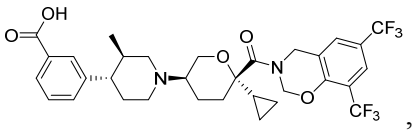
[0024] In addition to the compounds provided herein, the present disclosure further provides pharmaceutical compositions containing one or more of these compounds, as well as methods for the use of these compounds in therapeutic methods, primarily to treat diseases associated CCR2 signalling activity.

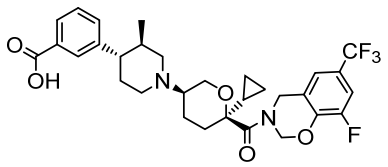
[0024a] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:



,

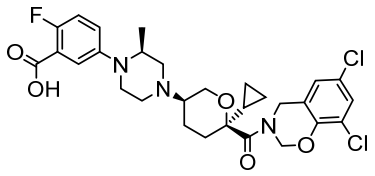
or a pharmaceutically acceptable salt thereof.

[0024b] In a further aspect of the present disclosure, there is provided a compound having the formula



or a pharmaceutically acceptable salt thereof.

[0024c] In another aspect of the present disclosure, there is provided a compound having the formula



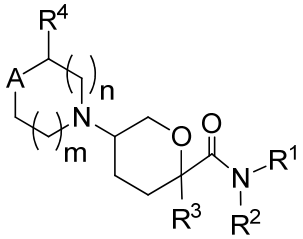
or a pharmaceutically acceptable salt thereof.

[0024d] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound disclosed herein.

[0025] The present disclosure also provides methods of diagnosing disease in an individual. In these methods, the compounds provided herein are administered in labeled form to a subject, followed by diagnostic imaging to determine the presence or absence of CCR2. There is also provided a method of diagnosing disease is carried out by contacting a tissue or blood sample with a labeled compound as provided herein and determining the presence, absence, or amount of CCR2 in the sample.

WHAT IS CLAIMED IS:

1. A compound having the formula



(I);

or a pharmaceutically acceptable salt, hydrate, stereoisomer or rotamer thereof; wherein

A is $C(R^5)(R^6)$ or $N(R^5)$

the subscripts m and n are each independently integers of from 0 to 2, and m + n is ≤ 3;

R^1 is selected from the group consisting of aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein the heteroaryl portion has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups or portions are optionally substituted with from 1 to 5 R^x substituents;

R^2 is selected from the group consisting of H, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein the heteroaryl portion has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups or portions are optionally substituted with from 1 to 4 R^x substituents;

or optionally, R^1 and R^2 are combined with the nitrogen atom to which each is attached to form a 6- to 11-membered monocyclic or fused bicyclic- heterocyclic or heteroaryl ring, wherein the $–NR^1R^2$ is optionally further substituted with from 1 to 4 R^x substituents;

R^3 is selected from the group consisting of H, C_{1-8} alkyl, C_{3-8} cycloalkyl and C_{3-8} cycloalkyl-C_{1-4} alkyl, each of which is optionally substituted with from 1-3 R^y substituents;

R^4 is selected from the group consisting of H, C_{1-8} alkyl optionally substituted with 1 to 2 R^y, and $–CO_2H$:

R^5 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyloxy, C_{3-8} cycloalkyl-C_{1-4} alkyl, C_{1-8} alkylamino, di-C_{1-8} alkylamino, aryl, aryloxy, arylamino, aryl-C_{1-4} alkyl, heteroaryl, heteroaryloxy, heteroarylamino and heteroaryl-C_{1-4} alkyl, each of which is optionally substituted with from 1 to 5 R^z substituents;

R^6 is selected from the group consisting of H, F, OH, C_{1-8} alkyl and C_{1-8} alkoxy, wherein the C_{1-8} alkyl and C_{1-8} alkoxy groups are optionally substituted with from 1 to 3 R^z substituents;

or optionally, R^5 and R^6 are joined to form a spirocyclic 5- or 6-membered cycloalkyl ring which is optionally unsaturated, and has a fused aryl group which is optionally substituted with from 1 to 4 R^z substituents;

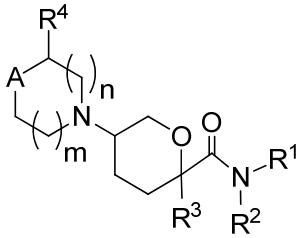
each R^x is independently selected from the group consisting of halogen, -CN, -R^c, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, -$OC(O)NR^aR^b$, -$NR^bC(O)R^a$, -$NR^bC(O)_2R^c$, -NR^a-$C(O)NR^aR^b$, -$NR^aC(O)NR^aR^b$, -NR^aR^b, -OR^a, -O-X^1-OR^a, -O-X^1-NR^aR^b, -O- X^1-CO_2R^a, -O-X^1-$CONR^aR^b$, -X^1-OR^a, -X^1-NR^aR^b, - X^1-CO_2R^a, -X^1-$CONR^aR^b$, -SF_5, -$S(O)_2NR^aR^b$, and 5- or 6-membered aryl or heteroaryl, wherein each X^1 is a C_{1-4} alkylene; each R^a and R^b is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^c is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl; and optionally when two R^x substituents are on adjacent atoms, are combined to form a fused five or six-membered carbocyclic ring, and wherein the aryl or heteroaryl groups are optionally substituted with 1-3 members selected from halogen, hydroxyl, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^y is independently selected from the group consisting of halogen, -CN, -R^f, -CO_2R^d, -$CONR^dR^e$, -$C(O)R^d$, -$OC(O)NR^dR^e$, -$NR^eC(O)R^d$, -$NR^eC(O)_2R^f$, -$NR^dC(O)NR^dR^e$, -$NR^dC(O)NR^dR^e$, -NR^dR^e, -OR^d, and -$S(O)_2NR^dR^e$; wherein each R^d and R^e is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S; each R^f is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl;

each R^z is independently selected from the group consisting of halogen, -CN, -R^i, -CO_2R^g, -$CONR^gR^h$, -$C(O)R^g$, -$OC(O)NR^gR^h$, -$NR^hC(O)R^g$, -$NR^hC(O)_2R^i$, -$NR^gC(O)NR^gR^h$, -NR^gR^h, -OR^g, -$S(O)_2NR^gR^h$, -X^1-R^j, -X^1-NR^gR^h, -X^1-CO NR^gR^h, -X^1-$NR^hC(O)R^g$, -NHR^j, -$NHCH_2R^j$, and tetrazole; wherein each R^g and R^h is

independently selected from hydrogen, C_{1-8} alkyl, C_{3-6} cycloalkyl and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S and is optionally substituted with one or two oxo; each R^i is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl; and each R^j is selected from the group consisting of C_{3-6} cycloalkyl, pyrrolinyl, piperidinyl, morpholinyl, tetrahydrofuranyl, and tetrahydropyranyl.

2. A compound having the formula



(I);

or a pharmaceutically acceptable salt, hydrate, stereoisomer or rotamer thereof; wherein

A is $C(R^5)(R^6)$ or $N(R^5)$

the subscripts m and n are each independently integers of from 0 to 2, and m + n is ≤ 3;

R^1 is selected from the group consisting of aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein the heteroaryl portion has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups or portions are optionally substituted with from 1 to 5 R^x substituents;

R^2 is selected from the group consisting of H, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein the heteroaryl portion has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups or portions are optionally substituted with from 1 to 4 R^x substituents;

or optionally, R^1 and R^2 are combined with the nitrogen atom to which each is attached to form a 6- to 11-membered heterocyclic or heteroaryl ring, optionally substituted with from 1 to 4 R^x substituents;

R^3 is selected from the group consisting of H, C_{1-8} alkyl, C_{3-8} cycloalkyl and C_{3-8} cycloalkyl-C_{1-4} alkyl, each of which is optionally substituted with from 1-3 R^y substituents;

R^4 is selected from the group consisting of H, C_{1-8} alkyl optionally substituted with 1 to 2 R^y, and $-CO_2H$:

R^5 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyloxy, C_{3-8} cycloalkyl-C_{1-4} alkyl, C_{1-8} alkylamino, di-C_{1-8} alkylamino, aryl, aryloxy, arylamino, aryl-C_{1-4} alkyl, heteroaryl, heteroaryloxy, heteroarylamino and heteroaryl-C_{1-4} alkyl, each of which is optionally substituted with from 1 to 5 R^z substituents;

R^6 is selected from the group consisting of H, F, OH, C_{1-8} alkyl and C_{1-8} alkoxy, wherein the C_{1-8} alkyl and C_{1-8} alkoxy groups are optionally substituted with from 1 to 3 R^z substituents;

or optionally, R^5 and R^6 are joined to form a spirocyclic 5- or 6-membered cycloalkyl ring which is optionally unsaturated, and has a fused aryl group which is optionally substituted with from 1 to 4 R^z substituents;

each R^x is independently selected from the group consisting of halogen, -CN, -R^c, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, -$OC(O)NR^aR^b$, -$NR^bC(O)R^a$, -$NR^bC(O)_2R^c$, -NR^a-$C(O)NR^aR^b$, -$NR^aC(O)NR^aR^b$, -NR^aR^b, -OR^a, and -$S(O)_2NR^aR^b$; wherein each R^a and R^b is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^c is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl; and optionally when two R^x substituents are on adjacent atoms, are combined to form a fused five or six-membered carbocyclic ring;

each R^y is independently selected from the group consisting of halogen, -CN, -R^f, -CO_2R^d, -$CONR^dR^e$, -$C(O)R^d$, -$OC(O)NR^dR^e$, -$NR^eC(O)R^d$, -$NR^eC(O)_2R^f$, -$NR^dC(O)NR^dR^e$, -$NR^dC(O)NR^dR^e$, -NR^dR^e, -OR^d, and -$S(O)_2NR^dR^e$; wherein each R^d and R^e is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S; each R^f is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl;

each R^z is independently selected from the group consisting of halogen, -CN, -R^i, -CO_2R^g, -$CONR^gR^h$, -$C(O)R^g$, -$OC(O)NR^gR^h$, -$NR^hC(O)R^g$, -$NR^hC(O)_2R^i$, -$NR^gC(O)NR^gR^h$, -NR^gR^h, -OR^g, -$S(O)_2NR^gR^h$, -X^1-R^j, -X^1-NR^gR^h, -X^1-$CONR^gR^h$, -X^1-$NR^hC(O)R^g$, -NHR^j and -$NHCH_2R^j$, wherein X^1 is a C_{1-4} alkylene; each R^g and R^h is independently selected from hydrogen, C_{1-8} alkyl, C_{3-6} cycloalkyl and C_{1-8}

haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S and is optionally substituted with one or two oxo; each R^i is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl; and each R^j is selected from the group consisting of C_{3-6} cycloalkyl, pyrrolinyl, piperidinyl, morpholinyl, tetrahydrofuranyl, and tetrahydropyranyl.

3. The compound of of any of claims **1** or **2**, wherein R^3 is a member selected from the group consisting of H, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, cyclopropyl, cyclopropylmethyl, cyclobutyl and cyclobutylmethyl.

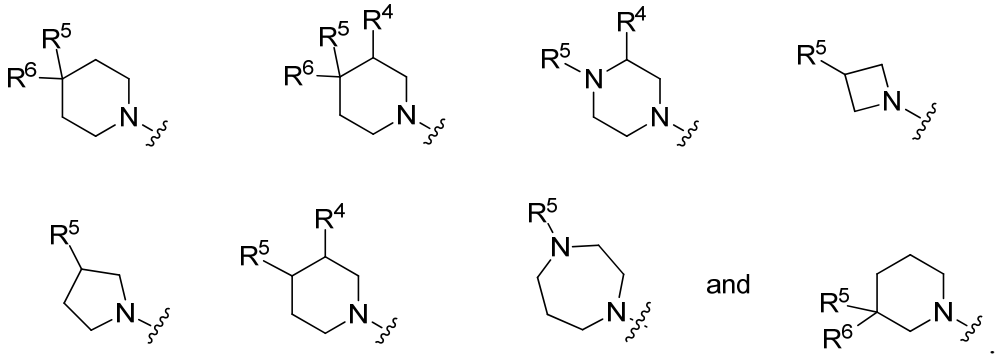
4. The compound of any one of claims **1** or **2**, wherein m and n are both 0.

5. The compound of any one of claims **1** or **2**, wherein m and n are both 1.

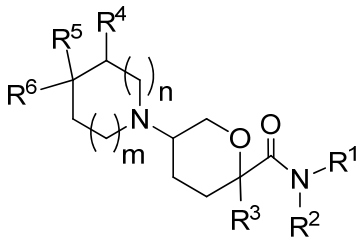
6. The compound of any one of claims **1** or **2**, wherein m is 1 and n is 0.

7. The compound of any one of claims **1** or **2**, wherein m is 1 and n is 2.

8. The compound of any one of claims **1**, **2**, **3**, **4**, **5, 6 or 7**, wherein the ring having vertex A is represented by a formula selected from the group consisting of:

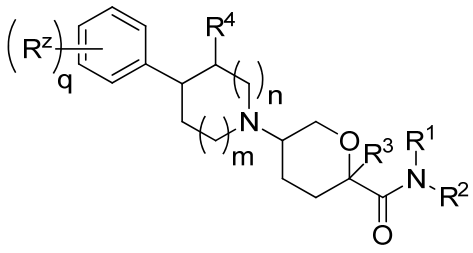


9. The compound of any one of claims **1** or **2**, having the formula:



(Ia).

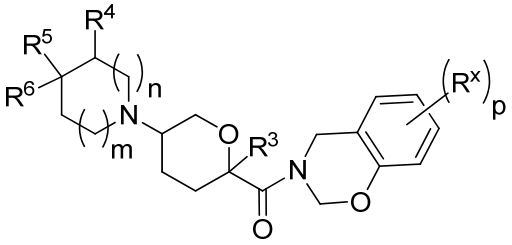
10. The compound of any one of claims **1**, **2** or **9**, having the formula:



(Ia1)

wherein the subscript q is an integer of from 1 to 5**.**

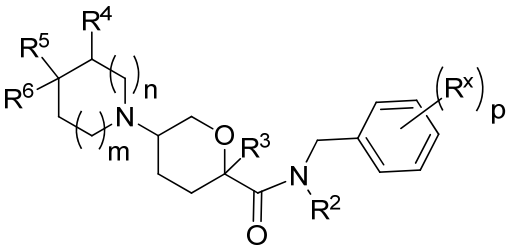
11. The compound of any one of claims **1**, **2** or **9**, having the formula:



(Ia2).

wherein the subscript p is an integer of from 1 to 4.

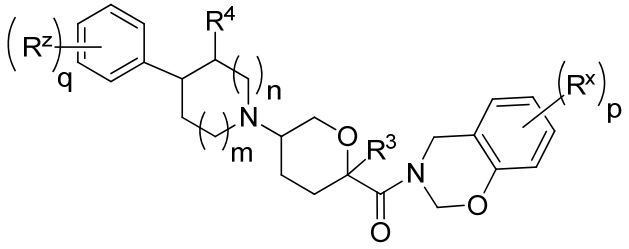
12. The compound of any one of claims **1**, **2** or **9**, having the formula:



(Ia3)

wherein the subscript p is an integer of from 1 to 5.

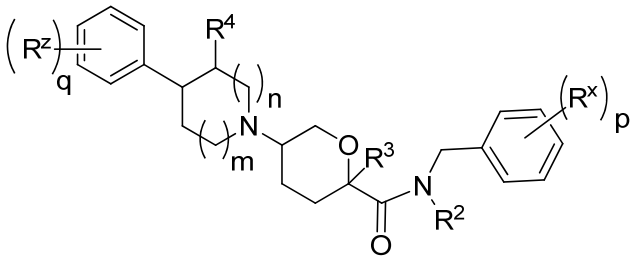
13. The compound of any one of claims **1**, **2, 9** or **11**, having the formula:



(Ia4)

wherein the subscript q is an integer of from 1 to 5, and the subscript p is an integer of from 1 to 4.

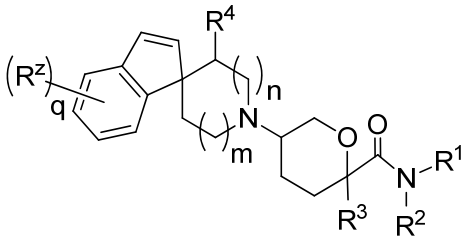
14. The compound of any one of claims **1**, **2, 9, 10** or **12**, having the formula:



(Ia5)

wherein the subscript q is an integer of from 1 to 5, and the subscript p is an integer of from 1 to 5.

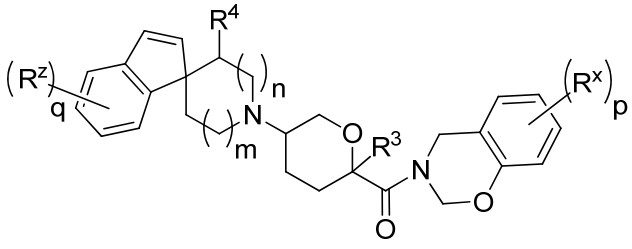
15. The compound of any one of claims **1**, **2** or **9**, having the formula:



(Ib)

wherein the subscript q is an integer of from 1 to 4.

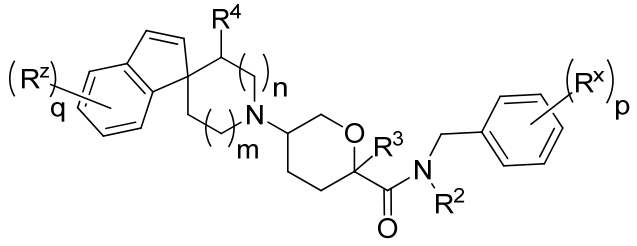
16. The compound of any one of claims **1**, **2**, **9** or **15**, having the formula:



(Ib1)

wherein the subscript q is an integer of from 1 to 4, and the subscript p is an integer of from 1 to 4.

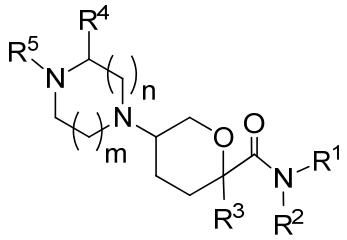
17. The compound of any one of claims **1**, **2**, **9** or **15**, having the formula:



(Ib2)

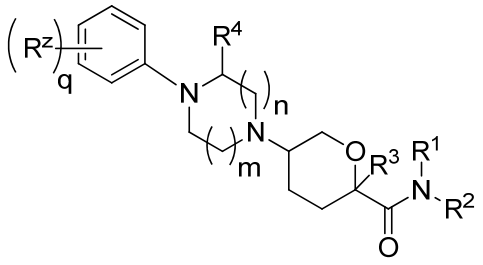
wherein the subscript q is an integer of from 1 to 4, and the subscript p is an integer of from 1 to 5:

18. The compound of any one of claims **1** or **2**, having the formula:



(Ic).

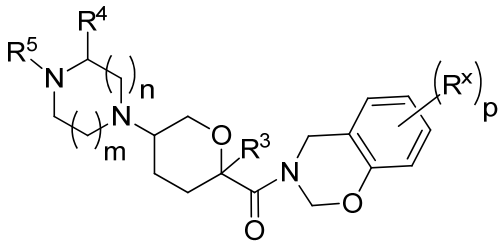
19. The compound of any one of claims **1**, **2** or **18**, having the formula:



(Ic1)

wherein the subscript q is an integer of from 1 to 5.

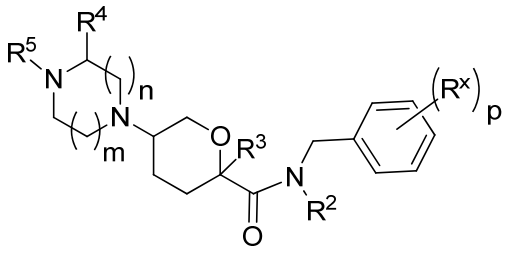
20. The compound of any one of claims **1**, **2** or **18**, having the formula:



(Ic2)

wherein the p is an integer of from 1 to 4.

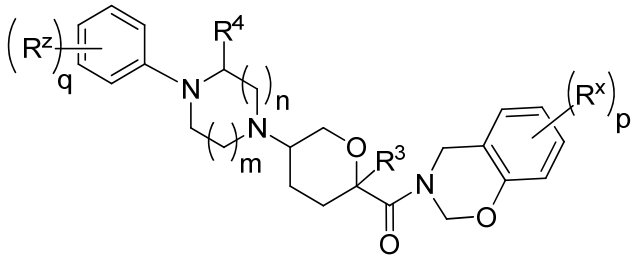
21. The compound of any one of claims **1**, **2** or **18**, having the formula:



(Ic3)

wherein the subscript p is an integer of from 1 to 5.

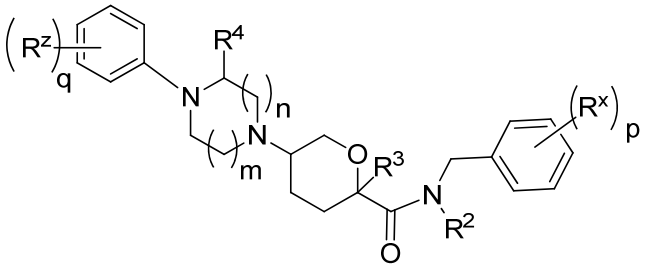
22. The compound of any one of claims **1**, **2**, **18** or **20**, having the formula:



(Ic4)

wherein the subscript q is an integer of from 1 to 5, and the subscript p is an integer of from 1 to 4.

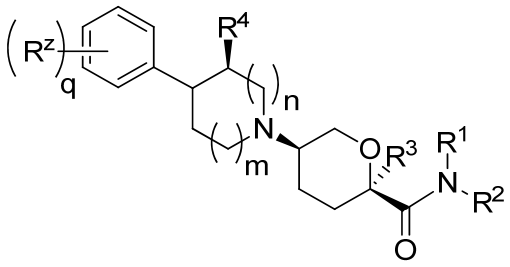
23. The compound of any one of claims **1**, **2**, **18** or **19**, having the formula:



(Ic5)

wherein the subscript q is an integer of from 1 to 5, and the subscript p is an integer of from 1 to 5.

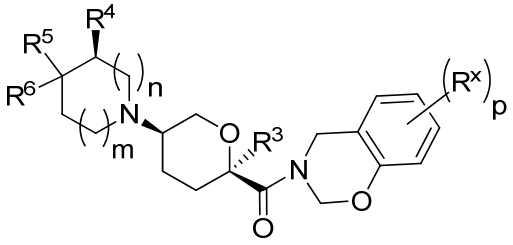
24. The compound of any one of claims **1**, **2**, **9** or **10**, having the formula:



(Ia1'),

wherein the subscript q is an integer of from 1 to 5, and wherein said compound is at least 90% free of other stereoisomers.

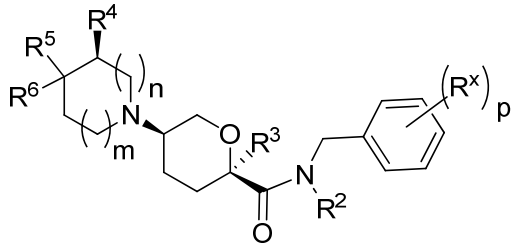
25. The compound of any one of claims **1**, **2**, **9** or **11**, having the formula:



(Ia2').

wherein the subscript p is an integer of from 1 to 4, and wherein said compound is at least 90% free of other stereoisomers.

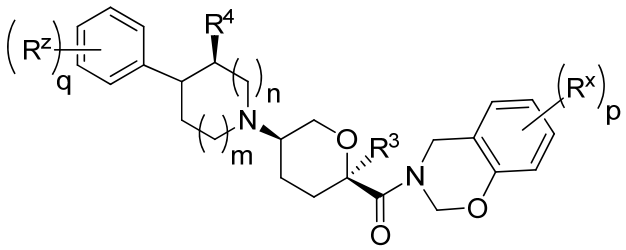
26. The compound of any one of claims **1**, **2** or **9**, having the formula:



(Ia3')

wherein the subscript p is an integer of from 1 to 5, and wherein said compound is at least 90% free of other stereoisomers.

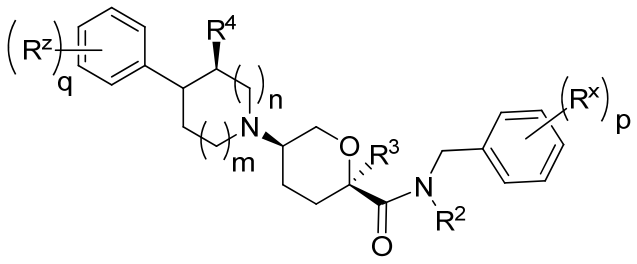
27. The compound of any one of claims **1**, **2**, **9** or **25**, having the formula:



(Ia4')

wherein the subscript q is an integer of from 1 to 5, the subscript p is an integer of from 1 to 4, and wherein said compound is at least 90% free of other stereoisomers.

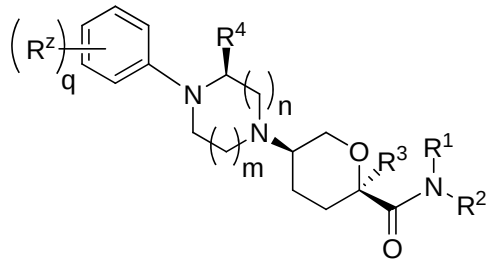
28. The compound of any one of claims **1**, **2**, **9** or **26**, having the formula:



(Ia5')

wherein the subscript q is an integer of from 1 to 5, the subscript p is an integer of from 1 to 5, and wherein said compound is at least 90% free of other stereoisomers.

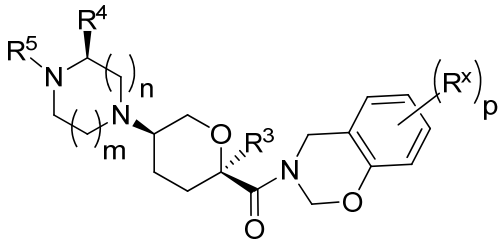
29. The compound of any one of claims **1**, **2**, **18** or **19**, having the formula:



(Ic1')

wherein said compound is at least 90% free of other stereoisomers.

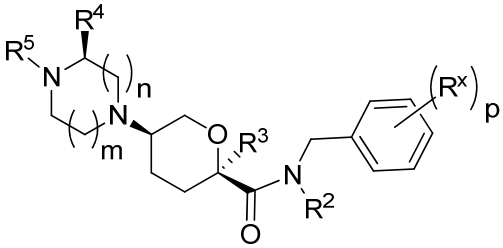
30. The compound of any one of claims **1**, **2**, or **20**, having the formula:



(Ic2')

wherein the subscript p is an integer of from 1 to 4, and wherein said compound is at least 90% free of other stereoisomers.

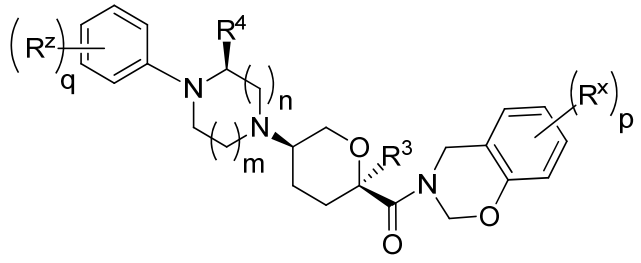
31. The compound of any one of claims **1**, **2**, **18** or **21**, having the formula:



(Ic3')

wherein the subscript p is an integer of from 1 to 5, and wherein said compound is at least 90% free of other stereoisomers.

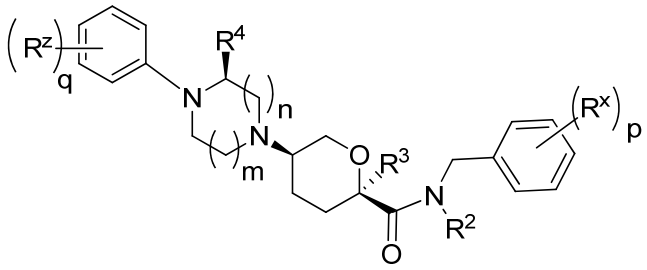
32. The compound of any one of claims **1**, **2**, **20** or **30**, having the formula:



(Ic4')

wherein the subscript q is an integer of from 1 to 5, the subscript p is an integer of from 1 to 4, and wherein said compound is at least 90% free of other stereoisomers.

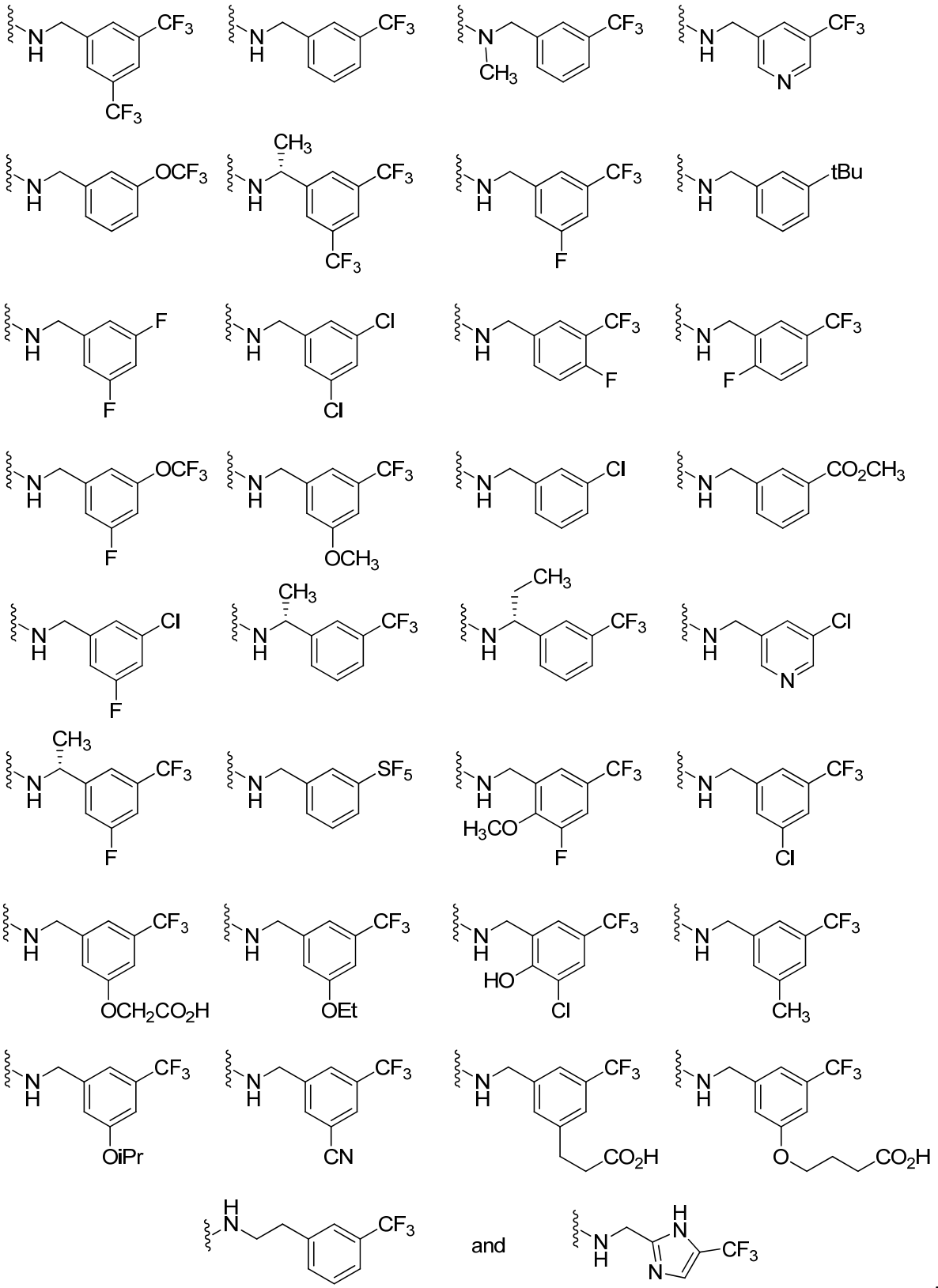
33. The compound of any one of claims **1**, **2**, **18**, **21** or **31**, having the formula:



(Ic5')

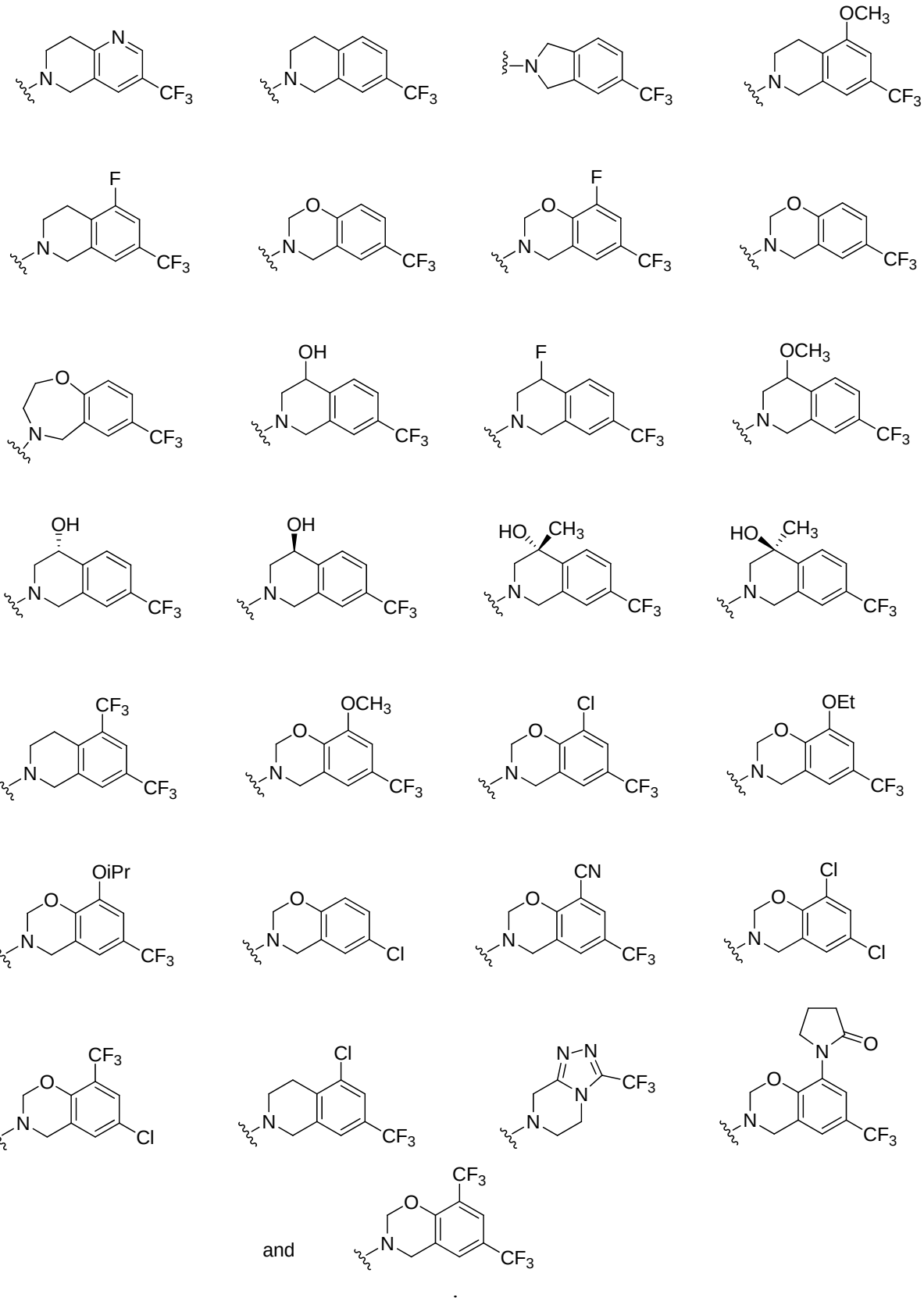
wherein the subscript q is an integer of from 1 to 5, the subscript p is an integer of from 1 to 5, and wherein said compound is at least 90% free of other stereoisomers.

34. The compound of any one of claims **1-7, 9-10, 15, 18, 19, 24,** or **29**, wherein $-N(R^1)(R^2)$ is selected from the group consisting of :



.

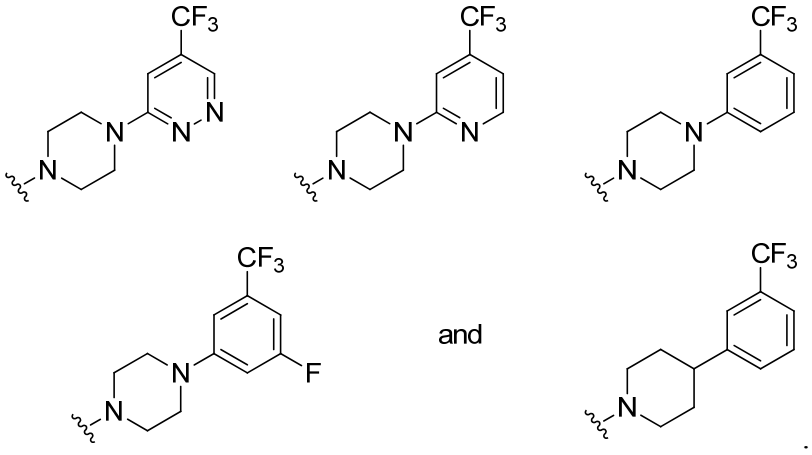
35. The compound of any one of claims **1 – 7, 9-10, 15, 18, 19, 24,** or **29**, wherein $-N(R^1)(R^2)$ is selected from the group consisting of:



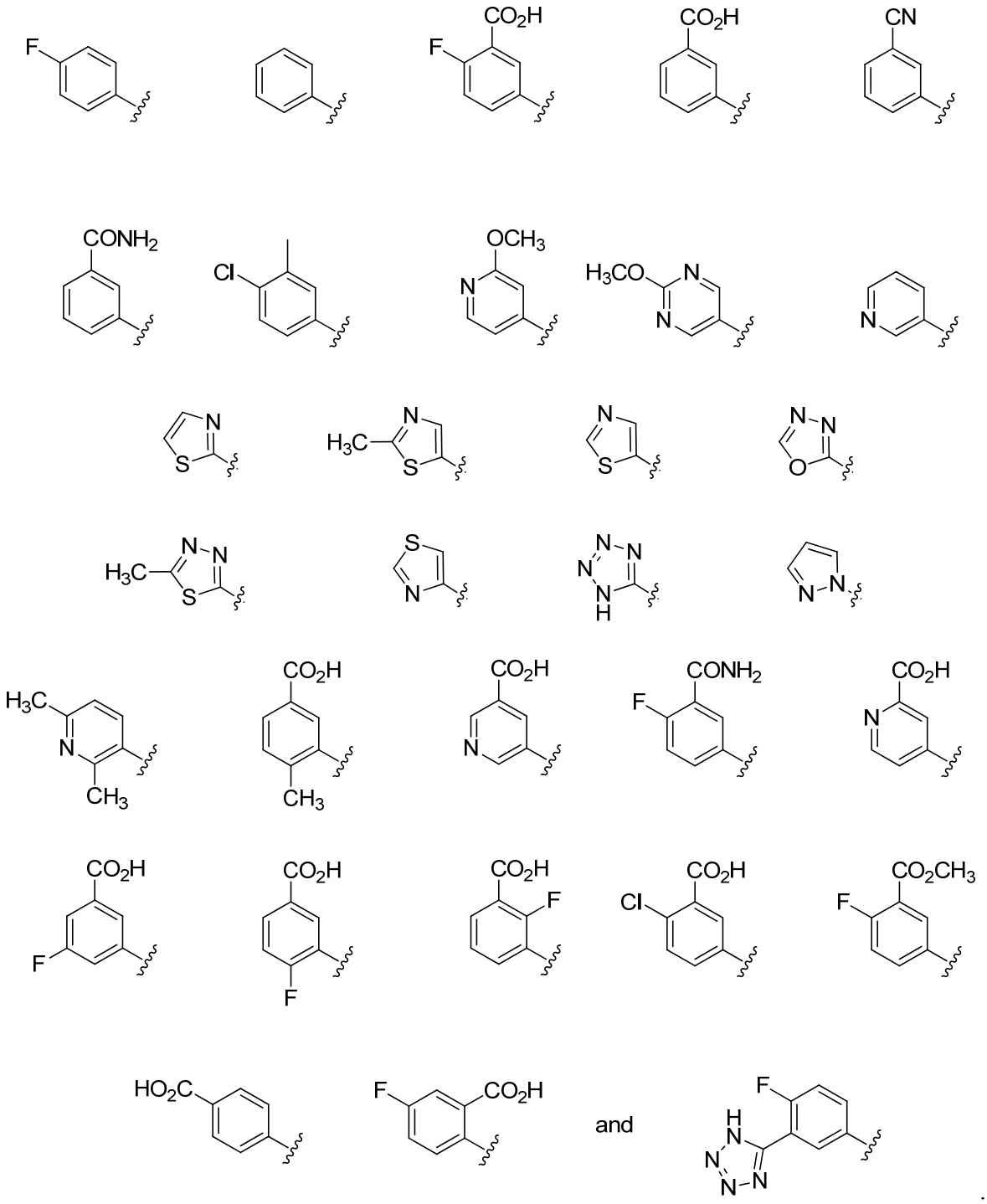
and

.

36. The compound of any one of claims **1 – 7, 15, 18, 19, 24,** or **29**, wherein -N(R^1)(R^2) is selected from the group consisting of:



37. The compound of any one of claims **1-7, 9, 11-12, or 25-26** , wherein A is $C(R^5)(R^6)$ wherein R^5 is selected from the group consisting of aryl, aryloxy, arylamino, aryl-C_{1-4} alkyl, heteroaryl, heteroaryloxy, heteroarylamino and heteroaryl-C_{1-4} alkyl, wherein the aryl or heteroaryl portions are selected from the group consisting of:

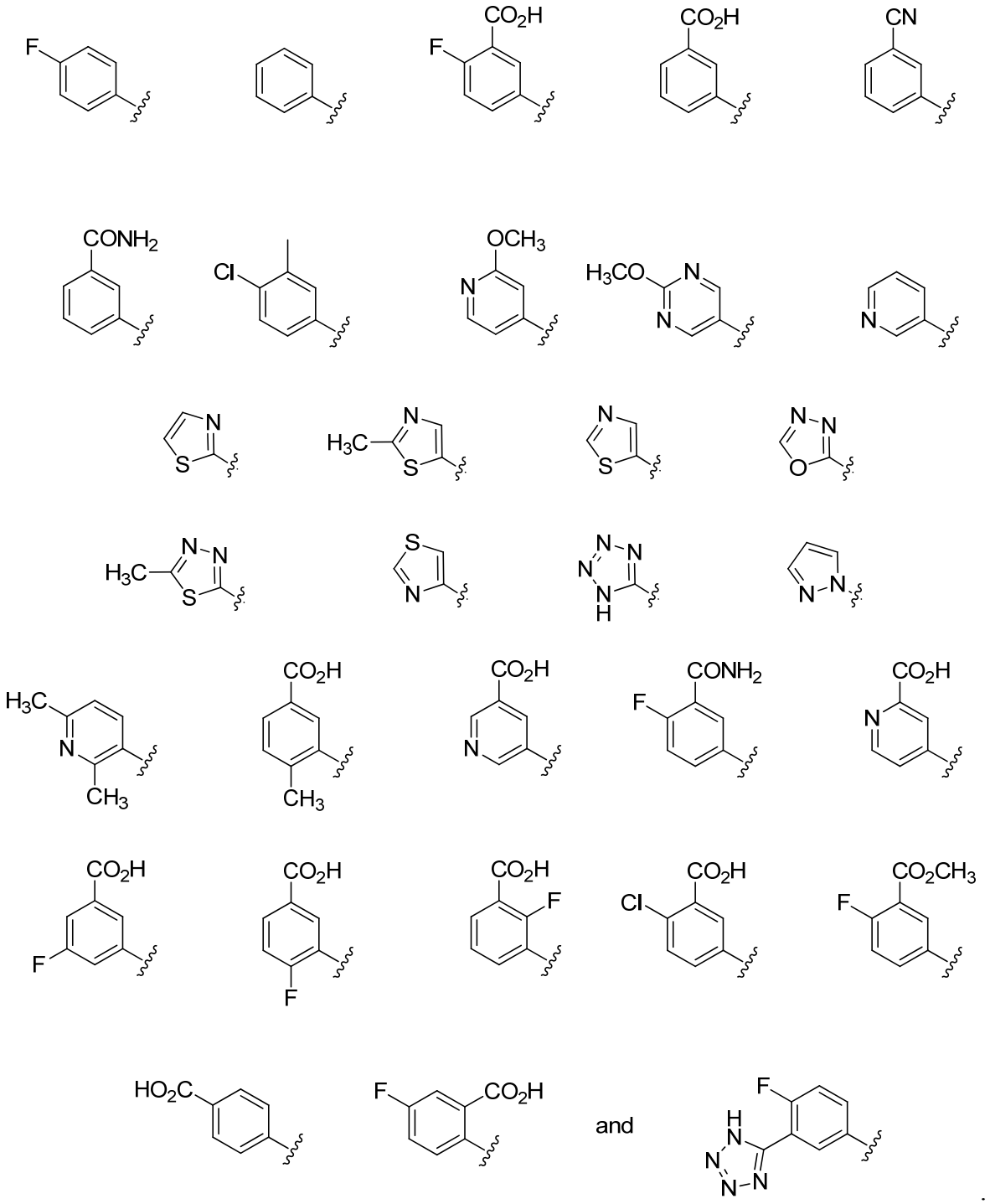


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38. The compound of claim **37**, wherein R^5 is selected from the group consisting of aryl, aryloxy, arylamino and aryl-C_{1-4} alkyl.

39. The compound of claim **37**, wherein R^5 is selected from the group consisting of heteroaryl, heteroaryloxy, heteroarylamino and heteroaryl-C_{1-4} alkyl.

40. The compound of any one of claims **1-7, 18, 20, 30,** or **31**, wherein A is N(R^5) wherein R^5 is selected from the group consisting of aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein the aryl or heteroaryl portions are selected from the group consisting of:



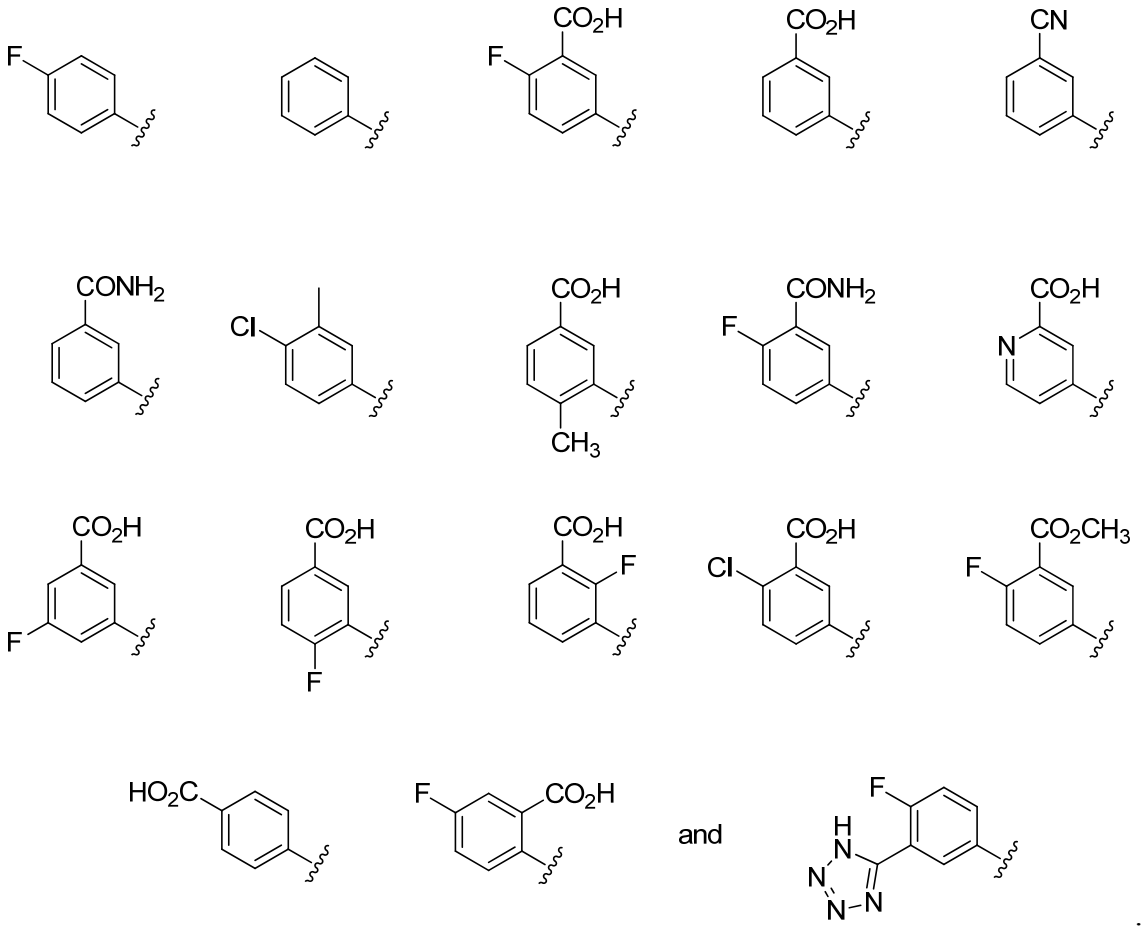
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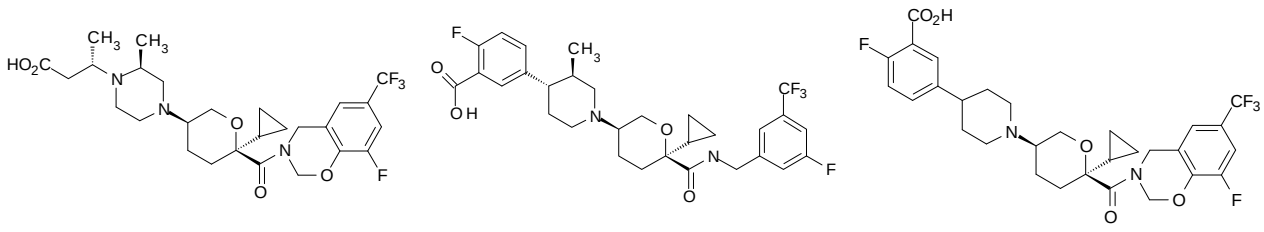
41. The compound of claim **40**, wherein R^5 is selected from the group consisting of aryl and aryl-C_{1-4} alkyl.

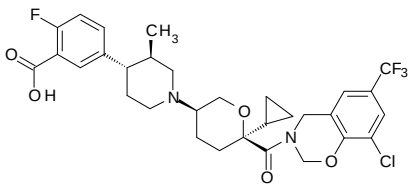
42. The compound of claim **40**, wherein R^5 is selected from the group consisting of heteroaryl and heteroaryl-C_{1-4} alkyl.

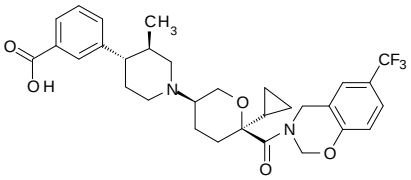
43. The compound of any one of claims **1-7, 18, 20, 30, or 31**, wherein A is N(R^5) wherein R^5 is selected from the group consisting of:

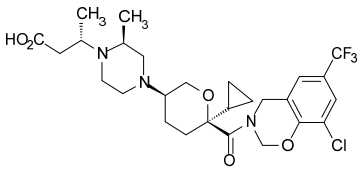


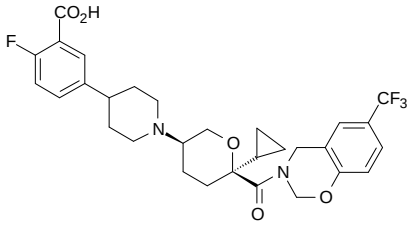
44. The compound of claim **1** or **2**, selected from the group consisting of:

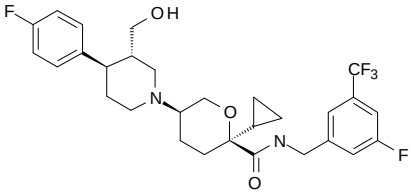


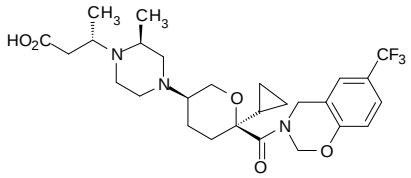


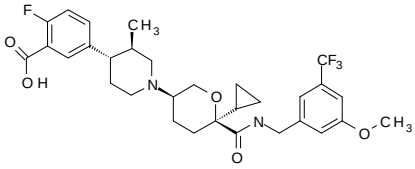


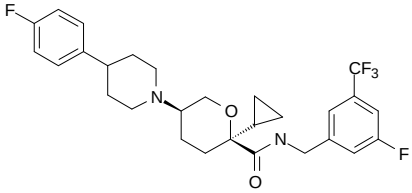


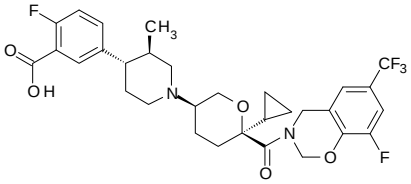


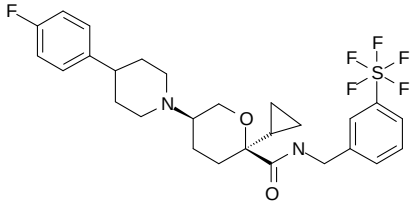


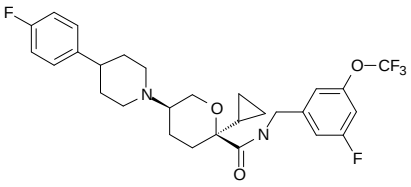


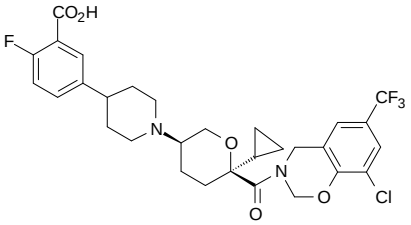


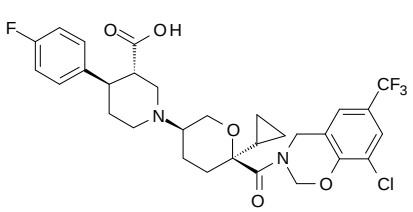


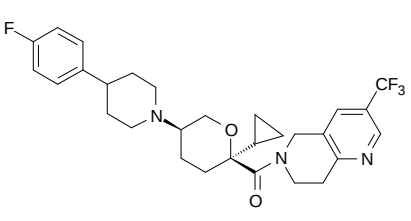




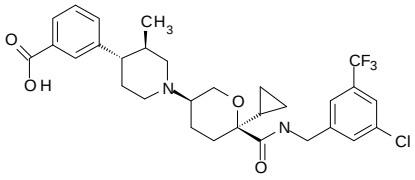
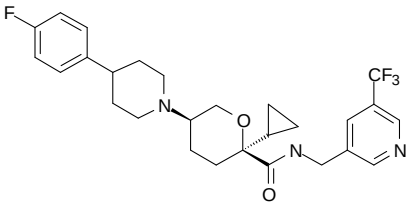
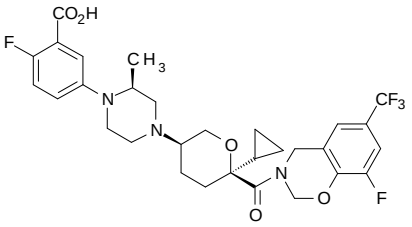
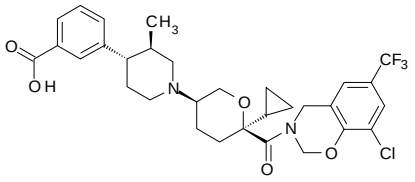
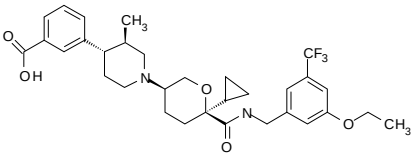
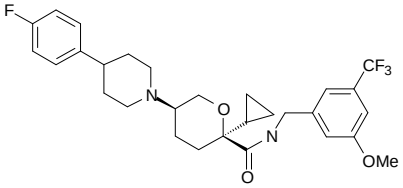
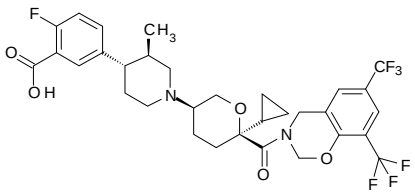
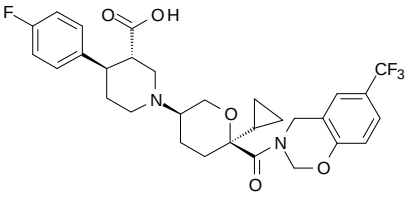
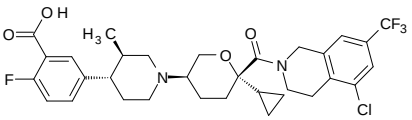
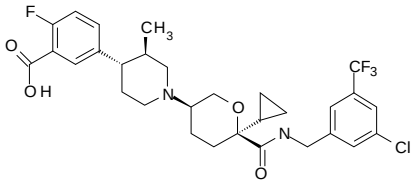
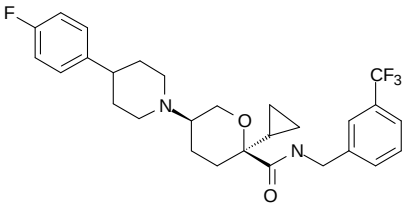
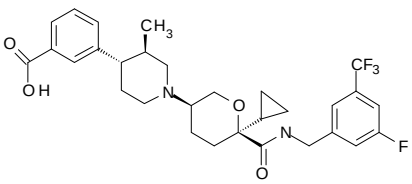
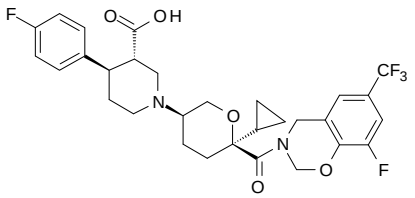
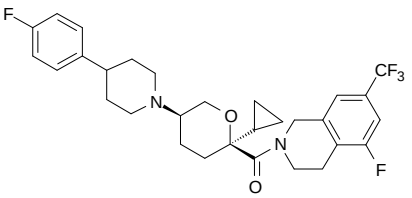
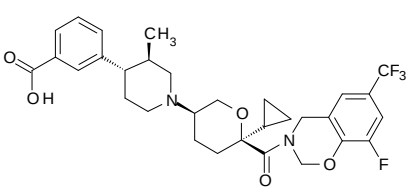




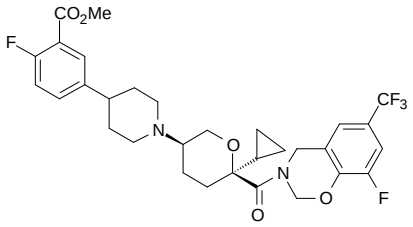


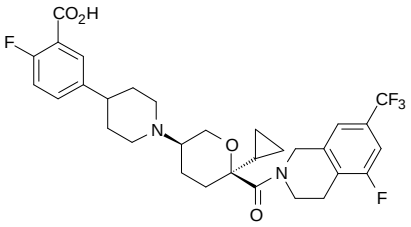


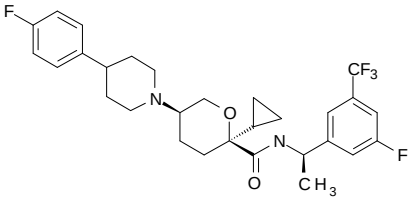


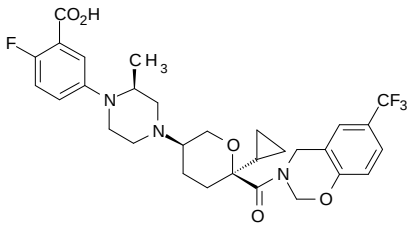
















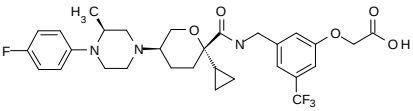


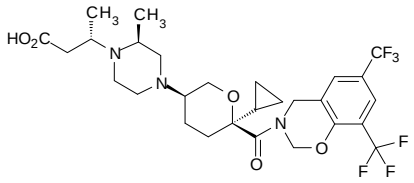


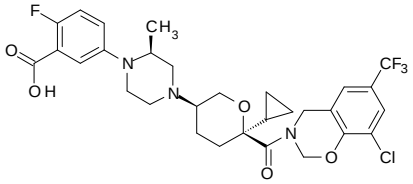


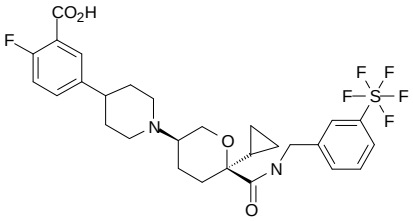


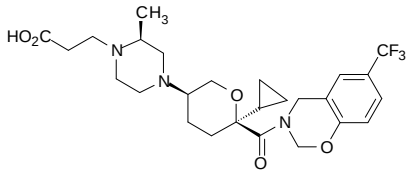


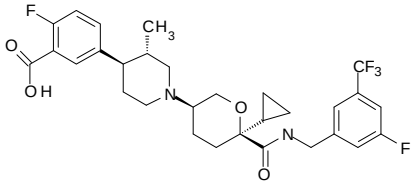


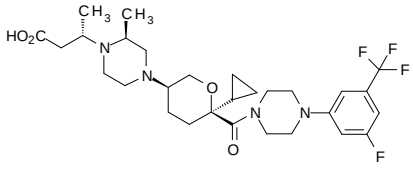


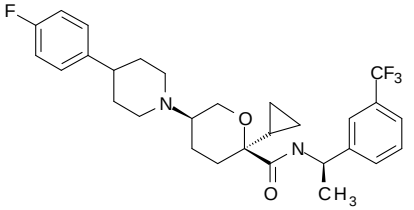


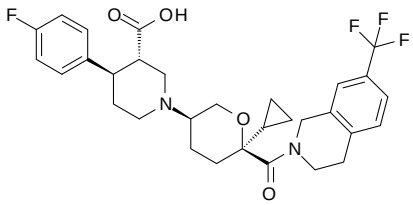


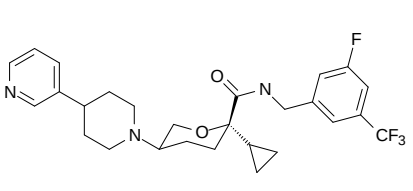


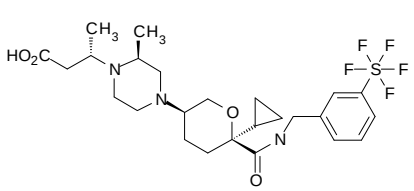




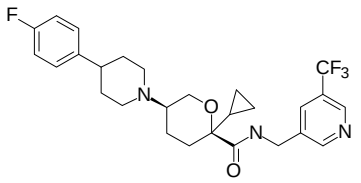


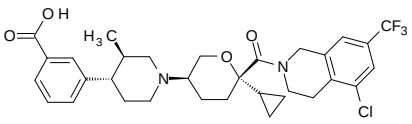


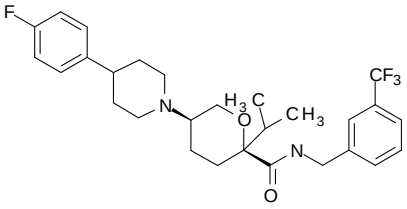


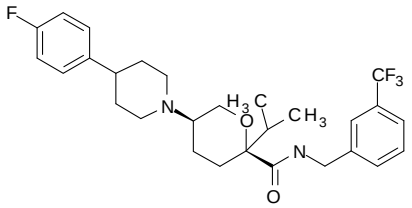


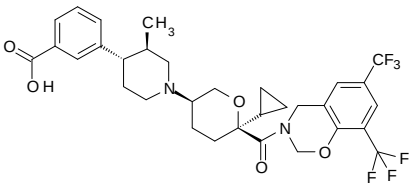


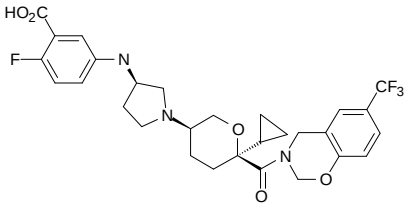


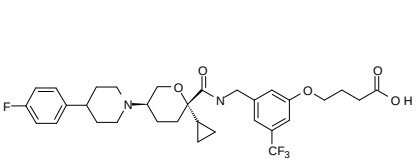


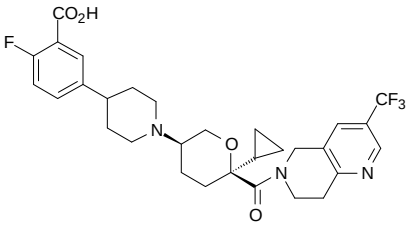


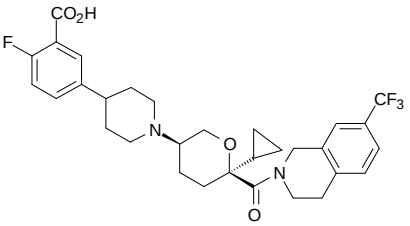


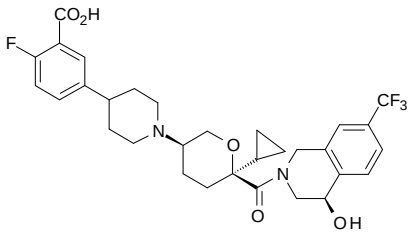


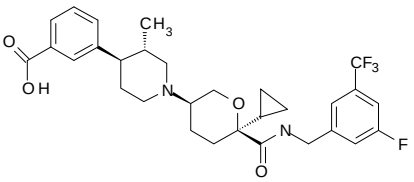


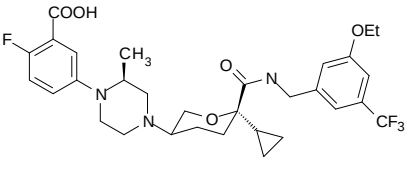


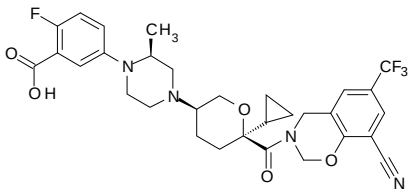


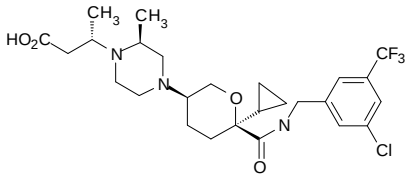


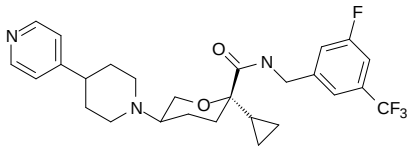


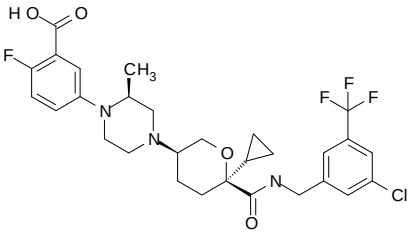


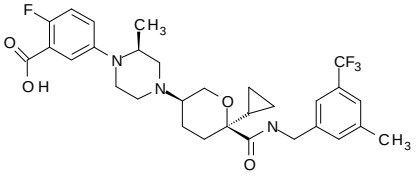


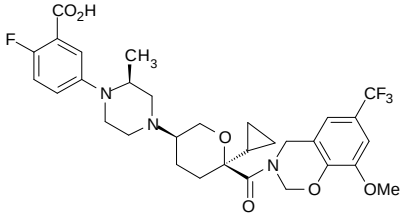


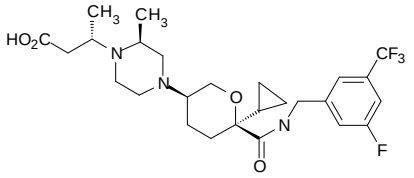


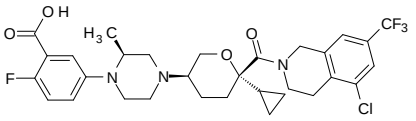


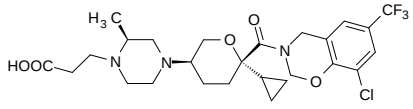


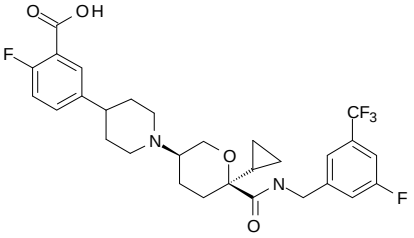


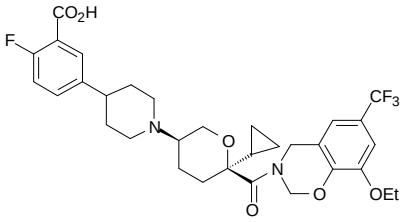


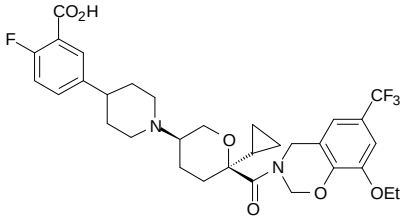


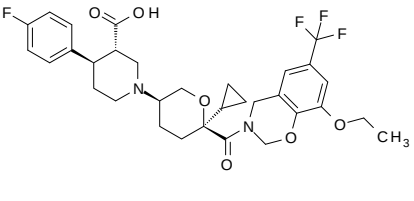


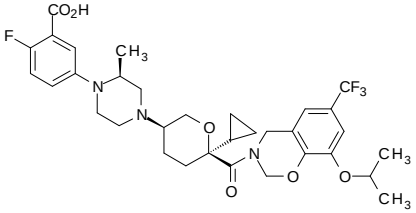


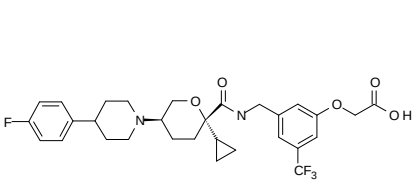


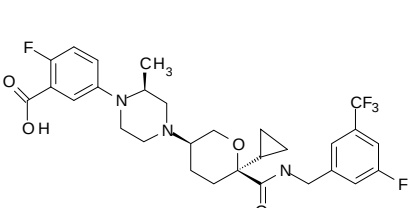


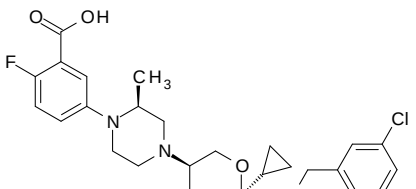


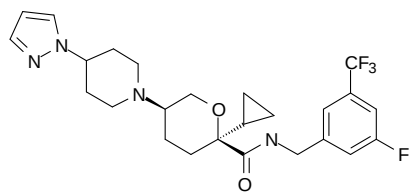


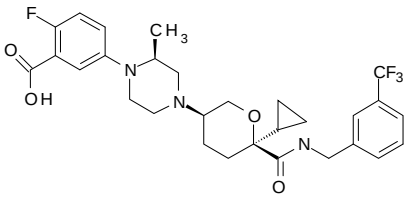


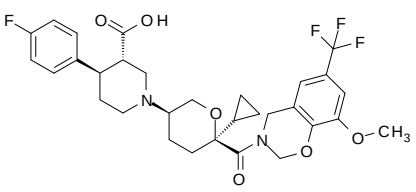


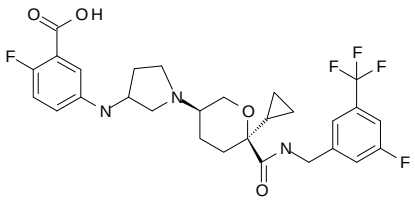


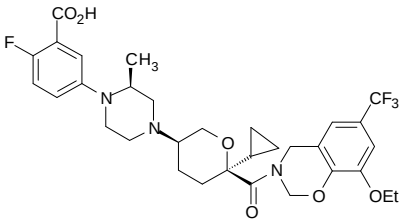


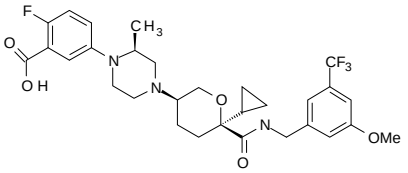


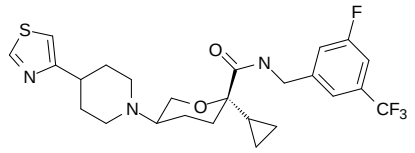


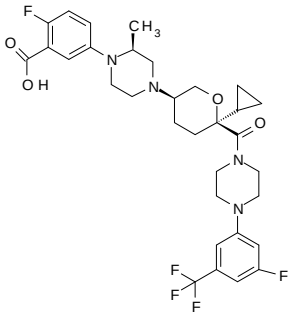


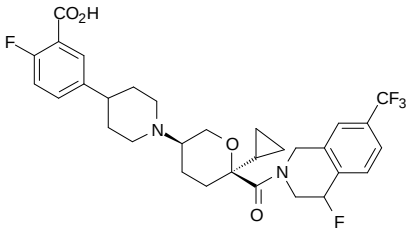


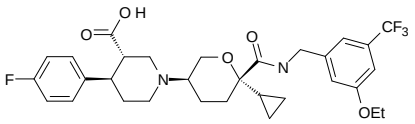


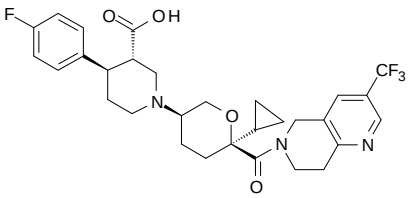


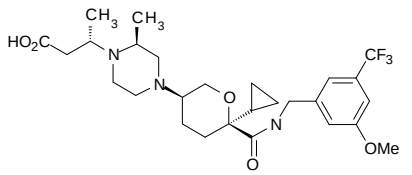


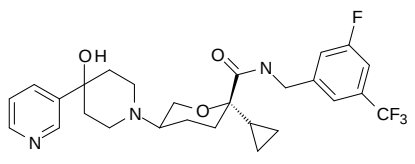


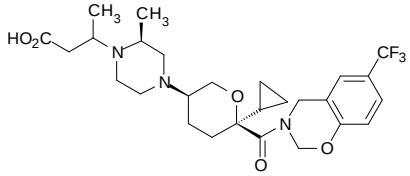


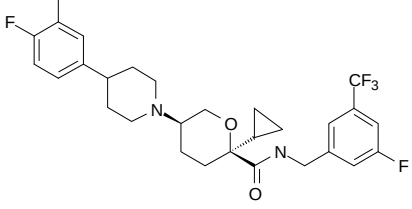


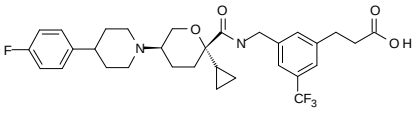


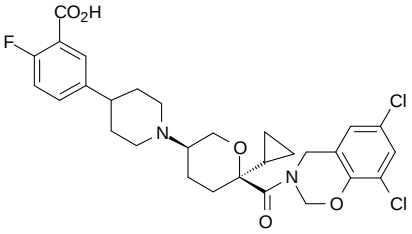


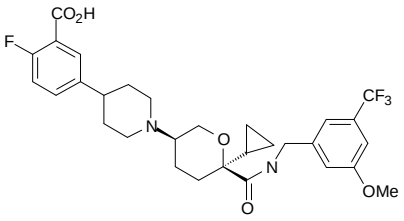


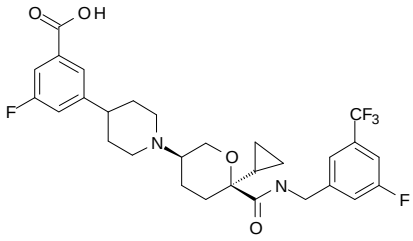


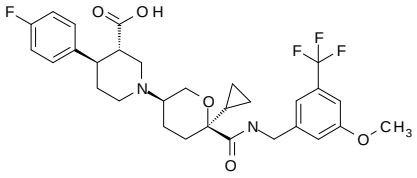


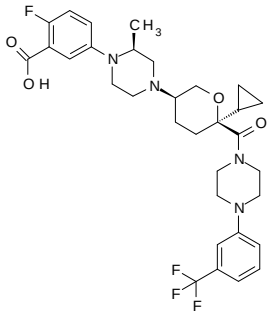


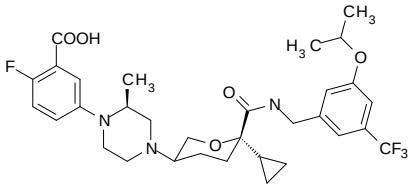


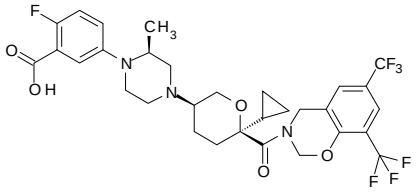


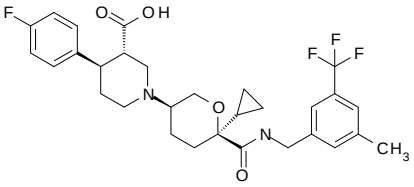


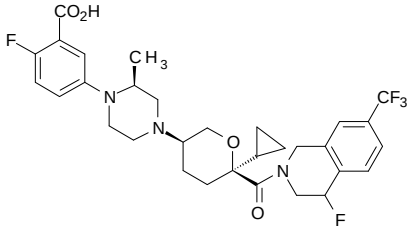


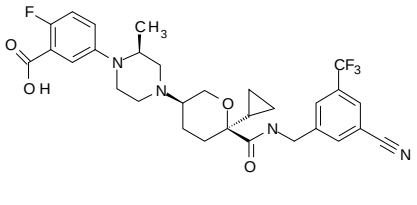


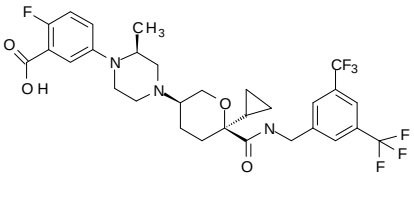


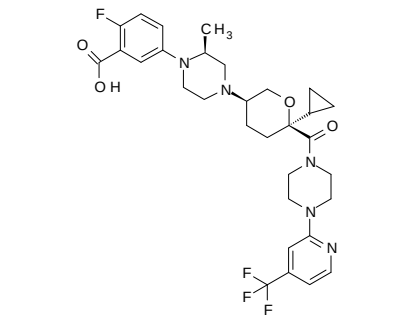


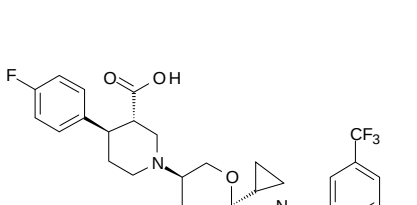


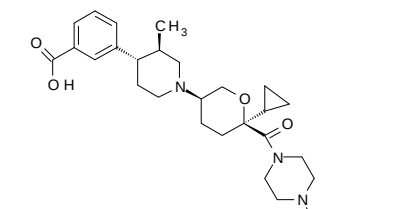


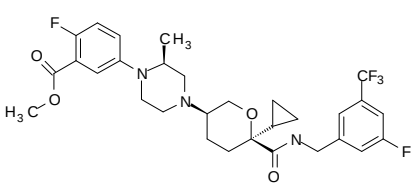


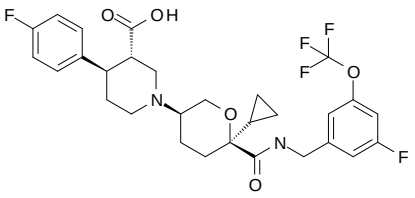


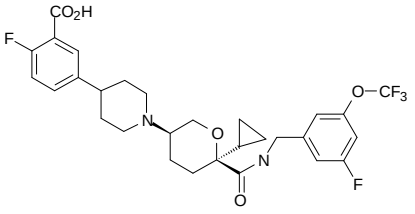


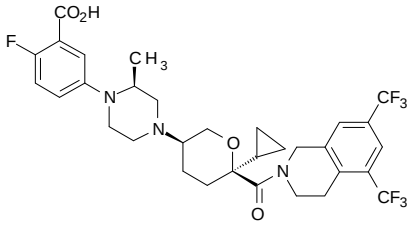


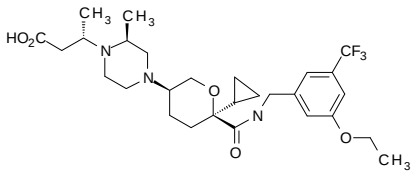


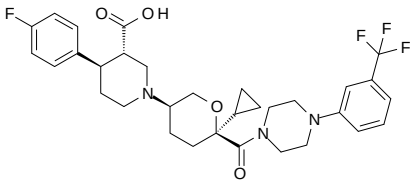


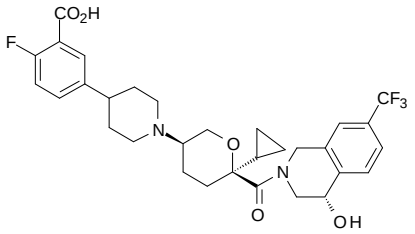


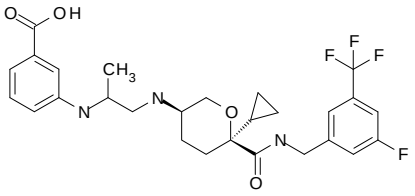


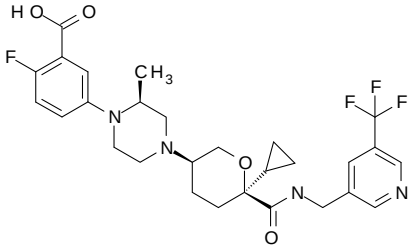


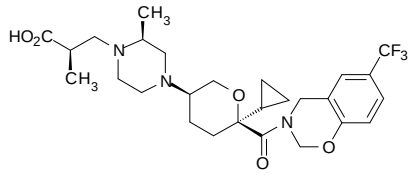


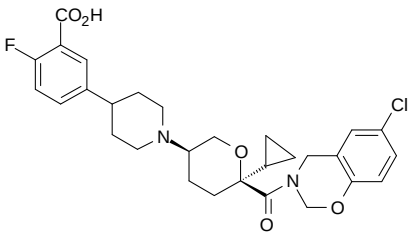


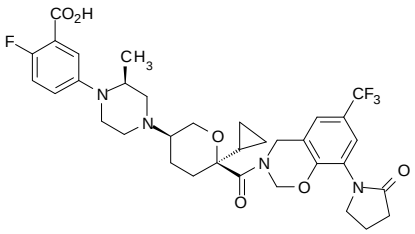


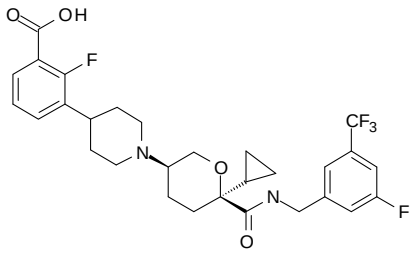


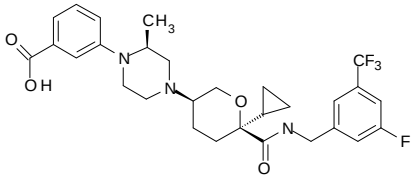
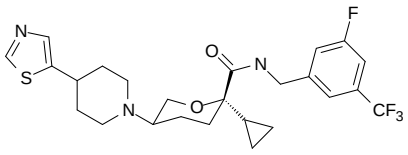
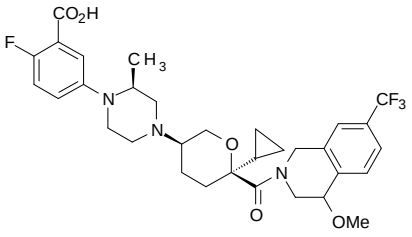
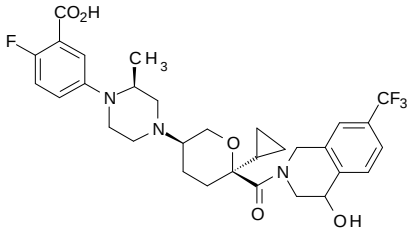
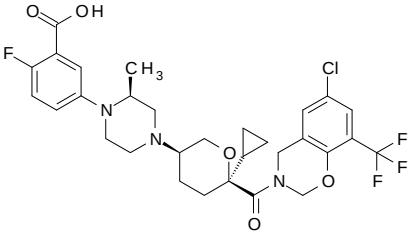
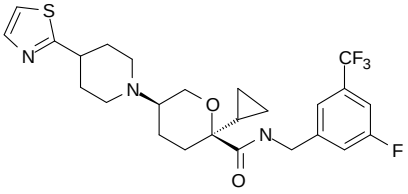
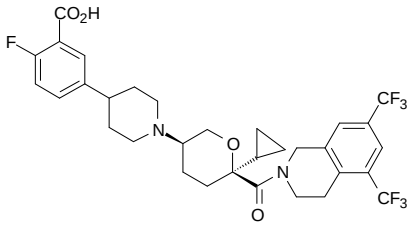
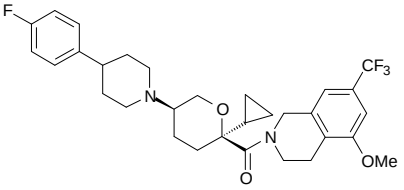
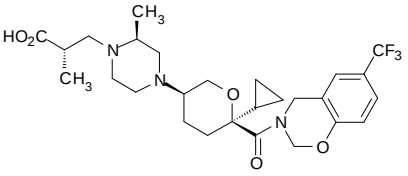
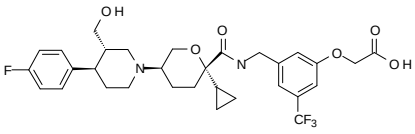
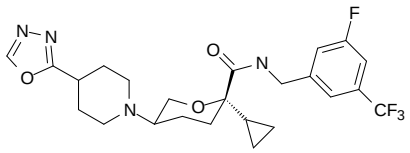
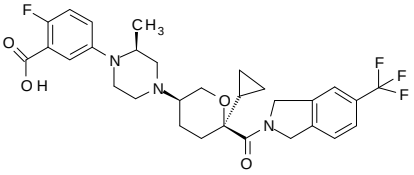
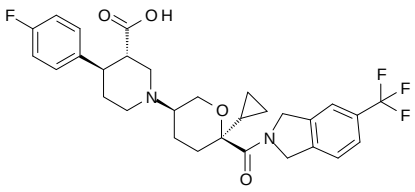
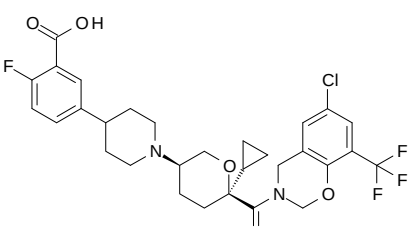
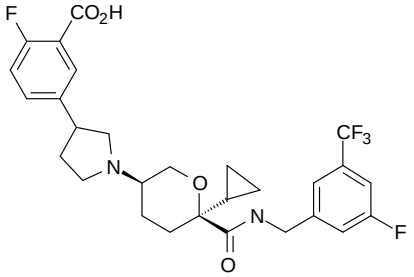


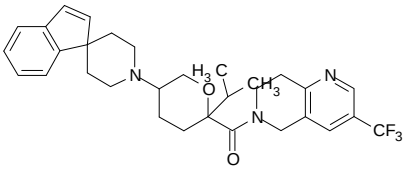


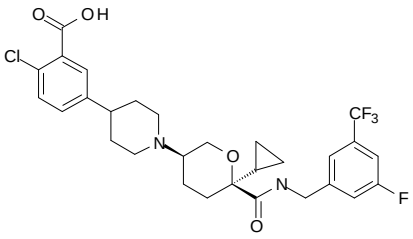


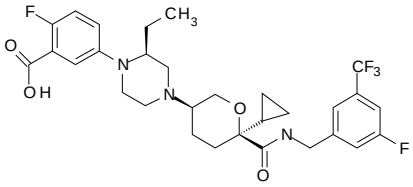


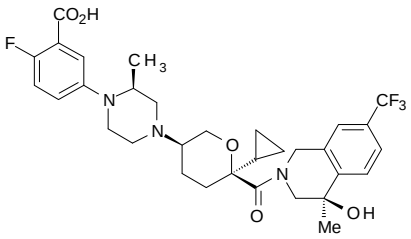


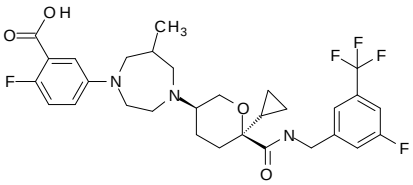
















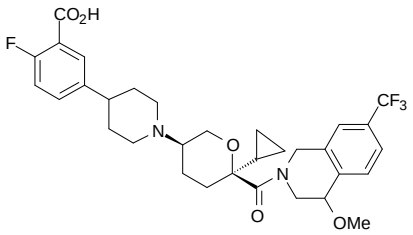


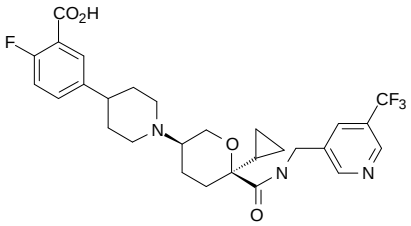


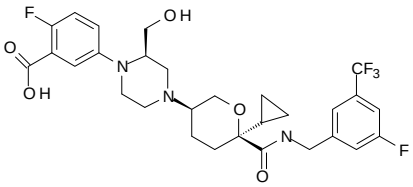


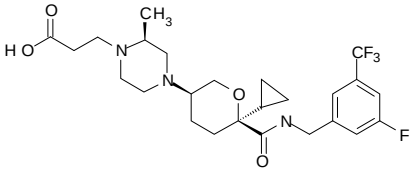


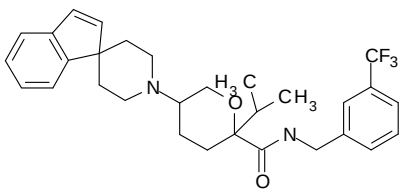


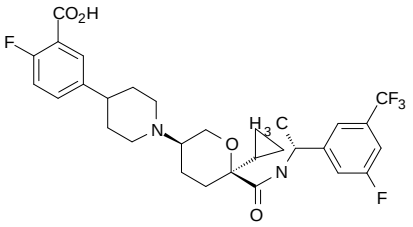


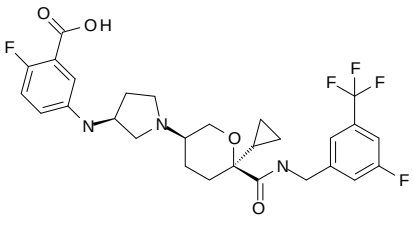


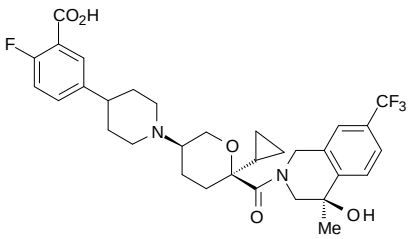


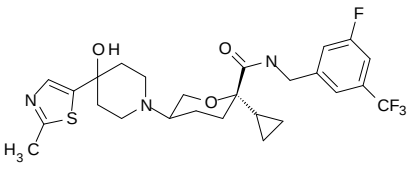


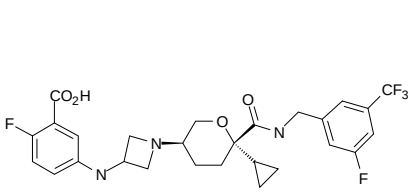


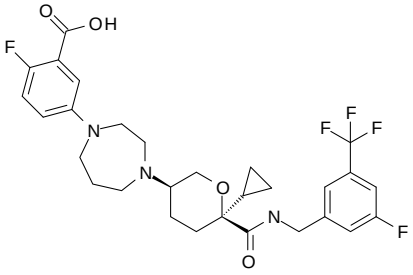


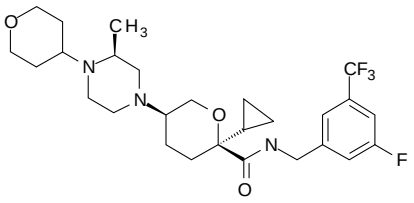


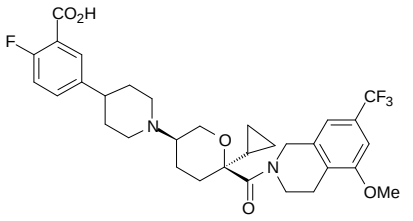


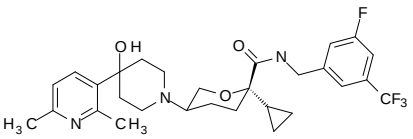


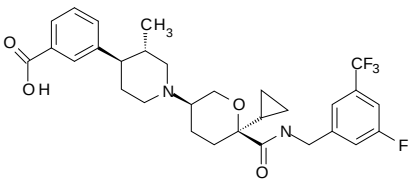


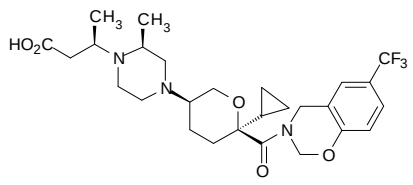


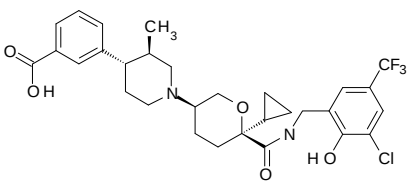


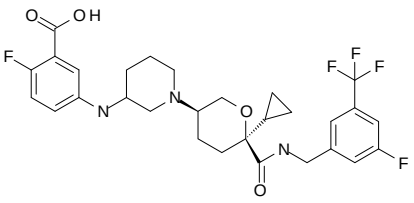


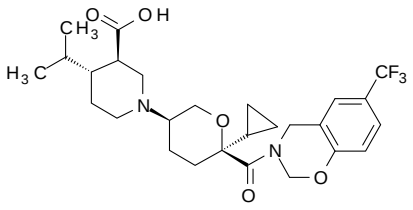


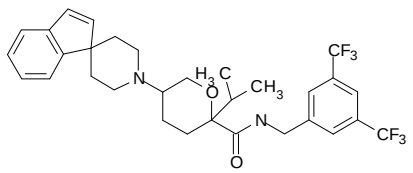


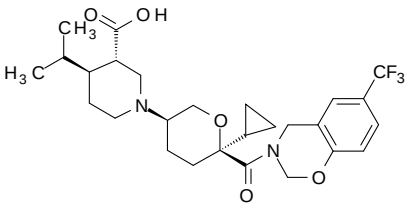


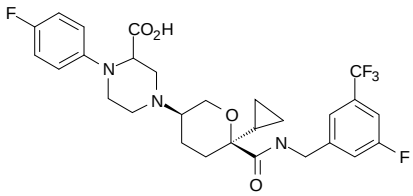


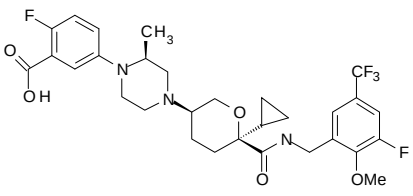


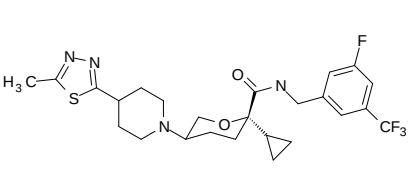


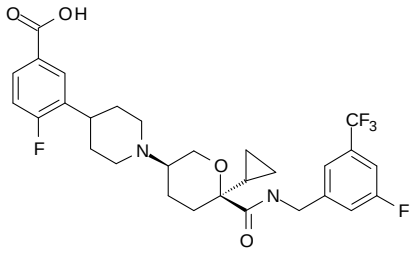


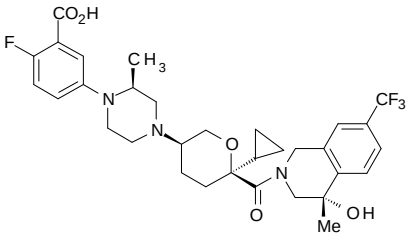


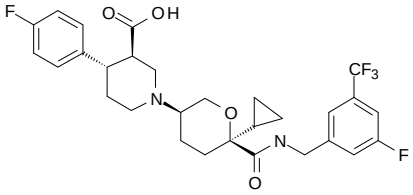


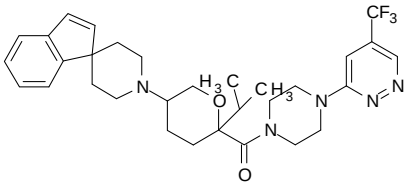


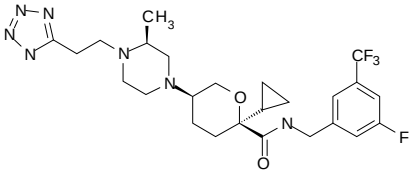


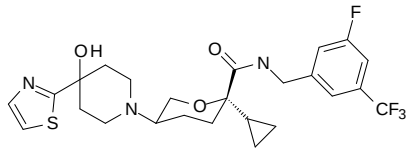


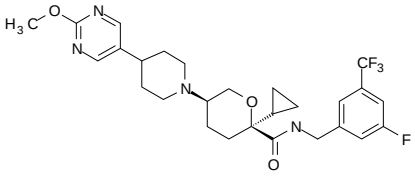


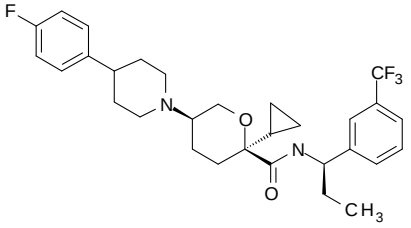


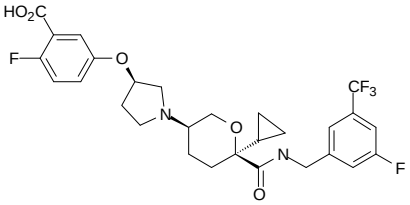


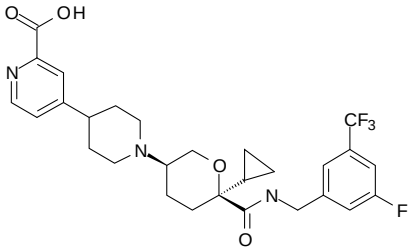


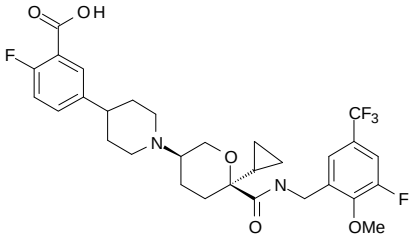


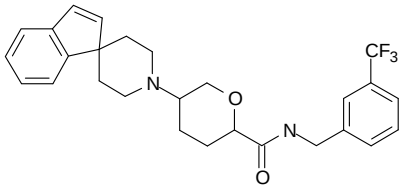


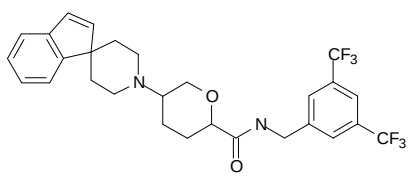


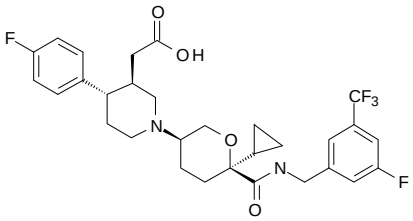


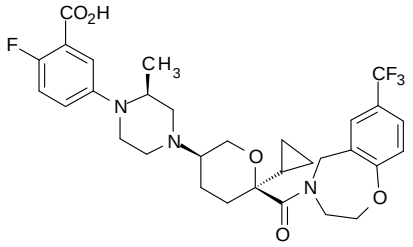


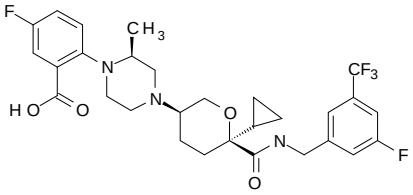


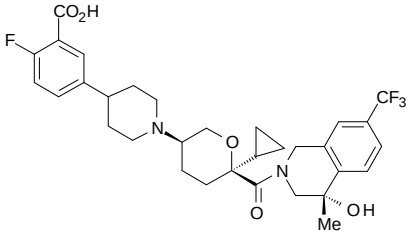


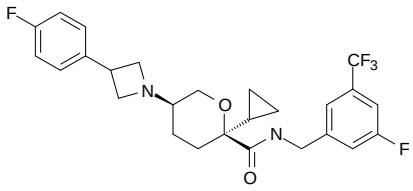


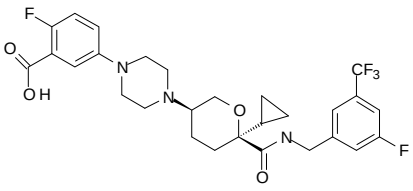


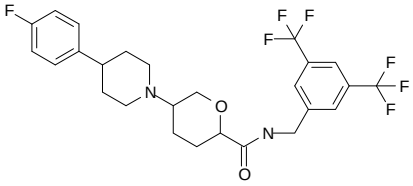


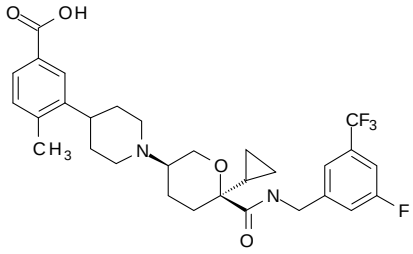


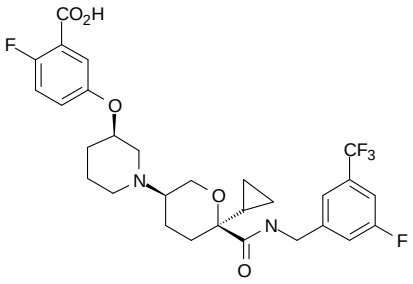


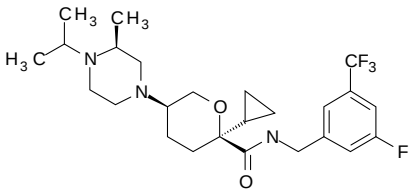


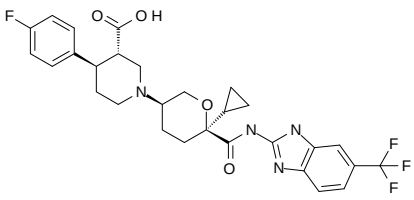


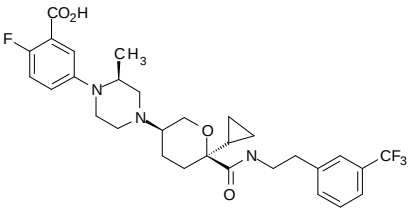


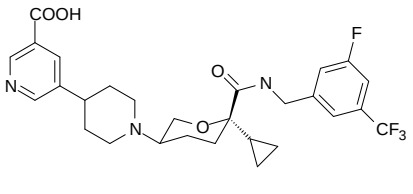


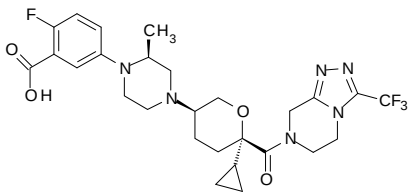


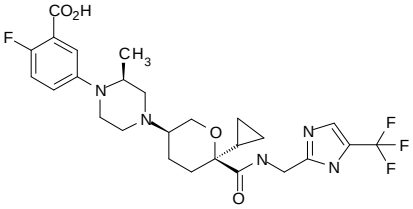


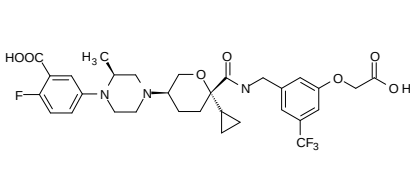


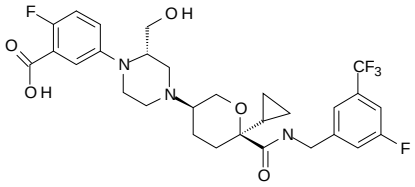


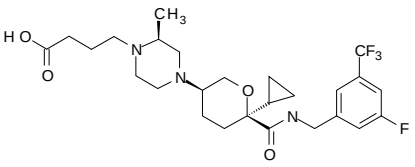


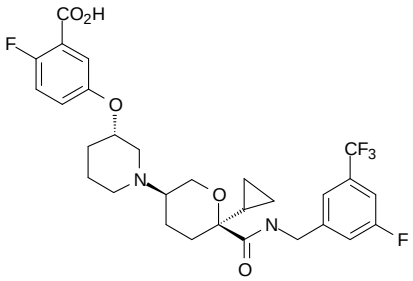


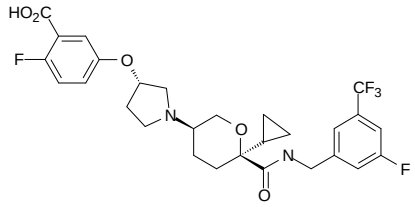


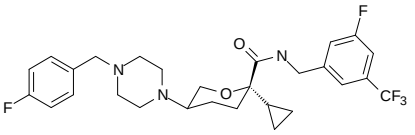


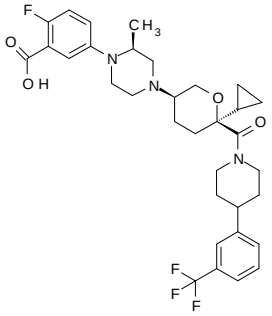


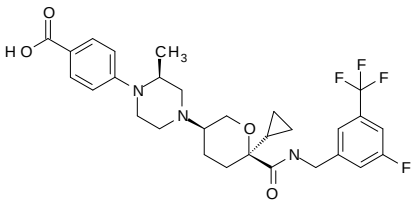


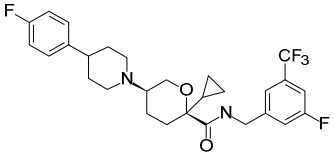


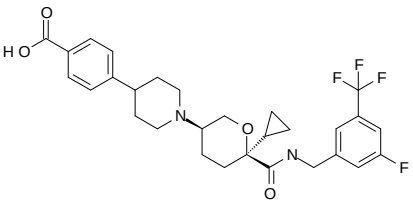


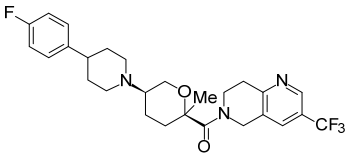


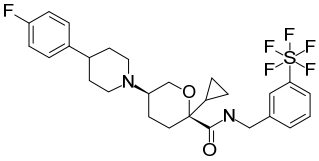


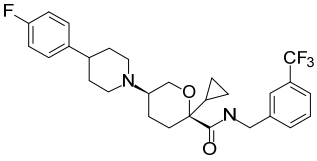


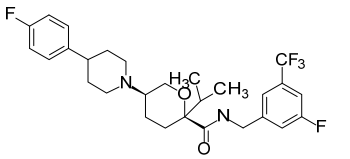


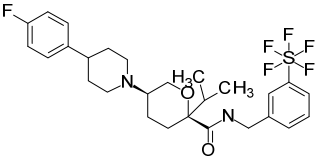


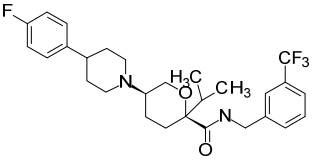


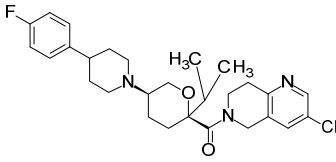


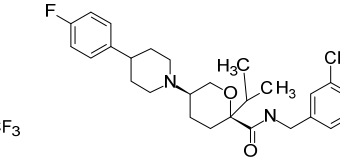


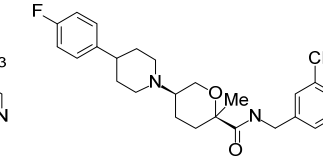


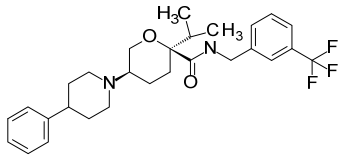


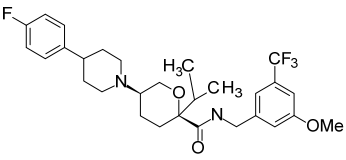


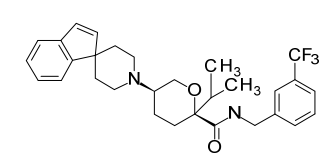


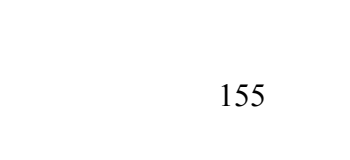


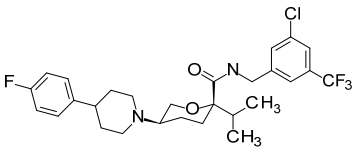
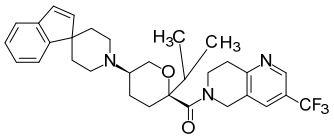
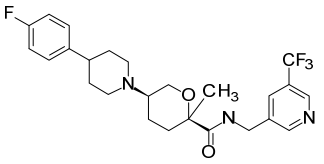
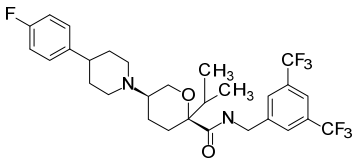
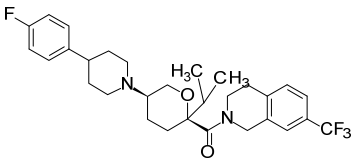
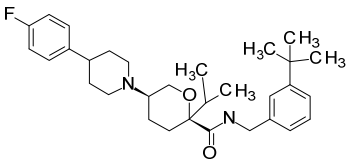
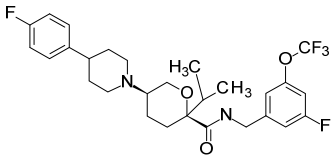
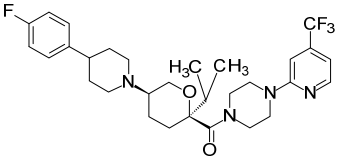
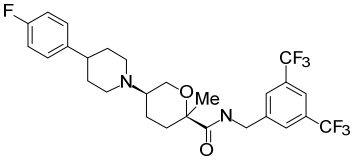
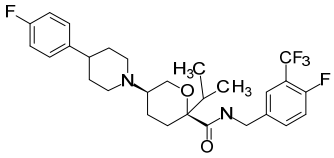
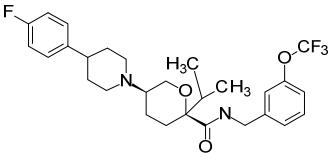
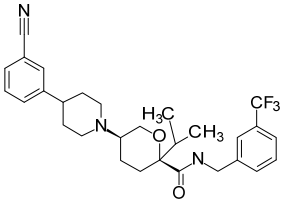
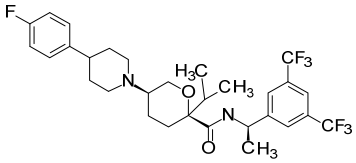
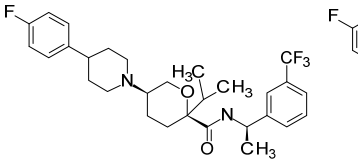
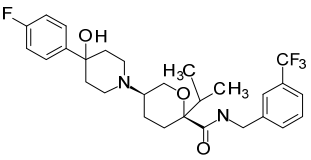
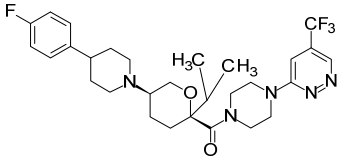
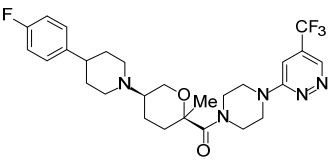
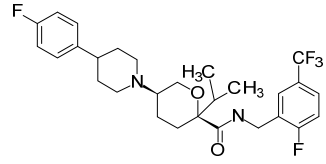
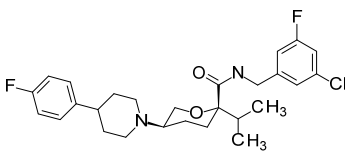
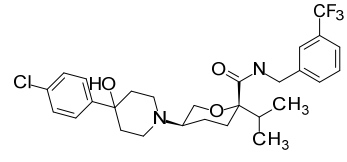
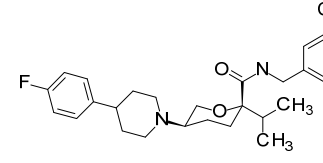
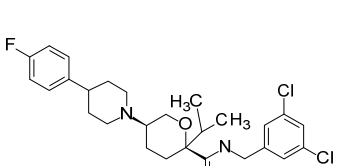
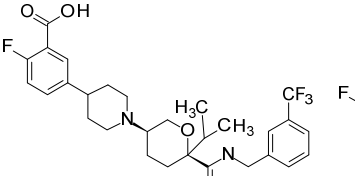
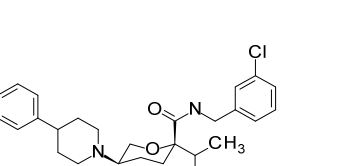
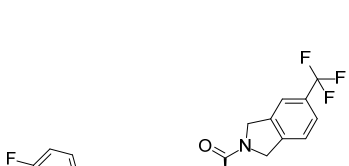
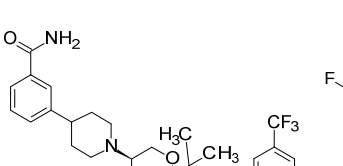
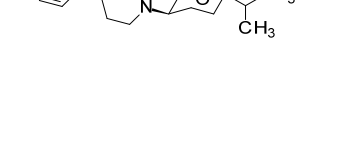
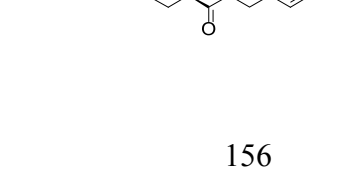
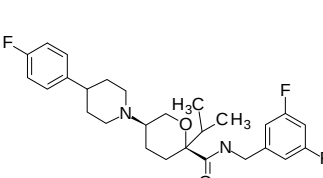


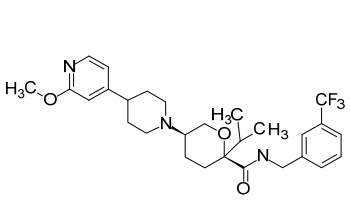
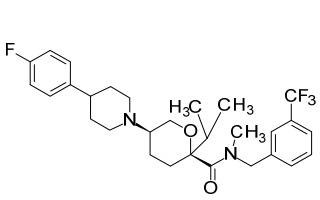
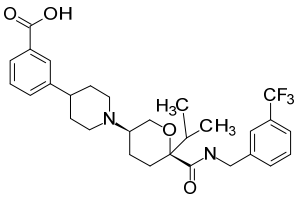
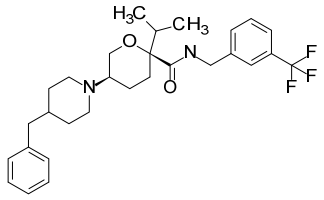
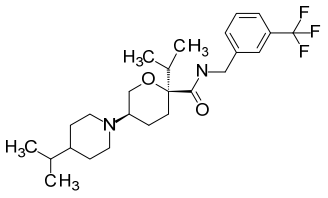
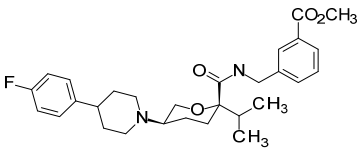






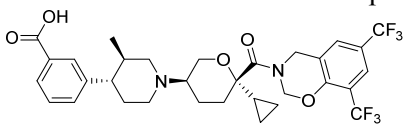







and


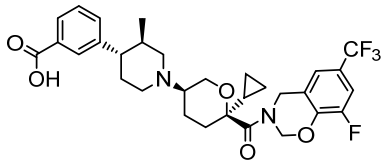
, or a pharmaceutically acceptable salt thereof.

45. A compound selected from the group consisting of:



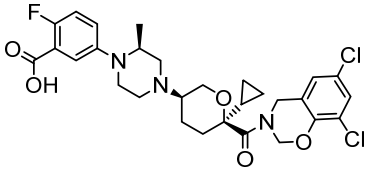
or a pharmaceutically acceptable salt thereof.

46. A compound having the formula


,

or a pharmaceutically acceptable salt thereof.

47. A compound having the formula



or a pharmaceutically acceptable salt thereof.

48. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any one of claims **1**-**47**.

49. The pharmaceutical composition of claim **48**, further comprising one or more additional therapeutic compounds.

50. The pharmaceutical composition of claim **49**, wherein the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a Thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a Kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a Poly ADP ribose polymerase inhibitor , a Poly ADP ribose polymerase 1 inhibitor, a Poly ADP ribose polymerase 2 inhibitor, a Poly ADP ribose polymerase 3 inhibitor, a Galactosyltransferase modulator, a Dihydropyrimidine dehydrogenase inhibitor, an Orotate phosphoribosyltransferase inhibitor, a Telomerase modulator, a Mucin 1 inhibitor, a Mucin inhibitor, a Secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an Interleukin 17E ligand, a Neurokinin receptor agonist, a Cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a Topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a Connective tissue growth factor ligand inhibitor, a Notch-2 receptor antagonist, a Notch-3 receptor antagonist, a Hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a Mesothelin modulator, an Asparaginase stimulator, a Caspase-3 stimulator; Caspase-9 stimulator, a PKN3 gene inhibitor, aHedgehog protein inhibitor; Smoothened receptor

antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a Thymidine kinase stimulator, a CD29 modulator, a Fibronectin modulator, an Interleukin-2 ligand, a Serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2 oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a Cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an Histone deacetylase inhibitor, a Cyclin-dependent kinase 4 inhibitor A modulator, an Estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor, a CD66e modulator, an Angiotensin II receptor antagonist, a Connective tissue growth factor ligand inhibitor, a Jak1 tyrosine kinase inhibitor, a Jak2 tyrosine kinase inhibitor, a dual Jak1/Jak2 tyrosine kinase inhibitor, an Angiotensin converting enzyme 2 stimulator, a Growth hormone receptor antagonist, a Galectin-3 inhibitor, a Sodium glucose transporter-2 inhibitor, a Endothelin ET-A antagonist, a Mineralocorticoid receptor antagonist, an Endothelin ET-B antagonist, an Advanced glycosylation product receptor antagonist, an Adrenocorticotrophic hormone ligand, a Farnesoid X receptor agonist, a G-protein coupled bile acid receptor 1 agonist, an Aldose reductase inhibitor, a Xanthine oxidase inhibitor, a PPAR gamma agonist, a Prostanoid receptor antagonist, a FGF receptor antagonist, a PDGF receptor antagonist, a TGF beta antagonist, a p38 MAP kinase inhibitor, a VEGF-1 receptor antagonist, a Protein tyrosine phosphatase beta inhibitor, a Tek tyrosine kinase receptor stimulator, a PDE 5 inhibitor, a Mineralocorticoid receptor antagonist, an ACE inhibitor, a I-kappa B kinase inhibitor, a NFE2L2 gene stimulator, a Nuclear factor kappa B inhibitor, a STAT3 gene inhibitor, a NADPH oxidase 1 inhibitor, a NADPH oxidase 4 inhibitor, a PDE 4 inhibitor, a Renin inhibitor, a MEKK-5 protein kinase inhibitor, a Membrane copper amine oxidase inhibitor, an Integrin alpha-V/beta-3 antagonist, an Insulin sensitizer, a Kallikrein 1 modulator, a Cyclooxygenase 1 inhibitor and a Phenylalanine hydroxylase stimulator.

51. The pharmaceutical composition of claim **49**, wherein the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-613, upamostat, CRS-207, NovaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell , oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase,

varlitinib, aglatimagene besadenovec, GBS-01, GI-4000, WF-10, galunisertib, afatinib, RX-0201, FG-3019, pertuzumab, DCVax-Direct, selinexor, glufosfamide, virulizin, yttrium (90Y) clivatuzumab tetraxetan, brivudine, nimotuzumab, algenpantucel-L, tegafur + gimeracil + oteracil potassium + calcium folinate, olaparib, ibrutinib, pirarubicin, Rh-Apo2L, tertomotide, tegafur + gimeracil + oteracil potassium, tegafur + gimeracil + oteracil potassium, masitinib, Rexin-G, mitomycin, erlotinib , adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane, paclitaxel, vinca alkaloids, vinblastine, anthracyclines, doxorubicin, epipodophyllotoxins, etoposide, cisplatin, rapamycin, methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents, chlorambucil, 5-fluorouracil, campthothecin, cisplatin, metronidazole, Gleevec, Avastin, Vectibix, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, AZD9291, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, nab-paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, rociletinib, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX, KY-1003, olmesartan medoxomil, candesartan, PBI-4050,

baricitinib, GSK-2586881, losartan, dapagliflozin propanediol, pegvisomant, GR-MD-02, canagliflozin, irbesartan, FG-3019, atrasentan, finerenone, sparsentan, bosentan, defibrotide, fimasartan, azeliragon, pyridoxamine, corticotropin, INT-767, epalrestat, topiroxostat, SER-150-DN, pirfenidone, VEGFR-1 mAb, AKB-9778, PF-489791, SHP-627, CS-3150, imidapril, perindopril, captopril, enalapril, lisinopril, Zofenopril, Lisinopril, Quinapril, Benazepril, Trandolapril, Cilazapril, Fosinopril, Ramipril, bardoxolone methyl, irbesartan + propagermanium, GKT-831, MT-3995, TAK-648, TAK-272, GS-4997, DW-1029M, ASP-8232, VPI-2690B, DM-199, rhein, PHN-033, GLY-230, and sapropterin, sulodexide.

52. Use of a compound of any one of claims **1-47** or a pharmaceutical composition of any one of claims **48-51** in the manufacture of a medicament for treating a mammal suffering from or susceptible to a disease or disorder involving pathologic activation of CCR2 receptors, wherein the disease or disorder is an inflammatory disease or disorder, a cardiovascular or cerebrovascular disorder, an autoimmune disorder, a cancer or a solid tumor.

53. An in vitro method of inhibiting CCR2 receptor-mediated cellular chemotaxis comprising contacting mammalian white blood cells with a CCR2 receptor modulatory amount of a compound of any one of claims **1-47** or a pharmaceutical composition of any one of claims **48-51**.

54. The use of claim **52**, wherein the disease or disorder is selected from the group consisting of diabtetic nephropathy, nephropathy, neutropenia, neutrophilia, Albuminuria, Diabetic retinopathy, Focal segmental glomerulosclerosis, glomerulosclerosis, Allergy, fibrosis, NASH, Hemolytic uremic syndrome, atypical hemolytic uremic syndrome (aHUS), C3-glomerulopathy, C3-glomerulonephritis, dense deposit disease, membranoproliferative glomerulonephritis, sepsis, septic shock, Alzheimer's disease, multiple sclerosis, stroke, inflammatory bowel disease, chronic obstructive pulmonary disorder, inflammation associated with burns, lung injury, osteoarthritis, atopic dermatitis, chronic urticaria, ischemia-reperfusion injury, acute respiratory distress syndrome, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, tissue graft rejection, Graft versus host disease, hyperacute rejection of transplanted organs, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion,

artherosclerosis, traumatic central nervous system injury, ischemic heart disease, rheumatoid arthritis, systemic lupus erythematosus, Guillain-Barre syndrome, pancreatitis, lupus nephritis, lupus glomerulonephritis, psoriasis, Crohn's disease, vasculitis, Anca-vasculitis, irritable bowel syndrome, dermatomyositis, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, myasthenia gravis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, immunovasculitis, tissue graft rejection, hyperacute rejection of transplanted organs, Melanoma, Small Cell Lung Carcinoma, Non Small Cell Lung Carcinoma, Pancreatic Cancer, Breast Cancer, Bladder Cancer, Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma, Head and Neck Squamous Cell Carcinoma, Esophageal Cancer, Ovarian Cancer, Prostate Cancer, Gastric Cancer, Acute myelogenous leukemia, leukemia, a pathologic sequelae associated with the group consisting of insulin-dependent diabetes, mellitus, lupus nephropathy, Heyman nephritis, membranous nephritis, glomerulonephritis, contact sensitivity responses, and inflammation resulting from contact of blood with artificial surfaces.

55. The use of claim **52**, wherein one or more additional therapeutic compounds is to be further administered.

56. The use of claim **55**, wherein the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a Thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a Kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a Poly ADP ribose polymerase inhibitor , a Poly ADP ribose polymerase 1 inhibitor, a Poly ADP ribose polymerase 2 inhibitor, a Poly ADP ribose polymerase 3 inhibitor, a Galactosyltransferase modulator, a Dihydropyrimidine dehydrogenase inhibitor, an Orotate phosphoribosyltransferase inhibitor, a Telomerase modulator, a Mucin 1 inhibitor, a Mucin inhibitor, a Secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an Interleukin 17E ligand, a Neurokinin receptor agonist, a Cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a Topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a Connective tissue growth factor ligand inhibitor, a Notch-2 receptor antagonist, a Notch-3 receptor antagonist, a Hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2

protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a Mesothelin modulator, an Asparaginase stimulator, a Caspase-3 stimulator; Caspase-9 stimulator, a PKN3 gene inhibitor, a Hedgehog protein inhibitor; Smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a Thymidine kinase stimulator, a CD29 modulator, a Fibronectin modulator, an Interleukin-2 ligand, a Serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2 oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a Cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an Histone deacetylase inhibitor, a Cyclin-dependent kinase 4 inhibitor A modulator, an Estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor, a CD66e modulator, an Angiotensin II receptor antagonist, a Connective tissue growth factor ligand inhibitor, a Jak1 tyrosine kinase inhibitor, a Jak2 tyrosine kinase inhibitor, a dual Jak1/Jak2 tyrosine kinase inhibitor, an Angiotensin converting enzyme 2 stimulator, a Growth hormone receptor antagonist, a Galectin-3 inhibitor, a Sodium glucose transporter-2 inhibitor, a Endothelin ET-A antagonist, a Mineralocorticoid receptor antagonist, an Endothelin ET-B antagonist, an Advanced glycosylation product receptor antagonist, an Adrenocorticotrophic hormone ligand, a Farnesoid X receptor agonist, a G-protein coupled bile acid receptor 1 agonist, an Aldose reductase inhibitor, a Xanthine oxidase inhibitor, a PPAR gamma agonist, a Prostanoid receptor antagonist, a FGF receptor antagonist, a PDGF receptor antagonist, a TGF beta antagonist, a p38 MAP kinase inhibitor, a VEGF-1 receptor antagonist, a Protein tyrosine phosphatase beta inhibitor, a Tek tyrosine kinase receptor stimulator, a PDE 5 inhibitor, a Mineralocorticoid receptor antagonist, an ACE inhibitor, a I-kappa B kinase inhibitor, a NFE2L2 gene stimulator, a Nuclear factor kappa B inhibitor, a STAT3 gene inhibitor, a NADPH oxidase 1 inhibitor, a NADPH oxidase 4 inhibitor, a PDE 4 inhibitor, a Renin inhibitor, a MEKK-5 protein kinase inhibitor, a Membrane copper amine oxidase inhibitor, an Integrin alpha-V/beta-3 antagonist, an Insulin sensitizer, a Kallikrein 1 modulator, a Cyclooxygenase 1 inhibitor and a Phenylalanine hydroxylase stimulator.

57. The use of claim **55**, wherein the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-

613, upamostat, CRS-207, NovaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell, oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase, varlitinib, aglatimagene besadenovec, GBS-01, GI-4000, WF-10, galunisertib, afatinib, RX-0201, FG-3019, pertuzumab, DCVax-Direct, selinexor, glufosfamide, virulizin, yttrium (90Y) clivatuzumab tetraxetan, brivudine, nimotuzumab, algenpantucel-L, tegafur + gimeracil + oteracil potassium + calcium folinate, olaparib, ibrutinib, pirarubicin, Rh-Apo2L, tertomotide, tegafur + gimeracil + oteracil potassium, tegafur + gimeracil + oteracil potassium, masitinib, Rexin-G, mitomycin, erlotinib , adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane, paclitaxel, vinca alkaloids, vinblastine, anthracyclines, doxorubicin, epipodophyllotoxins, etoposide, cisplatin, rapamycin, methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents, chlorambucil, 5-fluorouracil, campthothecin, cisplatin, metronidazole, Gleevec, Avastin, Vectibix, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, AZD9291, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, nab-paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, rociletinib, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308,

mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX, KY-1003, olmesartan medoxomil, candesartan, PBI-4050, baricitinib, GSK-2586881, losartan, dapagliflozin propanediol, pegvisomant, GR-MD-02, canagliflozin, irbesartan, FG-3019, atrasentan, finerenone, sparsentan, bosentan, defibrotide, fimasartan, azeliragon, pyridoxamine, corticotropin, INT-767, epalrestat, topiroxostat, SER-150-DN, pirfenidone, VEGFR-1 mAb, AKB-9778, PF-489791, SHP-627, CS-3150, imidapril, perindopril, captopril, enalapril, lisinopril, Zofenopril, Lisinopril, Quinapril, Benazepril, Trandolapril, Cilazapril, Fosinopril, Ramipril, bardoxolone methyl, irbesartan + propagermanium, GKT-831, MT-3995, TAK-648, TAK-272, GS-4997, DW-1029M, ASP-8232, VPI-2690B, DM-199, rhein, PHN-033, GLY-230, and sapropterin, sulodexide.

58. A compound of any one of claims **1-47** or a pharmaceutical composition of any one of claims **48-51** for use in treating a mammal suffering from or susceptible to a disease or disorder involving pathologic activation of CCR2 receptors.

59. A compound of any one of claims **1-47** or a pharmaceutical composition of any one of claims **48-51** for use in inhibiting CCR2 receptor-mediated cellular chemotaxis.