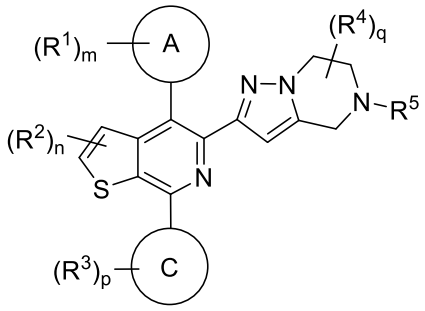
CLAIMS

1. A compound of Formula IC2'-b:



IC2'-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, pyridine, or a 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

Ring C is selected from the group consisting of phenyl; 9- to 10-membered bicyclic aryl ring, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur; 9- to 10-membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur; 3- to 7-membered carbocyclic ring; 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur; 6- to 11-membered bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur; and 12- to 13-membered polycyclic heterocyclic ring having 1-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

each R^1 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} alkyl, cycloalkyl, –CN, –C(O)OR, –C(O)NR_2, –CH_2NR_2, –N(R^7)$_2$, -N=S(R^7)$_2$, –SR^7, –(C_{1-4} alkylene)OR, and –OR^7, wherein a sulfur atom in R^1 can be oxidized;

each R^7 is independently selected from the group consisting of hydrogen, optionally substituted C_{1-6} aliphatic, –(C_{1-4} alkylene)OR, –(C_{1-4} alkylene)NR_2, optionally substituted 3- to 6-membered carbocyclic ring, optionally substituted 4- to 7-membered heteroaryl ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

or two R^7 groups, together with the atom(s) to which they are attached, form a 4- to 6-membered heterocyclic ring having 0-1 additional heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

each R^2 is independently selected from the group consisting of halogen, optionally substituted C_{1-6} aliphatic, and -OR;

each R^3 is independently selected from the group consisting of oxo, halogen, -CN, -OR, -C(O)R, -C(O)N$(R)_2$, -$(CH_2)_x$C(O)OR, -$(CH_2)_x$C(O)N$(R)_2$, -$(CH_2)_x$N(R)C(O)R, -$(CH_2)_x$Cy, -O$(CH_2)_x$Cy, -C(O)Cy, optionally substituted carbocyclic ring, and optionally substituted C_{1-6} aliphatic;

each R^4 is independently optionally substituted C_{1-6} aliphatic;

R^5 is optionally substituted C_{1-6} aliphatic, -C(O)R^9, -$(CH_2)_x$N(R)C(O)R^9, or -CN;

R^9 is optionally substituted C_{2-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or a 4-membered bicyclic carbocyclic ring;

m is 0, 1, 2, or 3;

n is 0, 1, or 2;

p is 0, 1, 2, or 3;

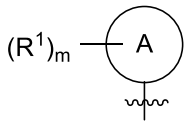
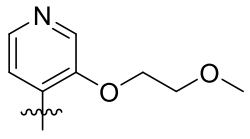
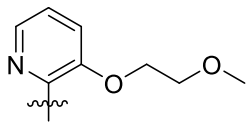
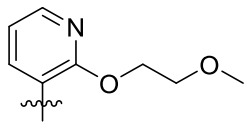
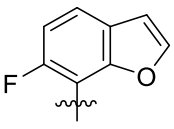
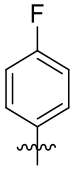
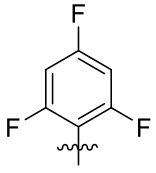
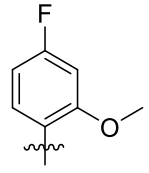
q is 0, 1, or 2;

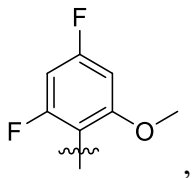
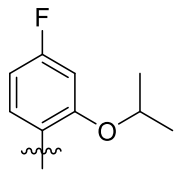
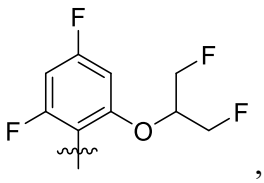
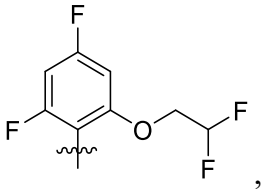
each x is independently 0, 1, or 2;

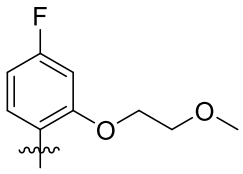
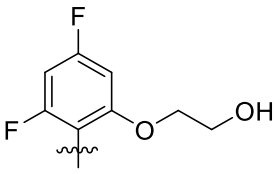
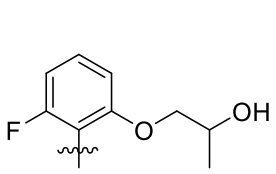
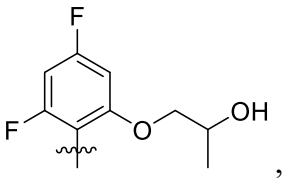
each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

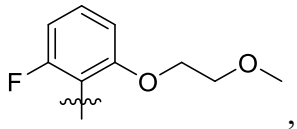
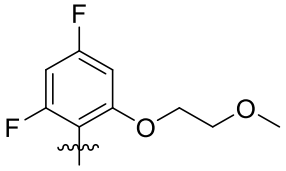
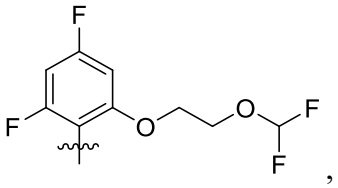
each Cy is independently selected from the group consisting of phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein each Cy is substituted with 0-3 instances of R^8; and

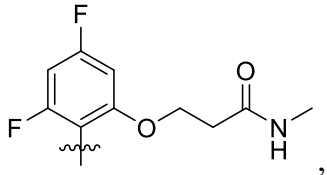
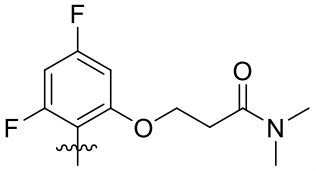
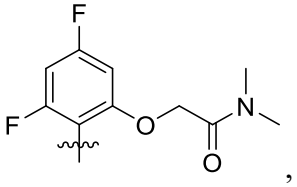
each R^8 is independently selected from the group consisting of oxo, halogen, and optionally substituted C_{1-6} aliphatic.

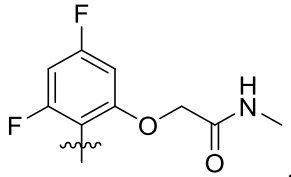
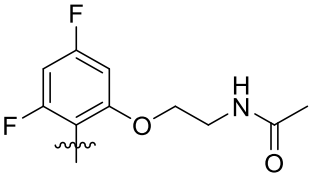
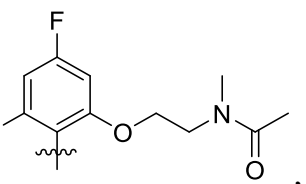
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein a moiety  is selected from the group consisting of: , , , , , , ,

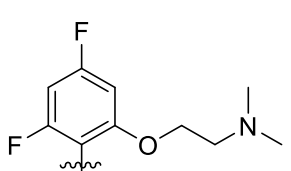
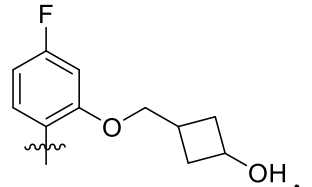
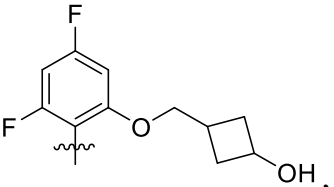
, , , ,

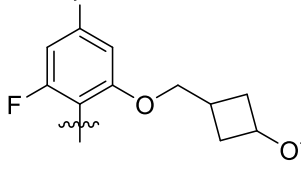
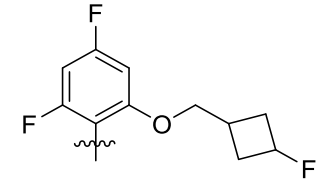
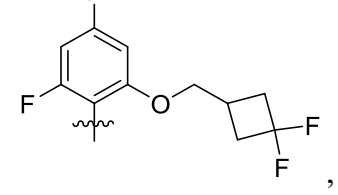
, , , ,

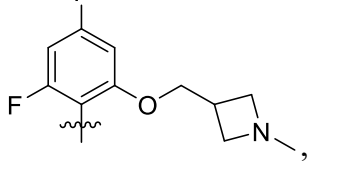
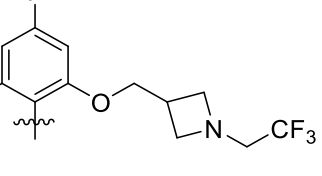
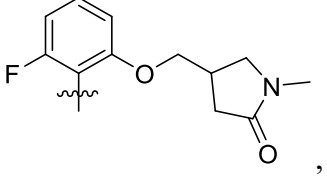
, , ,

, , ,

, , ,

, , ,

, , ,

, , ,

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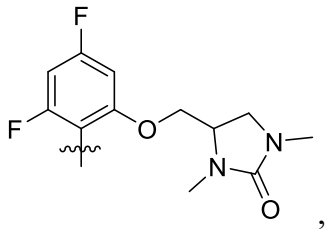
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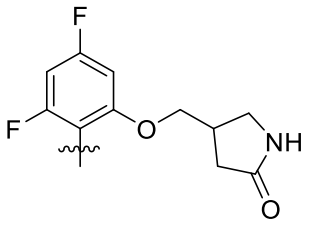
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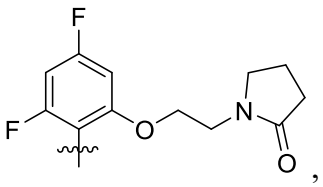
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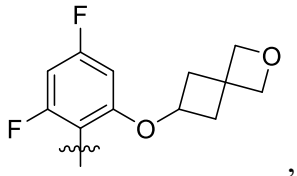
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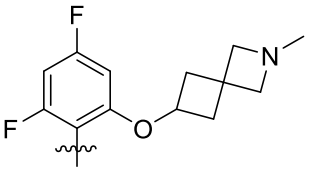
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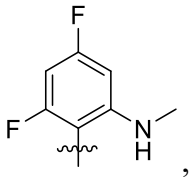
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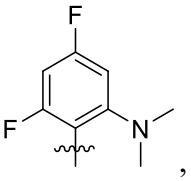
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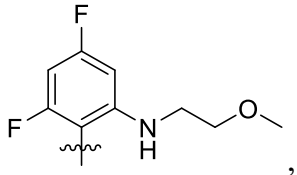
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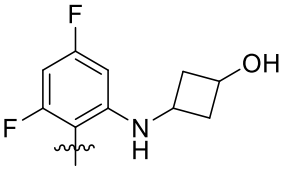
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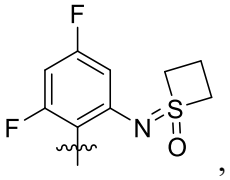
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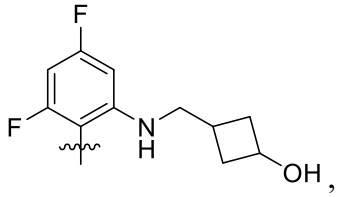
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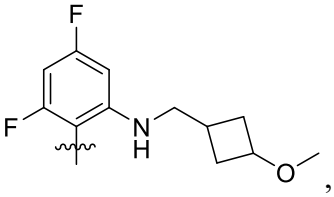
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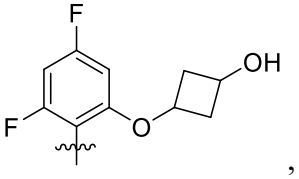
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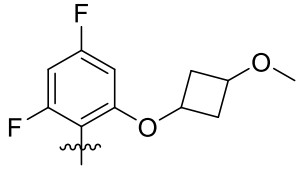
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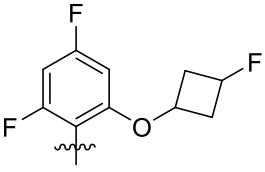
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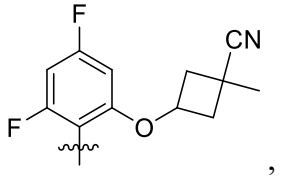
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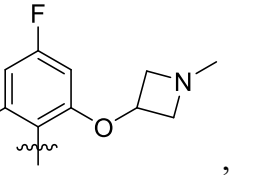
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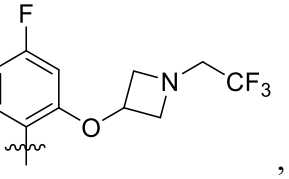
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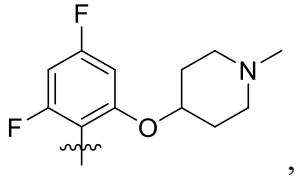
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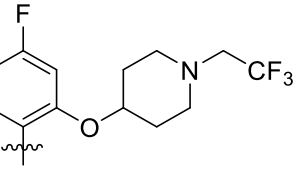
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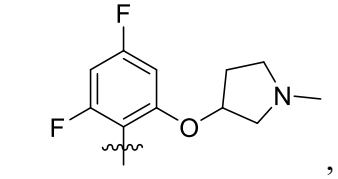
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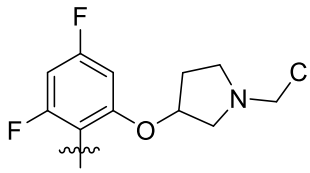
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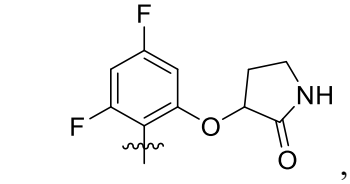
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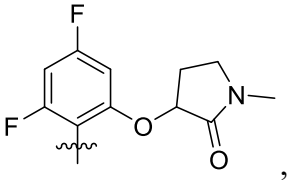
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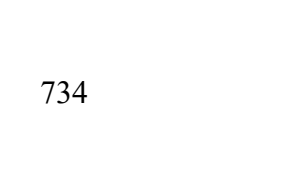
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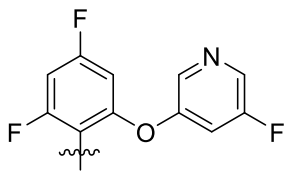
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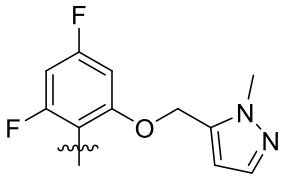
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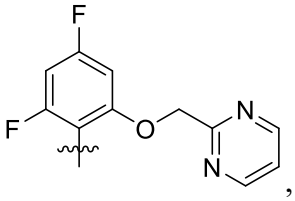
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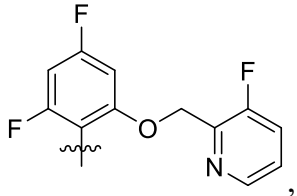
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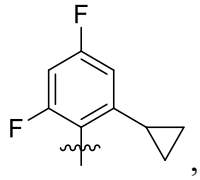
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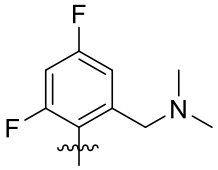
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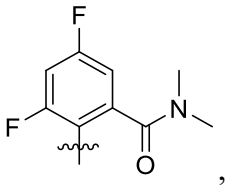
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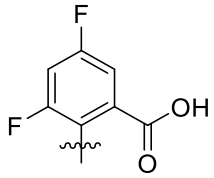
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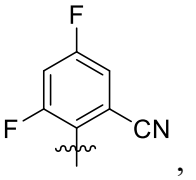
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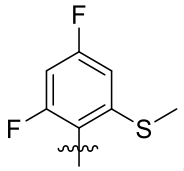
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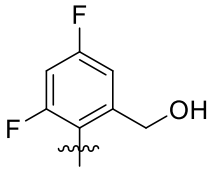
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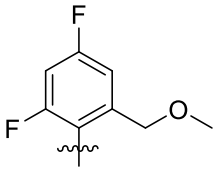
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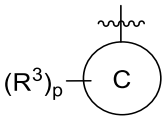
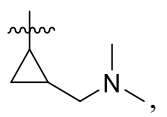
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein a moiety



is selected from the group consisting of: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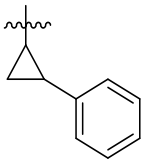
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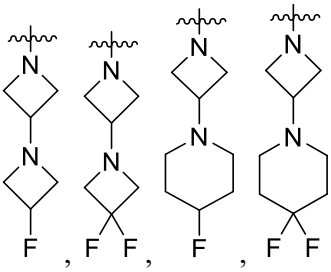
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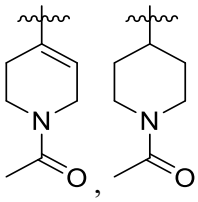
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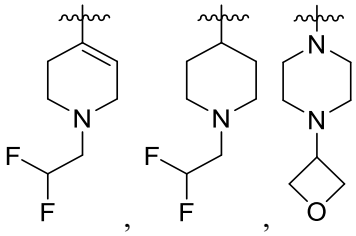
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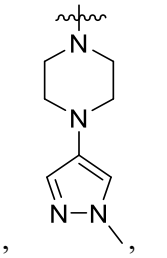
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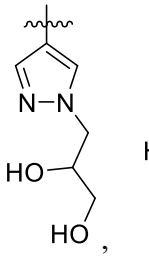
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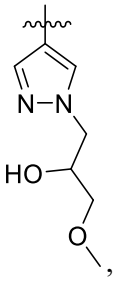
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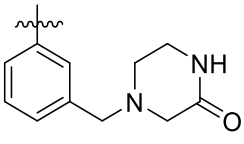
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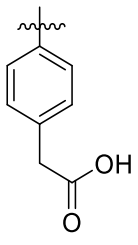
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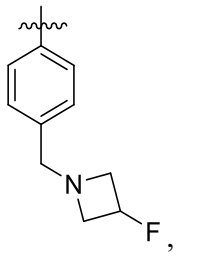
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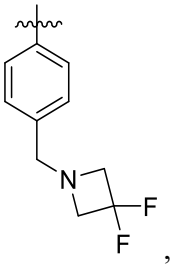
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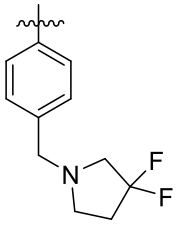
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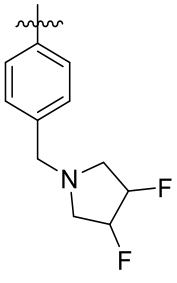
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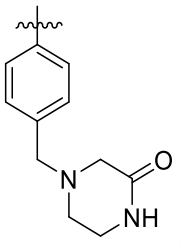
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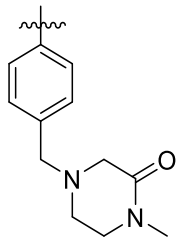
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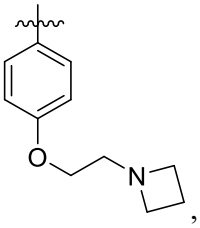
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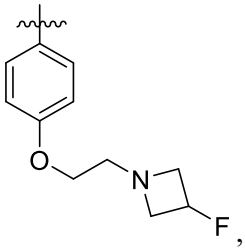
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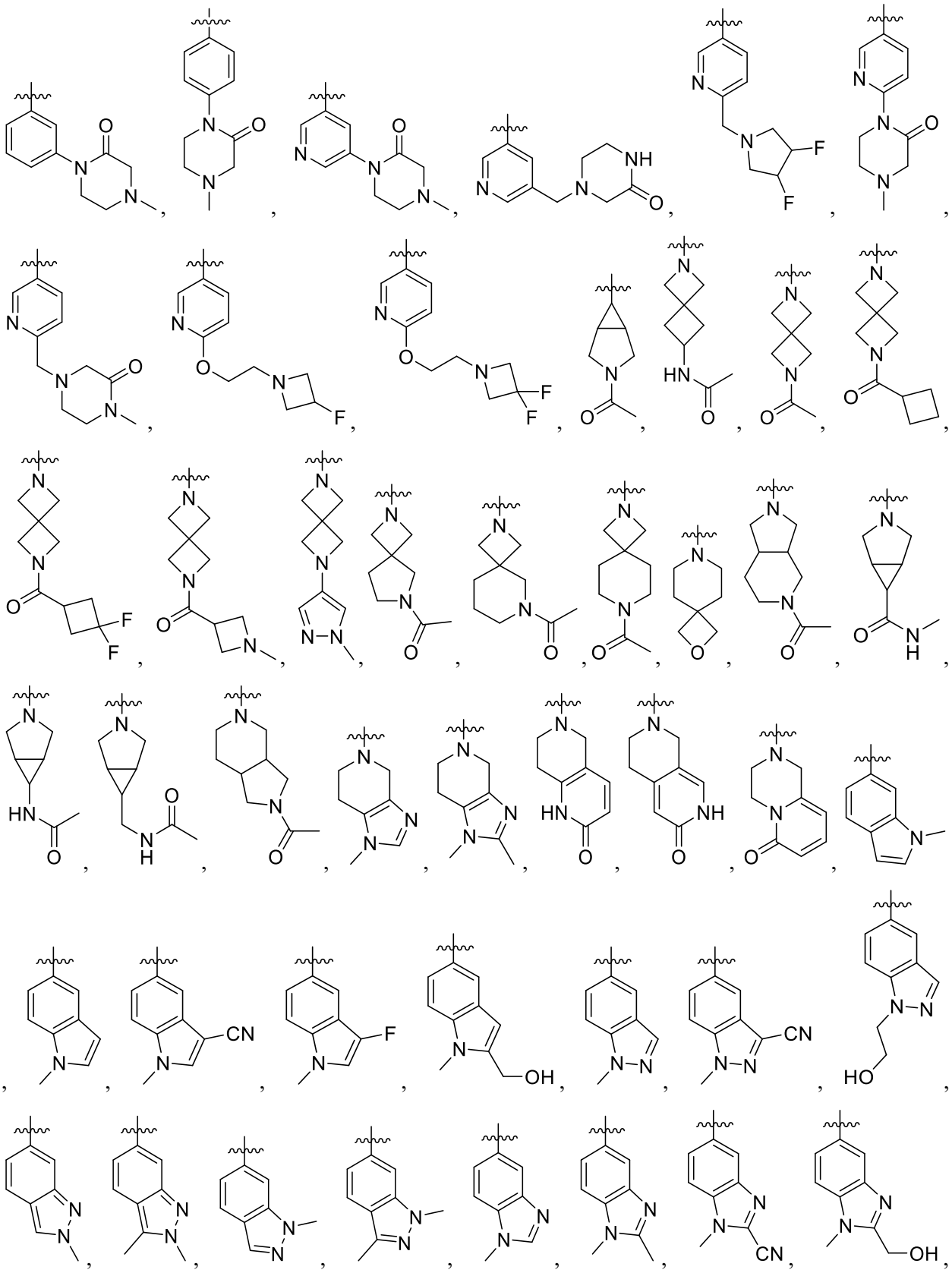
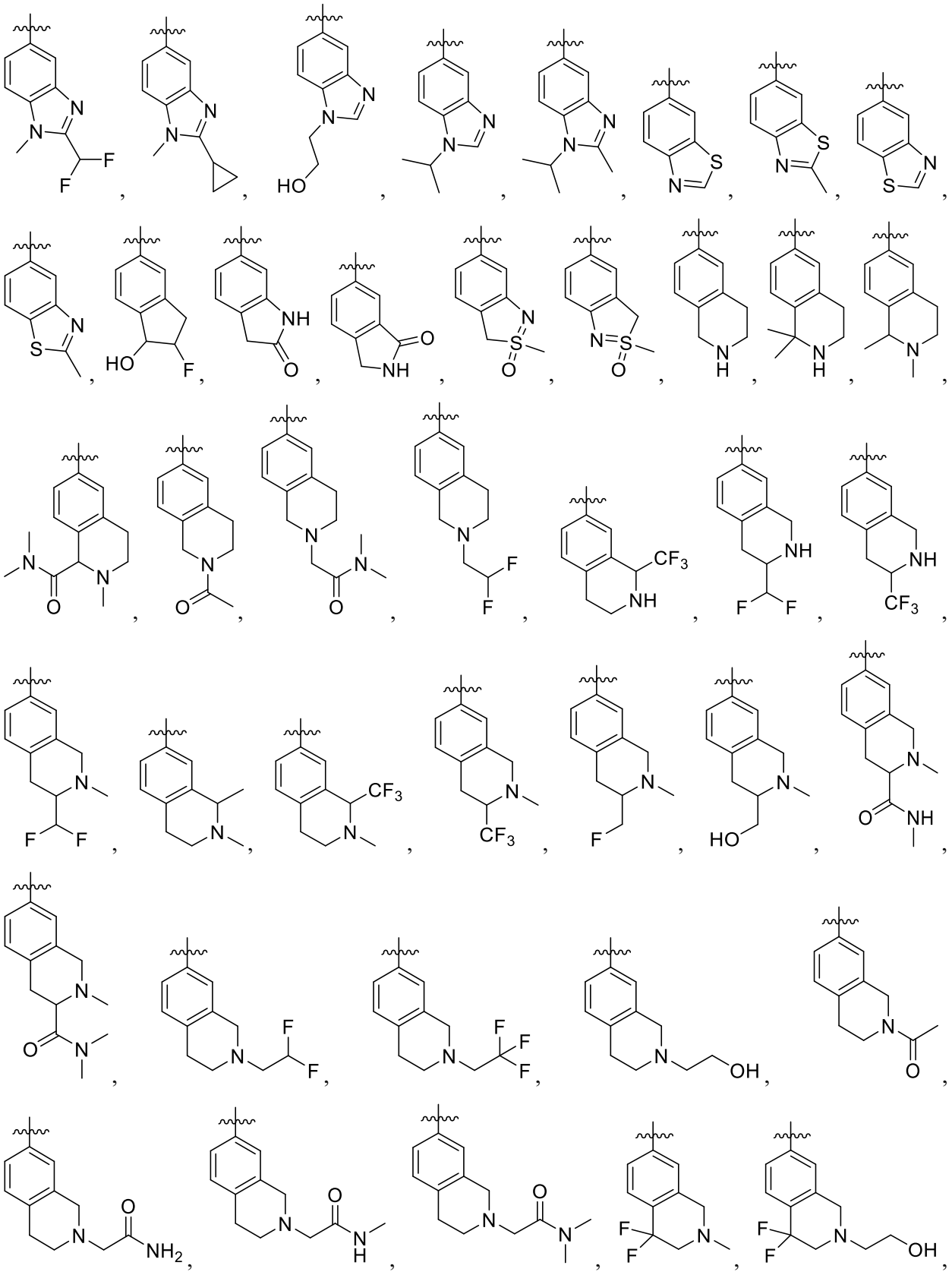
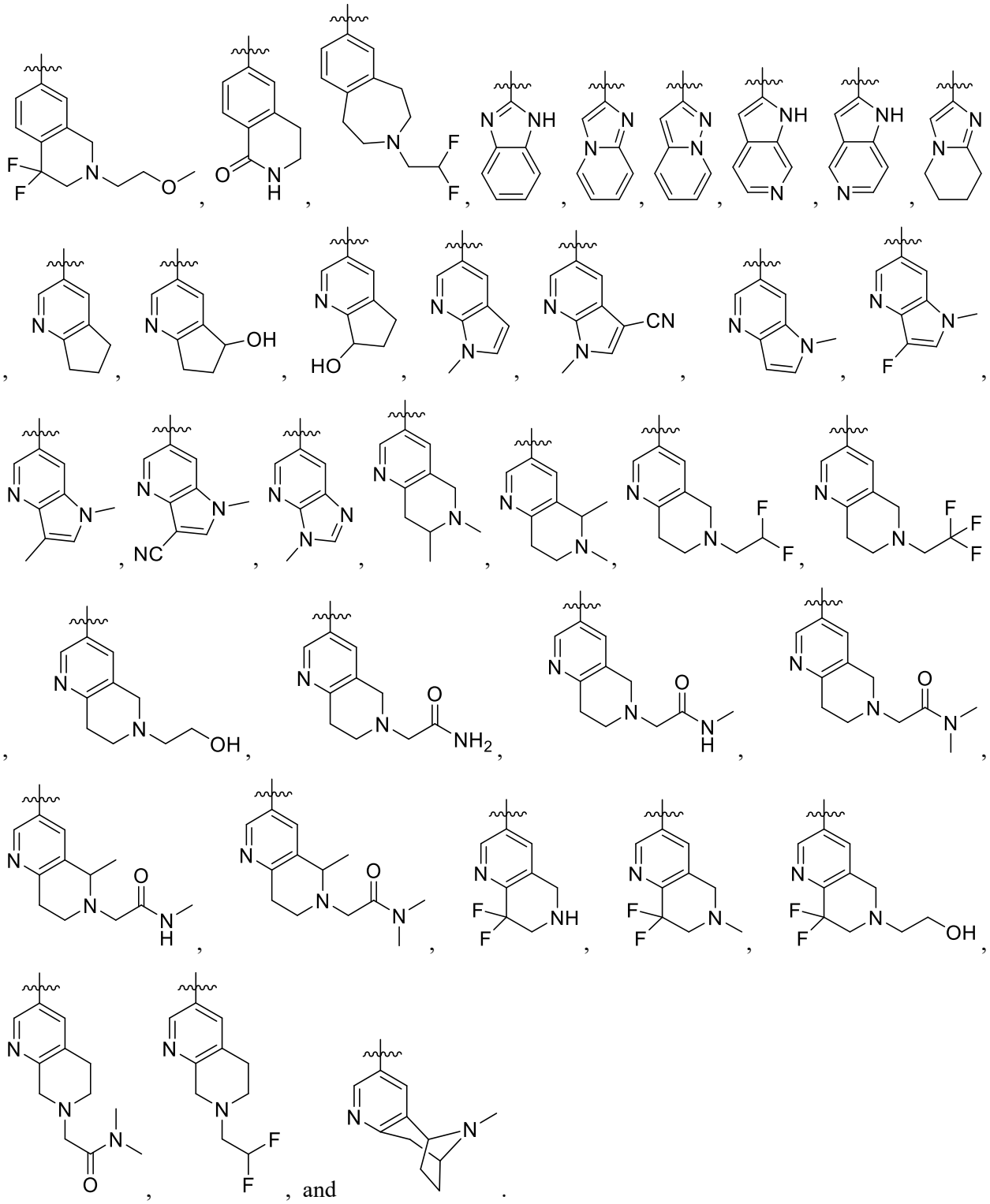
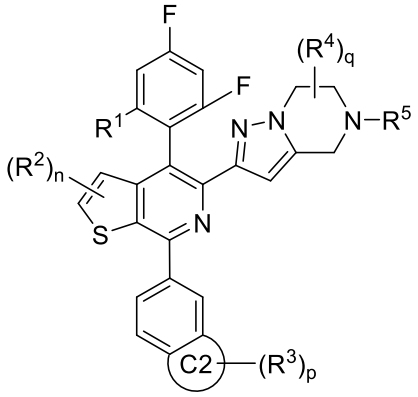






4. The compound of claim 1, wherein the compound is a compound of Formula IF':



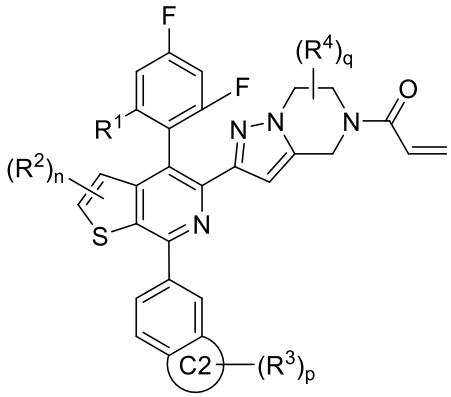
IF'

or a pharmaceutically acceptable salt thereof, wherein:

Ring C2 is selected from the group consisting of phenyl, 5- to 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, 3- to 7-membered carbocyclic ring, and 4- to 7-membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur; and

n is 0 or 1.

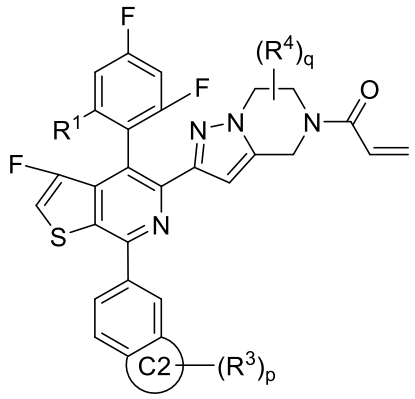
5. The compound of claim 4, wherein the compound is a compound of Formula IF1':



IF1'

or a pharmaceutically acceptable salt thereof.

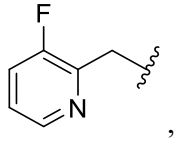
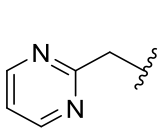
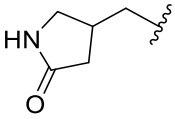
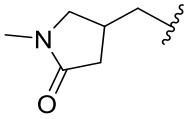
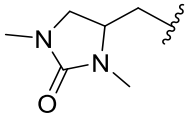
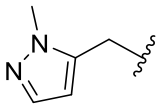
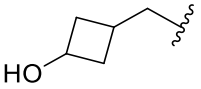
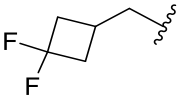
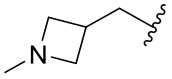
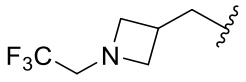
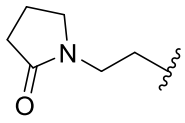
6. The compound of claim 4 or 5, wherein the compound is a compound of Formula IF2':

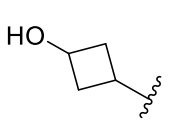
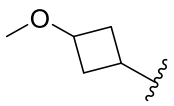
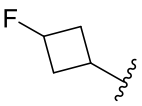
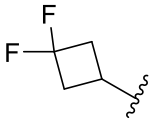
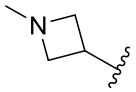
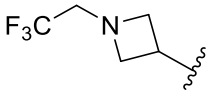
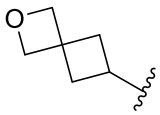
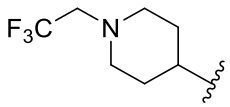
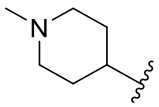
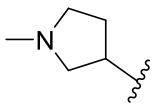
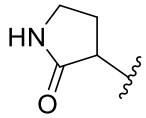
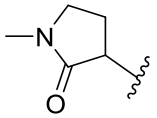
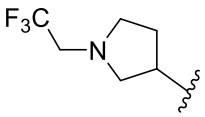
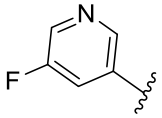


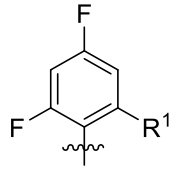
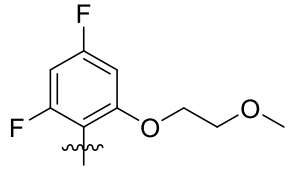
IF2'

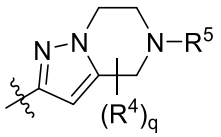
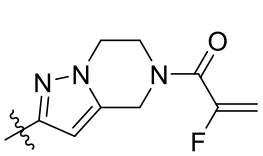
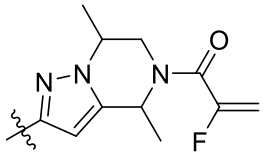
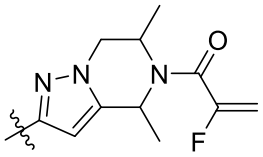
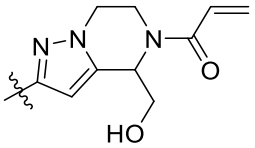
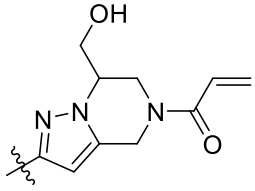
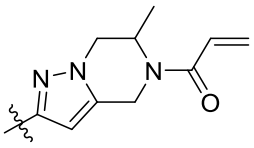
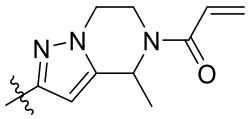
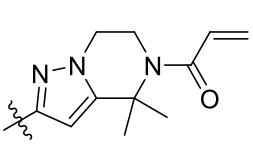
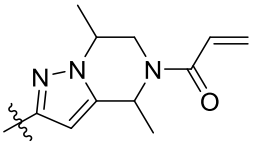
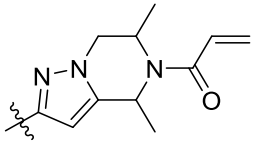
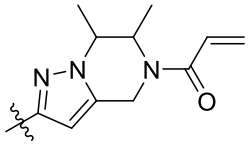
or a pharmaceutically acceptable salt thereof.

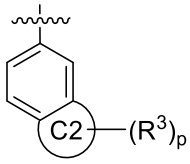
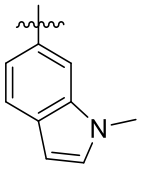
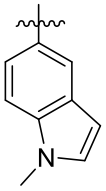
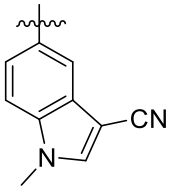
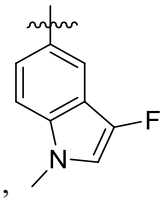
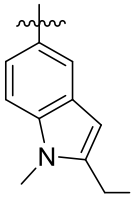
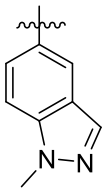
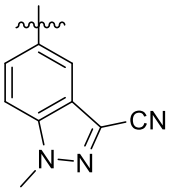
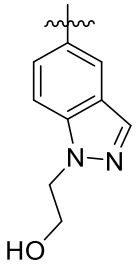
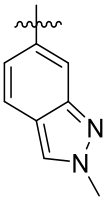
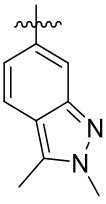
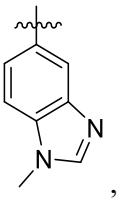
7. The compound of any one of claims 4 to 6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $-OR^7$.

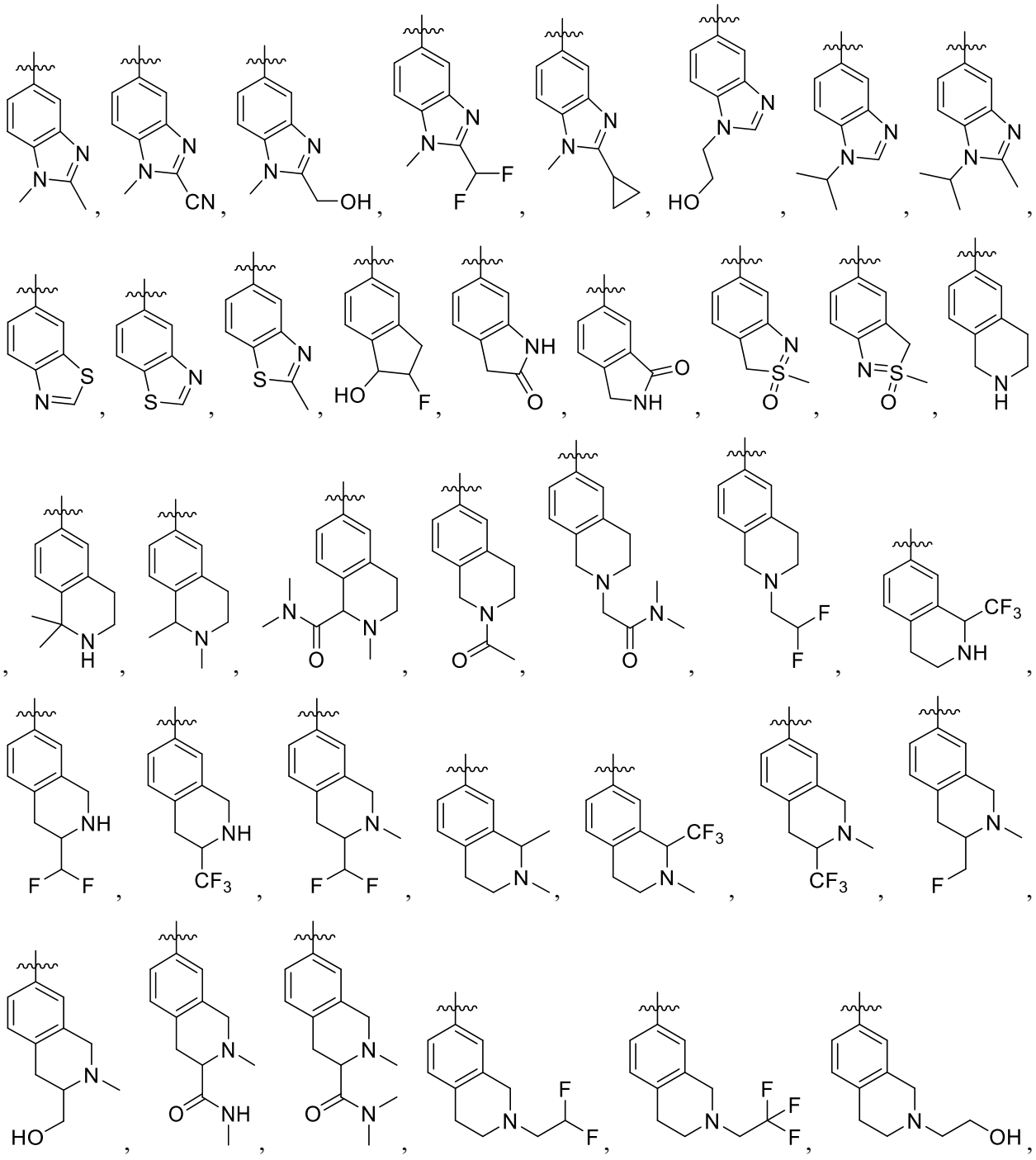
8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from the group consisting of: , , , , , , , , , , and .

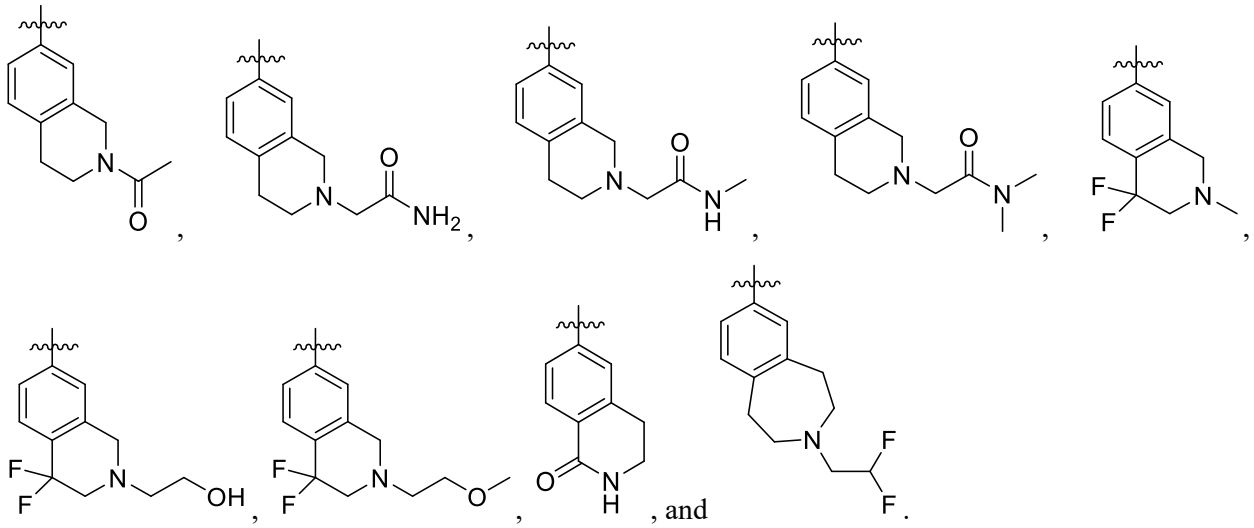
9. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from the group consisting of: , , , , , , , , , , , , , and .

10. The compound of any one of claims 4 to 6, or a pharmaceutically acceptable salt thereof, wherein a moiety  is .

11. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein  is selected from the group consisting of: , , , , , , , , , , and .

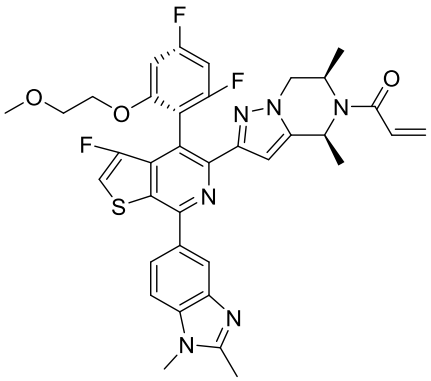
12. The compound of any one of claims 4 to 11, or a pharmaceutically acceptable salt thereof, wherein a moiety  is selected from the group consisting of: , , , , , , , , , , ,





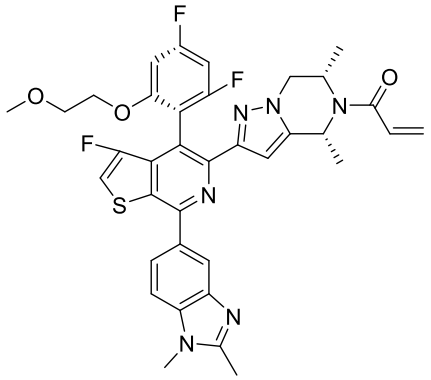
13. A compound selected from Table 1, Table 2, or Table 3, or a pharmaceutically acceptable salt thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

14. The compound of claim 13, having the structure:



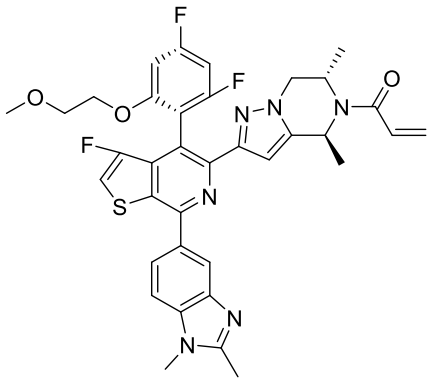
or a pharmaceutically acceptable salt thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

15. The compound of claim 13, having the structure:



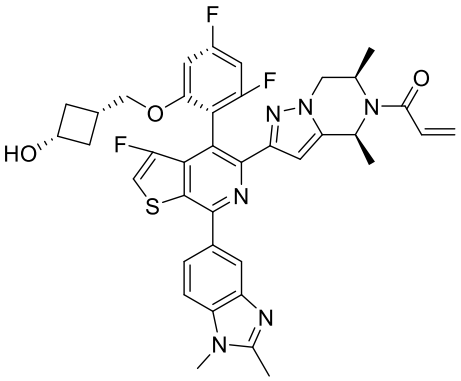
or a pharmaceutically acceptable salt thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

16. The compound of claim 13, having the structure:



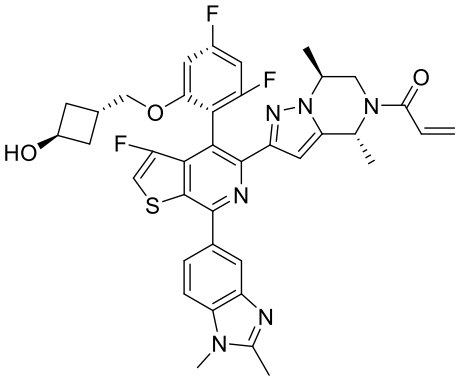
or a pharmaceutically acceptable salt thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

17. The compound of claim 13, having the structure:



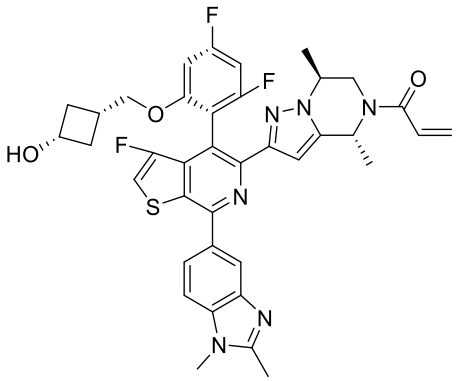
or a pharmaceutically acceptable salt thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

18. The compound of claim 13, having the structure:



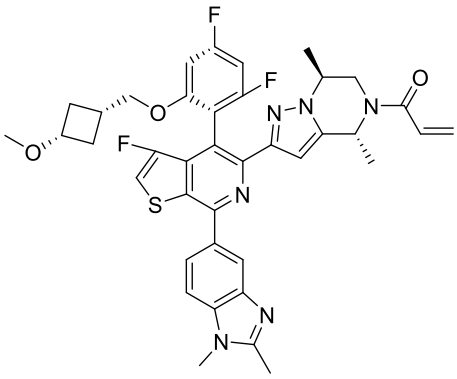
or a pharmaceutically acceptable salt thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

19. The compound of claim 13, having the structure:



or a pharmaceutically acceptable salt thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

20. The compound of claim 13, having the structure:



or a pharmaceutically acceptable salt thereof, or an atropisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

21. A pharmaceutical composition comprising a compound according to any one of claims 1-20, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

22. Use of a compound according to any one of claims 1-20 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease, disorder, or condition ameliorated by disruption, inhibition, and/or prevention of an interaction between a small GTPase and a PI3Kα protein.

23. The use of claim 22, wherein the small GTPase is Rac1, CDC42, or a RAS protein.

24. The use of claim 23, wherein the small GTPase is a RAS protein selected from the group consisting of KRAS, NRAS, HRAS, RRAS, RRAS2, MRAS, and RIT1.

25. The use of any one of claims 22-24, wherein the subject has a cancer.

26. Use of a compound according to any one of claims 1-20 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for disrupting, inhibiting, and/or preventing an interaction between a small GTPase and a PI3Kα protein.

27. Use of a compound according to any one of claims 1-20 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a cancer.

28. A compound according to any one of claim 1-20 or a pharmaceutically acceptable salt thereof for use in treating a cancer.

29. The use according to claim 25 or 27, or the compound for use according to claim 28, wherein the cancer is associated with and/or characterized by aberrant activation of PI3Kα and/or a mutation in PI3Kα.

30. The use or compound for use according to claim 29, wherein the PI3Kα protein comprises a N345K, E726K, C420R, Q546R, G118D, E453K, Q546K, G1049R, M1043I, K111E, K111N, E81K, E545A, E545G, N1044K, E110del, Q546P, E542K, E545K, H1047R, and/or H1047L mutation.

31. The use according to any one of claims 25, 27, 29, or 30, or a compound for use according to any one of claims 28-30, wherein the cancer is characterized by a mutation in a RAS protein.

32. The use or compound for use according to claim 31, wherein the RAS protein comprises a mutation in codon 12, 13, or 61.

33. The use or compound for use according to claim 31 or 32, wherein the RAS protein is KRAS.

34. The use or compound for use according to claim 33, wherein the KRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13A, G13C, G13R, G13S, G13V, Q61E, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

35. The use or compound for use according to claim 33, wherein the KRAS protein comprises a G12C or G12D mutation.

36. The use or compound for use according to claim 31 or 32, wherein the RAS protein is HRAS or NRAS.

37. The use or compound for use according to claim 36, wherein the HRAS or NRAS protein comprises a G12C, G12D, G12S, G12V, G12R, G12A, G13D, G13C, G13R, G13S, G13V, Q61K, Q61L, Q61P, Q61R, and/or Q61H mutation.

38. The use according to any one of claims 25, 27, or 29-37, or a compound for use according to any one of claims 28-37, wherein the cancer is selected from pancreatic cancer; colon cancer; rectal cancer; colorectal cancer; bowel cancer; breast cancer; ovarian cancer; endometrial cancer; lung cancer; prostate cancer; cancers of the oral cavity and pharynx (lip, tongue, mouth, larynx, pharynx), esophagus, stomach, small intestine, large intestine, liver and biliary passages, bone,

connective tissue, skin, cervix, uterus, corpus endometrium, testis, bladder, kidney and other urinary tissues, including renal cell carcinoma (RCC); cancers of the eye, brain, spinal cord, and other components of the central and peripheral nervous systems, as well as associated structures such as the meninges; cancers of the thyroid and other endocrine glands; Hodgkin's disease; non-Hodgkin's lymphomas; multiple myeloma; and hematopoietic malignancies including leukemias (Chronic Lymphocytic Leukemia (CLL), Acute Lymphocytic Leukemia (ALL), Chronic Myelogenous Leukemia (CML), Acute Myelogenous Leukemia (AML),) and lymphomas including lymphocytic, granulocytic and monocytic lymphomas.

39. The use or compound for use according to claim 38, wherein the cancer is selected from breast cancer, lung cancer (e.g., non-small cell lung cancer), endometrial cancer, esophageal cancer, ovarian cancer, colorectal cancer, gastric cancer, squamous cell carcinoma, prostate cancer, and pancreatic cancer.