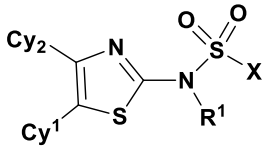
plasma membrane, is instead retained in the endoplasmic reticulum and targeted for degradation by the ubiquitin-proteasome system.

The loss of a functional CFTR channel at the plasma membrane disrupts ionic homeostasis and airway surface hydration leading to reduced lung function. Reduced periciliary liquid volume and increased mucus viscosity impede mucociliary clearance resulting in chronic infection and inflammation. In the lung, the loss of CFTR-function leads to numerous physiological effects downstream of altered anion conductance that result in the dysfunction of additional organs such as the pancreas, intestine and gall bladder.

Guided, in part, by studies of the mechanistic aspects of CFTR misfoldingand dysfunction, small molecule CFTR modulators have been identified, that can increase CFTR channel function. Despite the identification of compounds that modulate CFTR, there is no cure for this fatal disease and identification of new compounds and new methods of therapy are needed as well as new methods for treating or lessening the severity of cystic fibrosis and other CFTR mediated conditions and diseases in a patient.

SUMMARY

In one aspect of the present disclosure, there is provided a compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen or C_{1-6} alkyl;

X is phenyl, each of which is substituted with 0-3 occurrences of R^2;

Cy^1 is phenyl, each of which is substituted with 0-3 occurrences of R^3;

Cy^2 is phenyl, each of which is substituted with 1-3 occurrences of R^4;

each R^2 is independently hydroxyl, halo, $-NH_2$, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 4-10 membered heterocycloalkyl, 5-6 membered heteroaryl, C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, $-C(O)NH_2$, $-N(R^a)(R^5)$, $-N(R^a)C(O)-R^5$, $-N(R^a)SO_2-R^5$, $-SO_2-R^5$, $-C(O)N(R^a)(R^5)$, $-S(O)-R^5$, $-N(R^a)S(O)(NH)-R^5$ or $-P(O)(R^5)_2$, wherein each C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-9} cycloalkyl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^5;

each R^3 is independently halo, C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{3-9} cycloalkyl, C_{1-4} alkyl-C_{3-9} cycloalkyl, C_{1-4} alkoxy-C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{3-9}

cycloalkenyl, 5-6 membered aryl, aralkyl, aralkoxy, 5-6 membered heteroaryl, 4-10 membered heterocycloalkyl, -C(O)-R^7, -C(O)N(R^a)(R^7) or -N(R^a)(R^8), wherein each C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{1-8} haloalkoxy, C_{1-8} alkoxy, 4-10 membered heterocycloalkyl, 5-6 membered aryl, 5-6 membered heteroaryl, cycloalkenyl, C_{1-4} alkyl-C_{3-9} cycloalkyl or C_{1-4} alkoxy-C_{3-9} cycloalkyl is further substituted with 0-3 occurrences of R^7;

each R^4 is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, N(R^a)$_2$ or 4-10 membered heterocycloalkyl, wherein each 4-10 membered heterocycloalkyl may be further substituted with 0-3 R^b;

each R^5 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-9} cycloalkyl, hydroxyl, -SO_2-R^6, -CO_2H, -NH_2, -CO_2-C_{1-4} alkyl or 4-10 membered heterocycloalkyl, wherein each C_{1-6} alkyl, C_{3-9} cycloalkyl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^6;

each R^6 is independently hydroxyl, -NH_2, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, -CO_2H or -CO_2-(C_{1-4} alkyl);

each R^7 is independently halo, C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} haloalkyl, C_{1-5} haloalkoxy, C_{1-5} haloalkenyl, C_{3-7} cycloalkyl, hydroxyl, 5-6 membered aryl, aralkyl, aralkoxy, -C(O)-O-C_{1-4}alkyl, -C(O)N(R^a)(C_{1-4} alkyl), 5-6 membered heteroaryl or 4-10 membered heterocycloalkyl, wherein each C_{3-7} cycloalkyl, 5-6 membered aryl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^8;

each R^8 is independently halo, C_{1-4} alkyl, C_{1-4} haloalkoxy, C(O)-C_{1-4} alkyl or C(O)N(R^a)(C_{1-4} alkyl);

each R^a is independently H or C_{1-6} alkyl; and

each R^b is C_{1-4} alkyl;

wherein

a) if Cy^1 is phenyl and has 3 occurrences of R^3, then each R^3 is not methoxy;

b) when X and Cy^2 are each phenyl, then R^2 and R^4 are not each methyl;

c) R^3 and R^4 are not simultaneously tert-butyl or simultaneously methoxy; and

d) when Cy^1 and Cy^2 are mono-substituted phenyl, then R^2 is not OH, R^3 is not Cl and R^4 is not OMe.

In another aspect of the present disclosure, there is provided a compound selected from any compound given in Table 1.

In a further aspect of the present disclosure, there is provided a compound selected from any compound given in Table 2.

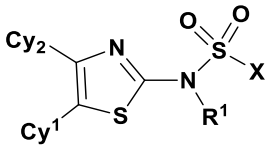
In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier or excipient.

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 treating deficient CFTR activity in a cell.

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 or a symptom thereof in a subject.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, for use in therapy.

In certain examples, the present application is directed to a compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen or C_{1-6} alkyl;

X is C_{1-6} alkyl, 5-6 membered aryl, 4-10 membered heterocycloalkyl, or 5-6 membered heteroaryl, each of which is substituted with 0-3 occurrences of R^2;

Cy^1 is C_{3-9} cycloalkyl, 5-6 membered aryl, 4-10 membered heterocycloalkyl or 5-6 membered heteroaryl, each of which is substituted with 0-3 occurrences of R^3;

Cy^2 is C_{3-9} cycloalkyl, 5-6 membered aryl, 4-10 membered heterocycloalkyl, or 5-6 membered heteroaryl, each of which is substituted with 1-3 occurrences of R^4;

d) when Cy^1 and Cy^2 are mono-substituted phenyl, then X is not thienyl; and

e) when Cy^1 and Cy^2 are mono-substituted phenyl, then R^2 is not OH, R^3 is not Cl and R^4 is not OMe.

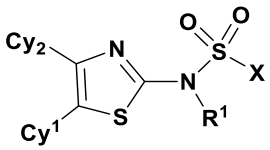
Disclosed herein are methods of treating deficient CFTR activity, thereby treating a disease or condition mediated by deficient CFTR activity. Such diseases and conditions include, but are not limited to, cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, congenital pneumonia, intestinal malabsorption, celiac disease, nasal polyposis, non-tuberculous mycobacterial infection, pancreatic steatorrhea, intestinal atresia, chronic obstructive pulmonary disease (COPD), chronic sinusitis, dry eye disease, protein C deficiency, abetalipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolyis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, and Sjogren's syndrome. In some examples, the disease is cystic fibrosis.

In certain examples, the present disclosure provides a pharmaceutical composition suitable for use in a subject in the treatment or prevention of disease and conditions associate with deficient CFTR activity, comprising an effective amount of any of the compounds described herein (e.g., a compound of the present disclosure, such as a compound of formula (I)), and one or more pharmaceutically acceptable excipients. In certain examples, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein.

Provided herein are combination therapies of compounds of formula (I) with CFTR-active agents that can enhance the therapeutic benefit beyond the ability of the primary therapy alone.

DETAILED DESCRIPTION

In certain aspects, the present application is directed to a compound of Formula (**I**):



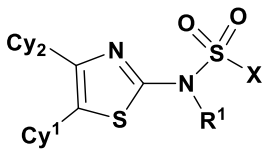
(**I**)

or a pharmaceutically acceptable salt thereof,

wherein:

CLAIMS

1. A compound of Formula (**I**):



(**I**)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen or C_{1-6} alkyl;

X is phenyl, each of which is substituted with 0-3 occurrences of R^2;

Cy^1 is phenyl, each of which is substituted with 0-3 occurrences of R^3;

Cy^2 is phenyl, each of which is substituted with 1-3 occurrences of R^4;

each R^2 is independently hydroxyl, halo, $-NH_2$, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, 4-10 membered heterocycloalkyl, 5-6 membered heteroaryl, C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, $-C(O)NH_2$, $-N(R^a)(R^5)$, $-N(R^a)C(O)-R^5$, $-N(R^a)SO_2-R^5$, $-SO_2-R^5$, $-C(O)N(R^a)(R^5)$, $-S(O)-R^5$, $-N(R^a)S(O)(NH)-R^5$ or $-P(O)(R^5)_2$, wherein each C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{3-9} cycloalkyl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^5;

each R^3 is independently halo, C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{3-9} cycloalkyl, C_{1-4} alkyl-C_{3-9} cycloalkyl, C_{1-4} alkoxy-C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{3-9} cycloalkenyl, 5-6 membered aryl, aralkyl, aralkoxy, 5-6 membered heteroaryl, 4-10 membered heterocycloalkyl, $-C(O)-R^7$, $-C(O)N(R^a)(R^7)$ or $-N(R^a)(R^8)$, wherein each C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{1-8} haloalkoxy, C_{1-8} alkoxy, 4-10 membered heterocycloalkyl, 5-6 membered aryl, 5-6 membered heteroaryl, cycloalkenyl, C_{1-4} alkyl-C_{3-9} cycloalkyl or C_{1-4} alkoxy-C_{3-9} cycloalkyl is further substituted with 0-3 occurrences of R^7;

each R^4 is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, $N(R^a)_2$ or 4-10 membered heterocycloalkyl, wherein each 4-10 membered heterocycloalkyl may be further substituted with 0-3 R^b;

each R^5 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-9} cycloalkyl, hydroxyl, $-SO_2-R^6$, $-CO_2H$, $-NH_2$, $-CO_2-C_{1-4}$ alkyl or 4-10 membered heterocycloalkyl, wherein each C_{1-6} alkyl, C_{3-9} cycloalkyl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^6;

each R^6 is independently hydroxyl, -NH_2, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, -CO_2H or -CO_2-(C_{1-4} alkyl);

each R^7 is independently halo, C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-5} haloalkyl, C_{1-5} haloalkoxy, C_{1-5} haloalkenyl, C_{3-7} cycloalkyl, hydroxyl, 5-6 membered aryl, aralkyl, aralkoxy, -C(O)-O-C_{1-4}alkyl, -C(O)N(R^a)(C_{1-4} alkyl), 5-6 membered heteroaryl or 4-10 membered heterocycloalkyl, wherein each C_{3-7} cycloalkyl, 5-6 membered aryl or 4-10 membered heterocycloalkyl is further substituted by 0-3 occurrences of R^8;

each R^8 is independently halo, C_{1-4} alkyl, C_{1-4} haloalkoxy, C(O)-C_{1-4} alkyl or C(O)N(R^a)(C_{1-4} alkyl);

each R^a is independently H or C_{1-6} alkyl; and

each R^b is C_{1-4} alkyl;

wherein

a) if Cy^1 is phenyl and has 3 occurrences of R^3, then each R^3 is not methoxy;

b) when X and Cy^2 are each phenyl, then R^2 and R^4 are not each methyl;

c) R^3 and R^4 are not simultaneously tert-butyl or simultaneously methoxy; and

d) when Cy^1 and Cy^2 are mono-substituted phenyl, then R^2 is not OH, R^3 is not Cl and R^4 is not OMe.

2. The compound of claim 1, wherein R^1 is H.

3. The compound of claim 1, wherein R^1 is C_{1-6} alkyl.

4. The compound of claim 1, wherein X is phenyl substituted with 0 occurrences of R^2.

5. The compound of claim 1, wherein X is phenyl substituted with 1 occurrence of R^2.

6. The compound of claim 5, wherein R^2 is heteroaryl substituted with 0-3 occurrences of R^5.

7. The compound of claim 5, wherein R^2 is -N(R^a)(R^5).

8. The compound of claim 7, wherein R^a is H or C_{1-6} alkyl, and R^5 is C_{1-6} alkyl

9. The compound of claim 7, wherein R^a is H and R^5 is selected from C_{1-6} haloalkyl , heterocycloalkyl , and C_{3-9} cycloalkyl , substituted with 0 or 1 R^6.

10. The compound of claim 9, wherein R^6 is selected from -CO_2H, -$C(O)_2$-C_{1-4} alkyl, hydroxyl, and C_{1-4} alkyl.

11. The compound of claim 5, wherein R^2 is $-N(R^a)C(O)-R^5$.

12. The compound of claim 11, wherein R^a is H and R^5 is selected from C_{1-6} alkyl and C_{3-9} cycloalkyl, each substituted with 0-3 occurrences of R^6.

13. The compound of claim 12, wherein R^6 is selected from $-NH_2$, hydroxyl, halo, and C_{1-4} haloalkyl.

14. The compound of claim 5, wherein R^2 is heterocycloalkyl substituted with 0-3 occurrences of R^5.

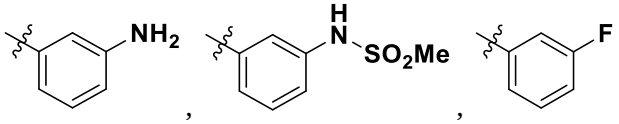
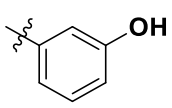
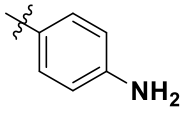
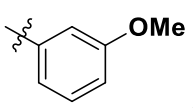
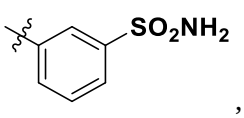
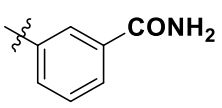
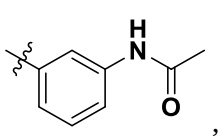
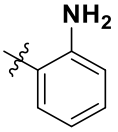
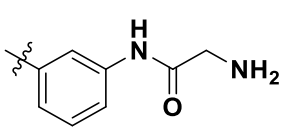
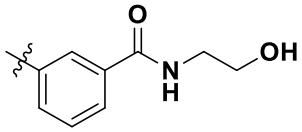
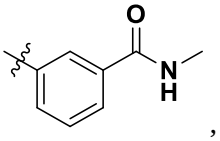
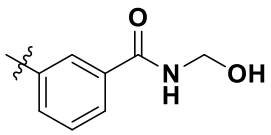
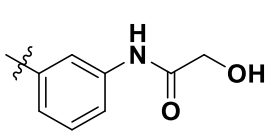
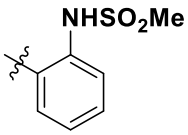
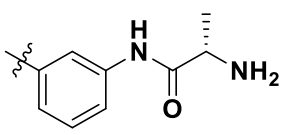
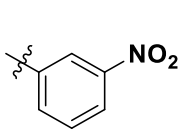
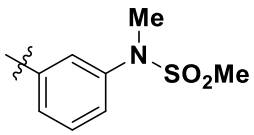
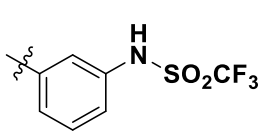
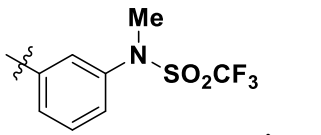
15. The compound of claim 14, wherein each R^5 is selected from C_{1-6} alkyl substituted with 0-3 occurrences of R^6.

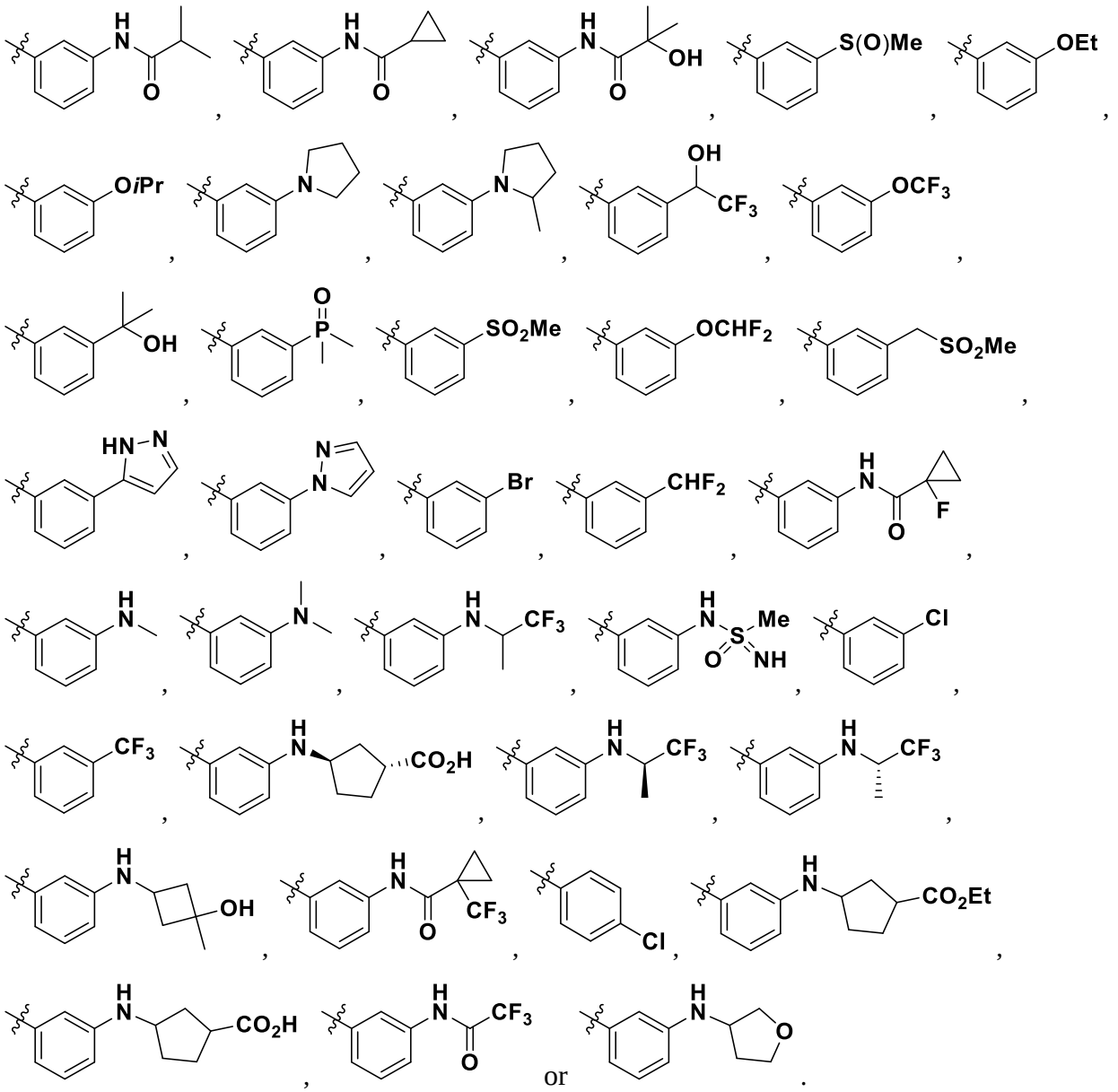
16. The compound of claim 5, wherein R^2 is $-C(O)-N(R^a)(R^5)$.

17. The compound of claim 16, wherein R^a is H and R^5 is C_{1-6} alkyl substituted with 0-3 occurrences of R^6.

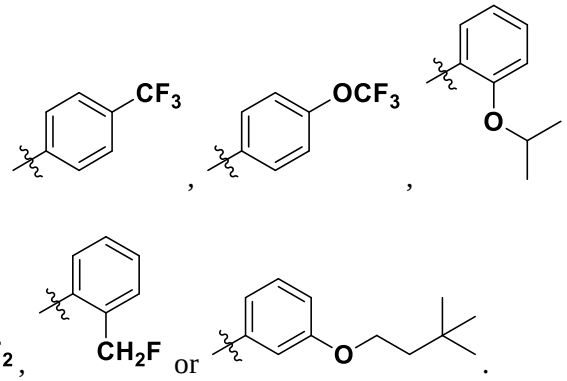
18. The compound of claim 5, wherein R^2 is $-N(R^a)S(O)(NH)-R^5$.

19. The compound of claim 18, wherein R^a is H and R^5 is C_{1-6} alkyl substituted with 0-3 occurrences of R^6.

20. The compound of claim 5, wherein X is , , , , , , , , , , , , , , , , , , , , .

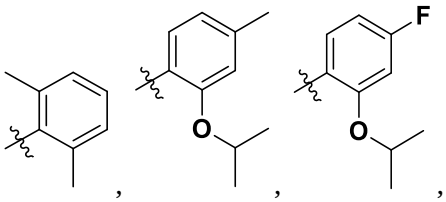
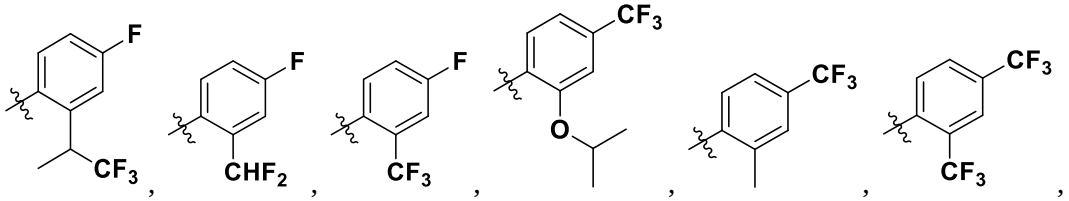
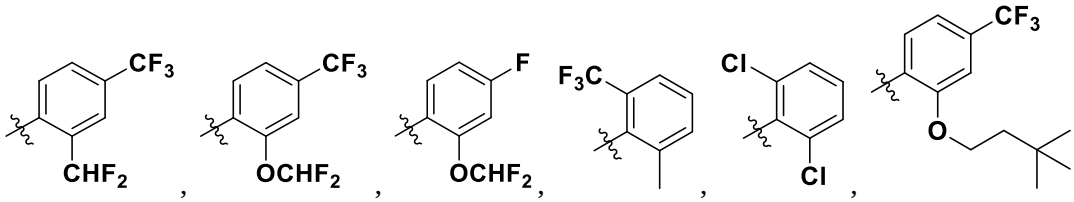
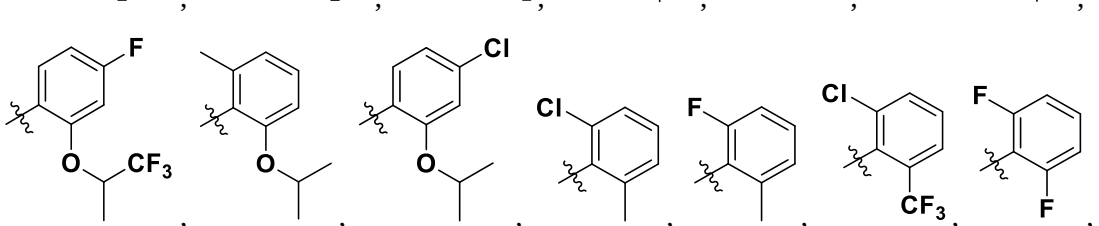
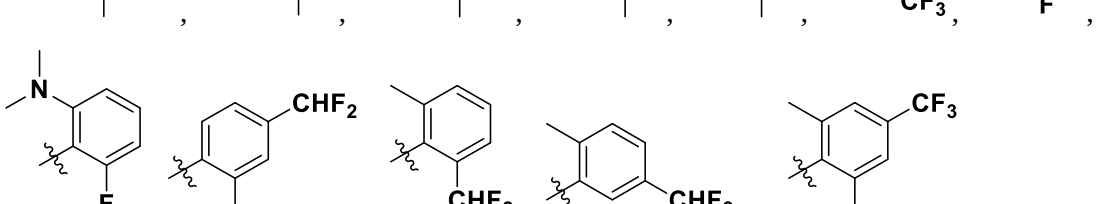
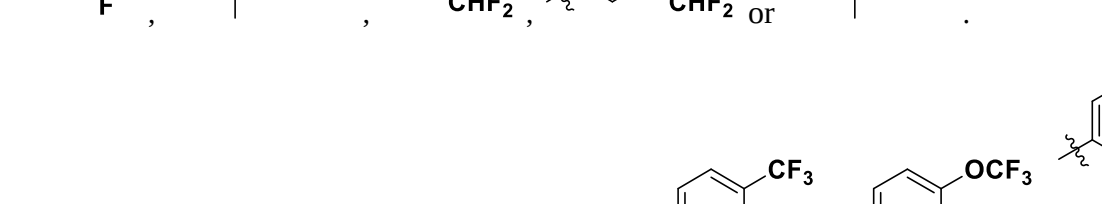
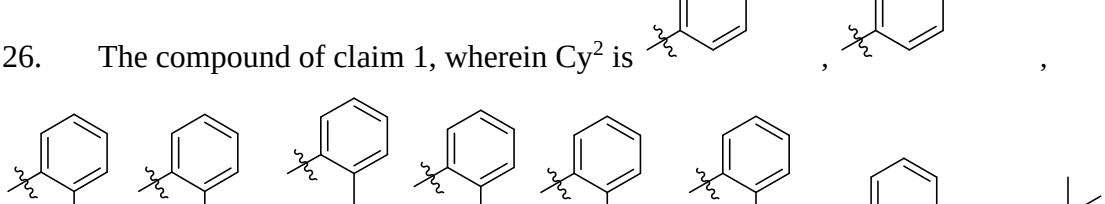
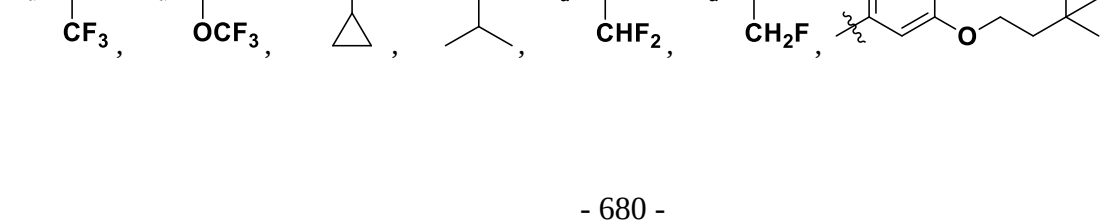
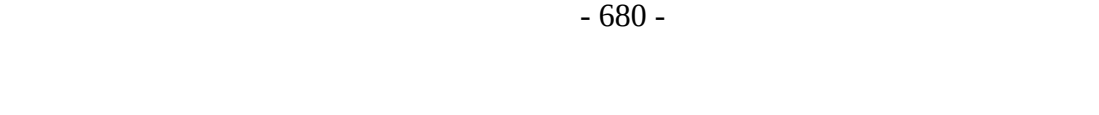


21. The compound of claim 1, wherein R^4 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy and C_{3-6} cycloalkyl.

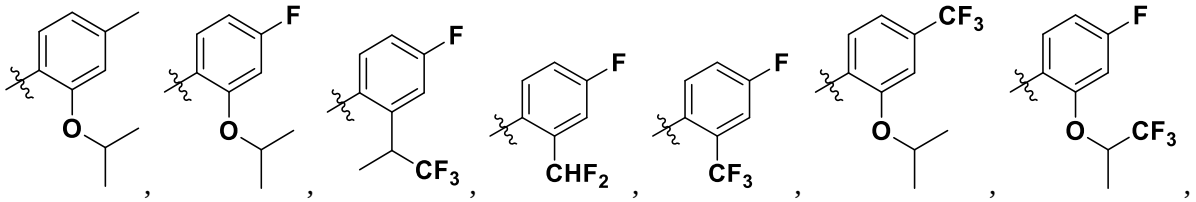
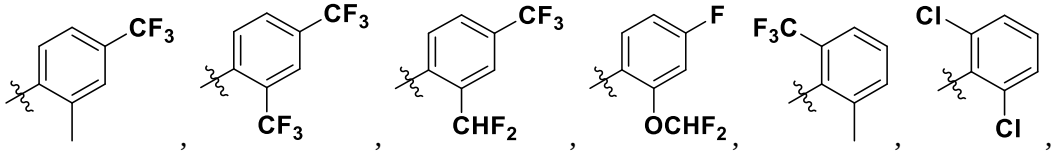
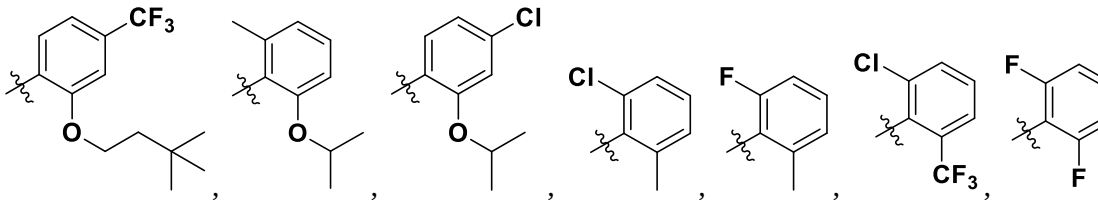
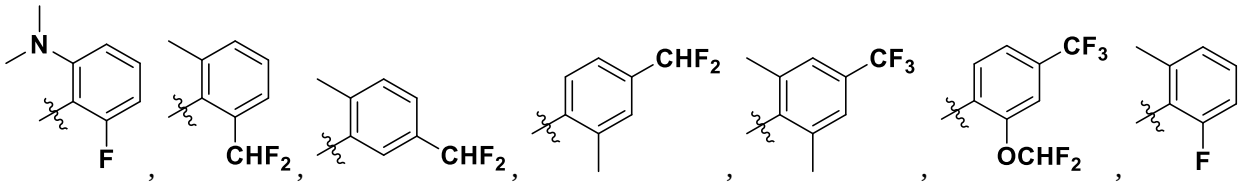
22. The compound of claim 21, wherein Cy^2 is 

23. The compound of claim 21, wherein Cy^2 is phenyl substituted with 2 or 3 occurrences of R^4.

24. The compound of claim 23, wherein R^4 is selected from halo, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy and $-N(R^a)_2$.

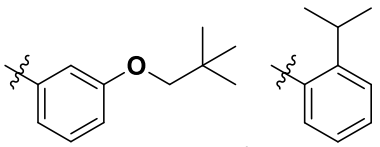
25. The compound of claim 21, wherein Cy^2 is , , , , , , , , , or .

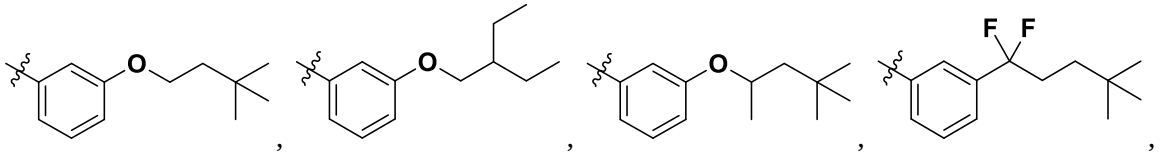
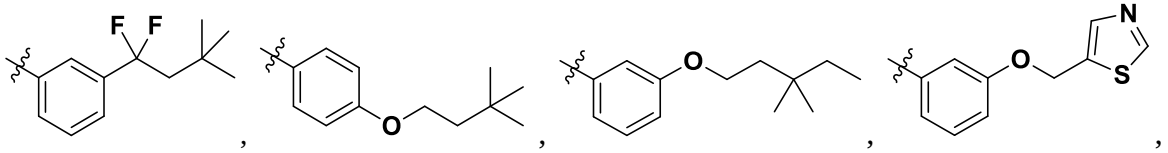
26. The compound of claim 1, wherein Cy^2 is , .

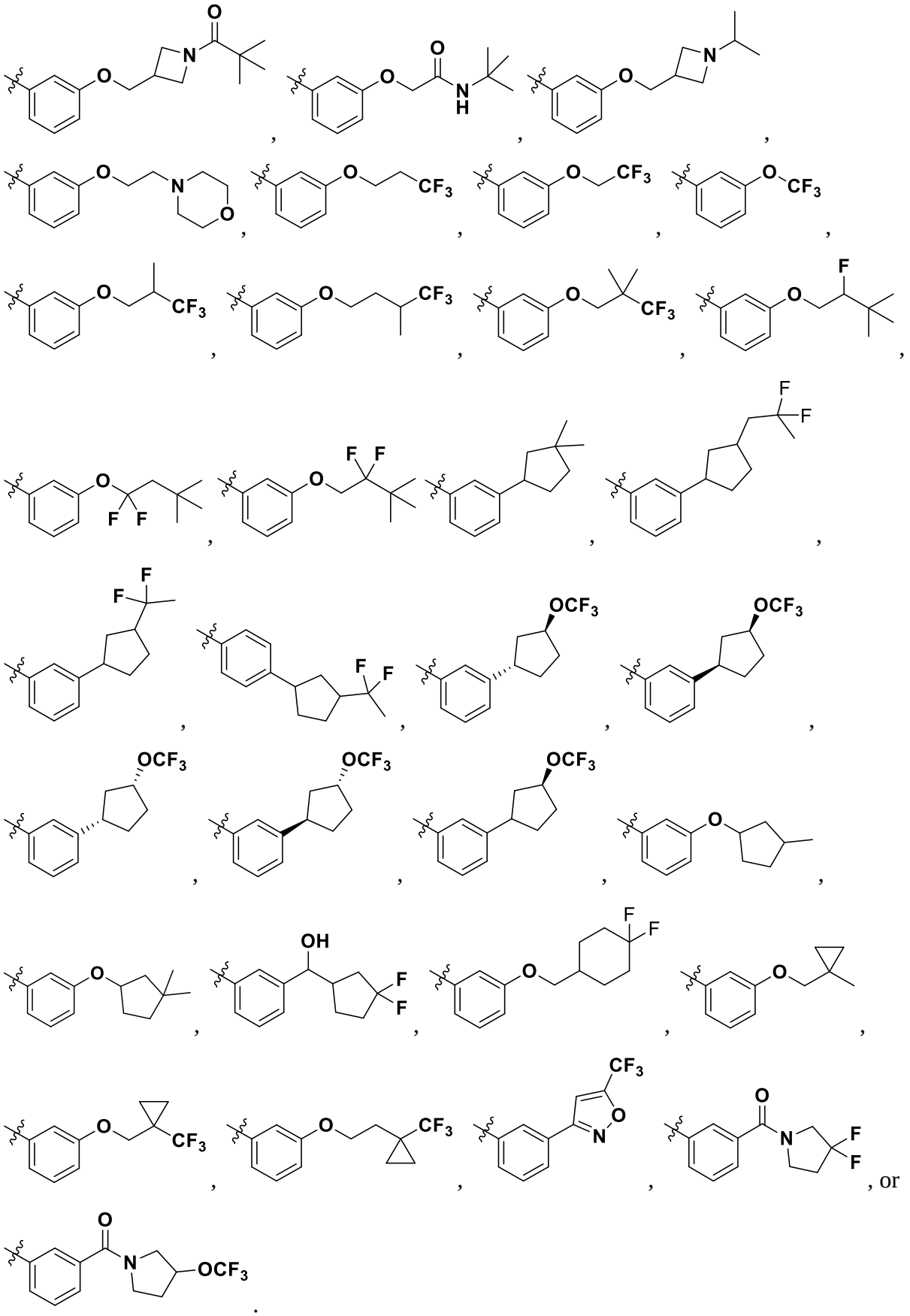





, or .

27. The compound of claim 1, wherein R^3 is selected from C_{1-8} alkyl, C_{1-8} haloalkyl, and C_{1-8} alkoxy.

28. The compound of claim 1, wherein Cy^1 is 

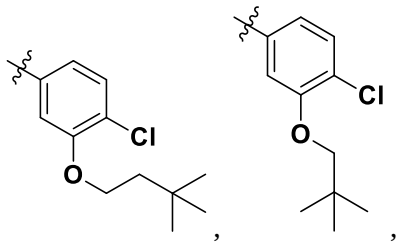
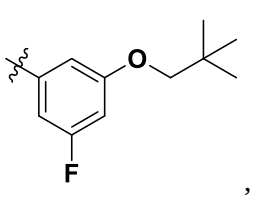
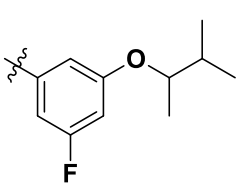
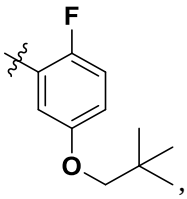
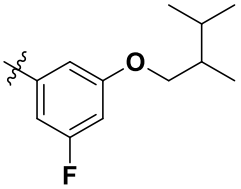
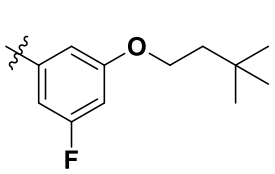
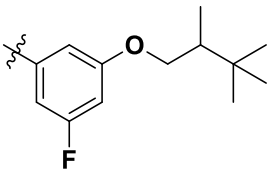
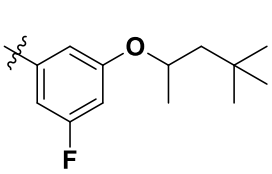
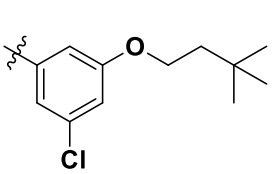
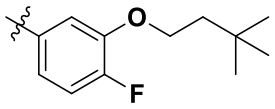
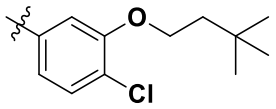
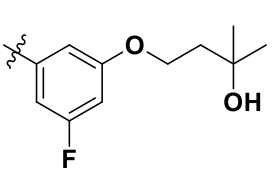
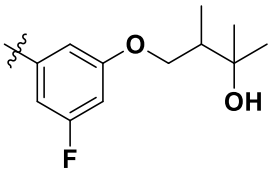
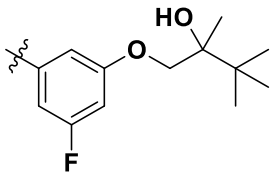
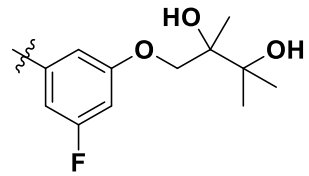
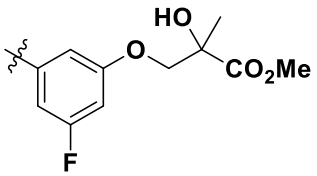
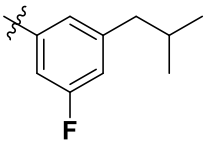
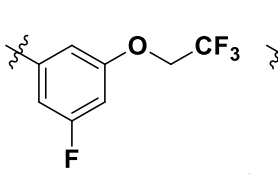
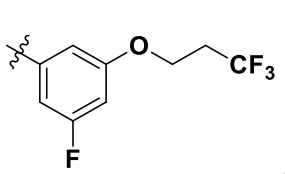
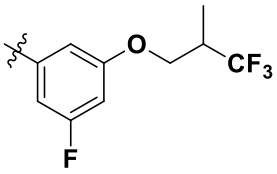
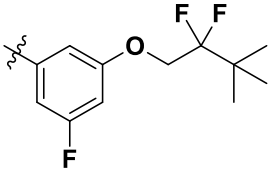
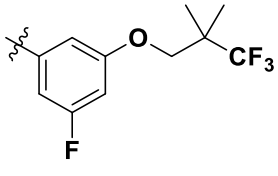
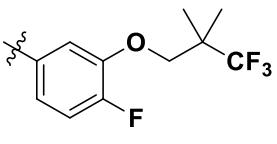
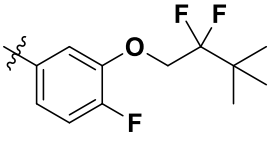
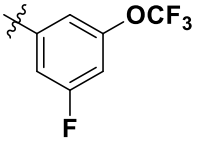



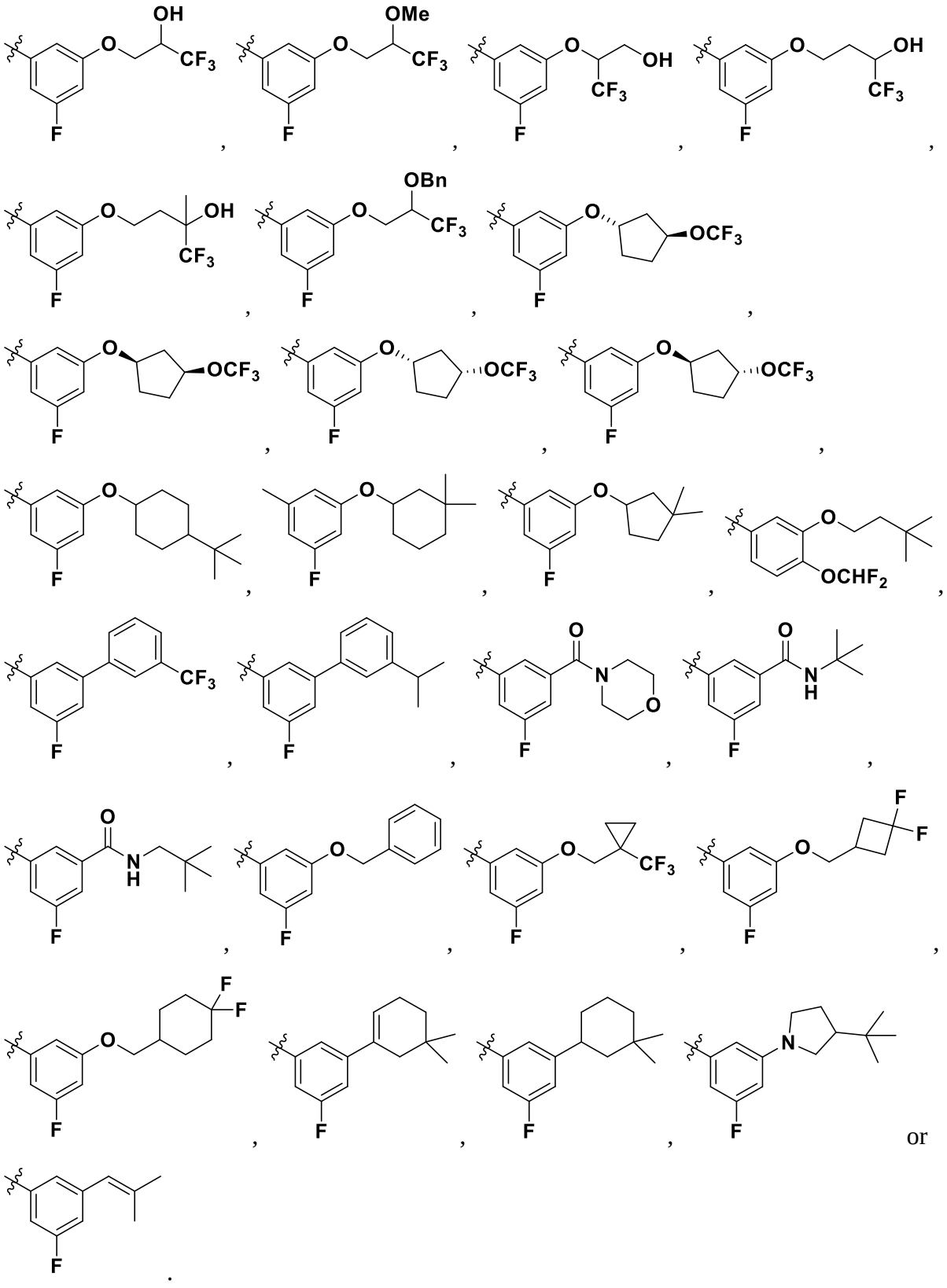


29. The compound of claim 1, wherein Cy^1 is phenyl substituted with 2 occurrences of R^3.

30. The compound of claim 29, wherein each R^3 is independently selected from halo, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-9} cycloalkyl, C_{1-8} alkoxy, C_{3-9} alkoxy, C_{1-8} haloalkoxy, C_{1-4} alkoxy-C_{3-9} cycloalkyl , C_{3-9} cycloalkenyl, aryl, heterocycloalkyl, -C(O)R^7, and-C(O)N(R^a)(R^7).

31. The compound of claim 30, wherein R^3 is further substituted with at least one R^7 selected from hydroxyl, -C(O)-O-C_{1-4} alkyl, C_{1-4} alkyl, C_{1-8} alkenyl, C_{1-4} alkoxy, aralkoxy, C_{1-4} haloalkoxy, and heterocycloalkyl.

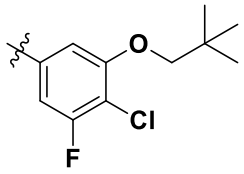
32. The compound of claim 30, wherein Cy^1 is , , , , , , , , , , , , , , , , , , , , , , , , , .

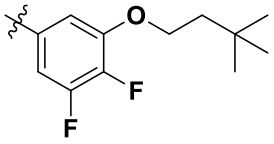


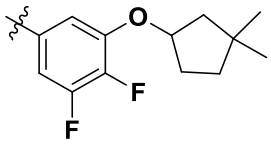
33. The compound of claim 27, wherein Cy^1 is phenyl substituted with 3 occurrences of R^3.

34. The compound of claim 33, wherein each R^3 is independently selected from halo, C_{1-8} alkoxy, and C_{3-9} cycloalkoxy.

35. The compound of claim 34, wherein R^3 is further substituted with at least one R^7 selected from C_{1-5} alkyl.

36. The compound of claim 34, wherein Cy^1 is 

, 

or 

.

37. A compound selected from any compound given in Table 1.

38. A compound selected from any compound given in Table 2.

39. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier or excipient.

40. The pharmaceutical composition of claim 39, further comprising one or more CFTR therapeutic agents.

41. Use of a compound of claim 1 in the manufacture of a medicament for treating deficient CFTR activity in a cell.

42. The use of claim 41, wherein the use treats a CFTR-mediated condition and/or disease.

43. The use of claim 42, wherein the disease or condition is selected from cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), congenital pneumonia, intestinal malabsorption, celiac disease, nasal polyposis, non-tuberculous mycobacterial infection, pancreatic steatorrhea, intestinal atresia, liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies,

familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, 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, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders, Huntington's, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, myotonic dystrophy, spongiform encephalopathies, hereditary Creutzfeldt-Jakob disease, Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, Sjogren's disease, Osteoporosis, Osteopenia, bone healing and bone growth, bone repair, bone regeneration, reducing bone resorption, increasing bone deposition, Gorham's Syndrome, chloride channelopathies, myotonia congenita, Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, Primary Ciliary Dyskinesia (PCD), PCD with situs inversus, PCD without situs inversus and ciliary aplasia.

44. The use of claim 43, wherein the disease or condition is selected from cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic pancreatitis, disseminated bronchiectasis, asthma, allergic pulmonary aspergillosis, congenital pneumonia, intestinal malabsorption, celiac disease, nasal polyposis, non-tuberculous mycobacterial infection, pancreatic steatorrhea, intestinal atresia, chronic obstructive pulmonary disease (COPD), chronic rhinosinusitis, dry eye disease, protein C deficiency, abetalipoproteinemia, lysosomal storage disease, type 1 chylomicronemia, mild pulmonary disease, lipid processing deficiencies, type 1 hereditary angioedema, coagulation-fibrinolyis, hereditary hemochromatosis, CFTR-related metabolic syndrome, chronic bronchitis, constipation, pancreatic insufficiency, hereditary emphysema, and Sjogren's syndrome.

45. The use of claim 43, wherein the disease or condition is cystic fibrosis.

46. Use of a compound of claim 1 in the manufacture of a medicament for treating cystic fibrosis or a symptom thereof in a subject.

47. The use of claim 46, wherein the subject is human.

48. The use according to claim 46 or 47, wherein said subject is at risk of developing cystic fibrosis, and wherein the compound is to be administered prior to the onset of symptoms of cystic fibrosis in said subject.

49. A compound of any one of claims 1-38, for use in therapy.