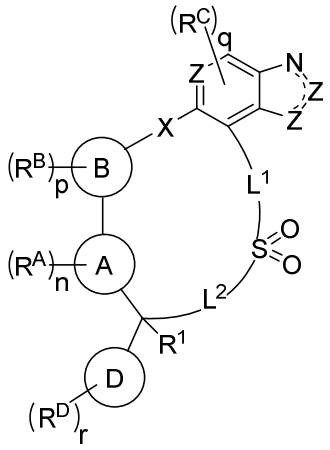
Claims

We claim:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof,

wherein

L^1 is an optionally substituted C_{1-6} alkylene chain wherein 1-3 of the methylene units is optionally and independently replaced by -O-, -N(R^2), -C(O)-, -S-, -S(O)-, -S(O)$_2$-, an optionally substituted 3-6 membered carbocyclyl, , optionally substituted C_2 alkenylene, or optionally substituted 5-6-membered heteroaryl;

L^2 is an optionally substituted C_{1-6} alkylene chain wherein 1-3 of the methylene units is optionally and independently replaced by -C(CD_3)$_2$-, -O-, -N(R^2)-, -C(O)-, -S-, -S(O)-, an optionally substituted 3-6 membered carbocyclyl, -S(O)$_2$-, optionally substituted C_2 alkenylene, or optionally substituted 5-6-membered heteroaryl;

Ring A is an optionally substituted 5-membered heteroaryl comprising 1-4 heteroatoms selected from the group consisting of N, O or S;

Ring B is optionally substituted phenyl or optionally substituted 6-membered heteroaryl;

Ring D is optionally substituted phenyl or optionally substituted 5-6-membered heteroaryl;

X is selected from the group consisting of -O-, -S-, -CH_2-, -C(OH)H-, -$CHCH_3$, -SO-, -CO-, -SO_2-, -CFH-, -CF_2-, and -$N(R^2)$-;

each R^A is independently selected from the group consisting of halogen, cyano, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_6 alkoxy, and -CD_3;

each R^B is independently selected from the group consisting of halogen, cyano, -$C(O)N(R^2)_2$, $C(O)OR^2$, -OR^2, -$N(R^2)_2$, optionally substituted C_1-C_6 aliphatic and optionally substituted C_1-C_6 alkoxy;

each R^C is independently selected from the group consisting of hydrogen, halogen, cyano, -$(CH_2)_{0-3}C(O)OH$, optionally substituted C_1-C_6 aliphatic or optionally substituted C_1-C_6 alkoxy;

each R^D is independently selected from the group consisting of halogen, cyano, -$C(O)N(R^2)_2$, -$C(O)OR^2$, -OR^2, -$N(R^2)_2$, optionally substituted C_1-C_6 aliphatic, optionally substituted C_1-C_3 alkoxy, optionally substituted 5-6-membered heteroaryl, and optionally substituted 3-6-membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O or S, wherein each R^D is optionally substituted with 1-6 instances of R^d;

wherein two instances of R^D may be taken together to form an optionally substituted 5-7 membered carbocyclic ring, optionally substituted 5-6-membered heteroaryl, and optionally substituted 3-6-membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O or S;

each R^d is independently selected from the group consisting of hydrogen, -OH, -CD_3, -$C(O)N(R^2)_2$, $C(O)OR^2$, -OR^2, -$N(R^2)_2$, -$S(O)_2R^2$ optionally substituted C_1-C_6 aliphatic, optionally substituted 5-6-membered heteroaryl, and optionally substituted 3-6-membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O or S;

R^1 is selected from the group consisting of hydrogen, cyano, -OR^2, -$(CH_2)_{0-3}N(R^2)_2$, optionally substituted C_1-C_3 aliphatic, 3-6-membered heterocyclyl comprising 1-3 heteroatoms selected from the group consisting of N, O or S, and -CD_3;

each R^2 is independently selected from hydrogen, optionally substituted C_1-C_6 aliphatic, -OH, C_1-C_6 alkoxy, -$S(O)_2$(optionally substituted C_1-C_6 aliphatic);

each Z independently is -CH=, -N= or -NH-;

n is 0, 1, 2 or 3;

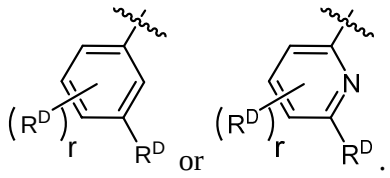
p is 0, 1, 2, 3 or 4;

q is 0, 1 2, or 3; and

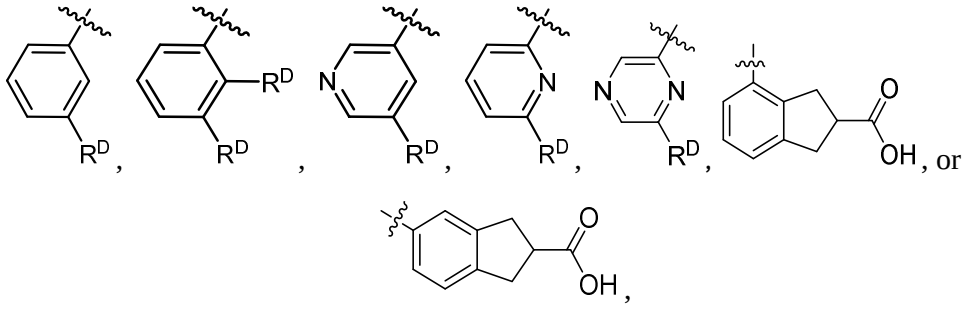
r is 0, 1, 2, 3, 4 or 5.

2. The compound of claim 1, wherein Ring D is optionally substituted phenyl or optionally substituted pyridine.

3. The compound of claim 2, wherein Ring D is

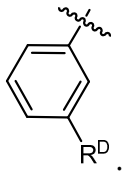


4. The compound of any of the previous claims, wherein Ring D is



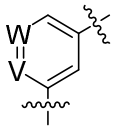
.

5. The compound of any of the previous claims, wherein Ring D is



6. The compound of any of the previous claims, wherein Ring B is optionally substituted phenyl, optionally substituted pyridine, or optionally substituted pyridone.

7. The compound of any of the previous claims, wherein Ring B is



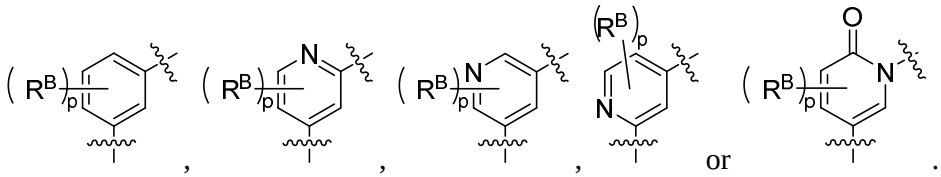
,

wherein

W is -CH=, -C(R^B)= or -N=; and

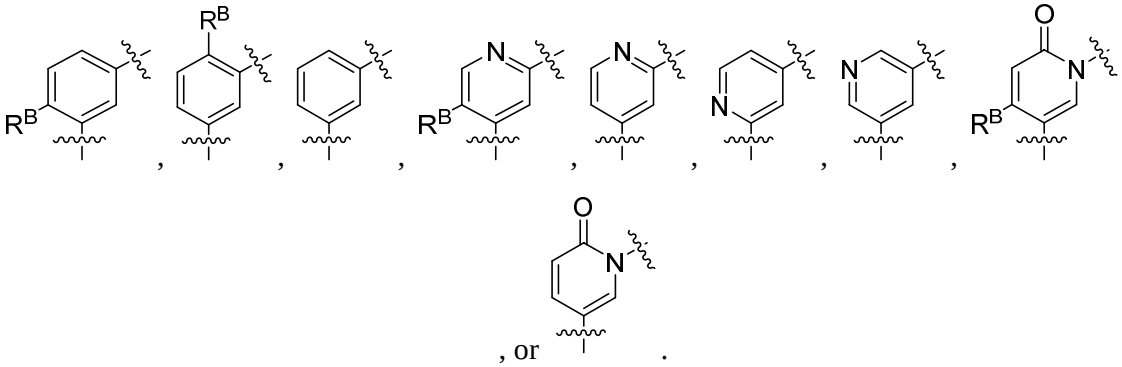
V is -CH=, -C(R^B)= or -N=.

8. The compound of any of the previous claims, wherein Ring B is



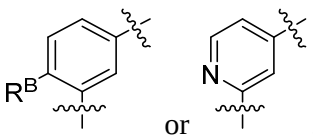
, , , , or .

9. The compound of any of the previous claims, wherein Ring B is



, , , , , , , , , or .

10. The compound of any of the previous claims, wherein Ring B is



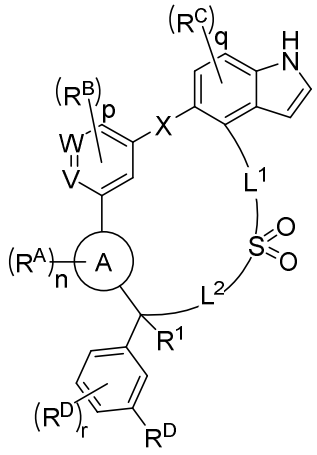
or .

11. The compound of any of the previous claims, wherein R^B is halogen or optionally substituted C_1-C_3 alkyl.

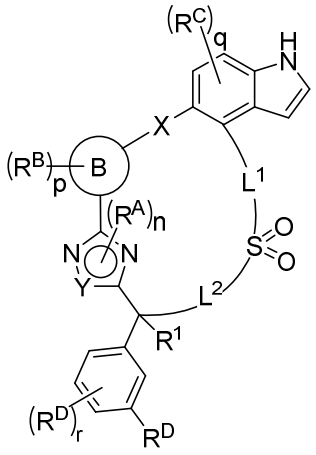
12. The compound of any of the previous claims, wherein R^B is halogen.

13. The compound of any of the previous claims, wherein R^B is fluoro.

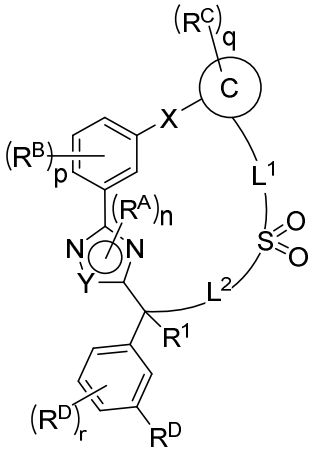
14. The compound of any of the previous claims, wherein the compound is of formula (I-a), (I-b), (I-c) or (I-d):



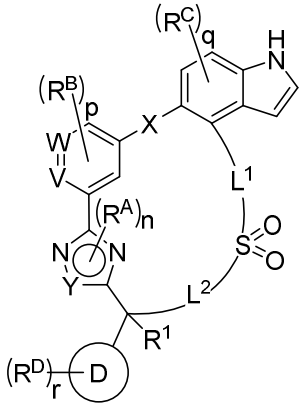
(I-a),



(I-b), or



(I-c)



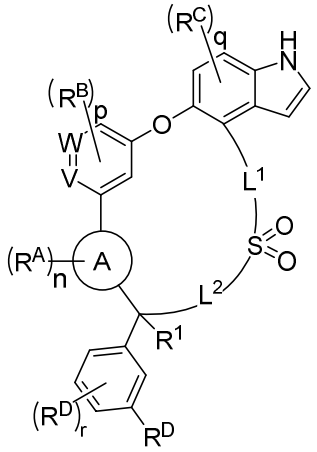
(I-d)

or a pharmaceutically acceptable salt thereof

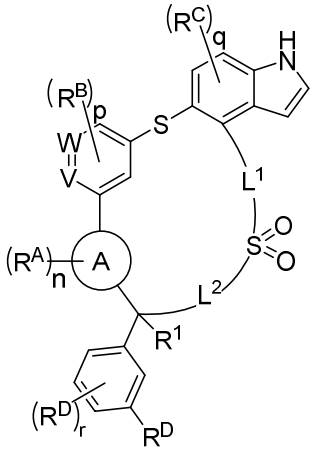
wherein

Y is C or N.

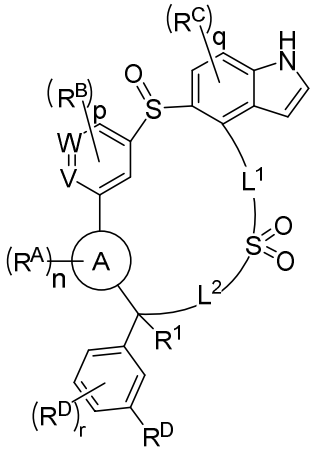
15. The compound of any of the previous claims wherein the compound is of formula (I-a1), (I-a2), (I-a3), (I-a4), or (I-a5):



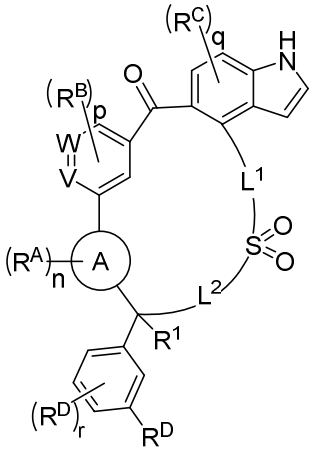
(I-a1),



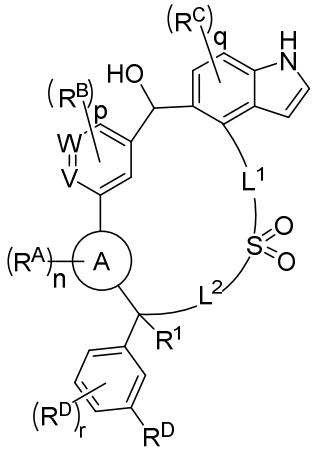
(I-a2),



(I-a3),



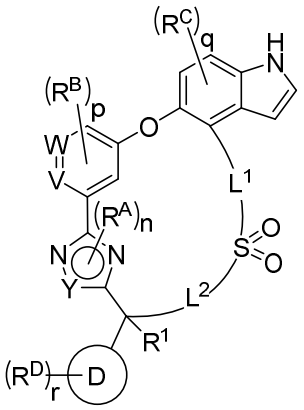
(I-a4), or



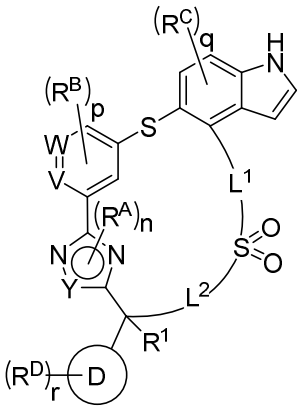
(I-a5),

or a pharmaceutically acceptable salt thereof.

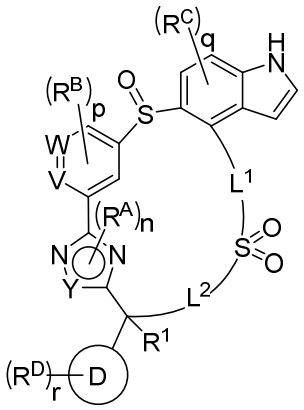
16. The compound of any of the previous claims wherein the compound is of formula (I-d1), (I-d2), (I-d3), (I-d4), or (I-d5)



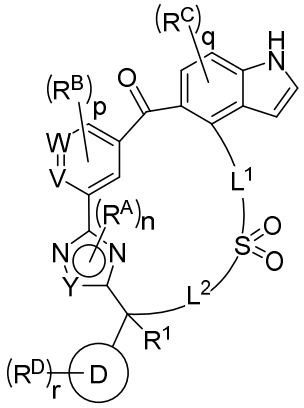
(I-d1)



(I-d2)

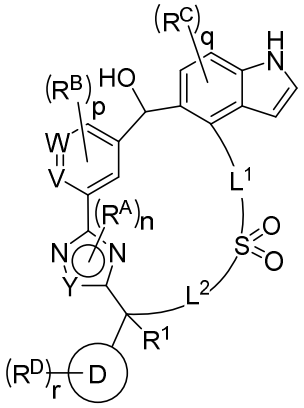


(I-d3)



(I-d4)

or



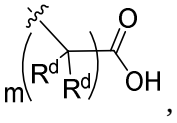
(I-d5),

or a pharmaceutically acceptable salt thereof.

17. The compound of any of the previous claims, wherein Ring C is selected from optionally substituted indole, optionally substituted indazole, optionally substituted benzimidazole, optionally substituted 6-azaindole, and optionally substituted 7-azaindole.

18. The compound of any of the previously claims, wherein Ring C is optionally substituted indole.

19. The compound of any the previous claims, wherein at least one instance of R^D is



,

wherein

each R^d is independently selected from hydrogen, optionally substituted methyl, -OH, -OMe, or $-CD_3$;

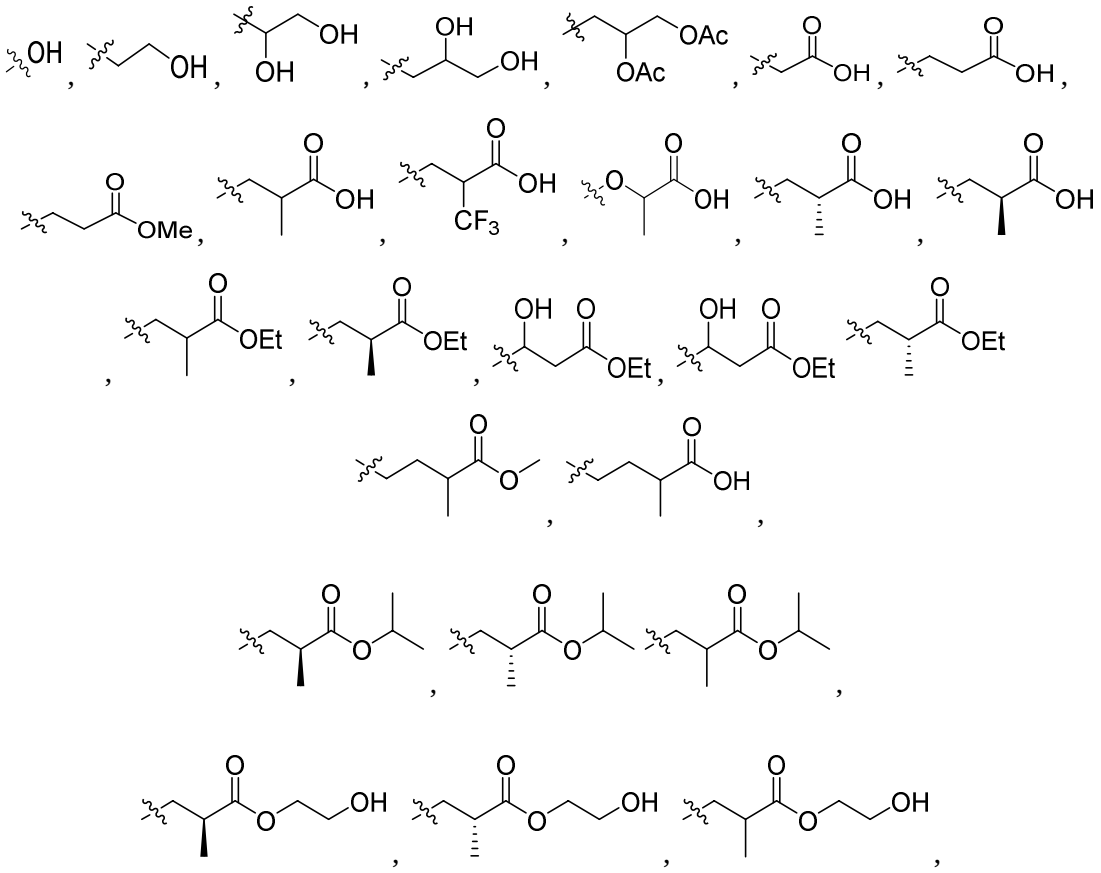
wherein, two instances R^d may, with the atoms on which they are attached, form a cyclopropyl ring; and

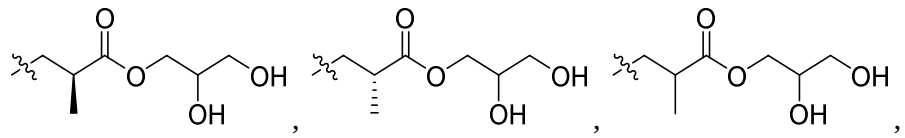
m is 0, 1, 2, or 3.

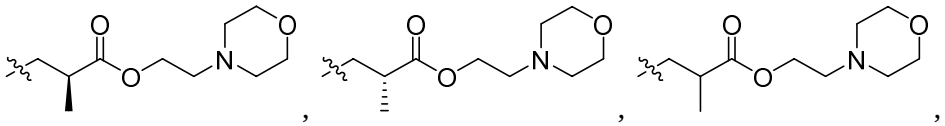
20. The compound of claim 16, wherein each R^d is independently selected from hydrogen, methyl, $-CF_3$, $-CF_2H$, or $-CFH_2$.

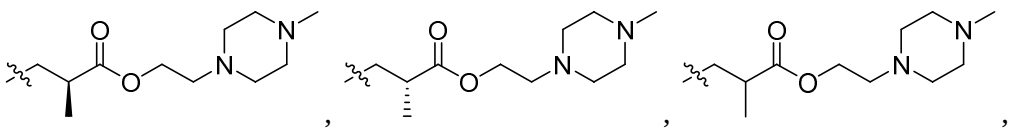
21. The compound of claim 17, wherein each R^d is independently selected from hydrogen and methyl.

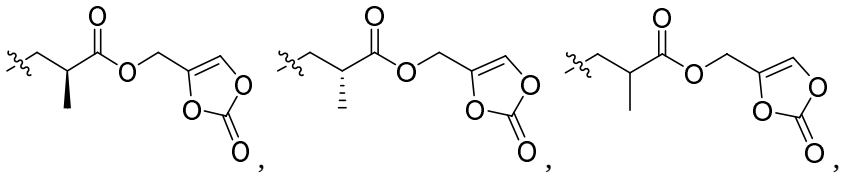
22. The compound of any of the previous claims, wherein at least one instance of R^D is selected from the group consisting of

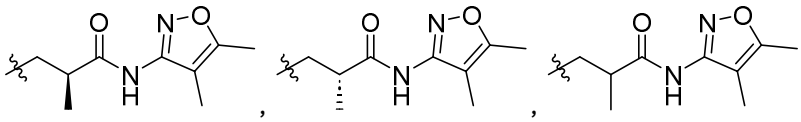


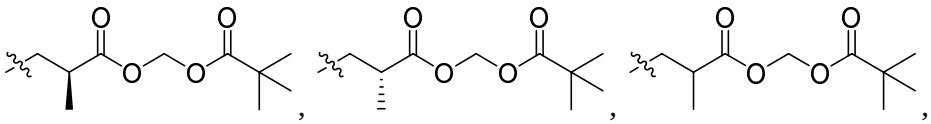


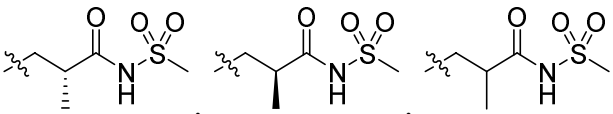


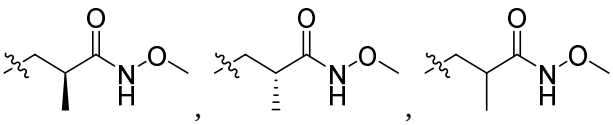


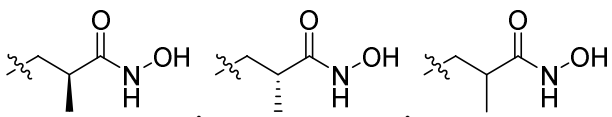


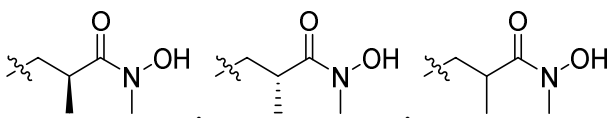


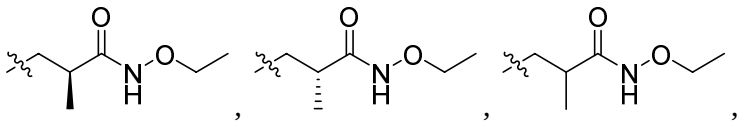


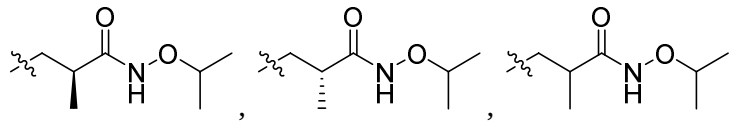


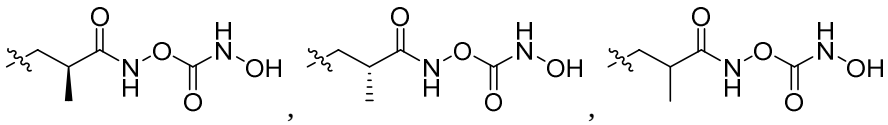


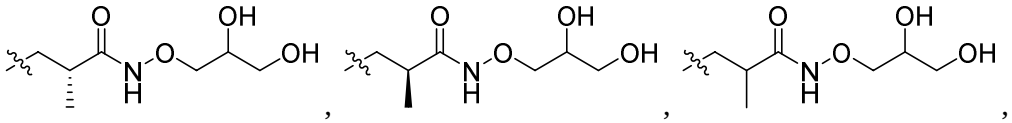


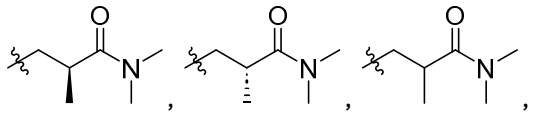


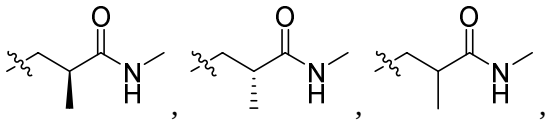


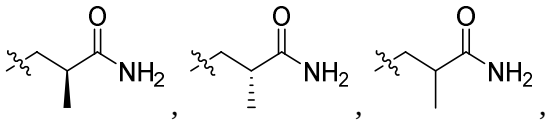


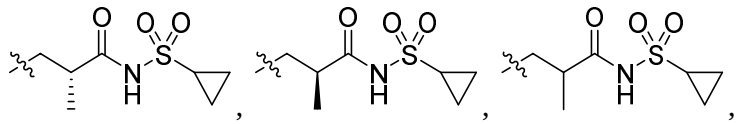


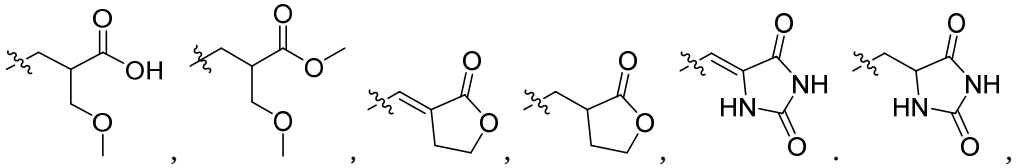


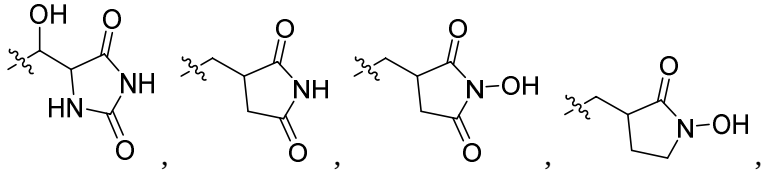


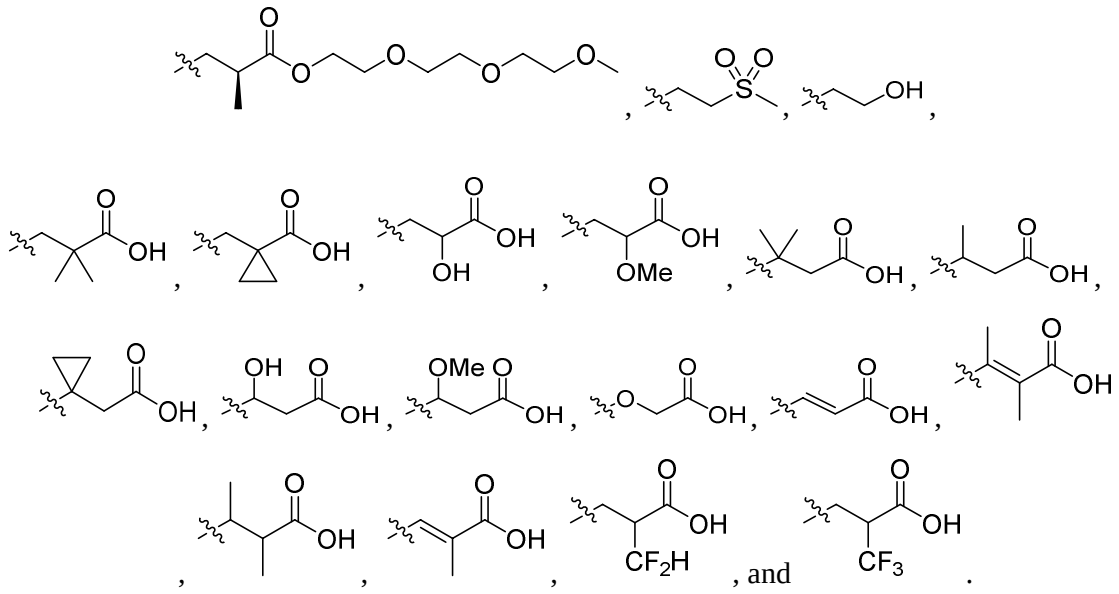




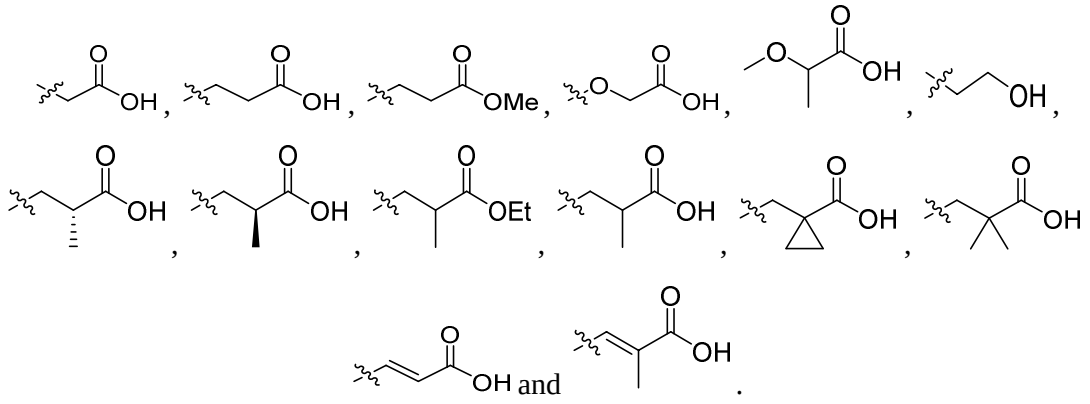




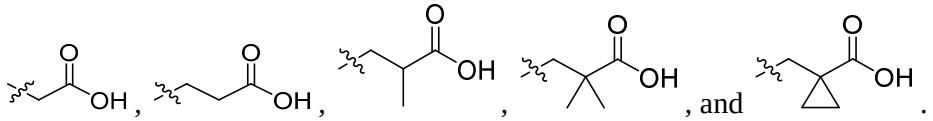




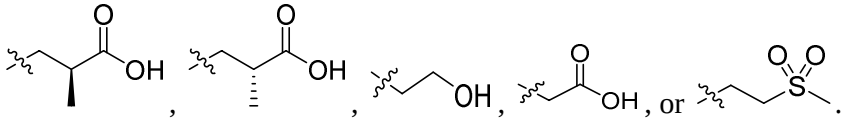
23. The compound of claim 19, wherein at least one instance of R^D is selected from the group consisting of



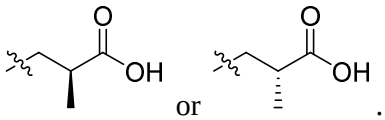
24. The compound of claim 20, wherein R^D is



25. The compound of claim 21, wherein R^D is



26. The compound of claim 21, wherein R^D is

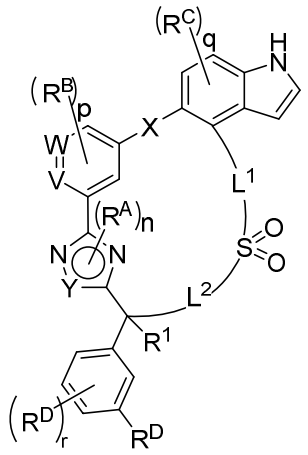


.

27. The compound of any of the previous claims wherein, ring A is selected from the group consisting of imidazole, pyrazole, tetrazole, oxazole, thiazole, and 1, 2, 4 triazole.

28. The compound of any of the previous claims, wherein each R^A is independently selected from hydrogen, methyl and $-CD_3$.

29. The compound of any of the previous claims, wherein the compound is of formula (I-e):



(I-e),

or a pharmaceutically acceptable salt thereof.

30. The compound of any of the previous claims, wherein L^1 is an optionally substituted C_{1-6} alkylene chain and L^2 is an optionally substituted C_{1-6} alkylene chain, wherein one of the methylene units of L^2 is optionally replaced with -O-.

31. The compound of any of the previous claims, wherein L^1 is a C_{1-6} alkylene chain substituted with 1-3 instances of methyl, and L^2 is C_{1-6} alkylene chain, wherein one of the methylene units of L^2 is optionally replaced with -O- and wherein L^2 is optionally substituted with 1-3 instances of methyl.

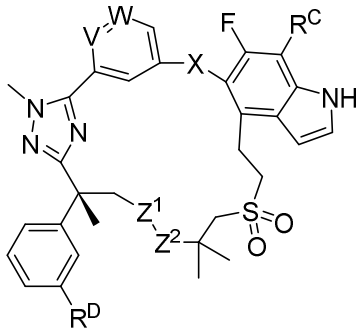
32. The compound of any of the previous claims, wherein L^1 is an unsubstituted C_2 alkylene chain.

33. The compound of any of the previous claims, wherein L^2 is an C_5 alkylene chain, wherein one of the methylene units of L^2 is optionally replaced with -O- and wherein L^2 is optionally substituted with 1-3 instances of methyl.

34. The compound of any of the previous claims, wherein L^2 is a C_5 alkylene chain, wherein L^2 is optionally substituted with 1-3 instances of methyl.

35. The compound of any of the previous claims, wherein L^2 is a C_5 alkylene chain, wherein L^2 is optionally substituted with 1-3 instances of methyl.

36. The compound of any of the previous claims, wherein the compound is of formula (I-f):



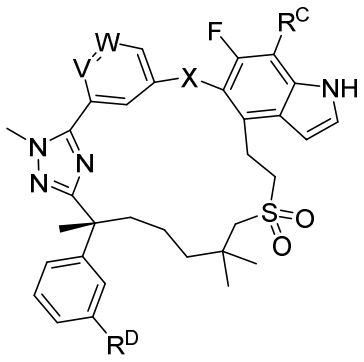
(I-f),

or a pharmaceutically acceptable salt thereof

wherein Z^1 is $-CH_2-$ or -O-; and

Z^2 is $-CH_2-$ or -O-.

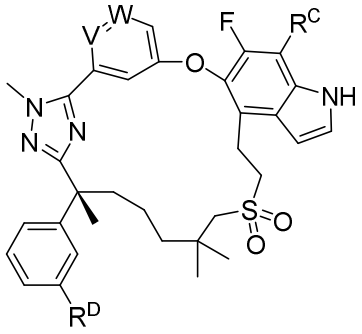
37. The compound of any of the previous claims, wherein the compound is of formula (I-g)



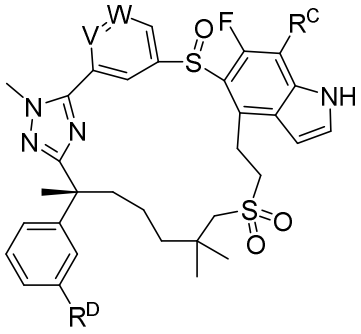
(I-g),

or a pharmaceutically acceptable salt thereof.

38. The compound of any of the previous claims, wherein the compound is of formula (I-g1) or (I-g2)



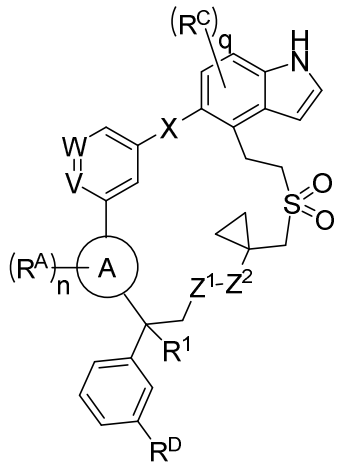
or



(I-g1) (I-g2)

or a pharmaceutically acceptable salt thereof.

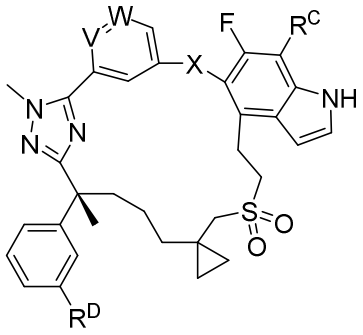
39. The compound of any of the previous claims, wherein the compound is of formula (I-h):



(I-h),

or a pharmaceutically acceptable salt thereof.

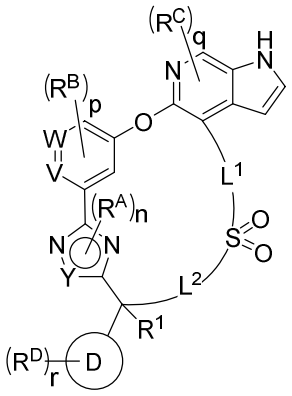
40. The compound of any of the previous claims, wherein the compound is of formula (I-i)



(I-i),

or a pharmaceutically acceptable salt thereof.

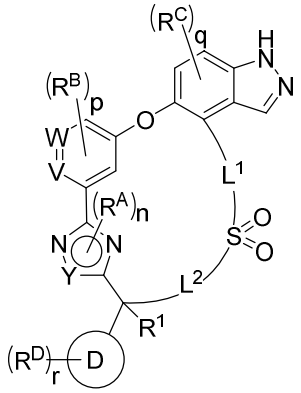
41. The compound of any of the previous claims, wherein the compound is of formula (I-j)



(I-j),

or a pharmaceutically acceptable salt thereof.

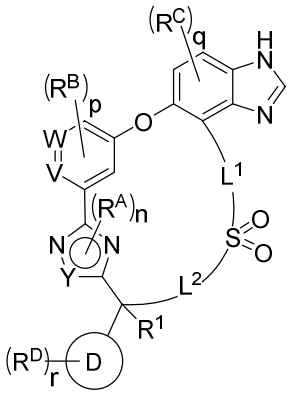
42. The compound of any of the previous claims, wherein the compound is of formula (I-k)



(I-k),

or a pharmaceutically acceptable salt thereof.

43. The compound of any of the previous claims, wherein the compound is of formula (I-m)



(I-m),

or a pharmaceutically acceptable salt thereof.

44. The compound of any of the previous claims, wherein Z^1 is -O- and Z^2 is -CH_2-.

45. The compound of any of the previous claims, wherein Z^1 is -CH_2- and Z^2 is –O-.

46. The compound of any of the previous claims, wherein Z^1 is -CH_2- and Z^2 is -CH_2-.

47. The compound of any of the previous claims, wherein R^1 is optionally substituted C_1-C_3 aliphatic.

48. The compound of any of the previous claims, wherein R^1 is optionally substituted methyl or -CD_3.

49. The compound of any of the previous claims, wherein each R^d is independently hydrogen or optionally substituted C_1-C_3 aliphatic.

50. The compound of any of the previous claims, wherein at least one R^d is optionally substituted C_1-C_3 aliphatic.

51. The compound of any of the previous claims, wherein at least one R^d is methyl.

52. The compound of any of the previous claims, wherein each R^A is independently optionally substituted C_1-C_3 aliphatic.

53. The compound of any of the previous claims, wherein each R^A is independently, methyl or -CD_3.

54. The compound of any of the previous claims, wherein R^C is halogen.

55. The compound of any of the previous claims, wherein R^C is independently fluoro or chloro.

56. The compound of any of the previous claims, wherein R^D is -COOH.

57. The compound of any of the previous claims, wherein R^D is halogen.

58. The compound of any of the previous claims, wherein R^D is fluoro.

59. The compound of any of the previous claims, wherein R^C is hydrogen.

60. A compound selected from a compound of Table 1 or a pharmaceutically acceptable salt thereof.

61. A pharmaceutical composition comprising a compound of any of the previous claims and a pharmaceutically acceptable excipient.

62. Use of a compound any of claims 1-60 or a pharmaceutical composition of claim 61, in the manufacture of a medicament for treating a CFTR-mediated disease or disorder.

63. The use of claim 62, 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), 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, myeloperoxidase 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, spinocerebellar 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.

64. The use of claim 62 or 63, 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, 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.

65. The use of any one of claims 62-64, wherein the disease or condition is cystic fibrosis.

66. Use of a compound of any one of claims 1-60, or the pharmaceutical composition of claim 61, in the manufacture of a medicament for treating cystic fibrosis in a subject.

67. The use of claim 66, wherein the subject is human.