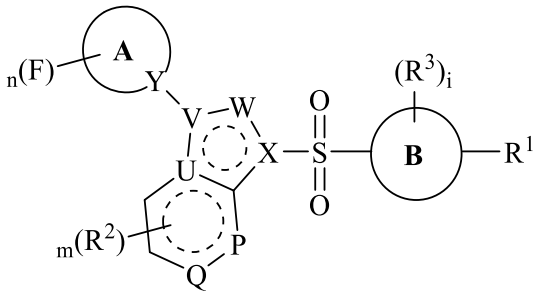
What is claimed:

CLAIMS

1. A compound having the structure of formula (**I**):



(**I**)

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

Ring A is a 4- to 9-membered carbocycle or heterocycle substituted with 1-8 F's;

Ring B is a substituted or unsubstituted phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, or thiophene, or a substituted or unsubstituted bi- or multi-cyclic carbocyclic or heterocyclic ring system;

P is CH, N or CR^2;

Q is CH, N or CR^2;

U is C or N;

V is C or N;

W is CH, N, C(=O), C(=S) or $CR^{W1}R^{W2}$, wherein each of R^{W1} and R^{W2} is independently H or $C_{1\text{-}6}$ alkyl;

X is C or N;

Y is C, CR^Y or N, wherein R^Y is H, F or $C_{1\text{-}6}$ alkyl;

R^1 is selected from the group consisting of F, CHF_2, $-CF_3$, $-CH_2CF_3$, CF_2CH_3, CF_2CH_2F, CF_2CHF_2, $-CF(CH_3)_2$, $-OCF_3$ and $-OCH(CH_3)_2$;

each R^2 is independently selected from the group consisting of halogen, unsubstituted or substituted $C_{1\text{-}6}$ alkyl and $C_{1\text{-}6}$ alkoxy, OH, CN, NRR', N(R)C(=O)RR', C(=O)R, and C(=O)NRR';

each R^3 is independently selected from the group consisting of halogen, CN, CF_3,

C_{1-5} alkyl, C_{3-7} cycloalkyl and heterocyclic;

each of R and R' is independently H, or C_{1-6} alkyl or cycloalkyl, optionally, R and R', together with the nitrogen or carbon atom to which they are attached, form a 3- to 6-membered ring, each optionally substituted with 0-3 substituents independently selected from the group consisting of C_{1-3} alkyl, halogen, OH, OC_{1-3} alkyl, and CN;

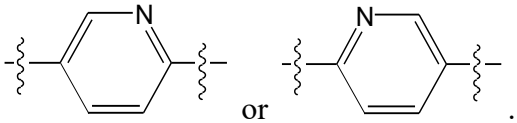
m is 0, 1, 2, 3 or 4;

n is 1, 2, 3, 4, 5, 6, 7 or 8; and

i is 0, 1 or 2.

2. The compound of claim 1, wherein Ring B is a substituted or unsubstituted phenyl.

3. The compound of claim 1, wherein Ring B is an unsubstituted pyridinyl:



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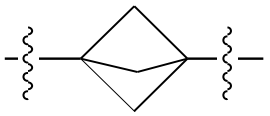
4. The compound of claim 1, wherein Ring B is a substituted or unsubstituted thiophene.

5. The compound of claim 1, wherein Ring B is a substituted or unsubstituted pyrrole.

6. The compound of claim 1, wherein Ring B is bicyclo[1.1.1]pentane:



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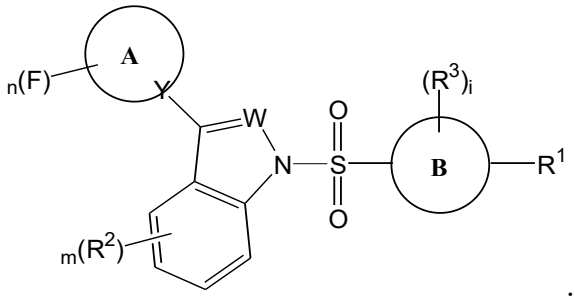
7. The compound of any one of claims 1-6, wherein X is N.

8. The compound of claim 7, wherein P is CH, Q is CH, U is C and V is C:



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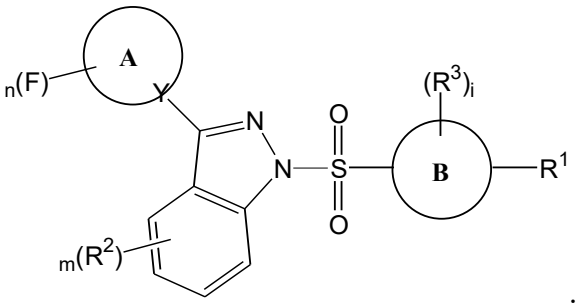
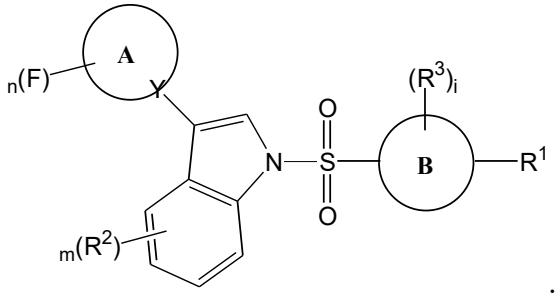
(I_a)

9. The compound of claim 8, wherein W is N:



(**Ib**)

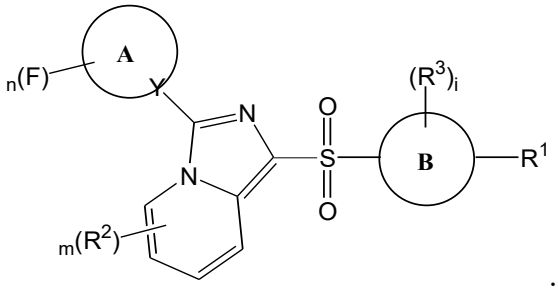
10. The compound of claim 8, wherein W is CH:



(**Ic**)

11. The compound of any one of claims 1-6, wherein X is C.

12. The compound of claim 11, wherein P is CH, Q is CH, U is N, V is C and W is N:



(**Id**)

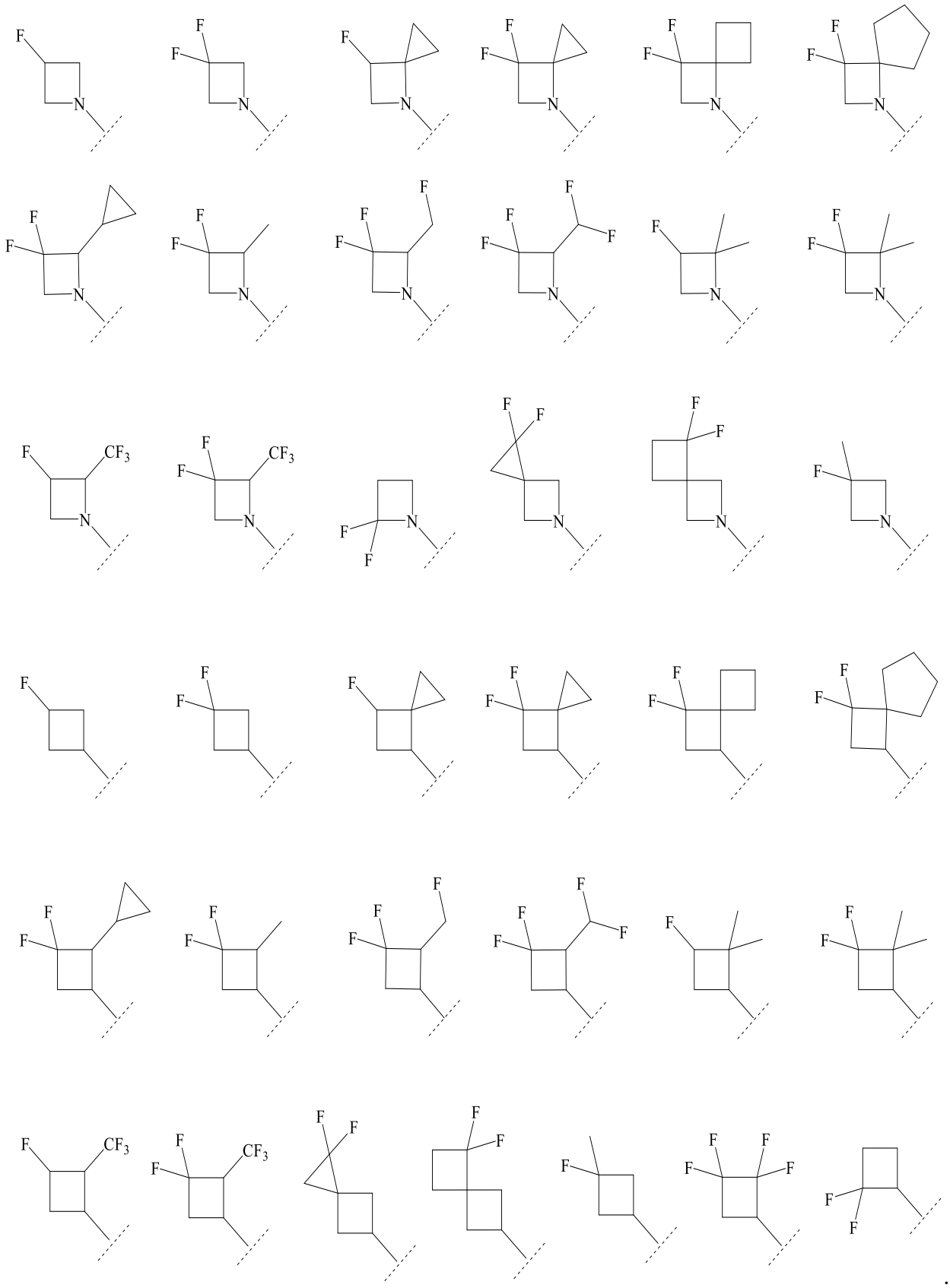
13. The compound of any one of claims 1-12, wherein Y is N.

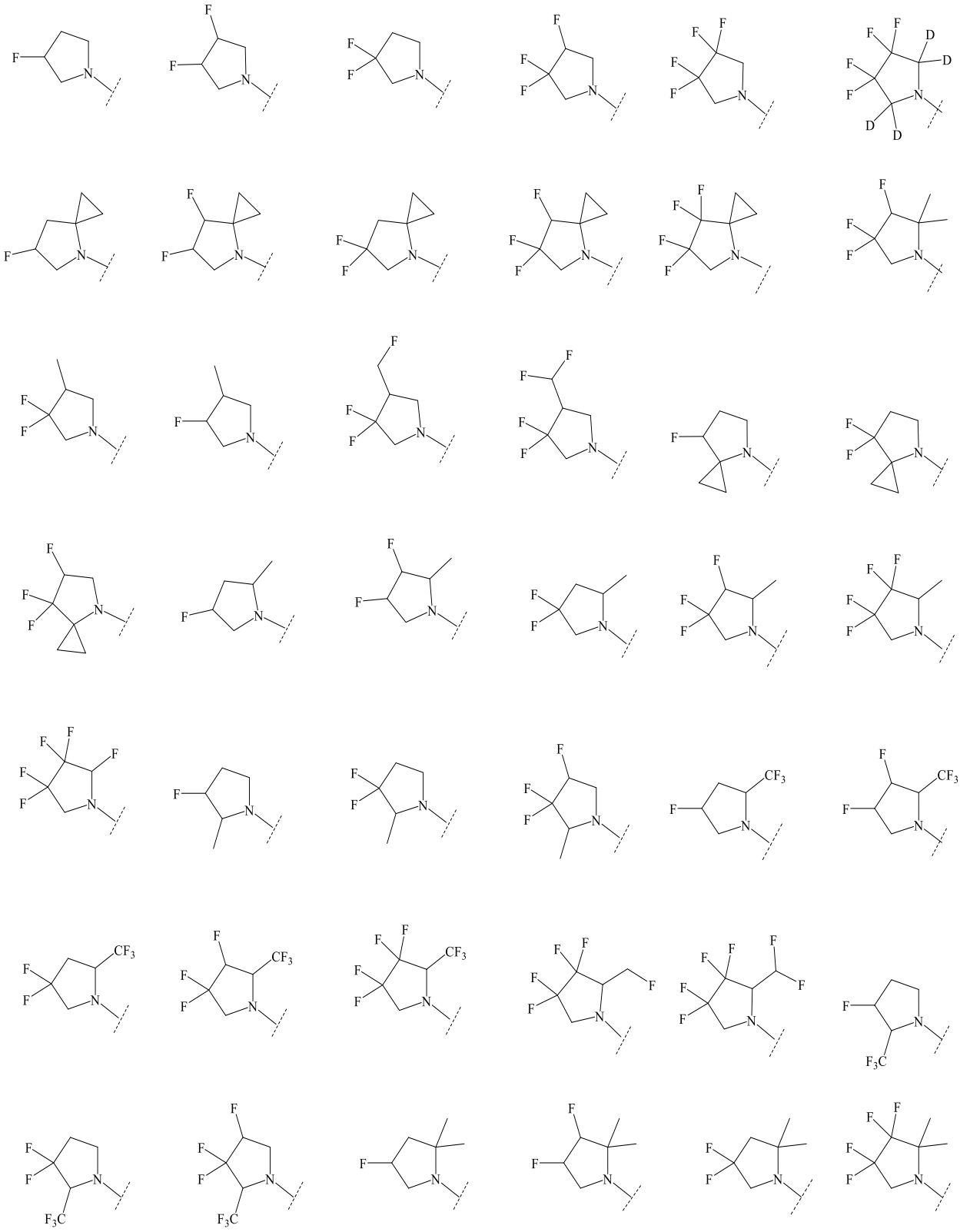
14. The compound of any one of claims 1-12, wherein Y is C or CH.

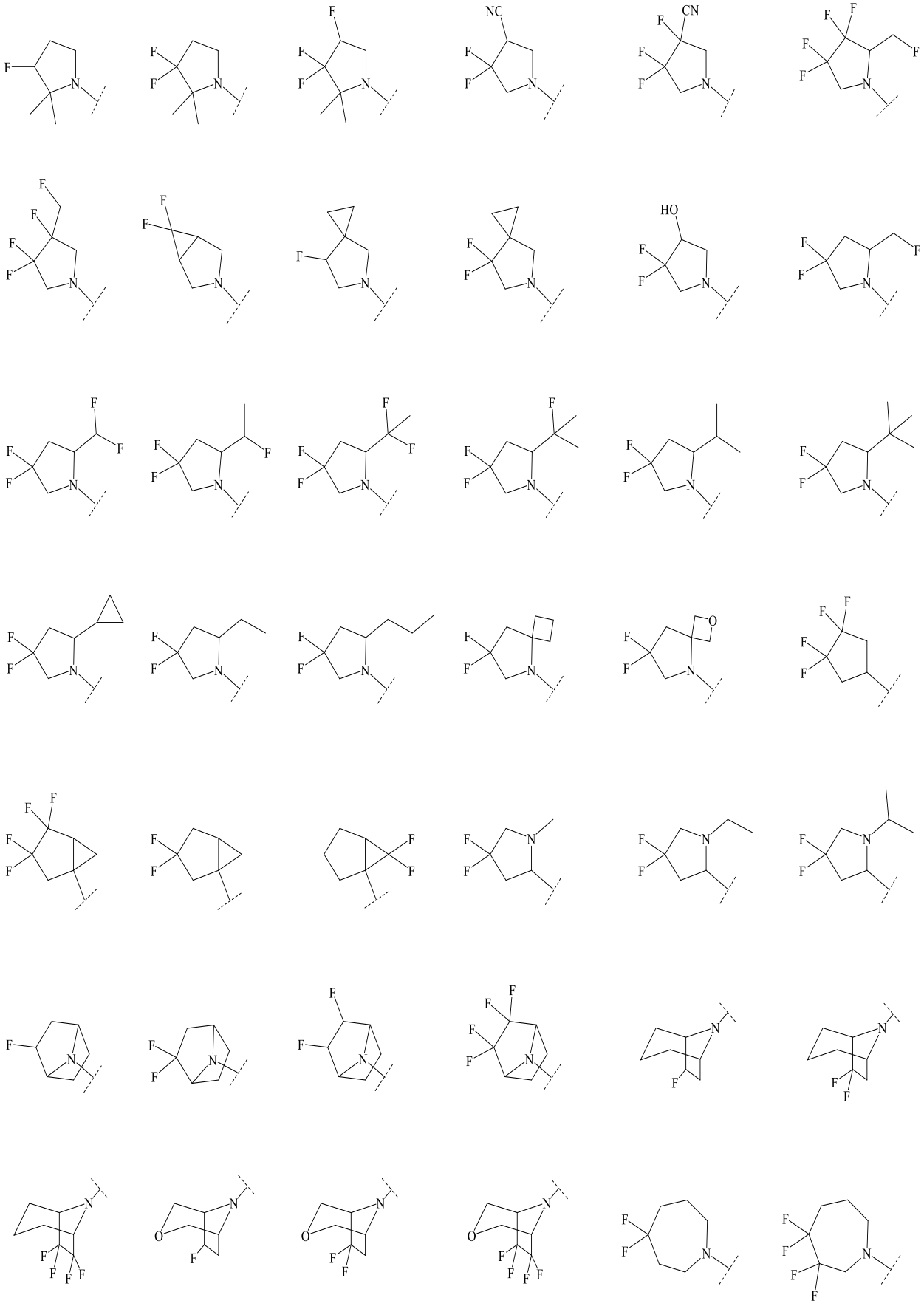
15. The compound of any one of claims 1-14, wherein Ring A is a 4-, 5- or 6-membered carbocyclic or heterocycle substituted with one or more F's.

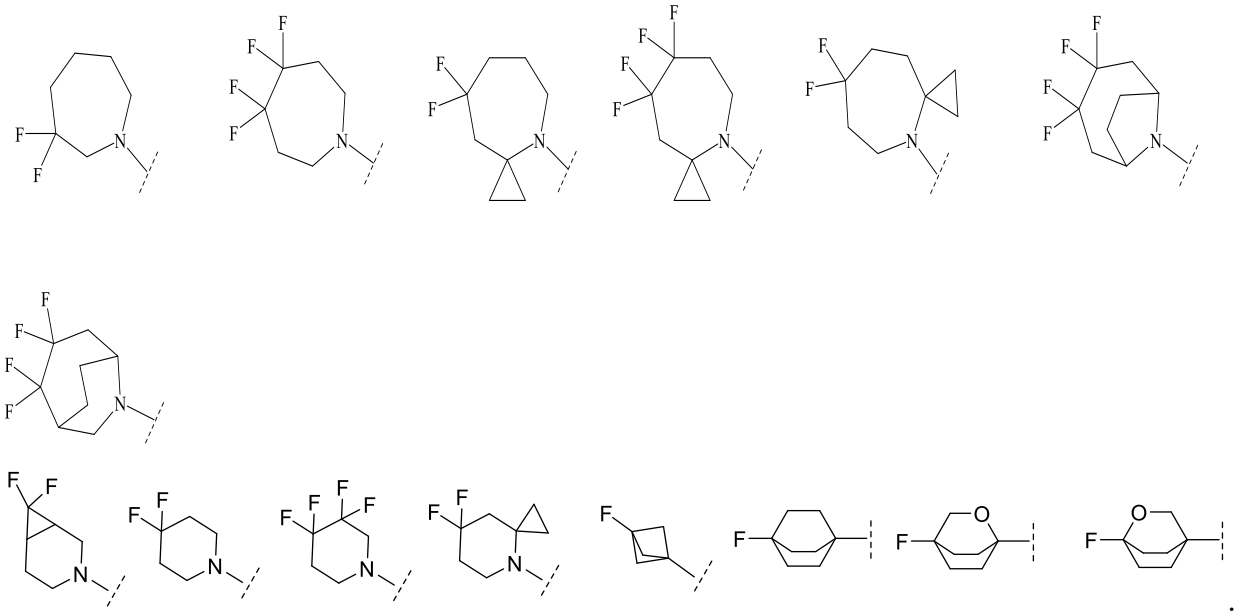
16. The compound of any one of claims 1-14, wherein Ring A is a heterobicycle substituted with one or more F's.

17. The compound of any one of claims 1-14, wherein Ring A has a structural formula selected from:

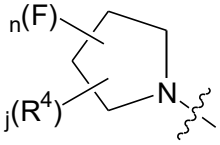








18. The compound of any one of claims 1-14, wherein Ring A is:



wherein

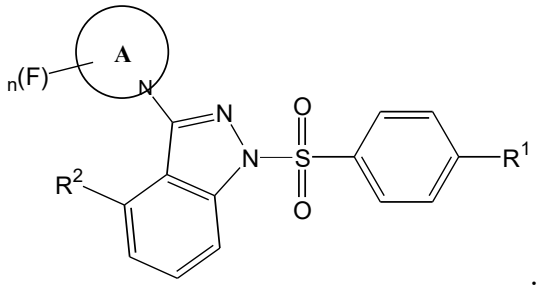
each R^4 is independently D, OH, CN, or $C_{1\text{-}2}$ alkyl optionally substituted with 0-3 F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic ring, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 7-membered carbocyclic or heterocyclic ring

n is 1, 2, 3, 4, 5 or 6; and

j is 0, 1, 2, 3 or 4.

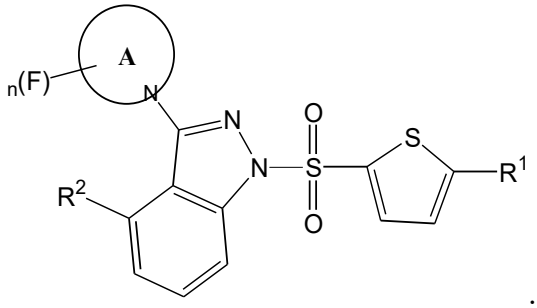
19. The compound of any one of claims 1-18, wherein R^1 is CHF_2, CF_2CH_3, CF_2CH_2F, CF_2CHF_2, or F.

20. The compound of claim 1, having the structural formula:



(**Ie**)

21. The compound of claim 1, having the structural formula:



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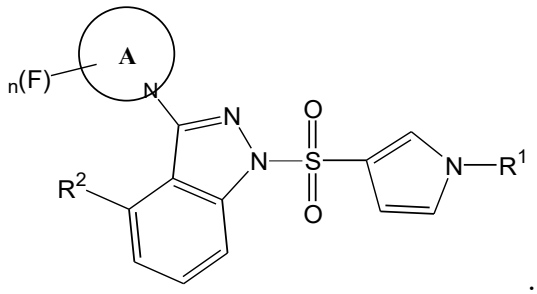
(**If**)

22. The compound of claim 1, having the structural formula:



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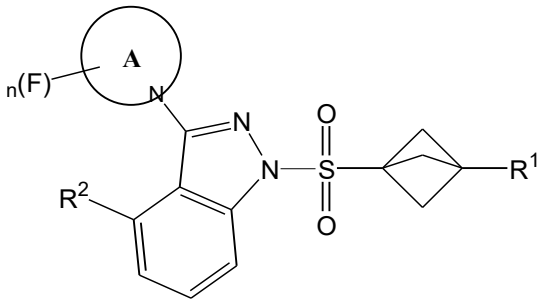
(**Ig**)

23. The compound of claim 1, having the structural formula:



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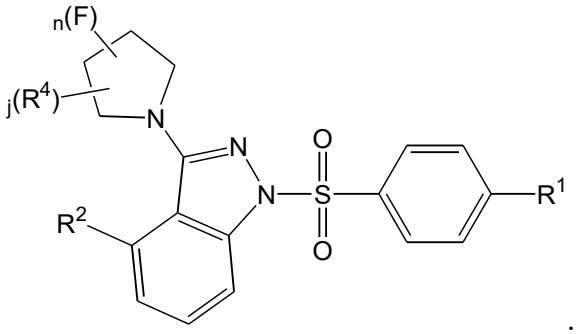
(**Ih**)

24. The compound of claim 1, having the structural formula:



(**I_m**)

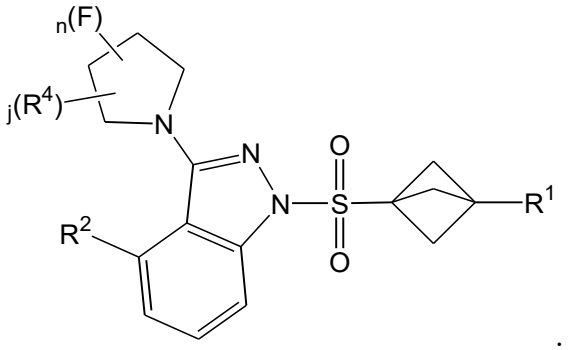
wherein

each R^4 is independently $C_{1\text{-}2}$ alkyl optionally substituted with 0-3 F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 6-membered carbocyclic or heterocyclic ring;

n is 1, 2, 3, 4, 5 or 6; and

j is 0, 1, 2, 3 or 4.

25. The compound of claim 1, having the structural formula:



(**I_n**)

wherein

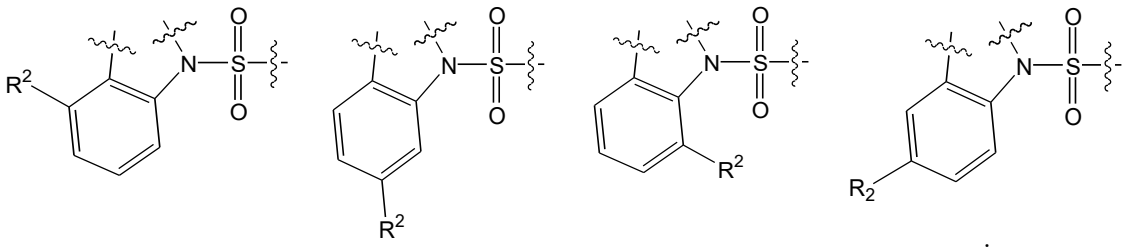
each R^4 is independently $C_{1\text{-}2}$ alkyl optionally substituted with 0-3 F's, or two R^4's along with the carbon atom they are bound to form a 3- or 4-membered carbocyclic or heterocyclic, or two R^4's along with the carbon atoms they are bound to atom for a 3- to 6-membered carbocyclic or heterocyclic ring;

n is 1, 2, 3, 4, 5 or 6; and

j is 0, 1, 2, 3 or 4.

26. The compound of any one of claims 1-25, wherein *m* is 1.

27. The compound of claim 26, wherein R^2 has a positioning selected from:



28. The compound of claim 27, wherein R^2 is a halogen.

29. A compound selected from **Table 1**.

30. The compound of any of claims 1-29, having one or more deuterium atoms in place of one or more hydrogen atoms.

31. A pharmaceutical composition comprising a compound of any of claims 1-30.

32. The compound of any one of claims 1-30 for use in treating or reducing a disease or disorder mediated by loss-of-function in TRPML1.

33. The compound for use of claim 32, wherein the disease or disorder is mucolipidosis type IV (ML4), lysosome storage disease, a neurodegenerative disease, a neuronal ceroid lipofuscinoses (NCLs) or Batten disease, Niemann–Pick type C (NPC), Charcot-Marie-Tooth disease (CMT), age-related macular degeneration (AMD), cystic fibrosis (CF), autosomal dominant polycystic kidney disease (ADPKD), cancers in which TRPML1 is overexpressed in cancer cells, muscular dystrophy, oxidative stress or reactive oxygen species (ROS), the effect of aging, or a related disease or disorder.

34. The compound for use claim 32, wherein the disease or disorder is Alzheimer's disease, Parkinson's disease, and Huntington's disease, amyotrophic lateral sclerosis (ALS) or frontotemporal dementia, or a related disease or disorder.

35. Use of a compound of any of claims 1-30, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.