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(54) **Title**: METHODS OF TREATING HYPERALGESIA

(57) **Abstract**: This application describes compounds and methods that can be used to treat, reverse, or avoid hyperalgesia.

Methods of Treating Hyperalgesia

[0001] Cross-Reference To Related Applications

[0002] This application claims priority to U.S. Provisional Application No. 62/267,144, filed December 14, 2015, which is incorporated by reference in its entirety. The present application is also related to U.S. Non-Provisional Application No. 13/428,849, filed March 23, 2012, Provisional Application No. 61/596,808 filed February 9, 2012, and U.S. Provisional Application No. 61/466,809 filed March 23, 2011, each of which is incorporated herein by reference in its entirety.

[0003] Field

[0004] This application relates to a family of compounds acting as opioid receptor ligands and methods of using such compounds for treating or reversing hyperalgesia, induced hyperalgesia, decreasing nociceptive sensitization, and the like.

[0005] Background

[0006] Opioid receptors (ORs) mediate the actions of morphine and morphine-like opioids, including most clinical analgesics. Three molecularly and pharmacologically distinct opioid receptor types have been described: δ, κ and μ. Furthermore, each type is believed to have sub-types. All three of these opioid receptor types appear to share the same functional mechanisms at a cellular level. For example, activation of the opioid receptors causes inhibition of adenylate cyclase, and recruits β-arrestin.

[0007] When therapeutic doses of morphine are given to patients with pain, the patients report that the pain is less intense, less discomforting, or entirely gone. In addition to experiencing relief of distress, some patients experience euphoria. However, when morphine in a selected pain-relieving dose is given to a pain-free individual, the experience is not always pleasant; nausea is common, and vomiting may also occur. Drowsiness, inability to concentrate, difficulty in mentation, apathy, lessened physical activity, reduced visual acuity, and lethargy may ensue. Additionally, those administered morphine and similar non-biased ligands can suffer from hyperalgesia. If the cause is

due to an opioid therapeutic, it can be referred to as Opioid Induced Hyperalgesia (OIH).

[0008] There is a continuing need for new OR modulators to be used as therapeutics that do not cause hyperalgesia or that can be used to treat people that suffer from hyperalgesia, induced by opioids or otherwise. The present embodiments satisfy these needs as well as other.

[0009] SUMMARY

[0010] This application describes opioid receptor (OR) ligands. It also describes methods of treating or reversing hyperalgesia, such as but not limited to, opioid induced hyperalgesia. Accordingly, in some embodiments, methods of treating hyperalgesia in a subject are provided. In some embodiments, methods of reversing hyperalgesia, including but not limited to, opioid induced hyperalgesia, in a subject are provided. In some embodiments, the methods comprise administering to the subject a compound of any formula described herein, or a pharmaceutically acceptable salt thereof.

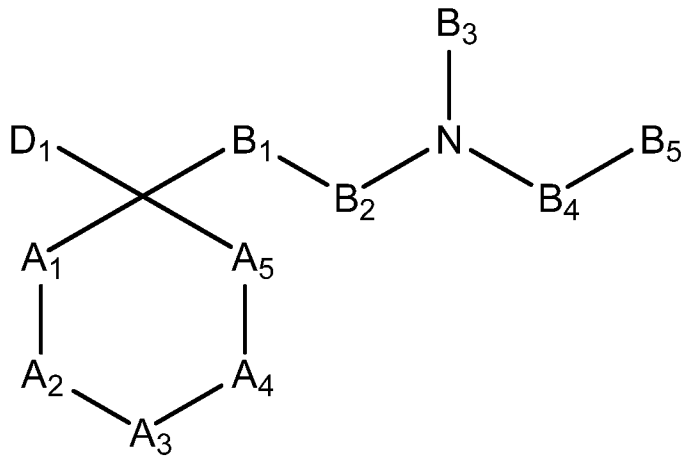
[0011] In some embodiments, methods of decreasing nociceptive sensitization in a subject are provided. In some embodiments, the methods comprise administering to the subject a compound of any formula described herein, or a pharmaceutically acceptable salt thereof.

[0012] In some embodiments, methods of treating pain in a subject are provided. In some embodiments, the methods comprise administering an opioid agonist to the subject until the first opioid increases nociceptive sensitization in the subject; and administering to the subject with increased nociceptive sensitization a compound of any formula described herein, or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, methods of treating pain in an opioid exposed subject are provided. In some embodiments, the methods comprise administering an opioid agonist to the subject; and administering to the subject of step a compound of any formula described herein, or a pharmaceutically acceptable salt thereof in the absence of the opioid.

[0014] In some embodiments, the compound of any formula or described herein, or a

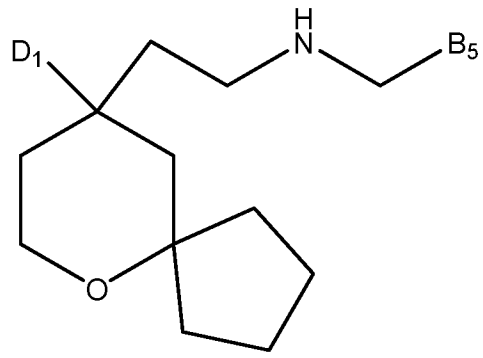
pharmaceutically acceptable salt thereof has a formula of Formula I:



I

[0015] In the structure above, variables A_1, A_2, A_3, A_4, A_5, B_1, B_2, B_3, B_4, B_5, and D_1 can be selected from the respective groups of chemical moieties later described. OR ligand derivatives and mimetics are also provided.

[0016] In some embodiments, the compound has a formula of



, or a pharmaceutically acceptable salt thereof,

wherein D_1 is an optionally substituted aryl; and B_5 is an optionally substituted pyridyl.

[0017] This application also describes pharmaceutical compositions comprising one or more compounds as described in this application a pharmaceutically acceptable carrier. Naturally, the compounds described herein can be employed in any form, such as a solid or solution (*e.g.*, aqueous solution) as is described further below. The compounds described herein, for example, can be obtained and employed in a lyophilized form alone

or with suitable additives.

[0018] In some embodiments, uses of the compounds, or pharmaceutically acceptable salts thereof, in the preparation of a medicament for the treatment or reversal of hyperalgesia, opioid induced hyperalgesia, and the like are provided.

[0019] **BRIEF DESCRIPTION OF DRAWINGS**

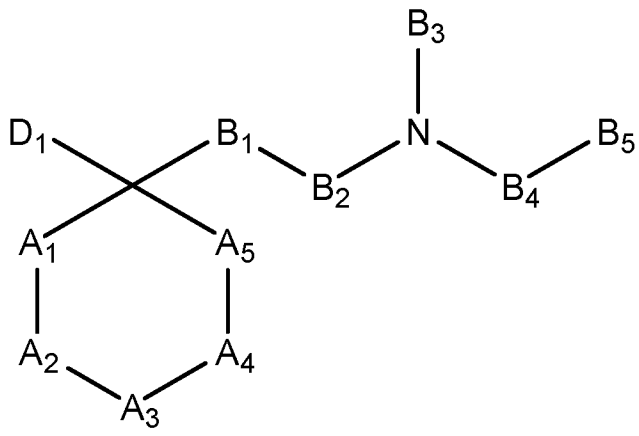
[0020] Fig. 1 illustrates that biased ligands described herein do not induce hyperalgesia.

[0021] Fig. 2 illustrates that biased ligands can reverse opioid induce hyperalgesia.

[0022] DETAILED DESCRIPTION

[0023] This application describes a family of compounds, OR ligands, with a unique profile. The compounds described herein act as agonists or antagonists of opioid receptor (OR)-mediated signal transduction. The ligands of these receptors can be used to treat pathologies associated with ORs including pain and pain related disorders, such as, but not limited to, opioid induced hyperalgesia and nociceptive sensitization.

[0024] In some embodiments, compounds also comprise Formula I:



;

wherein: A_1 is null, CH_2, CHR_1, CR_1R_2, CH, CR_1, O, S, SO, SO_2, NH or NR_1; A_2 is null, CH_2, CHR_5, CR_5R_6, CH, CR_5, O, S, SO, SO_2, NH or NR_5; A_3 is null, CH_2, CHR_7, CR_7R_8, O, S, SO, SO_2, NH, NR_7, CH or CR_7; A_4 is null, CH_2, cycle of the formula $C(CH_2)_n$, where n = 2-5, CHR_9, CR_9R_{10}, O, S, SO, SO_2, NH, NR_9, CH or CR_9; and A_5 is null, CH_2,

CHR_{11}, $CR_{11}R_{12}$, CH_2CH_2, $CHR_{11}CH_2$, CH_2CHR_{11}, $CHR_{11}CHR_{12}$, O, S, SO, SO_2, NH, NR_{11}, CH or CR_{11}.

[0025] No more than 2 out of 5 A_a (specifically A_1, A_2, A_3, A_4, A_5) can be null at the same time. The number of heteroatoms from A_1 to A_5 cannot exceed 2 at the same time, and O-O, S-O; S-S; S-N fragments in the ring structure are excluded from this composition.

[0026] The ring containing A_1, A_2, A_3, A_4, A_5 and the carbon connected to D_1 can be fused with another ring, such as benzene, pyridine, pyrimidine, furan, thiophene or pyridazine, but not limited to these ezamples, where the resulting bicycle is chemically stable and synthetically accessible. It is also understood that the above-mentioned fused rings could be multiply substituted with cyano, halogen, alkyl, branched alkyl, halogenated alkyl, hydroxyl, alkyloxy, formyl, acetyl, amino, alkylamino, dialkylamino, mercaptanyl, alkylmercaptanyl, and other small substitution groups. The bonds between $A_1$and A_2, A_2 and A_3, A_3 and A_4, A_4 and A_5 can independently be a single bond or a double bond. The bonds between A_1 and A_2, A_2 and A_3, A_3 and A_4, A_4 and A_5 cannot be a double bond at the same time.

[0027] A_2 and A_4 can be connected by a carbon bridge. Examples of such a bridge include –CH_2-, and -CH_2CH_2-.

[0028] B_1 is CH_2, CHR_{13}, $CR_{13}R_{14}$, O, S, SO, SO_2, NH, NR_{13}, CR_{13} or CO. B_2 is CH_2, CHR_{15}, $CR_{15}R_{16}$, CR_{15} or CO. B_3 is H, alkyl, branched alkyl, halogenated alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or alkylsulfonyl. B_4 is null, C_1-C_6 alkyl, CH_2, CH_2CH_2, CHR_{19}, $CR_{19}R_{20}$ or CO. In some embodiments, when B_4 is an alkyl one or more of the hydrogens can be replaced with a deuterium. B_5 is alkyl, branched alkyl, halogenated alkyl, carbocycle-substituted alkyl, aryl, carbocycle or arylalkyl.

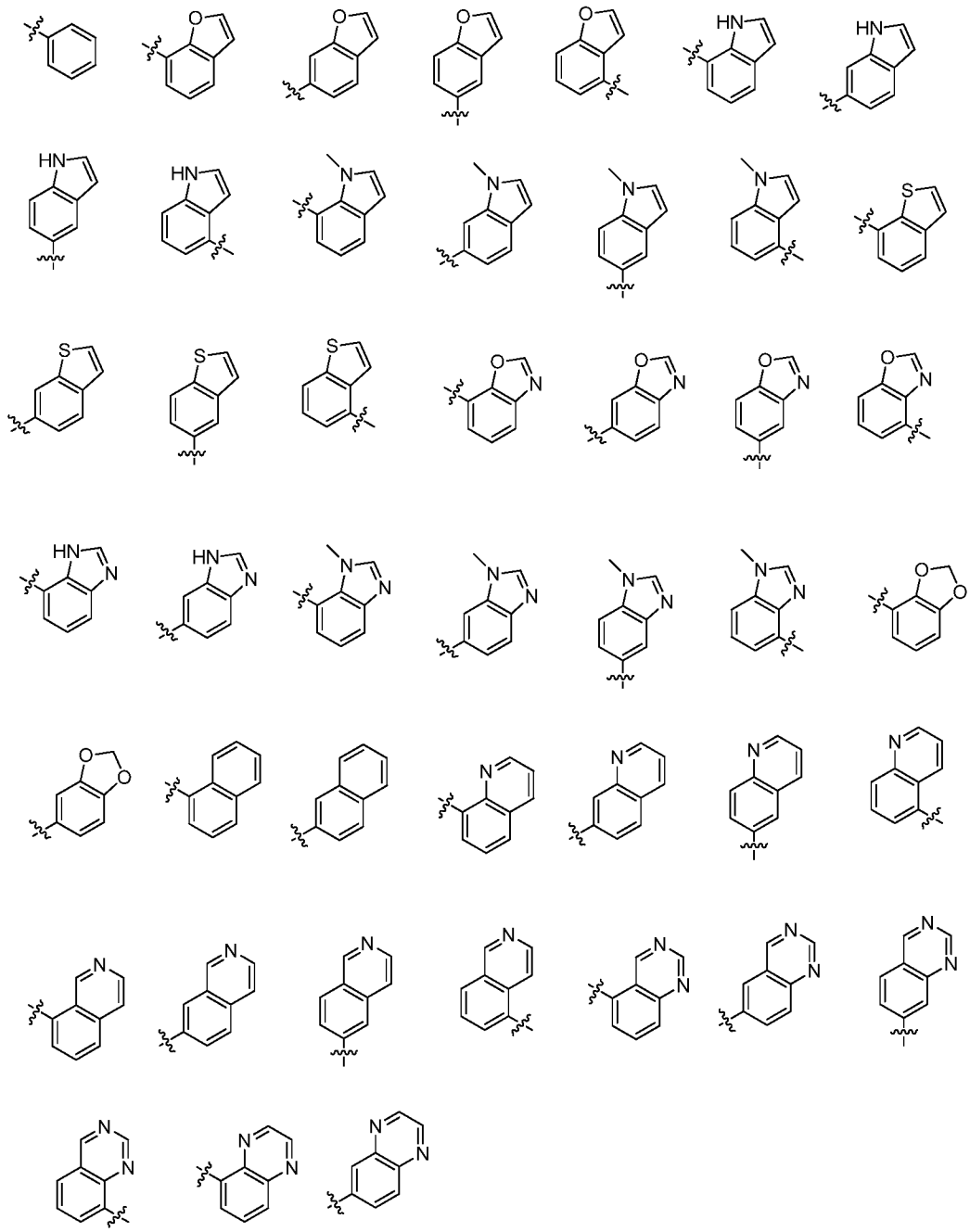
[0029] Aryl, carbocycle (non-aromatic)/heterocycle (non-aromatic with 1-3 heteroatoms, including O, N, S) are either unsubstituted, or substituted with small substitution groups. Small substitution groups can be cyano, halogen, alkyl, branched alkyl, halogenated alkyl, hydroxyl, alkyloxy, amino, alkylamino, dialkylamino, mercaptanyl,

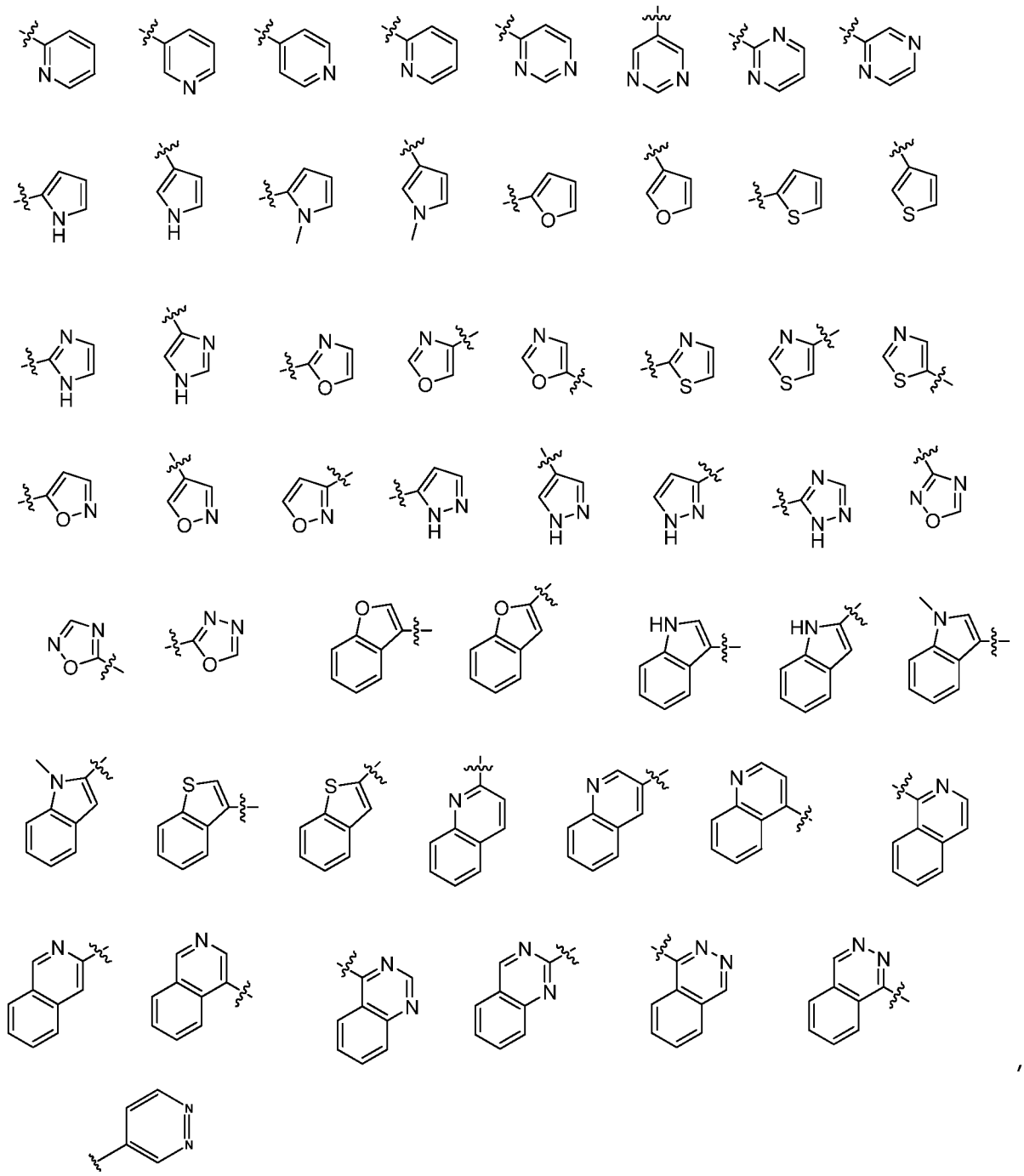
alkylmercaptanyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aryl, arylalkyl, carbocycle or carbocycle-alkyl. In some embodiments, the small substitution groups are selected from F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, NH_2, NHMe, NMe_2, methoxycarbonyl, methanesuflonyl, Ph, benzyl, $MeSO_2$, formyl, and acetyl.

[0030] Carbocycle may contain double bonds, but they should not be aromatic.

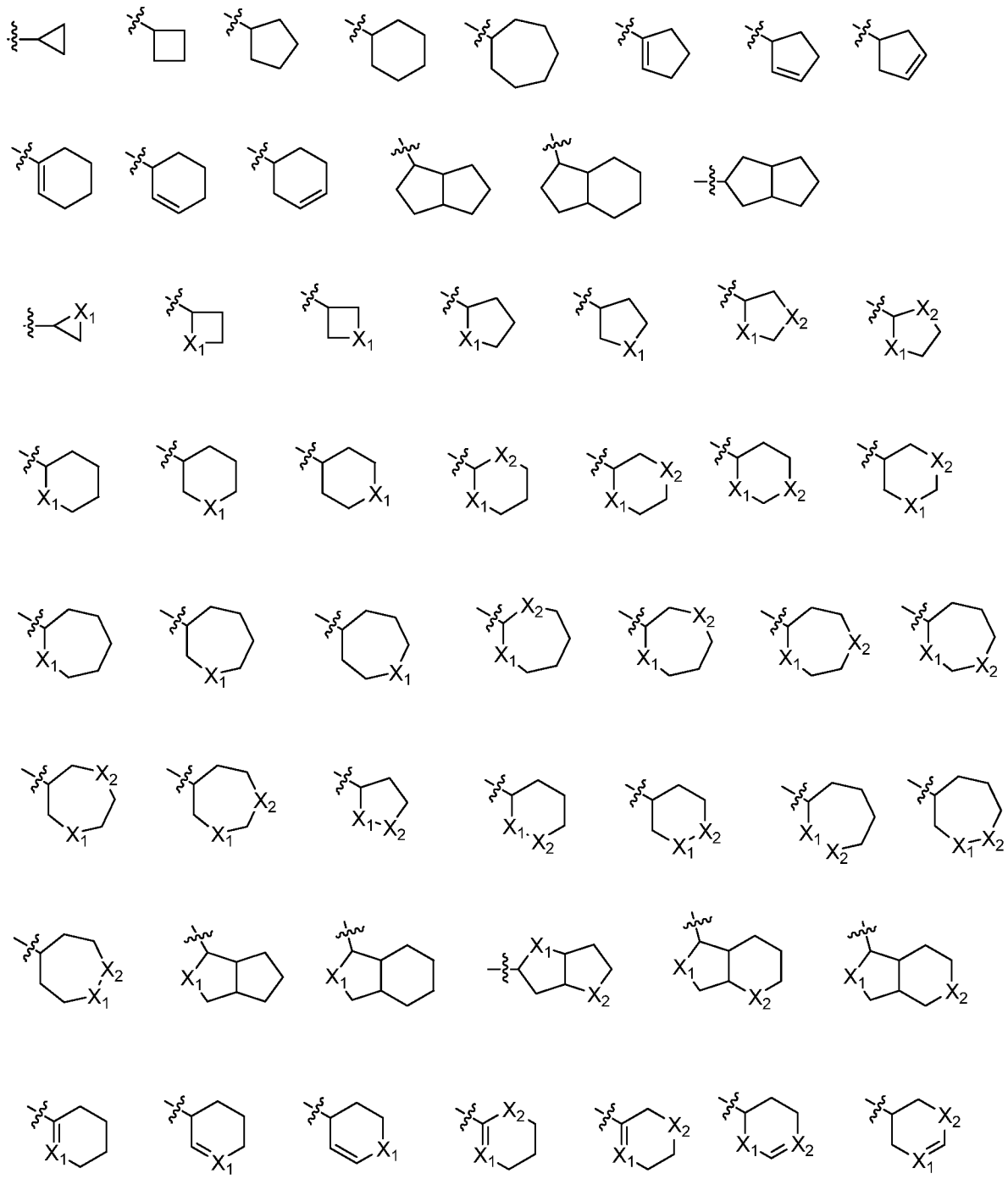
[0031] D_1 is an aryl group or a carbocycle.

[0032] An aryl group is either a monocyclic aromatic group or a bicyclic aromatic group, which may contain heteroatoms in the aromatic group (*e.g.* heteroaryl). The following structures are some examples of representive aryl groups, but the aryl groups are not limited to those examples:





[0033] Carbocycle is either a monocyclic or a bicyclic non-aromatic ring system. The following structures are some examples of representative carbocycle, but the carbocycle is not limited to those examples:



wherein X_1, and X_2 in the carbocycle examples are independently O, S, N, NH or NR_{18}.

[0034] The aryl groups can be independently mono or multiply substituted with cyano, halogen, alkyl, branched alkyl, halogenated alkyl, hydroxyl, alkyloxy, amino, alkylamino, dialkylamino, mercaptanyl, alkylmercaptanyl, alkylsulfonyl, aminosulfonyl,

alkylaminosulfonyl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aryl, arylalkyl, carbocycle, carbocycle-alkyl, and/or other small substitution groups. In some embodiments, the small substitution groups are selected from F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, NH_2, NHMe, NMe_2, methoxycarbonyl, methanesulfonyl, Ph, benzyl, formyl, and acetyl.

[0035] In some embodiments,D_1 is an aryl, or a carbocycle.

[0036] In some embodiments, R_1, R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, and R_{20} are independently: cyano, halogen, hydroxyl, alkyloxy, alkyl, branched alkyl, halogenated alkyl, branched halogenated alkyl, aryl, arylalkyl, carbocycle, carbocycle-alkyl, alkylcarbonyl, branched alkylcarbonyl, halogenated alkylcarbonyl, branched halogenated alkylcarbonyl, arylcarbonyl or alkoxycarbonyl. In some embodiments, R_1, R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, and R_{20} are independently F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-i-Pr, methoxycarbonyl, phenyl, benzyl, formyl or acetyl, whenever the resulting structure is stable.

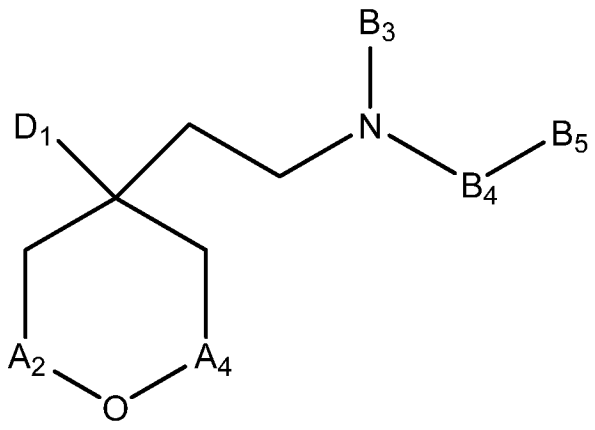
[0037] In some embodiments, R_1 and R_2, R_5 and R_6, R_7 and R_8, R_9 and R_{10}, R_{11} and R_{12}, R_{13} and R_{14}, R_{15} and R_{16}, R_{19} and R_{20}, or R_{15} and R_{19} can form a monocycle.

[0038] In some embodiments, Me is methyl; Et is ethyl; i-Pr is i-propyl; t-Bu is t-butyl; Ph is phenyl.

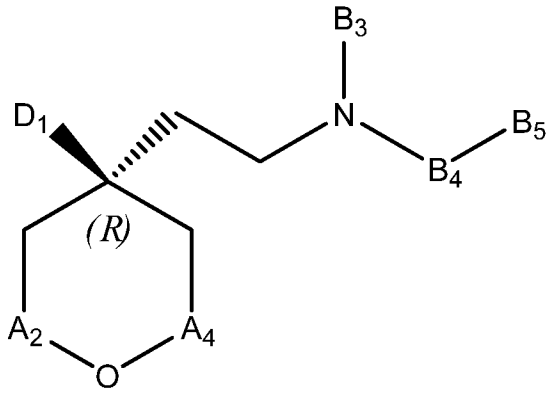
[0039] In some embodiments, the following compounds can be excluded from the genus of compounds:2-[({2-[2-Ethyl-2-methyl-4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol; 2-[({2-[2-Ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}amino)methyl]phenol; {2-[2,2-Dimethyl-4-(4-methylphenyl)oxan-4yl]ethyl}[(4-methoxyphenyl)methyl]amine; {2-[(4S*, 4R*)-2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(1R)-1-phenylethyl]amine; {2-[(4S*, 4R*)-2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(1S)-1-phenylethyl]amine; Benzyl({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine; 2-[({2-[2-Ethyl-4-(4-fluorophenyl)-2-

methyloxan-4-yl]ethyl}amino)methyl]phenol; Benzyl[2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl]amine; {2-[2-Ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}[(4-methoxyphenyl)methyl]amine; [(3,4-Dimethoxyphenyl)methyl]({2-[4-(4-fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; {2-[4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(1-phenylethyl)amine; [(4-Chlorophenyl)methyl]({2-[4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; Benzyl({2-[2-ethyl-4-(2-methoxyphenyl)-2-methyloxan-4-yl]ethyl})amine; [(3,4-dimethoxyphenyl)methyl]({2-[2-ethyl-4-(2-methoxyphenyl)-2-methyloxan-4-yl]ethyl})amine; 4-[({2-[4-(2-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}amino)methyl]-N,N-dimethylaniline; Benzyl({2-[4-(4-fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; {2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}(1-phenylethyl)amine; [2-(2,2-Dimethyl-4-phenyloxan-4-yl)ethyl][(4-methoxyphenyl)methyl]amine; {2-[4-(4-Fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl}[(4-methoxyphenyl)methyl]amine; [(3,4-Dimethoxyphenyl)methyl][2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl]amine

[0040] This application also describes compounds having the formula of Formula II-1 and II-2:



II-1



II-2

wherein A_2 is CH_2, CHR_5, CR_5R_6; A_4 is CH_2, CHR_9, CR_9R_{10} or a cycle of the formula $C(CH_2)_n$, where n = 2-5.

[0041] Further, in some embodiments, R_5 R_6, R_9, and R_{10} are independently CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, or phenyl. Further, R_5 and R_6, or R_9 and R_{10} can form a monocyclic carbocycle.

[0042] In some embodiments, A_2 and A_4 can be connected by a carbon bridge. This bridge can be $-CH_2-$ or $-CH_2CH_2-$.

[0043] Further, in some embodiments, B_3 is selected from the following: H, alkyl, branched alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, and alkylsulfonyl. In some embodiments, B_3 is C_1-C_5 alkyl. In some embodiments, B_3 is H.

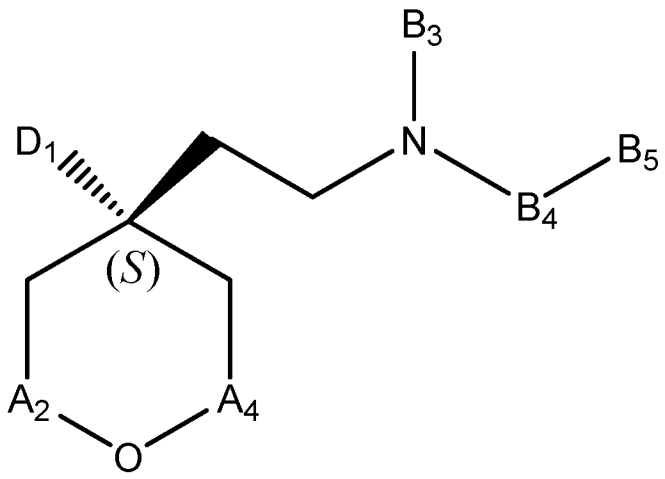
[0044] Further, in some embodiments, B_4 is null, C_1-C_6 alkyl, CH_2, CH_2CH_2, CHR_{19}, $CR_{19}R_{20}$ or CO. Further, R_{19} and R_{20} can form a monocycle of the formula $(CH_2)_n$, where n = 2-4. B_5 is alkyl, branched alkyl, carbocycle, carbocycle-substituted alkyl, aryl or arylalkyl.

[0045] In some embodiments, Further D_1 is an aryl. Examples of the aryl groups are shown above.

[0046] Each aryl group can be independently mono or multiply substituted with F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, NH_2, NHMe, NMe_2, methoxycarbonyl, Ph, benzyl, formyl, or acetyl. That is, each aryl group may be multiply substituted with the same substituent (i.e., 2 chloro

groups) or just be multiply substituted, albeit with different groups (*e.g.* an aryl group with 1 chloro and 1 methyl group would be considered multiply substituted).

[0047] This application also provides compounds having the structure of Formula III:



III

wherein A_2 is CH_2, CHR_5 or CR_5R_6; A_4 is CH_2, CHR_9, CR_9R_{10} or a cycle of the formula $C(CH_2)_n$, where n = 2-5.

[0048] Further R_5, R_6, R_9, and R_{10} are independently CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, or phenyl. R_5 and R_6, or R_9 and R_{10} can form a monocyclic carbocycle.

[0049] A_2 and A_4 can be connected by a carbon bridge. The bridge can be $-CH_2-$ or $-CH_2CH_2-$.

[0050] Further B_3 is selected from H, alkyl, branched alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl or alkylsulfonyl.

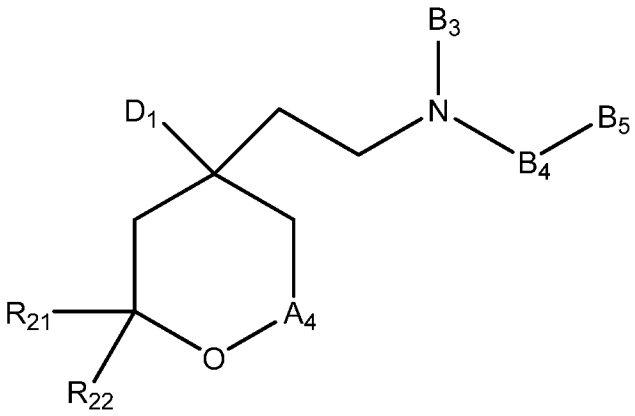
[0051] Further B_4 is null, C_1-C_6 alkyl, CH_2, CH_2CH_2, CHR_{19}, $CR_{19}R_{20}$ or CO. Further, R_{19} and R_{20} can form a monocycle of the formula $(CH_2)_n$, where n = 2-4. B_5 is alkyl, branched alkyl, carbocycle, carbocycle-substituted alkyl, aryl or arylalkyl.

[0052] Further D_1 is an aryl. Examples of the aryl groups are shown above.

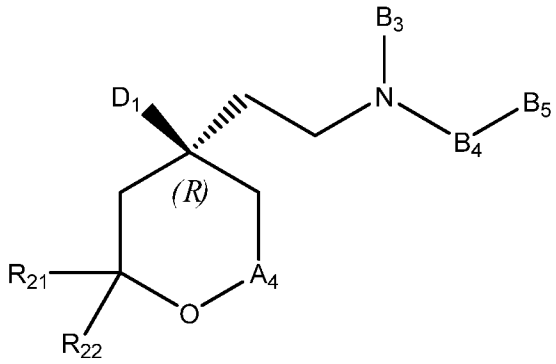
[0053] The aryl groups can be mono or multiply substituted with F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, NH_2,

NHMe, NMe_2, methoxycarbonyl, Ph, benzyl, formyl, or acetyl.

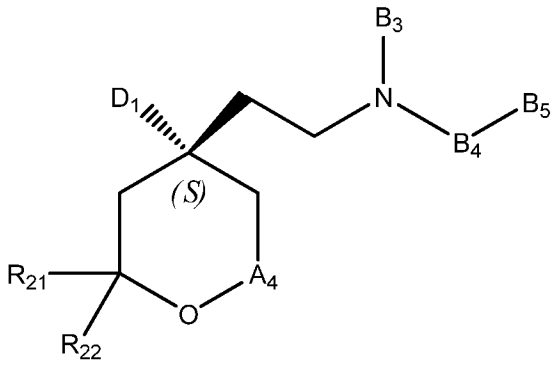
[0054] This application also provides compounds having the formula of Formula IV-1, IV-2, or IV-3, V, or VI:



IV-1



IV-2



IV-3

wherein R_{21} and R_{22} are, independently, H or CH_3; A_4 is CH_2, CR_9R_{10} or a cycle of the formula $C(CH_2)_n$, where n = 2-5.

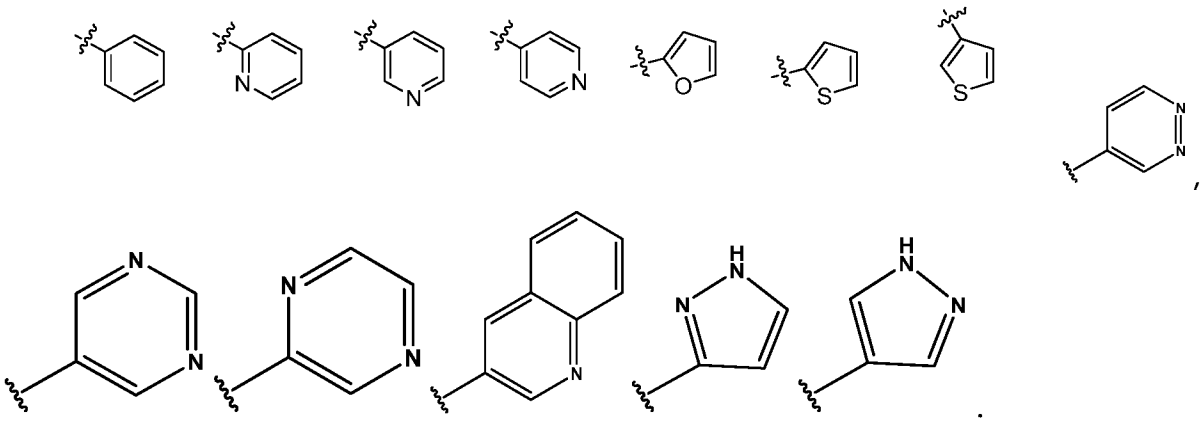
[0055] Further R_9 and R_{10} are independently CH_3 or CH_2CH_3.

[0056] Further B_3 is H, C_1-C_6 alkyl or branched alkyl.

[0057] Further B_4 is null, C_1-C_6 alkyl, CH_2, CH_2CH_2,or -$CHCH_3$.

[0058] B_5 is -$(CH_2)_nCH_3$, where n = 2-3, -$C(CH_3)_3$, cyclohexyl, cyclopentyl, aryl or arylalkyl.

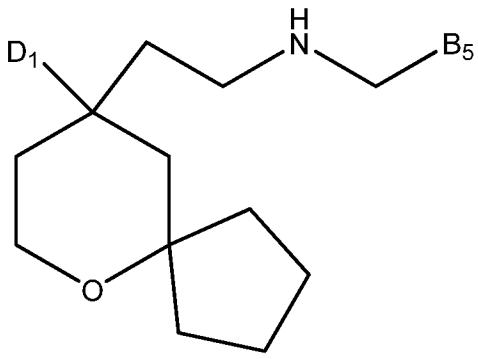
In some embodiments, the aryl group is selected from the list below:



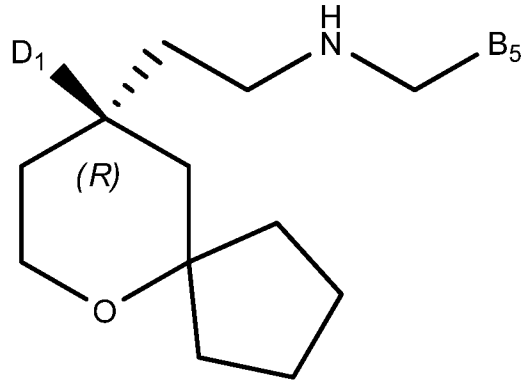
Each aryl groups can be mono or multiply substituted with, for example, F, I, Cl, Br, CH_3, CN, OH, OMe, OEt, OCF_3, CF_3, or methanesulfonyl.

[0059] Further, in some embodiments, D_1 is a phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl which can be independently mono or multiply substituted with F, Cl, Br, OCF_3, CF_3, or CH_3.

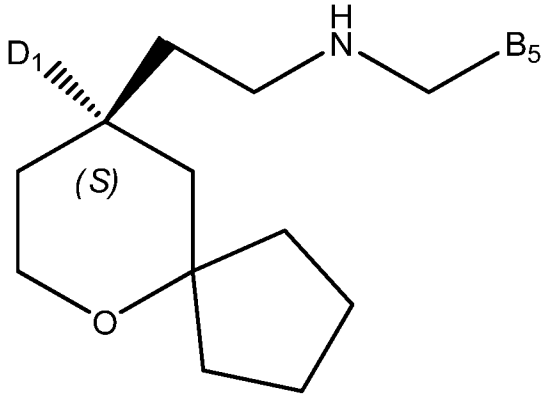
[0060] This application also provides compounds having the structure of Formula V-1, V-2, V-3, VI-1, VI-2, or VI-3:



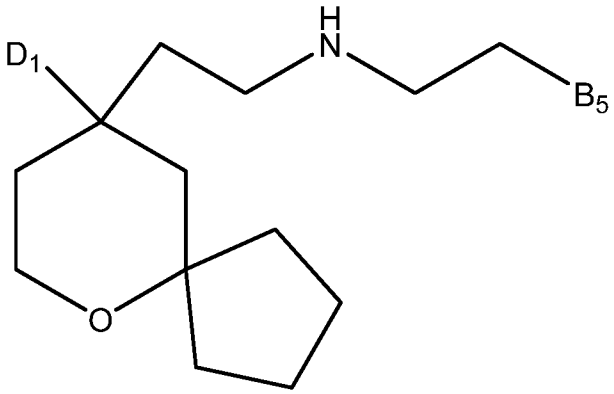
V-1,



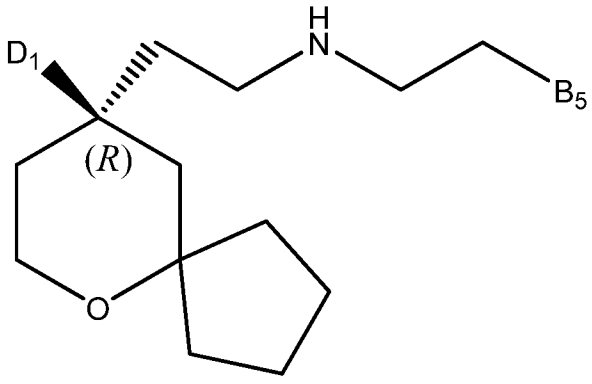
V-2,



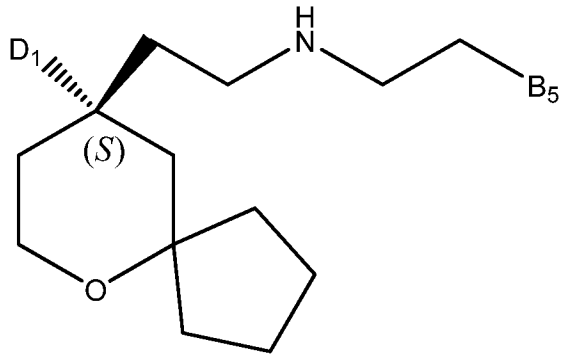
V-3,



VI-1,



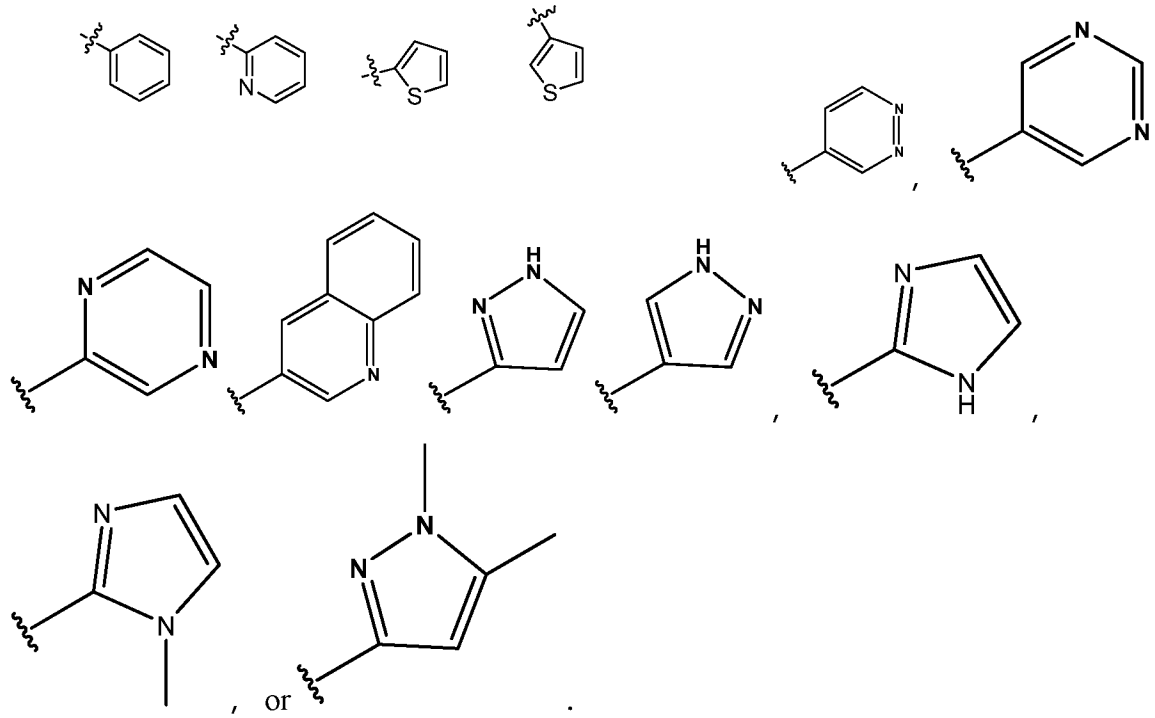
VI-2, or



VI-3

wherein D_1 is an aryl; B_5 is an aryl or carbocycle.

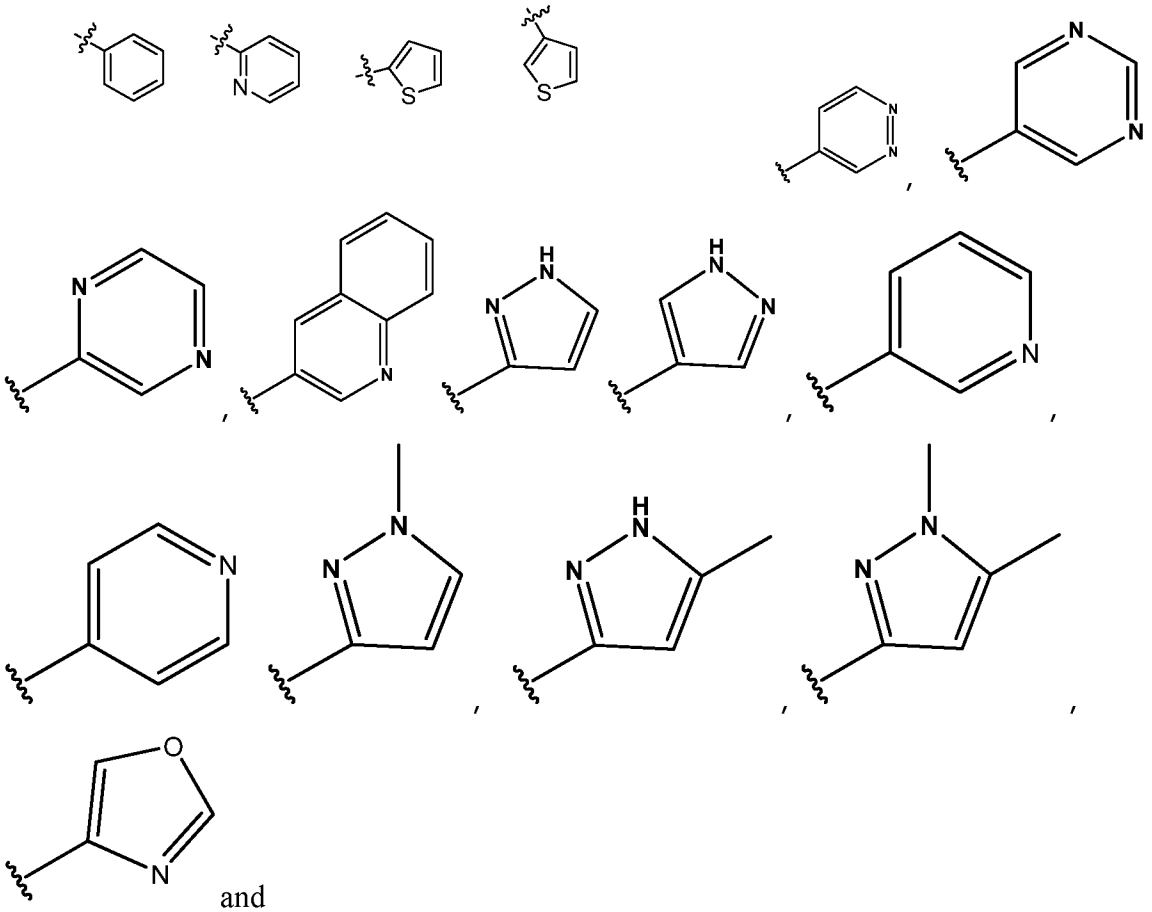
[0061] In some embodiments, each aryl group is independnetly selected from the list below:



[0062] In some embodiments, each aryl group is idependently mono or multiply substituted. In some embodiments, each aryl group can be independently mono or multiply substituted with I, F, Cl, Br, CH_3, CN, OH, OMe, OEt, OCF_3, CF_3, or methane sulfonyl. Further, in some embodiments, the carbocycle is cyclohexyl, cyclohexenyl or cyclopentyl.

[0063] In some embodiments, D_1 is an optionally mono or multiply substituted aryl. In some embodiments, B_5 is an optionally mono or multiply substituted aryl or carbocycle. In

some embodiments, D_1 or B_5 is independently selected from the group consisiting of:

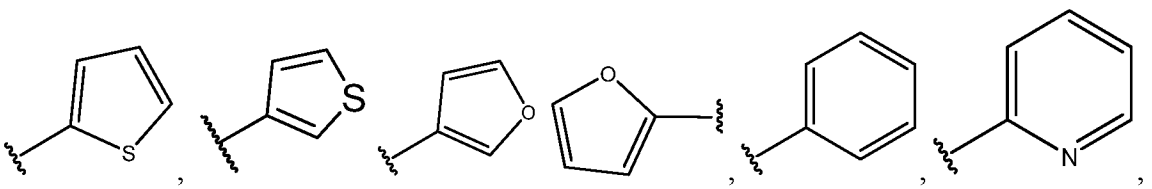


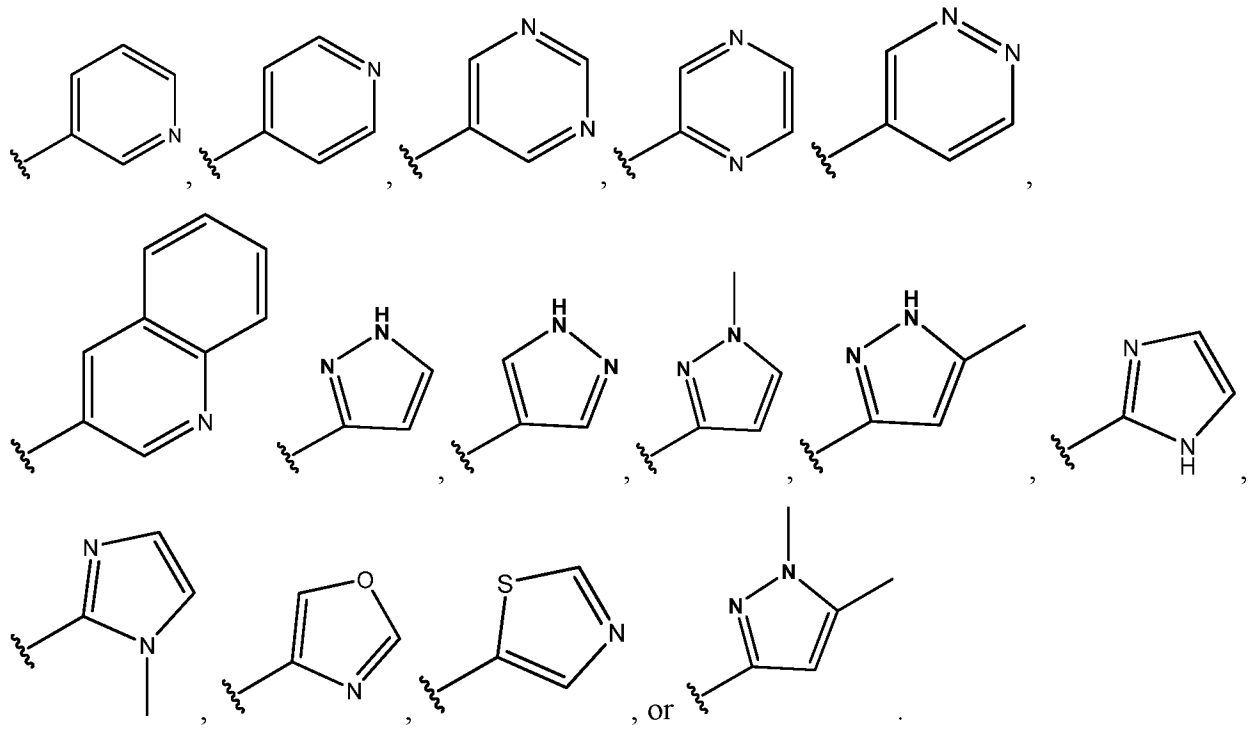
and

wherein the cabocycle is cyclohexyl, cyclohexenyl or cyclopentyl.

[0064] In some embodiments, D_1 is optionally mono or multiply substituted phenyl, 2-pyridil, 3-pyridyl, or 4-pyridyl. In some embodimetns, D_1 is optionally substituted with one or more of F, Cl, Br, I, OCF_3, CH_3, and CF_3. In some embodiments, D_1 is not substituted.

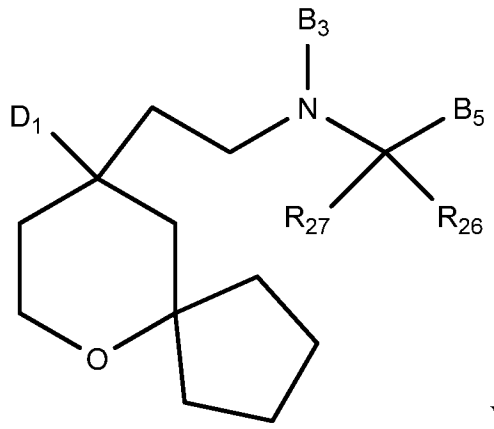
[0065] In some embodiments, B_5 is optionally mono or multiply substituted



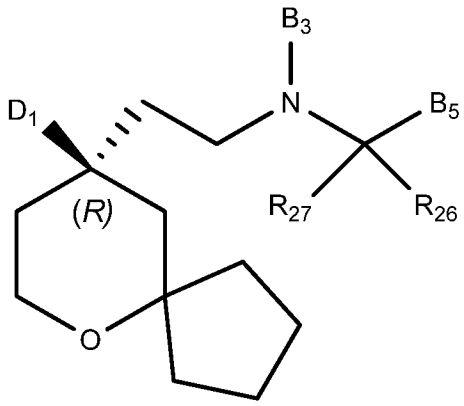


[0066] In some embodiments, B_5 is substituted with one or more of Cl, Br, F, I, OMe, CN, CH_3, methanesulfonyl, and CF_3. In some embodiments, B_5 is substituted with two or more of Cl, Br, F, I, OMe, CN, CH_3, CF_3, and methanesulfonyl, or a combination thereof. That is B_5 can have two or more substituents but not all of the plurality of substituents needs to be the same.

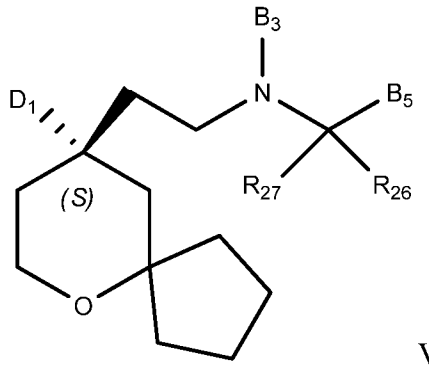
[0067] In some embodiments, compounds having stuctures of Formula VII-1, VII-2., or VII-3



VII-1,



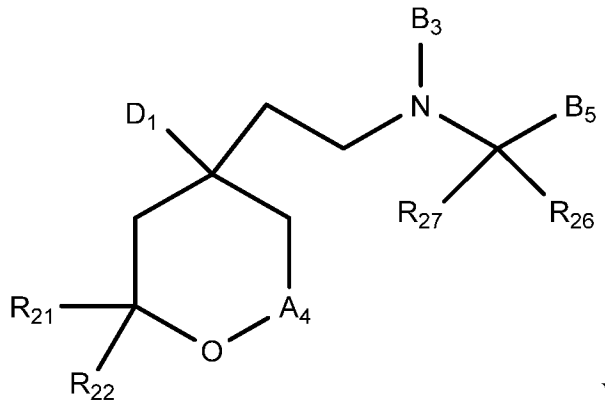
VII-2,



or VII-3

are provided, wherein D_1 is an optionally substituted heteroaryl or aryl, B_3 is H or alkyl, B_5 is an optionally substituted aryl or heteroaryl, and R_{26} and R_{27} are each hydrogren or an isotope thereof. In some embodiments, R_{26} and R_{27} are deuterium. In some embodiments, R_{26} or R_{27} are independently alkyl. In some embodiments, B_3 is C_1-C_5 alkyl.

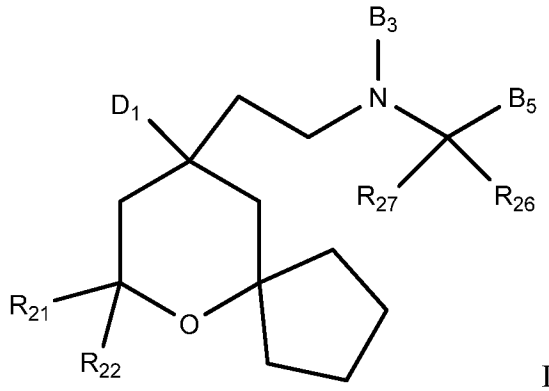
[0068] In some embodiments, the compound has a structure of Formula VIII or an enantiomer thereof



VIII, wherein D1 is an optionally substituted heteroaryl or aryl, B3 is H or alkyl, B5 is an optionally substituted aryl or heteroaryl, and R26 and R27 are each hydrogren or an isotope thereof. In some embodiments, R26 and R27 are deuterium. In some embodiments, R26 or R27 are independently alkyl. A4 is as described herein. In some embodiments, B3 is C1-C5 alkyl. In some embodiments, the enantiomer is the R or S enantiomer at the carbon that is connected to D1.

[0069] In some embodiments, a compound has the structure of Formula IX or an enantiomer

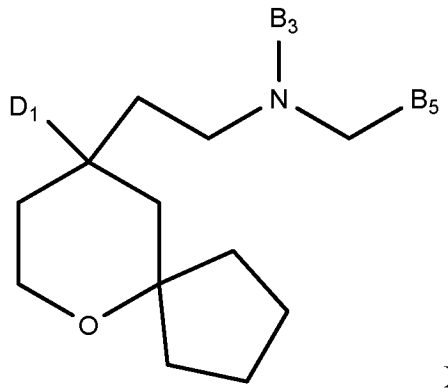
thererof



IX.

In some embodiments, the enantiomer is the *R* or *S* enantiomer at the carbon that is connected to D_1.

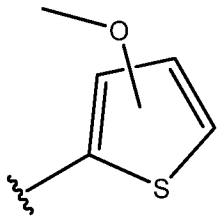
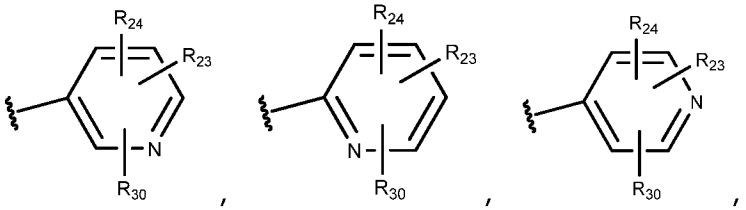
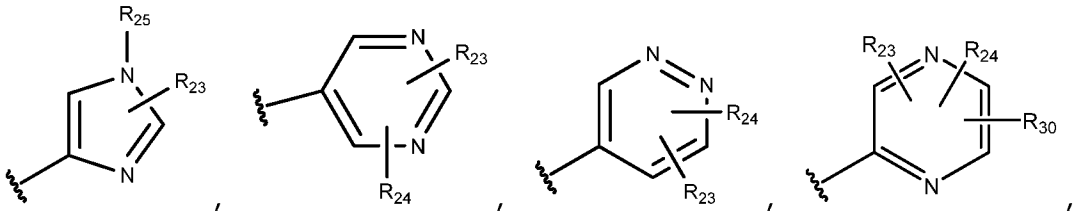
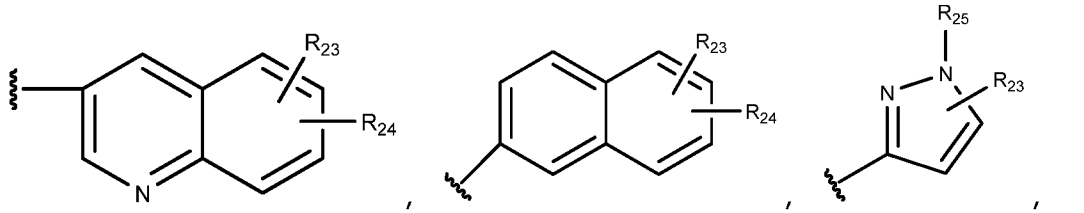
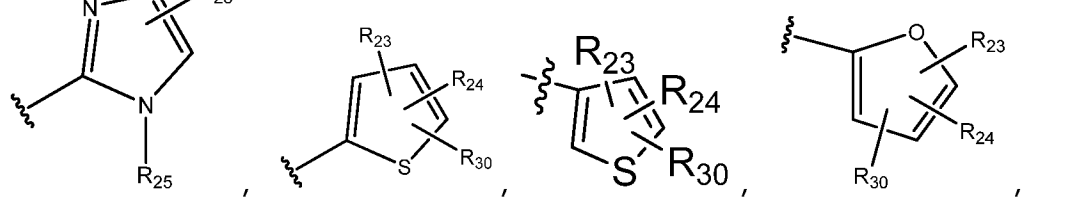
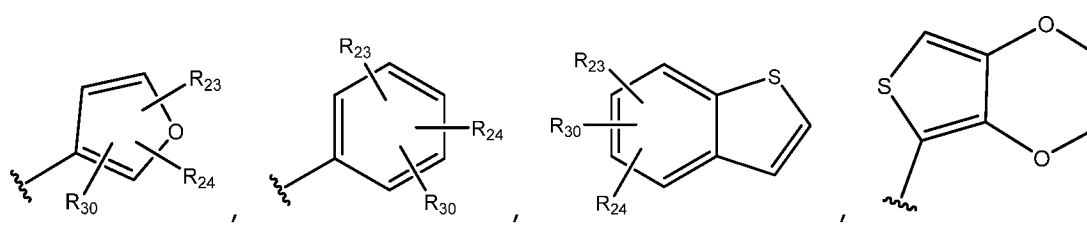
[0070] In some embodiments, a compound has the structure of Formula X or an enantiomer thereof

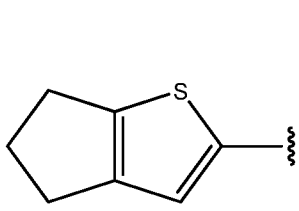


X.

In some embodiments, the enantiomer is the R or S enantiomer at the carbon that is connected to D1.

[0071] In some embodiments of the structures described herein, D1 is an optionally substiuted pyridyl group or phenyl group. In some embodiments, D1 is an optionally substiuted 2-pyridyl, 3-pyridyl, or 4-pyridyl group or phenyl group. In some embodiments, D1 is optionally substituted with one or more of, H, OH, alkyl alcohol, halo, alkyl, amine, amide, cyano, alkoxy, haloalkyl, or aklylsulfonyl. In some embodiments, D1 is optionally subsituted with one or more of H, OH, Cl, Br, F, I, OMe, CN, CH_3, CF_3.

[0072] In some embodiments of the strucutres described herein, B_5 is an optionally substituted thiophene group. In some embodiments, B_5 is substituted with an alkoxy group. In some embodiments, B_5 is substituted with a C_1-C_5 alkoxy group. In some embodiments, B_5 is substituted with a methoxy group. In some embodiments, B_5 is  . In some embodiments, B_5 is  ,  ,  ,  ,  .



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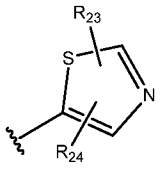

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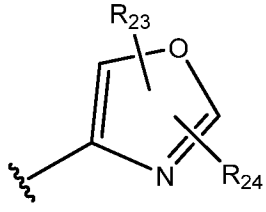
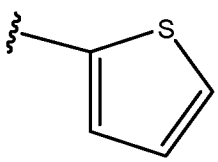


, wherein R_{23}, R_{24}, and R_{30} are each independently null, H, OH, cycle, aryl, branched or unbranched alkyl alcohol, halo, branched or unbranched alkyl, amine, amide, cyano, alkoxy, haloalkyl, aklylsulfonyl, nitrite, alkylsulfanyl, and R_{25} is H or alkyl. In some embodiments, R_{23} and R_{24} together form a aryl or cycle that is attached to one or more of the atoms of B_5. R_{23} R_{24}, and R_{30} can also be further substituted. In some embodiments, R_{23}, R_{24}, and R_{30} are each independently H, NH_2, OH, Cl, Br, F, I, OMe, CN, CH_3, phenyl, C_3-C_6 carbocycle, methanesulfonyl, CF_3,


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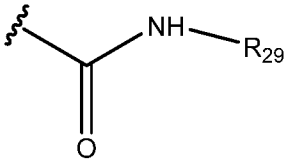

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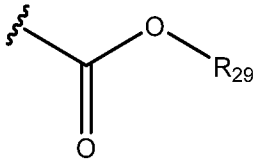


wherein R_{29} is H or an alkyl. In some embodiments, R_{29} is a C_1-C_6 alkyl. In some embodiments, one of R_{23}, R_{24}, and R_{30} is H. In some embodiments, at least one of R_{23}, R_{24}, and R_{30} is H. In some embodiments, two of R_{23}, R_{24}, and R_{30} are H.

[0073] The following compounds and others described herein have agonist activity for OR mediated signal transduction:[(4-chlorophenyl)methyl]({2-[4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; [(3,4-dimethoxyphenyl)methyl][2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl]amine; 2-[({2-[2-ethyl-2-methyl-4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol; [2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl][(2-fluorophenyl)methyl]amine; 4-[({2-[4-(2-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}amino)methyl]-N,N-dimethylaniline; 2-[({2-[2-ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}amino)methyl]phenoll;[(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine. Other examples include the compounds, and pharmaceutically acceptable salts thereof, described herein.

[0074] In some embodiments, compounds, such as the ones described herein are provided. In some embodiments, a compound selected from the compounds described in the Examples is provided. The compounds can be used in any of the methods described herein,

including, but not limited to, treating pain. For example, the compounds can be used for treating or reversing hyperalgesia, induced hyperalgesia, decreasing nociceptive sensitization, and the like. The compounds can be also be used in the preparation of a medicament for the same. In some embodiments, uses of the compounds for treating pain, treating or reversing hyperalgesia, induced hyperalgesia, decreasing nociceptive sensitization, and the like, are providedd.

[0075] Thus, the application provides methods of generating agonist activity in OR mediated signal transduction through administration of one or more of the above recited compounds to a subject or subject in need thereof.

[0076] Various atoms in the compositions described herein can be isotopes that occur at lower frequency. Hydrogen can be replaced at any position in the compositions described herein with deuterium. Optionally, hydrogen can also be replaced with tritium. Carbon (^{12}C) can be replaced at any position in the compositions described herein with ^{13}C or ^{14}C. Nitrogen (^{14}N) can be replaced with ^{15}N. Oxygen (^{16}O) can be replaced at any position in the compositions described herein with ^{17}O or ^{18}O. Sulfur (^{32}S) can be replaced at any position in the compositions described herein with ^{33}S, ^{34}S or ^{36}S. Chlorine (^{35}Cl) can be replaced at any position in the compositions described herein with ^{37}Cl. Bromine (^{79}Br) can be replaced at any position in the compositions described herein with ^{81}Br.

[0077] Selected compounds described herein are agonists and antagonists of Opioid Receptors (ORs). The ability of the compounds to stimulate OR mediated signaling may be measured using any assay known in the art to detect OR mediated signaling or OR activity, or the absence of such signaling/activity. "OR activity" refers to the ability of an OR to transduce a signal. Such activity can be measured, *e.g.*, in a heterologous cell, by coupling an OR (or a chimeric OR) to a downstream effector such as adenylate cyclase.

[0078] A "natural ligand-induced activity" as used herein, refers to activation of the OR by a natural ligand of the OR. Activity can be assessed using any number of endpoints to measure OR activity.

[0079] Generally, assays for testing compounds that modulate OR-mediated signal transduction include the determination of any parameter that is indirectly or directly under the influence of a OR, *e.g.*, a functional, physical, or chemical effect.

[0080] Samples or assays comprising ORs that are treated with a potential activator, inhibitor, or modulator are compared to control samples without the inhibitor, activator, or modulator to examine the extent of inhibition. Control samples (untreated with inhibitors) are assigned a relative OR activity value of 100%. Inhibition of an OR is achieved when the OR activity value relative to the control is about 80%, 50%, or 25%. Activation of an OR is achieved when the OR activity value relative to the control (untreated with activators) is 110%, 150%, 200-500% (*i.e.*, two to five fold higher relative to the control) or, 1000-3000% or higher.

[0081] The effects of the compounds upon the function of an OR can be measured by examining any of the parameters described above. Any suitable physiological change that affects OR activity can be used to assess the influence of a compound on the ORs and natural ligand-mediated OR activity. When the functional consequences are determined using intact cells or animals, one can also measure a variety of effects such as changes in intracellular second messengers such as cAMP.

[0082] Modulators of OR activity are tested using OR polypeptides as described above, either recombinant or naturally occurring. The protein can be isolated, expressed in a cell, expressed in a membrane derived from a cell, expressed in tissue or in an animal. For example, neuronal cells, cells of the immune system, transformed cells, or membranes can be used to test the GPCR polypeptides described above. Modulation is tested using one of the *in vitro* or *in vivo* assays described herein. Signal transduction can also be examined *in vitro* with soluble or solid state reactions, using a chimeric molecule such as an extracellular domain of a receptor covalently linked to a heterologous signal transduction domain, or a heterologous extracellular domain covalently linked to the transmembrane and or cytoplasmic domain of a receptor. Furthermore, ligand-binding domains of the protein of interest can be used *in vitro* in soluble or solid state reactions to assay for ligand binding.

[0083] Ligand binding to an OR, a domain, or chimeric protein can be tested in a number of formats. Binding can be performed in solution, in a bilayer membrane, attached to a solid phase, in a lipid monolayer, or in vesicles. Typically, in an assay described herein, the binding of the natural ligand to its receptor is measured in the presence of a candidate modulator. Alternatively, the binding of the candidate modulator may be measured in the presence of the natural ligand. Often, competitive assays that measure the ability of a compound to compete with binding of the natural ligand to the receptor are used. Binding can be tested by measuring, *e.g.*, changes in spectroscopic characteristics (*e.g.*, fluorescence, absorbance, refractive index), hydrodynamic (*e.g.*, shape) changes, or changes in chromatographic or solubility properties.

[0084] Modulators may also be identified using assays involving β-arrestin recruitment. β-arrestin serves as a regulatory protein that is distributed throughout the cytoplasm in unactivated cells. Ligand binding to an appropriate OR is associated with redistribution of β-arrestin from the cytoplasm to the cell surface, where it associates with the OR. Thus, receptor activation and the effect of candidate modulators on ligand-induced receptor activation, can be assessed by monitoring β-arrestin recruitment to the cell surface. This is frequently performed by transfecting a labeled β-arrestin fusion protein (*e.g.*, β-arrestin-green fluorescent protein (GFP)) into cells and monitoring its distribution using confocal microscopy (see, *e.g.*, Groarke *et al.*, J. Biol. Chem. 274(33):23263 69 (1999)).

[0085] Another technology that can be used to evaluate OR-protein interactions in living cells involves bioluminescence resonance energy transfer (BRET). A detailed discussion regarding BRET can be found in Kroeger *et al.*, J. Biol. Chem., 276(16):12736 43 (2001).

[0086] Other assays can involve determining the activity of receptors which, when activated by ligand binding, result in a change in the level of intracellular cyclic nucleotides, *e.g.*, cAMP, by activating or inhibiting downstream effectors such as adenylate cyclase. Changes in intracellular cAMP can be measured using immunoassays. The method described in Offermanns & Simon, J. Biol. Chem. 270:15175 15180 (1995) may be used to determine the level of cAMP. Also, the method described in Felley-Bosco *et al.*, Am.

J. Resp. Cell and Mol. Biol. 11:159 164 (1994) may be used to determine the level of cGMP. Further, an assay kit for measuring cAMP a is described in U.S. Pat. No. 4,115,538, herein incorporated by reference.

[0087] Transcription levels can be measured to assess the effects of a test compound on ligand-induced signal transduction. A host cell containing the protein of interest is contacted with a test compound in the presence of the natural ligand for a sufficient time to effect any interactions, and then the level of gene expression is measured. The amount of time to effect such interactions may be empirically determined, such as by running a time course and measuring the level of transcription as a function of time. The amount of transcription may be measured by using any method known to those of skill in the art to be suitable. For example, mRNA expression of the protein of interest may be detected using northern blots or their polypeptide products may be identified using immunoassays. Alternatively, transcription based assays using reporter genes may be used as described in U.S. Pat. No. 5,436,128, herein incorporated by reference. The reporter genes can be, *e.g.*, chloramphenicol acetyltransferase, firefly luciferase, bacterial luciferase, β-galactosidase and alkaline phosphatase. Furthermore, the protein of interest can be used as an indirect reporter via attachment to a second reporter such as green fluorescent protein (see, *e.g.*, Mistili & Spector, Nature Biotechnology 15:961 964 (1997)).

[0088] The amount of transcription is then compared to the amount of transcription in either the same cell in the absence of the test compound, or it may be compared with the amount of transcription in a substantially identical cell that lacks the protein of interest. A substantially identical cell may be derived from the same cells from which the recombinant cell was prepared but which had not been modified by introduction of heterologous DNA. Any difference in the amount of transcription indicates that the test compound has in some manner altered the activity of the protein of interest.

[0089] Pharmaceutical Compositions/ Formulations

[0090] Pharmaceutical compositions can be formulated by standard techniques using one or more physiologically acceptable carriers or excipients. The formulations may contain a buffer and/or a preservative. The compounds and their physiologically acceptable salts

and solvates can be formulated for administration by any suitable route, including via inhalation, topically, nasally, orally, parenterally (*e.g.*, intravenously, intraperitoneally, intravesically or intrathecally) or rectally in a vehicle comprising one or more pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice.

[0091] Pharmaceutical compositions can include effective amounts of one or more compound(s) described herein together with, for example, pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or other carriers. Such compositions may include diluents of various buffer content (*e.g.*, TRIS or other amines, carbonates, phosphates, amino acids, for example, glycinamide hydrochloride (especially in the physiological pH range), N-glycylglycine, sodium or potassium phosphate (dibasic, tribasic), *etc.* or TRIS-HCl or acetate), pH and ionic strength; additives such as detergents and solubilizing agents (*e.g.*, surfactants such as Pluronics, Tween 20, Tween 80 (Polysorbate 80), Cremophor, polyols such as polyethylene glycol, propylene glycol, *etc.*), anti-oxidants (*e.g.*, ascorbic acid, sodium metabisulfite), preservatives (*e.g.*, Thimersol, benzyl alcohol, parabens, *etc.*) and bulking substances (*e.g.*, sugars such as sucrose, lactose, mannitol, polymers such as polyvinylpyrrolidones or dextran, *etc.*); and/or incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, *etc.* or into liposomes. Hyaluronic acid may also be used. Such compositions can be employed to influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of a compound described herein. See, *e.g.*, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712 which are herein incorporated by reference. The compositions can, for example, be prepared in liquid form, or can be in dried powder, such as lyophilized form. Particular methods of administering such compositions are described *infra*.

[0092] Where a buffer is to be included in the formulations described herein, the buffer can be selected from sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium

phosphate, and tris(hydroxymethyl)-aminomethane, or mixtures thereof. The buffer can also be glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium phosphate or mixtures thereof.

[0093] Where a pharmaceutically acceptable preservative is to be included in a formulation of one of the compounds described herein, the preservative can be selected from phenol, m-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, or mixtures thereof. The preservative can also be phenol or m-cresol.

[0094] The preservative is present in a concentration from about 0.1 mg/ml to about 50 mg/ml, in a concentration from about 0.1 mg/ml to about 25 mg/ml, or in a concentration from about 0.1 mg/ml to about 10 mg/ml.

[0095] The use of a preservative in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

[0096] The formulation may further comprise a chelating agent where the chelating agent may be selected from salts of ethlenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof.

[0097] The chelating agent can be present in a concentration from 0.1 mg/ml to 5 mg/ml, from 0.1 mg/ml to 2 mg/ml or from 2 mg/ml to 5 mg/ml.

[0098] The use of a chelating agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

[0099] The formulation of the compounds described herein may further comprise a stabilizer selected from high molecular weight polymers and low molecular compounds where such stabilizers include, but are not limited to, polyethylene glycol (*e.g.* PEG 3350), polyvinylalcohol (PVA), polyvinylpyrrolidone, carboxymethylcellulose, different salts (*e.g.* sodium chloride), L-glycine, L-histidine, imidazole, arginine, lysine, isoleucine,

aspartic acid, tryptophan, and threonine or any mixture thereof. The stabilizer can also be L-histidine, imidazole or arginine.

[0100] The high molecular weight polymer can be present in a concentration from 0.1 mg/ml to 50 mg/m, from 0.1 mg/ml to 5 mg/ml, from 5 mg/ml to 10 mg/ml, from 10 mg/ml to 20 mg/ml, from 20 mg/ml to 30 mg/ml or from 30 mg/ml to 50 mg/ml.

[0101] The low molecular weight compound can be present in a concentration from 0.1 mg/ml to 50 mg/ml, from 0.1 mg/ml to 5 mg/ml, from 5 mg/ml to 10 mg/ml, from 10 mg/ml to 20 mg/ml, from 20 mg/ml to 30 mg/ml or from 30 mg/ml to 50 mg/ml.

[0102] The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

[0103] The formulation of the compounds described herein may further include a surfactant. IN some embodiments, the surfactant may be selected from a detergent, ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, such as 188 and 407, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives such as alkylated and alkoxylated derivatives (tweens, *e.g.* Tween-20, or Tween-80), monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, glycerol, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids, glycerophospholipids (lecithins, kephalins, phosphatidyl serine), glyceroglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, docusate calcium, docusate potassium, SDS (sodium dodecyl sulfate or sodium lauryl sulfate), dipalmitoyl phosphatidic acid, sodium caprylate, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (*e.g.* 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, *e.g.*

lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, zwitterionic surfactants (*e.g.* N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (*e.g.* cetyl-trimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl β-D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35), fusidic acid derivatives--(*e.g.* sodium tauro-dihydrofusidate *etc.*), long-chain fatty acids and salts thereof C6-C12 (*e.g.* oleic acid and caprylic acid), acylcarnitines and derivatives, N_α -acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N_α-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N_α-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof.

[0104] The use of a surfactant in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

[0105] Pharmaceutically acceptable sweeteners can be part of the formulation of the compounds described herein. Pharmaceutically acceptable sweeteners include at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose), saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel, and honey.

[0106] Intense sweeteners are conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v) based on the total volume of the final formulation, or is about 0.06% in the low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener can effectively be used in larger quantities ranging from about 10% to about 35%, or from about 10% to 15% (w/v).

[0107] The formulations of the compounds described herein may be prepared by conventional techniques, *e.g.* as described in Remington's Pharmaceutical Sciences, 1985 or in Remington: The Science and Practice of Pharmacy, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product.

[0108] The phrase "pharmaceutically acceptable" or "therapeutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and preferably do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human. As used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a State government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia (*e.g.*, Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985)) for use in animals, and more particularly in humans.

[0109] Administration of the compounds described herein may be carried out using any method known in the art. For example, administration may be transdermal, parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intracerebroventricular, intrathecal, intranasal, aerosol, by suppositories, or oral administration. A pharmaceutical composition of the compounds described herein can be for administration for injection, or for oral, pulmonary, nasal, transdermal, ocular administration.

[0110] For oral administration, the pharmaceutical composition of the compounds described herein can be formulated in unit dosage forms such as capsules or tablets. The tablets or

capsules may be prepared by conventional means with pharmaceutically acceptable excipients, including binding agents, for example, pregelatinised maize starch, polyvinylpyrrolidone, or hydroxypropyl methylcellulose; fillers, for example, lactose, microcrystalline cellulose, or calcium hydrogen phosphate; lubricants, for example, magnesium stearate, talc, or silica; disintegrants, for example, potato starch or sodium starch glycolate; or wetting agents, for example, sodium lauryl sulphate. Tablets can be coated by methods well known in the art. Liquid preparations for oral administration can take the form of, for example, solutions, syrups, or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives, for example, suspending agents, for example, sorbitol syrup, cellulose derivatives, or hydrogenated edible fats; emulsifying agents, for example, lecithin or acacia; non-aqueous vehicles, for example, almond oil, oily esters, ethyl alcohol, or fractionated vegetable oils; and preservatives, for example, methyl or propyl-p-hydroxybenzoates or sorbic acid. The preparations can also contain buffer salts, flavoring, coloring, and/or sweetening agents as appropriate. If desired, preparations for oral administration can be suitably formulated to give controlled release of the active compound.

[0111] For topical administration, the pharmaceutical composition of the compounds described herein can be formulated in a pharmaceutically acceptable vehicle containing 0.1 to 10 percent, or 0.5 to 5 percent, of the active compound(s). Such formulations can be in the form of a cream, lotion, sublingual tablet, aerosols and/or emulsions and can be included in a transdermal or buccal patch of the matrix or reservoir type as are conventional in the art for this purpose.

[0112] For parenteral administration, the compounds described herein are administered by either intravenous, subcutaneous, or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. The compounds can be formulated for parenteral administration by injection, for example, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, for example, in ampoules or in multi-dose containers, with an added preservative. The compositions can

take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents, for example, suspending, stabilizing, and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, for example, sterile pyrogen-free water, before use.

[0113] For administration by injection, the compound(s) can be used in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic. The pharmaceutical compositions of the compounds described herein may be formulated with a pharmaceutically acceptable carrier to provide sterile solutions or suspensions for injectable administration. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspensions in liquid prior to injection or as emulsions. Suitable excipients are, for example, water, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, or the like. In addition, if desired, the injectable pharmaceutical compositions may contain minor amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like. If desired, absorption enhancing preparations (*e.g.*, liposomes) may be utilized. Suitable pharmaceutical carriers are described in "Remington's pharmaceutical Sciences" by E. W. Martin.

[0114] For administration by inhalation, the compounds may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base, for example, lactose or starch. For intranasal administration the compounds described herein may be used, for example, as a liquid spray, as a powder or in the form of drops.

[0115] The compounds can also be formulated in rectal compositions, for example, suppositories or retention enemas, for example, containing conventional suppository bases, for example, cocoa butter or other glycerides.

[0116] Furthermore, the compounds can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0117] The compositions can, if desired, be presented in a pack or dispenser device that can contain one or more unit dosage forms containing the active ingredient. The pack can, for example, comprise metal or plastic foil, for example, a blister pack. The pack or dispenser device can be accompanied by instructions for administration.

[0118] The compounds described herein also include derivatives referred to as prodrugs, which can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Examples of prodrugs include compounds of the invention as described herein that contain one or more molecular moieties appended to a hydroxyl, amino, sulfhydryl, or carboxyl group of the compound, and that when administered to a patient, cleaves in vivo to form the free hydroxyl, amino, sulfhydryl, or carboxyl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention. Preparation and use of prodrugs is discussed in T. Higuchi et al., "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference in their entireties.

[0119] Dosages

[0120] The compounds described herein may be administered to a patient at therapeutically effective doses to prevent, treat, or control one or more diseases and disorders mediated, in whole or in part, by an OR-ligand interaction. Pharmaceutical compositions comprising one or more of compounds described herein may be administered to a patient in an amount sufficient to elicit an effective protective or therapeutic response in the patient. An amount adequate to accomplish this is defined as "therapeutically effective dose." The dose will be determined by the efficacy of the particular compound employed and the condition of the subject, as well as the body weight or surface area of the area to be treated. The size of the dose also will be determined by the existence, nature, and extent of any adverse effects that accompany the administration of a particular compound or vector in a particular subject.

[0121] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, for example, by determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio, LD50/ED50. In some embodiments, compounds that exhibit large therapeutic indices are used. While compounds that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue to minimize potential damage to normal cells and, thereby, reduce side effects.

[0122] The data obtained from cell culture assays and animal studies can be used to formulate a dosage range for use in humans. In some embodiments, the dosage of such compounds lies within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration. For any compound described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (the concentration of the test compound that achieves a half-

maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography (HPLC). In general, the dose equivalent of a modulator is from about 1 ng/kg to 10 mg/kg for a typical subject.

[0123] The amount and frequency of administration of the compounds described herein and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. In general it is contemplated that an effective amount would be from 0.001 mg/kg to 10 mg/kg body weight, and in particular from 0.01 mg/kg to 1 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.01 to 500 mg, and in particular 0.1 mg to 200 mg of active ingredient per unit dosage form.

[0124] In some embodiments, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, *e.g.*, an effective amount to achieve the desired purpose. The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, from about 0.01 mg to about 750 mg, from about 0.01 mg to about 500 mg, or from about 0.01 mg to about 250 mg, according to the particular application. The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total dosage may be divided and administered in portions during the day as required.

[0125] In some embodiments, one or more compounds described herein are administered with

another compound. The administration may be sequentially or concurrently. The combination may be in the same dosage form or administered as separate doses. In some embodiments, the another compound is another analgesic or pain reliever. In some embodiments, the another compound is a non-opioid analgesic. Examples of useful non-opioid analgesics include, but are not limited to, non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, and pharmaceutically acceptable salts thereof, and mixtures thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophenol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more detailed description of the NSAIDs, see Paul A. Insel, Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics 617-57 (Perry B. Molinhoff and Raymond W. Ruddon eds., 9.sup.th ed 1996); and Glen R. Hanson, Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II 1196-1221 (A. R. Gennaro ed. 19.sup.th ed. 1995), which are hereby incorporated by reference in their entireties.

[0126] The compounds described herein can also be administered Cox-II inhibitors. Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Pat. No. 6,136,839, which is hereby incorporated by reference in its

entirety. Examples of Cox-II inhibitors include, but are not limited to, rofecoxib and celecoxib.

[0127]The compounds described herein can also be administered with antimigraine agents. Examples of useful antimigraine agents include, but are not limited to, alpiropride, bromocriptine, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergonovine, ergot, ergotamine, flumedroxone acetate, fonazine, ketanserin, lisuride, lomerizine, methylergonovine, methysergide, metoprolol, naratriptan, oxetorone, pizotyline, propranolol, risperidone, rizatriptan, sumatriptan, timolol, trazodone, zolmitriptan, and mixtures thereof.

[0128] The compounds described herein can also be administered with anti-constipation agents. Examples of anti-constipation agents include, but are not limited to, laxatives or stool softners. Examples of anti-constipation agents include, but are not limited to, be docusate, poloxamer 188, psyllium, methylcellulose, carboxymethyl cellulose, polycarbophil, bisacodyl, castor oil, magnesium citrate, magnesium hydroxide, magnesium sulfate, dibasic sodium phosphate, monobasic sodium phosphate, sodium biphosphate or any combination thereof.

[0129] Medical Use

[0130] The compositions described herein may be useful for treating pain or pain associated disorders. The compositions described herein may be useful for treating immune dysfunction, inflammation, esophageal reflux, neurological and psychiatric conditions, urological and reproductive conditions, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents and agents for the treatment of respiratory diseases and cough.

[0131] In some embodiments, methods of treating pain are provided. In some embodiments, one or more compound described herein are administered to a subject to treat the pain. In some embodiments, the pain can be post-operative pain. In some embodiments, the pain is caused by cancer. In some embodiments, the pain is neuropathic pain. In some embodiments, the pain is caused by trauma, such as but not limited to, blunt force trauma. In some embodiments, the pain is caused by inflammation.

[0132] In some embodiments, the one or more compounds can used for treating or reversing hyperalgesia. Accordingly, in some embodiments, methods of treating or reversing hyperalgesia are provided. In some embodiments, the methods comprise administering to a subject one or more compounds described herein, or pharmaceutically acceptable salts thereof. In some embodiments, a pharmaceutical composition comprising the one or more compounds, or pharmaceutically acceptable salts thereof are administered. As used herein, hyprealgesia refers to a condition where a subject has an increased sensitivity to pain. The increase sensitivity can occur at the site of a previous injury or pain sensation or can be at a different site. In some embodiments, the hyperalgesia is diffuse hyperlagesia (i.e. in more than one site on the subject) or is focal, (i.e. at a discrete site on the subject). In some embodiments, the subject has been administered a first opioid prior to being administered the one or more compounds described herein, or a pharmaceutically acceptable salt thereof.

[0133] In some embodiments, the hyperalgesia is opioid induced hyperalgesia, which can also be referred to as opioid-induced abnormal pain sensitivity or paradoxical hyperalgesia, which is described as a condition that results from the use of opioids. For example, individuals taking opioids can develop an increasing sensitivity to noxious stimuli, even evolving a painful response to previously non-noxious stimuli (allodynia). This is a result of the subject being exposed to opioids. Opioid induced hyperalgesia ("OIH") is distinct and different from what is known as "tolerance." Without being bound to any particular theory, tolerance is due to desensitization of antinociceptive mechanisms whereas OIH is due to sensitization of pronociceptive mechanisms. Therefore, where opioid tolerance is identified as a condition in a subject the tolerance can be minimized by increasing the dose of the opioid. In contrast, increasing the dose of an opioid in a subject suffering from OIH will only worsen the condition. In some embodiments, the compounds described herein are used for the preparation of a medicament for treating hyperalgesia or opioid induced hyperalgesia.

[0134] In some embodiments, the opioid induced hyperalgesia is morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, alfentanil, remifentanil, sufentanil, etorphine, buprenorphine, methadone, and/or heroin induced hyperalgesia. In some

embodiments, the OIH is induced by a combination of more than one opioid. In some embodiments, the OIH is morphine induced OIH. In some embodiments, the OIH is oxycodone induced OIH. In some embodiments, the OIH is hydrocodone induced OIH. In some embodiments, the OIH is hydromorphone induced OIH. In some embodiments, the OIH is fentanyl induced OIH. In some embodiments, the OIH is buprenorphine induced OIH. In some embodiments, the OIH is heroin induced OIH.

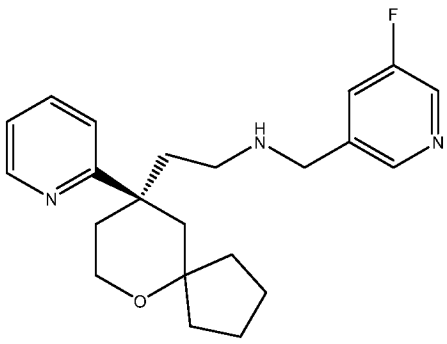
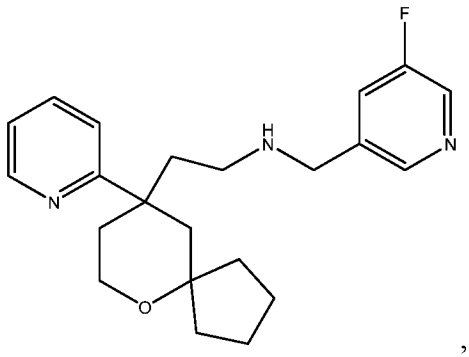
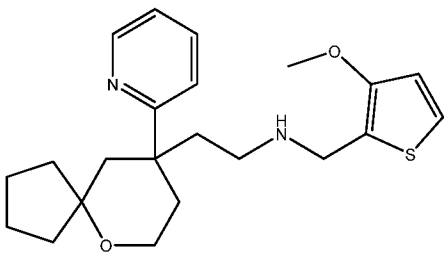
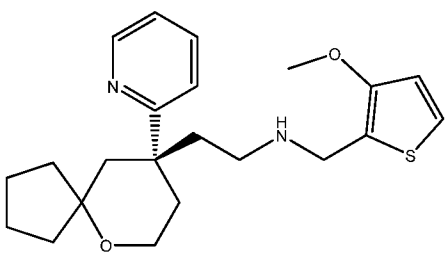
[0135] In some embodiments, methods of decreasing nociceptive sensitization in a subject are provided. In some embodiments, the methods comprise administering to a subject one or more compounds described herein, or pharmaceutically acceptable salts thereof. In some embodiments, a pharmaceutical composition comprising the one or more compounds, or pharmaceutically acceptable salts thereof are administered. In some embodiments, the the subject has increased nociceptive sensitization. In some embodiments, the nociceptive sensitization is induced by another therapeutic. In some embodiments, the nociceptive sensitization is opioid induced nociceptive sensitization. In some embodiments, the opioid induced nociceptive sensitization is morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, alfentanil, remifentanil, sufentanil, etorphine, buprenorphine, methadone, and/or heroin, or a pharmaceutically acceptable salt thereof, induced nociceptive sensitization.

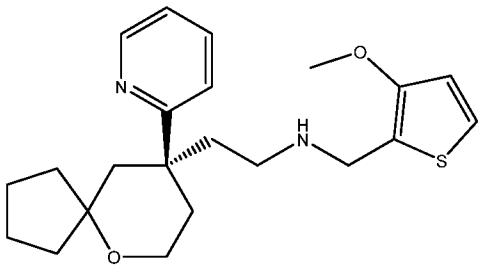
[0136] In some embodiments, methods of treating pain in a subject are provided, wherein the method comprises administering an opioid agonist to the subject until the opioid increases nociceptive sensitization in the subject; and then administering to the subject with increased nociceptive sensitization one or more compounds described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the opioid agonist is morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, alfentanil, remifentanil, sufentanil, etorphine, buprenorphine, methadone, and/or heroin, or pharmaceutically acceptable salts thereof. In some embodiments, a pharmaceutical composition comprising the one or more compounds, or pharmaceutically acceptable salts thereof are administered.

[0137] In some embodiments, methods of treating pain are provided, wherein the methods

comprising administering administering an opioid agonist to the subject; and then administering to the subject in the absence of the opioid and then administering to the subject one or more compounds described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the opioid agonist is morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, alfentanil, remifentanil, sufentanil, etorphine, buprenorphine, methadone, and/or heroin, or pharmaceutically acceptable salts thereof. In some embodiments, a pharmaceutical composition comprising the one or more compounds, or pharmaceutically acceptable salts thereof are administered.

[0138] In some embodiments, the compounds are used in the preparation of a medicament for treating or reversing OIH, such as opioid induced OIH. In some embodiments, uses of a compound, or pharmaceutically acceptable salt thereof, for treating or reversing OIH are provided. Non-limiting exmaples of opioid induced OIH are described above. In some embodiments, the compounds are used in the preparation of a medicament for treating nociceptive sensitization. In some embodiments, uses of a compound, or pharmaceutically acceptable salt thereof, for treating nociceptive sensitization are provided. In some embodiments, the nociceptive sensitization is opioid induced. Non-limiting exmaples of opioid that can induce nociceptive sensitization are provided herein.

[0139] In some embodiments, the compound that is used in the methods, uses, or preparation of a medicament is  ,  ,  ,  ,



, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is a compound as described in Examples 1-4, or a pharmaceutically acceptable salt thereof.

[0140] In some embodiments, 2-[({2-[2-Ethyl-2-methyl-4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol; 2-[({2-[2-Ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}amino)methyl]phenol; {2-[2,2-Dimethyl-4-(4-methylphenyl)oxan-4yl]ethyl}[(4-methoxyphenyl)methyl]amine; {2-[(4S*, 4R*)-2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(1R)-1-phenylethyl]amine; {2-[(4S*, 4R*)-2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(1S)-1-phenylethyl]amine; Benzyl({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine; 2-[({2-[2-Ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}amino)methyl]phenol; Benzyl[2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl]amine; {2-[2-Ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}[(4-methoxyphenyl)methyl]amine; [(3,4-Dimethoxyphenyl)methyl]({2-[4-(4-fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; {2-[4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(1-phenylethyl)amine; [(4-Chlorophenyl)methyl]({2-[4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; Benzyl({2-[2-ethyl-4-(2-methoxyphenyl)-2-methyloxan-4-yl]ethyl})amine; [(3,4-dimethoxyphenyl)methyl]({2-[2-ethyl-4-(2-methoxyphenyl)-2-methyloxan-4-yl]ethyl})amine; 4-[({2-[4-(2-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}amino)methyl]-N,N-dimethylaniline; Benzyl({2-[4-(4-fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; {2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}(1-phenylethyl)amine; [2-(2,2-Dimethyl-4-phenyloxan-4-yl)ethyl][(4-methoxyphenyl)methyl]amine; {2-[4-(4-Fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl}[(4-methoxyphenyl)methyl]amine; [(3,4-Dimethoxyphenyl)methyl][2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl]amine, or any combination thereof is not administered.

[0141] In some embodiments, a compound of formula N-((3-methoxythiophen-2-yl)methyl)-2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethanamine; N-((5-fluoropyridin-3-

yl)methyl)-2-(9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl)ethanamine, or any stereoisomer thereof. For example, in some embodiments, the compound is Compound 54, 135, 140, 150, 155, 215, 265, 270, 500, or any combination thereof.

[0142] In some embodiments, the one or more compounds described herein can be administered by any suitable route, including, but not limited to, via inhalation, topically, nasally, orally, parenterally (*e.g.*, intravenously, intraperitoneally, intravesically or intrathecally) or rectally in a vehicle comprising one or more pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard practice.

Definitions

[0143] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the compositions and compounds described herein, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only not intended to be limiting. Other features and advantages of the compositions and compounds described herein will be apparent from the following detailed description and claims.

[0144] As used herein, the phrase "in need thereof" means that the subject, animal or mammal has been identified as having a need for the particular method or treatment. In some embodiments, the identification can be by any means of diagnosis. In any of the methods and treatments described herein, the subject, animal or mammal can be in need thereof. In some embodiments, the subject has been identified has having hyperalgesia, such as but not limited to, opioid induced hyperalgeisa. In some embodiments, the subject has been identified as having increased nociceptive sensitization. In some embodiments, the increased nociceptive sensitization is opioid induced nociceptive sensitization.

[0145] The general chemical terms used throughout have their usual meanings. For example, the

term alkyl refers to a branched or unbranched saturated hydrocarbon group. The term "*n*-alkyl" refers to an unbranched alkyl group. The term "C_x-C_y alkyl" refers to an alkyl group having from x to y carbon atoms, inclusively, in the branched or unbranched hydrocarbon group. By way of illustration, but without limitation, the term "C_1-C_4 alkyl" refers to a straight chain or branched hydrocarbon moiety having from 1 to 4 carbon atoms, including methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl. The term "C_1-C_4 *n*-alkyl" refers to straight chain hydrocarbon moieties having from 1 to 4 carbon atoms including methyl, ethyl, *n*-propyl, and *n*-butyl. C_x-C_y x can be from 1 to 10 and y is from 2 to 20. The term "C_3-C_6 cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The term "C_3-C_7 cycloalkyl" also includes cycloheptyl. Cycloalkylalkyl refers to cycloalkyl moieties linked through an alkyl linker chain, as for example, but without limitation, cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexylethyl, and cyclohexylpropyl. Each alkyl, cycloalkyl, and cycloalkylalkyl group may be optionally substituted, such as, but not limited to, as specified herein. In some embodiments, the alkyl is a C_1-C_3, C_1-C_4, C_1-C_6, C_4-C_6, or C_1-C_{10} alkyl.

[0146] The terms "alkoxy", "phenyloxy", "benzoxy" and "pyrimidinyloxy" refer to an alkyl group, phenyl group, benzyl group, or pyrimidinyl group, respectively, that is bonded through an oxygen atom. Each of these groups may be optionally substituted.

[0147] The terms "alkylthio", "phenylthio", and "benzylthio" refer to an alkyl group, phenyl group, or benzyl group, respectively, that is bonded through a sulfur atom. Each of these groups may be optionally substituted.

[0148] The term "C_1-C_4 acyl" refers to a formyl group or a C_1-C_3 alkyl group bonded through a carbonyl moiety. The term "C_1-C_4 alkoxycarbonyl" refers to a C_1-C_4 alkoxy group bonded through a carbonyl moiety.

[0149] The term "halo" refers to fluoro, chloro, bromo, or iodo. In some embodiments, the halo groups are fluoro, chloro, and bromo. In some embodiments, the halo groups are fluoro

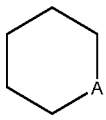
and chloro.

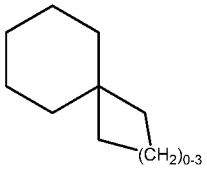
[0150] As used herein, “carbocycle” or "carbocyclic ring" is intended to mean, unless otherwise specified, any stable 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12-membered monocyclic, bicyclic or tricyclic ring, any of which can be saturated, unsaturated (including partially and fully unsaturated), or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. In some embodiments, the bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring can also be present on the bridge. Fused (*e.g.*, naphthyl and tetrahydronaphthyl) and spiro rings are also included.

[0151] The term "heterocycle" is taken to mean a saturated or unsaturated 5- or 6-membered ring containing from 1 to 3 heteroatoms selected from nitrogen, oxygen and sulfur, said ring optionally being benzofused. Exemplary heterocycles include furanyl, thiophenyl (thienyl), pyrrolyl, pyrrolidinyl, pyridinyl, N-methylpyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, thiazolidinyl, N-acetylthiazolidinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and the like. Benzofused heterocyclic rings include isoquinolinyl, benzoxazolyl, benzodioxolyl, benzothiazolyl, quinolinyl, benzofuranyl, benzothiophenyl, indolyl, and the like, all of which may be optionally substituted, which also of course includes optionally substituted on the benzo ring when the heterocycle is benzofused.

[0152] The term “cycle” group is taken to mean a carbocylic ring, a carbocycle or a heterocarbocyle.

[0153] As used herein, the phrase a “cycle of the formula” refers to a ring that can be formed

with the variable referred to. For example, in the structure 

, wherein A can be a cycle of the formula $C(CH_2)_n$, where n = 2-5, it means that A is a carbon and forms a ring with itself with 2-5 CH_2 groups, which could also be represented structurally as 

. The variable "A" is not limited to carbon and can be another atom, such as, but not limited to, a heteroatom, but the context in which the variable is used will indicate the type of atom "A" could be. This is just a non-limiting example. Additionally, the ring that is formed with "A" can also be substituted. Exemplary substituents are described herein.

[0154] In some embodiments, heterocycles include, but are not limited to, pyridinyl, indolyl, furanyl, benzofuranyl, thiophenyl, benzodioxolyl, and thiazolidinyl, all of which may be optionally substituted.

[0155] As used herein, the term "aromatic heterocycle" or "heteroaryl" is intended to mean a stable 5, 6, 7, 8, 9, 10, 11, or 12-membered monocyclic or bicyclic aromatic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. In the case of bicyclic heterocyclic aromatic rings, only one of the two rings needs to be aromatic (*e.g.*, 2,3-dihydroindole), though both can be (*e.g.*, quinoline). The second ring can also be fused or bridged as defined above for heterocycles. The nitrogen atom can be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, as defined). The nitrogen and sulfur heteroatoms can optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p = 1 or 2). In certain compounds, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0156] Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl,

benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0157] Substituted alkyl, cycloalkyl, cycloalkylalkyl, alkoxy, or alkylthio, means an alkyl, cycloalkyl, cycloalkylalkyl, alkoxy, or alkythio group, respectively, substituted one or more times independently with a substituent selected from the group consisting of halo, hydroxy, and C_1-C_3 alkoxy. By way of illustration, but without limitation, examples include trifluoromethyl, pentafluoroethyl, 5-fluoro-2-bromopentyl, 3-hydroxypropyloxy, 4-hydroxycyclohexyloxy, 2-bromoethylthio, 3-ethoxypropyloxy, 3-ethoxy-4-chlorocyclohexyl, and the like. In some embodiments, substitutions include substitution 1-5 times with halo, each independently selected, or substituted 1-3 times with halo and 1-2 times independently with a group selected from hydroxy and C_1-C_3 alkoxy, or substituted 1-3 times independently with a group selected from hydroxy and C_1-C_3 alkoxy, provided that no more than one hydroxy and/or alkoxy substituent may be attached through the same carbon.

[0158] The terms “substituted phenyl” and “substituted heterocycle” are taken to mean that the cyclic moiety in either case is substituted. They can be substituted independently with one or more substituents. They can be substituted independently with 1, 2, 3, 4, 5, 1-3, 1-4, or 1-5 substituents. The substitution can be, independently, halo, alkyl, such as, but not limited to, C_1-C_4 alkyl, alkoxy, such as but not limited to, C_1-C_4 alkoxy, and alklylthio, such as but not limited to, C_1-C_4 alkylthio, wherein each alkyl, alkoxy and alkylthio substituent can be further substituted independently with C_1-C_2 alkoxy or with one to five halo groups; or substituted with one substituent selected from the group consisting of phenyloxy, benzyloxy, phenylthio, benzylthio, and pyrimidinyloxy, wherein the phenyloxy, benzyloxy, phenylthio, benzylthio, and pyrimidinyloxy moiety can be further substituted with one to two substituents selected from the group consisting of halo, C_1-C_2 alkyl, and C_1-C_2 alkoxy; or substituted with one substituent selected from the group consisting of C_1-C_4 acyl and C_1-C_4 alkoxycarbonyl, and further substituted with zero to one substituent selected from the group consisting of halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_1-C_4 alkylthio. When a substituent is halo, in some embodiments, the halo groups are fluoro, chloro, and bromo. The halo can also be iodo.

[0159] DMF means N,N-dimethylformamide.

[0160] As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0161] By "pharmaceutical formulation" it is further meant that the carrier, solvent, excipients and salt must be compatible with the active ingredient of the formulation (*e.g.* a compound described herein). It is understood by those of ordinary skill in this art that the terms “pharmaceutical formulation” and “pharmaceutical composition” are generally interchangeable, and they are so used for the purposes of this application.

[0162] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts

thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic. The present disclosure includes pharmaceutically acceptale salts of any compound(s) described herein. In some embodiments, the pharmaceutically acceptable salt is a hydrochloric salt.

[0163] Pharmaceutically acceptable salts can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, and the like. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, USA, p. 1445 (1990).

[0164] Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, *etc.*) the compounds described herein can be delivered in prodrug form and can be administered in this form for the treatment of disease. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of described herein *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs are prepared by modifying functional groups present in the

compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds described herein wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds described herein.

[0165] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0166] As used herein, “treating” or “treatment” includes any effect *e.g.*, lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder, *etc.* “Treating” or “treatment” of a disease state means the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting an existing disease-state, *i.e.*, arresting its development or its clinical symptoms; and/or (c) relieving the disease-state, *i.e.*, causing regression of the disease state.

[0167] As used herein, “preventing” means causing the clinical symptoms of the disease state not to develop *i.e.*, inhibiting the onset of disease, in a subject that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state.

[0168] As used herein, “mammal” refers to human and non-human patients.

[0169] As used herein, the term "therapeutically effective amount" refers to a compound, or a combination of compounds, described herein present in or on a recipient in an amount sufficient to elicit biological activity, *e.g.* pain relief. In some embodiments, the combination of compounds is a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* vol. 22, pp. 27-55 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a

synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased decrease in pain, or some other beneficial effect of the combination compared with the individual components.

[0170] All percentages and ratios used herein, unless otherwise indicated, are by weight.

[0171] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions described herein also consist essentially of, or consist of, the recited components, and that the processes described herein also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the process remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0172] All enantiomers, diastereomers, and mixtures thereof, are included within the scope of compounds described herein. In some embodiments, a composition comprising the *R* enantiomer is free or substantially free of the *S* enantiomer. In some embodiments, a composition comprising the *S* enantiomer is free or substantially free of the *R* enantiomer. In some embodiments, a composition comprises an enantiomeric excess of at least, or about, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% of either the *R* or the *S* enantiomer.

[0173] As used throughout this disclosure, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to “a composition” includes a plurality of such compositions, as well as a single composition, and a reference to “a therapeutic agent” is a reference to one or more therapeutic and/or pharmaceutical agents and equivalents thereof known to those skilled in the art, and so forth. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

[0174] The compounds described herein and used in various embodiments described herein can

be prepared according to any method, and for example, as described in U.S. Patent No. 8,835,488, which is hereby incorporated by reference in its entirety.

[0175] The following compounds, or pharmaceutically acceptable salts thereof, can be used in any of the methods and embodiments described herein. These compounds are also described, for exmaplle, in U.S. Patent No. 8,835,488, which is hereby incorporated by reference in its entirety.

Compound.	Name	Compound	Name
1	2-[9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethan-1-amine	11	2-[({2-[4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol
2	2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethan-1-amine	12	2-[({2-[4-(4-fluorophenyl)oxan-4-yl]ethyl}amino)methyl]phenol
3	2-[9-(2-aminoethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-4-ol	13	benzyl({2-[3-(pyridin-2-yl)-1-oxaspiro[4.4]nonan-3-yl]ethyl})amine
4	6-[9-(2-aminoethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-3-ol	14	benzyl({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine
5	6-[9-(2-aminoethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-2-ol	15	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}(pyridin-2-ylmethyl)amine
6	2-[(9R)-9-(2-aminoethyl)-6-oxaspiro[4.5]decan-9-yl]-1-oxidopyridin-1-ium	16	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}(pyridin-3-ylmethyl)amine
7	benzyl({2-[1-(4-fluorophenyl)cyclohexyl]ethyl})amine	17	[(2-methoxyphenyl)methyl]({2-[4-(4-methylphenyl)oxan-4-yl]ethyl})amine
8	benzyl({2-[4-(4-fluorophenyl)oxan-4-yl]ethyl})amine	18	(furan-3-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

9	[(2-methylphenyl)methyl]({2-[4-(4-methylphenyl)oxan-4-yl]ethyl})amine	19	(1H-imidazol-2-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
10	N-{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}aniline	20	(1,3-oxazol-4-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
21	{2-[3-(pyridin-2-yl)-1-oxaspiro[4.4]nonan-3-yl]ethyl}(thiophen-2-ylmethyl)amine	31	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(2-methylphenyl)methyl]amine
22	{2-[3-(pyridin-2-yl)-1-oxaspiro[4.4]nonan-3-yl]ethyl}(thiophen-3-ylmethyl)amine	32	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(3-methylphenyl)methyl]amine
23	(cyclopentylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	33	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(4-methylphenyl)methyl]amine
24	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}(thiophen-2-ylmethyl)amine	34	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(1R)-1-phenylethyl]amine
25	{2-[4-(4-fluorophenyl)oxan-4-yl]ethyl}[(2-methoxyphenyl)methyl]amine	35	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(1S)-1-phenylethyl]amine
26	{2-[9-(1H-pyrazol-1-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine	36	benzyl({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})methylamine
27	benzyl({2-[(9S)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	37	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}(2-phenylethyl)amine

28	benzyl({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	38	(pyrazin-2-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
29	benzyl({2-[3-(pyridin-2-yl)-1-oxaspiro[4.5]decan-3-yl]ethyl})amine	39	benzyl({2-[2,2-diethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl})amine
30	benzyl({2-[9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	40	benzyl({2-[2,2,6,6-tetramethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl})amine
41	4-[({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol	50	benzyl(2-{9-cyclohexyl-6-oxaspiro[4.5]decan-9-yl}ethyl)amine
42	2-[({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol	51	{2-[3-(pyridin-2-yl)-1-oxaspiro[4.5]decan-3-yl]ethyl}(thiophen-2-ylmethyl)amine
43	3-[({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol	52	{2-[3-(pyridin-2-yl)-1-oxaspiro[4.5]decan-3-yl]ethyl}(thiophen-3-ylmethyl)amine
44	[(5-methylfuran-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	53	{2-[9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine
45	[(5-methylfuran-2-yl)methyl]({2-[9-(pyrazin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	54	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine
46	benzyl({2-[9-(thiophen-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	55	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-3-ylmethyl)amine

47	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(2-fluorophenyl)methyl]amine	56	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(1,3-thiazol-2-ylmethyl)amine
48	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(3-fluorophenyl)methyl]amine	57	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(1,3-thiazol-5-ylmethyl)amine
49	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(4-fluorophenyl)methyl]amine	58	{2-[9-(pyrazin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine
59	{2-[2,2-diethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl}(thiophen-3-ylmethyl)amine	69	2-{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}-2,3-dihydro-1H-isoindole
60	{2-[2,2-diethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl}(thiophen-2-ylmethyl)amine	70	{2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl}dipropylamine
61	{2-[2,2,6,6-tetramethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl}(thiophen-2-ylmethyl)amine	71	(2-phenylethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
62	{2-[2,2,6,6-tetramethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl}(thiophen-3-ylmethyl)amine	72	(2-phenylethyl)({2-[9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
63	{2-[9-(thiophen-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine	73	benzyl({2-[9-(6-methylpyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
64	{2-[9-(thiophen-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-3-ylmethyl)amine	74	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}(2-phenylpropan-2-yl)amine

65	(cyclopentylmethyl)({2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl})amine	75	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[2-(pyridin-3-yl)ethyl]amine
66	(cyclopentylmethyl)({2-[4-(4-fluorophenyl)-2,2,6,6-tetramethyloxan-4-yl]ethyl})amine	76	[(2-methylpyrimidin-5-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
67	(2-{9-cyclohexyl-6-oxaspiro[4.5]decan-9-yl}ethyl)(thiophen-2-ylmethyl)amine	77	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(2-methoxyphenyl)methyl]amine
68	(2-{9-cyclohexyl-6-oxaspiro[4.5]decan-9-yl}ethyl)(thiophen-3-ylmethyl)amine		
78	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(3-methoxyphenyl)methyl]amine	87	benzyl({2-[4-(4-fluorophenyl)-2,2,6,6-tetramethyloxan-4-yl]ethyl})amine
79	benzyl({2-[9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	88	[(2,3-dimethoxyphenyl)methyl]({2-[4-(4-methylphenyl)oxan-4-yl]ethyl})amine
80	benzyl({2-[(9S)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	89	[(3-methylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
81	benzyl({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	90	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[2-(thiophen-2-yl)ethyl]amine
82	2-[(9R)-9-(2-{4H,5H,6H-thieno[2,3-c]pyrrol-5-yl}ethyl)-6-oxaspiro[4.5]decan-9-yl]pyridine	91	[(2-methylthiophen-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

83	[(4,5-dimethylfuran-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	92	[(5-methylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
84	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyridin-4-ylmethyl)amine	93	{2-[9-(6-methylpyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-3-ylmethyl)amine
85	2-[({2-[4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}amino)methyl]phenol	94	{2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl}(1H-pyrrol-2-ylmethyl)amine
86	benzyl({2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl})amine	95	{2-[9-(6-methylpyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine
96	[(4-methylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	105	6-[9-{2-[(thiophen-2-ylmethyl)amino]ethyl}-6-oxaspiro[4.5]decan-9-yl]pyridin-2-ol
97	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(5-methylfuran-2-yl)methyl]amine	106	[(5-methylthiophen-2-yl)methyl]({2-[2,2,6,6-tetramethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl})amine
98	[(4-methyl-1,3-thiazol-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	107	2-(9-{2-[(thiophen-2-ylmethyl)amino]ethyl}-6-oxaspiro[4.5]decan-9-yl)pyridin-4-ol
99	[(2-methyl-1,3-thiazol-5-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	108	[(4-methylthiophen-2-yl)methyl]({2-[2,2,6,6-tetramethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl})amine
100	[(4-methyl-1,3-thiazol-5-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	109	dibutyl({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

101	[(2-chlorophenyl)methyl]({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine	110	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-3-ylmethyl)amine
102	[(3-chlorophenyl)methyl]({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine	111	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine
103	[(4-chlorophenyl)methyl]({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine	112	(cyclopentylmethyl)({2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl})amine
104	6-[9-{2-[(thiophen-2-ylmethyl)amino]ethyl}-6-oxaspiro[4.5]decan-9-yl]pyridin-3-ol	113	{2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl}(thiophen-3-ylmethyl)amine
114	{2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl}(thiophen-2-ylmethyl)amine	123	benzyl({2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl})amine
115	{2-[4-(4-fluorophenyl)-2,2,6,6-tetramethyloxan-4-yl]ethyl}(thiophen-3-ylmethyl)amine	124	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(1R)-1-phenylethyl]amine
116	{2-[4-(4-fluorophenyl)-2,2,6,6-tetramethyloxan-4-yl]ethyl}(thiophen-2-ylmethyl)amine	125	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(1S)-1-phenylethyl]amine
117	benzyl({2-[9-(2-methoxyphenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	126	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(2-nitrophenyl)methyl]amine
118	benzyl({2-[9-(6-methoxypyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	127	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(3-nitrophenyl)methyl]amine

119	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(2-methoxyphenyl)methyl]methylamine	128	2-[({2-[9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]phenol
120	{2-[9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(3-methylphenyl)methyl]amine	129	{2-[4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}[(2-methoxyphenyl)methyl]amine
121	{2-[(9S)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(3-methylphenyl)methyl]amine	130	[(5-ethylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
122	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(3-methylphenyl)methyl]amine	131	[(3,5-dimethylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
132	{2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl}[(6-methylpyridin-3-yl)methyl]amine	140	[(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
133	{2-[4-(4-fluorophenyl)-2,2,6,6-tetramethyloxan-4-yl]ethyl}[(6-methylpyridin-3-yl)methyl]amine	141	[(3-methoxythiophen-2-yl)methyl]({2-[9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
134	[(4,5-dimethylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	142	{2-[9-(6-methoxypyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine
135	[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	143	{2-[9-(6-methoxypyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-3-ylmethyl)amine

136	{2-[9-(pyrazin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine	144	{2-[4-(4-chlorophenyl)-2,2-dimethyloxan-4-yl]ethyl}[(2-methoxyphenyl)methyl]amine
137	[(4,5-dimethylfuran-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	145	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(5-methylthiophen-2-yl)methyl]amine
138	{2-[9-(2-methoxyphenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-2-ylmethyl)amine	146	{2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl}(thiophen-3-ylmethyl)amine
139	{2-[9-(2-methoxyphenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(thiophen-3-ylmethyl)amine	147	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(3-methylthiophen-2-yl)methyl]amine
148	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(4-methylthiophen-2-yl)methyl]amine	156	{2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl}[(6-methylpyridin-3-yl)methyl]amine
149	{2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl}(thiophen-2-ylmethyl)amine	157	[(2,3-dimethoxyphenyl)methyl]({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine
150	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(4-methyl-1,3-thiazol-2-yl)methyl]amine	158	[(2,4-dimethoxyphenyl)methyl]({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine
151	{2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl}[(5-methylthiophen-2-yl)methyl]amine	159	{2-[9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(4-methoxyphenyl)methyl]amine

152	[(5-chlorothiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	160	[(5-propylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
153	dibutyl({2-[4-(4-fluorophenyl)-2,2,6,6-tetramethyloxan-4-yl]ethyl})amine	161	1-{5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]thiophen-2-yl}ethan-1-ol
154	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(2-phenylpropan-2-yl)amine	162	6-[9-(2-{[(4,5-dimethylthiophen-2-yl)methyl]amino}ethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-3-ol
155	{4H,5H,6H-cyclopenta[b]thiophen-2-ylmethyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	163	6-[9-(2-{[(4,5-dimethylthiophen-2-yl)methyl]amino}ethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-2-ol
164	2-[9-(2-{[(4,5-dimethylthiophen-2-yl)methyl]amino}ethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-4-ol	171	6-[9-(2-{[(3-methoxythiophen-2-yl)methyl]amino}ethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-3-ol
165	[(5-nitrothiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	172	6-[9-(2-{[(3-methoxythiophen-2-yl)methyl]amino}ethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-2-ol
166	[(3,5-dimethylthiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	173	2-[(9R)-9-(2-{[(3-methoxythiophen-2-yl)methyl]amino}ethyl)-6-oxaspiro[4.5]decan-9-yl]-1-oxidopyridin-1-ium

167	[(5-ethylthiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	174	2-[9-(2-{[(3-methoxythiophen-2-yl)methyl]amino}ethyl)-6-oxaspiro[4.5]decan-9-yl]pyridin-4-ol
168	{2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl}[(5-methylthiophen-2-yl)methyl]amine	175	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(3-methoxythiophen-2-yl)methyl]amine
169	[(4,5-dimethylthiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	176	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}({[3-(trifluoromethyl)phenyl]methyl})amine
170	{[5-(methylsulfanyl)thiophen-2-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	177	(1-benzothiophen-2-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
178	(1-benzothiophen-3-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	185	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({2H,3H-thieno[3,4-b][1,4]dioxin-5-ylmethyl})amine
179	[(5-chlorothiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	186	{2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(2-methanesulfonylphenyl)methyl]amine
180	2-{[(2-{2,2-dimethyl-4-[4-(trifluoromethyl)phenyl]oxan-4-yl}ethyl)amino]methyl}phenol	187	[(4-bromofuran-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

181	[(5-chlorothiophen-2-yl)methyl]({2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl})amine	188	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(methylsulfanyl)thiophen-2-yl]methyl})amine
182	{[5-(2-methylpropyl)thiophen-2-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	189	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[6-(trifluoromethyl)pyridin-3-yl]methyl})amine
183	[(5-butylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	190	[(5-bromofuran-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
184	{4H,5H,6H-cyclopenta[b]thiophen-2-ylmethyl}({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	191	(2-{2,2-dimethyl-4-[4-(trifluoromethyl)phenyl]oxan-4-yl}ethyl)[(2-methoxyphenyl)methyl]amine
192	{2-[2,2,6,6-tetramethyl-4-(pyridin-2-yl)oxan-4-yl]ethyl}({[6-(trifluoromethyl)pyridin-3-yl]methyl})amine	199	[(4-phenylphenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
193	{[5-(furan-2-yl)thiophen-2-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	200	[(3-phenylphenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
194	[(5-chlorothiophen-2-yl)methyl]({2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl})amine	201	benzyl({2-[9-(4-bromophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

195	(1-benzothiophen-2-ylmethyl)({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	202	2-amino-4-chloro-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]thiophene-3-carbonitrile
196	(1-benzothiophen-3-ylmethyl)({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	203	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({2H,3H-thieno[3,4-b][1,4]dioxin-5-ylmethyl})amine
197	[(5-fluoro-1-benzothiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	204	[(4-phenylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
198	[(5-cyclopentylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	205	[(5-phenylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
206	[(5-methanesulfonylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	213	[(4-bromofuran-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
207	[(4-bromothiophen-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	214	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(thiophen-2-yl)thiophen-2-yl]methyl})amine
208	[(4-bromothiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	215	{2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl}({[6-(trifluoromethyl)pyridin-3-yl]methyl})amine

209	[(5-bromothiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	216	[(5-chloro-1-benzothiophen-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
210	[(2-bromothiophen-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	217	[(5-bromo-4-methylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
211	[(5-bromofuran-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	218	[(4-bromo-5-methylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
212	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[6-(trifluoromethyl)pyridin-3-yl]methyl})amine	219	[(3-bromo-5-methylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
220	[(4-bromo-3-methylthiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	227	[(4-bromo-3-methylthiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
221	{2-[4-(4-fluorophenyl)-1-oxaspiro[5.5]undecan-4-yl]ethyl}({[6-(trifluoromethyl)pyridin-3-yl]methyl})amine	228	[(4-bromo-5-methylthiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
222	[(4-bromothiophen-3-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	229	[(3-bromo-5-methylthiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

223	[(4-bromothiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	230	[(5-bromo-4-methylthiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
224	[(5-bromothiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	231	{2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl}bis(thiophen-2-ylmethyl)amine
225	dibenzyl({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	232	[(4,5-dibromothiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
226	dibenzyl({2-[2,2-diethyl-4-(4-fluorophenyl)oxan-4-yl]ethyl})amine	233	[(3,4-dibromothiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
234	[(4,5-dibromothiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	240	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[2-(trifluoromethyl)phenyl]methyl})amine
235	[(3,4-dibromothiophen-2-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	241	2-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]phenol
236	[(2-fluorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	242	[(2-methoxyphenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

237	[(2-bromophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	243	[(3-fluorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
238	[(2-chlorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	244	[(3-bromophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
239	[(2-methylphenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	245	[(3-chlorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
246	[(3-methylphenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	252	N-methyl-3-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]benzamide
247	methyl 3-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]benzoate	253	N-ethyl-3-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]benzamide
248	3-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]phenol	254	[(4-methoxyphenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

249	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[3-(trifluoromethyl)phenyl]methyl})amine	255	4-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]phenol
250	N-methyl-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]thiophene-2-carboxamide	256	[(2,3-difluorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
251	N-ethyl-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]thiophene-2-carboxamide	257	[(2,4-difluorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
258	[(2,5-difluorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	264	2-methoxy-4-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]phenol
259	[(2,6-difluorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	265	[(5-fluoropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
260	[(3,4-difluorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	266	[(5-bromopyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

261	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	267	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
262	[(2,3-dimethoxyphenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	268	[(5-methoxypyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
263	[(3,4-dimethoxyphenyl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	269	5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-3-carbonitrile
270	[(5-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	275	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[3-(trifluoromethyl)pyridin-2-yl]methyl})amine
271	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine	276	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine

272	{[6-chloro-5-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	277	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-2-yl]methyl})amine
273	{[2-fluoro-5-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	500	[(4-chlorophenyl)methyl]({2-[4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl})amine
274	{[6-fluoro-5-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine	501	[(3,4-dimethoxyphenyl)methyl][2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl]amine
502	2-[({2-[2-ethyl-2-methyl-4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol	503	[2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl][(2-fluorophenyl)methyl]amine
504	4-[({2-[4-(2-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}amino)methyl]-N,N-dimethylaniline	505	2-[({2-[2-ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}amino)methyl]phenol

Compound	Name
506.	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyrimidin-5-ylmethyl)amine

Compound	Name
507.	[(2-methylpyrimidin-5-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
508.	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[2-(trifluoromethyl)pyrimidin-5-yl]methyl})amine
509.	[(2-methoxypyrimidin-5-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
510.	(pyridazin-4-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
511.	[(6-methylpyridazin-4-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
512.	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[6-(trifluoromethyl)pyridazin-4-yl]methyl})amine
513.	[(6-methoxypyridazin-4-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
514.	(pyrazin-2-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
515.	[(6-methylpyrazin-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
516.	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[6-(trifluoromethyl)pyrazin-2-yl]methyl})amine
517.	[(6-methoxypyrazin-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
518.	[(5-methylpyrazin-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
519.	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyrazin-2-yl]methyl})amine

Compound	Name
520.	[(5-methoxypyrazin-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
521.	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(quinolin-3-ylmethyl)amine
522.	(1H-pyrazol-3-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
523.	[(1-methyl-1H-pyrazol-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
524.	[(5-methyl-1H-pyrazol-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
525.	[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
526.	(1H-pyrazol-4-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
527.	[(1-methyl-1H-pyrazol-4-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
528.	[(5-methyl-1H-pyrazol-4-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
529.	[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
530.	[(5,6-difluoropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
531.	[(5-chloro-6-fluoropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
532.	[(5-bromo-6-fluoropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
533.	[(6-fluoro-5-iodopyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
534.	[(6-fluoro-5-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
535.	[(6-fluoro-5-methoxypyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
536.	2-fluoro-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-3-carbonitrile
537.	[(6-chloro-5-fluoropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
538.	[(5,6-dichloropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
539.	[(5-bromo-6-chloropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
540.	[(6-chloro-5-iodopyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
541.	[(6-chloro-5-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
542.	[(6-chloro-5-methoxypyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
543.	2-chloro-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-3-carbonitrile

Compound	Name
544.	3-fluoro-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-2-carbonitrile
545.	3-chloro-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-2-carbonitrile
546.	3-bromo-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-2-carbonitrile
547.	3-iodo-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-2-carbonitrile
548.	3-methyl-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-2-carbonitrile
549.	3-methyl-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-2-carbonitrile

Compound	Name
550.	5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-2,3-dicarbonitrile
551.	5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]-3-(trifluoromethyl)pyridine-2-carbonitrile
552.	{[5-fluoro-6-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
553.	{[5-chloro-6-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
554.	{[5-bromo-6-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
555.	{[5-iodo-6-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
556.	{[5-methyl-6-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
557.	{[5-methoxy-6-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
558.	5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]-2-(trifluoromethyl)pyridine-3-carbonitrile
559.	{[5,6-bis(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
560.	[(5-fluoro-6-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
561.	[(5-chloro-6-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
562.	[(5-bromo-6-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
563.	[(5-iodo-6-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
564.	[(5,6-dimethylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
565.	[(5-methoxy-6-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
566.	2-methyl-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-3-carbonitrile
567.	{[6-methyl-5-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
568.	[(5-fluoro-6-methoxypyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
569.	[(5-chloro-6-methoxypyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
570.	[(5-bromo-6-methoxypyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
571.	[(5-iodo-6-methoxypyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-l]ethyl})amine

Compound	Name
572.	[(6-methoxy-5-methylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
573.	[(5,6-dimethoxypyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
574.	2-methoxy-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-3-carbonitrile
575.	2-methoxy-5-[({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amino)methyl]pyridine-3-carbonitrile
576.	{[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]methyl}({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
576	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-phenyl-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
577	{2-[(9R)-9-phenyl-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine
578	{2-[(9R)-9-phenyl-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine
579	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-phenyl-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
580	[(3-methylphenyl)methyl]({2-[(9R)-9-phenyl-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
581	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
582	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amin
583	{2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine
584	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-(4-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
585	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-[4-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
586	{2-[(9R)-9-[4-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine
587	{2-[(9R)-9-[4-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine

Compound	Name
588	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-[4-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
589	[(3-methylphenyl)methyl]({2-[(9R)-9-[4-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
590	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-3-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
591	{2-[(9R)-9-(pyridin-3-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine
592	{2-[(9R)-9-(pyridin-3-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine
593	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-(pyridin-3-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
594	[(3-methylphenyl)methyl]({2-[(9R)-9-(pyridin-3-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
595	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-4-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
596	{2-[(9R)-9-(pyridin-4-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine
597	{2-[(9R)-9-(pyridin-4-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine
598	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-(pyridin-4-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
599	[(3-methylphenyl)methyl]({2-[(9R)-9-(pyridin-4-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
600	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-(3-methylphenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
601	{2-[(9R)-9-(3-methylphenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine
602	{2-[(9R)-9-(3-methylphenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine
603	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-(3-methylphenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
604	{2-[(9R)-9-(3-methylphenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(3-methylphenyl)methyl]amine
605	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-[3-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
606	{2-[(9R)-9-[3-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine
607	{2-[(9R)-9-[3-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine
608	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-[3-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
609	[(3-methylphenyl)methyl]({2-[(9R)-9-[3-(trifluoromethoxy)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
610	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-[4-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
611	{2-[(9R)-9-[4-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine

Compound	Name
612	{2-[(9R)-9-[4-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine
613	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-[4-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
614	[(3-methylphenyl)methyl]({2-[(9R)-9-[4-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
615	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-(3-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
616	{2-[(9R)-9-(3-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine
617	{2-[(9R)-9-(3-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine

Compound	Name
618	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-(3-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
619	{2-[(9R)-9-(3-fluorophenyl)-6-oxaspiro[4.5]decan-9-yl]ethyl}[(3-methylphenyl)methyl]amine
620	[(5-chloropyridin-3-yl)methyl]({2-[(9R)-9-[3-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
621	{2-[(9R)-9-[3-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-3-yl]methyl})amine
622	{2-[(9R)-9-[3-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl}({[4-(trifluoromethyl)pyridin-3-yl]methyl})amine
623	[(3,5-difluorophenyl)methyl]({2-[(9R)-9-[3-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
624	[(3-methylphenyl)methyl]({2-[(9R)-9-[3-(trifluoromethyl)phenyl]-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
625	[(5-chloropyridin-3-yl)methyl](methyl){2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amine
626	methyl({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}){[5-(trifluoromethyl)pyridin-3-yl]methyl}amine
627	[(5-chloropyridin-3-yl)methyl-(2H2)]{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}amine
628	({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}){[5-(trifluoromethyl)pyridin-3-yl]methyl-(2H2)}amine
629	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[6-(trifluoromethyl)pyridin-2-yl]methyl})amine

Compound	Name
630	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[5-(trifluoromethyl)pyridin-2-yl]methyl})amine
631	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyridin-2-ylmethyl)amine
632	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyridin-3-ylmethyl)amine
633	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}(pyridin-4-ylmethyl)amine
634	(1H-imidazol-4-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
635	[(2-methylpyridin-4-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
636	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({[2-(trifluoromethyl)pyridin-4-yl]methyl})amine
637	[(6-chloropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
638	[(1-methyl-1H-imidazol-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
639	(naphthalen-2-ylmethyl)({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
640	[(6-bromo-5-fluoropyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
641	[(5-methanesulfonylpyridin-3-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

Compound	Name
642	[2-(3-methylphenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
643	[2-(3-chlorophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
644	[2-(3-bromophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
645	[2-(3-fluorophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
646	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({2-[3-(trifluoromethyl)phenyl]ethyl})amine

Compound	Name
647	[2-(3-methoxyphenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
648	[2-(4-methylphenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
649	[2-(4-chlorophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
650	[2-(4-bromophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
651	[2-(4-fluorophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
652	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({2-[4-(trifluoromethyl)phenyl]ethyl})amine

Compound	Name
653	[2-(4-methoxyphenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
654	[2-(2-methylphenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
655	[2-(2-chlorophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
656	[2-(2-bromophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
657	[2-(2-fluorophenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine
658	{2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl}({2-[2-(trifluoromethyl)phenyl]ethyl})amine

Compound	Name
659	[2-(2-methoxyphenyl)ethyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine

[0176] **Examples**

[0177] Example 1: Biased ligands do not induce hyperalgesia. Compounds were tested for their potential to induce hyperalgesia in a mouse model of opioid induced hyperalgesia. In this test mice (n=8/group) are given subcutaneous injections of vehicle or mu opioid agonists twice per day for four days. On each of the four drug treatment days a measurement of mechanical allodynia was obtained using a method of repeated stimulation with a single von Frey monofilament (0.4 g). On the fifth day animals are again tested with no additional drug treatments. For testing, the monofilament is delivered to the hind paw for approximately 1-2 seconds. If there is a withdrawal response, that is recorded as a positive response. This is repeated ten times for each mouse. The final measurement for each mouse is the % non-response to stimulation for the ten trials. The results are shown in Figure 1. Compound A is Compund 265 and Compound B is Compound 54.

[0178] The figures illustrate the percent of non-responses to 10 applications of a 0.4 g von Frey filament in mice treated with indicated mu-opioid agonists or vehicle over 4 days. Oxycodone and fentanyl decreased the % non-responses, an indication of increased sensitivity (hyperalgesia) to the von Frey filament, while the biased mu-opioid agonists Compound A and B, did not.

[0179] These results demonstrate that the biased ligands that target the mu-opioid receptor do not induce hyperalgesia as compared to the non-biased ligands that are fentanyl and oxycodone. These results were surprising and unexpected. Therefore, based upon these results it is expected that the compounds can be used to treat hyperalgesia or subjects that have hyperalgesia or increased nociceptive sensitization as described herein.

[0180] Example 2: Biased ligand reverse opioid induced hyperalgesia. In a mouse model of opioid induced hyperalgesia, compounds were tested for their potential to reverse opioid induced hyperalgesia. In this test mice (n=8/group) were given subcutaneous injections of vehicle or a reference mu opioid agonist twice per day for four days. On each of the four drug treatment days a measurement of mechanical allodynia was obtained using a method of repeated stimulation with a single von Frey monofilament (0.4 g). After behavioral testing on the fifth day animals that had received a reference mu opioid agonist were switched onto Compound B. Twice daily subcutaneous injections continued through Day 12. A behavioral assessment of mechanical allodynia was made on days 5, 6, 7, 8, 10 and 12. For testing, the monofilament is delivered to the hind paw for approximately 1-2 seconds. If there was a withdrawal response, that was recorded as a positive response. This was repeated ten times for each mouse. The final measurement for each mouse is the % non-response to stimulation for the ten trials. Compound B (Compound 54) was able to reverse of opioid induced hyperalgesic activity. Similar results would be expected for Compound 140 and Compound 265 because they are also biased ligands like Compound 54. Accordingly, the results that were produced demonstrate that the biased ligands provided herein can reverse opioid induced hyperalgesic activity. Accordingly, the compounds described herein can be used to reverse opioid induced hyperalgesic activity in humans or other mammals.

[0181] Example 3: A human subject who is prescribed morphine presents with symptoms of opioid induced hyperalgesia. The subject stops being administered the morphine and is administered Compound 140 or Compound 265. The subject's opioid induced hyperalgesia is treated and reduced. The subject continues taking Compound 140 or Compound 265 and does not suffer from hyperalgesia while maintaining the pain relief.

[0182] Example 4: A subject is identified as having increased nociceptive sensitization due to being administered an opioid for pain relief. The subject is switched from the opioid to a pharmaceutical composition comprising Compound 140 or Compound 265. The subject's nociceptive sensitization is decreased while maintaining the pain relief.

[0183] The foregoing examples demonstrate that the compounds described herein do not induce

OIH in subjects being administered one or more of the compounds described herein and can be used to treat pain in subjects without causing hyperalgesia or increased nociceptive sensitization. The examples also demonstrate that the biased ligans provided herein can be used to reverse opioid induced hyperalgesic activity in a mammal, such as humans.

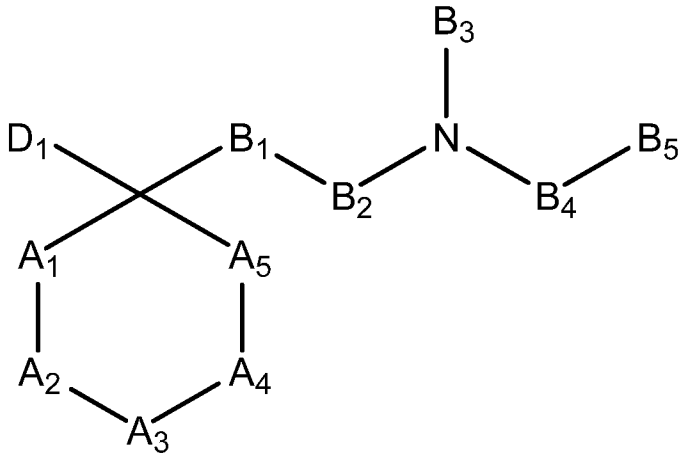
[0184] While the compounds and methods describd herein have been described with reference to examples, those skilled in the art recognize that various modifications may be made without departing from the spirit and scope thereof.

[0185] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety.

CLAIMS

What is claimed is:

1. A method of treating or reversing hyperalgesia in a subject comprising administering to the subject a compound of Formula I, or a pharmaceutically acceptable salt thereof:



;

I

wherein:

A_1 is selected from the group consisting of null, CH_2, CHR_1, CR_1R_2, CH, CR_1, O, S, SO, SO_2, NH and NR_1;

A_2 is selected from the group consisting of null, CH_2, CHR_5, CR_5R_6, CH, CR_5, O, S, SO, SO_2, NH and NR_5;

A_3 is selected from the group consisting of null, CH_2, CHR_7, CR_7R_8, O, S, SO, SO_2, NH, NR_7, CH and CR_7;

A_4 selected from the group consisting of is null, CH_2, cycle of the formula $C(CH_2)_n$, where n = 2-5, CHR_9, CR_9R_{10}, O, S, SO, SO_2, NH, NR_9, CH and CR_9;

A_5 is selected from the group consisting of null, CH_2, CHR_{11}, $CR_{11}R_{12}$, CH_2CH_2, $CHR_{11}CH_2$, CH_2CHR_{11}, $CHR_{11}CHR_{12}$, O, S, SO, SO_2, NH, NR_{11}, CH and CR_{11};

B_1 is selected from the group consisting of CH_2, CHR_{13}, $CR_{13}R_{14}$, O, S, SO, SO_2, NH, NR_{13}, CR_{13} and CO;

B_2 is selected from the group consisting of CH_2, CHR_{15}, $CR_{15}R_{16}$, CR_{15} and CO;

B_3 is selected from the group consisting of H, alkyl, branched alkyl, halogenated alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, and

alkylsulfonyl;

B_4 is selected from the group consisting of null, C_1-C_6 alkyl, CH_2, CH_2CH_2, CHR_{19}, $CR_{19}R_{20}$ and CO;

B_5 is selected from the group consisting of alkyl, branched alkyl, halogenated alkyl, carbocycle-substituted alkyl, aryl, carbocycle and arylalkyl;

D_1 is an aryl group or a cycle;

R_1, R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{19}, and R_{20} are independently selected from the group consisting of cyano, halogen, hydroxyl, alkyloxy, alkyl, branched alkyl, halogenated alkyl, branched halogenated alkyl, aryl, arylalkyl, carbocycle, carbocycle-alkyl, alkylcarbonyl, branched alkylcarbonyl, halogenated alkylcarbonyl, branched halogenated alkylcarbonyl, arylcarbonyl and alkoxycarbonyl;

wherein no more than 2 out of 5 of A_1, A_2, A_3, A_4, and A_5 can be null at the same time,

wherein the number of heteroatoms in A_1, A_2, A_3, A_4, A_5 cannot exceed 2 at the same time;

wherein the bonds between A_1, A_2, A_3, A_4 and A_5 cannot be S-O, S-S, or S-N; and

wherein alkyl is a linear carbon chain having from 1 to 10 carbon atoms; wherein the cycle is not aromatic;

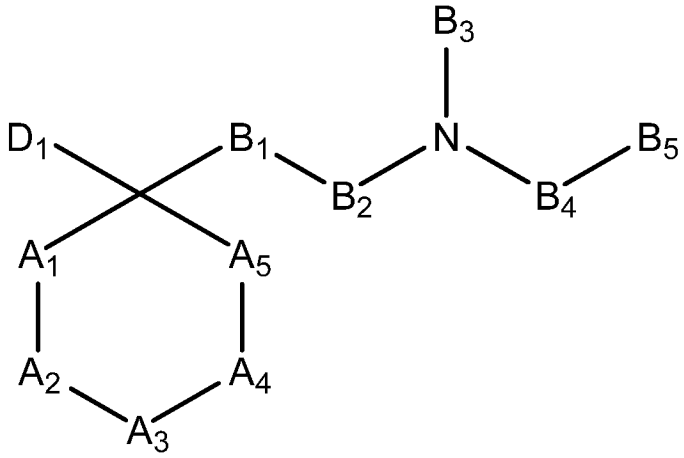
wherein each aryl group is a monocyclic aromatic group or a bicyclic aromatic group; wherein each cycle is a monocyclic or a bicyclic non-aromatic ring system.

2. The method of claim 1, wherein the hyperalgesia is opioid induced hyperalgesia.

3. The method of claim 2, wherein the opioid induced hyperalgesia is morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, alfentanil, remifentanil, sufentanil, etorphine, buprenorphine, methadone, and/or heroin induced hyperalgesia.

4. The method of claim 1, wherein the subject has been administered an opioid prior to being administered the compound of Formula I, or a pharmaceutically acceptable salt thereof.

5. A method of decreasing nociceptive sensitization in a subject comprising administering to the subject a compound of Formula I, or a pharmaceutically acceptable salt thereof:



;

I

wherein:

A_1 is selected from the group consisting of null, CH_2, CHR_1, CR_1R_2, CH, CR_1, O, S, SO, SO_2, NH and NR_1;

A_2 is selected from the group consisting of null, CH_2, CHR_5, CR_5R_6, CH, CR_5, O, S, SO, SO_2, NH and NR_5;

A_3 is selected from the group consisting of null, CH_2, CHR_7, CR_7R_8, O, S, SO, SO_2, NH, NR_7, CH and CR_7;

A_4 selected from the group consisting of is null, CH_2, cycle of the formula $C(CH_2)_n$, where n = 2-5, CHR_9, CR_9R_{10}, O, S, SO, SO_2, NH, NR_9, CH and CR_9;

A_5 is selected from the group consisting of null, CH_2, CHR_{11}, $CR_{11}R_{12}$, CH_2CH_2, $CHR_{11}CH_2$, CH_2CHR_{11}, $CHR_{11}CHR_{12}$, O, S, SO, SO_2, NH, NR_{11}, CH and CR_{11};

B_1 is selected from the group consisting of CH_2, CHR_{13}, $CR_{13}R_{14}$, O, S, SO, SO_2, NH, NR_{13}, CR_{13} and CO;

B_2 is selected from the group consisting of CH_2, CHR_{15}, $CR_{15}R_{16}$, CR_{15} and CO;

B_3 is selected from the group consisting of H, alkyl, branched alkyl, halogenated alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, and alkylsulfonyl;

B_4 is selected from the group consisting of null, C_1-C_6 alkyl, CH_2, CH_2CH_2, CHR_{19}, $CR_{19}R_{20}$ and CO;

B_5 is selected from the group consisting of alkyl, branched alkyl, halogenated alkyl, carbocycle-substituted alkyl, aryl, carbocycle and arylalkyl;

D_1 is an aryl group or a cycle;

R_1, R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{19}, and R_{20} are independently selected from the group consisting of cyano, halogen, hydroxyl, alkyloxy, alkyl, branched alkyl, halogenated alkyl, branched halogenated alkyl, aryl, arylalkyl, carbocycle, carbocycle-alkyl, alkylcarbonyl, branched alkylcarbonyl, halogenated alkylcarbonyl, branched halogenated alkylcarbonyl, arylcarbonyl and alkoxycarbonyl;

wherein no more than 2 out of 5 of A_1, A_2, A_3, A_4, and A_5 can be null at the same time,

wherein the number of heteroatoms in A_1, A_2, A_3, A_4, A_5 cannot exceed 2 at the same time;

wherein the bonds between A_1, A_2, A_3, A_4 and A_5 cannot be S-O, S-S, or S-N; and

wherein alkyl is a linear carbon chain having from 1 to 10 carbon atoms; wherein the cycle is not aromatic;

wherein each aryl group is a monocyclic aromatic group or a bicyclic aromatic group; wherein each cycle is a monocyclic or a bicyclic non-aromatic ring system.

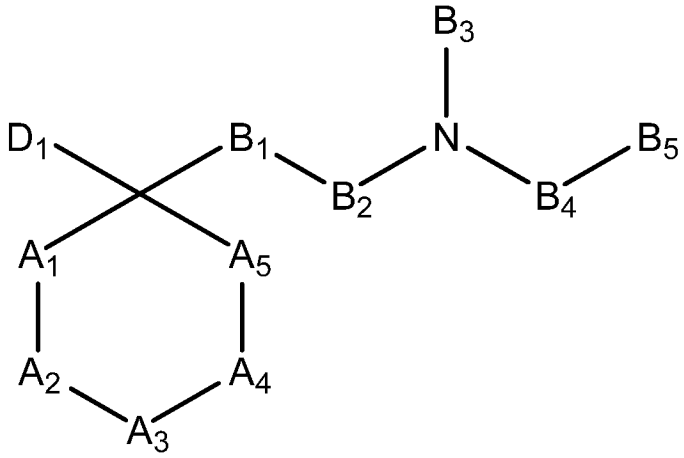
6. The method of claim 5, wherein the subject has opioid induced nociceptive sensitization.

7. The method of claim 5, wherein the opioid induced nociceptive sensitization is morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, alfentanil, remifentanil, sufentanil, etorphine, buprenorphine, methadone, and/or heroin, or a pharmaceutically acceptable salt thereof, induced nociceptive sensitization.

8. A method of treating pain in a subject comprising:

administering an opioid agonist to the subject until the opioid increases nociceptive sensitization in the subject; and

administering to the subject with increased nociceptive sensitization a compound of Formula I, or a pharmaceutically acceptable salt thereof:



;

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wherein:

A_1 is selected from the group consisting of null, CH_2, CHR_1, CR_1R_2, CH, CR_1, O, S, SO, SO_2, NH and NR_1;

A_2 is selected from the group consisting of null, CH_2, CHR_5, CR_5R_6, CH, CR_5, O, S, SO, SO_2, NH and NR_5;

A_3 is selected from the group consisting of null, CH_2, CHR_7, CR_7R_8, O, S, SO, SO_2, NH, NR_7, CH and CR_7;

A_4 selected from the group consisting of is null, CH_2, cycle of the formula $C(CH_2)_n$, where n = 2-5, CHR_9, CR_9R_{10}, O, S, SO, SO_2, NH, NR_9, CH and CR_9;

A_5 is selected from the group consisting of null, CH_2, CHR_{11}, $CR_{11}R_{12}$, CH_2CH_2, $CHR_{11}CH_2$, CH_2CHR_{11}, $CHR_{11}CHR_{12}$, O, S, SO, SO_2, NH, NR_{11}, CH and CR_{11};

B_1 is selected from the group consisting of CH_2, CHR_{13}, $CR_{13}R_{14}$, O, S, SO, SO_2, NH, NR_{13}, CR_{13} and CO;

B_2 is selected from the group consisting of CH_2, CHR_{15}, $CR_{15}R_{16}$, CR_{15} and CO;

B_3 is selected from the group consisting of H, alkyl, branched alkyl, halogenated alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, and alkylsulfonyl;

B_4 is selected from the group consisting of null, C_1-C_6 alkyl, CH_2, CH_2CH_2, CHR_{19}, $CR_{19}R_{20}$ and CO;

B_5 is selected from the group consisting of alkyl, branched alkyl, halogenated alkyl, carbocycle-substituted alkyl, aryl, carbocycle and arylalkyl;

D_1 is an aryl group or a cycle;

R_1, R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{19}, and R_{20} are independently selected from the group consisting of cyano, halogen, hydroxyl, alkyloxy, alkyl, branched alkyl, halogenated alkyl, branched halogenated alkyl, aryl, arylalkyl, carbocycle, carbocycle-alkyl, alkylcarbonyl, branched alkylcarbonyl, halogenated alkylcarbonyl, branched halogenated alkylcarbonyl, arylcarbonyl and alkoxycarbonyl;

wherein no more than 2 out of 5 of A_1, A_2, A_3, A_4, and A_5 can be null at the same time,

wherein the number of heteroatoms in A_1, A_2, A_3, A_4, A_5 cannot exceed 2 at the same time;

wherein the bonds between A_1, A_2, A_3, A_4 and A_5 cannot be S-O, S-S, or S-N; and

wherein alkyl is a linear carbon chain having from 1 to 10 carbon atoms; wherein the cycle is not aromatic;

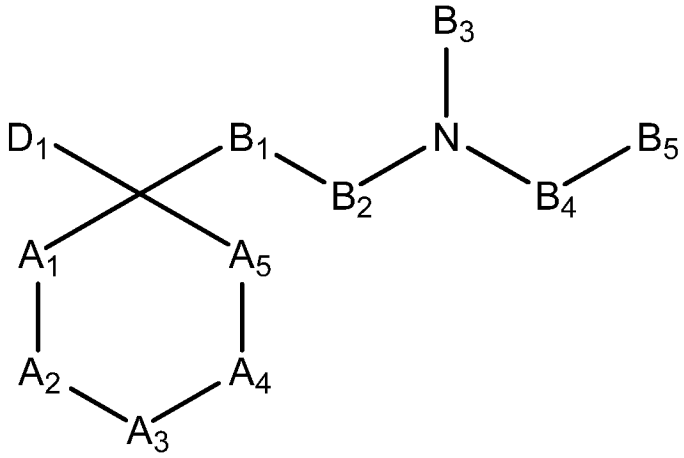
wherein each aryl group is a monocyclic aromatic group or a bicyclic aromatic group; wherein each cycle is a monocyclic or a bicyclic non-aromatic ring system.

9. The method of claim 8, wherein the opioid agonist is morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, alfentanil, remifentanil, sufentanil, etorphine, buprenorphine, methadone, and/or heroin, or a pharmaceutically acceptable salt thereof.

10. A method of treating pain in an opioid exposed subject comprising:

a) administering an opioid agonist to the subject;

b) administering to the subject of step a), in the absence of the opioid administered in step a), a compound of Formula I, or a pharmaceutically acceptable salt thereof:



;

I

wherein:

A_1 is selected from the group consisting of null, CH_2, CHR_1, CR_1R_2, CH, CR_1, O, S, SO, SO_2, NH and NR_1;

A_2 is selected from the group consisting of null, CH_2, CHR_5, CR_5R_6, CH, CR_5, O, S, SO, SO_2, NH and NR_5;

A_3 is selected from the group consisting of null, CH_2, CHR_7, CR_7R_8, O, S, SO, SO_2, NH, NR_7, CH and CR_7;

A_4 selected from the group consisting of is null, CH_2, cycle of the formula $C(CH_2)_n$, where n = 2-5, CHR_9, CR_9R_{10}, O, S, SO, SO_2, NH, NR_9, CH and CR_9;

A_5 is selected from the group consisting of null, CH_2, CHR_{11}, $CR_{11}R_{12}$, CH_2CH_2, $CHR_{11}CH_2$, CH_2CHR_{11}, $CHR_{11}CHR_{12}$, O, S, SO, SO_2, NH, NR_{11}, CH and CR_{11};

B_1 is selected from the group consisting of CH_2, CHR_{13}, $CR_{13}R_{14}$, O, S, SO, SO_2, NH, NR_{13}, CR_{13} and CO;

B_2 is selected from the group consisting of CH_2, CHR_{15}, $CR_{15}R_{16}$, CR_{15} and CO;

B_3 is selected from the group consisting of H, alkyl, branched alkyl, halogenated alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, and alkylsulfonyl;

B_4 is selected from the group consisting of null, C_1-C_6 alkyl, CH_2, CH_2CH_2, CHR_{19}, $CR_{19}R_{20}$ and CO;

B_5 is selected from the group consisting of alkyl, branched alkyl, halogenated alkyl, carbocycle-substituted alkyl, aryl, carbocycle and arylalkyl;

D_1 is an aryl group or a cycle;

R_1, R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{19}, and R_{20} are independently selected from the group consisting of cyano, halogen, hydroxyl, alkyloxy, alkyl, branched alkyl, halogenated alkyl, branched halogenated alkyl, aryl, arylalkyl, carbocycle, carbocycle-alkyl, alkylcarbonyl, branched alkylcarbonyl, halogenated alkylcarbonyl, branched halogenated alkylcarbonyl, arylcarbonyl and alkoxycarbonyl;

wherein no more than 2 out of 5 of A_1, A_2, A_3, A_4, and A_5 can be null at the same time,

wherein the number of heteroatoms in A_1, A_2, A_3, A_4, A_5 cannot exceed 2 at the same time;

wherein the bonds between A_1, A_2, A_3, A_4 and A_5 cannot be S-O, S-S, or S-N; and

wherein alkyl is a linear carbon chain having from 1 to 10 carbon atoms; wherein the cycle is not aromatic;

wherein each aryl group is a monocyclic aromatic group or a bicyclic aromatic group; wherein each cycle is a monocyclic or a bicyclic non-aromatic ring system.

11. The method of claim 11, wherein the opioid is morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, alfentanil, remifentanil, sufentanil, etorphine, buprenorphine, methadone, and/or heroin, or a pharmaceutically acceptable salt thereof.

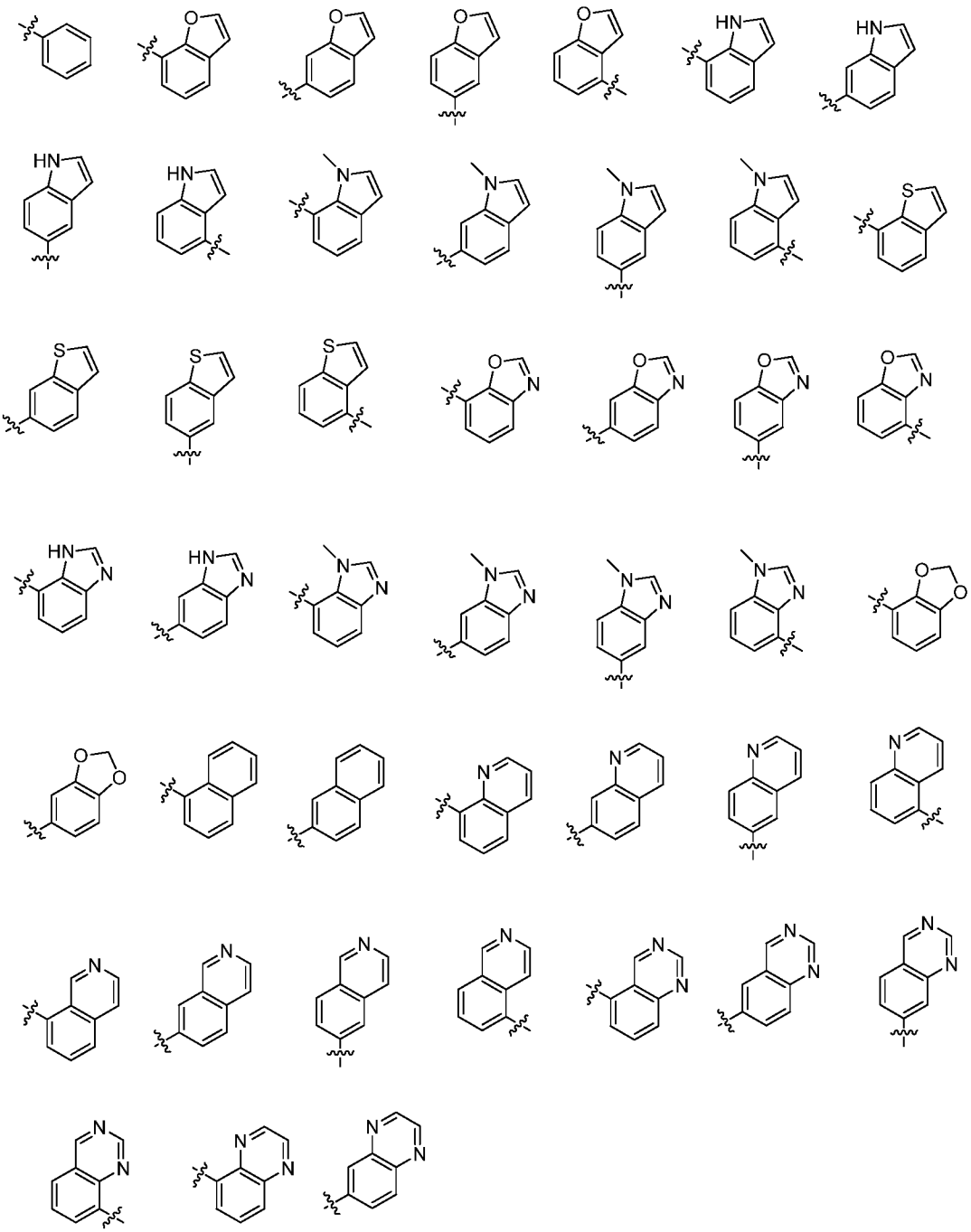
12. The method of any of claims 1-11, wherein the compound of Formula I is not 2-[({2-[2-Ethyl-2-methyl-4-(4-methylphenyl)oxan-4-yl]ethyl}amino)methyl]phenol; 2-[({2-[2-Ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}amino)methyl]phenol; {2-[2,2-Dimethyl-4-(4-methylphenyl)oxan-4yl]ethyl}[(4-methoxyphenyl)methyl]amine; {2-[(4S*, 4R*)-2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(1R)-1-phenylethyl]amine; {2-[(4S*, 4R*)-2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}[(1S)-1-phenylethyl]amine; Benzyl({2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl})amine; 2-[({2-[2-Ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}amino)methyl]phenol; Benzyl[2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl]amine; {2-[2-Ethyl-4-(4-fluorophenyl)-2-methyloxan-4-yl]ethyl}[(4-methoxyphenyl)methyl]amine; [(3,4-Dimethoxyphenyl)methyl]({2-[4-(4-fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; {2-[4-(4-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}(1-phenylethyl)amine; [(4-Chlorophenyl)methyl]({2-[4-(4-methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; Benzyl({2-[2-ethyl-4-(2-methoxyphenyl)-2-methyloxan-4-yl]ethyl})amine; [(3,4-

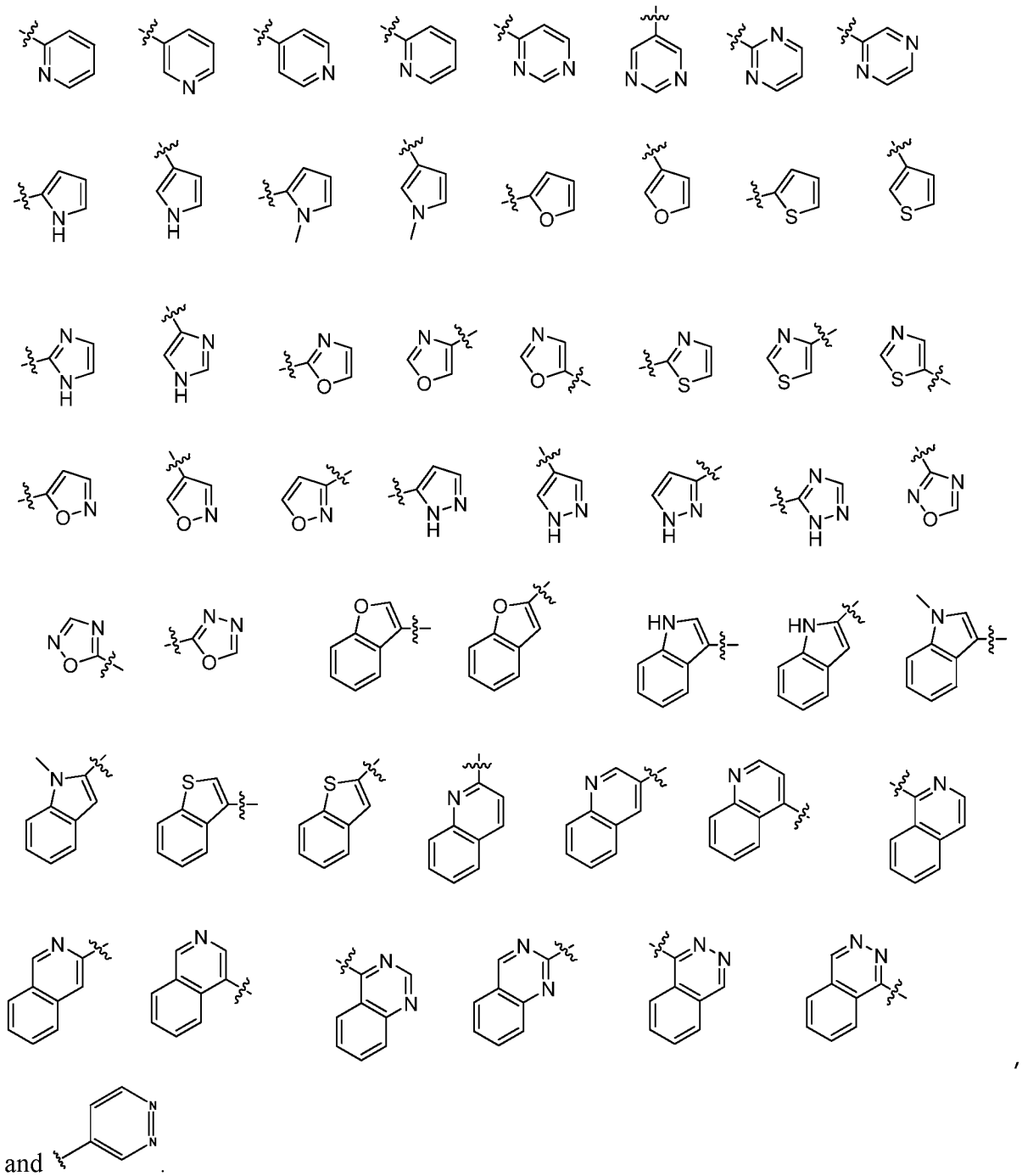
dimethoxyphenyl)methyl]({2-[2-ethyl-4-(2-methoxyphenyl)-2-methyloxan-4-yl]ethyl})amine; 4-[({2-[4-(2-Methoxyphenyl)-2,2-dimethyloxan-4-yl]ethyl}amino)methyl]-N,N-dimethylaniline; Benzyl({2-[4-(4-fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl})amine; {2-[2,2-dimethyl-4-(4-methylphenyl)oxan-4-yl]ethyl}(1-phenylethyl)amine; [2-(2,2-Dimethyl-4-phenyloxan-4-yl)ethyl][(4-methoxyphenyl)methyl]amine; {2-[4-(4-Fluorophenyl)-2,2-dimethyloxan-4-yl]ethyl}[(4-methoxyphenyl)methyl]amine; and [(3,4-Dimethoxyphenyl)methyl][2-(2,2-dimethyl-4-phenyloxan-4-yl)ethyl]amine.

13. The method of any one of claims 1-12, wherein the aryl groups or cycle groups have 1-3 heteroatoms, wherein the heteroatoms are selected from the group consisting of O, N and S.

14. The method of any one of claims 1-13, wherein each aryl group or each cycle group is independently substituted with one or more substitution groups selected from the group consisting of F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, methoxycarbonyl, methanesulfonyl, Ph, benzyl, formyl, and acetyl.

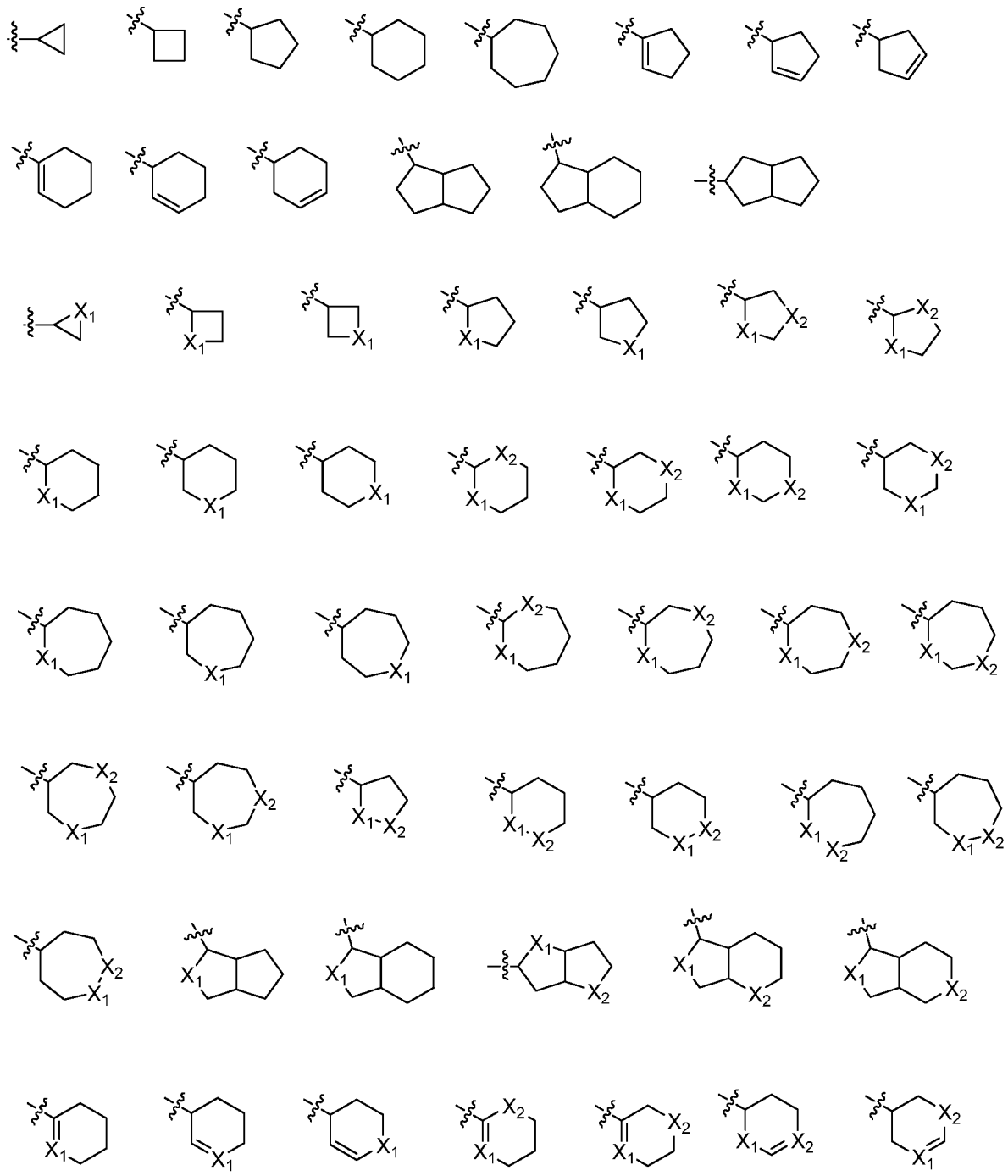
15. The method of any one of claims 1-14, wherein the each aryl group is independently selected from the group consisting of:





and .

16. The method of any one of claims 1-15, wherein the cycle is selected from the group consisting of:



;

wherein X_1 and X_2 in the cycle are independently selected from the group consisting of O, S, N, NH, and NR_{18}, wherein R_{18} is selected from the group consisting of cyano, halogen, hydroxyl, alkyloxy, alkyl, branched alkyl, halogenated alkyl, branched halogenated alkyl, aryl, arylalkyl,

carbocycle, carbocycle-alkyl, alkylcarbonyl, branched alkylcarbonyl, halogenated alkylcarbonyl, branched halogenated alkylcarbonyl, arylcarbonyl and alkoxycarbonyl.

17. The method of any one of claims 1-16, wherein A_2 and A_4 are connected by a carbon bridge.

18. The method of claim 16, wherein the bridge comprises $–CH_2-$ or $-CH_2CH_2-$.

19. The method of any one of claims 1-16, wherein when the carbon connected to D_1 is fused with another ring, A_1, A_2, A_3, A_4, A_5 form a ring selected from the group consisting of benzene, pyridine, pyrimidine, furan, thiophene and pyridazine.

20. The method of claim 19, wherein the ring formed by A_1, A_2, A_3, A_4, A_5 is independently multiply substituted with a member of the group consisting of cyano, halogen, alkyl, branched alkyl, halogenated alkyl, hydroxyl, alkyloxy, formyl, acetyl, amino, alkylamino, dialkylamino, mercaptanyl, and alkylmercaptanyl.

21. The method of any one of claims 1-20, wherein R_1, R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, and R_{20} are independently selected from the group consisting of F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-propyl, n-butyl, isobutyl, sec-buytyl, isopropyl, tert-butyl, CN, OH, OCH_3 OCH_2CH_3, O-i-propyl, methoxycarbonyl, phenyl, benzyl, CHO, and $COCH_3$.

22. The method of any one of claims 1-20, wherein R_1 and R_2, R_5 and R_6, R_7 and R_8, R_9 and R_{10}, R_{11} and R_{12}, R_{13} and R_{14}, R_{15} and R_{16}, R_{19} and R_{20}, or R_{15} and R_{19}, independently, form a monocyclic cycle or heterocycle.

23. The method of any one of claims 1-22, wherein each aryl is independently multiply substituted with groups selected from cyano, halogen, alkyl, branched alkyl, halogenated alkyl, hydroxyl, alkyloxy, amino, alkylamino, dialkylamino, mercaptanyl, alkylmercaptanyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aryl, arylalkyl, cycle and cycle-alkyl.

24. The method of any one of claims 1-23, wherein each cycle is independently multiply

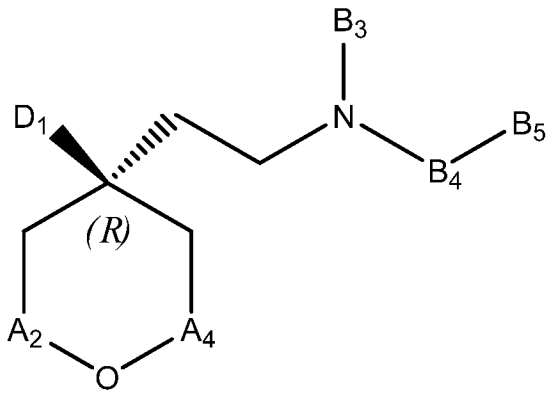
substituted with groups selected from cyano, halogen, alkyl, branched alkyl, halogenated alkyl, hydroxyl, alkyloxy, amino, alkylamino, dialkylamino, mercaptanyl, alkylmercaptanyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aryl, arylalkyl, cycle and cycle-alkyl.

25. The method of any one of claims 1-24, wherein the bonds between A_1 and A_2, A_2 and A_3, A_3 and A_4, A_4 and A_5, A_5 and A_6, A_6 and A_1 and A_6 and A_7 are independently a single bond or a double bond.

26. The method of any one of claims 1-25, wherein the bonds between $A_1$and A_2, A_2 and A_3, A_3 and A_4, A_4 and A_5, A_5 and A_6, A_6 and A_1 and A_6 and A_7 are not simulataneously double bonds.

27. The method of any one of claims 1-26, wherein R_1, R_2, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, and R_{20} are independently selected from the group consisting of F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-propyl, n-butyl, isobutyl, sec-butyl, i-propyl, t-butyl, CN, OH, OCH_3, OCH_2CH_3, O-i-propyl, methoxycarbonyl, phenyl, benzyl, formyl, and acetyl.

28. The method of any one of claims 1, 5, 8, or 10, wherein the compound has a formula of Formula II-2, or a pharmaceutically acceptable salt thereof:



II-2

wherein:

A_2 is selected from the group consisting of CH_2, CHR_5 and CR_5R_6;

A_4 is elected from the group consisting of CH_2, CHR_9, CR_9R_{10} and a cycle of the formula

$C(CH_2)_n$, where n = 2-5;

R_5, R_6, R_9 and R_{10} are independently selected from the group consisting of CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu and phenyl;

B_3 is selected from the group consisting of H, alkyl, branched alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl and alkylsulfonyl;

B_4 is selected from the group consisting of null, CH_2, CHR_{19}, $CR_{19}R_{20}$ and CO;

B_5 is selected from the group consisting of alkyl, branched alkyl, carbocycle, carbocycle-substituted alkyl, aryl and arylalkyl; and

D_1 is aryl.

29. The method of claim 28, wherein each aryl group is independently substituted with one or more of F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, NH_2, NHMe, NMe_2, methoxycarbonyl, methanesulfonyl, Ph, benzyl, formyl and acetyl.

30. The method of claim 28, wherein N is not bonded directely to a heteroatom.

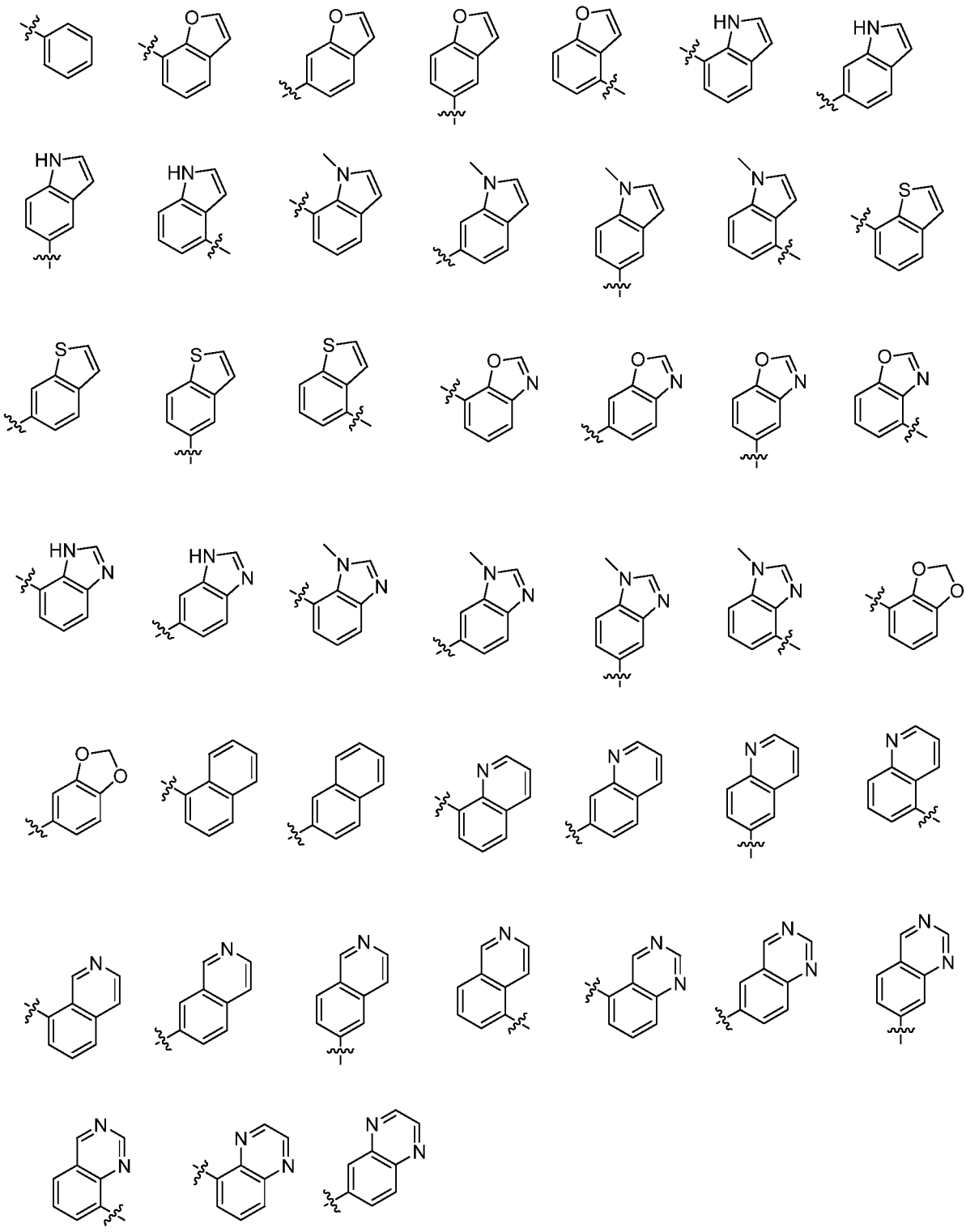
31. The method of claim 28, wherein R_5 and R_6, or R_9 and R_{10} form a monocyclic carbocycle.

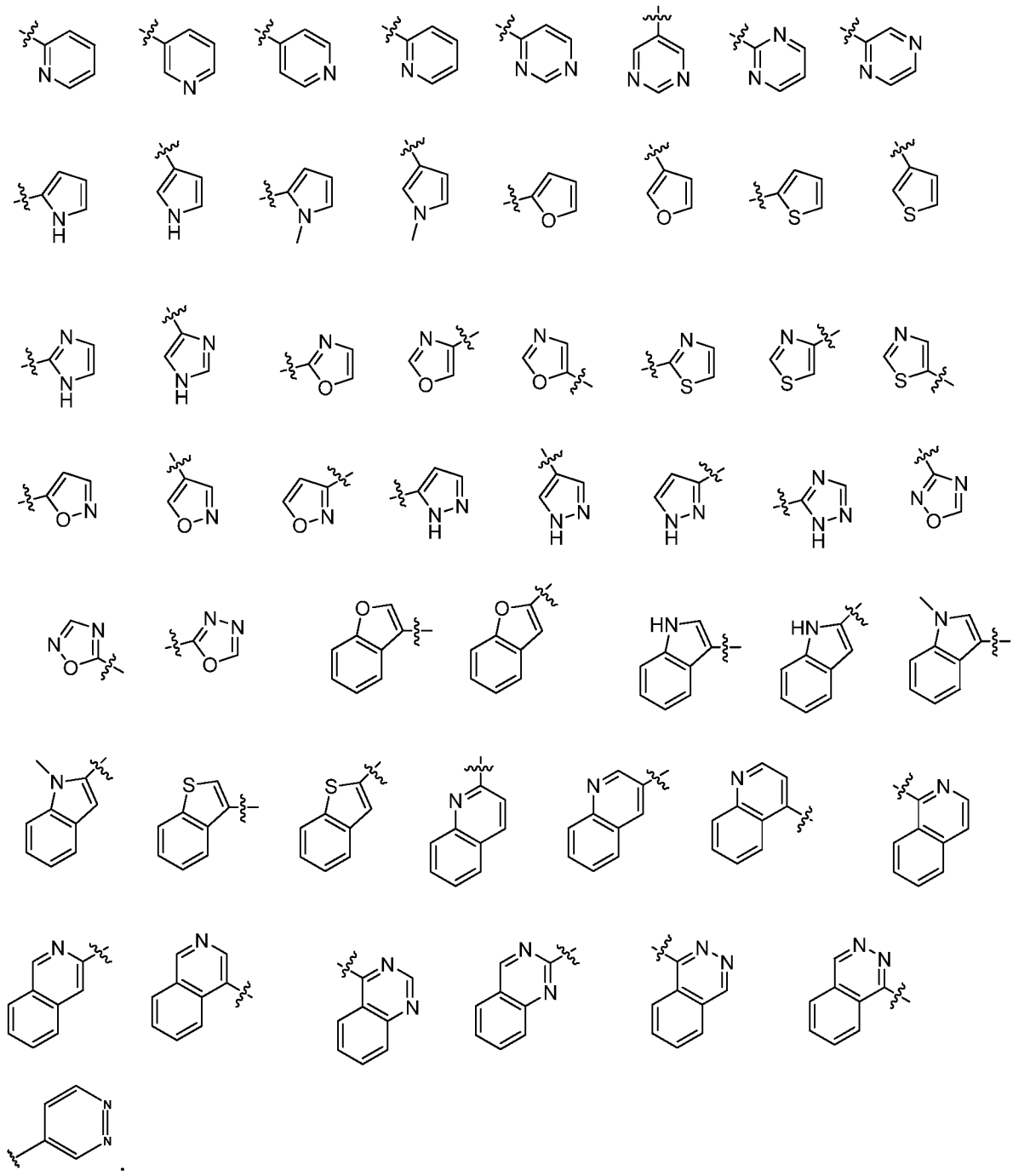
32. The method of claim 28, wherein A_2 and A_4 are connected by a carbon bridge.

33. The method of claim 28, wherein the bridge comprises $–CH_2-$ or $-CH_2CH_2-$.

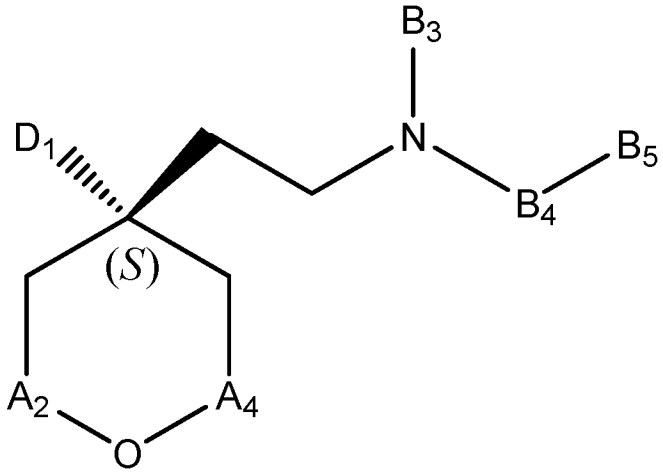
34. The method of claim 28, wherein each aryl or cycle independently has 1-3 heteroatoms, wherein the heteroatoms are selected from the group consisting of O, N and S, are unsubstituted, or substituted with substitution groups selected from the group consisting of F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, methoxycarbonyl, methanesulfonyl, Ph, benzyl, formyl, and acetyl.

35. The method of claim 28, wherein each aryl is independently selected from the group consisting of:





36. The method of any one of claims 1, 5, 8, or 10, wherein the compound has a formula of Formula III, or a pharmaceutically acceptable salt thereof:



III

wherein:

A_2 is selected from the group consisting of CH_2, CHR_5 and CR_5R_6;

A_4 is selected from the group consisting of CH_2, CHR_9, CR_9R_{10} and a cycle of the formula $C(CH_2)_n$, where n = 2-5;

R_5, R_6, R_9 and R_{10} are independently selected from the group consisting of CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu and phenyl;

B_3 is selected from the group consisting of H, alkyl, branched alkyl, aryl, arylalkyl, alkylcarbonyl, branched alkylcarbonyl, arylcarbonyl, alkoxycarbonyl and alkylsulfonyl;

B_4 is selected from the group consisting of null, CH_2, CHR_{19}, $CR_{19}R_{20}$ and CO;

B_5 is selected from the group consisting of alkyl, branched alkyl, carbocycle, carbocycle-substituted alkyl, aryl and arylalkyl; and

D_1 is an aryl.

37. The method of claim 36, wherein each aryl group is independently substituted with one or more of F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, NH_2, NHMe and NMe_2, methoxycarbonyl, methanesulfonyl, Ph, benzyl, formyl, or acetyl.

38. The method of claim 36, wherein N is not bonded directely to a heteroatom.

39. The method of claim 36, wherein R_5 and R_6, or R_9 and R_{10} form a monocyclic carbocycle.

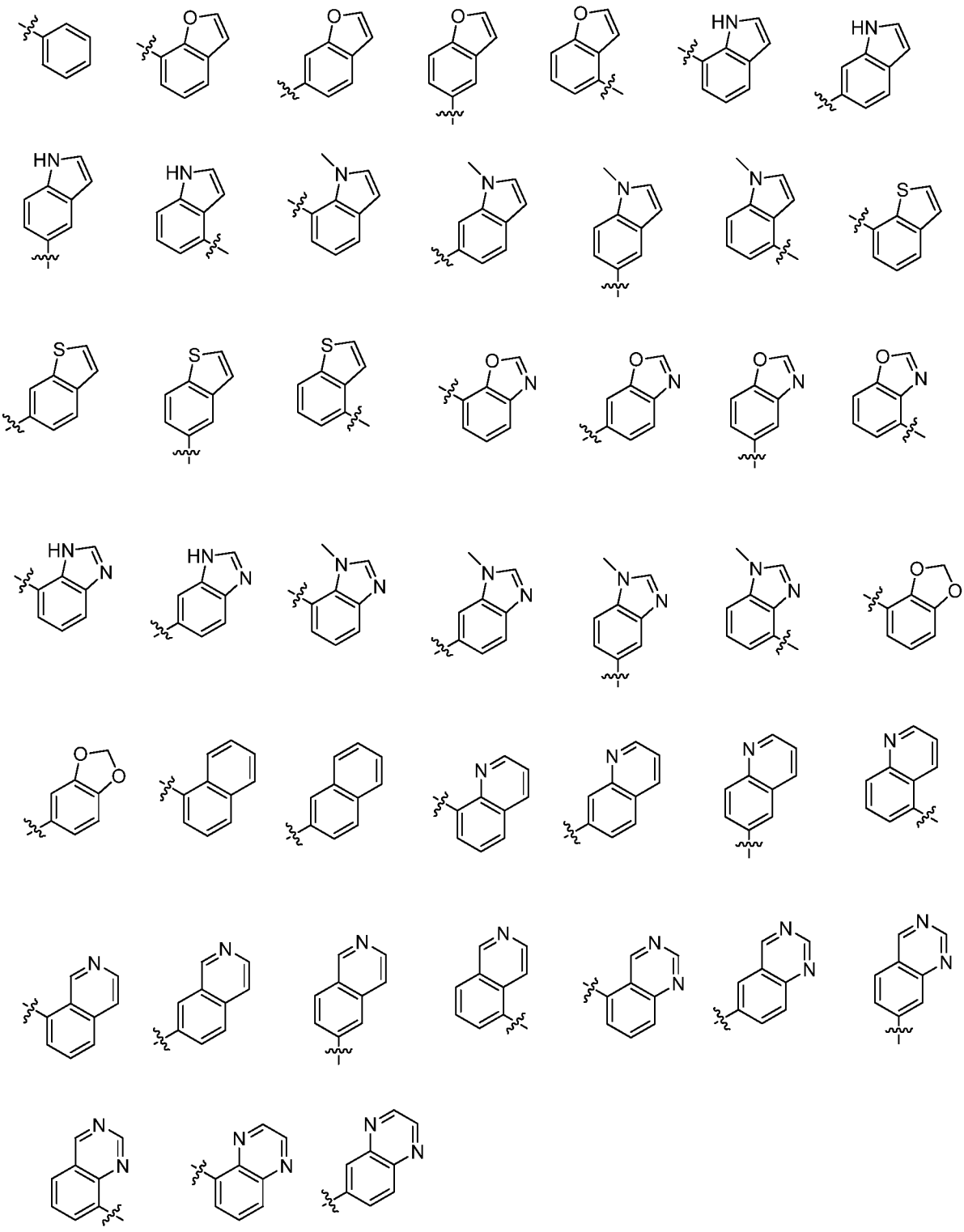
40. The method of claim 36, wherein A_2 and A_4 are connected by a carbon bridge.

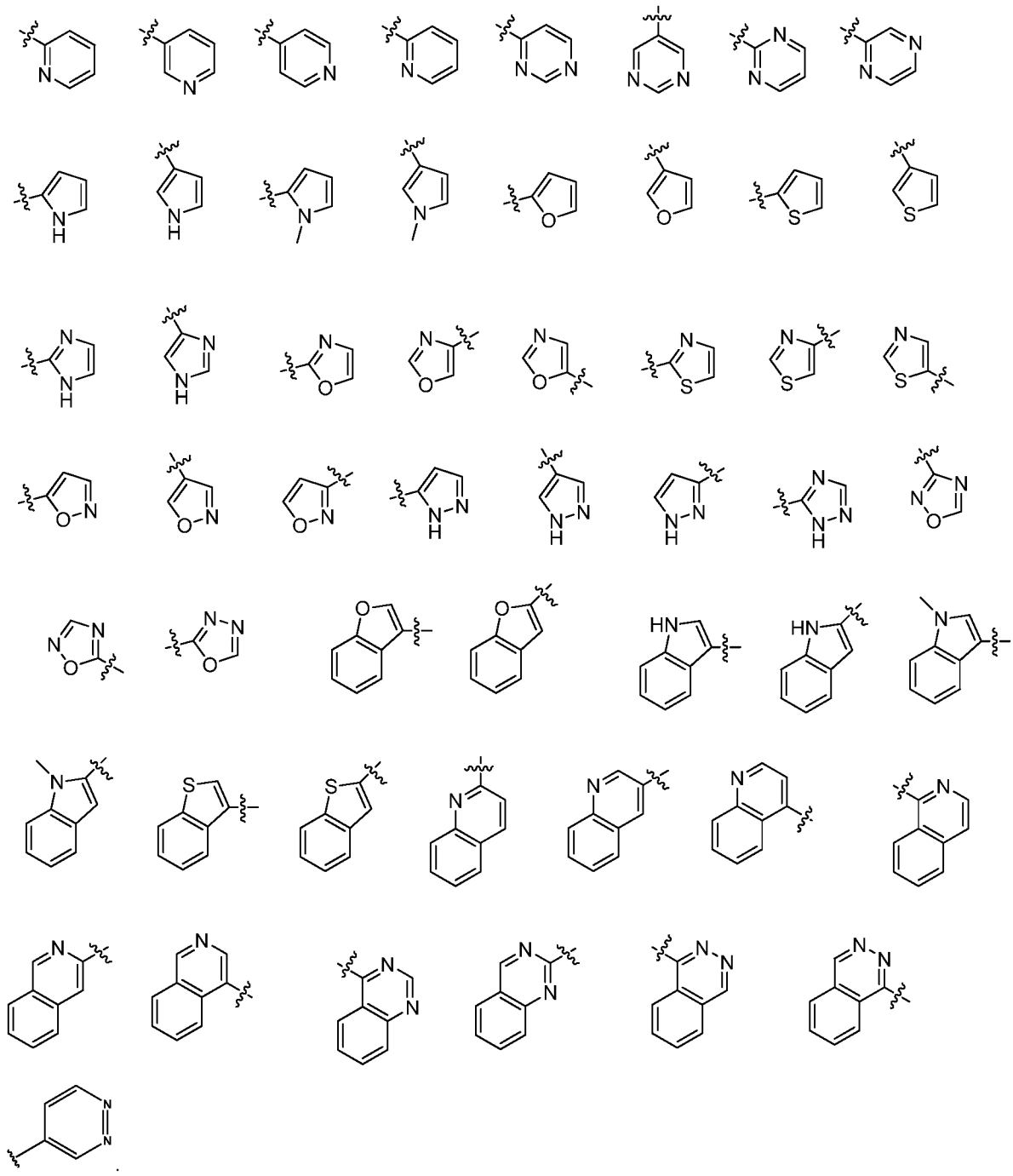
41. The compound of claim 40, wherein the bridge comprises $–CH_2-$ or $-CH_2CH_2-$.

42. The method of claim 36, wherein the aryl groups and/or cycle groups have 1-3 heteroatoms, wherein the heteroatoms are selected from the group consisting of O, N and S.

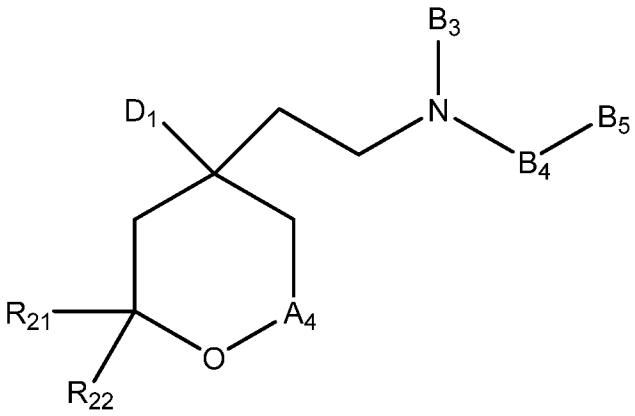
43. The method of claim 42, wherein each aryl group and/or cycle group is independently substituted with one or more of F, Cl, Br, CH_3, CH_2CH_3, CH_2F, CHF_2, CF_3, n-Pr, n-Bu, i-Bu, sec-Bu, i-Pr, t-Bu, CN, OH, OMe, OEt, O-iPr, OCF_3, methoxycarbonyl, methanesulfonyl, Ph, benzyl , formyl, and acetyl.

44. The method of claim 36, wherein each aryl is independently selected from the group consisting of:

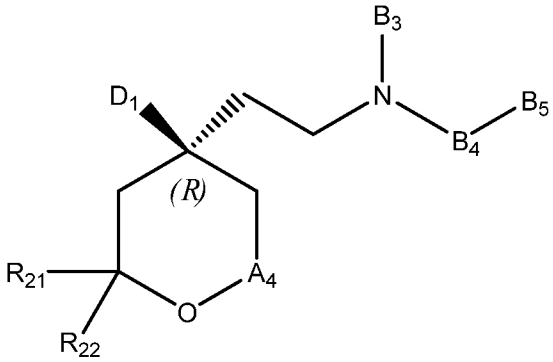




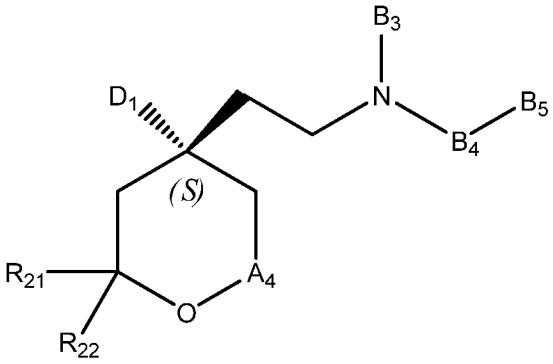
45. The method of any one of claims 1, 5, 8, or 10, wherein the compound has a formula of Formula IV-1, IV-2, or IV-3, or a pharmaceutically acceptable salt thereof:



IV-1



IV-2, or



IV-3

wherein R_{21} and R_{22} are independently H or CH_3;

A_4 is selected from the group consisting of CH_2, CR_9R_{10} and a cycle of the formula $C(CH_2)_n$, where n = 2-5;

R_9 and R_{10} are independently CH_3 or CH_2CH_3;

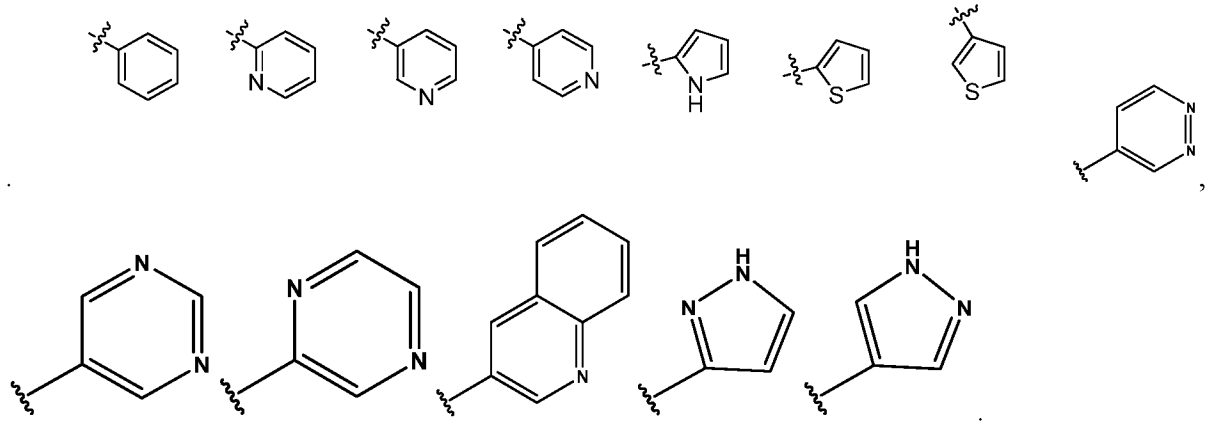
B_3 is H, CH_3, or $-(CH_2)_nCH_3$, where n = 2-3;

B_4 is selected from the group consisting of null, CH_2, C_1-C_6 alkyl, CH_2CH_2 or -$CHCH_3$;

B_5 is selected from the group consisting of -$(CH_2)_nCH_3$, where n = 2-3, -$C(CH_3)_3$, cyclohexyl, cyclopentyl, aryl and arylalkyl;

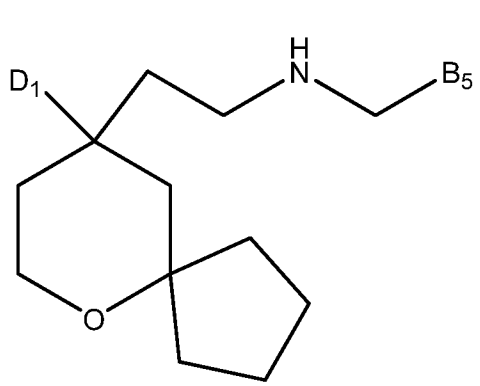
D_1 is a phenyl or 2-pyridyl, wherein the phenyl or 2-pyridyl can be independently mono or multiply substituted with a member of the group consisting of F, Cl, Br, CF_3, OCF_3 and CH_3; and

wherein the aryl group is selected from group consisting of

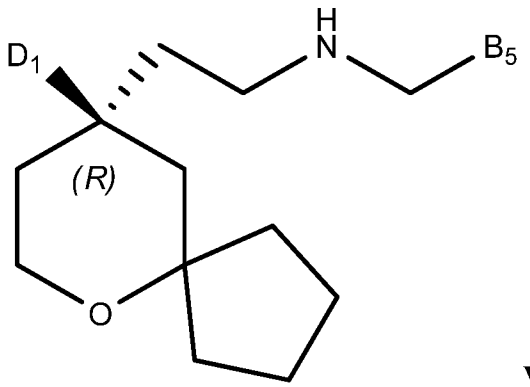


46. The method of claim 45, wherein each aryl group, phenyl, or 2-pyridyl is independently substituted with one or more of F, Cl, Br, CH_3, CN, OH, OMe, OEt, CF_3, OCF_3, or methanesulfonyl

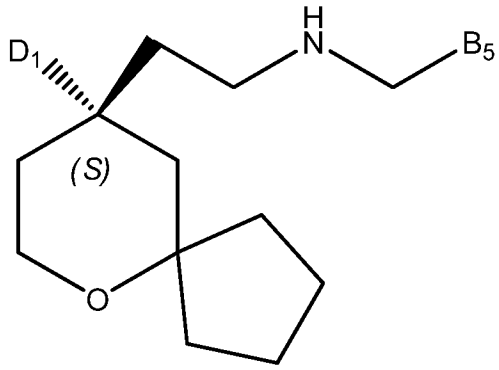
47. The method of any one of claims 1, 5, 8, or 10, wherein the compound has a formula of Formula V-1, V-2, V-3, VI-1, VI-2, or VI-3, or a pharmaceutically acceptable salt thereof:



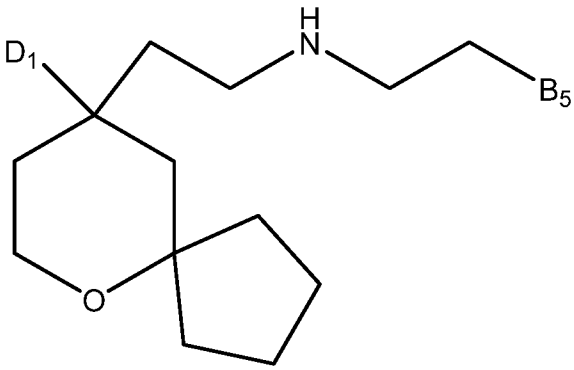
V-1,



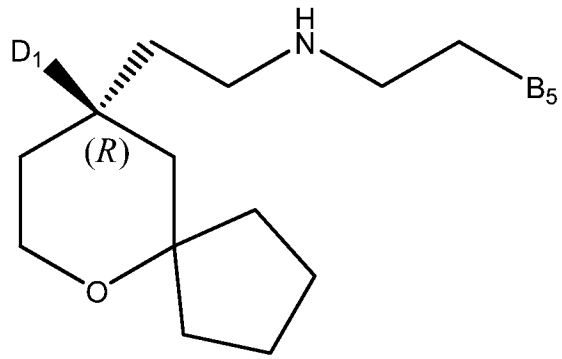
V-2,



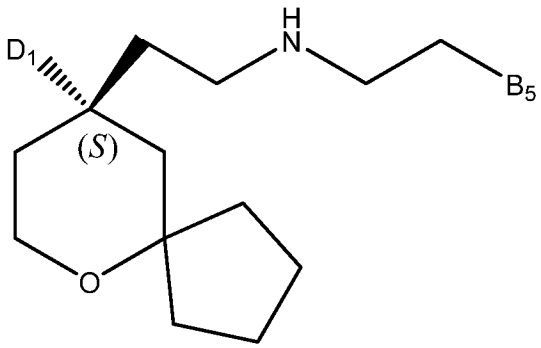
V-3,



VI-1,



VI-2,

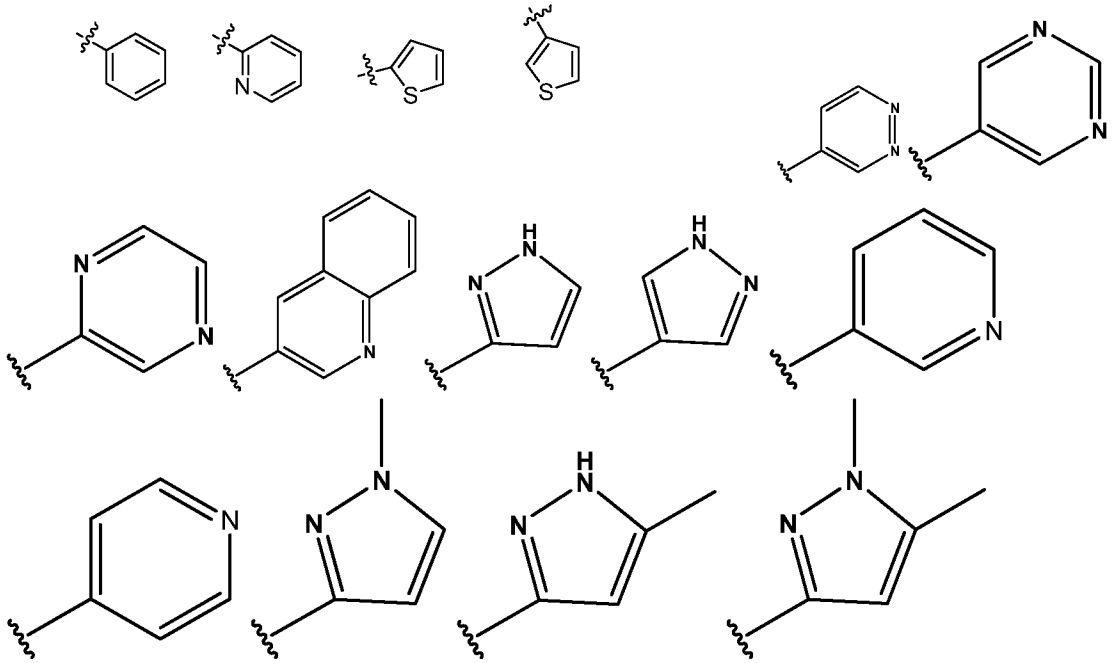


VI-3

wherein D_1 is an optionally mono or multiply substituted aryl;

B_5 is an optionally mono or multiply substituted aryl or carbocycle;

wherein aryl is selected from the group consisiting of:



and

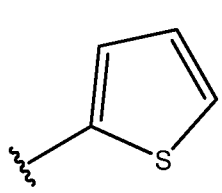
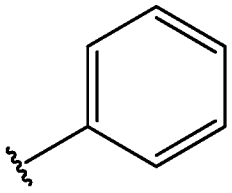
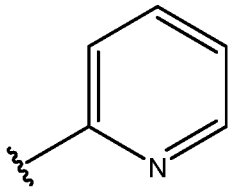
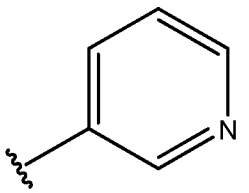
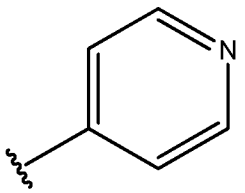
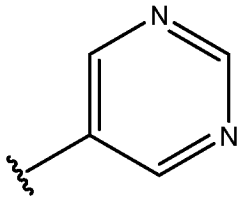
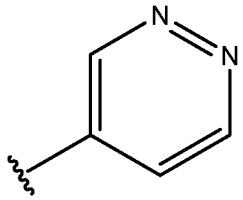
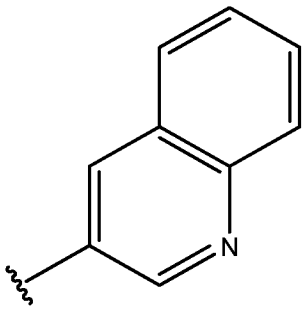
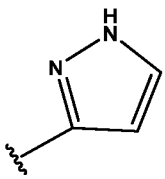
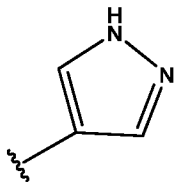
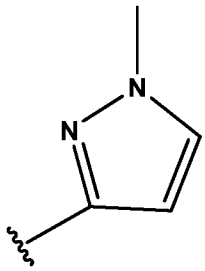
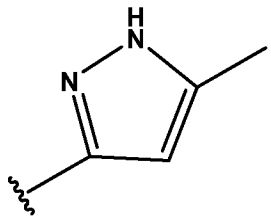
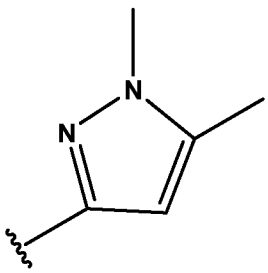
wherein the cabocycle is cyclohexyl, cyclohexenyl or cyclopentyl.

48. The method of claim 47, wherein D_1 is independently optionally mono or multiply substituted phenyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl.

49. The method of claims 47 or 48, wherein D_1 is optionally independently substituted with one or more of F, Cl, Br, I, OCF_3, CH_3, or CF_3.

50. The method of claims 47 or 48, wherein D_1 is not substituted.

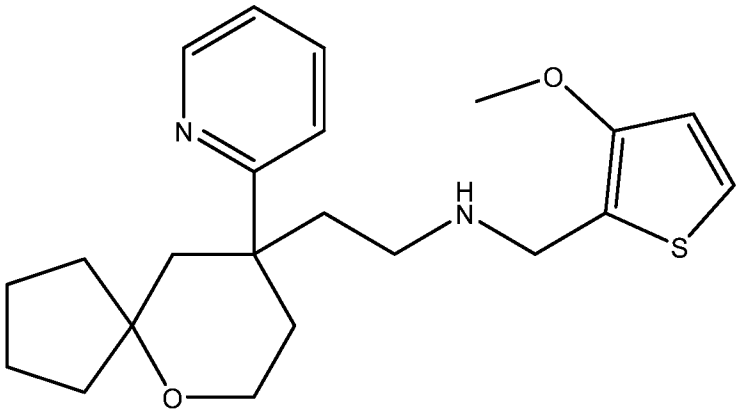
51. The method of any one of claims 47-50, wherein B_5 is independently optionally mono or

multiply substituted  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,or 

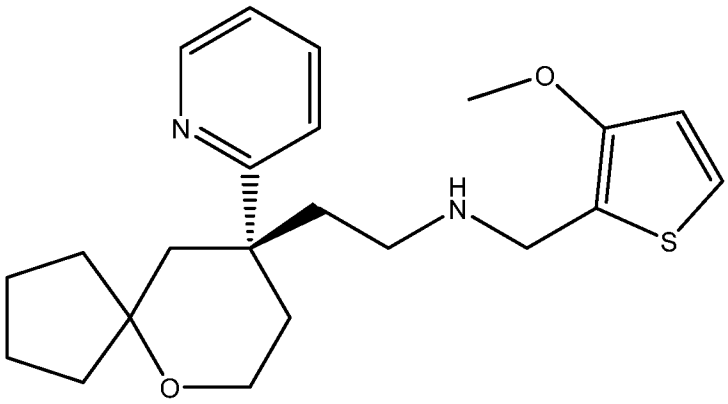
52. The method of any one of claims 47-51, wherein B_5 is independently substituted with one or more of Cl, Br, F, I, OMe, CN, CH_3, CF_3, or methane sulfonyl.

53. The method of any one of claims 47-52, wherein B_5 is independently substituted with two or more of Cl, Br, F, I, OMe, CN, CH_3, CF_3, or methane sulfonyl.

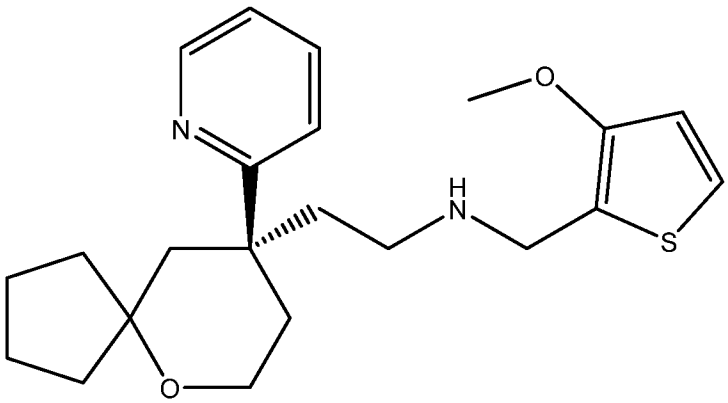
54. The method of any one of claims 1, 5, 8, or 10, wherein the compound has a formula of:



,

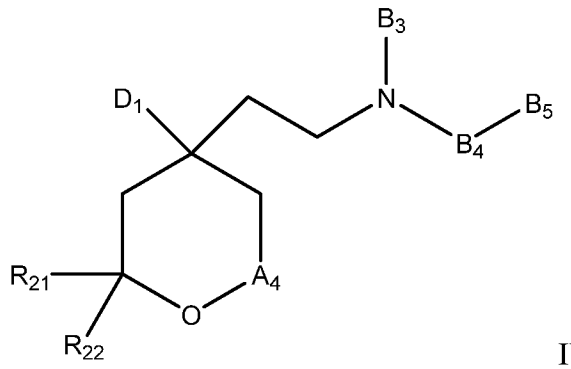


or



.

55. The method of any one of claims 1, 5, 8, or 10, wherein the compound has a formula of of Formula IV-1, or a pharmaceutically acceptable salt thereof:



IV-1

wherein:

R_{21} and R_{22} are independently H or CH_3;

A_4 is an optionally substituted cycle of the formula $C(CH_2)_n$, where n = 2-5;

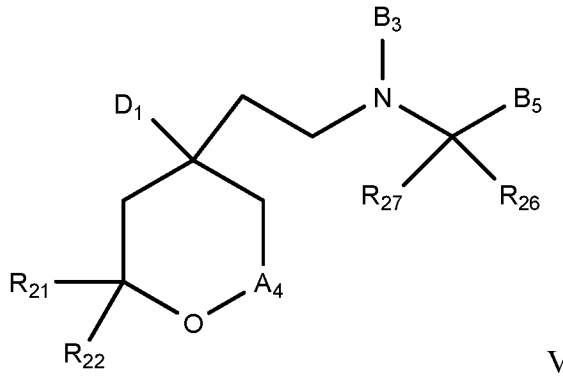
B_3 is H or an optionally substituted alkyl;

B_4 is C_1-C_6 alkyl;

D_1 is an optionally substituted aryl; and

B_5 is an optionally substituted aryl.

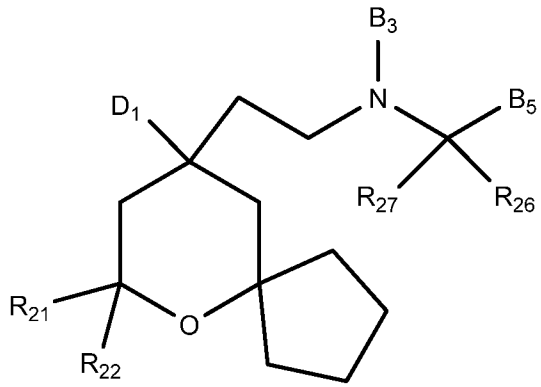
56. The method of claim 55, having the structure of Formula VII-1:



VIII,

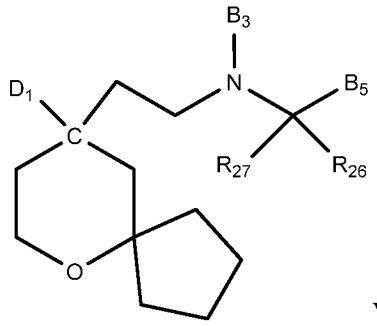
wherein R_{26} and R_{27} are independently H or an isotope thereof.

57. The method of claim 56, wherein the compound has the structure of Formula IX, or a pharmaceutically acceptable salt thereof:



IX.

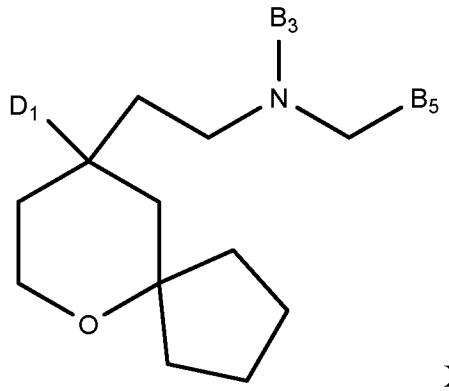
58. The method of claim 56, wherein the compound has the structure of Formula VII-1, or a pharmaceutically acceptable salt thereof.



VII-1.

59. The method of claim 58, wherein, R_{26} and R_{27} are H.

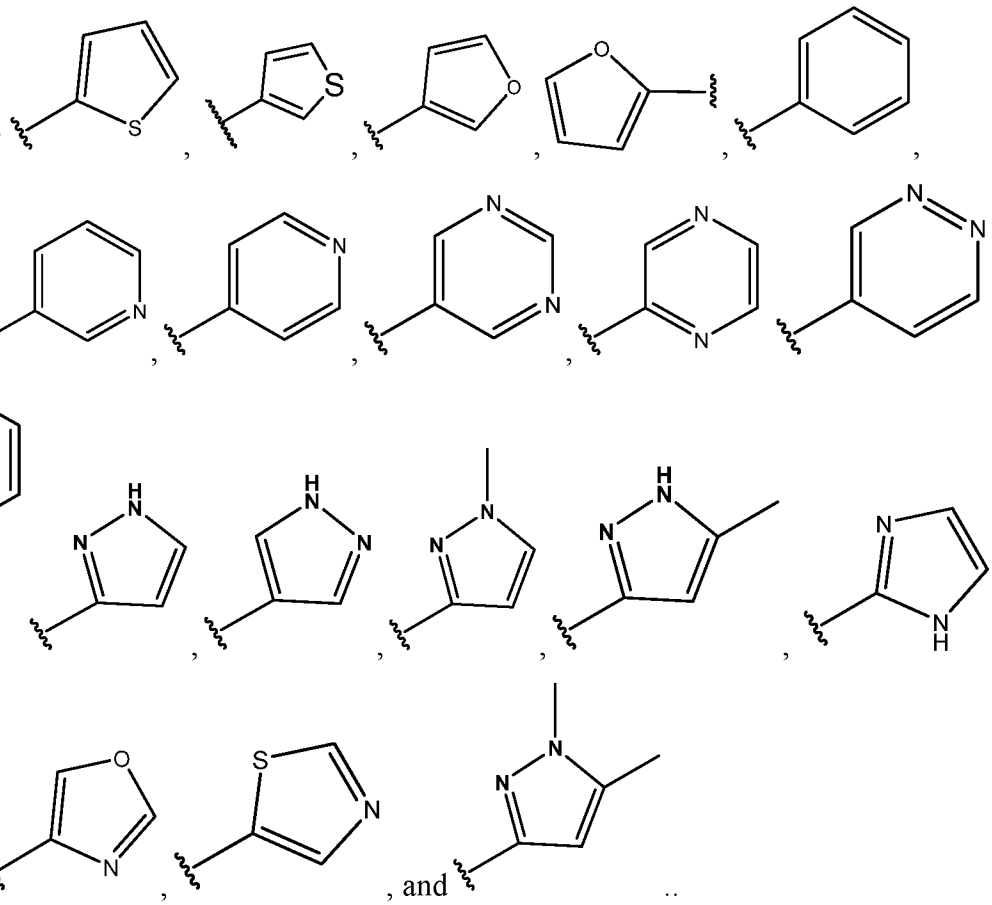
60. The method of claim 56, wherein the compound has the structure of Formula X, or a pharmaceutically acceptable salt thereof:

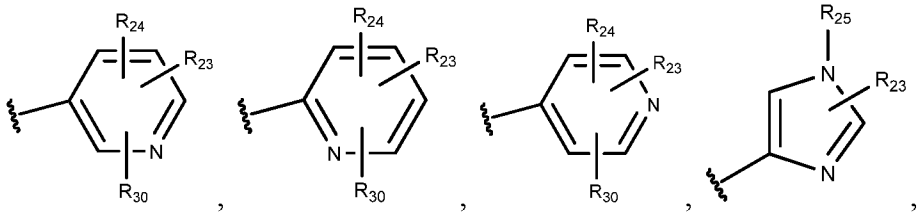


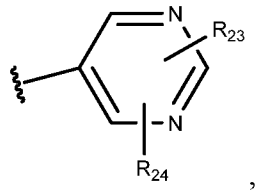
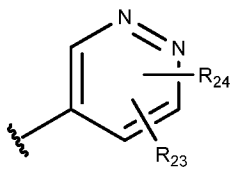
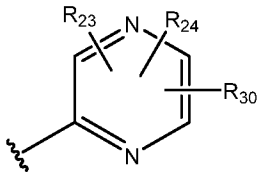
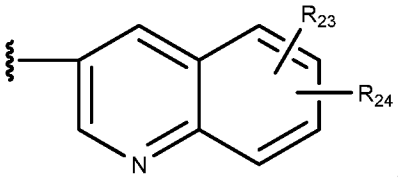
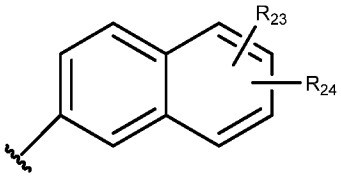
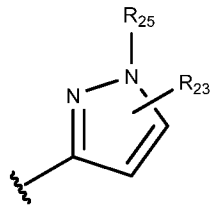
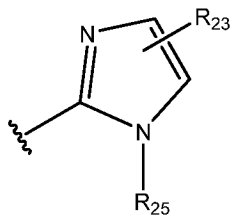
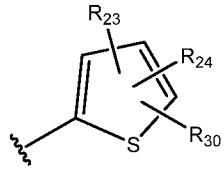
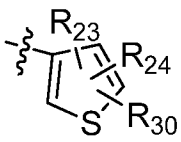
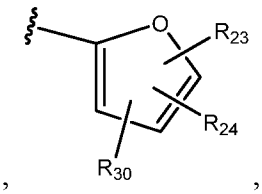
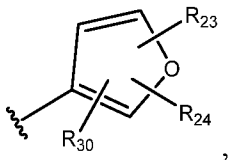
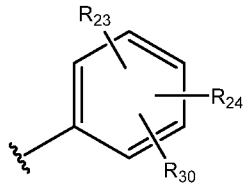
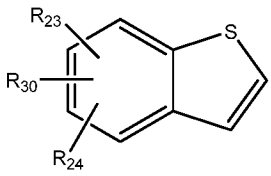
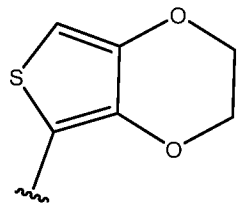
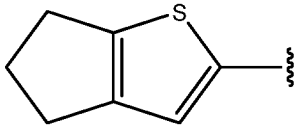
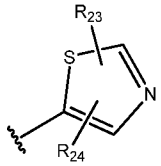
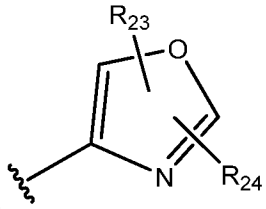
X.

61. The method of claim 55, wherein D1 is an optionally substituted phenyl or an optionally substituted pyridyl.

62. The method of claim 55, wherein B_5 is an optionally substituted heteroaryl.

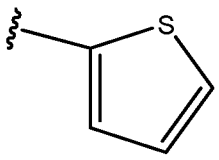
63. The method of claim 55, wherein B_5 is an optionally substituted aryl selected from the group consisting of  , and ..

64. The method of claim 55, wherein B_5 is an optionally substituted aryl selected from the group consisting of  .

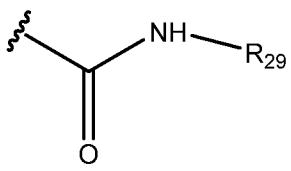
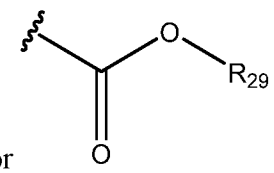


















, wherein R_{23}, R_{24}, and R_{30} are each independently null, H, OH, cycle, aryl, branched or unbranched alkyl alcohol, halo, branched or unbranched alkyl, amine, amide, cyano, alkoxy, haloalkyl, aklylsulfonyl, nitrite, alkylsulfanyl; or , R_{23} and R_{24} together form a aryl or cycle that is attached to one or more of the atoms of B_5; and R25 is H or an optionally substituted branched or unbranched alkyl.

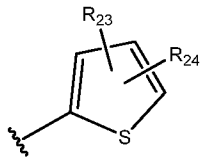
65. The method of claim 64, wherein R_{23}, R_{24}, and R_{30} are each independently H, NH_2, OH,

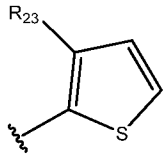


Cl, Br, F, I, OMe, CN, CH_3, phenyl, C_3-C_6 carbocycle, methanesulfonyl, CF_3,

, or ,wherein R_{29} is H or an optionally substituted branched or unbranched alkyl.

66. The method of claim 64, wherein B_5 is  .

67. The method of claim 64, wherein B_5 is  .

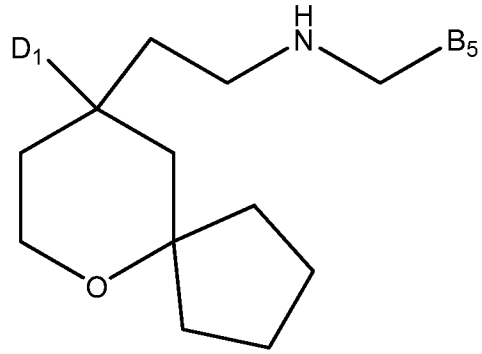
68. The method of claim 66, wherein R_{23} is alkoxy.

69. The method of claim 66, wherein R_{24} is H.

70. The method of claim 66, wherein R_{23} is methoxy.

71. The method of claim 55, wherein B_3 is H or C_1-C_5 alkyl.

72. The method of any one of claims 1, 5, 8, or 10, wherein the compound has a formula of:



, or a pharmaceutically acceptable salt thereof,

wherein:

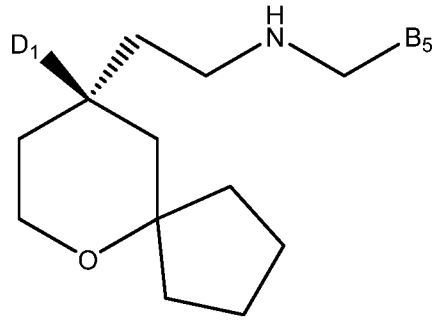
D_1 is an optionally substituted aryl; and

B_5 is an optionally substituted pyridyl.

73. The method of claim 72, wherein D_1 is an optionally substituted pyridyl.

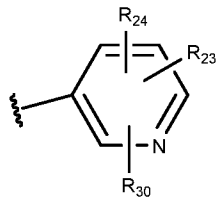
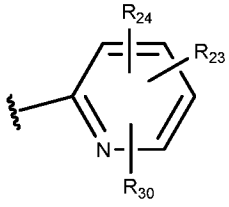
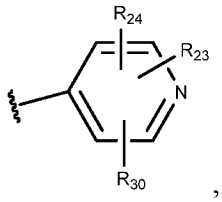
74. The method of claim 72, wherein D_1 is pyridyl.

75. The method of claim 72, wherein the compound has the formula of

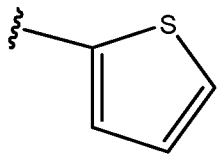
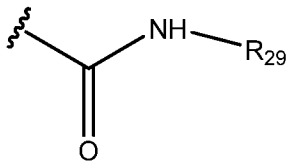
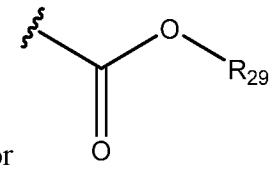


, or a pharmaceutically acceptable salt thereof.

76. The method of claim 72, wherein B_5 is


, 
, or 
,

wherein R_{23}, R_{24}, and R_{30} are each independently H, OH, cycle, aryl, branched or unbranched alkyl alcohol, halo, branched or unbranched alkyl, amine, amide, cyano, alkoxy, haloalkyl, aklylsulfonyl, nitrite, or alkylsulfanyl.

77. The method of claim 76, wherein R_{23}, R_{24}, and R_{30} are each independently H, NH_2, OH, 
, Cl, Br, F, I, OMe, CN, CH_3, phenyl, C_3-C_6 carbocycle, methanesulfonyl, CF_3, 
, or 
, wherein R_{29} is H or an alkyl.

78. The method of claim 76, wherein one of R_{23}, R_{24}, and R_{30} is H.

79. The method of claim 76, wherein two of R_{23}, R_{24}, and R_{30} are H.

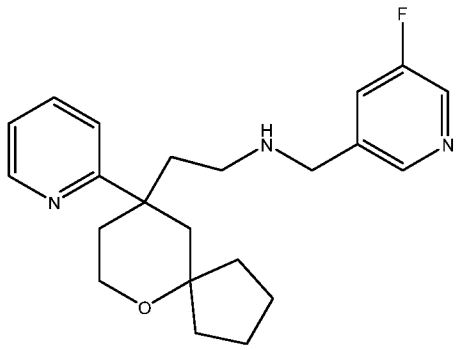
80. The method of claim 77, wherein R_{23} is F.

81. The method of claim 79, or a pharmaceutically acceptable salt thereof, wherein R_{23} is F, and R_{24} and R_{30} are H.

82. The method of claim 72, wherein the optionally substituted pyridyl is a halo substituted pyridyl.

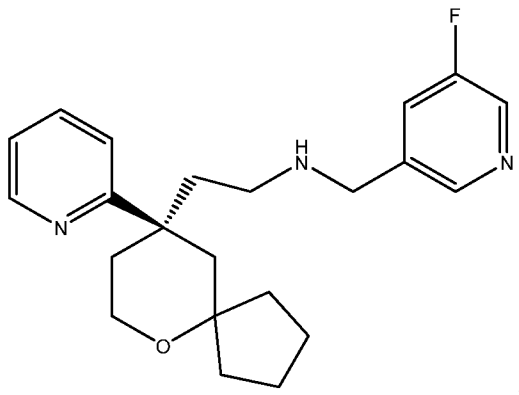
83. The method of claim 82, wherein the halo substituted pyridyl is a fluoro substituted pyridyl.

84. The method of claim 72, wherein the compound, has the formula of



, or a pharmaceutically acceptable salt thereof.

85. The method of claim 72, wherein the compound, has the formula of



, or a pharmaceutically acceptable salt thereof.

86. The method of any one of claims 1-85, wherein the compound, or a pharmaceutically

acceptable salt thereof is administered in a pharmaceutical composition.

87. The method of any one of claims 1-86, wherein the subject is a subject in need thereof.

88. The method of any one of claims 1-86, wherein the subject has been identified as having induced hyperalgesia.

89. The method of any one of claims 1-86, wherein the subject has been identified as having opioid induced hyperalgesia.

Fig. 1

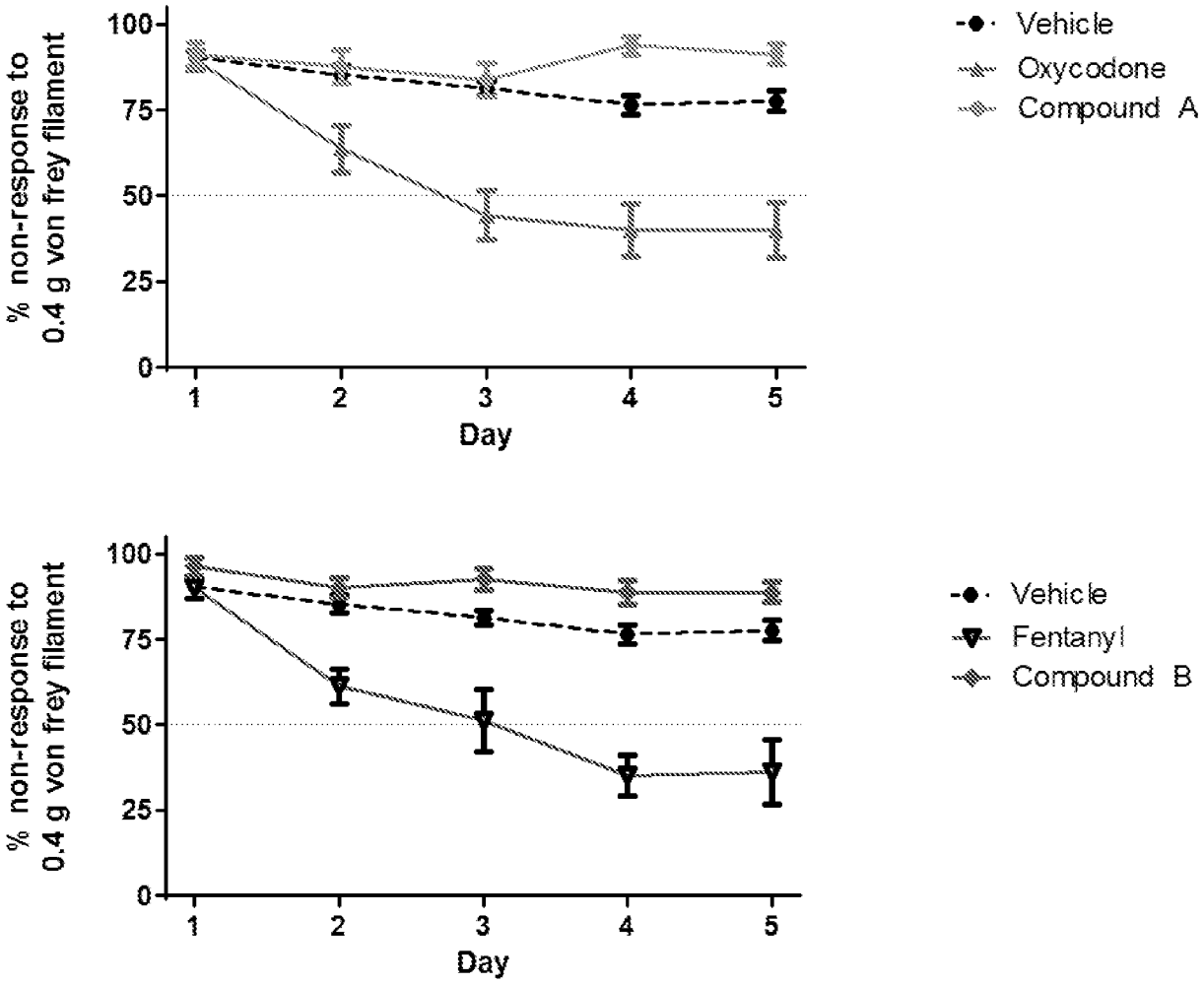
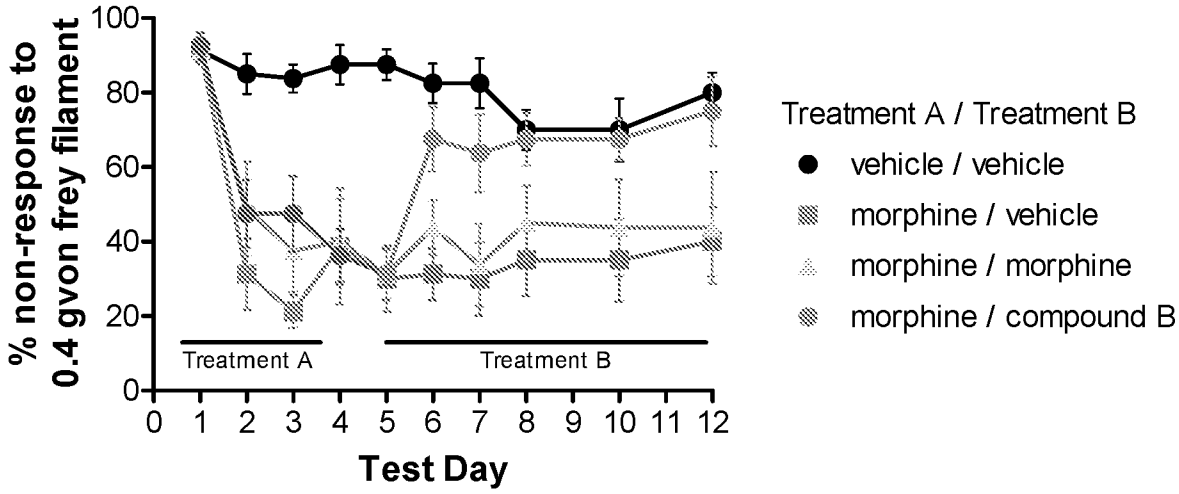

% non-response to 0.4 g von frey filament
100
75
50
25
0
1
2
3
4
5
Day
Vehicle
Oxycodone
Compound A
% non-response to 0.4 g von frey filament
100
75
50
25
0
1
2
3
4
5
Day
Vehicle
Fentanyl
Compound B

Fig. 2


% non-response to 0.4 gvon frey filament
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Test Day
Treatment A
Treatment B
Treatment A / Treatment B
vehicle / vehicle
morphine / vehicle
morphine / morphine
morphine / compound B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/66601

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/4433, 31/497; A61P 1/10; C07D 405/04 (2017.01)
CPC - A61K 31/4433, 31/35; C07D 405/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --	US 2012/0245181 A1 (YAMASHITA, D et al.) 27 September 2012; paragraphs [0010]-[0020], [0147], [0152]-[0153], [0158], [0160]	1, 5, 8-11, 12/1, 12/5, 12/8-11, 28/1, 28/5, 28/8, 28/10, 29/28/1, 29/28/5, 29/28/8, 29/28/10, 30/28/1, 30/28/5, 30/28/8, 30/28/10, 31/28/1, 31/28/5, 31/28/8, 31/28/10, 32/28/1, 32/28/5, 32/28/8, 32/28/10, 33/28/1, 33/28/5, 33/28/8, 33/28/10, 34/28/1, 34/28/5, 34/28/8, 34/28/10, 35/28/1, 35/28/5, 35/28/8, 35/28/10, 36/1, 36/5, 36/8, 36/10, 37/36/1, 37/36/5, 37/36/8, 37/36/10, 38/36/1, 38/36/5, 38/36/8, 38/36/10, 39/36/1, 39/36/5, 39/36/8, 39/36/10, 40/36/1, 40/36/5, 40/36/8, 40/36/10, 41/40/36/1,

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2017 (23.01.2017)	10 MAR 2017
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/66601

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
		41/40/36/5, 41/40/36/8, 41/40/36/10, 42/36/1, 42/36/5, 42/36/8, 42/36/10, 43/42/36/1, 43/42/36/5, 43/42/36/8, 43/42/36/10, 44/36/1, 44/36/5, 44/36/8, 44/36/10, 45/1, 45/5, 45/8, 45/10, 46/45/1, 46/45/5, 46/45/8, 46/45/10, 47/1, 47/5, 47/8, 47/10, 48/47/1, 48/47/5, 48/47/8, 48/47/10, 54/1, 54/5, 54/8, 54/10, 55/1, 55/5, 55/8, 55/10, 56/55/1, 56/55/5, 56/55/8, 56/55/10, 57/56/55/1, 57/56/55/5, 57/56/55/8, 57/56/55/10, 58/56/55/1, 58/56/55/5, 58/56/55/8, 58/56/55/10, 60/56/55/1, 60/56/55/5, 60/56/55/8, 60/56/55/10, 61/55/1, 61/55/5, 61/55/8, 61/55/10, 62/55/1, 62/55/5, 62/55/8, 62/55/10, 63/55/1, 63/55/5, 63/55/8, 63/55/10, 64/55/1, 64/55/5, 64/55/8, 64/55/10, 65/64/55/1, 65/64/55/5, 65/64/55/8, 65/64/55/10, 66/64/55/1, 66/64/55/5, 66/64/55/8, 66/64/55/10, 67/64/55/1, 67/64/55/5, 67/64/55/8, 67/64/55/10, 68/66/64/55/1, 68/66/64/55/5, 68/66/64/55/8, 68/66/64/55/10, 69/66/64/55/1, 69/66/64/55/5, 69/66/64/55/8, 69/66/64/55/10, 70/66/64/55/1, 70/66/64/55/5, 70/66/64/55/8, 70/66/64/55/10, 71/55/1, 71/55/5, 71/55/8, 71/55/10, 72/1, 72/5, 72/8, 72/10, 73/72/1, 73/72/5, 73/72/8, 73/72/10, 74/72/1, 74/72/5, 74/72/8, 74/72/10, 75/72/1, 75/72/5, 75/72/8, 75/72/10, 76/72/1, 76/72/5, 76/72/8, 76/72/10, 77/76/72/1, 77/76/72/5, 77/76/72/8, 77/76/72/10, 78/76/72/1, 78/76/72/5, 78/76/72/8, 78/76/72/10, 79/76/72/1, 79/76/72/5, 79/76/72/8, 79/76/72/10, 80/77/76/72/1, 80/77/76/72/5, 80/77/76/72/8, 80/77/76/72/10,

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/66601

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
		81/79/76/72/1, 81/79/76/72/5, 81/79/76/72/8, 81/79/76/72/10, 82/72/1, 82/72/5, 82/72/8, 82/72/10, 83/82/72/1, 83/82/72/5, 83/82/72/8, 83/82/72/10, 84/72/1, 84/72/5, 84/72/8, 84/72/10, 85/72/1, 85/72/5, 85/72/8, 85/72/10
Y		2-4, 6-7, 12/2-4, 12/6-7
Y	US 2013/0158033 A1 (VELA HERNANDEZ, JM et al.) 20 June 2013; abstract; paragraphs [0017], [0159], [0192]-[0196]	2-4, 6-7, 12/2-4, 12/6-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/66601

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 13-27, 49-53, 86-89
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.