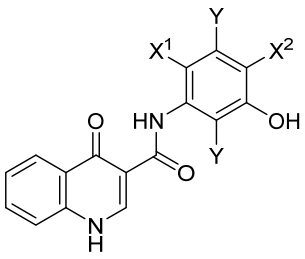
[0006] There remains a need in the art for compounds, compositions and methods of increasing CFTR activity as well as for methods of treating CF, other CFTR-related diseases, and other maladies of protein misfolding.

SUMMARY

[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 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 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.

[0007b] In another aspect of the present disclosure, there is provided a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from the group consisting of $–Si(R^3)_3$, $–C(CY_3)_3$, 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 be 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 $–Si(R^3)_3$ and $–C(CY_3)_3$;

wherein at least one of X^1 or X^2 is $–Si(R^3)_3$;

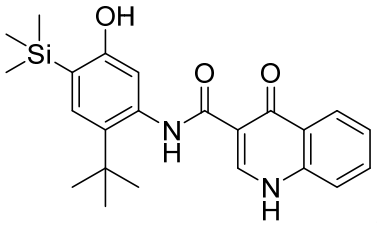
R^3 is independently selected for each occurrence from the group consisting of hydroxyl, C_{1-4}alkyl, C_{1-4}alkoxy, and phenyl, wherein C_{1-4}alkyl, C_{1-4}alkoxy, and phenyl may optionally be substituted by one, two, three or more deuterium atoms; or two R^3 groups together with the silicon to which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

[0007c] In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

3b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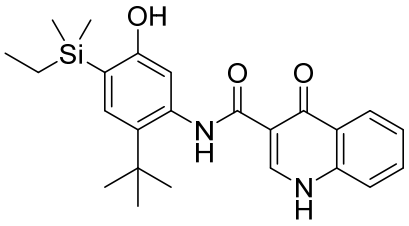
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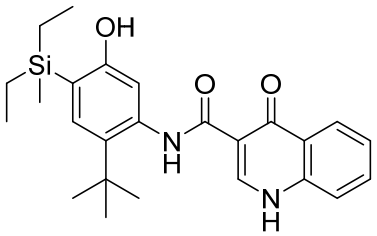
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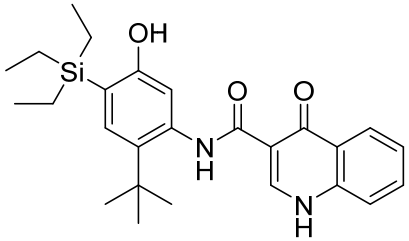
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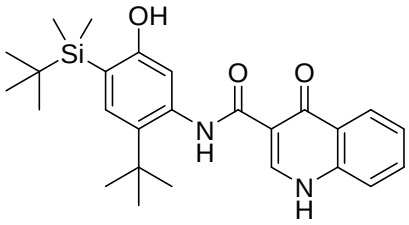
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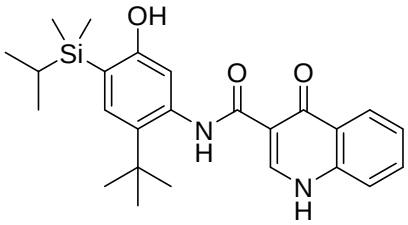
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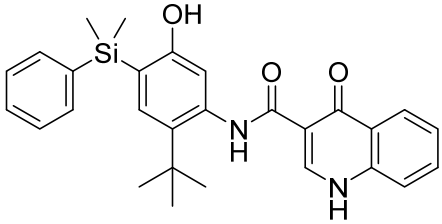
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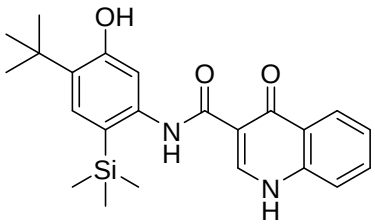
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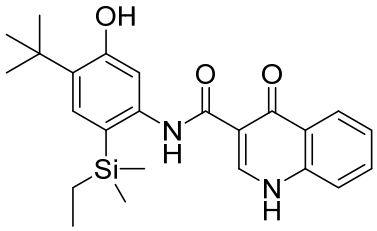
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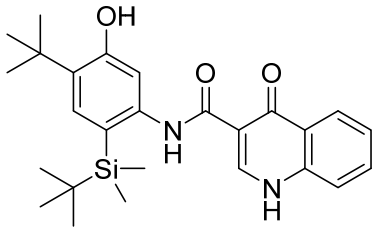
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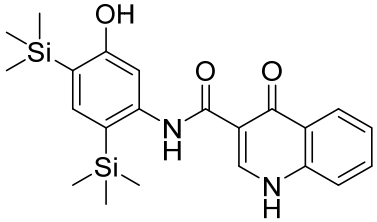
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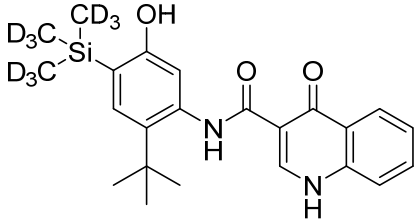
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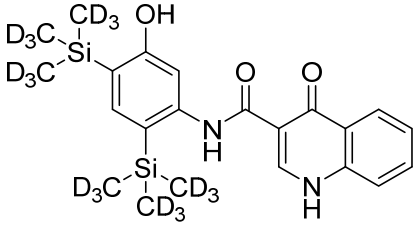
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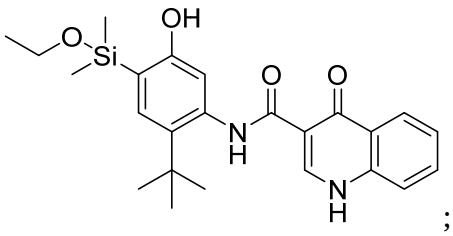
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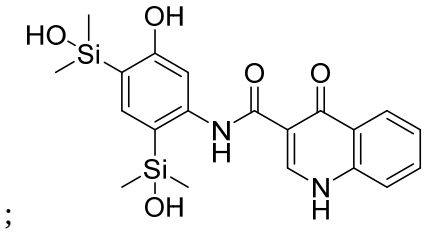
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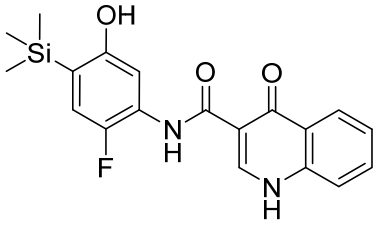
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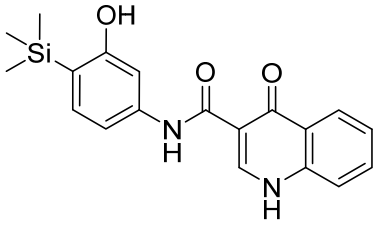
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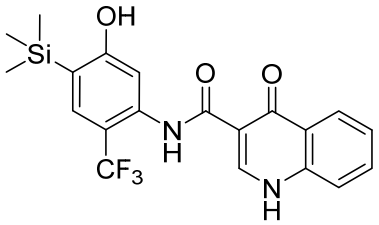
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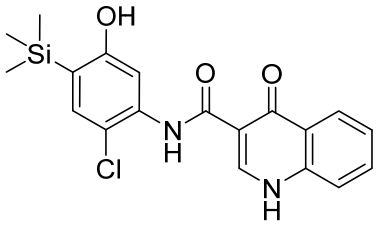
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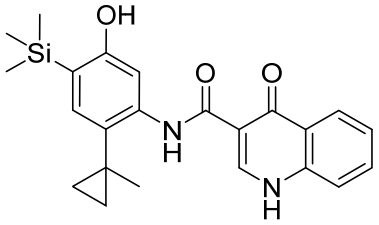
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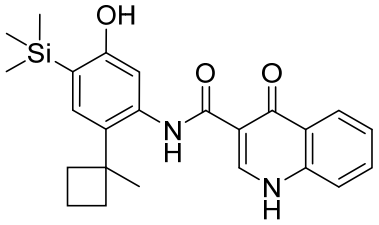
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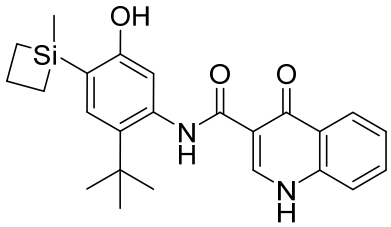
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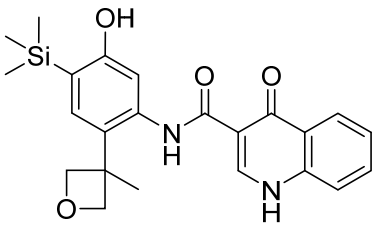
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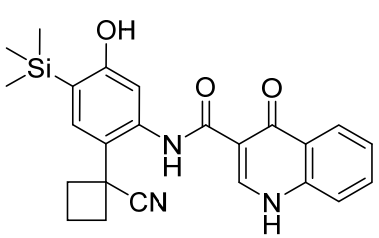
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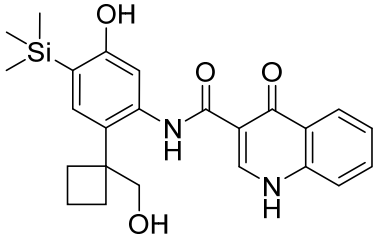
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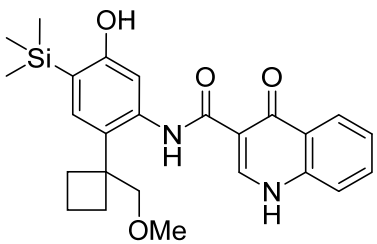
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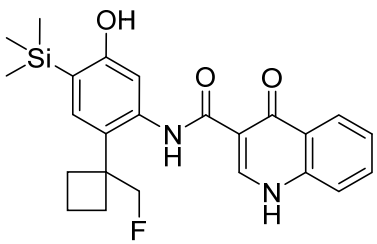
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and a pharmaceutically acceptable salt thereof; wherein any atom not designated as deuterium is present at its natural isotopic abundance.

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

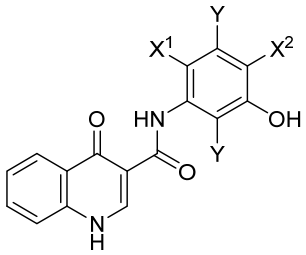
[0007e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof.

[0007f] 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.

[0007g] In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof.

[0007h] 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.

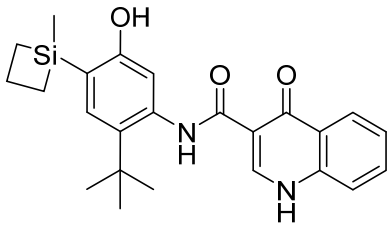
[0008] For example, disclosed herein are compounds having Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, in which X^1, X^2 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 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.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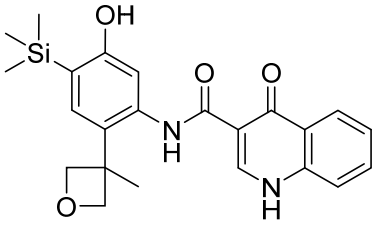
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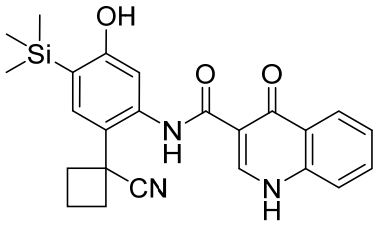
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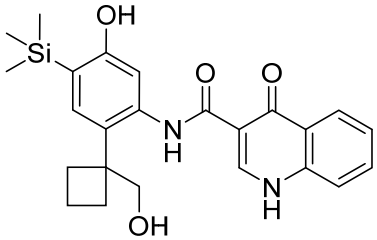
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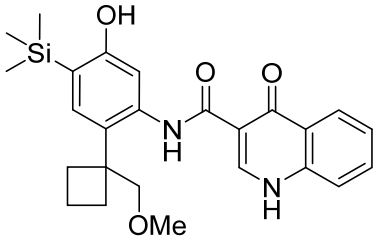
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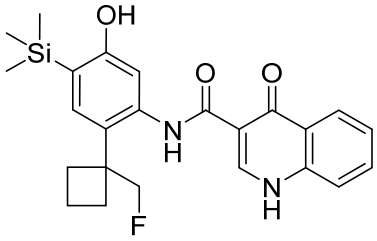
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and a pharmaceutically acceptable salt thereof; wherein any atom not designated as deuterium is present at its natural isotopic abundance.

16. A pharmaceutical composition comprising a compound of any one of claims 1 to 15 and a pharmaceutically acceptable excipient.

17. The pharmaceutical composition of claim 16, wherein the composition further comprises at least one additional CFTR modulator.

18. Use of a compound of any one of claims 1 to 15 in the manufacture of a medicament for enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof.

19. The use of claim 18, 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.

20. The use of claim 19, wherein G551D CFTR activity is enhanced.

21. The use of any one of claims 18-20, wherein the subject is suffering from a disease associated with decreased CFTR activity.

22. The use of claim 21, wherein the disease is selected from the group consisting of cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, A-β-lipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolyis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, Sjogren's syndrome, familial hypercholesterolemia, I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, nephrogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, Huntington's disease, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidoluysian, myotonic dystrophy, hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, cholestatic liver disease, and Straussler-Scheinker syndrome.

23. The use of claim 22, wherein the disease is cystic fibrosis.

24. The use of any one of claims 18-23, wherein the subject is a human patient.

25. The use of any one of claims 18-24, wherein the medicament is to be administered to the subject, and at least one or two additional CFTR modulators are to be further administered.

26. The use of claim 25, 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.

27. Use of a compound of any one of claims 1-15 in the manufacture of a medicament for treating cystic fibrosis in a patient in need thereof.

28. A compound of any one of claims 1 to 15 for use in enhancing cystic fibrosis transmembrane conductance regulator (CFTR) activity in a subject in need thereof.

29. A compound of any one of claims 1-15 for use in treating cystic fibrosis in a patient in need thereof.