroleum ether (1:2) affording 9.1 g of the title compound as a brown oil. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{12}H_{17}INO_3^+$: 350.0 (M+H); 350.0.

[0112] D. 4-tert-Butyl-2-iodo-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate. To a 250-mL round-bottom flask was placed a solution of 5-amino-4-tert-butyl-2-iodophenyl methyl carbonate (3.49 g, 10.00 mmol, as prepared in the previous step) and DIEA (3.225 g, 24.95 mmol) in DCM (100 mL) then 4-oxo-1,4-dihydroquinoline-3-carbonyl chloride (4.14 g, 19.94 mmol, as prepared in Step A) was added. The reaction was stirred for 2 days at rt, then washed with water (3x50 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography eluting with DCM/MeOH (20:1) affording 1.2 g of the title compound as a brown solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{22}H_{22}IN_2O_5^+$: 521.1 (M+H); Found: 521.0.

[0113] E. N-[2-tert-Butyl-4-(ethyldimethylsilyl)-5-hydroxyphenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 4-tert-butyl-2-iodo-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (200 mg, 0.38 mmol, as prepared in the previous step) in DMPU (2.5 mL) then ethyldimethylsilane (136 mg, 1.54 mmol), $[Rh(cod)_2]BF_4$ (8 mg, 0.02 mmol), and K_3PO_4 (123 mg, 0.58 mmol) were added. The reaction was stirred for 16 h at 60°C then cooled to rt and filtered. The filtrate was diluted with 50 mL of water then extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Bridge C18 OBD Prep Column, 10um, 19 mm X 250 mm; mobile phase, Water (10 mmol/L NH_4HCO_3) and MeCN (60.0% MeCN up to 81.0% in 10 min); Detector, UV 254/220 nm) affording 12.7 mg of the title compound as a gray solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{24}H_{31}N_2O_3Si^+$: 423.2 (M+H); Found: 423.2. 1H NMR (400 MHz, $DMSO-d_6$): δ 12.90 (d, $J = 6.8$ Hz, 1H), 11.90 (s, 1H), 9.25 (s, 1H), 8.70 (d, $J = 6.4$ Hz, 1H), 8.33 (d, $J = 8.4$ Hz, 1H), 7.90-7.70 (m, 2H), 7.52 (t, $J = 7.6$ Hz, 1H), 7.25 (s, 1H), 7.16 (s, 1H), 1.39 (s, 9H), 0.94 (t, $J = 7.6$ Hz, 3H), 0.76 (q, $J = 7.6$ Hz, 2H), 0.22 (s, 6H). HPLC purity (254 nm): 96.9%.

Example 3: Preparation of N-[2-tert-Butyl-4-[diethyl(methyl)silyl]-5-hydroxyphenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 3)

[0114] A. N-[2-tert-Butyl-4-[diethyl(methyl)silyl]-5-hydroxyphenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 4-tert-butyl-2-iodo-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (200 mg, 0.38 mmol, as prepared in Example 2, Step D) in DMPU (2.5 mL) then diethyl(methyl)silane (157 mg, 1.54 mmol), [Rh(cod)₂]BF₄ (7.8 mg, 0.02 mmol) and K₃PO₄ (123 mg, 0.58 mmol) were added. The reaction was stirred for 16 h at 60°C then cooled to rt and filtered. The filtrate was diluted with 50 mL of water then extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Bridge C18 OBD Prep Column, 10 µm, 19 mm X 250 mm; mobile phase, Water (10 mmol/L NH₄HCO₃) and MeCN (63.0% MeCN up to 85.0% in 10 min); Detector, UV 254/220 nm) affording 20.2 mg of the title compound as a gray solid. Mass Spectrum (LCMS, ESI pos): Calcd. for C₂₅H₃₃N₂O₃Si⁺: 437.2 (M+H); Found: 437.2. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.90 (d, *J* = 6.4 Hz, 1H), 11.90 (s, 1H), 9.23 (s, 1H), 8.87 (d, *J* = 6.8 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.90-7.70 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.25 (s, 1H), 7.17 (s, 1H), 1.39 (s, 9H), 0.94 (t, *J* = 8.0 Hz, 6H), 0.77 (q, *J* = 7.6 Hz, 4H), 0.20 (s, 3H). HPLC purity (254 nm): 98.7%.

Example 4: Preparation of N-(2-(tert-Butyl)-5-hydroxy-4-(triethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 4)

[0115] A. 5-Amino-2-bromo-4-tert-butylphenyl methyl carbonate. To a 100-mL round-bottom flask was placed a solution of 2-bromo-4-tert-butyl-5-nitrophenyl methyl carbonate (3.3 g, 10 mmol, as prepared in Example 1, Step B) in THF/AcOH (60/15 mL) then Fe (2.8 g, 50 mmol) was added. The reaction was stirred for 5 h at rt then the solids were removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (1:10) affording 2.6 g of the title

compound as a yellow solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{12}H_{17}BrNO_3^+$: 302.0 (M+H); Found: 302.1.

[0116] B. 2-Bromo-4-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-carboxamido)phenyl methyl carbonate. To a 100-mL round-bottom flask was placed a solution of 5-amino-2-bromo-4-tert-butylphenyl methyl carbonate (1.5 g, 5 mmol, as prepared in the previous step) in DMF (20 mL) then 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (1.5 g, 7.5 mmol), HATU (2.9 g, 7.5 mmol), and DIEA (19 g, 15 mmol) were added. The reaction was stirred for 16 h at rt then diluted with 100 mL of water, and extracted with EtOAc (3x100 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (1:5) affording 1.4 g of the title compound as a grey solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{22}H_{22}BrN_2O_5^+$: 473.1 (M+H); Found: 473.2.

[0117] C. N-(2-(tert-Butyl)-5-hydroxy-4-(triethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-bromo-4-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (600 mg, 1.27 mmol, as prepared in the previous step) in DMPU (4.5 mL) then $Pd_2(dba)_3 \cdot CHCl_3$ (39 mg, 0.04 mmol), JohnPhos (57 mg, 0.19 mmol), KF/Al_2O_3 (50%, 737 mg, 12.71 mmol), and triethylsilane (589 mg, 5.07 mmol) were added. The reaction was stirred for 16 h at 90°C, cooled to rt, and filtered. The filtrate was diluted with 100 mL of water and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Select CSH Prep C18 OBD Column, 5µm, 19*150mm; mobile phase, Water (10 mmol/L NH_4HCO_3) and MeCN (50.0% MeCN up to 76.0% in 1 min, up to 95.0% in 7 min); Detector, UV 254/220 nm) affording 8.6 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{26}H_{35}N_2O_3Si^+$: 451.2 (M+H); Found: 451.3. 1H NMR (400 MHz, $DMSO-d_6$): δ 12.94 (brs, 1H), 12.02 (s, 1H), 8.91 (s, 1H), 8.33 (d, $J = 7.2$ Hz, 1H), 7.85-7.70 (m, 2H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 2.8$ Hz, 1H), 7.25 (d, $J = 8.8$ Hz, 1H), 6.63 (dd, $J = 2.8, 8.4$ Hz,

1H), 1.41 (s, 9H), 0.96 (t, $J = 8.0$ Hz, 9H), 0.73 (q, $J = 8.0$ Hz, 6H). HPLC purity (254 nm): 95.7%.

Example 5: Preparation of N-(2-tert-Butyl-4-(tert-butyldimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 5)

5 [0118] A. N-(2-tert-butyl-4-(tert-butyldimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-bromo-4-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-carboxamido)phenyl methyl carbonate (300 mg, 0.63 mmol, as prepared in Example 4, Step B) in DMPU (4 mL) dimethyl(propan-2-yl)silane (294 mg, 2.53 mmol),
10 [Rh(cod)₂]BF₄ (13 mg, 0.03 mmol), and K₃PO₄ (200 mg, 0.95 mmol) were added. The reaction was stirred for 72 h at 90°C, cooled to rt, and filtered. The filtrate was diluted with 50 mL of water and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Bridge C18 OBD Prep Column, 10 μm, 19 mm X 250
15 mm; mobile phase, Water (10 mmol/L NH₄HCO₃) and MeCN (60.0% MeCN up to 80.0% in 8 min); Detector, UV 254/220 nm) affording 11.4 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for C₂₆H₃₅N₂O₃Si⁺: 451.2 (M+H); Found: 451.3. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.89 (s, 1H), 11.91 (s, 1H), 9.20 (s, 1H), 8.87 (s, 1H), 8.33 (d, $J = 7.2$ Hz, 1H), 7.90-7.70 (m, 2H), 7.52 (t, $J = 7.2$ Hz, 1H), 7.27 (s, 1H), 7.19 (s, 1H), 1.39 (s,
20 9H), 0.90 (s, 9H), 0.26 (s, 9H). HPLC purity (254 nm): 97.2%.

Example 6: Preparation of N-[2-tert-Butyl-4-[dimethyl(propan-2-yl)silyl]-5-hydroxyphenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 6)

[0119] A. N-[2-tert-Bbutyl-4-[dimethyl(propan-2-yl)silyl]-5-hydroxyphenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 20-mL sealed tube purged and maintained with an inert
25 atmosphere of nitrogen, was placed a solution of 4-tert-butyl-2-iodo-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (250 mg, 0.48 mmol, as prepared in Example 2, Step D) in DMPU (3 mL) dimethyl(propan-2-yl)silane (196 mg, 1.92 mmol), [Rh(cod)₂]BF₄ (9.7 mg, 0.02 mmol), and K₃PO₄ (153 mg, 0.72 mmol) were added. The

reaction was stirred for 16 h at 90°C, cooled to rt, and filtered. The filtrate was diluted with 50 mL of water and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Bridge C18 OBD Prep Column, 10 µm, 19 mm X 250 mm; mobile phase, Water (10 mmol/L NH₄HCO₃) and MeCN (65.0% MeCN up to 82.0% in 8 min); Detector, UV 254/220 nm) affording 20.7 mg of the title compound as a gray solid. Mass Spectrum (LCMS, ESI pos): Calcd. for C₂₅H₃₃N₂O₃Si⁺: 437.2 (M+H); 437.1. ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.90 (s, 1H), 9.21 (s, 1H), 8.85 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 7.85-7.70 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.24 (s, 1H), 7.16 (s, 1H), 1.37 (s, 9H), 1.30-0.93 (m, 1H), 0.93 (d, *J* = 7.2 Hz, 6H), 0.18 (s, 6H). HPLC purity (254 nm): 98.9%.

Example 7: N-(2-(tert-Butyl)-4-(dimethyl(phenyl)silyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 7)

[0120] A. N-(2-(tert-Butyl)-4-(dimethyl(phenyl)silyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 4-tert-butyl-2-iodo-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (250 mg, 0.48 mmol, as prepared in Example 2, Step D) in DMPU (3 mL), then dimethyl(phenyl)silane (261 mg, 1.92 mmol), [Rh(cod)₂]BF₄ (9.7 mg, 0.02 mmol), and K₃PO₄ (153 mg, 0.72 mmol) were added. The reaction was stirred for 16 h at 90°C, cooled to rt and the solids removed by filtration. The filtrate was diluted with water (50 mL) and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Column, X Bridge C18 OBD Prep Column, 10 µm, 19 mm X 250 mm; mobile phase, Water (10 mmol/L NH₄HCO₃) and ACN (50.0% ACN up to 75.0% in 9 min); Detector, UV 254/220 nm) affording 30.8 mg of the title compound as a gray solid. Mass Spectrum (LCMS, ESI pos): Calcd. for C₂₈H₃₁N₂O₃Si⁺: 471.2 (M+H); Found: 471.3. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.82 (br s, 1H), 11.91 (s, 1H), 9.33 (s, 1H), 8.85 (s, 1H), 8.30 (d, *J* = 8.1 Hz, 1H), 7.81-7.71 (m, 2H), 7.56-7.46 (m, 3H), 7.34 (d, *J* = 2.4 Hz, 3H), 7.18 (s, 1H), 7.13 (s, 1H), 1.30 (s, 9H), 0.50 (s, 6H). HPLC purity (254 nm): 98.9%.

Example 8: Preparation of N-[4-tert-Butyl-5-hydroxy-2-(trimethylsilyl)phenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 8)

[0121] A. 4-Bromo-2-tert-butylphenyl methyl carbonate. To a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 4-bromo-2-tert-butylphenol (1 g, 4.36 mmol), TEA (887 mg, 8.77 mmol), and DMAP (54 mg, 0.42 mmol) in DCM (10 mL) then the solution was cooled to 0°C and methyl chloroformate (494 mg, 5.23 mmol) was added. The reaction was stirred for 3 h at 0°C then quenched by the addition of 20 mL of water and extracted with DCM (3x20 mL). The organic extracts were combined and concentrated under reduced pressure affording 1.5 g of the title compound as a yellow oil.

[0122] B. 4-Bromo-2-tert-butyl-5-nitrophenyl methyl carbonate. To a 50-mL round-bottom flask was placed a solution of 4-bromo-2-tert-butylphenyl methyl carbonate (1.2 g, 4.18 mmol, as prepared in the previous step) in conc. sulfuric acid (5 mL) then the solution was cooled to 0°C and KNO₃ (0.55 g) was added in portions. The reaction was stirred for 2 h at rt then quenched by the addition of 30 mL of water/ice and extracted with DCM (3x30 mL). The organic extracts were combined and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (1:20) affording 1.1 g of the title compound as a yellow solid. ¹H NMR (300 MHz, CD₃OD): δ 7.87 (s, 1H), 7.77 (s, 1H), 3.91 (s, 3H), 1.35 (s, 9H).

[0123] C. 5-Amino-4-bromo-2-tert-butylphenyl methyl carbonate. To a 25-mL round-bottom flask was placed a solution of 4-bromo-2-tert-butyl-5-nitrophenyl methyl carbonate (664 mg, 2.00 mmol, as prepared in the previous step) in THF (10 mL) and AcOH (2 mL) then Fe powder (1000 mg, 17.91 mmol) was added in portions over 15 min at 66°C. The reaction was stirred for 8 h at 66°C, cooled to rt, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (1:1) affording 450 mg of the title compound as a yellow solid.

[0124] D. 4-Bromo-2-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate. To a 25-mL round-bottom flask was placed a solution of 5-amino-4-bromo-2-tert-

butylphenyl methyl carbonate (604 mg, 2.00 mmol, as prepared in the previous step) in DMF (10 mL) then 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (567 mg, 3.00 mmol), DIEA (516 mg, 3.99 mmol), and HATU (1524 mg, 4.00 mmol) were added. The reaction was stirred for 16 h at 65°C then quenched by the addition of 50 mL of water/ice and extracted with EtOAc (3x25 mL). The organic extracts were combined and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (1:1) affording 800 mg of the title compound as a yellow solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{22}H_{22}BrN_2O_5^+$: 473.1 (M+H); Found: 473.1.

[0125] E. N-[4-tert-Butyl-5-hydroxy-2-(trimethylsilyl)phenyl]-4-oxo-1,4-

dihydroquinoline-3-carboxamide. To a 40-mL sealed tube was placed a solution of 4-bromo-2-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (47.3 mg, 0.10 mmol, as prepared in the previous step) in DMPU (1 mL) then $[Rh(cod)_2]BF_4$ (20.3 mg, 0.05 mmol), hexamethyldisilane (1 mL), and K_3PO_4 (84.9 mg, 0.40 mmol) were added under nitrogen. The reaction was stirred for 16 h at 110°C then quenched by the addition of 10 mL of ice/water and extracted with EtOAc (3x10 mL). The organic extracts were combined, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Bridge Shield RP18 OBD Column, 19*250mm, 10um; mobile phase, Water (10 mmol/L NH_4HCO_3) and MeCN (60.0% MeCN up to 90.0% in 11 min); Detector, UV 254/220 nm) affording 10.1 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{23}H_{29}N_2O_3Si^+$: 409.2 (M+H); Found: 409.2. 1H NMR (300 MHz, $DMSO-d_6$): δ 11.73 (s, 1H), 8.96 (s, 1H), 9.51 (s, 1H), 8.43 (s, 1H), 8.30 (d, $J = 8.4$ Hz, 1H), 7.71-7.81 (m, 2H), 7.49 (t, $J = 8.1$ Hz, 1H), 7.29 (s, 1H), 7.21 (s, 1H), 1.34 (s, 9H), 0.28 (s, 9H). HPLC purity (254 nm): 98.1%.

Example 9: Preparation of N-(4-(tert-Butyl)-2-(ethyltrimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 9)

[0126] A. N-(4-(tert-Butyl)-2-(ethyltrimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 4-bromo-2-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (47.3 mg, 0.10 mmol, as prepared in

Example 8, Step D) in DMPU (0.2 mL), then ethyldimethylsilane (2 mL), Rh(cod)₂BF₄ (20 mg), and K₃PO₄ (84 mg, 0.40 mmol) were added. The reaction was stirred at 110°C for 16 h. This reaction was repeated 15 times. The 16 crude reactions were combined, diluted with EtOAc (5 mL), filtered, and concentrated under vacuum. The crude product was purified by
5 Prep-HPLC (Column, XBridge C18 OBD Prep Column, 10 µm, 19 mm×250 mm; mobile phase, Water(10 mmol/L NH₄HCO₃) and ACN (70% ACN up to 85% in 11 min); Detector, UV 254/220nm) affording 20 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI neg): Calcd. for C₂₄H₂₉N₂O₃Si⁻: 421.2 (M-H); Found: 421.3. ¹H NMR (300 MHz, DMSO-*d*₆): δ 12.72 (br s, 1H), 11.71 (s, 1H), 9.52 (s, 1H), 8.84 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 1H),
10 7.82-7.71 (m, 2H), 7.49 (t, *J* = 8.1 Hz, 1H), 7.28 (s, 1H), 7.20 (s, 1H), 1.34 (s, 9H), 0.95-0.77 (m, 5H), 0.28 (s, 6H). HPLC purity (254 nm): 99.0%.

Example 10: Preparation of N-(4-(tert-Butyl)-2-(tert-butyldimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 10)

[0127] A. N-(4-(tert-Butyl)-2-(tert-butyldimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-
15 dihydroquinoline-3-carboxamide. To a 10-mL sealed tube, was placed a solution of 4-bromo-2-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (47.3 mg, 0.10 mmol, as prepared in Example 8, Step D) in DMPU (1 mL), then tert-butyldimethylsilane (0.5 mL), Rh(cod)₂BF₄ (20 mg) and K₃PO₄ (84 mg, 0.40 mmol) were added under nitrogen. The reaction was stirred for 16 h at 110°C, then diluted with EtOAc (5 mL), filtered, and
20 concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Column, X Bridge C18 OBD Prep Column, 10 µm, 19 mm X 250 mm; mobile phase, Water (10MMOL/L NH₄HCO₃) and ACN (83.0% ACN up to 90.0% in 11 min); Detector, UV 254/220nm) affording 8.9 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for C₂₆H₃₅N₂O₃Si⁺: 451.2 (M+H); Found: 451.3. ¹H NMR (300 MHz,
25 DMSO-*d*₆): δ 12.81 (br s, 1H), 11.43 (s, 1H), 9.54 (s, 1H), 8.82 (s, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.81-7.71 (m, 2H), 7.51-7.46 (m, 1H), 7.22 (s, 1H), 7.05 (s, 1H), 1.34 (s, 9H), 0.86 (s, 9H), 0.25 (s, 6H). HPLC purity (254 nm): 98.2%.

Example 11: Preparation of N-(5-Hydroxy-2,4-bis(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 11)

[0128] A. N-(2,4-Dibromo-5-hydroxyphenyl)acetamide. To a 3000-mL round-bottom flask was placed a solution of N-(3-hydroxyphenyl)acetamide (15 g, 99.23 mmol) in MeOH (300 mL) and DCM (1.2 L) then $\text{Py} \cdot \text{Br}_3$ (70.18 g, 220.13 mmol) was added in portions at rt over 1 h. The reaction was stirred overnight at rt then concentrated under reduced pressure. The resulting mixture was diluted with 800 mL of water and extracted with EtOAc (2x1.5 L). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (1:1) affording 9 g of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_8\text{H}_8\text{Br}_2\text{NO}_2^+$: 307.9 (M+H); Found: 308.1.

10 [0129] B. 5-Amino-2,4-dibromophenol. To a 500-mL round-bottom flask was placed a solution of N-(2,4-dibromo-5-hydroxyphenyl)acetamide (10.4 g, 33.66 mmol, as prepared in the previous step) in H_2O (130 mL) then conc. HCl (46 mL) was added. The reaction was stirred for 3 h at 100°C then NaOAc was added to adjust the pH to 7. The solids were removed by filtration then the filtrate was extracted with EtOAc (3x300 mL). The organic extracts were
15 combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure affording 8.2 g of the title compound as a yellow solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_6\text{H}_6\text{Br}_2\text{NO}^+$: 265.9 (M+H); Found: 266.2.

[0130] C. N-(2,4-Dibromo-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 100-mL round-bottom flask was placed a solution of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (945 mg, 5.00 mmol) in DMF (25 mL) then 5-amino-2,4-dibromophenol (1.99 g, 7.46 mmol, as prepared in the previous step), HATU (3.8 g, 9.99 mmol), and DIEA (2 g, 15.48 mmol) were added. The reaction was stirred for 2 days at 85°C then diluted with 100 mL of water and extracted with EtOAc (3x200 mL). The organic extracts were combined and concentrated under reduced pressure. The crude product was triturated with EtOAc affording
20 1.1 g of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_{16}\text{H}_{11}\text{Br}_2\text{N}_2\text{O}_3^+$: 436.9 (M+H); Found: 437.1.

[0131] D. N-[5-Hydroxy-2,4-bis(trimethylsilyl)phenyl]-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of N-(2,4-dibromo-5-hydroxyphenyl)-4-oxo-1,4-

dihydroquinoline-3-carboxamide (200 mg, 0.46 mmol, as prepared in the previous step) in DMPU (3 mL) then hexamethyldisilane (533 mg, 3.64 mmol), $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (24 mg, 0.02 mmol), JohnPhos (20 mg, 0.07 mmol), and $\text{KF}/\text{Al}_2\text{O}_3$ (50%, 265 mg, 4.57 mmol) were added. The reaction was stirred for 16 h at 110°C, cooled to rt, and filtered. The filtrate was diluted with 50 mL of water and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (HPLC-10: Column, X Bridge C18 OBD Prep Column, 10 μm , 19 mm X 250 mm; mobile phase, Water (10 mmol/L NH_4HCO_3) and MeCN (60.0% MeCN up to 85.0% in 8 min); Detector, UV 254/220nm) affording 8.2 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_3\text{Si}_2^+$: 425.2 (M+H); Found: 425.1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.89 (br s, 1H), 11.86 (s, 1H), 9.60 (s, 1H), 8.87 (s, 1H), 8.32 (d, $J = 8.4$ Hz, 1H), 7.90-7.70 (m, 2H), 7.50 (t, $J = 7.6$ Hz, 1H), 7.35 (d, $J = 7.6$ Hz, 2H), 0.31 (s, 9H), 0.25 (s, 9H). HPLC purity (254 nm): 96.1%.

Example 12: Preparation of N-(2-(tert-Butyl)-5-hydroxy-4-(tris(methyl- d_3)silyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 12)

[0132] A. N-(2-(tert-Butyl)-5-hydroxy-4-(tris(methyl- d_3)silyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To an 8-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-bromo-4-tert-butyl-5-(4-oxo-1,4-dihydroquinoline-3-amido)phenyl methyl carbonate (50 mg, 0.11 mmol, as prepared in Example 4, Step B) in DMPU (3 mL) then d_{18} -hexamethyldisilane (52 mg, 0.32 mmol), $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (2.2 mg, 0.01 mmol), and K_3PO_4 (34 mg, 0.16 mmol) were added. The reaction was stirred for 16 h at 90°C, cooled to rt, and filtered. The filtrate was diluted with 50 mL of water and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. This reaction was repeated once more then the two batches were combined and purified by Prep-HPLC (HPLC-10: Column, X Bridge C18 OBD Prep Column, 10 μm , 19 mm X 250 mm; mobile phase, Water (10 mmol/L NH_4HCO_3) and MeCN (55.0% MeCN up to 87.0% in 7 min); Detector, UV 254/220 nm) affording 4.9 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_{23}\text{H}_{20}\text{D}_9\text{N}_2\text{O}_3\text{Si}^+$: 418.3 (M+H); Found: 418.1. ^1H NMR (400 MHz, $\text{DMSO}-d_6$):

δ 12.89 (br s, 1H), 11.91 (s, 1H), 9.26 (s, 1H), 8.87 (s, 1H), 8.34-8.32 (m, 1H), 7.90-7.70 (m, 2H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.25 (s, 1H), 7.15 (s, 1H), 1.39 (s, 9H). HPLC purity (254 nm): 95.3%.

Example 13: N-(5-Hydroxy-2,4-bis(tris(methyl- d_3)silyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 13)

[0133] A. N-(5-Hydroxy-2,4-bis(tris(methyl- d_3)silyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 40-mL sealed tube, purged and maintained with an inert atmosphere of N_2 , was placed a solution of N-(2,4-dibromo-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (50 mg, 0.11 mmol, as prepared in Example 9, Step C) in DMPU (1 mL), then
10 KF/ Al_2O_3 (100 mg, 1.72 mmol), $Pd_2(dba)_3CHCl_3$ (20 mg, 0.02 mmol), Johnphos (10 mg, 0.03 mmol) and d_{18} -hexamethyldisilane (74 mg, 0.45 mmol) were added. The reaction was stirred for 16 h at 110°C. This step was repeated 5 additional times, then the crude reactions were combined and purified by column chromatography eluting with EtOAc (100%). The resulting material was purified by Prep-HPLC (Column, Atlantis Prep T3 OBD Column, 19*250mm
15 10um; mobile phase, Water (10 mmol/L NH_4HCO_3) and ACN (75% ACN up to 90% in 8 min); Detector, UV 254/220 nm) affording 27.0 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for $C_{22}H_{11}D_{18}N_2O_3Si_2^+$: 443.3 (M+H); Found: 443.4. 1H NMR (400 MHz, $DMSO-d_6$): δ 12.90 (s, 1H), 11.82 (s, 1H), 9.61 (s, 1H), 8.87 (s, 1H), 8.32 (d, $J = 8.0$ Hz, 1H), 7.85-7.73 (m, 2H), 7.54 (t, $J = 7.8$ Hz, 1H), 7.36 (s, 1H), 7.33 (s, 1H). HPLC
20 purity (254 nm): 95.3%.

Example 14: N-(3-Hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 17)

[0134] A. 5-Nitro-2-(trimethylsilyl)phenol. To a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-bromo-5-nitrophenol (1.1 g, 5.05 mmol) in DMPU (10 mL) then hexamethyldisilane (14.7 g, 100.42
25 mmol), $Pd_2(dba)_3CHCl_3$ (520 mg, 0.50 mmol), JohnPhos (450 mg, 1.51 mmol), and KF (1.45 g, 25.00 mmol) were added. The reaction was stirred at 110°C for 16 h in an oil bath, then cooled to rt and filtered. The filtrate was diluted with water (100 mL), and extracted with EtOAc

(3x100 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (0-50%) affording 850 mg of as yellow oil. Mass Spectrum (LCMS, ESI neg): Calcd. for $\text{C}_9\text{H}_{12}\text{NO}_3\text{Si}^-$: 210.1 (M-H); Found: 210.0.

- 5 **[0135]** B. 5-Amino-2-(trimethylsilyl)phenol. To a 50-mL round-bottom flask, was placed a solution of 5-nitro-2-(trimethylsilyl)phenol (200 mg, 0.95 mmol, as prepared in the previous step) in methanol/THF (4/2 mL) then $\text{Ni}(\text{OAc})_2$ (168 mg, 0.95 mmol) was added followed by NaBH_4 (36 mg, 0.95 mmol), in portions at 0°C . The reaction was stirred at 0°C for 10 min in a water/ice bath then the solids were removed by filtration. The reaction was quenched by the
- 10 addition of water (50 mL) and the resulting solution was extracted with EtOAc (3x50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 , and diluted with DMF (6 mL). The resulting solution was concentrated under reduced pressure to remove EtOAc affording a DMF solution of the title compound, which was used directly in the next step without isolation. Mass Spectrum (LCMS, ESI pos): Calcd. for $\text{C}_9\text{H}_{16}\text{NOSi}^+$: 182.1 (M+H);
- 15 Found: 182.1.

- [0136]** C. N-(3-Hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 5-amino-2-(trimethylsilyl)phenol as in DMF (6 mL, as prepared in the previous step), then 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (180 mg,
- 20 0.95 mmol), HATU (543 mg, 1.43 mmol), and DIEA (245 mg, 1.90 mmol) were added. The reaction was stirred at rt for 16 h, then diluted with water (50 mL) and extracted with EtOAc (2x50 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified by re-crystallization from EtOAc affording 59.4 mg of the title compound as a white solid. Mass Spectrum (LCMS,
- 25 ESI pos): Calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3\text{Si}^+$: 353.1 (M+H); Found: 353.3. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.95 (s, 1H), 12.41 (s, 1H), 9.51 (s, 1H), 8.86 (s, 1H), 8.32 (d, $J = 7.5$ Hz, 1H), 7.82-7.74 (m, 2H), 7.54 (t, $J = 7.5$ Hz, 1H), 7.39 (s, 1H), 7.19 (d, $J = 7.8$ Hz, 1H), 7.02-7.69 (m, 1H), 0.23 (s, 9H). HPLC purity (254 nm): 99.2%.

Example 15: N-(3-Hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 18)

- [0137] A. 2-Bromo-4-fluorophenyl methyl carbonate. To a 100-mL round-bottom flask was placed a solution of 2-bromo-4-fluorophenol (1.9 g, 9.95 mmol) in DCM (20 mL) then
5 TEA (2.0 g, 19.76 mmol) and DMAP (120 mg, 0.98 mmol) were added, followed by the dropwise addition of methyl chloroformate (1.23 g, 13.02 mmol) with stirring at 0°C. The reaction was stirred at rt for 3 h, then quenched by the addition of water (100 mL) and extracted with DCM (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure affording 1.5 g of the title compound as a yellow oil.
- 10 [0138] B. 2-Bromo-4-fluoro-5-nitrophenyl methyl carbonate. To a 100-mL round-bottom flask, was placed a solution of 2-bromo-4-fluorophenyl methyl carbonate (1 g, 4.02 mmol, as prepared in the previous step) in DCM (10 mL), then HNO₃/H₂SO₄ (1:1) (5 mL) was added dropwise with stirring at 0°C. The reaction was stirred at rt for 2 h, then poured into 200 mL of water/ice and extracted with DCM (3x100 mL). The organic extracts were combined, dried
15 over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (2:1) affording 700 mg of the title compound as a light yellow solid. Mass Spectrum (LCMS, ESI pos): Calcd. for C₈H₆BrFNO₅⁺: 293.9 (M+H); Found: 294.0.
- [0139] C. 4-Fluoro-5-nitro-2-(trimethylsilyl)phenol. To a 20-mL sealed tube purged and
20 maintained with an inert atmosphere of nitrogen, was placed a solution of 2-bromo-4-fluoro-5-nitrophenyl methyl carbonate (300 mg, 1.02 mmol, as prepared in the previous step) in DMPU (3 mL) then hexamethyldisilane (2.98 g, 20.36 mmol), PdCl₂ (184 mg, 1.04 mmol), and K₃PO₄ (441 mg, 2.08 mmol) were added. The reaction was stirred at 110°C for 24 h in an oil bath, then cooled to rt and filtered. The filtrate was diluted with water (50 mL) and extracted with
25 EtOAc (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (0-60%) affording 150 mg of the title compound as a yellow oil. Mass Spectrum (LCMS, ESI neg): Calcd. for C₉H₁₁FNO₃Si⁻: 228.1 (M+H); Found: 228.0.

[0140] D. 5-Amino-4-fluoro-2-(trimethylsilyl)phenol. To a 50-mL round-bottom flask was placed a solution of 4-fluoro-5-nitro-2-(trimethylsilyl)phenol (150 mg, 0.65 mmol, as prepared in the previous step) in methanol/THF (2/2 mL), then Ni(OAc)₂ (116 mg, 0.66 mmol) was added followed by the addition of NaBH₄ (25 mg, 0.66 mmol) in portions at 0°C. The reaction was stirred at 0°C for 10 min then the solids were removed by filtration. The filtrate was diluted with water (20 mL) and extracted with EtOAc (3x20 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure affording 100 mg of the title compound as a yellow oil. Mass Spectrum (LCMS, ESI pos): Calcd. for C₉H₁₅FNOSi⁺: 200.1 (M+H); Found: 200.1.

[0141] E. N-(3-Hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 50-mL round-bottom flask was placed a solution of 5-amino-4-fluoro-2-(trimethylsilyl)phenol (100 mg, 0.50 mmol, as prepared in the previous step) in DMF (5 mL) then 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (95 mg, 0.50 mmol), HATU (285 mg, 0.75 mmol), and DIEA (129 mg, 1.00 mmol) were added. The reaction was stirred at rt for 16 h, then diluted with water (50 mL) and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Column, X Bridge C18 OBD Prep Column, 10 µm, 19 mm X 250 mm; mobile phase, Water (10 mM NH₄HCO₃) and ACN (50.0% ACN up to 83.0% in 8 min); Detector, UV 254/220nm) affording 68.2 mg of the title compound as an off-white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for C₁₉H₂₀FN₂O₃Si⁺: 371.1 (M+H); Found: 371.1. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.97 (s, 1H), 12.69 (d, *J* = 2.4 Hz, 1H), 9.48 (s, 1H), 8.88 (s, 1H), 8.35-8.32 (m, 1H), 8.08 (d, *J* = 6.0 Hz, 1H), 7.85-7.75 (m, 2H), 7.56-7.52 (m, 1H), 7.03 (d, *J* = 10.8 Hz, 1H), 0.24 (s, 9H). HPLC purity (254 nm): 99.1%.

Example 16: N-(5-Hydroxy-2-(trifluoromethyl)-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound 19)

[0142] A. 2-Bromo-4-(trifluoromethyl)phenyl methyl carbonate. To a 250-mL round-bottom flask was placed a solution of 2-bromo-4-(trifluoromethyl)phenol (4.8 g, 19.92 mmol) in DCM (100 mL) then TEA (4 g, 39.53 mmol) and DMAP (250 mg, 2.05 mmol) were added, followed by the dropwise addition of methyl chloroformate (3.8 g, 40.21 mmol) with stirring at

0°C. The reaction was stirred at rt for 3 h then quenched by the addition of water (100 mL) and extracted with DCM (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (0-5%) affording 4.0 g of the title compound as yellow oil.

[0143] B. 2-Bromo-5-nitro-4-(trifluoromethyl)phenyl methyl carbonate. To a 250-mL round-bottom flask was placed a solution of 2-bromo-4-(trifluoromethyl)phenyl methyl carbonate (4 g, 13.38 mmol, as prepared in the previous step) in H₂SO₄ (20 mL) then HNO₃/H₂SO₄ (1:1, 10 mL) was added dropwise with stirring at 0°C. The reaction was stirred at rt for 3 h then quenched by the addition of 300 mL of water/ice and extracted with DCM (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (0-50%) affording 1.0 g of the title compound as a light yellow solid.

[0144] C. 5-Nitro-4-(trifluoromethyl)-2-(trimethylsilyl)phenol. To a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-bromo-5-nitro-4-(trifluoromethyl)phenyl methyl carbonate (300 mg, 0.87 mmol, as prepared in the previous step) in DMPU (3 mL) then hexamethyldisilane (2.6 g, 17.76 mmol), PdCl₂ (154 mg, 0.87 mmol), and K₃PO₄ (369 mg, 1.74 mmol) were added. The reaction was stirred at 110°C for 24 h, then cooled and filtered. The filtrate was diluted with water (50 mL) and extracted with EtOAc (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (0-50%) affording 160 mg of the title compound as light yellow oil. Mass Spectrum (LCMS, ESI neg): Calcd. for C₁₀H₁₁F₃NO₃Si⁻: 278.0 (M+H); Found: 278.0.

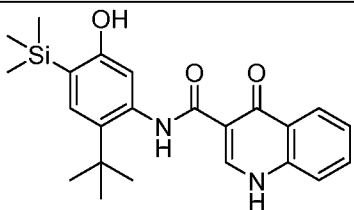
[0145] D. 5-Amino-4-(trifluoromethyl)-2-(trimethylsilyl)phenol. To a 25-mL round-bottom flask was placed a solution of 5-nitro-4-(trifluoromethyl)-2-(trimethylsilyl)phenol (160 mg, 0.57 mmol, as prepared in the previous step) and Ni(OAc)₂ (102 mg, 0.58 mmol) in methanol/THF (2 mL), then NaBH₄ (22 mg, 0.58 mmol) was added in portions at 0°C. The

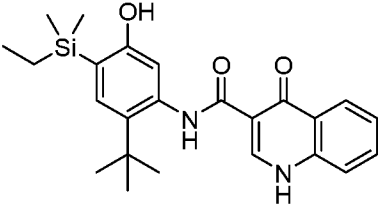
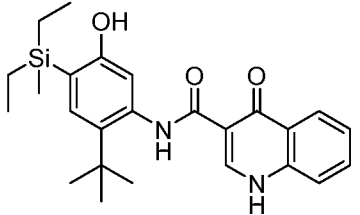
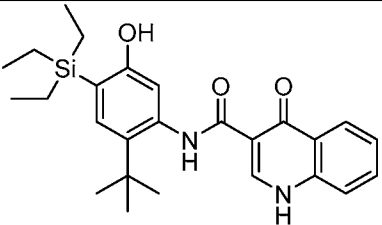
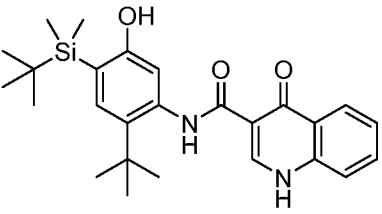
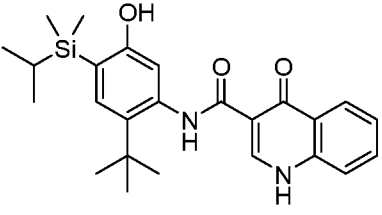
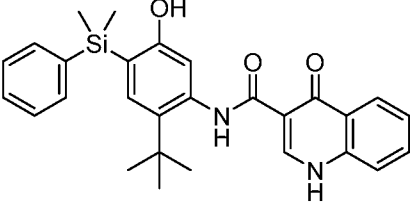
reaction was stirred at 0°C for 10 min, then filtered, diluted with water (100 mL), and extracted with EtOAc (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure affording 120 mg of the title compound as a yellow oil. Mass Spectrum (LCMS, ESI pos): Calcd. for C₁₀H₁₅F₃NOSi⁺: 250.1 (M+H); Found: 250.1.

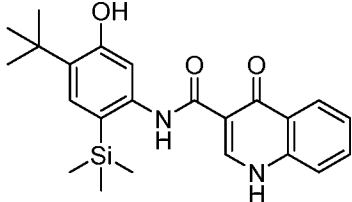
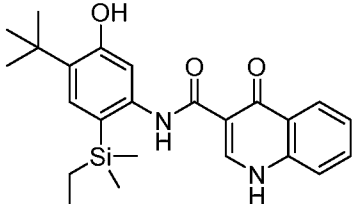
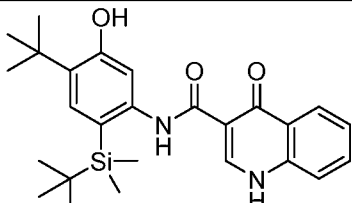
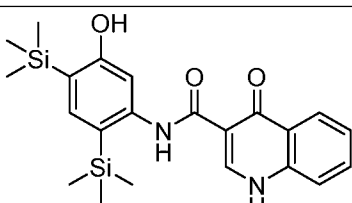
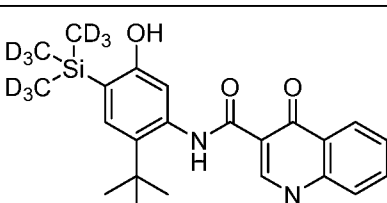
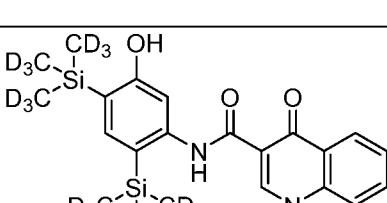
- 5 **[0146]** E. N-(5-Hydroxy-2-(trifluoromethyl)-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide. To a 100-mL round-bottom flask was placed a solution of 5-amino-4-(trifluoromethyl)-2-(trimethylsilyl)phenol (120 mg, 0.48 mmol, as prepared in the previous step) in DMF (10 mL), then 4-oxo-1,4-dihydroquinoline-3-carboxylic acid (137 mg, 0.72 mmol), HATU (365 mg, 0.96 mmol), and DIEA (186 mg, 1.44 mmol) were added. The reaction was stirred at rt for 16 h, diluted with water (100 mL), and extracted with EtOAc (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by Chiral-Prep-HPLC (Column, Chiralpak IA, 2*25cm, 5um; mobile phase, Hex- and ethanol- (hold 10.0% ethanol- in 13 min); Detector, UV 220/254nm) affording in 6.6 mg of the title compound as a white solid. Mass Spectrum (LCMS, ESI pos): Calcd. for C₂₀H₂₀F₃N₂O₃Si⁺: 421.1 (M+H); Found: 421.2. ¹H NMR (300 MHz, DMSO-*d*₆): δ 13.15 (br s, 1H), 12.67 (s, 1H), 10.37 (s, 1H), 8.86 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 7.99 (s, 1H), 7.84-7.73 (m, 2H), 7.54-7.49 (m, 1H), 7.45 (s, 1H), 0.25 (s, 9H). HPLC purity (254 nm): 99.8%.
- 10
- 15

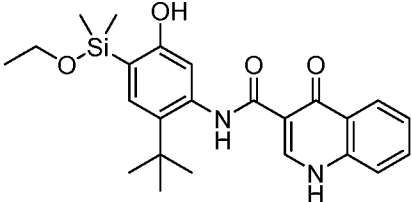
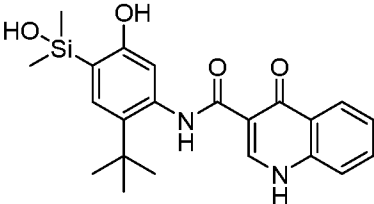
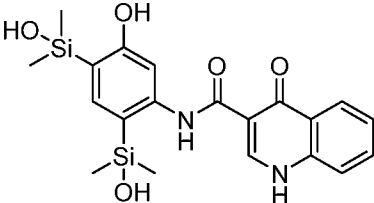
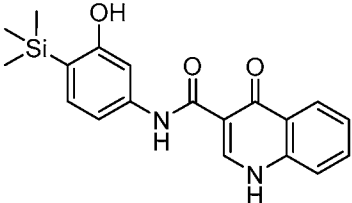
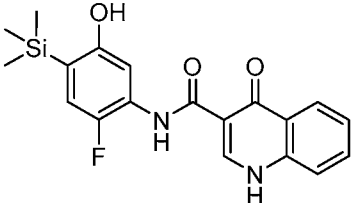
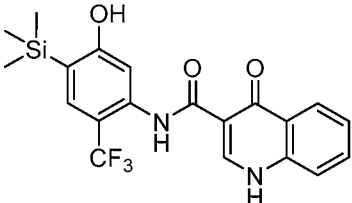
- [0147]** Exemplary compounds of the disclosure prepared by the above synthetic procedures are provided in Table 1:
- 20

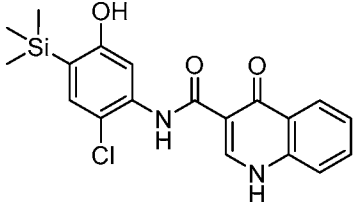
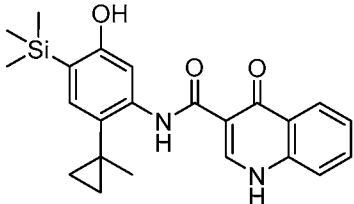
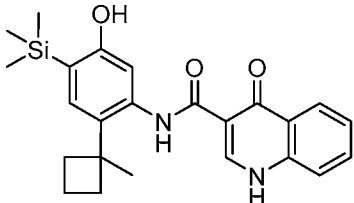
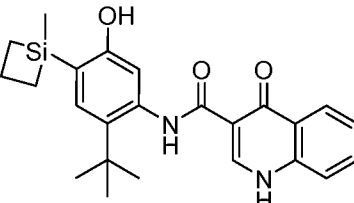
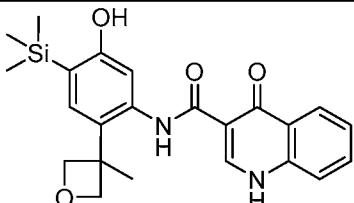
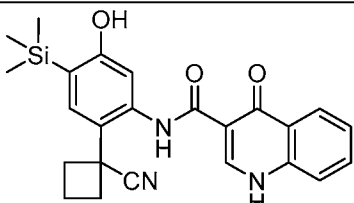
Table 1

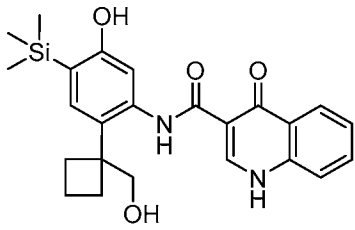
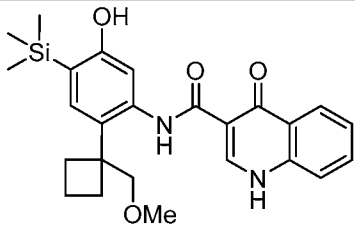
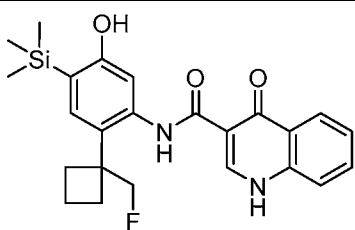
Compound	Structure	Name
1		N-(2-(tert-Butyl)-5-hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

2		N-(2-(tert-Butyl)-4-(ethyl(dimethyl)silyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
3		N-(2-(tert-Butyl)-4-(diethyl(methyl)silyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
4		N-(2-(tert-Butyl)-5-hydroxy-4-(triethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
5		N-(2-(tert-Butyl)-4-(tert-butyl(dimethyl)silyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
6		N-(2-(tert-Butyl)-5-hydroxy-4-(isopropyl(dimethyl)silyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
7		N-(2-(tert-Butyl)-4-(dimethyl(phenyl)silyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

8		N-(4-(tert-Butyl)-5-hydroxy-2-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
9		N-(4-(tert-Butyl)-2-(ethyl dimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
10		N-(4-(tert-Butyl)-2-(tert-butyl dimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
11		N-(5-Hydroxy-2,4-bis(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
12		N-(2-(tert-Butyl)-5-hydroxy-4-(tris(methyl-d3)silyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
13		N-(5-Hydroxy-2,4-bis(tris(methyl-d3)silyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

14		N-(2-(tert-Butyl)-4-(ethoxydimethylsilyl)-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
15		N-(2-(tert-Butyl)-5-hydroxy-4-(hydroxydimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
16		N-(5-Hydroxy-2,4-bis(hydroxydimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
17		N-(3-Hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
18		N-(2-Fluoro-5-hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
19		N-(5-Hydroxy-2-(trifluoromethyl)-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

20		N-(2-Chloro-5-hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
21		N-(5-Hydroxy-2-(1-methylcyclopropyl)-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
22		N-(5-Hydroxy-2-(1-methylcyclobutyl)-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
23		N-(2-(tert-Butyl)-5-hydroxy-4-(1-methylsiletan-1-yl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
24		N-(5-Hydroxy-2-(3-methyloxetan-3-yl)-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
25		N-(2-(1-Cyanocyclobutyl)-5-hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

26		N-(5-Hydroxy-2-(1-(hydroxymethyl)cyclobutyl)-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
27		N-(5-Hydroxy-2-(1-(methoxymethyl)cyclobutyl)-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide
28		N-(2-(1-(Fluoromethyl)cyclobutyl)-5-hydroxy-4-(trimethylsilyl)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

Example 17: CFTR activity assays

i. Ussing measurements

- 5 [0148] 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 $\Delta F508$ 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
- 10 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 ($V_{\text{hold}} = 0$ mV), and the entire assay is conducted at a temperature of 36°C -36.5°C. Once the voltages are
- 15 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:

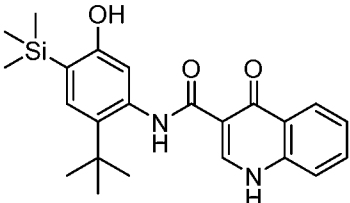
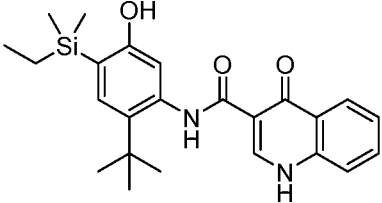
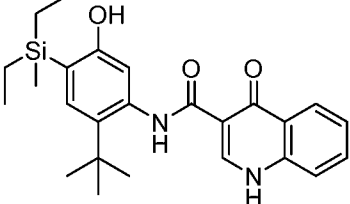
1. Benzamil to the apical chamber to inhibit ENaC sodium channel.
2. Forskolin to both chambers to activate $\Delta F508$ -CFTR by phosphorylation.
- 5 3. VX-770 to the apical chamber to potentiate $\Delta F508$ -CFTR channel opening.
4. CFTRinh-172 to the apical chamber to inhibit $\Delta F508$ -CFTR Cl⁻ conductance.

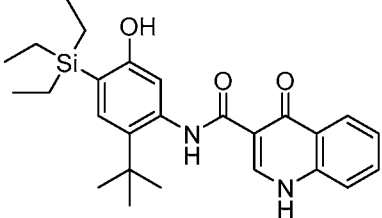
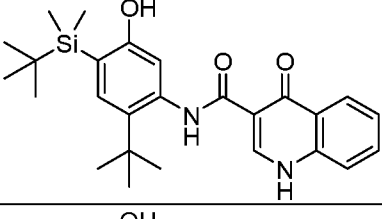
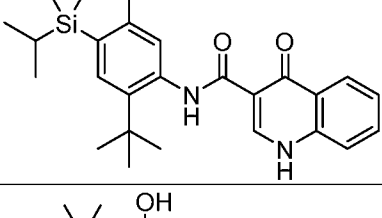
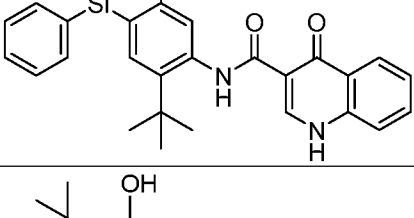
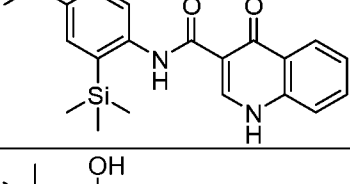
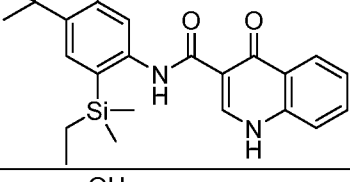
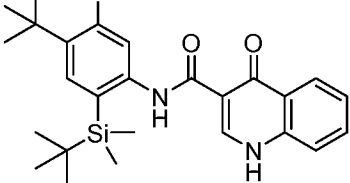
[0149] The inhibitable current (that current that is blocked by CFTRinh-172) is measured as the specific activity of the $\Delta F508$ -CFTR channel, and increases in response to compound in this activity over that observed in vehicle-treated samples are identified as the correction of
10 $\Delta F508$ -CFTR function imparted by the compound tested.

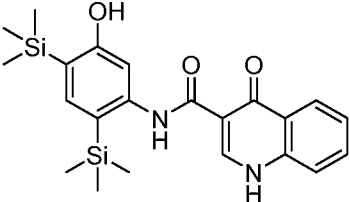
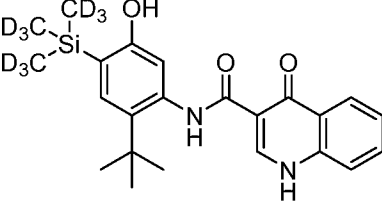
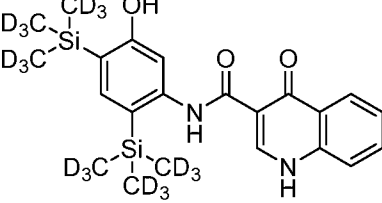
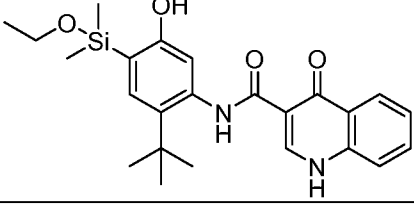
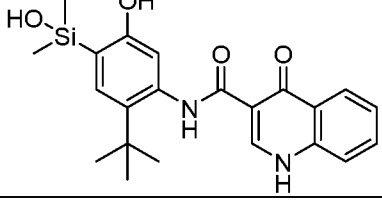
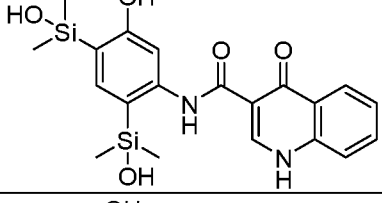
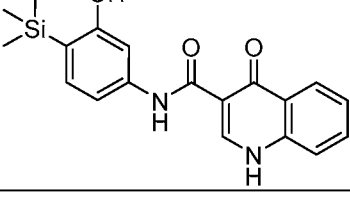
[0150] The results are shown below in Table 2. (+ indicates activity <200% of a corrector (VX-809 (3 μ M)) with compound at 1 μ M; ++ indicates activity >200% of a corrector (VX-809 (3 μ M)) with compound at 1 μ M.

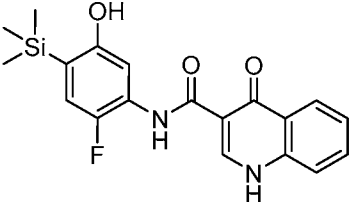
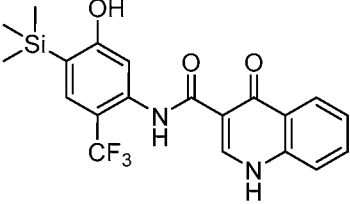
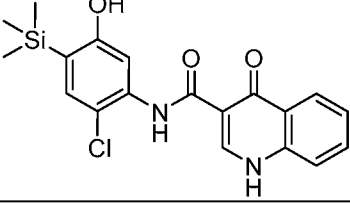
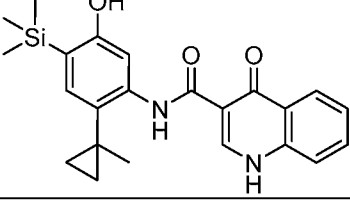
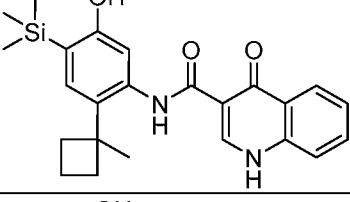
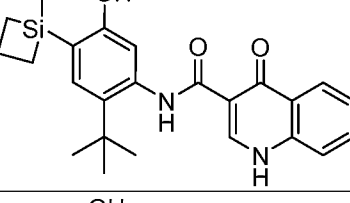
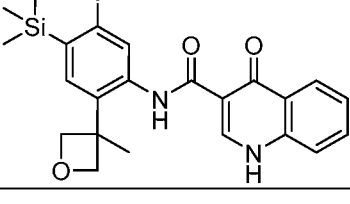
Table 2

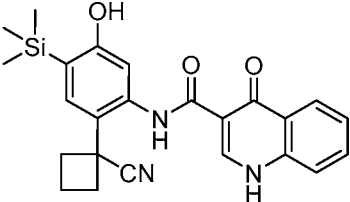
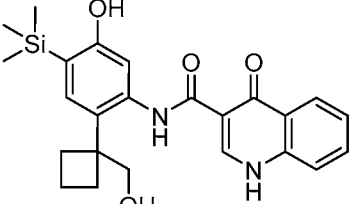
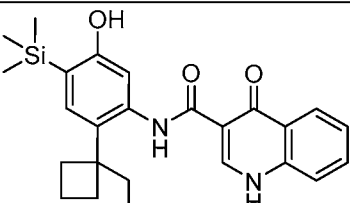
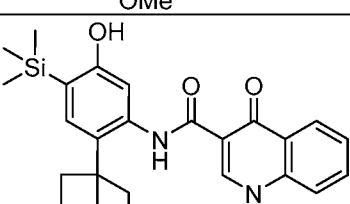
15

Compound	Structure	Activity
1		++
2		++
3		++

4		+
5		++
6		++
7		++
8		++
9		
10		++

11		++
12		++
13		++
14		
15		
16		
17		++

18		++
19		++
20		
21		
22		
23		
24		

25		
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28		

[0151] While this disclosure has been particularly shown and described with references to certain embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the disclosure encompassed by the appended claims.

INCORPORATION BY REFERENCE

[0152] 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.

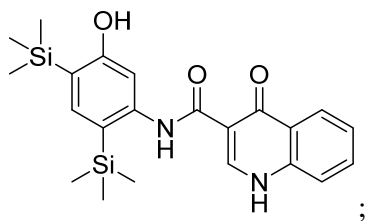
EQUIVALENTS

[0153] While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of
5 the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[0154] 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
10 contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure.

What is claimed is:

1. A compound represented by:



or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.
3. The pharmaceutical composition of claim 2, wherein the composition further comprises at least one additional CFTR modulator.
4. Use of a compound of claim 1 in the manufacture of a medicament for treating 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/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myeloperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, Huntington's disease, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidolulsian, myotonic dystrophy, hereditary Creutzfeldt-Jakob

disease (due to prion protein processing defect), Fabry disease, cholestatic liver disease, and Strausler-Scheinker syndrome, in a subject in need thereof.

5. The use of claim 4, wherein the subject has one or more mutations in the CFTR gene, wherein the mutations are each selected from the group consisting of S549N, G551D, G1244E, G1349D, G167R, G551S, S1251N, S1255P, S549R, G178R, G970R, and R117H.
6. The use of claim 5, wherein G551D CFTR activity is enhanced.
7. The use of claim 6, wherein the disease is cystic fibrosis.
8. The use of any one of claims 4-6, wherein the subject is a human patient.
9. The use of any one of claims 4-8, wherein the medicament is to be administered to the subject, and at least one or two additional CFTR modulators are to be further administered.
10. The use of claim 9, wherein one additional CFTR modulator is selected from the group consisting of VX-152, VX-440, VX-445, VX-659, VX-809 (lumacaftor), VX-661, FDL169, GLPG2851, GLPG2665, GLPG2737, and GLPG2222.
11. Use of a compound of claim 1 in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.
12. A compound of claim 1 for use in treating cystic fibrosis in a patient in need thereof.