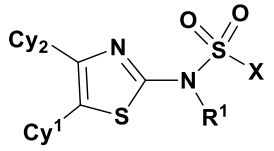
plasma membrane, is instead retained in the endoplasmic reticulum and targeted for degradation by the ubiquitin-proteasome system.

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.

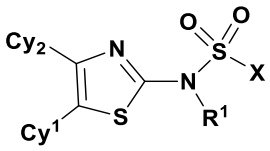
In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier or excipient.

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 ~~aspect~~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.

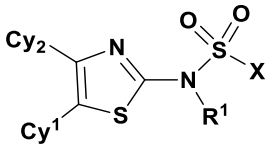
Disclosed herein are methods of treating deficient CFTR activity, thereby treating a disease or condition mediated by deficient CFTR activity. Such diseases and conditions include, but are not limited to, cystic fibrosis, congenital bilateral absence of vas deferens (CBAVD), acute, recurrent, or chronic 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 ~~embodiment~~examples, the disease is cystic fibrosis.

In certain ~~embodiment~~examples, the present ~~invention~~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 ~~invention~~present disclosure, such as a compound of formula (I)), and one or more pharmaceutically acceptable excipients. In certain ~~embodiment~~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**):



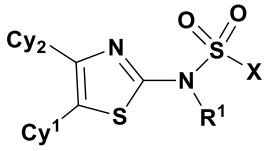
(**I**)

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~~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 phenyl~~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 phenyl~~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;

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 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.

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 ~~(e.g., methyl or ethyl)~~.

~~4. The compound of any one of claims 1-3, wherein X is aryl (e.g., phenyl) substituted with 0-3 occurrences of R^2.~~

4~~5~~. The compound of claim 4~~1~~, wherein X is phenyl substituted with 0 occurrences of R^2.

56. The compound of claim 41, wherein X is phenyl substituted with 1 occurrence of R^2.

67. The compound of claim 56, wherein R^2 is heteroaryl (e.g., 1-pyrazolyl or 5-pyrazolyl) substituted with 0-3 occurrences of R^5.

78. The compound of claim 56, wherein R^2 is $-N(R^a)(R^5)$.

89. The compound of claim 78, wherein R^a is H or C_{1-6} alkyl (e.g., methyl), and R^5 is C_{1-6} alkyl (e.g., methyl).

910. The compound of claim 78, wherein R^a is H and R^5 is selected from C_{1-6} haloalkyl (e.g., trifluoromethyl or 1,1,1-trifluoroisopropyl), heterocycloalkyl (e.g., 3-tetrahydrofuranyl), and C_{3-9} cycloalkyl (e.g., cyclobutyl or cyclopentyl), substituted with 0 or 1 R^6.

1011. The compound of claim 910, wherein R^6 is selected from $-CO_2H$, $-C(O)_2-C_{1-4}$ alkyl (e.g., $-CO_2Me$ or $-CO_2Et$), hydroxyl, and C_{1-4} alkyl (e.g., methyl).

1112. The compound of claim 56, wherein R^2 is $-N(R^a)C(O)-R^5$.

1213. The compound of claim 1112, wherein R^a is H and R^5 is selected from C_{1-6} alkyl (e.g., methyl, ethyl or isopropyl) and C_{3-9} cycloalkyl (e.g., cyclopropyl), each substituted with 0-3 occurrences of R^6.

1314. The compound of claim 1213, wherein R^6 is selected from $-NH_2$, hydroxyl, halo (e.g., fluoro), and C_{1-4} haloalkyl (e.g., trifluoromethyl).

1415. The compound of claim 56, wherein R^2 is heterocycloalkyl (e.g., N-pyrrolidinyl) substituted with 0-3 occurrences of R^5.

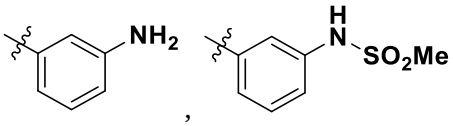
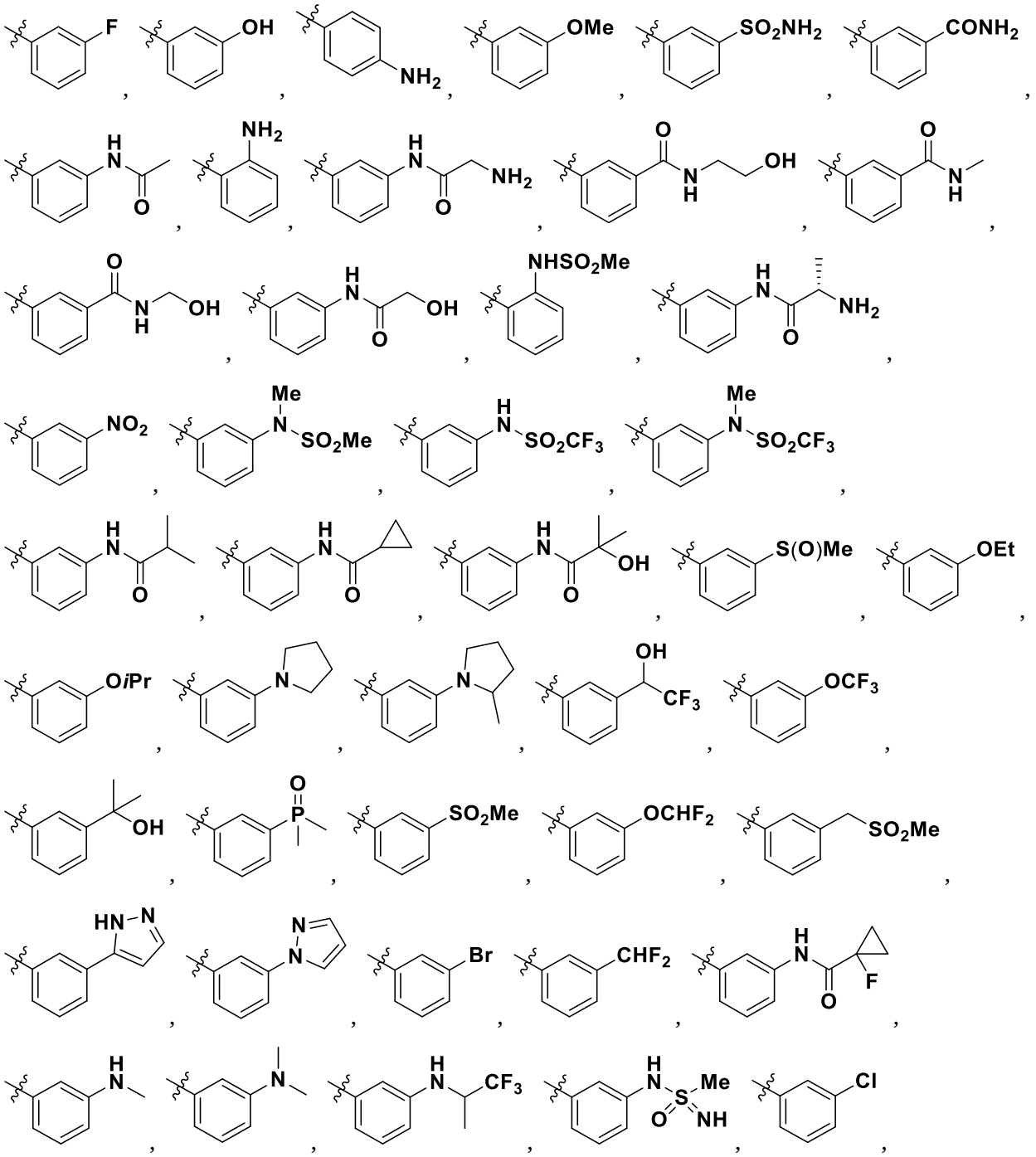
1516. The compound of claim 1415, wherein each R^5 is selected from C_{1-6} alkyl (e.g., methyl) substituted with 0-3 occurrences of R^6.

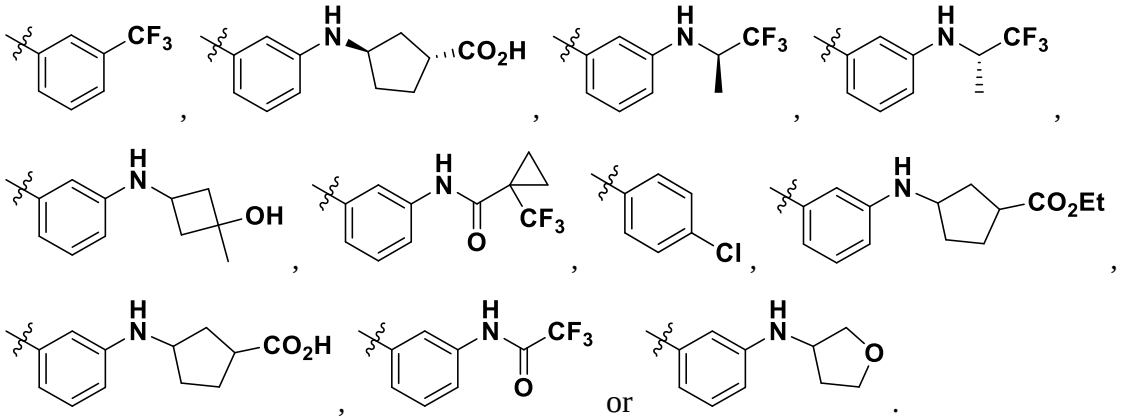
1617. The compound of claim 56, wherein R^2 is $-C(O)-N(R^a)(R^5)$.

1718. The compound of claim 1617, wherein R^a is H and R^5 is C_{1-6} alkyl (e.g., methyl or ethyl) substituted with 0-3 occurrences of R^6.

1819. The compound of claim 56, wherein R^2 is $-N(R^a)S(O)(NH)-R^5$.

1920. The compound of claim 1819, wherein R^a is H and R^5 is C_{1-6} alkyl ~~(e.g., methyl)~~ substituted with 0-3 occurrences of R^6.

2021. The compound of claim 56, wherein X is  , 



or .

~~22. The compound of claim 4, wherein X is phenyl substituted with 2 occurrences of R^2.~~

~~23. The compound of claim 22, wherein each R^2 is halo (e.g., fluoro or chloro).~~

~~24. The compound of claim 22, wherein one R^2 is $-NH_2$ and one R^2 is halo (e.g., fluoro).~~

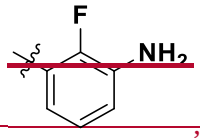
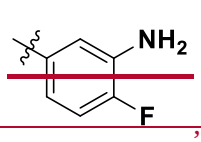
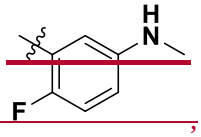
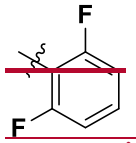
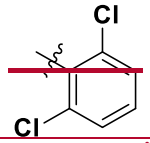
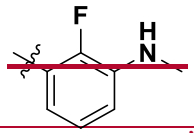
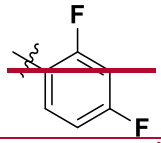
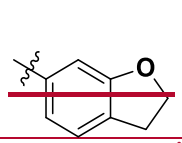
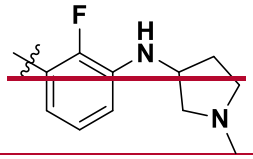
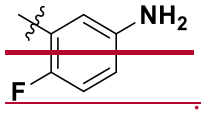
~~25. The compound of claim 22, wherein one R^2 is C_{1-6} alkyl (e.g., methyl) and the other R^2 is C_{1-6} haloalkyl (e.g., difluoromethyl).~~

~~26. The compound of claim 22, wherein one R^2 is halo (e.g., fluoro) and the other R^2 is $-N(R^a)(R^5)$ (e.g., –NHMe).~~

~~27. The compound of claim 26, wherein R^a is H and R^5 is C_{3-9} cycloalkyl (e.g., cyclopentyl) substituted with 0-3 occurrences of R^6.~~

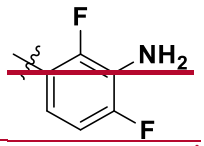
~~28. The compound of claim 26, wherein R^a is H and R^5 is heterocycloalkyl (e.g., 3-pyrrolidinyl) substituted with 0-3 occurrences of R^6.~~

~~29. The compound of claim 27 or 28, wherein R^6 is C_{1-6} alkyl (e.g., methyl).~~

30. The compound of claim 22, wherein X is  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

31. The compound of claim 4, wherein X is phenyl substituted with 3 occurrences of R^2.

32. The compound of claim 31, wherein two R^2 are halo (e.g., fluoro) and the remaining R^2 is $-NH_2$.

33. The compound of claim 32, wherein X is  .

34. The compound of any one of claims 1-3, wherein X is 5-6 membered heteroaryl substituted 0-3 occurrences of R^2.

35. The compound of claim 34, wherein X is selected from pyridinyl, pyrazolyl, isoxazolyl, pyrazolyl, indolyl, thiazolyl, thiophenyl or furanyl substituted with 0-3 occurrences of R^2.

36. The compound of claim 34, wherein X is 2-pyridinyl substituted with one R^2 selected from $-NH_2$, halo (e.g., fluoro or chloro), and C_{1-6} alkoxy (e.g., methoxy or isopropoxy) substituted with 0-3 occurrences of R^5.

37. The compound of claim 36, wherein R^5 is C_{3-9} cycloalkyl (e.g., cyclopropyl or cyclobutyl) substituted with 1 or 2 occurrences of R^6.

38. The compound of claim 37, wherein R^6 is selected from C_{1-4} haloalkyl (e.g., trifluoromethyl) and halo (e.g., fluoro).

39. The compound of claim 34, wherein R^2 is $-N(R^a)SO_2-R^5$.

~~40. The compound of claim 39, wherein R^a is H and R^5 is C_{1-6} alkyl (e.g., methyl) substituted with 0-3 occurrences of R^6.~~

~~41. The compound of claim 34, wherein R^2 is $-N(R^a)C(O)-R^5$ or $-N(R^a)(R^5)$.~~

~~42. The compound of claim 41, wherein R^a is H and R^5 is C_{1-6} alkyl (e.g., methyl or isopropyl, or neopentyl) substituted with 0-3 occurrences of R^6.~~

~~43. The compound of claim 41, wherein R^a is C_{1-6} alkyl (e.g., methyl or ethyl) and R^5 is C_{1-6} alkyl (e.g., methyl or isopropyl) substituted with 0-3 occurrences of R^6.~~

~~44. The compound of claim 41, wherein R^a is H and R^5 is C_{3-9} cycloalkyl (e.g., cyclopropyl or cyclopentyl) substituted with 0-3 occurrences of R^6.~~

~~45. The compound of claim 41, wherein R^a is H and R^5 is C_{1-6} haloalkyl (e.g., 1,1,1-trifluoroisopropyl) substituted with 0-3 occurrences of R^6.~~

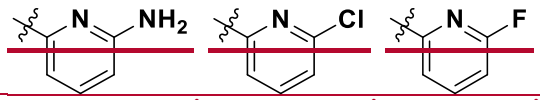
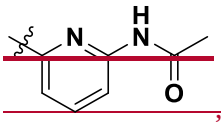
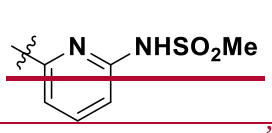
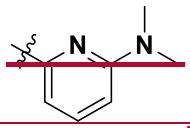
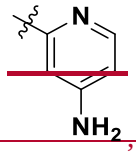
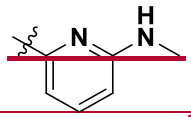
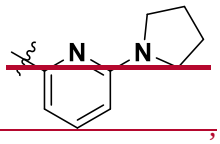
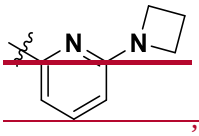
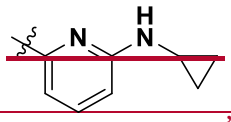
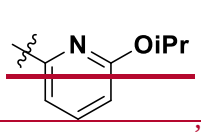
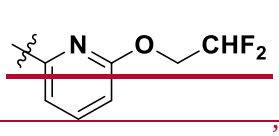
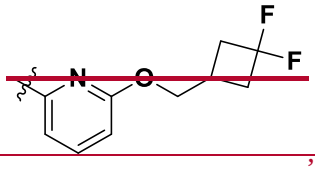
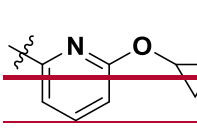
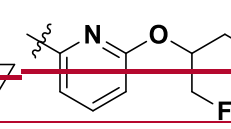
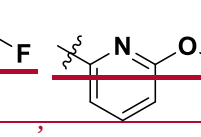
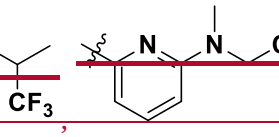
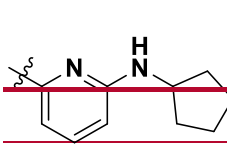
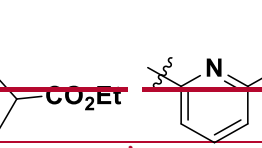
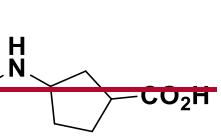
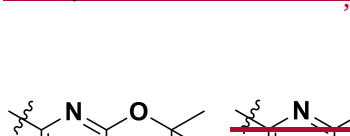
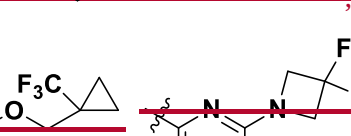
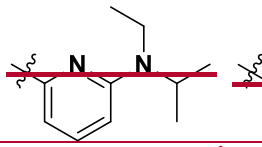
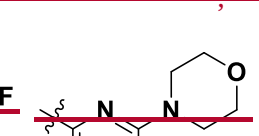
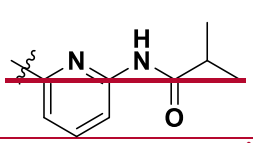
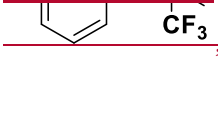
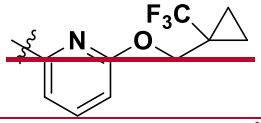
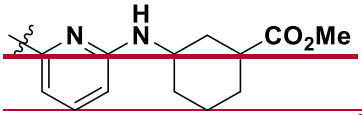
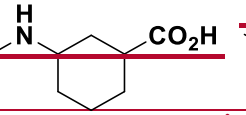
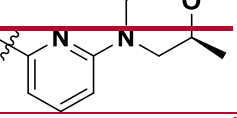
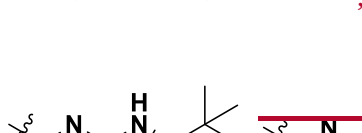
~~46. The compound of claim 41, wherein R^a is C_{1-6} alkyl (e.g., methyl) and R^5 is C_{1-6} haloalkyl (e.g., 2,2,2-trifluoroethyl) substituted with 0-3 occurrences of R^6.~~

~~47. The compound of any one of claims 42-47, wherein R^6 is $-CO_2H$ or $-CO_2-C_{1-4}$ alkyl (e.g., $-CO_2Me$ or $-CO_2Et$).~~

~~48. The compound of claim 34 wherein R^2 is selected from C_{3-9} cycloalkoxy (e.g., cyclopropoxy), C_{1-6} haloalkoxy (e.g., trifluoromethyl, 2,2-difluoroethyl, 1,1,1-trifluoroisopropyl, 1,1,1-trifluoro-tert-butyl or 1,3-difluoroisopropyl), and C_{3-9} cycloalkyl (e.g., cyclopentyl or cyclohexyl), substituted with 0-3 occurrences of R^5.~~

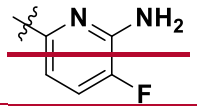
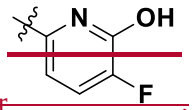
~~49. The compound of claim 34, wherein R^2 is heterocycloalkyl (e.g., azetidinyl, pyrrolidinyl, piperidinyl or morpholinyl) substituted with 0-3 occurrences of R^5.~~

~~50. The compound of claim 50, wherein R^5 is selected from halo (e.g., fluoro), C_{1-6} alkyl (e.g., methyl) substituted with 0-3 occurrences of R^6, wherein R^6 is selected from $-CO_2H$, and $-CO_2-C_{1-4}$ alkyl (e.g., $-CO_2Me$).~~

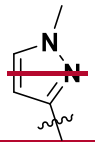
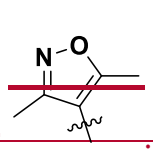
51. The compound of claim 34, wherein X is  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  ,  ,  ,  ,  , ,  ,  , , ,  , ,  ,  , ,  , , , , , , , , , , , , or .

52. The compound of claim 34, wherein X is 2-pyridinyl substituted with 2 occurrences of R^2.

53. The compound of claim 53, wherein R^2 is selected from $-NH_2$, hydroxyl, and halo (e.g., fluoro).

54. The compound of claim 53, wherein X is  or  .

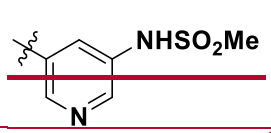
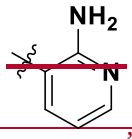
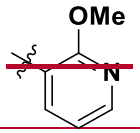
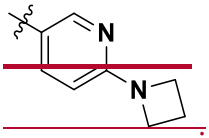
55. The compound of claim 34, wherein X is 3-pyrazolyl or 4-isoxazolyl substituted with 0-3 occurrences of R^2.

56. The compound of claim 56, wherein X is  or  .

57. The compound of claim 34, wherein X is 3-pyridinyl substituted with 0-3 occurrences of R^2.

58. The compound of claim 58, wherein R^2 is selected from $-NH_2$, $-N(R^a)SO_2-R^5$, C_{1-6} alkoxy (e.g., methoxy), and heterocycloalkyl (e.g., N-oxetanyl).

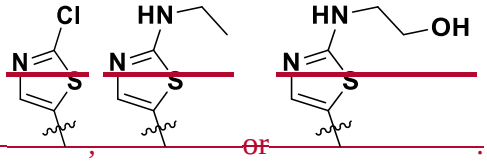
59. The compound of claim 59, wherein R^a is H and R^5 is C_{1-6} alkyl (e.g., methyl) substituted with 0-3 occurrences of R^6.

60. The compound of claim 58, wherein X is  ,  ,  or  .

61. The compound of claim 34, wherein X is 5-thiazolyl substituted with 0-3 occurrences of R^2.

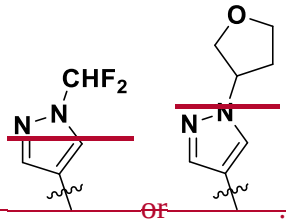
62. The compound of claim 62, wherein R^2 is selected from $-NH_2$, halo (e.g., chloro), and $-N(R^a)(R^5)$.

63. The compound of claim 63, wherein R^a is H and R^5 is C_{1-6} alkyl (e.g., ethyl) substituted with 0 or 1 occurrences of R^6.

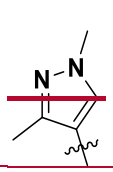
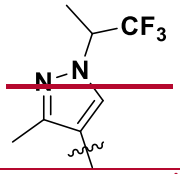
64. The compound of claim 62, wherein is  , , or .

65. The compound of claim 34, wherein X is 4-pyrazolyl substituted with 0-3 occurrences of R^2.

66. The compound of claim 62, wherein R^2 is selected from haloalkyl (e.g., difluoromethyl), and heterocycloalkyl (e.g., 3-tetrahydrofuranyl).

67. The compound of claim 66, wherein X is  or .

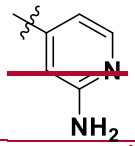
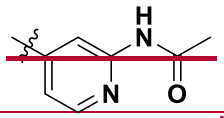
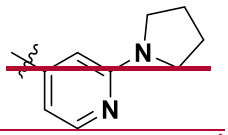
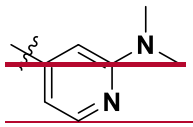
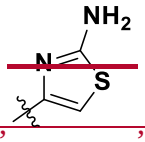
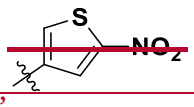
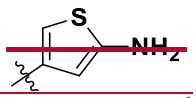
68. The compound of claim 34, wherein X is 4-pyrazolyl substituted with 2 occurrences of R^2 selected from C_{1-6} alkyl (e.g., methyl) and C_{1-6} haloalkyl (e.g., 1,1,1-trifluoroisopropyl).

69. The compound of claim 69 wherein X is  or  .

70. The compound of claim 34, wherein X is 6-indolyl, 3-thiazolyl, 4-thiazolyl, 3-thiophenyl, 4-pyridinyl substituted with 0-3 occurrences of R^2.

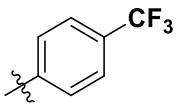
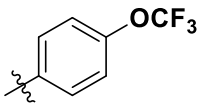
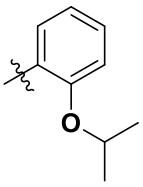
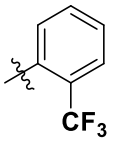
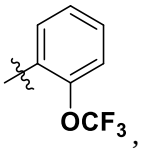
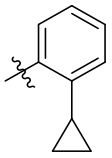
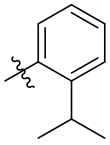
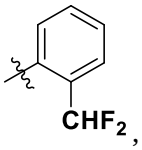
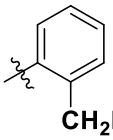
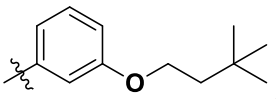
71. The compound of claim 71, wherein R^2 is selected from $-NH_2$, nitro, hydroxyl, $-N(R^a)(R^5)$, $-N(R^a)C(O)-R^5$, and heterocycloalkyl (e.g., N-pyrrolidinyl) substituted with 0-3 occurrences of R^5.

72. The compound of claim 72, wherein R^a is H or C_{1-6} alkyl (e.g., methyl) and R^5 is C_{1-6} alkyl (e.g., methyl) substituted with 0-3 occurrences of R^6.

73. The compound of claim 71, wherein X is       or  .

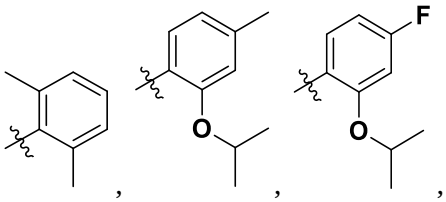
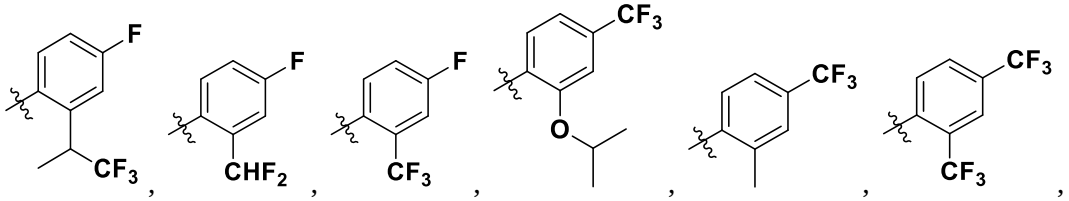
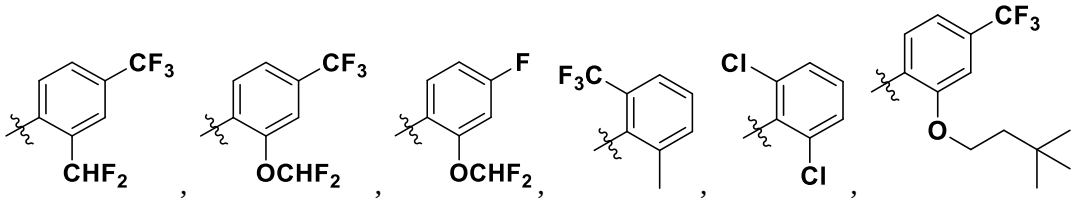
74. The compound of any one of claims 1-74, wherein Cy^2 is aryl substituted with 1-3 occurrences of R^4.

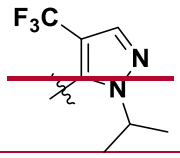
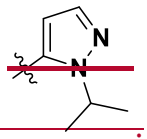
2175. The compound of claim 751, wherein R^4 is selected from C_{1-6} alkyl (e.g., methyl or isopropyl), C_{1-6} haloalkyl (e.g., trifluoromethyl, difluoromethyl, 2-fluoroisopropyl or fluoromethyl), C_{1-6} alkoxy (e.g., methoxy, isopropoxy or 3,3-dimethylbutoxy), C_{1-6} haloalkoxy (e.g., trifluoromethoxy) and C_{3-6} cycloalkyl (e.g., cyclopropyl).

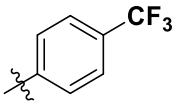
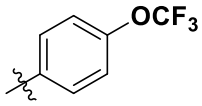
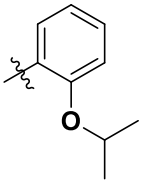
2276. The compound of claim 2175, wherein Cy^2 is          or  .

2377. The compound of claim 2175, wherein Cy^2 is phenyl substituted with 2 or 3 occurrences of R^4.

2478. The compound of claim 2378, wherein R^4 is selected from halo (e.g., fluoro or chloro), C_{1-6} haloalkyl (e.g., trifluoromethyl or difluoromethyl), C_{1-6} alkyl (e.g., methyl), C_{1-6} alkoxy (e.g., isopropoxy), C_{1-6} haloalkoxy (e.g., trifluoromethoxy, 1,1,1-trifluoroisopropoxy or difluoromethoxy) and $-N(R^a)_2$ (e.g., $N(CH_3)_2$).

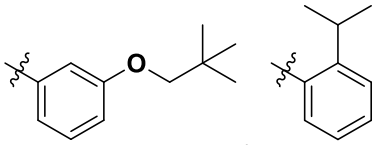
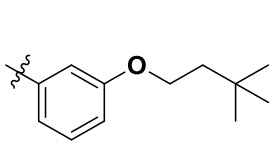
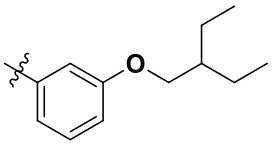
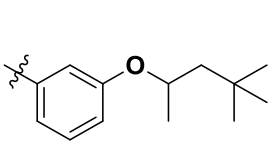
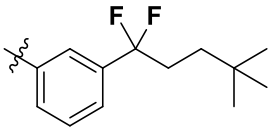
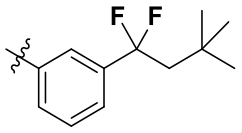
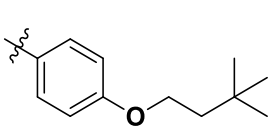
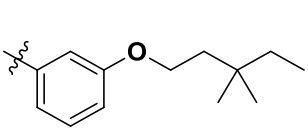
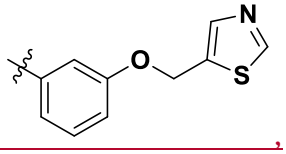
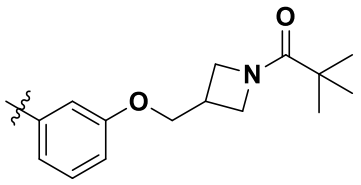
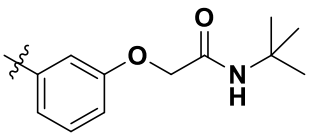
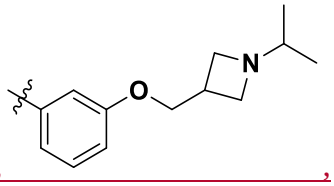
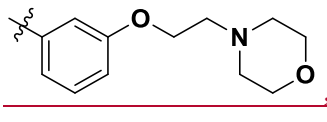
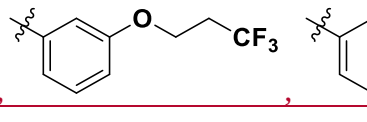
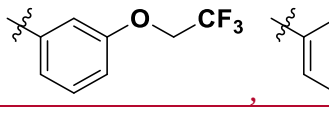
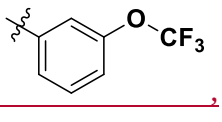
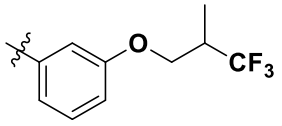
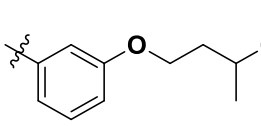
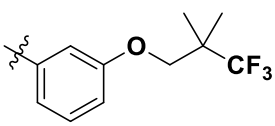
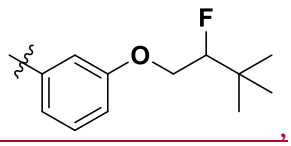
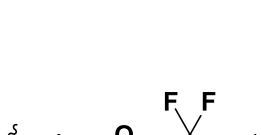
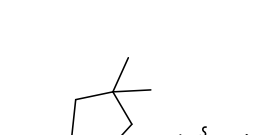
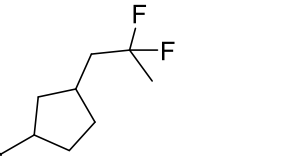
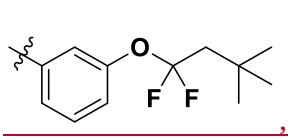
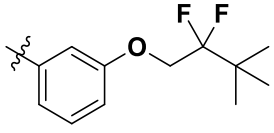
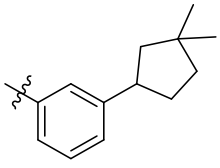
2579. The compound of claim 2175, wherein Cy^2 is  ,  ,  ,

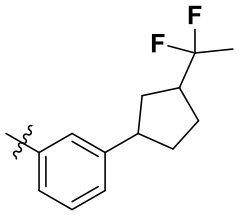
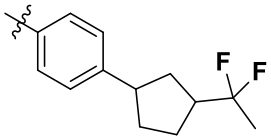
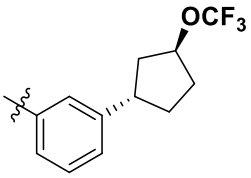
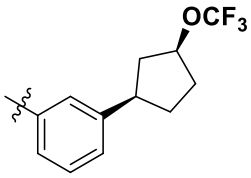
~~84. The compound of claim 84, wherein Cy^2 is  or  .~~

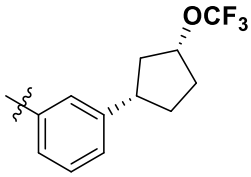
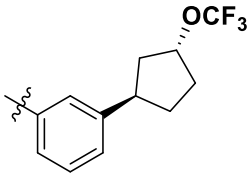
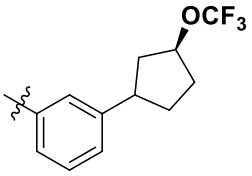
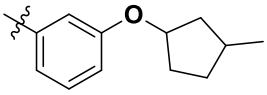
2685. The compound of ~~any one of~~ claim~~s~~ 1~~–74~~, wherein Cy^2 is  ,  ,  ,

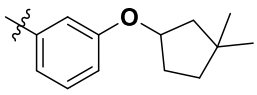
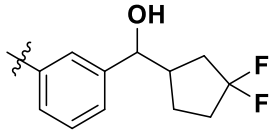
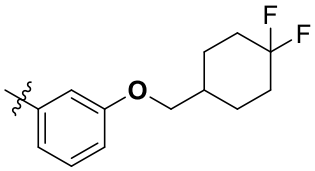
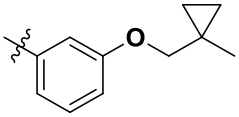
~~86. The compound of any one of claim 1-86, wherein Cy^1 is aryl (e.g. phenyl) substituted with 0-3 occurrences of R^3.~~

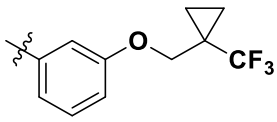
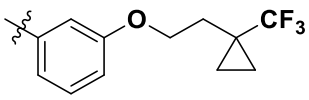
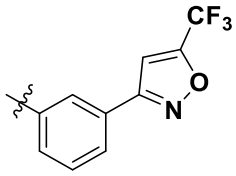
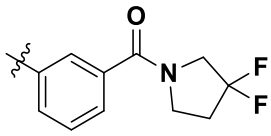
2787. The compound of claim 187, wherein R^3 is selected from C_{1-8} alkyl ~~(e.g., *o*-isopropyl)~~, C_{1-8} haloalkyl ~~(e.g., *m*-trifluoromethyl, *m*-1,1-difluoro-3,3-dimethylbutyl or *m*-1,1-difluoro-4,4-dimethylpentyl)~~, and C_{1-8} alkoxy ~~(e.g., *m*-methoxy, *m*-3,3-dimethylbutoxy, *p*-3,3-dimethylbutoxy, *m*-neopentyloxy, *m*-2-ethylbutoxy, *m*-(4,4-dimethylpentan-2-yl)oxy or *m*-(3,3-dimethylpentyl)oxy))~~.

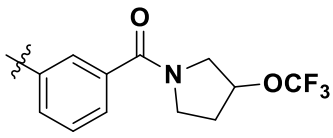
2888. The compound of claim ~~87~~1, wherein Cy^1 is  , ,  ,  ,  ,  ,  ,  , ~~or~~  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  , .

 ,  ,  ,  ,

 ,  ,  ,  ,

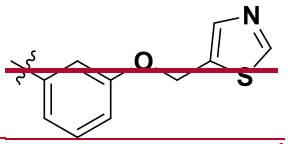
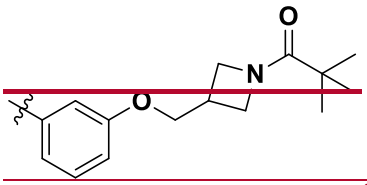
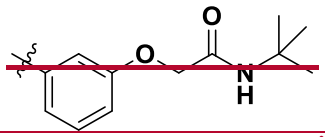
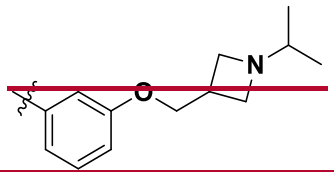
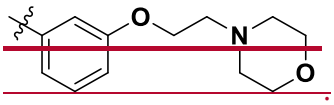
 ,  ,  ,  ,

 ,  ,  ,  , or

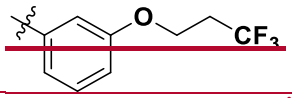
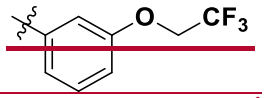
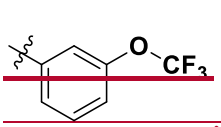
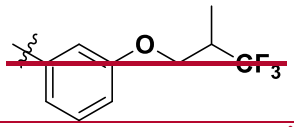
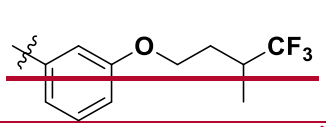
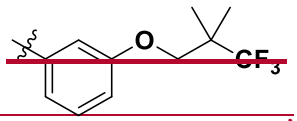
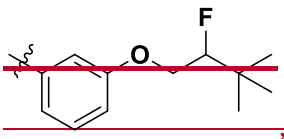
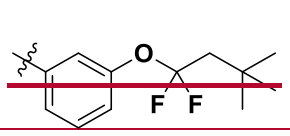
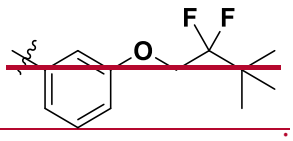
 .

~~89. The compound of claim 87, wherein R^3 is C_{1-8} alkoxy (e.g., methoxy or ethoxy) which is substituted with one occurrence of R^7 selected from 5-6 membered heteroaryl (e.g., 5-thiazolyl) and 4-10 membered heterocycloalkyl (e.g., 2-azetidinyl or N-morpholinyl).~~

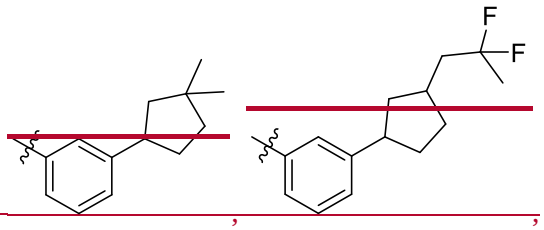
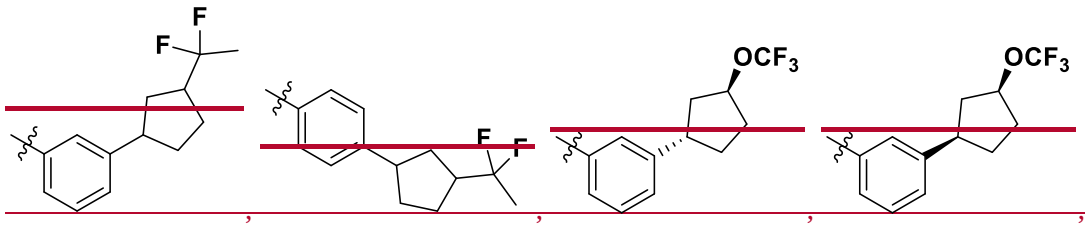
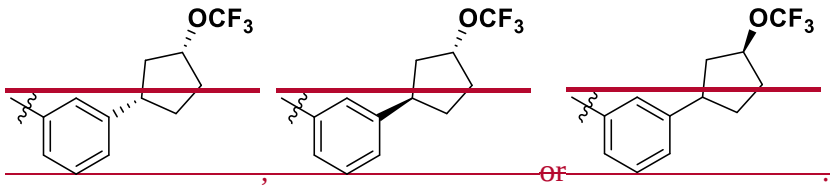
~~90. The compound of claim 90, wherein R^7 is further substituted with one R^8 selected from C_{1-4} alkyl (e.g., isopropyl), C(O)(C_{1-4} alkyl) (e.g., C(O)-t-butyl) and C(O)N(R^a)(C_{1-4} alkyl) (e.g., C(O)-NH-t-butyl).~~

91. The compound of claim 87, wherein Cy^1 is  ,  ,  ,  or  .

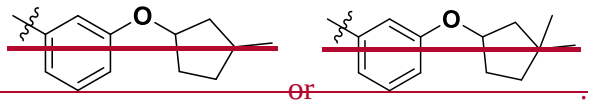
92. The compound of claim 87, wherein R^3 is C_{1-8} haloalkoxy (e.g., *m*-trifluoromethoxy, *m*-2,2,2-trifluoroethoxy, *m*-3,3,3-trifluoropropoxy, *m*-3,3,3-trifluoro-2-methylpropoxy, *m*-4,4,4-trifluoro-3-methylbutoxy, *m*-3,3,3-trifluoro-2,2-dimethylpropoxy, *m*-2-fluoro-3,3-dimethylbutoxy, *m*-1,1-difluoro-3,3-dimethylbutoxy or *m*-2,2-difluoro-3,3-dimethylbutoxy) or cycloalkyl (e.g., cyclopentyl).

93. The compound of claim 87, wherein Cy^1 is  ,  ,  ,  ,  ,  ,  ,  or  .

94. The compound of claim 87, wherein R^3 is m-cyclopentyl or p-cyclopentyl substituted with one occurrence of R^7 selected from C_{1-4} haloalkoxy (e.g., trifluoromethoxy), C_{1-4} haloalkyl (e.g., 1,1-difluoroethyl or 2-2-difluoropropyl) and C_{1-4} alkyl (e.g., methyl).

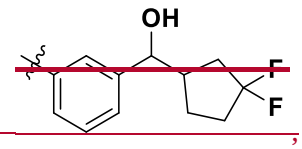
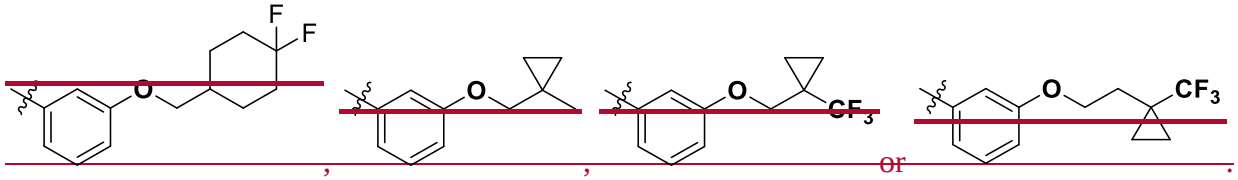
95. The compound of claim 95, wherein Cy^1 is  ,  ,  , or .

96. The compound of claim 87, wherein R^3 is C_{3-9} cycloalkoxy (e.g., cyclopentoxy) further substituted with 0-3 occurrences of R^7 selected from C_{1-4} alkyl (e.g., methyl).

97. The compound of claim 97, wherein Cy^1 is  or .

98. The compound of claim 87, wherein R^3 is C_{1-4} alkyl-C_{3-9} cycloalkyl (e.g., cyclopentylmethyl) or C_{1-4} alkoxy-C_{3-9} cycloalkyl (e.g., cyclohexylmethoxy, cyclopropylmethoxy or 2-cyclopropylethoxy) substituted with 0-3 occurrences of R^7.

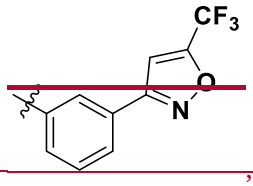
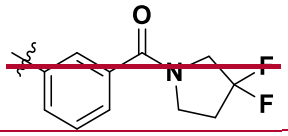
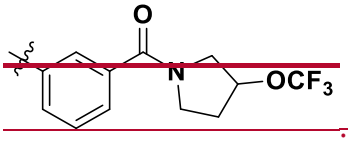
99. The compound of claim 99, wherein R^7 is selected from halo (e.g., fluoro), hydroxyl, C_{1-4} alkyl (e.g., methyl), and C_{1-4} haloalkyl (e.g., trifluoromethyl).

100. The compound of claim 99, wherein Cy^1 is  ,  , or .

~~101. The compound of claim 87, wherein R^3 is heteroaryl (e.g., 3-isoxazolyl) substituted with 0-3 occurrences of R^7 or -C(O)-R^7.~~

~~102. The compound of claim 102, wherein R^7 is C_{1-4} haloalkyl (e.g., trifluoromethyl) or heterocycloalkyl (e.g., N-pyrrolidinyl) substituted with 0-3 occurrences of R^8.~~

~~103. The compound of claim 103, wherein R^8 is C_{1-4} haloalkoxy (e.g., trifluoromethoxy) or halo (e.g., fluoro).~~

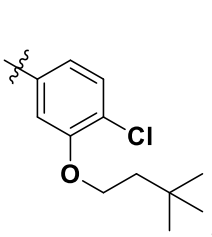
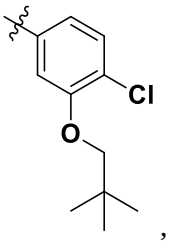
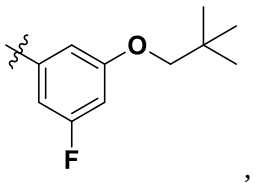
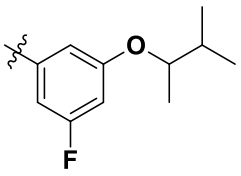
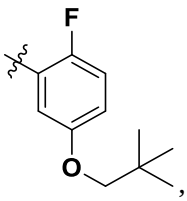
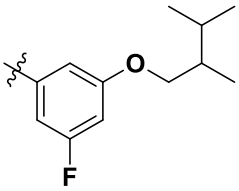
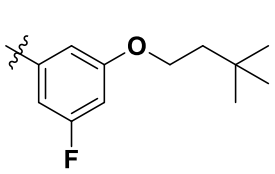
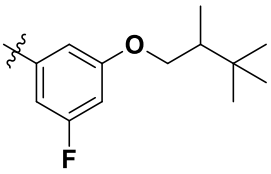
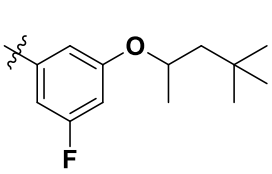
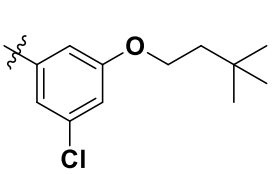
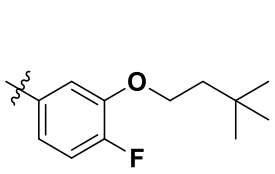
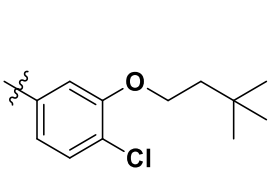
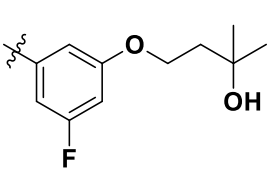
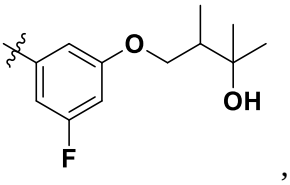
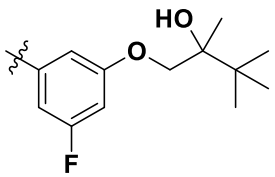
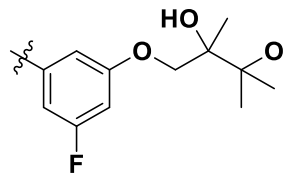
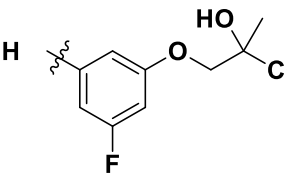
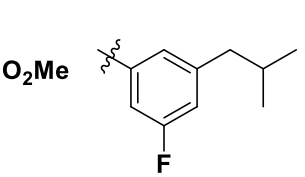
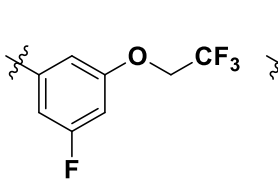
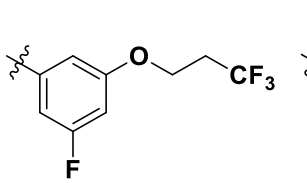
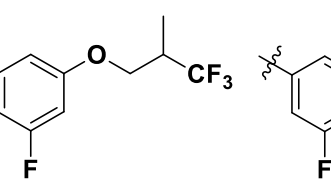
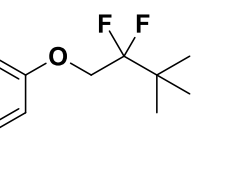
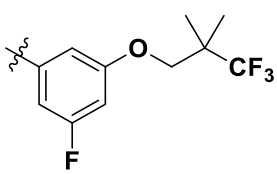
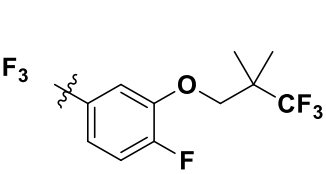
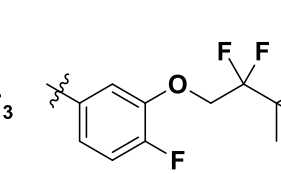
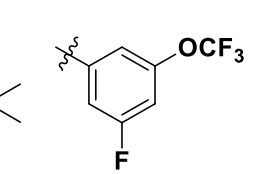
~~104. The compound of claim 102, wherein Cy^1 is~~  ,  ~~or~~  .

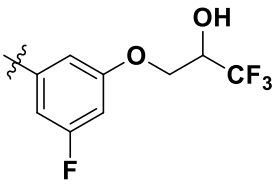
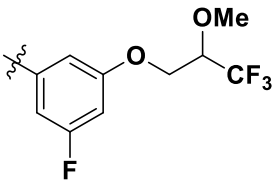
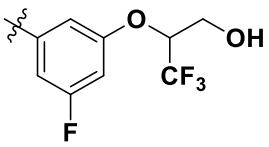
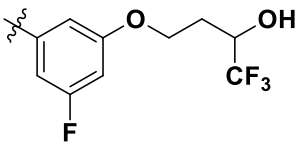
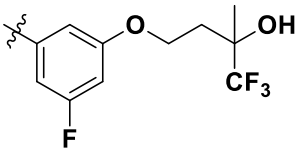
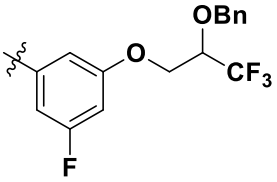
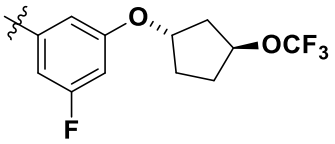
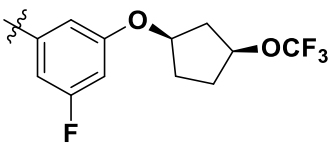
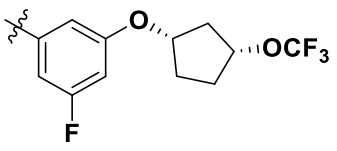
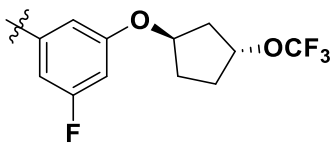
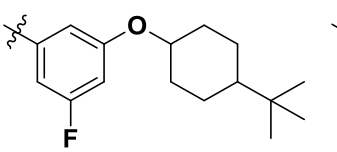
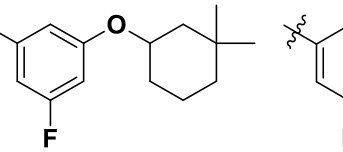
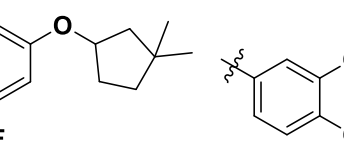
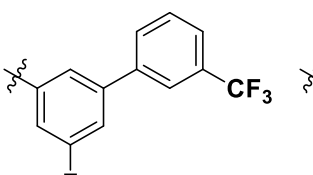
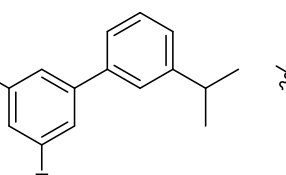
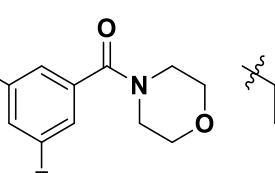
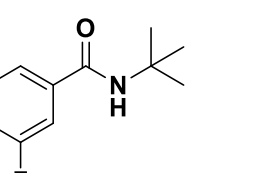
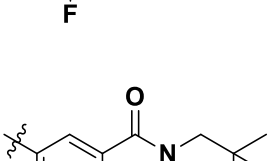
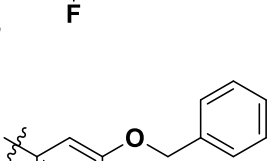
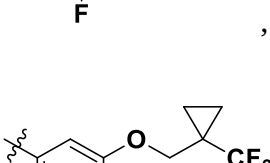
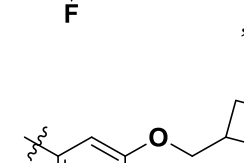
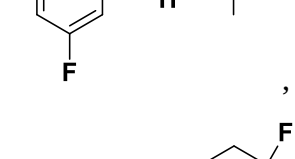
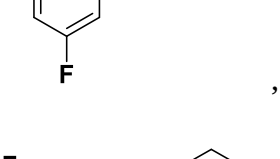
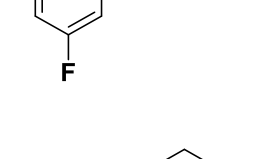
29~~105~~. The compound of claim 1~~87~~, wherein Cy^1 is phenyl substituted with 2 occurrences of R^3.

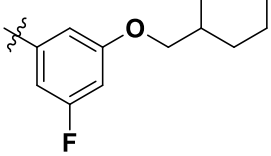
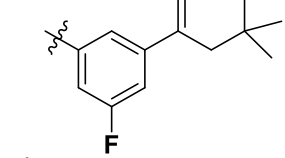
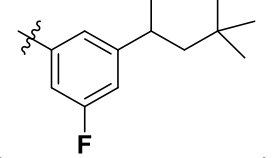
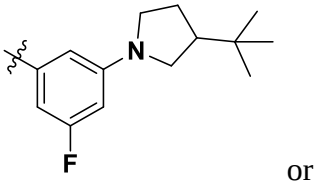
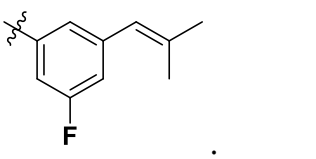
30~~106~~. The compound of claim 29~~106~~, wherein each R^3 is independently selected from halo ~~(e.g., fluoro or chloro)~~, C_{1-8} alkyl ~~(e.g., methyl, ethyl, isobutyl or neopentyl)~~, C_{1-8} haloalkyl ~~(e.g., difluoromethyl)~~, C_{3-9} cycloalkyl ~~(e.g., cyclohexyl)~~, C_{1-8} alkoxy ~~(e.g., methoxy, ethoxy, propoxy, 3,3-dimethylbutoxy, 2,3-dimethylbutoxy, neopentyloxy, (3-methylbutanyl-2-yl)oxy, 2,3,3-trimethylbutoxy, (4,4-dimethylpentan-2-yl)oxy, isopentyoxy, 2,3,3, trimethylbutoxy or 2,3-dimethylbutoxy)~~, C_{3-9} alkoxy ~~(e.g., cyclopentoxy or cyclohexyloxy)~~, C_{1-8} haloalkoxy ~~(e.g., trifluoromethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy, 2,2-difluoro-3,3-dimethylbutoxy, 3,3,3-trifluoro-2-methylpropoxy, (1,1,1-trifluoropropan-2-yl)oxy or 4,4,4-trifluoro-3-methylbutoxy)~~, C_{1-4} alkoxy-C_{3-9} cycloalkyl ~~(methoxycyclobutyl or methoxycyclohexyl)~~, C_{3-9} cycloalkenyl ~~(e.g., cyclohexenyl)~~, aryl ~~(e.g., phenyl)~~, heterocycloalkyl ~~(e.g., pyrrolidinyl)~~, -C(O)R^7, and-C(O)N(R^a)(R^7).

31~~107~~. The compound of claim 30~~107~~, wherein R^3 is further substituted with at least one R^7 selected from hydroxyl, -C(O)-O-C_{1-4} alkyl ~~(e.g., -CO_2Me)~~, C_{1-4} alkyl ~~(e.g., methyl, isopropyl, t-butyl, neopentyl)~~, C_{1-8} alkenyl ~~(e.g., 2-methylprop-1-en-1-yl)~~, C_{1-4} alkoxy ~~(e.g., methoxy)~~,

aralkoxy ~~(e.g., benzoxy)~~, C_{1-4} haloalkoxy ~~(e.g., trifluoromethoxy)~~, and heterocycloalkyl ~~(e.g., morpholinyl)~~.

32~~108~~. The compound of claim 30~~106~~, wherein Cy^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  , .

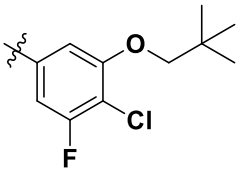
or

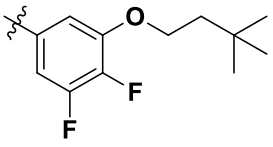
.

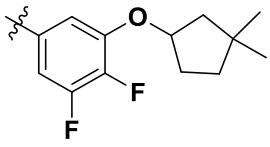
33109. The compound of claim 2787, wherein Cy^1 is phenyl substituted with 3 occurrences of R^3.

34110. The compound of claim 33110, wherein each R^3 is independently selected from halo ~~(e.g., fluoro)~~, C_{1-8} alkoxy ~~(e.g., neopentyloxy or 3,3-dimethylbutoxy)~~, and C_{3-9} cycloalkoxy ~~(e.g., cyclopentoxy)~~.

35111. The compound of claim 34111, wherein R^3 is further substituted with at least one R^7 selected from C_{1-5} alkyl ~~(e.g., methyl)~~.

36112. The compound of claim 34110, wherein Cy^1 is 

, 

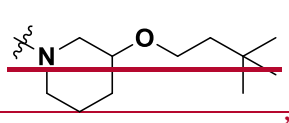
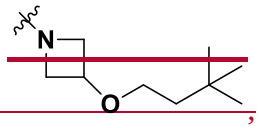
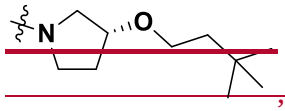
or 

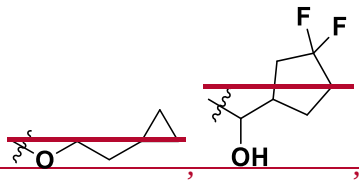
.

~~113. The compound of any one of claim 1-86, wherein Cy^1 is heterocycloalkyl substituted with 0-3 occurrences of R^3.~~

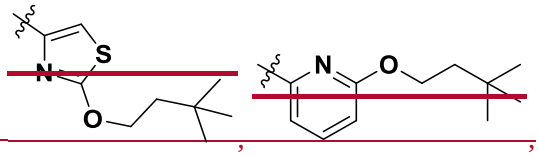
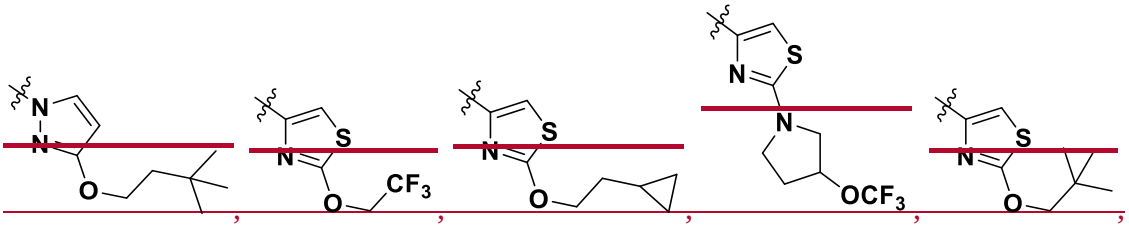
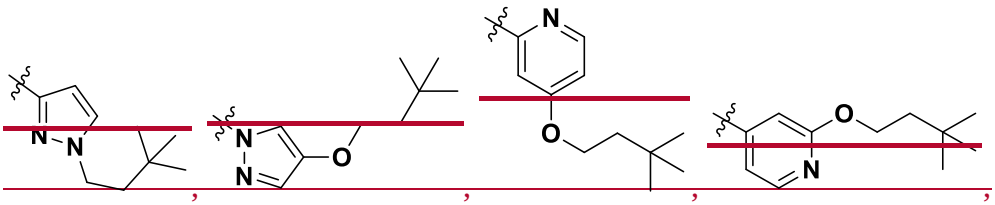
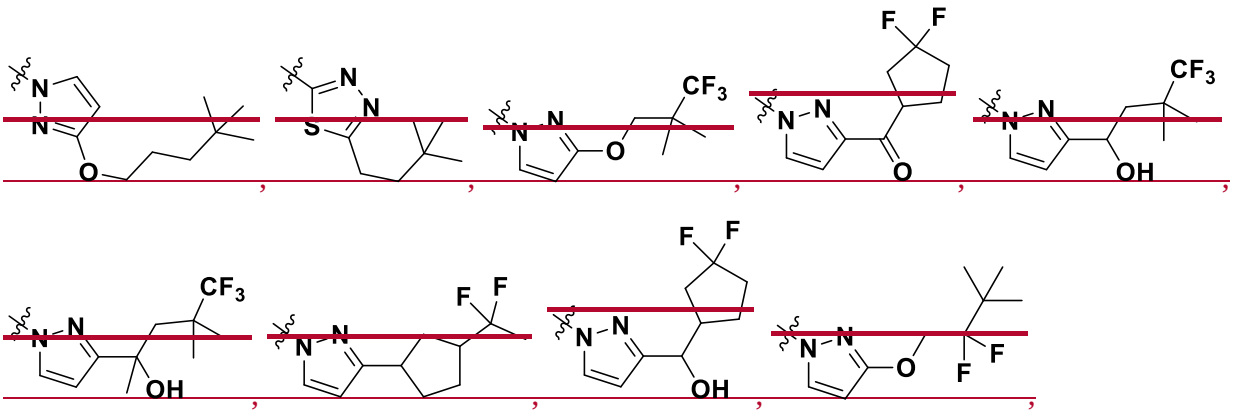
~~114. The compound of claim 114, wherein the heterocycloalkyl is selected from N-azetidinyl, N-pyrrolidinyl, N-morpholinyl, N-piperidinyl, N-piperidin-2-only, N-pyrrolidin-2-only, 3-tetrahydropyranyl, 3-(3,6-dihydro-2H-pyranyl), 2N-6-oxa-9-azaspiro[4.5]decanyl, 2N-6-oxa-2,9-diazaspiro[4.5]decanyl, 9-(oxa-9-azaspiro[4.5]decanyl) and 2-(3-oxa-1-azaspiro[4.4]non-1-enyl.~~

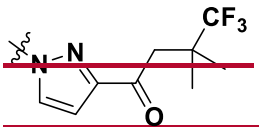
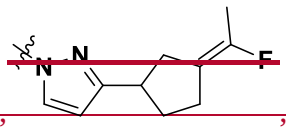
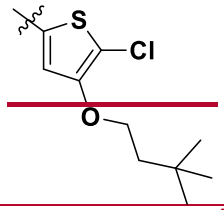
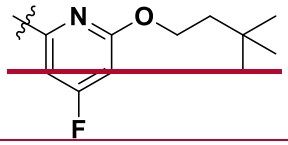
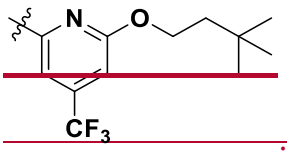
~~115. The compound of claim 114, wherein R^3 is selected from C_{1-8} alkyl (e.g., methyl, neopentyl, 4,4-dimethylpentyl, 3-methylbutyl or 3,3-dimethylbutyl), C_{1-8} alkoxy (e.g., 3,3-dimethylbutoxy, neopentyloxy or tert-butoxy), C_{1-8} haloalkoxy (e.g., trifluoromethoxy), and $-C(O)-R^7$.~~

116. The compound of claim 114, wherein Cy^1 is  ,  ,  ,

~~cycloalkyl (e.g., cyclohexyl), heterocycloalkyl (e.g., N-pyrrolidinyl), C_{1-4} alkyl-C_{3-9} cycloalkyl, C_{1-4} alkoxy-C_{3-9} cycloalkyl,~~  ~~, and -C(O)R^7.~~

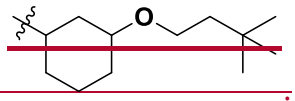
~~120. The compound of claim 120, wherein R^3 is substituted by at least one R^7 selected from halo (e.g., fluoro), hydroxyl, C_{1-5} haloalkyl (e.g., 1,1-difluoroethyl), C_{1-5} haloalkoxy (e.g., trifluoromethoxy), and C_{3-7} cycloalkyl (e.g., cyclopentyl).~~

~~121. The compound of claim 118, wherein Cy^1 is~~    

 ,  ,  ,  or  .

122. The compound of any one of claim 1-86, wherein Cy^1 is cycloalkyl substituted with 0-3 occurrences of R^3.

123. The compound of claim 123, wherein the cycloalkyl is cyclohexyl or cyclopentyl and R^3 is C_{1-8} alkoxy (e.g., 3,3-dimethybutoxy).

124. The compound of claim 123, wherein Cy^1 is  .

125. The compound of claim 1, wherein

R^1 is hydrogen;

X is 5-6 membered aryl or 5-6 membered heteroaryl, each of which is substituted with 0-3 occurrences of R^2;

Cy^1 is 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 5-6 membered aryl, which is substituted with 1-3 occurrences of R^4;

each R^2 is independently halo, $-NH_2$, C_{1-6} alkyl, C_{1-8} haloalkoxy, 5-6 membered heteroaryl, $-N(R^a)(R^5)$, $-N(R^a)C(O)-R^5$, $-SO-R^5$ or $-SO_2-R^5$;

each R^3 is independently halo, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, or 4-10 membered heterocycloalkyl, wherein each C_{3-9} cycloalkyl, C_{3-9} cycloalkoxy, C_{1-8} haloalkoxy, C_{1-8} alkoxy, and 4-10 membered heterocycloalkyl is further substituted with 0-3 occurrences of R^7;

each R^4 is independently halo, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} haloalkyl;

~~each R^5 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-9} cycloalkyl, hydroxyl, or $-CO_2H$, wherein each C_{1-6} alkyl, or C_{3-9} cycloalkyl is further substituted by 0-3 occurrences of R^6;~~

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

~~each R^7 is independently halo, C_{1-5} alkyl, C_{1-5} haloalkoxy, C_{3-7} cycloalkyl, and hydroxyl; and~~

~~each R^a is independently H or C_{1-6} alkyl.~~

37~~26~~. A compound selected from any compound given in Table 1.

38~~27~~. A compound selected from any compound given in Table 2.

~~128. The compound of any one of claims 1-128, wherein the compound is a CFTR corrector.~~

39~~29~~. A pharmaceutical composition comprising a compound of ~~any one of~~ claim~~s~~ 1~~-128~~, and a pharmaceutically acceptable carrier or excipient.

40~~30~~. The pharmaceutical composition of claim 39~~30~~, further comprising one or more CFTR therapeutic agents.

41~~31~~. Use of a compound of claim 1 in the manufacture of a medicament for~~A method of~~ treating deficient CFTR activity in a cell~~, comprising contacting the cell with a compound of any one of claims 1-128~~.

42~~32~~. The ~~method~~use of claim 41~~32~~, wherein the use~~contacting the cell occurs in a subject in need thereof, thereby treating~~ treats a CFTR-mediated condition and/or disease.

43~~33~~. The ~~method~~use of claim 42~~33~~, 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~~134~~. The ~~method~~use of claim 43~~133 or 134~~, 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~~135~~. The ~~method~~use of ~~any one of~~ claim~~s~~ 43~~133-135~~, wherein the disease or condition is cystic fibrosis.

46136. Use of a compound of claim 1 in the manufacture of a medicament for~~A method of~~ treating cystic fibrosis or a symptom thereof in a subject~~, comprising administering to the subject a therapeutically effective amount of a compound of claim 1~~.

47137. The ~~method~~use of claim 46~~137~~, wherein the subject is human.

48138. The use~~method~~ according to claim 46~~137~~ or 47~~138~~, wherein said subject is at risk of developing cystic fibrosis, and wherein the compound is to be administered~~said administering step is carried out~~ 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.