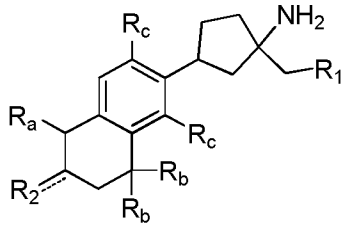
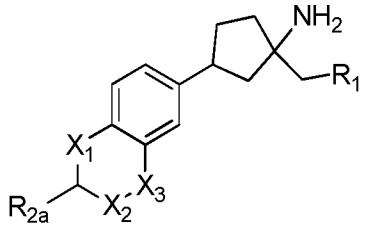
CLAIMS

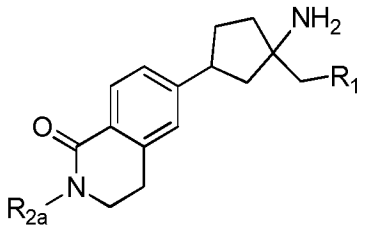
1. A compound of Formulas (I), (II), (III), (IV), or (V):



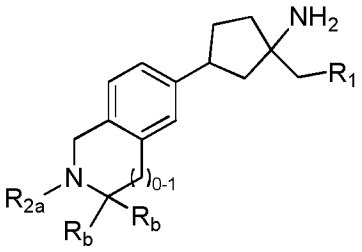
(I)



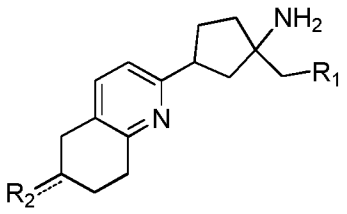
(II)



(III)



(IV)



(V)

or a salt thereof, wherein:

R_1 is -OH or $-OP(O)(OH)_2$;

X_1 is CH_2 or O;

X_2 is CH_2 or O;

X_3 is CH_2 or O, provided that X_2 is O only if both X_1 and X_3 are each CH_2;

R_2 is R_{2a} or R_{2b};

$\cdots$ represents either a single bond to R_{2a} or a double bond to R_{2b};

R_{2a}

is $-(CH_2)_{3\text{-}4}CH_3$, $-(CH_2)_{1\text{-}4}CH{=}CR_xR_x$, $-(CH_2)_{1\text{-}4}CH{=}CR_x(CH_2CH_3)$, $-CH{=}CH(CH_2)_{1\text{-}3}C(R_x)_3$, $-CH{=}CH(CH_2)_{1\text{-}3}OCH_3$, $-(CH_2)_{1\text{-}3}CH{=}CHCH{=}CR_xR_x$, $-CH{=}CH(CH_2)_{1\text{-}3}CH{=}CR_xR_x$, $-CH{=}CHR_z$, $-(CH_2)_{1\text{-}3}R_z$, $-(CH_2)_{1\text{-}3}O(CH_2)_{0\text{-}3}R_z$, $-(CH_2)_{1\text{-}3}S(CH_2)_{0\text{-}3}R_z$, $-CH_2S(O)R_z$, $-CH_2S(O)_2R_z$, $-O(CH_2)_{1\text{-}2}R_z$, $-O(CH_2)_{1\text{-}2}O(CH_2)_{0\text{-}2}R_z$, $-OC(O)R_z$, $-(CH_2)_{1\text{-}4}O(CH_2)_{0\text{-}9}C(R_x)_3$, $-(CH_2)_{1\text{-}4}O(CH_2)_{0\text{-}9}CF_3$, $-(CH_2)_{1\text{-}4}CR_xR_xO(CH_2)_{0\text{-}4}C(R_x)_3$, $-(CH_2)_{1\text{-}3}O(CH_2)_{1\text{-}4}CH{=}CR_x(CH_2)_{0\text{-}3}CH_3$, $-(CH_2)_{1\text{-}3}O(CH_2)_{1\text{-}4}CH{=}CR_xR_x$, $-(CH_2)_{1\text{-}3}O(CH_2)_{1\text{-}4}C(OH)R_xR_x$, $-(CH_2)_{1\text{-}3}O(CH_2)_{1\text{-}4}O(CH_2)_{0\text{-}3}CH_3$, $-(CH_2)_{1\text{-}3}S(CH_2)_{0\text{-}4}C(R_x)_3$, $-(CH_2)_{0\text{-}3}O(CH_2)_{1\text{-}4}S(CH_2)_{0\text{-}3}C(R_x)_3$, $-(CH_2)_{1\text{-}3}S($

$CH_2)_{1-4}Si(CH_3)_3$, $-(CH_2)_{1-3}S(O)(CH_2)_{0-4}C(R_x)_3$, $-(CH_2)_{1-3}S(O)_2(CH_2)_{0-4}C(R_x)_3$, $-(CH_2)_{1-5}N$ R_xR_x, $-O(CH_2)_{1-7}C(R_x)_3$, $-O(CH_2)_{1-4}O(CH_2)_{0-4}C(R_x)_3$, $-O(CH_2)_{1-4}CH{=}CR_x(CH_2)_{0-3}CH_3$, $-O$ $(CH_2)_{1-4}O(CH_2)_{0-3}C(R_x)_3$, $-O(CH_2)_{1-4}O(CH_2)_{1-3}CH{=}CR_xR_x$, $-O(CH_2)_{1-4}O(CH_2)_{1-3}C{\equiv}CR_x$, $-C(O)(CH_2)_{0-4}C(R_x)_3$, $-OC(O)(CH_2)_{0-4}C(R_x)_3$, $-OC(O)CR_xR_x(CH_2)_{0-4}C(R_x)_3$, $-OC(O)NR_x(C$ $H_2)_{0-5}C(R_x)_3$, $-NR_xC(O)NR_x(CH_2)_{0-5}C(R_x)_3$, $-C(CH_3){=}N{-}O(CH_2)_{0-5}C(R_x)_3$, $-C(CH_3){=}N{-}O($ $CH_2)_{1-2}$(phenyl), $-C(CH_3){=}N{-}O(CH_2)_{1-2}$(fluorophenyl), $-C(CH_3){=}N{-}O(CH_2)_{1-2}$(methoxyph enyl), phenyl, or pyridinyl;

R_{2b} is

(i) a 6-membered spiro-ring having one oxygen atom and substituted with R_b, wherein R_b is H or $-(CH_2)_3CH_3$; or

(ii) $=N{-}O{-}(CH_2)_3CH_3$, $=N{-}O{-}CH_2CH(CH_3)_2$, $=N{-}OCH_2CH_2$(phenyl), or $=N{-}O{-}CH_2CH_2CH_2$(phenyl);

R_a is H or -OH;

each R_b is independently H or $-CH_3$;

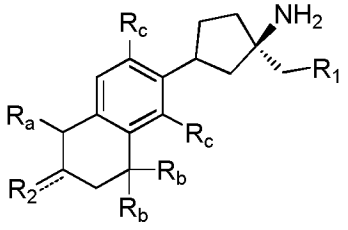
each R_c is independently H, Cl, I, or $-CH_3$;

each R_x is independently H or $-CH_3$; and

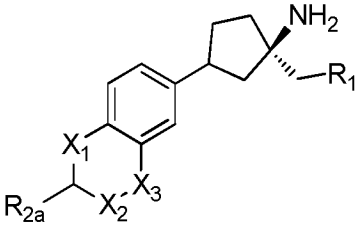
R_z is phenyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, thiophenyl, thiazolyl, oxetanyl, C_{3-6} cycloalkyl, adamantanyl, or tetrahydropyranyl, each substituted with zero to 4 substituents independently selected from F, Cl, I, C_{1-4} alkyl, $-O(C_{1-3}$ alkyl), $-CF_3$, $-OCF_3$, $-(CH_2)_{1-6}OCH_3$, $-CH_2NR_xR_x$, $-C(O)NR_xR_x$, $-C(O)NR_x(C_{1-4}$ alkyl), and $-CH_2C(O)NR_xR_x$.

with the provisos that if said compound has the structure of Formula (I) and R_2 is $-(CH_2)_5CH_3$, then at least one of R_b and R_c is not H; and (ii) if said compound has the structure of Formula (II) and X_1, X_2, and X_3 are each CH_2, then R_{2a} is not $-(CH_2)_5CH_3$.

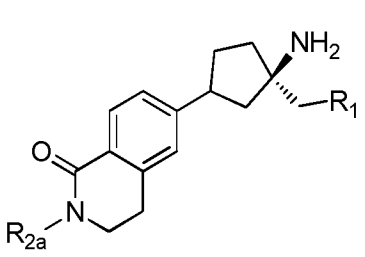
2. The compound according to claim 1, wherein said compound has the structure of Formula (Ic), (IIc), (IIIc), (IVc), or (Vc):



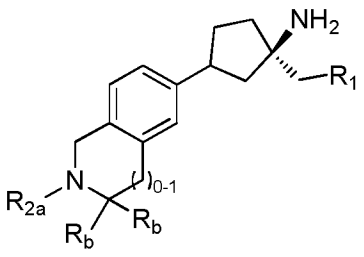
(Ic)



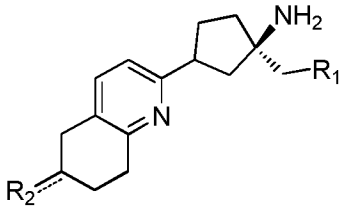
(IIc)



(IIIc)



(IVc)



(Vc).

3. The compound according to any one of claims 1 to 2, having the structure of Formula (I) or a salt thereof, wherein:

R_1 is -OH or $-OP(O)(OH)_2$;

R_2 is R_{2a} or R_{2b};

R_{2a}

is $-(CH_2)_3CH_3$, $-(CH_2)_5CH_3$, $-CH_2CH=CHCH_2CH_3$, $-CH_2CH_2CH=CHCH_2CH_3$, $-(CH_2)_3CH=CHCH_3$, $-(CH_2)_3CH=C(CH_3)_2$, $-(CH_2)_4CH=CH_2$, $-(CH_2)_4CH=CHCH_3$, $-CH=CH(CH_2)_3CH_3$, $-CH=CH(CH_2)_3OCH_3$, $-CH=CHCH_2CH_2CH(CH_3)_2$, $-CH=CHCH_2CH_2CH_2OCH_3$, $-CH_2CH=CHCH=CHCH_3$, $-CH=CHCH_2CH_2CH=CH_2$, -CH=CH(phenyl) wherein said phenyl is substituted with $-CH_3$ or $-OCH_3$; -CH=CH(tetrahydropyranyl), $-(CH_2)_{1-3}$(phenyl) wherein said phenyl is substituted with zero to 2 substituents independently selected from F, I, $-CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, and $-CH_2C(O)N(CH_3)_2$; $-(CH_2)_2$(methyl imidazolyl), $-(CH_2)_2$(methyl pyrazolyl), $-(CH_2)_{1-2}$(pyridinyl) wherein said pyridinyl is substituted with zero to 1 substituent selected from $-OCH_3$; $-(CH_2)_2$(pyrimidinyl), $-(CH_2)_2$(quinolinyl), $-(CH_2)_{2-3}$(tetrahydropyranyl), $-CH_2O(CH_2)_{3-4}CH_3$, $-CH_2OCH_2CH_2CH(CH_3)_2$, $-CH_2OCH_2CH_2C(CH_3)_3$, $-CH_2O(CH_2)_9CH_3$, $-CH_2OCH_2CH_2CH_2CF_3$, $-CH_2OCH_2CH=CHCH_2CH_3$, $-CH_2OCH_2CH=C(CH_3)_2$, $-CH_2OCH_2CH=CHCH_2CH_2CH_3$, $-CH_2OCH_2CH_2CH=CH_2$, $-CH_2OCH_2CH_2CH_2CH=CH_2$, $-CH_2OCH_2CH_2CH=C(CH_3)_2$, $-CH_2OCH_2CH_2CH(OH)CH_3$, $-CH_2OCH_2CH_2CH_2CH_2OH$, $-CH_2OCH_2CH_2CH_2C(CH_3)_2(OH)$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2OCH_2CH_2CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_2CH_2CH_3$, $-CH_2O$(phenyl) wherein said phenyl is substituted with zero to 3 substituents independently selected from F,

Cl, $-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-OCH_3$, $-OCF_3$, $-(CH_2)_{1-6}OCH_3$, $-C(O)N(CH_3)_2$, $-CH_2N(CH_3)_2$, $-C(O)N(CH_2CH_3)(CH_3)$, $-C(O)N(CH_3)(CH_2CH_2CH_2CH_3)$, and $-C(O)N(CH_3)(CH_2CH(CH_3)_2)$; $-CH_2O$(methoxy pyridinyl), $-CH_2O$(tetrahydropyranyl), $-CH_2O$(trifluoromethyl, methyl pyrazolyl), $-CH_2OCH_2$(phenyl) wherein said phenyl is substituted with zero to 1 substituent selected from $-CH_3$ and $-OCH_3$; $-CH_2OCH_2$(methyl pyrazolyl), $-CH_2OCH_2$(tetrahydropyranyl), $-CH_2OCH_2$(thiophenyl), $-CH_2OCH_2$(trifluoro methyl thiophenyl), $-CH_2OCH_2$(ethyl thiophenyl), $-CH_2OCH_2$(dimethyl thiophenyl), $-CH_2CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH(CH_3)_2$, $-CH_2CH_2O$(methoxyphenyl), $-CH_2CH_2OCH_2$(cyclopropyl), $-CH_2CH_2SCH(CH_3)_2$, $-(CH_2)_3OCH_2CH_3$, $-(CH_2)_3OCH(CH_3)_2$, $-(CH_2)_3OCH_2CH_2CH=CH_2$, $-(CH_2)_3O$(oxetanyl), $-(CH_2)_3O$(tetramethyl cyclohexyl), $-(CH_2)_3OCH_2SCH_3$, $-CH_2S(CH_2)_{2-4}CH_3$, $-CH_2SCH(CH_3)_2$, $-CH_2SCH_2CH(CH_3)_2$, $-CH_2SCH_2C(CH_3)_3$, $-CH_2SCH_2CH_2CH(CH_3)_2$, $-CH_2SCH_2CH_2C(CH_3)_3$, $-CH_2SCH_2CH_2Si(CH_3)_3$, $-CH_2CH_2S(CH_2)_{1-2}CH_3$, $-CH_2CH_2SCH_2CH(CH_3)_2$, $-CH_2S$(phenyl) wherein said phenyl is substituted with zero to 2 substituents independently selected from $-CH_3$, $-CH(CH_3)_2$, and $-OCH_3$; $-CH_2S$(adamantanyl), $-CH_2S$(pyridinyl), $-CH_2S$(methyl pyridinyl), $-CH_2SCH_2CH_2$(phenyl), $-CH_2SCH_2CH_2$(pyrazinyl), $-CH_2SCH_2CH_2$(pyridinyl), $-CH_2S(O)(CH_2)_3CH_3$, $-CH_2S(O)_2(CH_2)_3CH_3$, $-CH_2S(O)$(phenyl), $-CH_2S(O)_2$(phenyl), $-(CH_2)_4OCH(CH_3)_2$, $-(CH_2)_4CH(CH_3)OCH_3$, $-(CH_2)_4C(CH_3)_2OCH_3$, $-(CH_2)_5N(CH_3)_2$, $-O(CH_2)_{4-7}CH_3$, $-OCH_2CH_2O(CH_2)_{2-4}CH_3$, $-OCH_2CH_2OCH_2CH(CH_3)_2$, $-OCH_2CH=CH(CH_2)_{2-3}CH_3$, $-OCH_2CH_2OCH_2CH=CH_2$, $-OCH_2CH_2OCH_2CH=CH(CH_3)$, $-OCH_2CH_2OCH_2CH=C(CH_3)_2$, $-OCH_2CH_2OCH_2CH_2C\equiv CH$, $-OCH_2CH_2O(CH_2)_{2-3}CH(CH_3)_2$, $-OCH_2CH_2S(CH_2)_2CH_3$, $-OCH_2$(cyclohexyl), $-OCH_2$(tetrahydropyranyl), $-OCH_2$(phenyl) wherein said phenyl is substituted with zero to 1 substituent selected from $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCF_3$, and $-OCH_2CH_3$; $-OCH_2CH_2O$(cyclohexyl), $-OCH_2CH_2O$(methyl phenyl), $-OCH_2CH_2OCH_2$(cyclobutyl), $-OCH_2CH_2OCH_2$(phenyl), $-OCH_2CH_2OCH_2$(thiazolyl), $-OCH_2CH_2OCH_2$(thiophenyl), $-OC(O)(CH_2)_4CH_3$, $-OC(O)C(CH_3)_2(CH_2)_3CH_3$, $-OC(O)$(phenyl), $-OC(O)NH(CH_2)_3CH_3$, $-OC(O)NH(CH_2)_5CH_3$, $-OC(O)N(CH_3)(CH_2)_3CH_3$, $-OC(O)N(CH_3)(CH_2)_4CH_3$, $-NHC(O)NH(CH_2)_3CH_3$, $-C(CH_3)=N-O(CH_2)_3CH_3$, $-C(CH_3)=N-OCH_2$(phenyl), $-C(CH_3)=N-OCH_2$(fluorophenyl), $-C(CH_3)=N-OCH_2$(methoxyphenyl), $-C(CH_3)=N-OCH_2CH_2$(phenyl), $-OC(O)NH(CH_2)_3CH_3$, $-OC(O)NH(CH_2)_5CH_3$, $-OC(O)N$

$(CH_3)(CH_2)_{3-4}CH_3$, -NHC(O)NH$(CH_2)_3CH_3$, phenyl, or pyridinyl;

R_{2b} is:

(i) 6-membered spiro-ring having one oxygen atom and substituted with R_b, wherein R_b is H or -$(CH_2)_3CH_3$; or

(ii) =N-O-$(CH_2)_3CH_3$, =N-O-$CH_2CH(CH_3)_2$, =N-OCH_2CH_2(phenyl), or =N-O-$CH_2CH_2CH_2$(phenyl);

R_a is H or -OH;

each R_b is independently H or -CH_3; and

each R_c is independently H, Cl, I, or -CH_3;

with the proviso that if R_2 is -$(CH_2)_6CH_3$, then at least one of R_b and R_c is not H.

4. The compound according to any one of claims 1 to 2, having the structure of Formula (II) or a salt thereof; wherein:

R_1 is -OH or -OP(O)$(OH)_2$;

X_1 is CH_2 or O;

X_2 is CH_2 or O;

X_3 is CH_2 or O; provided that X_2 is O only if both X_1 and X_3 are each CH_2; and

R_{2a} is -$(CH_2)_{5-6}CH_3$ or -$CH_2O(CH_2)_{3-4}CH_3$.

5. The compound according to any one of claims 1 to 2 having a structure of Formula (III), Formula (IV), or Formula (V) or a salt thereof; wherein:

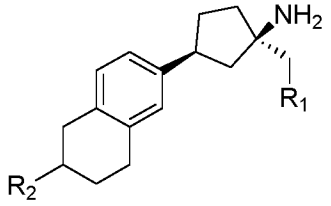
R_1 is -OH or -OP(O)$(OH)_2$;

R_2 is R_{2a};

R_{2a} is -$(CH_2)_3CH_3$, -$(CH_2)_5CH_3$, -$(CH_2)_3$(phenyl), or -C(O)$(CH_2)_4CH_3$; and

each R_b is -CH_3.

6. The compound according to claim 1 having the structure:

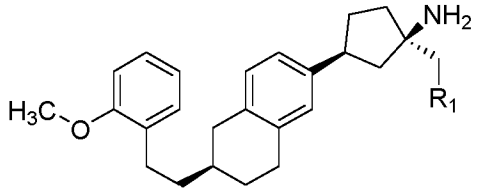


or a salt thereof; wherein:

R_1 is -OH or -OP(O)$(OH)_2$; and

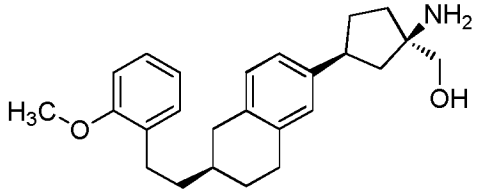
R_2 is $-(CH_2)_5OCH3$, $-(CH_2)_3OCH_2CH_3$, $-CH_2O$(methoxyphenyl),
or $-CH_2CH_2$(methoxyphenyl).

7. The compound according to any one of claims 1 to 3 and 6 having the structure:



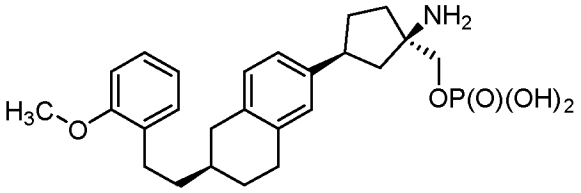
or a salt thereof; wherein:
R_1 is -OH or $-OP(O)(OH)_2$.

8. The compound according to any one of claims 1 to 3 and 6 to 7 having the structure:



or a salt thereof.

9. The compound according to any one of claims 1 to 3 and 6 to 7 having the structure:



or a salt thereof.

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition according to claim 10 wherein R_1 is -OH in the compound or pharmaceutically acceptable salt thereof.

12. A compound according to any one claims 1 to 10 or a pharmaceutically acceptable salt thereof for use as a medicament.

13. A compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof for use in the treatment of a disease or disorder associated with the activity of G protein-coupled receptor $S1P_1$.

14. A compound for use according to claim 13 or a pharmaceutically acceptable salt thereof, for the treatment of an autoimmune disease or a chronic inflammatory disease.