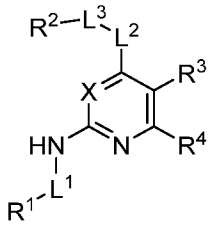
WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

L^1 is an optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 4-8-membered heterocyclylene, or optionally substituted C_{3-8} carbocyclylene;

R^1 is SO_2R^{10}, $SO_2NR^{11}R^{12}$, $S(O)(NH)R^{10}$, or $C(O)NR^{11}R^{12}$;

X is N or CR^{13};

L^2 is a bond, $-N(R^{14})-$, or -O-;

L^3 is a bond, an optionally substituted C_{1-4} alkylene or an optionally substituted C_{1-4} heteroalkylene;

R^2 is hydrogen, an optionally substituted C_{3-8} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-10 membered heteroaryl;

R^3 is hydrogen, halogen (e.g., F), CN, $C(O)NR^{11}R^{12}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} heteroalkyl, OR^A, COR^B, $COOR^A$, $NR^{11}R^{12}$, optionally substituted C_{3-8} carbocyclyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5-10 membered heteroaryl;

R^4 is hydrogen, halogen (e.g., F), optionally substituted C_{1-6} alkyl, or $NR^{11}R^{12}$;

or L^2 and R^3, together with the intervening atoms, form an optionally substituted 4-8 membered ring structure; or R^3 and R^4, together with the intervening atoms, form an optionally substituted 4-8 membered ring structure;

wherein:

R^{10} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), or optionally substituted 4-10 membered heterocyclyl;

each of R^{11} and R^{12}, at each occurrence, is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), optionally substituted 4-10 membered heterocyclyl; or a nitrogen protecting group; or R^{11} and R^{12} can be joined to form an optionally substituted 4-10 membered heterocyclyl or 5- or 6-membered heteroaryl;

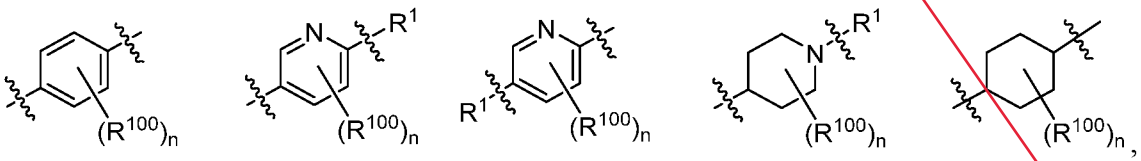
R^A is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), optionally substituted 4-10 membered heterocyclyl; or an oxygen protecting group;

R^B is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl);

R^{13} is hydrogen, F, CN, -OH, an optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} heteroalkyl, optionally substituted C_{3-8} carbocyclyl, or optionally substituted 4-10 membered heterocyclyl; and

R^{14} is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), optionally substituted 4-10 membered heterocyclyl; or a nitrogen protecting group.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^1 is selected from:



wherein:

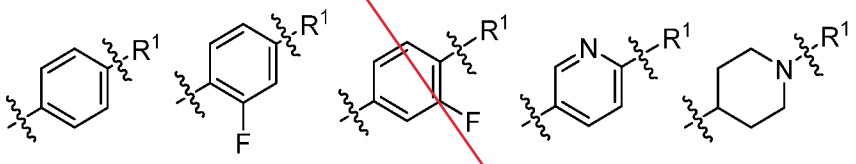
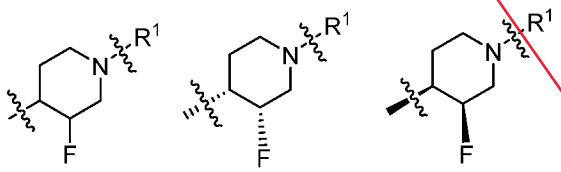
n is 0, 1, 2, 3, or 4, as valency permits; and

R^{100} at each occurrence is independently selected from halogen (e.g., F or Cl), CN, OH, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} alkoxy, and optionally substituted C_{1-4} heteroalkyl.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein n is 0.

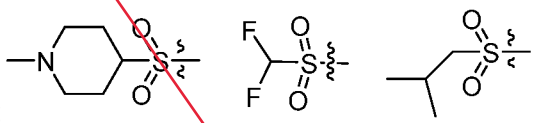
4. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, and R^{100} at each occurrence is independently selected from F, Cl, CN, OH, C_{1-4} alkyl optionally substituted with F, C_{1-4} alkoxy optionally substituted with F, and C_{1-4} heteroalkyl optionally substituted with F.

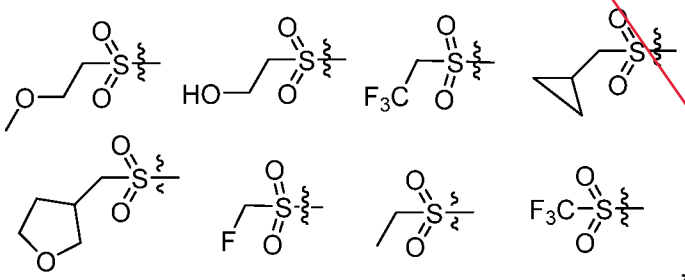
5. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein n is 1, and R^{100} is F, Cl, CN, OH, methyl, fluorine-substituted methyl such as CF_3, methoxy, or fluorine-substituted methoxy.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^1 is selected from:  or L^1 is selected from: .

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is SO_2R^{10}, wherein R^{10} is an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted 4-8 membered heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S, or R^{10} is an optionally substituted 5 or 6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, O, and S.

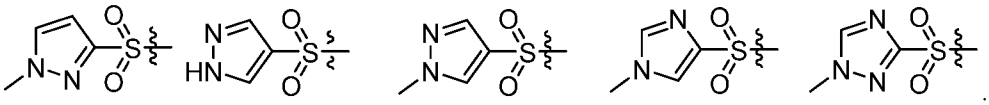
8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is SO_2R^{10}, wherein R^{10} is C_{1-4} alkyl, (C_{1-4} alkylene)$_j$-C_{3-6} cycloalkyl, (C_{1-4} alkylene)$_j$-4-8 membered monocyclic heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S, or (C_{1-4} alkylene)$_j$-(5 or 6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, O, and S),
wherein j is 0 or 1, and the C_{1-4} alkylene is straight or branched alkyelene chain optionally substituted with F; and
wherein each of the C_{1-4} alkyl, C_{3-6} cycloalkyl, 5 or 6 membered heteroaryl and 4-8 membered monocyclic heterocyclyl is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, halo (e.g., F), G^1, OH, O-G^1, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or R^{10} is an optionally substituted 5 or 6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, O, and S.

9. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is SO_2Me or selected from: , or R^1 is selected from



,

or R^1 is selected from



10. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $S(O)(NH)R^{10}$, wherein R^{10} is an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted 4-8 membered heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S.

11. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $S(O)(NH)R^{10}$, wherein R^{10} is C_{1-4} alkyl, $(C_{1-4}$ alkylene$)_j$-C_{3-6} cycloalkyl, $(C_{1-4}$ alkylene$)_j$-4-8 membered monocyclic heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S, or R^{10} is $(C_{1-4}$ alkylene$)_j$-(5 or 6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, O, and S), wherein j is 0 or 1, and the C_{1-4} alkylene is straight or branched alkyelene chain optionally substituted with F; and
wherein each of the C_{1-4} alkyl, C_{3-6} cycloalkyl, 5 or 6 membered heteroaryl and 4-8 membered monocyclic heterocyclyl is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, F, G^1, OH, O-G^1, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl.

12. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is S(O)(NH)Me.

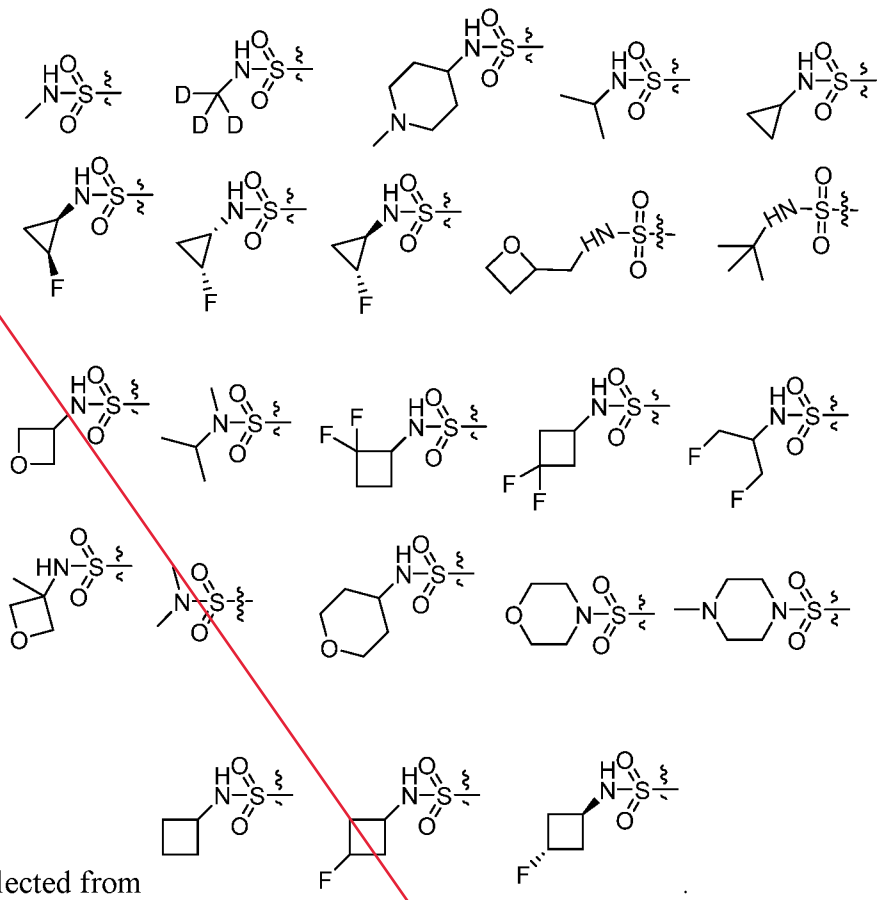
13. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are independently hydrogen, an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted 4-8 membered heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S.

14. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are independently hydrogen, C_{1-4} alkyl, (C_{1-4} alkylene)$_j$-C_{3-6} cycloalkyl, (C_{1-4} alkylene)$_j$-4-8 membered monocyclic heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S, wherein j is 0 or 1, and the C_{1-4} alkylene is straight or branched alkyelene chain optionally substituted with F; and
wherein each of the C_{1-4} alkyl, C_{3-6} cycloalkyl, and 4-8 membered monocyclic heterocyclyl is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, deuterium, F, G^1, OH, O-G^1, NH_2, NH(G^1), and N(G^1)(G^1), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

15. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are joined to form an optionally substituted 4-8 membered heterocyclyl having, in addition to the nitrogen atom both R^{11} and R^{12} are attached to, 0 or 1 ring heteroatom selected from N, O, and S.

16. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are joined to form a 4-8 membered monocyclic heterocyclyl having, in addition to the nitrogen atom both R^{11} and R^{12} are attached to, 0 or 1 ring heteroatom selected from N, O, and S, which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, deuterium, F, G^1, OH, O-G^1, NH_2, NH(G^1), and N(G^1)(G^1), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

17. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is SO_2NH_2 or R^1 is selected from:



or R^1 is selected from .

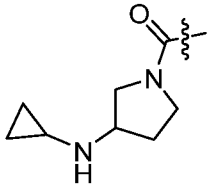
18. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $C(O)NR^{11}R^{12}$, wherein R^{11} and R^{12} are independently hydrogen, an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted 4-8 membered heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S.

19. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $C(O)NR^{11}R^{12}$, wherein R^{11} and R^{12} are independently hydrogen, C_{1-4} alkyl, (C_{1-4} alkylene)$_j$-C_{3-6} cycloalkyl, (C_{1-4} alkylene)$_j$-4-8 membered monocyclic heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S, wherein j is 0 or 1, and the C_{1-4} alkylene is straight or branched alkyelene chain optionally substituted with F; and
wherein each of the C_{1-4} alkyl, C_{3-6} cycloalkyl, and 4-8 membered monocyclic heterocyclyl is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, deuterium, F, G^1, OH, O-G^1, NH_2, $NH(G^1)$, and

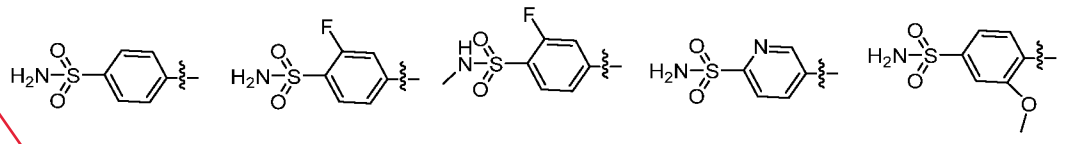
$N(G^1)(G^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

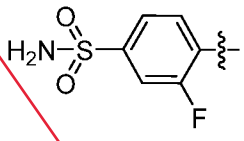
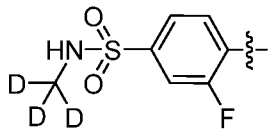
20. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $C(O)NR^{11}R^{12}$, wherein R^{11} and R^{12} are joined to form an optionally substituted 4-8 membered heterocyclyl having, in addition to the nitrogen atom both R^{11} and R^{12} are attached to, 0 or 1 ring heteroatom selected from N, O, and S.

21. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is $C(O)NR^{11}R^{12}$, wherein R^{11} and R^{12} are joined to form a 4-8 membered monocyclic heterocyclyl having, in addition to the nitrogen atom both R^{11} and R^{12} are attached to, 0 or 1 ring heteroatom selected from N, O, and S, which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, deuterium, F, G^1, OH, O-G^1, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

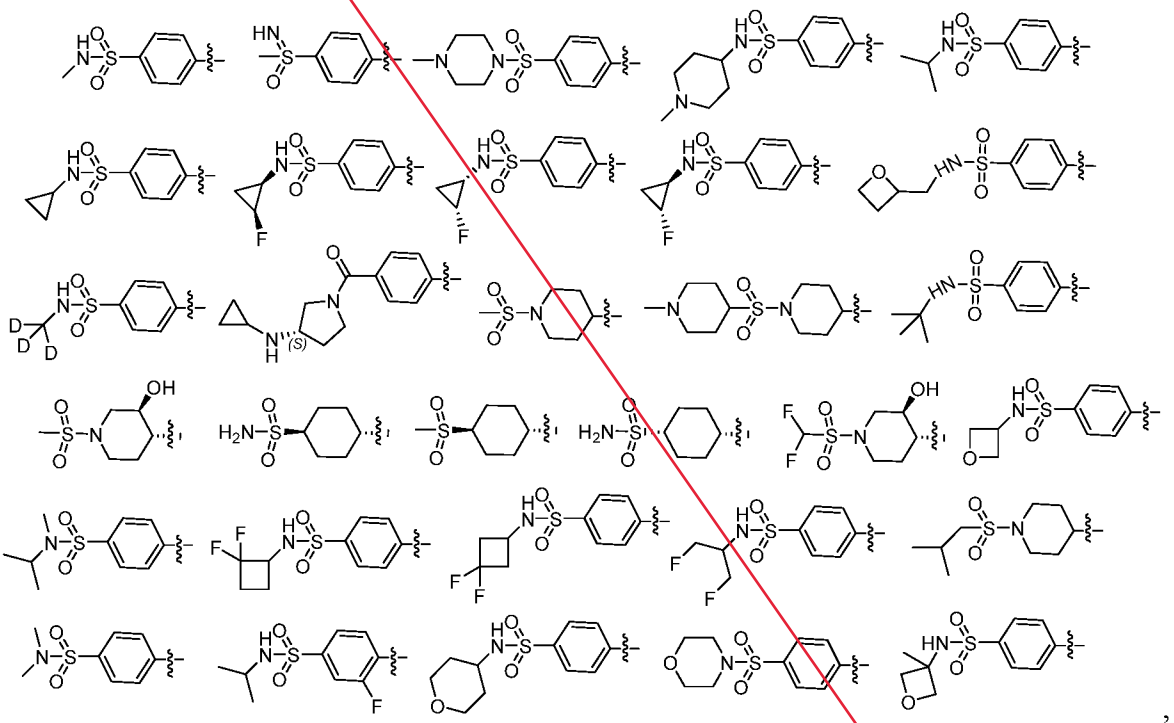
22. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is C(O)NHMe or .

23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^1-R^1 in Formula I is selected from:

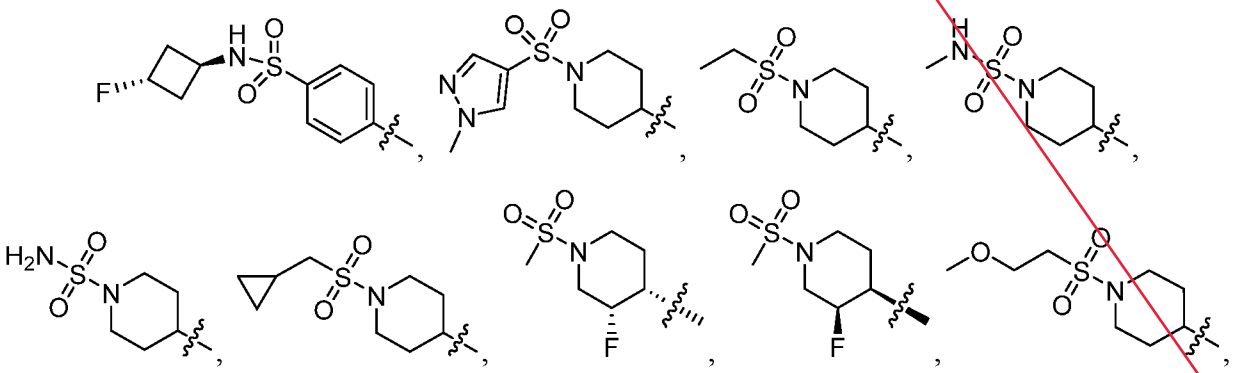


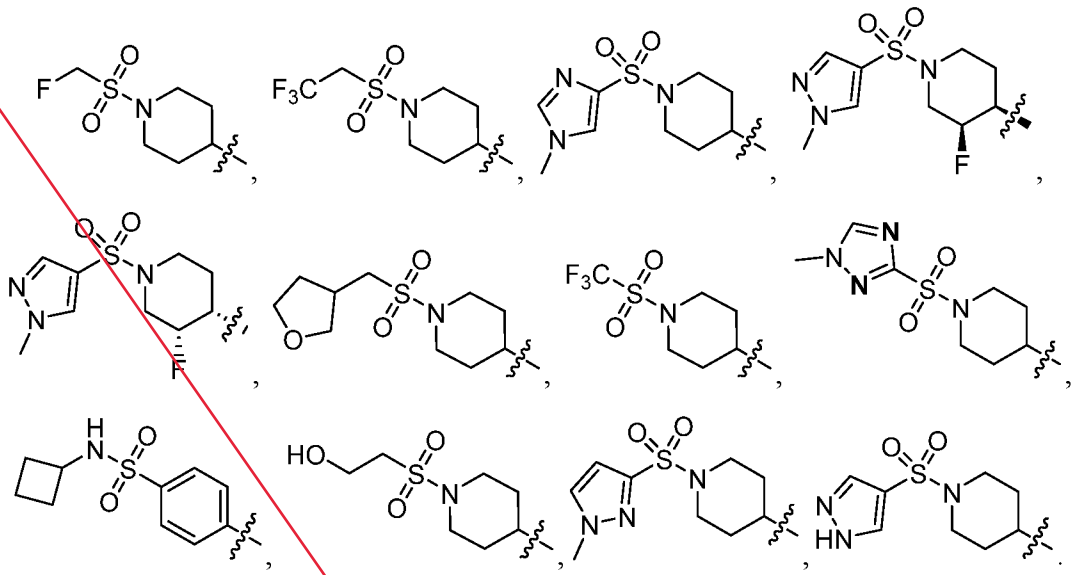
or L^1-R^1 is  or .

24. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^1-R^1 in Formula I is selected from:



or L^1-R^1 in Formula I is selected from:



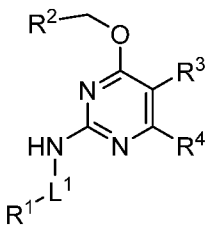


25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein X is N.

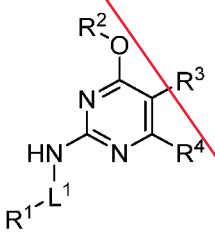
26. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein X is CH.

27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein L^2 is -O- and L^3 is a bond or a C_{1-4} alkylene (e.g., CH_2) optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, OH, and protected OH.

28. The compound of claim 27, or a pharmaceutically acceptable salt thereof, characterized as having Formula I-1 or I-2:



Formula I-1

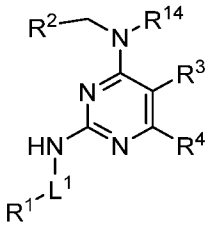


Formula I-2

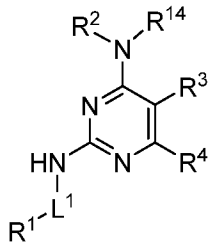
29. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein L^2 is $–N(R^{14})-$ and L^3 is a bond or a C_{1-4} alkylene optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, OH, and protected OH.

30. The compound of any one of claims 1-26 and 29, or a pharmaceutically acceptable salt thereof, wherein L^2 is $–N(R^{14})-$, wherein R^{14} is hydrogen or a C_{1-4} alkyl optionally substituted with oxo, F, CN, G^1, OH, O-G^1, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl.

31. The compound of claim 29 or 30, or a pharmaceutically acceptable salt thereof, characterized as having Formula I-3 or I-4:



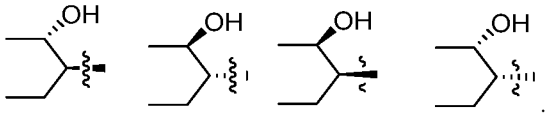
Formula I-3



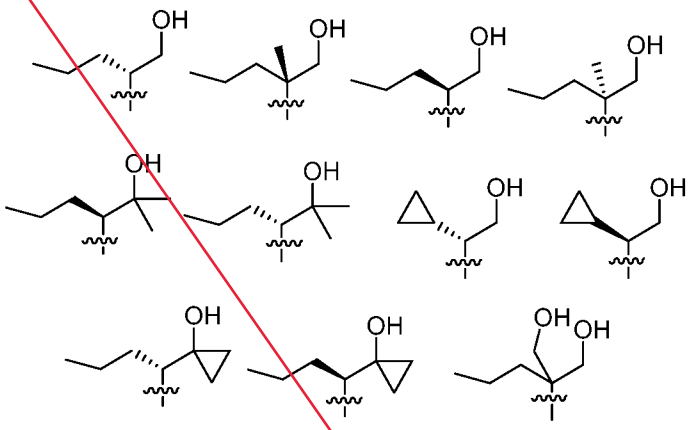
Formula I-4

32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is a C_{3-8} alkyl substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, F, G^1, CN, OH, O-G^1, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, wherein two optional substituents of the C_{3-8} alkyl, together with the intervening atom(s), can optionally be joined to form a ring structure.

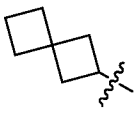
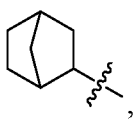
33. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



34. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:

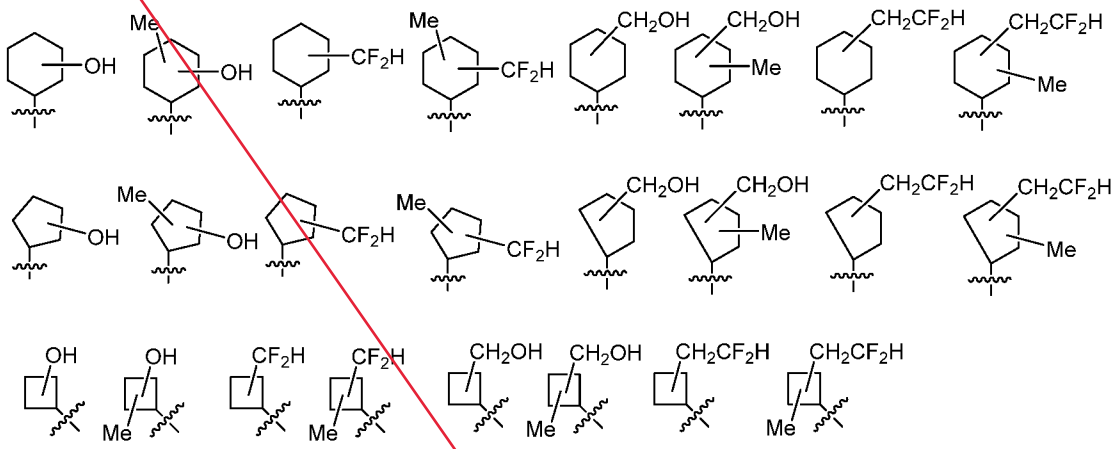


35. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is a C_{3-8} cycloalkyl optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, CN, G^1, OH, COOH, C(O)-G^1, O-G^1, C(O)-O-G^1, NH_2, NH(G^1), N(G^1)(G^1), C(O)-NH_2, C(O)-NH(G^1), C(O)-N(G^1)(G^1), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl.

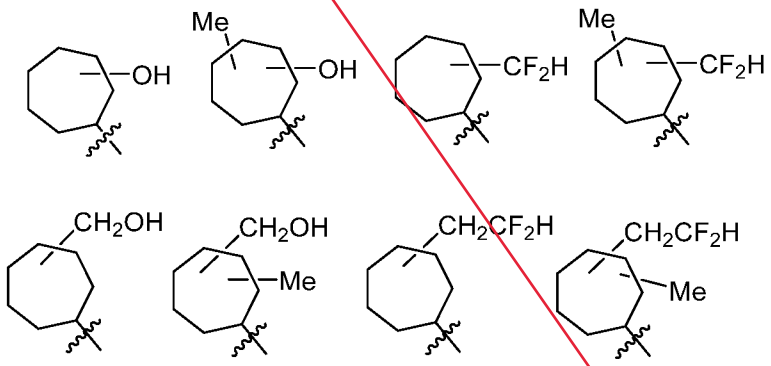
36. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is a C_{3-6} cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or a spiro, fused, or bridged C_{6-8} cycloalkyl, such as  or , wherein the cycloalkyl is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, methyl, ethyl, hydroxyethyl (e.g., -CH_2CH_2OH or -

$CH(OH)CH_3$), $-C(O)CH_3$, OH, $-CH_2OH$, fluorine substituted methyl (e.g., $-CF_2H$), and fluorine substituted ethyl (e.g., $-CH_2CF_2H$).

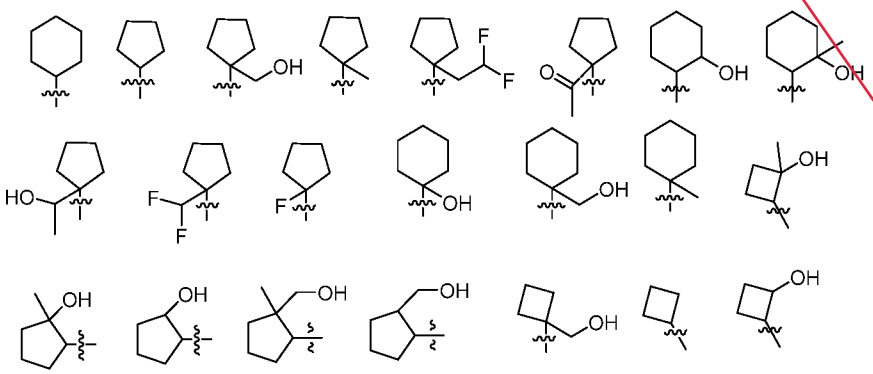
37. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



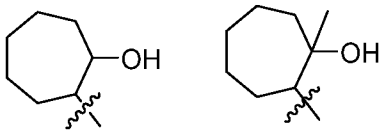
or R^2 is selected from:



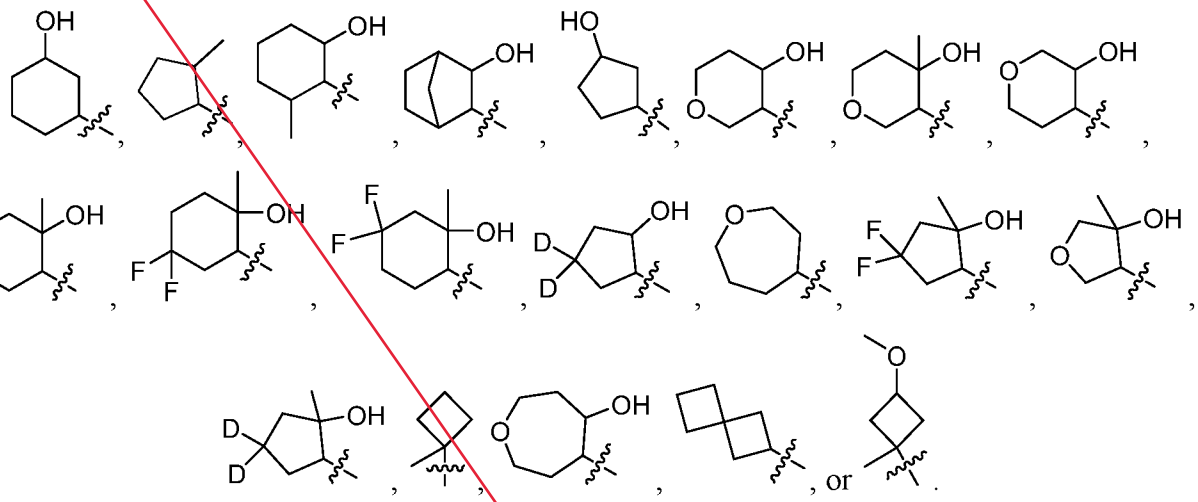
38. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



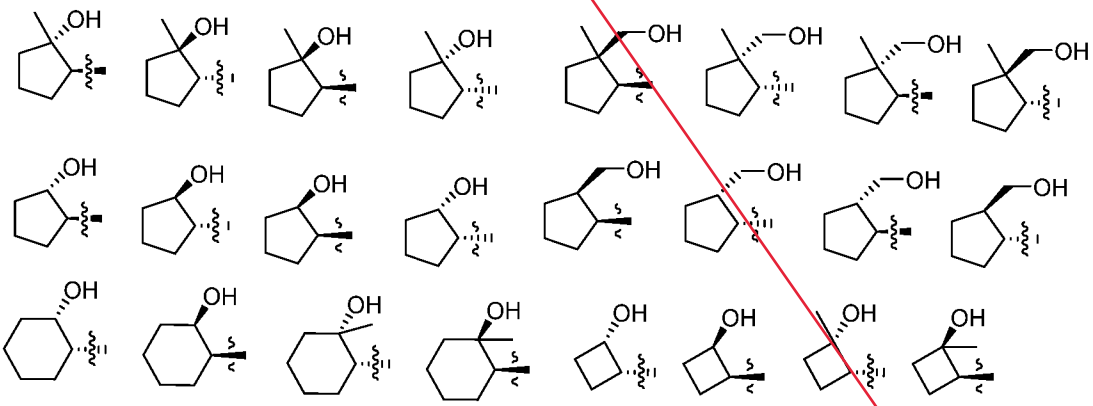
or R^2 is selected from:



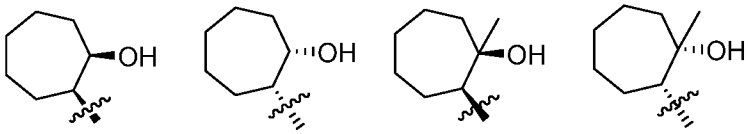
or R^2 is selected from:



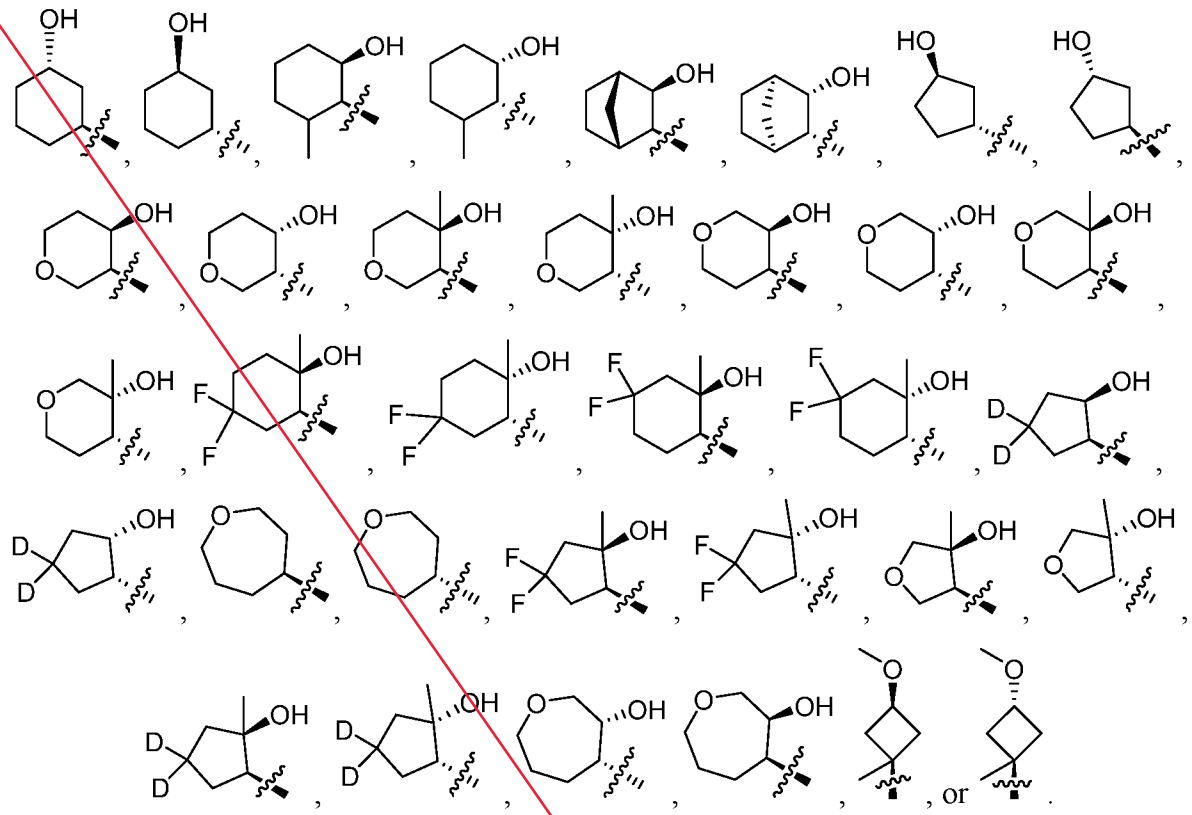
39. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



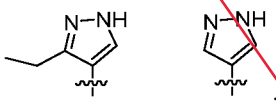
or R^2 is selected from:



or R^2 is selected from:



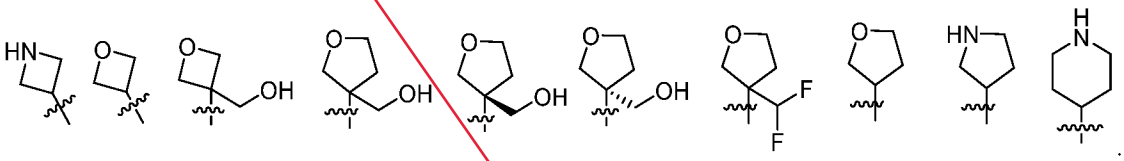
40. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



41. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4-8 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, F, CN, G^1, OH, COOH, C(O)-G^1, O-G^1, C(O)-O-G^1, NH_2, NH(G^1), N(G^1)(G^1), C(O)-NH_2, C(O)-NH(G^1), C(O)-N(G^1)(G^1), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl.

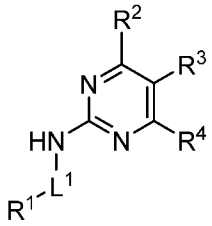
42. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4-6 or 7 membered monocyclic heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, such as oxetane, azetidine, tetrahydrofuran, tetrahydropyran, oxepane, pyrrolidine, piperidine, etc., which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, F, methyl, ethyl, hydroxyethyl (e.g., $-CH_2CH_2OH$ or $-CH(OH)CH_3$), $-C(O)CH_3$, OH, $-CH_2OH$, fluorine substituted methyl (e.g., $-CF_2H$), and fluorine substituted ethyl (e.g., $-CH_2CF_2H$).

43. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



44. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein L^2 and L^3 are both a bond.

45. The compound of claim 44, or a pharmaceutically acceptable salt thereof, characterized as having Formula I-5:



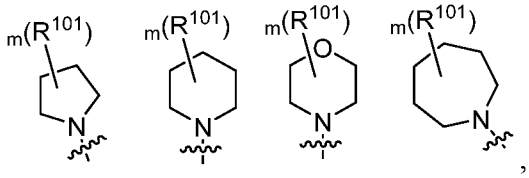
I-5.

46. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4-10 membered heterocyclyl having 1-4 ring heteroatoms independently selected from N, O, and S, which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, F, CN, G^1, OH, COOH, C(O)-G^1, O-G^1, C(O)-O-G^1, NH_2, NH(G^1), N(G^1)(G^1), C(O)-NH_2, C(O)-NH(G^1), C(O)-N(G^1)(G^1), G^2, O-

G^2, $NH(G^2)$, $N(G^1)(G^2)$, $C(O)$-$NH(G^2)$, and $C(O)$-$N(G^1)(G^2)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G^2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), F, CN, G^1, OH, O-G^1, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$; and wherein two optional substituents of the 4-10 membered heterocyclyl, together with the intervening atom(s), can optionally be joined to form a fused, bridged, or spiro ring structure.

47. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 4-8 membered monocyclic, saturated or partially unsaturated, heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, such as pyrrolidine, piperidine, azepane, etc., which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from oxo, F, CN, G^1, OH, COOH, C(O)-G^1, O-G^1, C(O)-O-G^1, NH_2, $NH(G^1)$, $N(G^1)(G^1)$, C(O)-NH_2, C(O)-$NH(G^1)$, C(O)-$N(G^1)(G^1)$, G^2, O-G^2, $NH(G^2)$, $N(G^1)(G^2)$, C(O)-$NH(G^2)$, and C(O)-$N(G^1)(G^2)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G^2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), F, CN, G^1, OH, O-G^1, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$; and wherein two optional substituents of the 4-8 membered heterocyclyl, together with the intervening atom(s), can optionally be joined to form a fused, bridged, or spiro ring structure.

48. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



wherein:

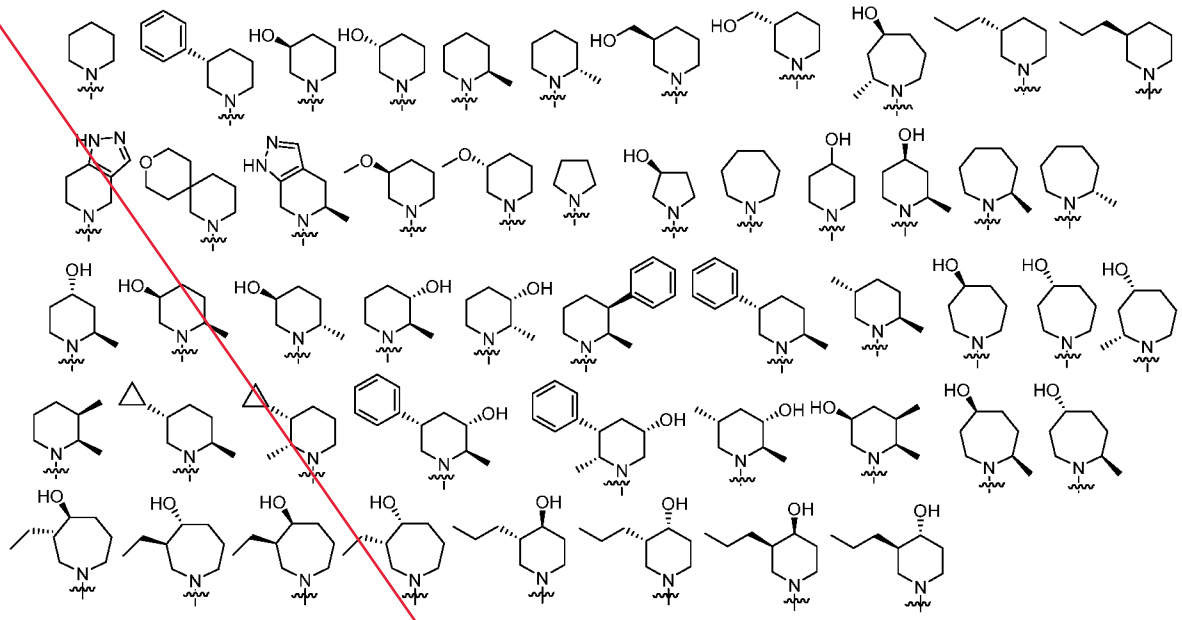
m is 0, 1, 2, 3, or 4;

R^{101} at each occurrence is independently oxo, F, CN, G^1, G^2, OH, O-G^1, and O-G^2, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G^2 at each occurrence is independently 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, each of which is optionally substituted with 1-3 substituents independently selected from F, CN, G^1, OH, and O-G^1; wherein two R^{101}, together with the intervening atom(s), can optionally be joined to form a fused, bridged, or spiro ring structure.

49. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein R^{101} at each occurrence is independently F, OH, CN, C_{1-4} alkyl (e.g., methyl, ethyl, propyl, etc.) phenyl, cyclopropyl, hydroxymethyl (-CH_2OH), methoxy, fluorine substituted methoxy, fluorine substituted C_{1-4} alkyl, such as fluorine substituted methyl such as CF_2H, or fluorine substituted ethyl (e.g., CH_2CF_2H).

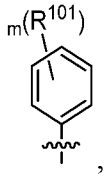
50. The compound of claim 48 or 49, or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, or 3.

51. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



52. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is a phenyl optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, CN, G^1, OH, COOH, C(O)-G^1, O-G^1, C(O)-O-G^1, NH_2, NH(G^1), N(G^1)(G^1), C(O)-NH_2, C(O)-NH(G^1), C(O)-N(G^1)(G^1), G^2, O-G^2, NH(G^2), N(G^1)(G^2), C(O)-NH(G^2), and C(O)-N(G^1)(G^2), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G^2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), F, CN, G^1, OH, O-G^1, NH_2, NH(G^1), and N(G^1)(G^1); wherein two optional substituents of the phenyl group, together with the intervening atom(s), can optionally be joined to form a fused ring structure.

53. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is:



wherein:

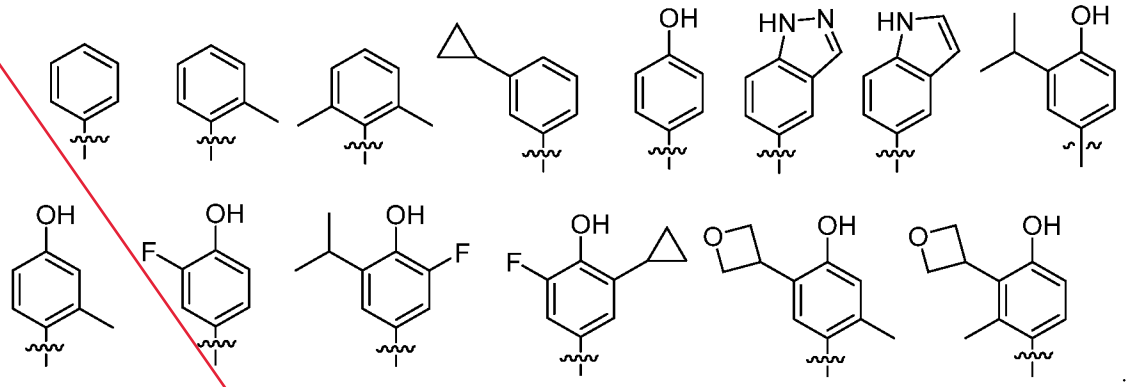
m is 0, 1, 2, or 3;

R^{101} at each occurrence is independently F, CN, G^1, G^2, OH, O-G^1, O-G^2, NH_2, NH(G^1), NH(G^2), N(G^1)(G^1), and N(G^1)(G^2), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, OH, and C_{1-4} heteroalkyl or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, OH, and C_{1-4} heteroalkyl; wherein G^2 at each occurrence is independently 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, each of which is optionally substituted with 1-3 substituents independently selected from F, CN, G^1, OH, and O-G^1; wherein two R^{101}, together with the intervening atom(s), can optionally be joined to form a fused ring structure.

54. The compound of claim 53, or a pharmaceutically acceptable salt thereof, wherein m is 1, 2, or 3.

55. The compound of claim 53 or 54, or a pharmaceutically acceptable salt thereof, wherein R^{101} at each occurrence is independently F, C_{1-4} alkyl (e.g., methyl, ethyl, n-propyl, etc.), OH, cyclopropyl, cyclobutyl, oxetanyl, or CN.

56. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



57. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 5-10 membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, CN, G^1, OH, COOH, C(O)-G^1, O-G^1, C(O)-O-G^1, NH_2, NH(G^1), N(G^1)(G^1), C(O)-NH_2, C(O)-NH(G^1), C(O)-N(G^1)(G^1), G^2, O-G^2, NH(G^2), N(G^1)(G^2), C(O)-NH(G^2), and C(O)-N(G^1)(G^2), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G^2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), F, CN, G^1, OH, O-G^1, NH_2, NH(G^1), and N(G^1)(G^1); and wherein two optional substituents of the heteroaryl group, together with the intervening atom(s), can optionally be joined to form a fused ring structure.

58. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 5- or 6-membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, such as pyridyl (e.g., 2-, 3-, or 4-pyridyl), which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, CN, G^1, OH, COOH, C(O)-G^1, O-G^1, C(O)-O-G^1, NH_2, NH(G^1), N(G^1)(G^1), C(O)-NH_2, C(O)-NH(G^1), C(O)-N(G^1)(G^1), G^2, O-G^2, NH(G^2), N(G^1)(G^2), C(O)-NH(G^2), and C(O)-N(G^1)(G^2), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4}

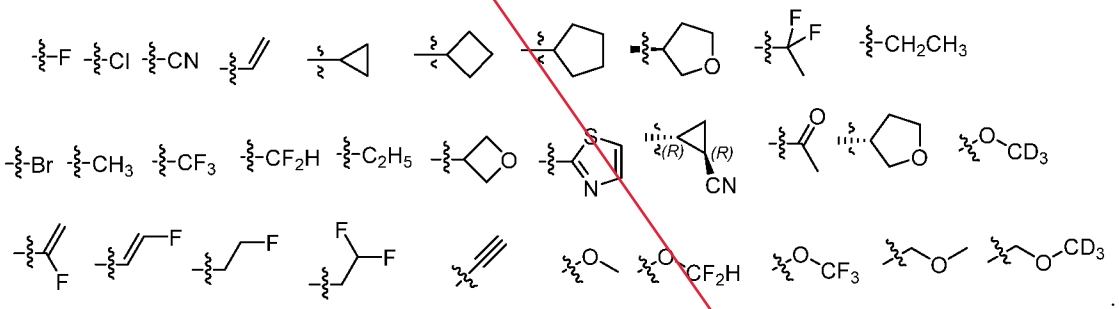
heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G^2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), F, CN, G^1, OH, O-G^1, NH_2, NH(G^1), and N(G^1)(G^1); and wherein two optional substituents of the heteroaryl group, together with the intervening atom(s), can optionally be joined to form a fused ring structure.

59. The compound of claim 44 or 45, or a pharmaceutically acceptable salt thereof, wherein R^2 is a 8-10-membered bicyclic heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, such as indolyl, indazolyl, etc., which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, CN, G^1, OH, COOH, C(O)-G^1, O-G^1, C(O)-O-G^1, NH_2, NH(G^1), N(G^1)(G^1), C(O)-NH_2, C(O)-NH(G^1), C(O)-N(G^1)(G^1), G^2, O-G^2, NH(G^2), N(G^1)(G^2), C(O)-NH(G^2), and C(O)-N(G^1)(G^2), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G^2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), F, CN, G^1, OH, O-G^1, NH_2, NH(G^1), and N(G^1)(G^1); and wherein two optional substituents of the heteroaryl group, together with the intervening atom(s), can optionally be joined to form a fused ring structure.

60. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt thereof wherein R^3 is hydrogen, F, Cl, Br, C_{1-4} alkyl optionally substituted with F and/or deuterium (e.g., methyl, CD_3, ethyl, CHF_2, CF_2CH_3, CH_2CH_2F, CH_2CF_2H, or CF_3), or CN.

61. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt thereof wherein R^3 is a C_{3-6} cycloalkyl, 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, or 5-6 membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), deuterium, F, CN, G^1, OH, O-G^1, NH_2, NH(G^1), N(G^1)(G^1), C(O)-NH_2, C(O)-NH(G^1), and C(O)-N(G^1)(G^1), wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

62. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt thereof wherein R^3 is selected from:



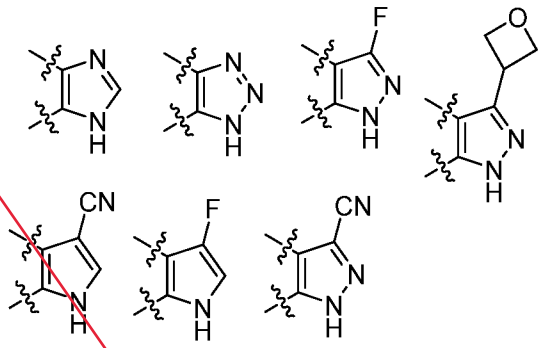
63. The compound of any one of claims 1-62, or a pharmaceutically acceptable salt thereof wherein R^4 is hydrogen.

64. The compound of any one of claims 1-62, or a pharmaceutically acceptable salt thereof wherein R^4 is NH_2.

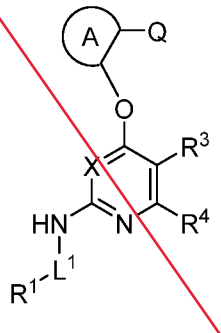
65. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt thereof wherein R^3 and R^4 are joined to form a 5- or 6-membered heteroaryl structure, which has 1-3 ring heteroatoms independently selected from N, O, and S, which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, CN, OH, and 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently

selected from N, O, and S, which is optionally substituted with 1-3 substituents independently selected from oxo, F, CN, and OH.

66. The compound of any one of claims 1-59, or a pharmaceutically acceptable salt thereof wherein R^3 and R^4 are joined to form



67. A compound of Formula II, or a pharmaceutically acceptable salt thereof:



Formula II

wherein:

L^1 is an optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 4-8-membered heterocyclylene, or optionally substituted C_{3-8} carbocyclylene;

R^1 is SO_2R^{10}, $SO_2NR^{11}R^{12}$, $S(O)(NH)R^{10}$, or $C(O)NR^{11}R^{12}$;

X is N or CR^{13};

Ring A is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring having one or more (e.g., 1 or 2) ring heteroatoms independently selected from O, N, and S;

Q is hydrogen, OR^A, optionally substituted C_{1-4} alkyl, halogen, CN, or COR^B;

R^3 is hydrogen, halogen (e.g., F), CN, $C(O)NR^{11}R^{12}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally

substituted C_{1-4} heteroalkyl, OR^A, COR^B, $COOR^A$, $NR^{11}R^{12}$, optionally substituted C_{3-8} carbocyclyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5-10 membered heteroaryl;

R^4 is hydrogen, halogen (e.g., F), optionally substituted C_{1-6} alkyl, or $NR^{11}R^{12}$;

or R^3 and R^4, together with the intervening atoms, form an optionally substituted 4-8 membered ring structure;

wherein:

R^{10} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), or optionally substituted 4-10 membered heterocyclyl;

each of R^{11} and R^{12}, at each occurrence, is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), optionally substituted 4-10 membered heterocyclyl; or a nitrogen protecting group; or R^{11} and R^{12} can be joined to form an optionally substituted 4-10 membered heterocyclyl or 5- or 6-membered heteroaryl;

R^A at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl), optionally substituted 4-10 membered heterocyclyl; or an oxygen protecting group;

R^B at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted heteroaryl (e.g., 5- or 6-membered heteroaryl); and

R^{13} is hydrogen, F, CN, -OH, an optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} heteroalkyl, optionally substituted C_{3-8} carbocyclyl, or optionally substituted 4-10 membered heterocyclyl.

68. The compound of claim 67, or a pharmaceutically acceptable salt thereof, wherein X is N.

69. The compound of claim 67 or 68, or a pharmaceutically acceptable salt thereof, wherein Ring A is an optionally substituted C_{4-10} cycloalkyl or optionally substituted 4-10

membered heterocyclic ring having 1-4 ring heteroatoms independently selected from O, S, and N.

70. The compound of claim 67 or 68, or a pharmaceutically acceptable salt thereof, wherein Ring A is an optionally substituted monocyclic C_{4-8} cycloalkyl.

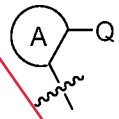
71. The compound of claim 67 or 68, or a pharmaceutically acceptable salt thereof, wherein Ring A is an optionally substituted fused, bridged, or spiro bicyclic C_{6-10} cycloalkyl.

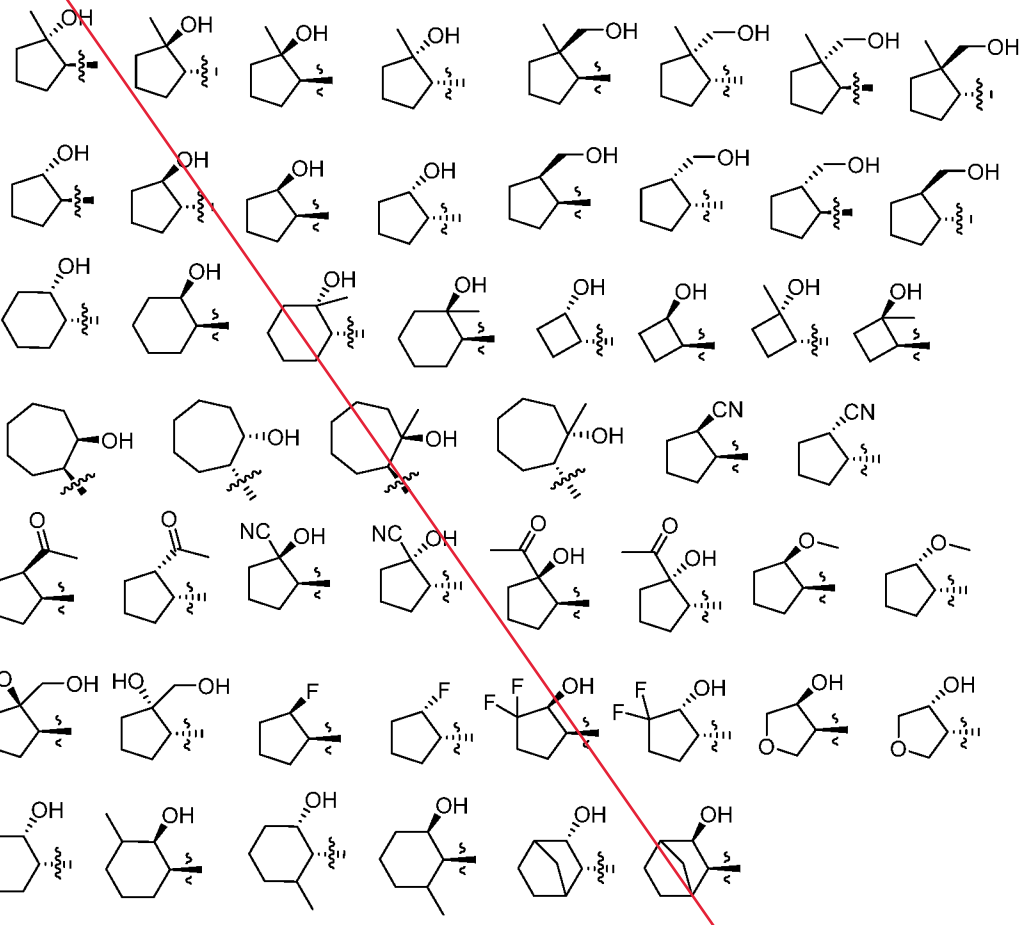
72. The compound of claim 67 or 68, or a pharmaceutically acceptable salt thereof, wherein Ring A is an optionally substituted monocyclic 4-8 membered heterocyclic ring having one ring heteroatom selected from O and N.

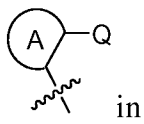
73. The compound of claim 67 or 68, or a pharmaceutically acceptable salt thereof, wherein Ring A is an optionally substituted fused, bridged, or spiro bicyclic 6-10 membered heterocyclic ring having one or two ring heteroatoms independently selected from O, S, and N.

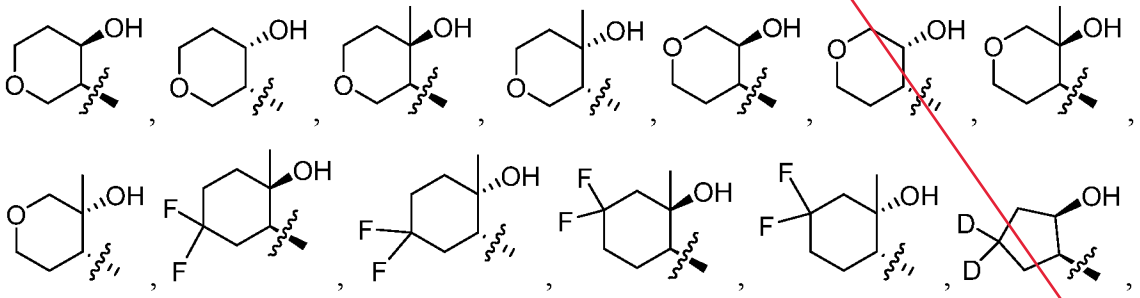
74. The compound of any one of claims 67-73, or a pharmaceutically acceptable salt thereof, wherein Ring A is optionally substituted with 1-3 substituents independently selected from oxo, halogen (e.g., F), CN, G^1, C(O)H, $C(O)G^1$, OH, $O\text{-}G^1$, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl.

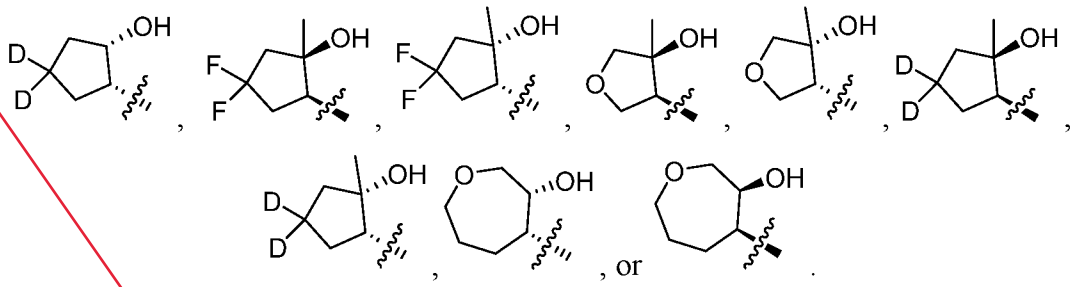
75. The compound of any one of claims 67-74, or a pharmaceutically acceptable salt thereof, wherein Q is OH, F, CN, C(O)H, C(O)-(C_{1-4} alkyl optionally substituted with F), CH_2OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} alkoxy optionally substituted with F.

76. The compound of claim 67 or 68, or a pharmaceutically acceptable salt thereof, wherein  in Formula II is selected from:

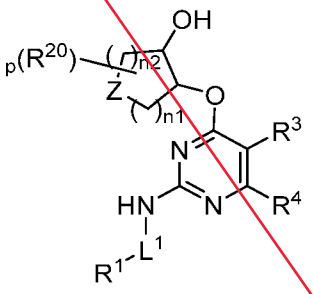


 or in Formula II is selected from:

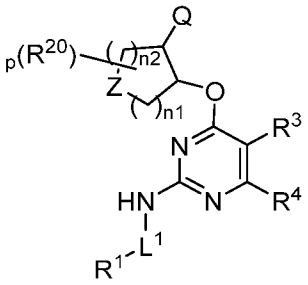




77. The compound claim 67, or a pharmaceutically acceptable salt thereof, characterized as having the following Formula II-1 or II-2:



Formula II-1,



Formula II-2

wherein:

n1 and n2 are independently 0, 1, 2, or 3,

Z is $CR^{21}R^{22}$, O, or NR^{23},

p is 0, 1, 2, 3, or 4, as valency permits,

R^{20} at each occurrence is independently oxo, halogen (e.g., F), CN, G^1, C(O)H, $C(O)G^1$, OH, O-G^1, NH_2, $NH(G^1)$, and $N(G^1)(G^1)$, wherein G^1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl,

or two geminal R^{20} form an oxo group, or two R^{20} together with the intervening atoms form an optionally substituted ring structure,

R^{21} and R^{22} are each independently hydrogen or R^{20},

or R^{21} and R^{22} together form an oxo group or an optionally substituted ring structure,

or one of R^{21} and R^{22} with one R^{20} group together with the intervening atoms form an optionally substituted ring structure,

R^{23} is hydrogen or R^{20},

or R^{23} and one R^{20} group together with the intervening atoms form an optionally substituted ring structure,
wherein Q, L^1, R^1, and R^3 are as defined in claim 67.

78. The compound of claim 77, or a pharmaceutically acceptable salt thereof, wherein n2 is 1.

79. The compound of claim 77 or 78, or a pharmaceutically acceptable salt thereof, wherein n1 is 0, 1, 2, or 3.

80. The compound of any one of claims 77-79, or a pharmaceutically acceptable salt thereof, wherein Z is CH_2, O, or NR^{23}, wherein R^{23} is hydrogen or a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, and OH.

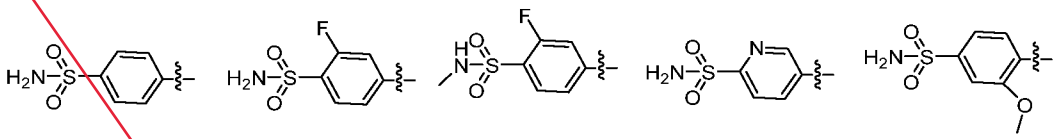
81. The compound of any one of claims 77-80, or a pharmaceutically acceptable salt thereof, wherein p is 0.

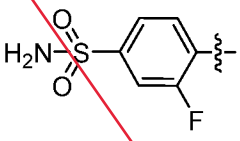
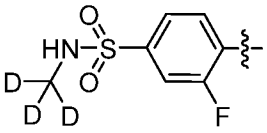
82. The compound of any one of claims 77-80, or a pharmaceutically acceptable salt thereof, wherein p is 1 or 2, and R^{20} at each occurrence is independently halogen (e.g., F), CN, G^1, C(O)H, $C(O)G^1$, OH, or O-G^1.

83. The compound of any one of claims 77-80, or a pharmaceutically acceptable salt thereof, wherein p is 1 or 2, and R^{20} at each occurrence is independently halogen (e.g., F), CN, CH_2OH, G^1, C(O)H, $C(O)G^1$, OH, or O-G^1, wherein G^1 is a C_{1-4} alkyl optionally substituted with 1-3 F.

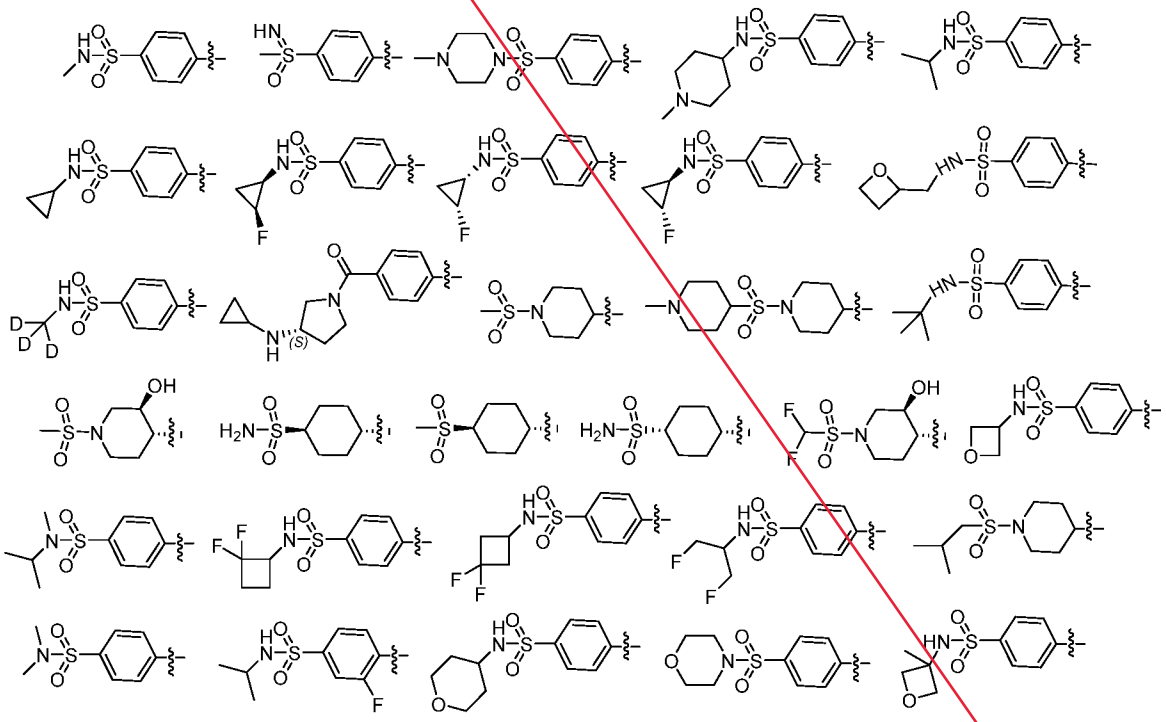
84. The compound of any one of claims 77-83, or a pharmaceutically acceptable salt thereof, which has a formula according to Formula II-2, wherein Q is F, CN, C(O)H, C(O)-(C_{1-4} alkyl optionally substituted with F), CH_2OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} alkoxy optionally substituted with F.

85. The compound of any one of claims 67-84, or a pharmaceutically acceptable salt thereof, wherein L^1-R^1 in Formula II is selected from:

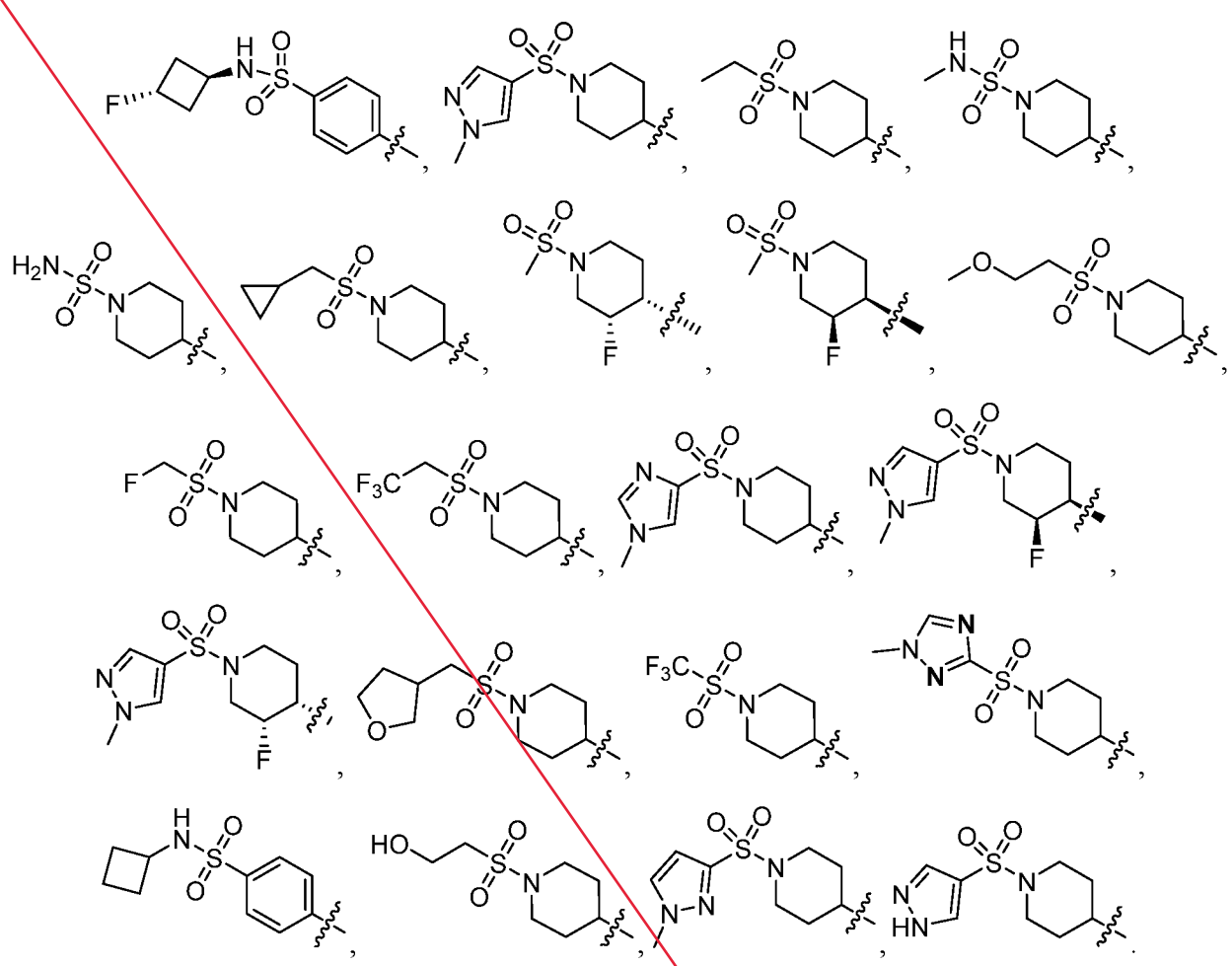


or L^1-R^1 is  or .

86. The compound of any one of claims 67-84, or a pharmaceutically acceptable salt thereof, wherein L^1-R^1 in Formula II is selected from:



or L^1-R^1 in Formula II is selected from:



87. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen, F, Cl, Br, C_{1-4} alkyl optionally substituted with F and/or deuterium (e.g., methyl, CD_3, ethyl, CHF_2, CF_2CH_3, CH_2CH_2F, CH_2CF_2H, or CF_3), or CN.

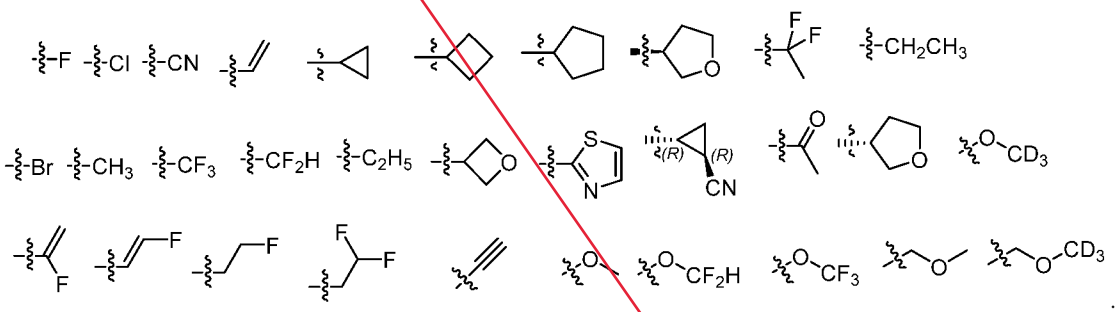
88. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt thereof, wherein R^3 is OR^A.

89. The compound of claim 88, or a pharmaceutically acceptable salt thereof, wherein R^A is hydrogen, C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

90. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt thereof, wherein R^3 is $C(O)R^B$.

91. The compound of claim 90, or a pharmaceutically acceptable salt thereof, wherein R^B is hydrogen, C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

92. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from:

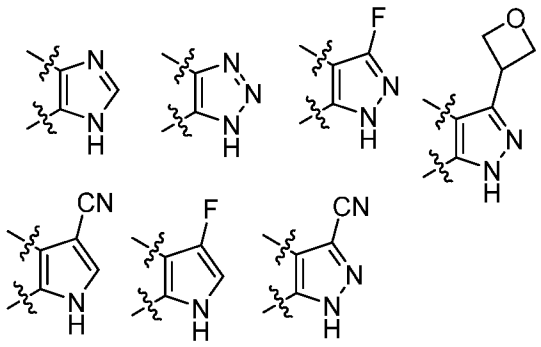


93. The compound of any one of claims 67-92, or a pharmaceutically acceptable salt thereof wherein R^4 is hydrogen.

94. The compound of any one of claims 67-92, or a pharmaceutically acceptable salt thereof wherein R^4 is NH_2.

95. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt thereof wherein R^3 and R^4 are joined to form a 5- or 6-membered heteroaryl structure, which has 1-3 ring heteroatoms independently selected from N, O, and S, which is optionally substituted with one or more (e.g., 1, 2, or 3) substituents independently selected from F, CN, OH, and 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, which is optionally substituted with 1-3 substituents independently selected from oxo, F, CN, and OH.

96. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt thereof wherein R^3 and R^4 are joined to form



97. A compound selected from Examples 1-155 or the compounds shown in Table 1A or 1B herein, a stereoisomer thereof, a deuterated analog thereof, or a pharmaceutically acceptable salt thereof.

98. A pharmaceutical composition comprising the compound of any one of claims 1-97, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

99. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-97, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 98.

100. The method of claim 99, wherein the cancer is breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer (including NSCLC, SCLC, squamous cell carcinoma or adenocarcinoma), esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer (including RCC), liver cancer (including HCC), pancreatic cancer, stomach (i.e., gastric) cancer and/or thyroid cancer.

101. The method of claim 99, wherein the cancer is breast cancer selected from ER-positive/HR-positive, HER2-negative breast cancer; ER-positive/HR-positive, HER2-positive breast cancer; triple negative breast cancer (TNBC); and inflammatory breast cancer.

102. The method of claim 99, wherein the cancer is breast cancer selected from endocrine resistant breast cancer, trastuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition.

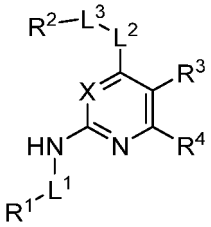
103. The method of claim 99, wherein the cancer is advanced or metastatic breast cancer.

104. The method of claim 99, wherein the cancer is ovarian cancer.

105. The method of any one of claims 99-104, wherein the cancer is characterized by an amplification or overexpression of cyclin E1 and/or cyclin E2.

WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

L_1 is an optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 4-8-membered heterocyclylene, or optionally substituted C_{3-8} carbocyclylene;

R_1 is SO_2R_{10}, $SO_2NR_{11}R_{12}$, $S(O)(NH)R_{10}$, or $C(O)NR_{11}R_{12}$;

X is N or CR_{13};

L_2 is a bond, $-N(R_{14})-$, or -O-;

L_3 is a bond, an optionally substituted C_{1-4} alkylene or an optionally substituted C_{1-4} heteroalkylene;

R_2 is hydrogen, an optionally substituted C_{3-8} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted 4-10 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-10 membered heteroaryl;

R_3 is hydrogen, halogen, CN, $C(O)NR_{11}R_{12}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} heteroalkyl, OR_A, COR_B, $COOR_A$, $NR_{11}R_{12}$, optionally substituted C_{3-8} carbocyclyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5-10 membered heteroaryl;

R_4 is hydrogen, halogen, optionally substituted C_{1-6} alkyl, or $NR_{11}R_{12}$; or L_2 and R_3, together with the intervening atoms, form an optionally substituted 4-8 membered ring structure; or R_3 and R_4, together with the intervening atoms, form an optionally substituted 4-8 membered ring structure;

wherein:

R_{10} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, or optionally substituted 4-10 membered heterocyclyl; each of R_{11} and R_{12}, at each occurrence, is independently

hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl; or a nitrogen protecting group; or R_{11} and R_{12} can be joined to form an optionally substituted 4-10 membered heterocyclyl or 5- or 6-membered heteroaryl;

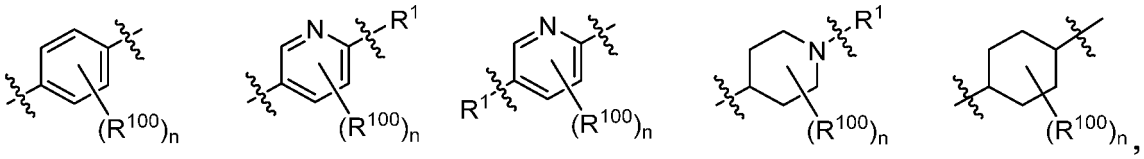
R_A is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted heteroaryl 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl; or an oxygen protecting group;

R_B is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl;

R_{13} is hydrogen, F, CN, -OH, an optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} heteroalkyl, optionally substituted C_{3-8} carbocyclyl, or optionally substituted 4-10 membered heterocyclyl; and

R_{14} is hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl; or a nitrogen protecting group.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L_1 is selected from:



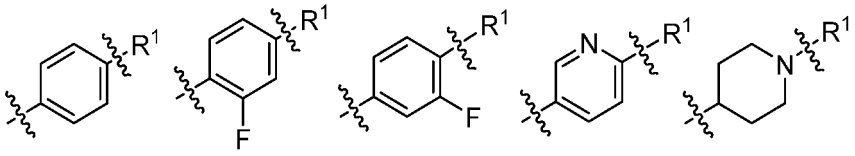
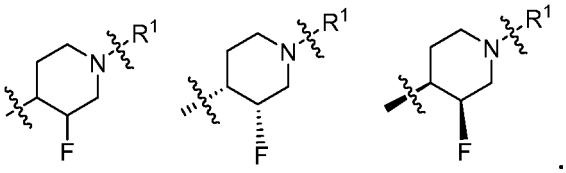
wherein:

n is 0, 1, 2, 3, or 4, as valency permits; and

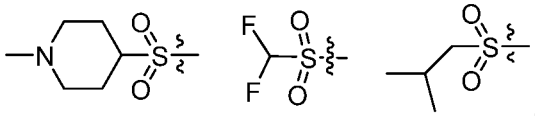
R_{100} at each occurrence is independently selected from halogen, CN, OH, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} alkoxy, and optionally substituted C_{1-4} heteroalkyl.

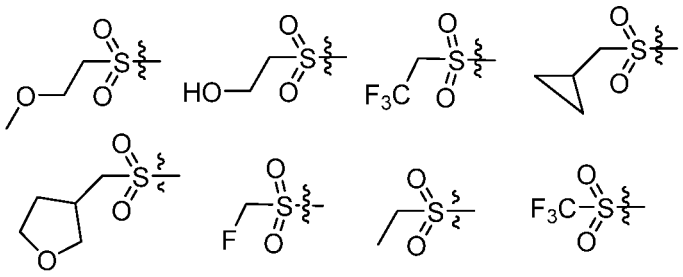
3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein n is 0, 1 or 2, and R_{100} at each occurrence is independently selected from F, Cl, CN, OH, C_{1-4} alkyl optionally

substituted with F, C_{1-4} alkoxy optionally substituted with F, and C_{1-4} heteroalkyl optionally substituted with F.

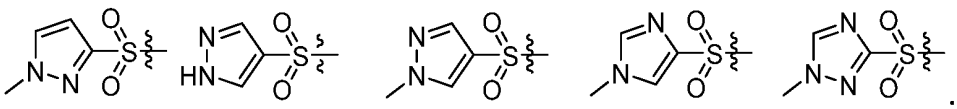
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L_1 is selected from:  or L^1 is selected from: .

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R_1 is SO_2R_{10}, wherein R_{10} is an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted 4-8 membered heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S, or R_{10} is an optionally substituted 5 or 6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, O, and S.

6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^1 is SO_2Me or selected from: , or R^1 is selected from

.

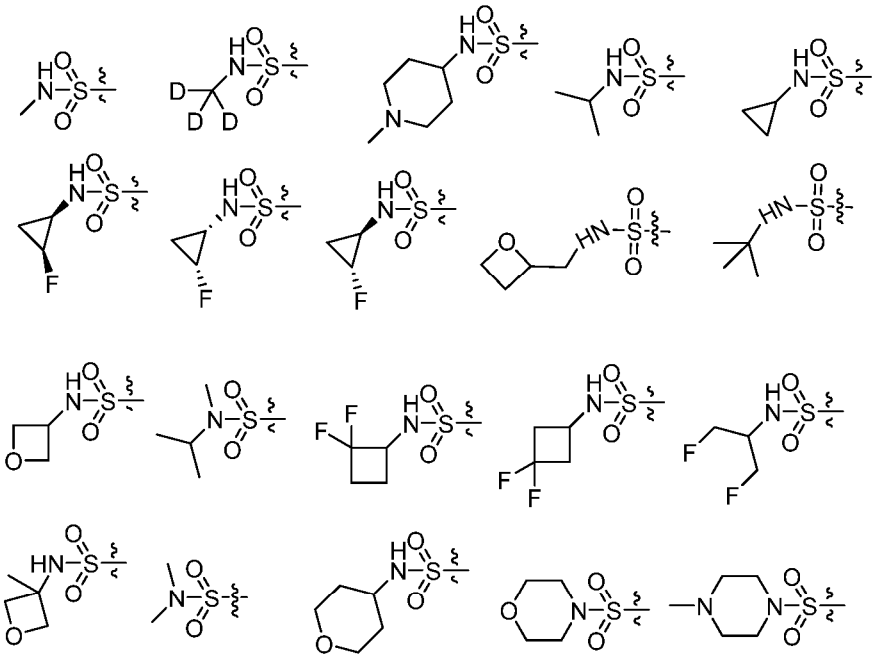
or R_1 is selected from

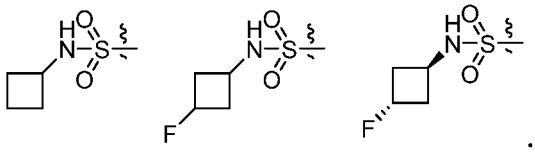


7. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R_1 is $S(O)(NH)R_{10}$, wherein R_{10} is an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted 4-8 membered heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S.

8. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R_1 is $SO_2NR_{11}R_{12}$, wherein R_{11} and R_{12} are independently hydrogen, an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted 4-8 membered heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S.

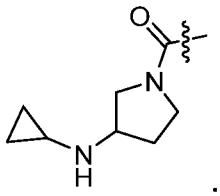
9. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R_1 is SO_2NH_2 or R_1 is selected from:



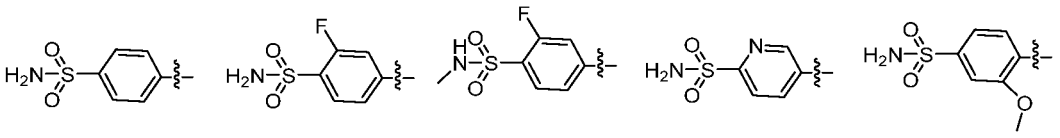
or R^1 is selected from .

10. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R_1 is $C(O)NR_{11}R_{12}$, wherein R_{11} and R_{12} are independently hydrogen, an optionally substituted C_{1-4} alkyl, optionally substituted C_{3-6} cycloalkyl, or optionally substituted 4-8 membered heterocyclyl having one or two ring heteroatoms independently selected from N, O, and S.

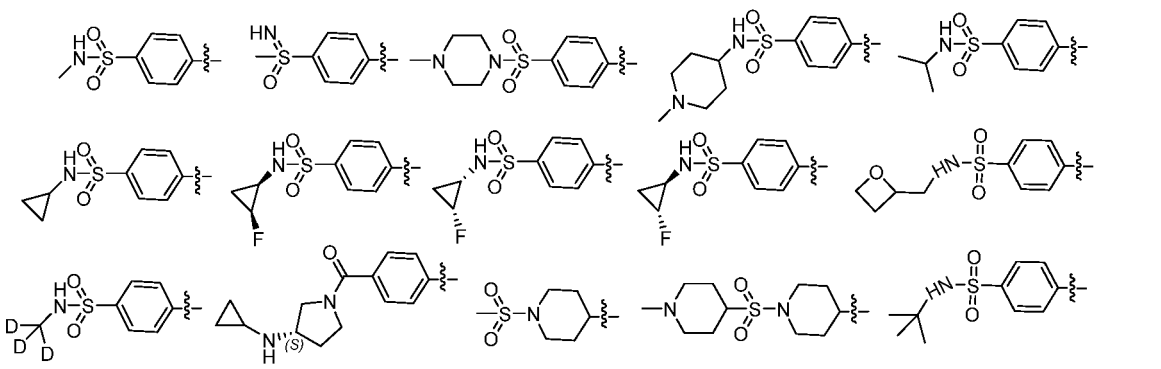
11. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof,

wherein R^1 is C(O)NHMe or .

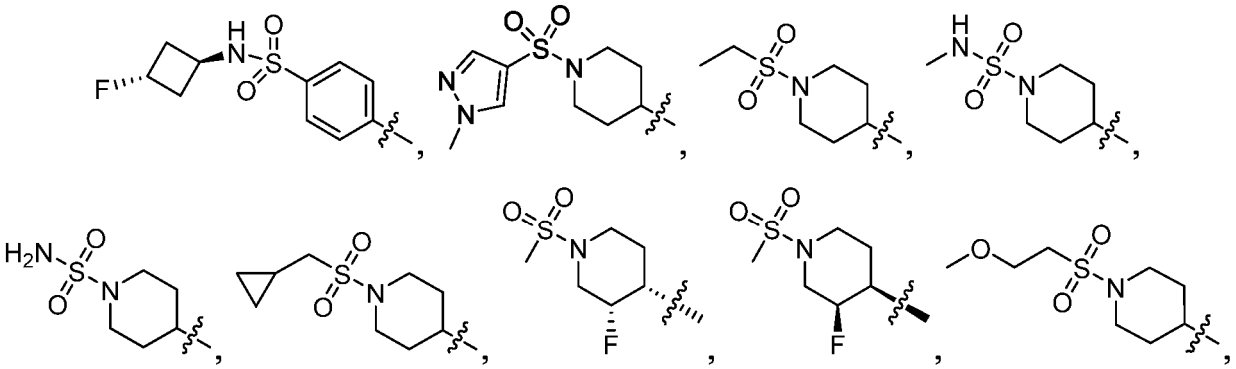
12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L_1-R_1 in Formula I is selected from:

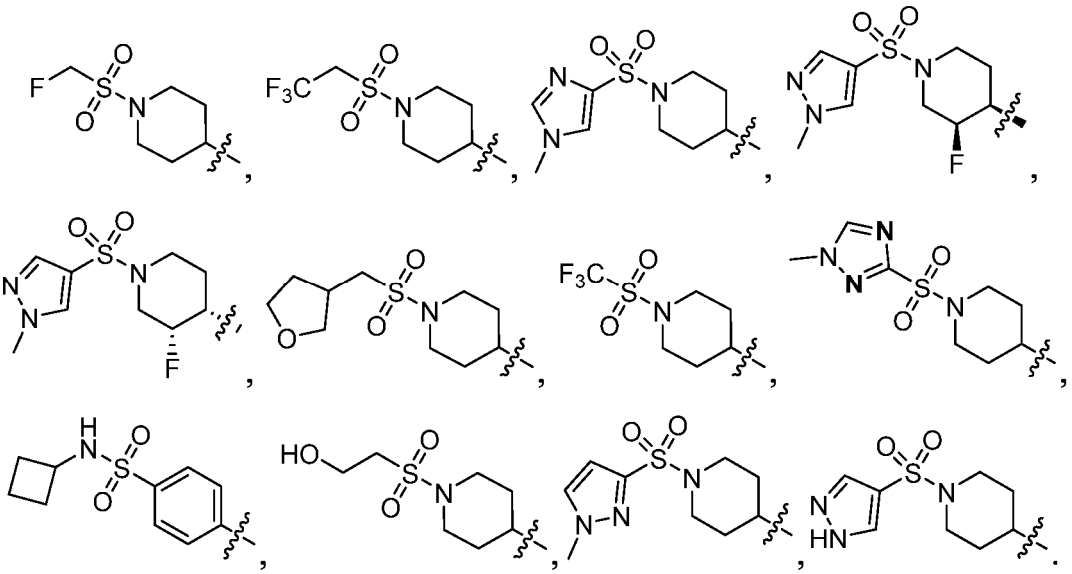


or L^1-R^1 is



or L_1-R_1 in Formula I is selected from:



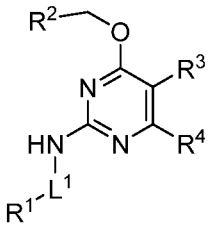


13 The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein X is N or CH.

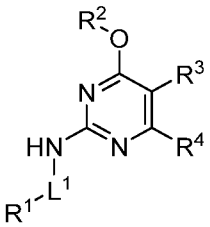
14 The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein L_2 is -O- and L_3 is a bond or a C_{1-4} alkylene optionally substituted with 1, 2, or 3 substituents independently selected from F, OH, and protected OH.

15 The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein L_2 is –N(R_{14})- and L_3 is a bond or a C_{1-4} alkylene optionally substituted with 1, 2, or 3 substituents independently selected from F, OH, and protected OH.

16. The compound of claim 14 or 15, or a pharmaceutically acceptable salt thereof, characterized as having Formula I-1 or I-2:



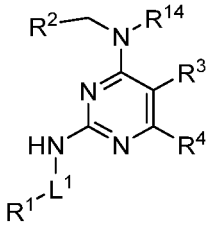
Formula I-1



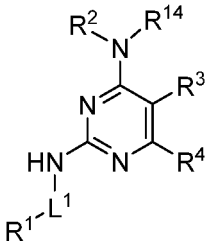
Formula I-2

; or

characterized as having Formula I-3 or I-4:



Formula I-3

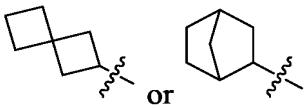


Formula I-4

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R_2 is a C_{3-8} alkyl substituted with 1, 2, or 3 substituents independently selected from oxo, F, G_1, CN, OH, O-G_1, NH_2, NH(G_1), and N(G_1)(G_1), wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 13 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, wherein two optional substituents of the C_{3-8} alkyl, together with the intervening atom(s), can optionally be joined to form a ring structure.

18. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R_2 is a C_{3-8} cycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from F, CN, G_1, OH, COOH, C(O)-G_1, O-G_1, C(O)O-G_1, NH_2, NH(G_1), N(G_1)(G_1), C(O)-NH_2, C(O)-NH(G_1), C(O)-N(G_1)(G_1), wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl.

19. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R_2 is a C_{3-6} cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,



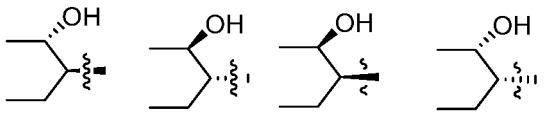
or a spiro, fused, or bridged C_{6-8} cycloalkyl, such as , wherein the cycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from F, methyl, ethyl, hydroxyethyl(, -C(O)CH_3, OH, -CH_2OH, fluorine substituted methyl, and fluorine substituted ethyl.

20. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R_2 is a 4-8 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O,

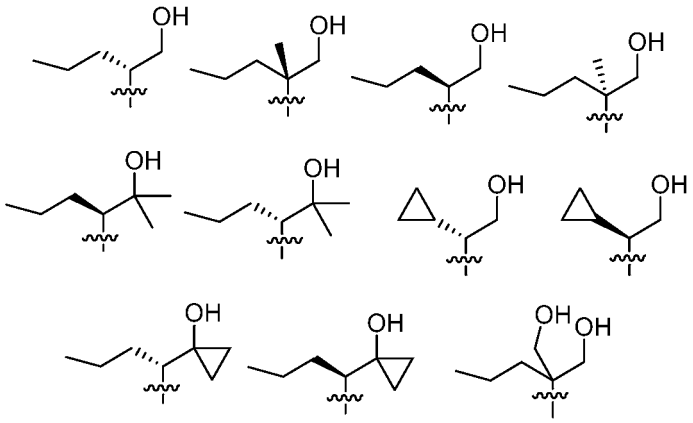
and S, which is optionally substituted with 1, 2, or 3 substituents independently selected from oxo, F, CN, G_1, OH, COOH, C(O)-G_1, O-G_1, C(O)-O-G_1, NH_2, NH(G_1), N(G_1)(G_1), C(O)-NH_2, C(O)-NH(G_1), C(O)-N(G_1)(G_1), wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 13 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl.

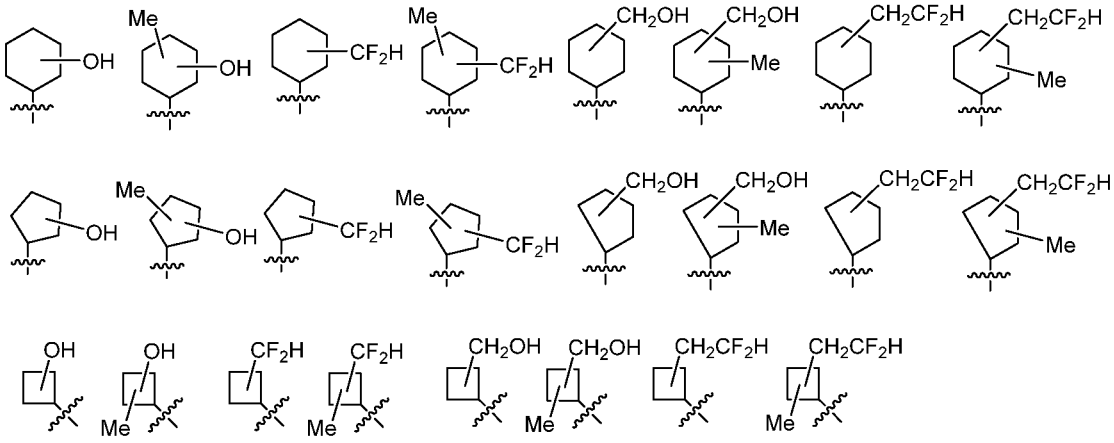
21. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R_2 is a 4-6 or 7 membered monocyclic heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, such as oxetane, azetidine, tetrahydrofuran, tetrahydropyran, oxepane, pyrrolidine, piperidine, etc., which is optionally substituted with 1, 2, or 3 substituents independently selected from oxo, F, methyl, ethyl, hydroxyethyl, -C(O)CH_3, OH, - CH_2OH, fluorine substituted methyl, and fluorine substituted ethyl.

22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from:

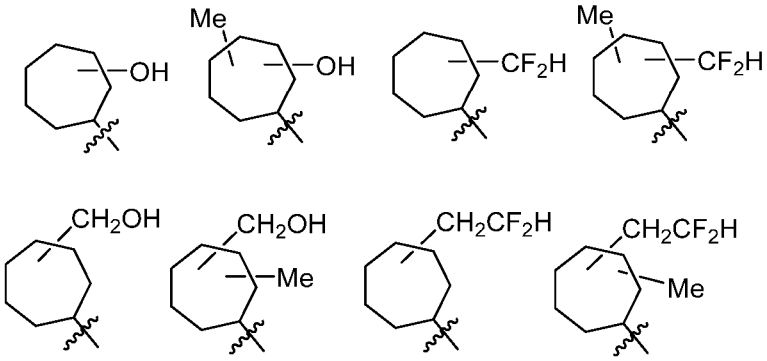


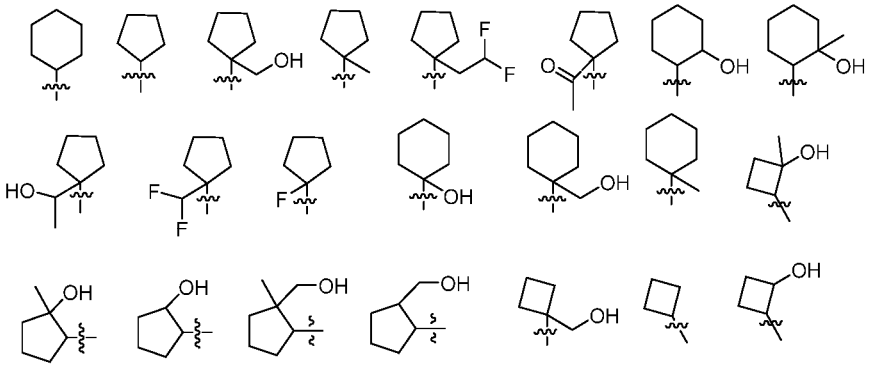
or R^2 is selected from:



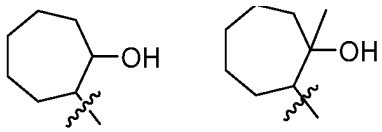


or R^2 is selected from:

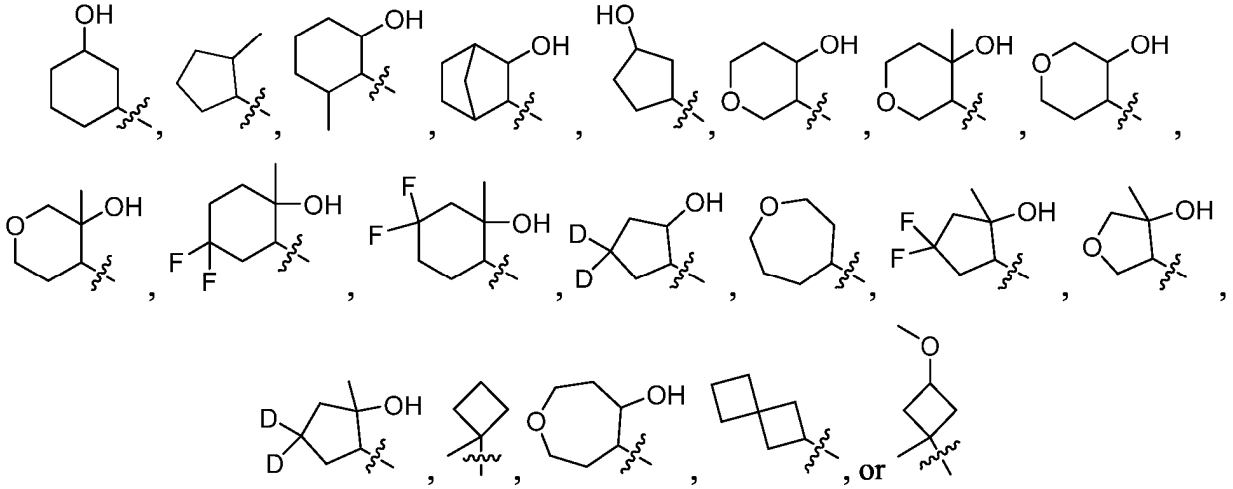




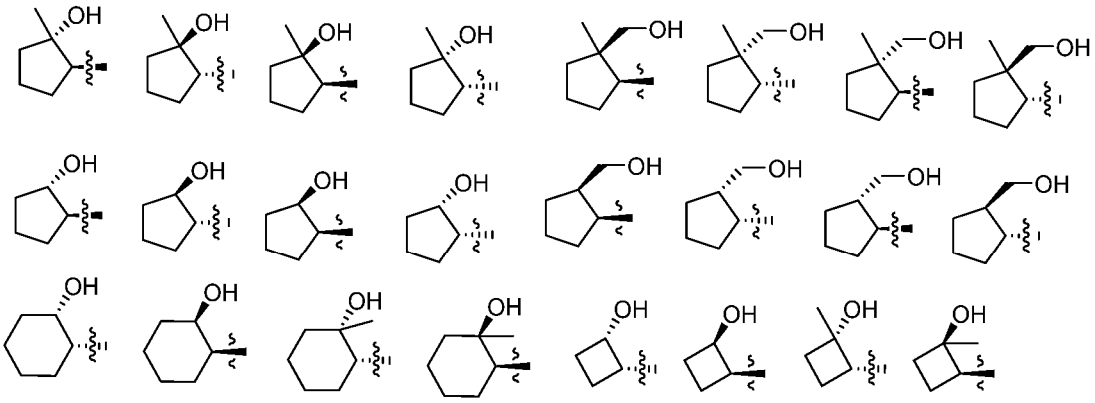
or R^2 is selected from:



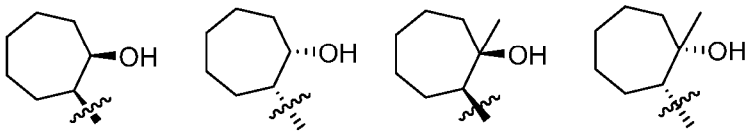
or R^2 is selected from:



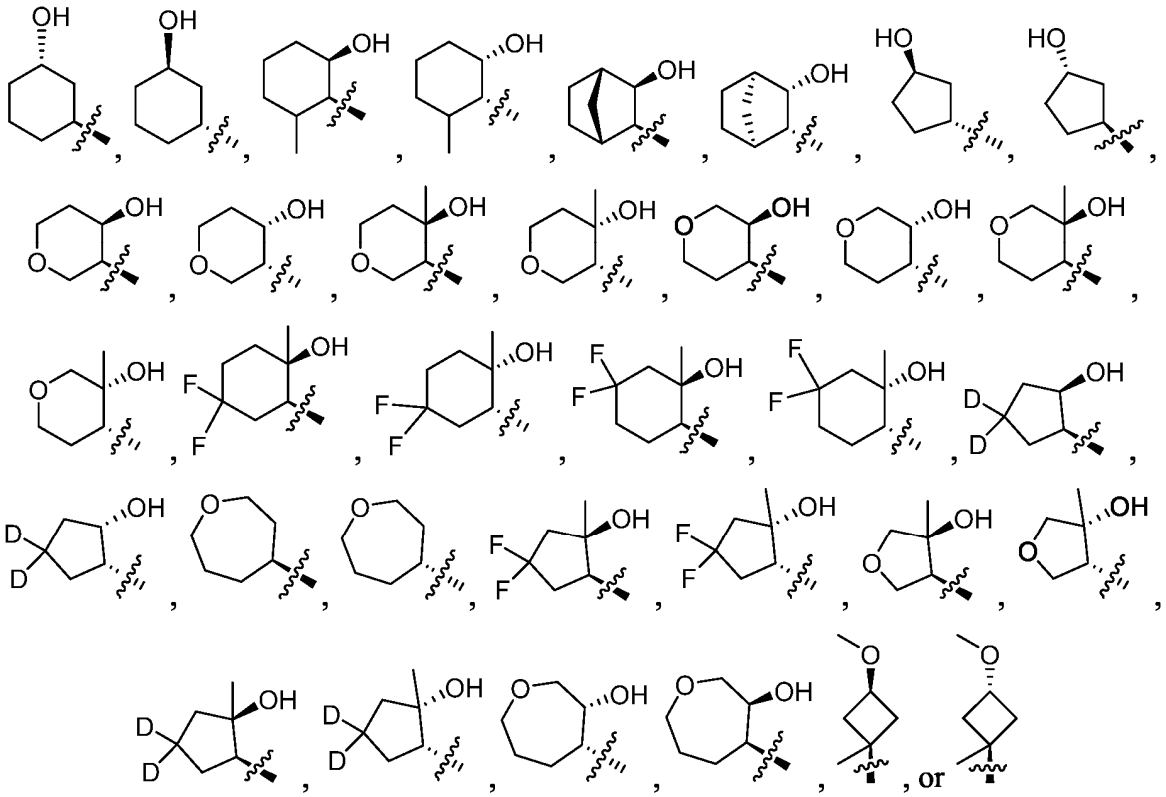
, or



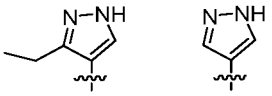
or R^2 is selected from:



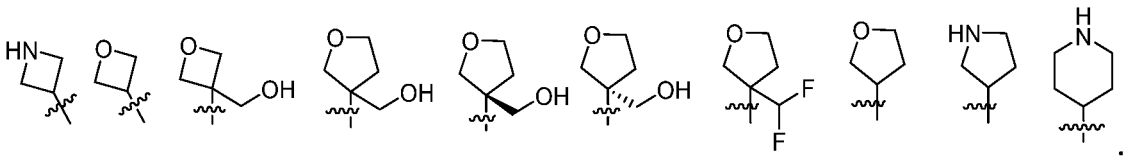
or R^2 is selected from:



or R^2 is selected from:

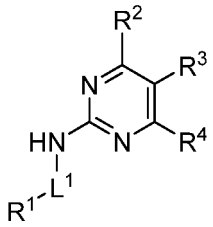


or R^2 is selected from:



23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein L_2 and L_3 are both a bond.

24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, characterized as having Formula I-5:

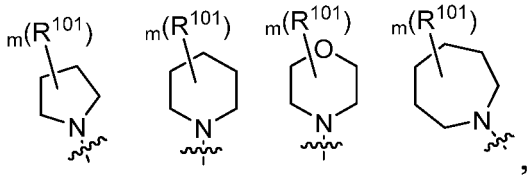


I-5.

25. The compound of claim 23 or 24, or a pharmaceutically acceptable salt thereof, wherein R_2 is a 4-10 membered heterocyclyl having 1-4 ring heteroatoms independently selected from N, O, and S, which is optionally substituted with 1, 2, or 3 substituents independently selected from oxo, F, CN, G_1, OH, COOH, C(O)-G_1, O-G_1, C(O)-O-G_1, NH_2, NH(G_1), N(G_1)(G_1), C(O)-NH_2, C(O)-NH(G_1), C(O)-N(G_1)(G_1), G_2, O- G_2, NH(G_2), N(G_1)(G_2), C(O)-NH(G_2), and C(O)-N(G_1)(G_2), wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G_2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), F, CN, G_1, OH, O-G_1, NH_2, NH(G_1), and N(G_1)(G_1); and wherein two optional substituents of the 4-10 membered heterocyclyl, together with the intervening atom(s), can optionally be joined to form a fused, bridged, or spiro ring structure; or
R_2 is a 4-8 membered monocyclic, saturated or partially unsaturated, heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, such as pyrrolidine, piperidine, azepane, etc., which is optionally substituted with 1, 2, or 3 substituents independently selected from oxo, F, CN, G_1, OH, COOH, C(O)-G_1, O-G_1, C(O)-O-G_1, NH_2, NH(G_1), N(G_1)(G_1), C(O)-NH_2, C(O)-NH(G_1), C(O)-N(G_1)(G_1), G_2, O-G_2, NH(G_2), N(G_1)(G_2), C(O)-NH(G_2), and C(O)-N(G_1)(G_2), wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G_2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected

from oxo (as applicable), F, CN, G_1, OH, O-G_1, NH_2, NH(G_1), and N(G_1)(G_1); and wherein two optional substituents of the 4-8 membered heterocyclyl, together with the intervening atom(s), can optionally be joined to form a fused, bridged, or spiro ring structure; or

R_2 is selected from:



,

wherein:

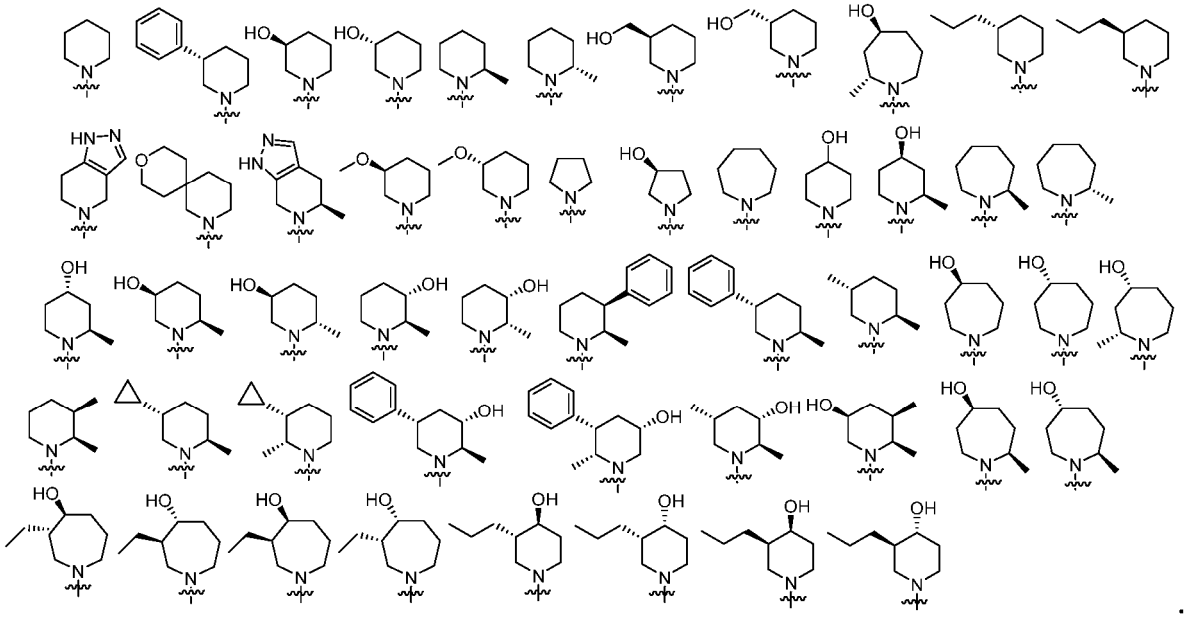
m is 0, 1, 2, 3, or 4;

R_{101} at each occurrence is independently oxo, F, CN, G_1, G_2, OH, O-G_1, and O-G_2, wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 13 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G_2 at each occurrence is independently 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, each of which is optionally substituted with 1-3 substituents independently selected from F, CN, G_1, OH, and O-G_1; wherein two R_{101}, together with the intervening atom(s), can optionally be joined to form a fused, bridged, or spiro ring structure.

26. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein R_{101} at each occurrence is independently F, OH, CN, C_{1-4} alkyl, phenyl, cyclopropyl, hydroxymethyl), methoxy, fluorine substituted methoxy, fluorine substituted C_{1-4} alkyl, such as fluorine substituted methyl such as CF_2H, or fluorine substituted ethyl.

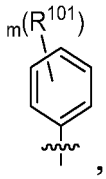
27. The compound of claim 25 or 26, or a pharmaceutically acceptable salt thereof, wherein m is 0, 1, 2, or 3.

28. The compound of claim 24 or 25, or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from:



29. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein R_2 is:

wherein:

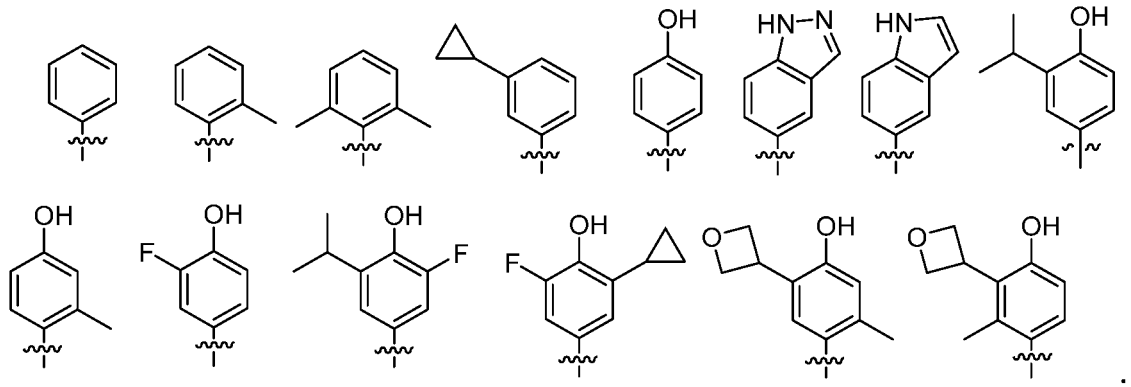


m is 0, 1, 2, or 3;

R_{101} at each occurrence is independently F, CN, G_1, G_2, OH, O-G_1, O-G_2, NH_2, NH(G_1), NH(G_2), N(G_1)(G_1), and N(G_1)(G_2), wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, OH, and C_{1-4} heteroalkyl or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, OH, and C_{1-4} heteroalkyl; wherein G_2 at each occurrence is independently 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, each of which is optionally substituted with 1-3 substituents independently selected from F, CN, G_1, OH, and O-G_1; wherein two R_{101}, together with the intervening atom(s), can optionally be joined to form a fused ring structure.

30. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein R_{101} at each occurrence is independently F, C_{1-4} alkyl, OH, cyclopropyl, cyclobutyl, oxetanyl, or CN.

31. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein R_2 is selected from:

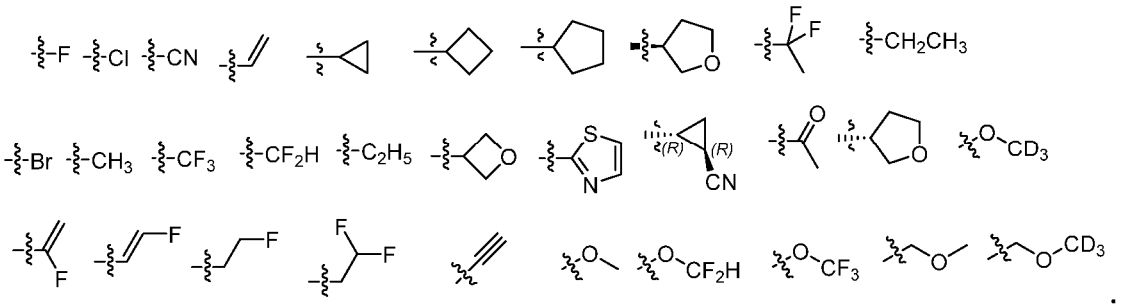


32. The compound of claim 24 or 25, or a pharmaceutically acceptable salt thereof, wherein R_2 is a 5-10 membered heteroaryl or a 8-10-membered bicyclic heteroaryl, each having 1-4 ring heteroatoms independently selected from N, O, and S, which is optionally substituted with 1, 2, or 3 substituents independently selected from F, CN, G_1, OH, COOH, C(O)-G_1, O-G_1, C(O)O-G_1, NH_2, NH(G_1), N(G_1)(G_1), C(O)-NH_2, C(O)-NH(G_1), C(O)-N(G_1)(G_1), G_2, O-G_2, NH(G_2), N(G_1)(G_2), C(O)-NH(G_2), and C(O)-N(G_1)(G_2), wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl; wherein G_2 at each occurrence is independently a 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, phenyl or 5- or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from oxo (as applicable), F, CN, G_1, OH, O-G_1, NH_2, NH(G_1), and N(G_1)(G_1); and wherein two optional substituents of the heteroaryl group, together with the intervening atom(s), can optionally be joined to form a fused ring structure.

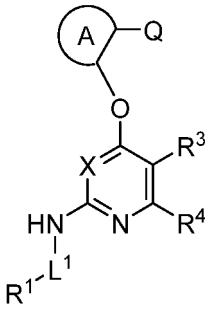
33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt thereof wherein R_3 is hydrogen, F, Cl, Br, C_{1-4} alkyl optionally substituted with F and/or deuterium, or CN; or R_3 is a C_{3-6} cycloalkyl, 4-6 membered heterocyclyl having 1-2 ring heteroatoms independently selected from N, O, and S, or 5-6 membered heteroaryl having 1-4 ring heteroatoms independently selected from N, O, and S, each of which is optionally substituted with 1-3

substituents independently selected from oxo (as applicable), deuterium, F, CN, G_1, OH, O-G_1, NH_2, NH(G_1), N(G_1)(G_1), C(O)-NH_2, C(O)-NH(G_1), and C(O)-N(G_1)(G_1), wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof wherein R_3 is selected from:



35. A compound of Formula II, or a pharmaceutically acceptable salt thereof:



Formula II

wherein:

L_1 is an optionally substituted phenylene, optionally substituted 5- or 6-membered heteroarylene, optionally substituted 4-8-membered heterocyclylene, or optionally substituted C_{3-8} carbocyclylene;

R_1 is SO_2R_{10}, $SO_2NR_{11}R_{12}$, S(O)(NH)R_{10}, or C(O)$NR_{11}R_{12}$;

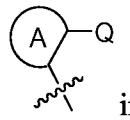
X is N or CR_{13};

Ring A is an optionally substituted carbocyclic ring or optionally substituted heterocyclic ring having 1 or 2 ring heteroatoms independently selected from O, N, and S;

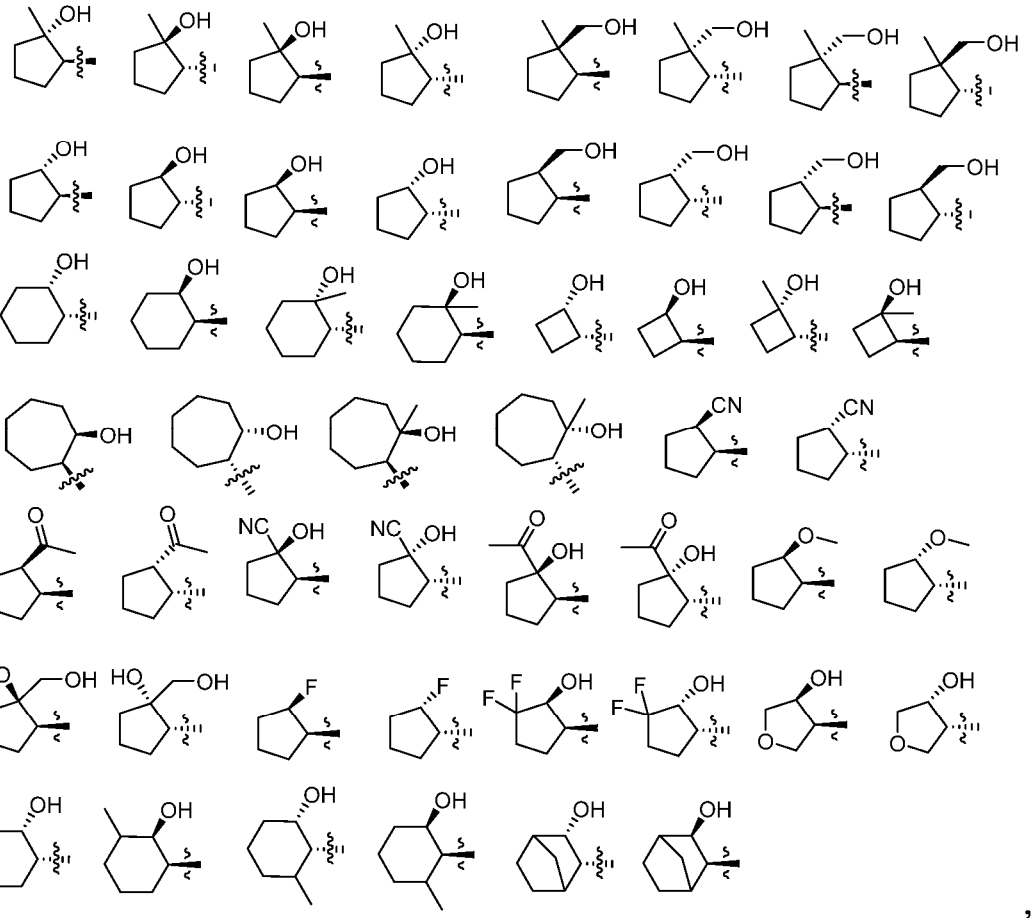
Q is hydrogen, OR_A, optionally substituted C_{1-4} alkyl, halogen, CN, or COR_B;
R_3 is hydrogen, halogen, CN, $C(O)NR_{11}R_{12}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} heteroalkyl, OR_A, COR_B, $COOR_A$, $NR_{11}R_{12}$, optionally substituted C_{3-8} carbocyclyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5-10 membered heteroaryl;
R_4 is hydrogen, halogen, optionally substituted C_{1-6} alkyl, or $NR_{11}R_{12}$; or R_3 and R_4, together with the intervening atoms, form an optionally substituted 4-8 membered ring structure;
wherein:
R_{10} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, or optionally substituted 4-10 membered heterocyclyl; each of R_{11} and R_{12}, at each occurrence, is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl; or a nitrogen protecting group; or R_{11} and R_{12} can be joined to form an optionally substituted 4-10 membered heterocyclyl or 5- or 6-membered heteroaryl;
R_A at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 5- or 6-membered heteroaryl, optionally substituted 4-10 membered heterocyclyl; or an oxygen protecting group;
R_B at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} carbocyclyl, optionally substituted phenyl, optionally substituted 4-10 membered heterocyclyl, or optionally substituted 5- or 6-membered heteroaryl; and
R_{13} is hydrogen, F, CN, -OH, an optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} heteroalkyl, optionally substituted C_{3-8} carbocyclyl, or optionally substituted 4-10 membered heterocyclyl.

36. The compound of claim 35, or a pharmaceutically acceptable salt thereof, wherein X is N.

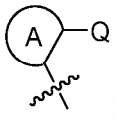
37. The compound of claim 35 or 36, or a pharmaceutically acceptable salt thereof, wherein



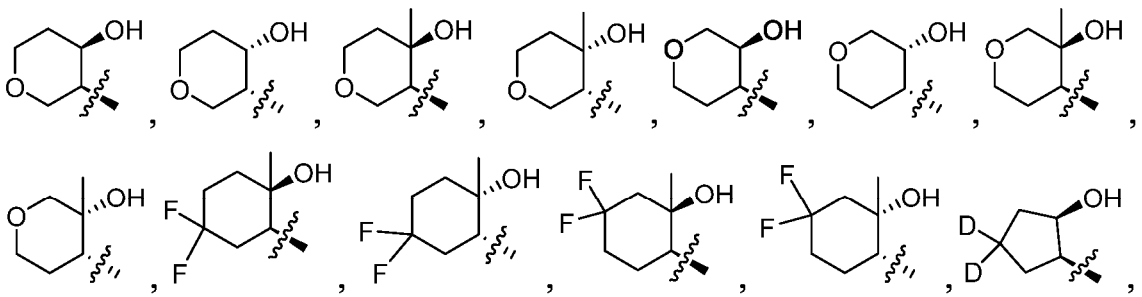
in Formula II is selected from:

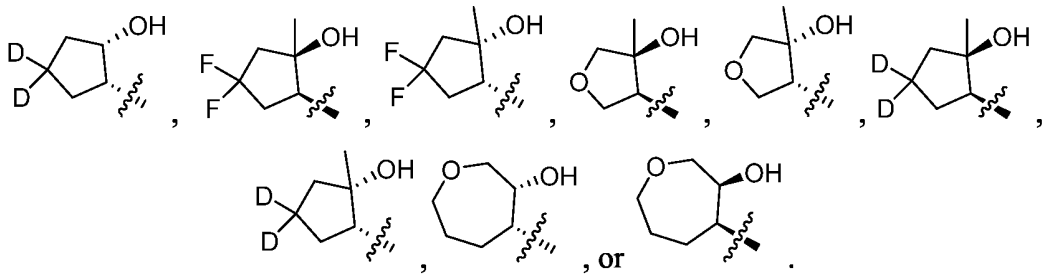


,

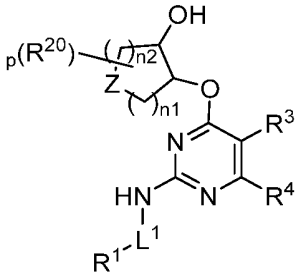


or in Formula II is selected from:

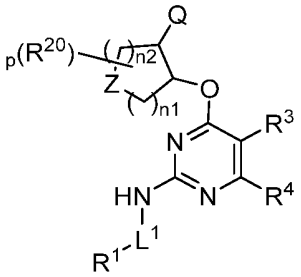




38. The compound claim 35, or a pharmaceutically acceptable salt thereof, characterized as having the following Formula II-1 or II-2:



Formula II-1,



Formula II-2

wherein:

n1 and n2 are independently 0, 1, 2, or 3,

Z is $CR_{21}R_{22}$, O, or NR_{23},

p is 0, 1, 2, 3, or 4, as valency permits,

R_{20} at each occurrence is independently oxo, halogen, CN, G_1, C(O)H, $C(O)G_1$, OH, O-G_1, NH_2, $NH(G_1)$, and $N(G_1)(G_1)$, wherein G_1 at each occurrence is independently a C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from F, CN, OH, and C_{1-4} heteroalkyl, or two geminal R_{20} form an oxo group, or two R_{20} together with the intervening atoms form an optionally substituted ring structure,

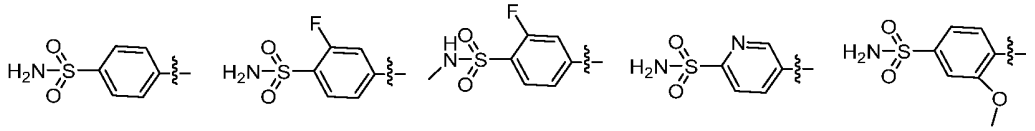
R_{21} and R_{22} are each independently hydrogen or R_{20}, or R_{21} and R_{22} together form an oxo group or an optionally substituted ring structure, or one of R_{21} and R_{22} with one R_{20} group together with the intervening atoms form an optionally substituted ring structure,

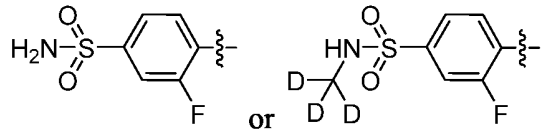
R_{23} is hydrogen or R_{20},

or R_{23} and one R_{20} group together with the intervening atoms form an optionally substituted ring structure,

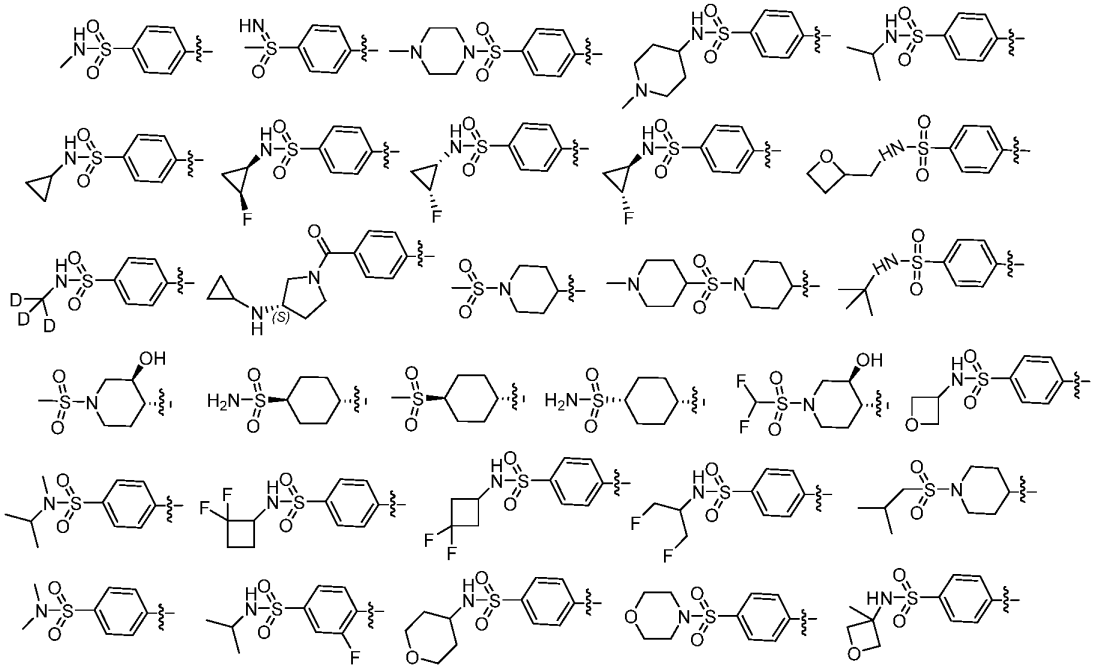
wherein Q, L_1, R_1, and R_3 are as defined in claim 35.

39. The compound of any one of claims 35-38, or a pharmaceutically acceptable salt thereof, wherein L_1-R_1 in Formula II is selected from:

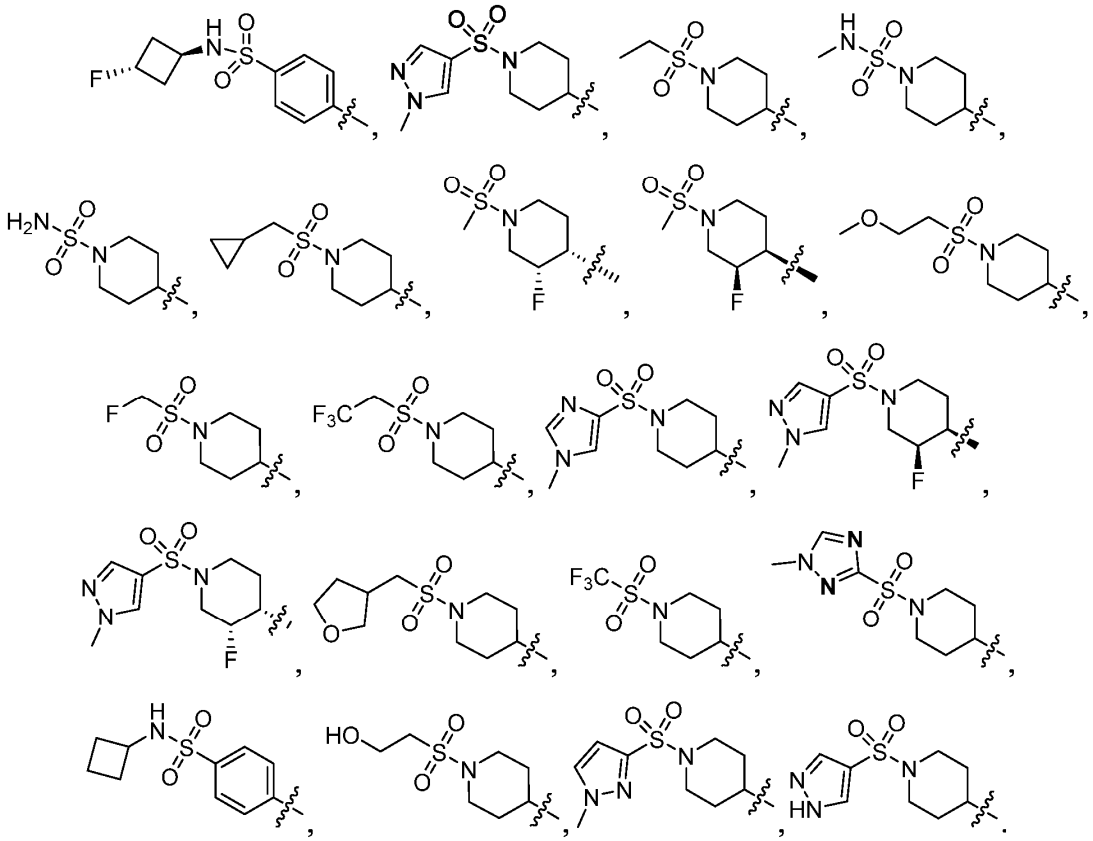


or L^1-R^1 is  or

or L_1-R_1 in Formula II is selected from:

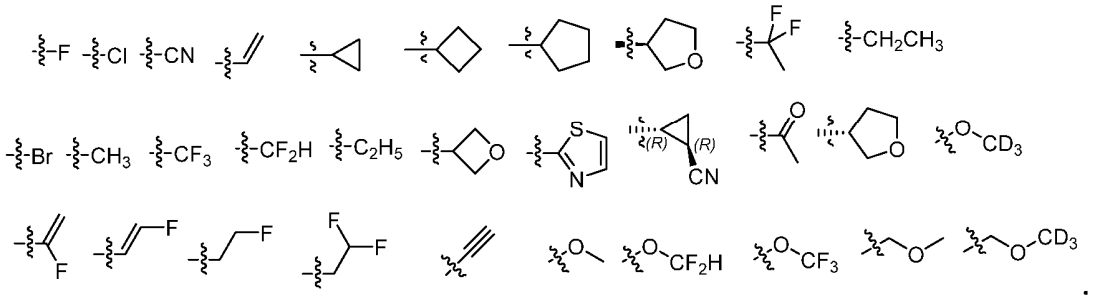


or L_1-R_1 in Formula II is selected from:

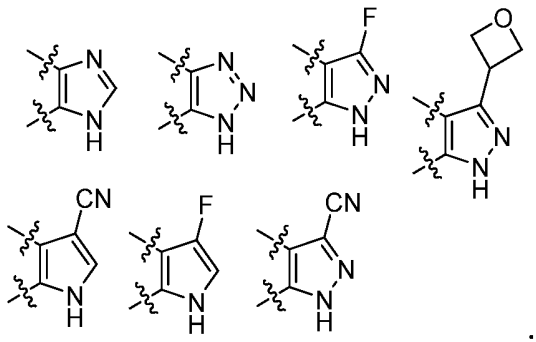


40. The compound of any one of claims 35-39, or a pharmaceutically acceptable salt thereof, wherein R_3 is hydrogen, F, Cl, Br, C_{1-4} alkyl optionally substituted with F and/or deuterium, or CN; or R_3 is OR_A wherein R_A is hydrogen, C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl; or R_3 is $C(O)R_B$, wherein R_B is hydrogen,
C_{1-4} alkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl, or a C_{3-6} cycloalkyl optionally substituted with 1-3 substituents independently selected from deuterium, F, CN, OH, and C_{1-4} heteroalkyl.

41 The compound of any one of claims 1-40, or a pharmaceutically acceptable salt thereof, wherein R_3 is selected from:



42. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt thereof wherein R_4 is hydrogen, NH_2, or R_3 and R_4 are joined to form



43. A pharmaceutical composition comprising the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

44. Use of the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 43, in the manufacture of a medicament for treating cancer.

45. The use of claim 44, wherein the cancer is breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer), esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer, liver cancer, pancreatic cancer, stomach cancer and/or thyroid cancer.

46. The use of any one of claims 44-45, wherein the cancer is characterized by an amplification or overexpression of cyclin E1 and/or cyclin E2.

47. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 43, for use as a medicament.