TITLE

Heterocyclic Compounds Useful in the Treatment of Disease

CROSS REFERENCE TO RELATED APPLICATIONS

[1] This application claims the benefit of U.S. Provisional Patent Application Serial No. 61/801,426, filed March 15, 2013, U.S. Provisional Patent Application Serial No. 61/801,231, filed March 15, 2013, U.S. Provisional Patent Application Serial No. 61/827,409, filed May 24, 2013, the entire contents of which are hereby incorporated by reference herein.

STATEMENT OF GOVERNMENT INTEREST

[2] This invention was made with government support under Grants DK092005 and CA174019 awarded by the National Institutes of Health. The US government has certain rights in the invention.

FIELD OF THE INVENTION

[3] The present invention relates to compounds having pharmacological activity, to processes for preparation of such compounds, to pharmaceutical compositions comprising them, and to their use in therapy and prophylaxis of disease in a subject in need thereof, in particular for human and veterinarian treatments of pain, pruritus, cancer, inflammation and fibrotic diseases.

BACKGROUND OF THE INVENTION

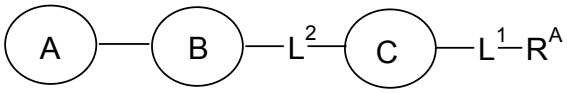
[4] Lysophospholipids affect fundamental cellular functions that include proliferation, differentiation, survival, migration, adhesion, invasion, and morphogensis. Abnormal functions influence many biological processes leading to disease that include, but are not limited to fibrotic disease, inflammation, cancer and peripheral nerve injury. Lysophosphatidic acid (LPA) is a lysophospholipid that has been shown to act through specific G protein-coupled receptors (GPCRs) in an autocrine and paracrine fashion. Antagonists of the LPA receptors find use in the treatment of diseases, disorders or conditions in which LPA plays a role.

[5] Agents that interact with the lysophosphatidic acid receptors [LPARs] to reduce signal transduction through those receptors (i.e., by competitive or noncompetitive inhibition or acting as inverse agonists) reduce manifestations of the diseases described herein. Diseases and conditions whose etiology, progression or persistence is effected by in whole or in part by signaling through the lysophosphatidic acid receptor subtype 1

CLAIMS

What is claimed is:

1. A compound wherein the compound has the structure of Formula I

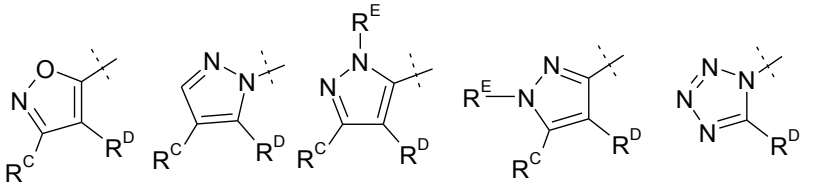


Formula I

,

or a pharmaceutically acceptable salt, wherein

Ring A is a 5-membered heteroarene selected from one of:



,

wherein the dashed line indicates the point of attachment of Ring A to Ring B;

Ring B is substituted or unsubstituted 1,4-arylene, where if ring B is substituted then ring B is substituted with 1, 2, or 3 independently selected R^H;

Ring C is absent;

L^1 is -UV-Z-;

UV is -OW-, -WO-, -N(R^J)W-, -WN(R^J)- or -C(=O)N(R^J)-, wherein W is substituted or unsubstituted C_1-C_3 alkylene, wherein each R^J is independently substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_1-C_6 fluoroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_4 alkylene-(substituted or unsubstituted C_3-C_6 cycloalkyl), -C_1-C_4 alkylene-(substituted or unsubstituted heterocycloalkyl), -C_1-C_4 alkylene-(substituted or unsubstituted aryl), or -C_1-C_4 alkylene-(substituted or unsubstituted heteroaryl); and

W is substituted or unsubstituted C_1-C_3 alkylene or substituted or unsubstituted C_3-C_6 cycloalkylene, or W is -C(R^L)$_2$- or

UV is -WN(R^J)- or -C(=O)N(R^J)-, wherein R^J is –H or –CH_3; and

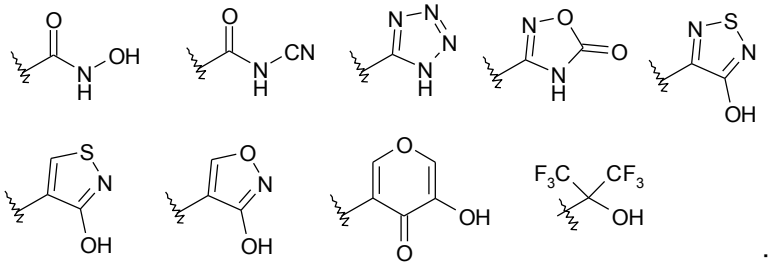
W is substituted or unsubstituted C_1-C_3 alkylene;

and

Z is substituted or unsubstituted C_1-C_6 alkylene, substituted or unsubstituted C_3-C_6 cycloalkylene, or C_1-C_6 fluoroalkylene or Z is -C(R^L)$_2$-;

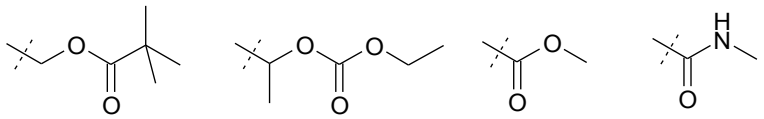
L^2 is absent;

R^A is $-CO_2H$, $-CO_2R^B$, -CN, tetrazolyl, $-C(=O)NH_2$, $-C(=O)NHR^B$, $-C(=O)NHSO_2R^B$ or $-C(=O)NHCH_2CH_2SO_3H$ or a carboxylic acid isostere having the structure of one of:



;

R^B is -H or $-C_1$-C_4 alkyl, or has the structure of one of:



;

R^C is -H, -CN, -F, -Cl, -Br, -I, $-OC_1$-C_4 alkyl, $-C_1$-C_4 alkyl, $-C_3$-C_6 cycloalkyl, or $-C_1$-C_4 fluoroalkyl;

R^D is $-N(R^F)$-$C(=O)XCH(R^G)$-CY, $-N(R^F)C(=O)XC(R^G)_2$-CY, $-N(R^F)C(=O)X$-CY, wherein R^F and each R^G independently are -H or C_1-C_4 alkyl.

R^E is -H, $-C_1$-C_4 alkyl or $-C_1$-C_4 fluoroalkyl;

R^F is -H or C_1-C_4 alkyl;

R^G is independently selected R^E, or one R^G is C_1-C_4 alkyl and is taken together with CY and the carbon atom to which R^G and CY are attached to define a substituted or unsubstituted carbocycle or a substituted or unsubstituted heterocycle, and the other R^G, if present, is as defined for R^E;

CY is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_2-C_{10} heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein if CY is substituted then CY is substituted with 1, 2, or 3 independently selected R^H;

wherein each R^H is independently selected from -H, halogen, -CN, $-NO_2$, -OH, $-OR^J$, $-SR^J$, $-S(=O)R^J$, $-S(=O)_2R^J$, $-N(R^J)S(=O)_2R^J$, $-S(=O)_2N(R^L)_2$, $-C(=O)R^J$, $OC(=O)R^J$, $-C(=O)OR^J$, $-OC(=O)OR^J$, $-N(R^L)_2$, $-C(=O)N(R^L)_2$, $-OC(=O)N(R^L)_2$, $-N(R^J)C(=O)N(R^L)_2$, $-N(R^J)C(=O)R^J$, $-N(R^J)C(=O)OR^J$, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, C_1-C_4 alkoxy, and C_1-C_4 heteroalkyl,

wherein each R^L is independently -H, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_1-C_6 fluoroalkyl,

substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -C_1-C_4 alkylene-(substituted or unsubstituted cycloalkyl), -C_1-C_4 alkylene-(substituted or unsubstituted heterocycloalkyl), -C_1-C_4 alkylene(substituted or unsubstituted aryl), or -C_1-C_4 alkylene-(substituted or unsubstituted heteroaryl),

or when R^H is -$S(=O)_2N(R^L)_2$, -$N(R^L)_2$, -$C(=O)N(R^L)_2$, -$OC(=O)N(R^L)_2$ or $N(R^J)C(=O)N(R^L)_2$, each R^L is independently -H or C_1-C_6 alkyl, or the R^L groups independently are C_1-C_6 alkyl which are taken together with the N atom to which they are attached to define a substituted or unsubstituted heterocycle,

or when W is -$C(R^L)_2$- or Z is -$C(R^L)_2$-, each R^L is independently -H or C_1-C_6 alkyl, or the R^L groups independently are C_1-C_6 alkyl which are taken together with the carbon atom to which they are attached to define a carbocycle;

2. The compound of claim 1 wherein L^1 is -UV-Z- wherein -UV- is defined by -OW-, -WO-, -$N(R^J)$W-, -$WN(R^J)$- or -$C(=O)N(R^J)$-, wherein W is substituted or unsubstituted C_1-C_3 alkylene.

3. The compound of claim 2 wherein Z is substituted or unsubstituted C_1-C_6 alkylene.

4. The compound of claim 2 wherein Z is substituted or unsubstituted C_1-C_6 alkylene and R^A is -CO_2H or -CO_2R^B.

5. The compound of claim 2, wherein L^1 is -UV-Z-, wherein -UV- is defined by -$C(=O)N(R^J)$-, wherein R^J is -H or -CH_3.

6. The compound of claim 2 wherein L^1 is UV-Z-, wherein -UV-, is defined by -WO-.

7. The compound of claim 2 wherein L^1 is UV-Z-, wherein -UV-, is defined by - $WN(R^J)$-, wherein R^J is -H or -CH_3.

8. The compound of claim 1 wherein R^C is -H, -CN, -CH_3, -F or -CF_3, R^D is -$N(R^F)C(=O)XCH(R^G)$-CY, -$N(R^F)C(=O)XC(R^G)_2$-CY, or -$N(R^F)C(=O)$X-CY and L^1 is -UV-Z- wherein -UV- is defined by -WO -, -$WN(R^J)$- or -$C(=O)N(R^J)$-.

9. The compound of claim 8 wherein R^C is -H, $-CH_3$, -F or $-CF_3$; and R^D is $-N(R^F)C(=O)XCH(R^G)$-CY.

10. The compound of claim 9 wherein R^D is $-N(R^F)C(=O)XCH(R^G)$-CY, wherein -X- is $-N(R^F)$- or -O-; and wherein R^G and each R^F, independently selected, are -H or $-CH_3$.

11. The compound of claim 10 wherein R^G is $-CH_3$, in the *R* or *S* configuration, and CY is substituted or unsubstituted phenyl or substituted or unsubstituted heteroaryl.

12. The compound of claim 10 wherein R^D is $-N(R^F)C(=O)OCH(R^G)$-CY, wherein CY is substituted or unsubstituted phenyl, wherein substituted phenyl is phenyl that is substituted with one or two of independently selected R^J.

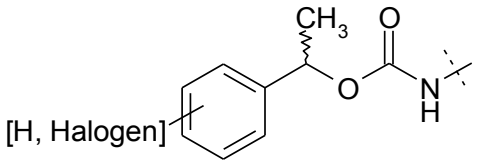
13. The compound of claim 10 wherein R^D is $-N(R^F)C(=O)OCH(CH_3)$-CY, wherein R^F is -H, and wherein CY is unsubstituted phenyl.

14. The compound of claim 10 wherein R^D is $-N(R^F)$-C(=O)$OCH(CH_3)$-CY, wherein R^F is -H, and wherein CY is substituted phenyl, wherein substituted phenyl is phenyl that is substituted with one or two of independently selected R^H, wherein R^H are halogens.

15. The compound of claim 14 wherein R^D is -NH-C(=O)$OCH(CH_3)$-CY wherein CY is substituted phenyl, wherein substituted phenyl is phenyl that is substituted with one R^J, wherein R^J is -F, -Cl or -Br.

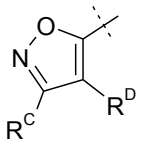
16. The compound of claim 14 wherein R^D is -NH-C(=O)$OCH(CH_3)$-CY, wherein CY is substituted phenyl, wherein substituted phenyl is phenyl that is substituted with one R^J, wherein R^J is -Cl.

17. The compound of claim 14 wherein R^D is $-NHC(=O)OCH(CH_3)$-CY having the structure of



18. The compound of claim 14 wherein R^D is -NHC(=O)OCH(CH_3)-CY wherein the methyl group in R^D is in the *R* configuration.

19. The compound of any one of claims 1-18 wherein Ring A has the structure of:



and Ring B is substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

20. The compound of claim 19 wherein R^C is -H, -CH_3 or -CF_3, and R^D is -NH-C(=O)OCH(R^G)-CY, wherein R^G is -H or -CH_3, in the *R* or *S* configuration, and -CY is substituted or unsubstituted phenyl.

21. The compound of claim 19 wherein L^1 is -UV-Z-, wherein -UV-, is -WO-, -WN(R^J)- or -C(=O)N(R^J)-.

22. The compound of claim 19 wherein L^1 is -UV-Z-, wherein -UV-, is -WN(R^J)- or -C(=O)N(R^J)-, wherein R^J is -H or -CH_3.

23. The compound of claim 22 wherein L^1 is -UV-Z-, wherein -UV- is defined by -C(=O)NH-, and wherein Z is substituted or unsubstituted C_1-C_6 alkylene.

24. The compound of claim 22 wherein L^1 is -UV-Z-, wherein -UV- is defined by -WO-, wherein W is substituted or unsubstituted C_1-C_3 alkylene, and wherein Z is substituted or unsubstituted C_1-C_6 alkylene.

25 The compound of claim 22 wherein L^1 is -UV-Z-, wherein -UV- is defined by

-W-NH-, wherein W is substituted or unsubstituted C_1-C_3 alkylene, and wherein Z is substituted or unsubstituted C_1-C_6 alkylene.

26. The compound of claim 22 wherein L^1 is -UV-Z-, wherein -UV- is defined by -WO-, -WN(R^J)- or -C(=O)N(R^J), wherein R^J is -H or -CH_3, and wherein Z is substituted or unsubstituted C_1-C_6 alkylene, wherein the alkylene is -CH(CH_2-cyclopropyl)-, -CH(CH_2-aryl) or -CH(CH_2-heteroaryl), wherein the aryl or heteroaryl is substituted or unsubstituted.

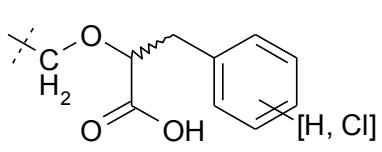
27. The compound of claim 26 wherein L^1 is -UV-Z-, wherein -UV- is defined by -C(=O)NH-, -WO- or -W-NH-, wherein -W- is -CH_2-; and R^A is -CO_2H or -CO_2R^B.

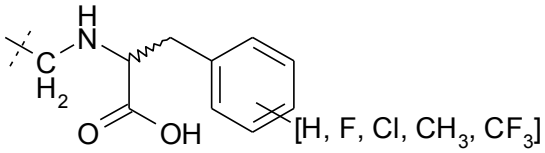
28. The compound of claim 26 wherein L^1 is -UV-Z-, wherein -UV- is defined by –WO- or –W-NH-, wherein –WO- is -CH_2O-, and –W-NH- is -CH_2-NH- or UV is defined by -C(=O)NH-; and

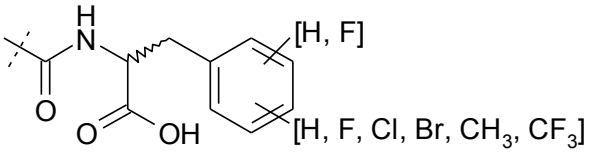
wherein Z is substituted or unsubstituted C_1-C_6 alkylene, wherein the alkylene is -CH(CH_2-cyclopropyl)-, -CH(CH_2-aryl) or -CH(CH_2-heteroaryl), wherein the aryl or heteroaryl is unsubstituted or substituted with 1, 2, or 3 independently selected substituted or unsubstituted C_1-C_4 alkyl or halogen.

29. The compound of claim 28 wherein said substituted or unsubstituted C_1-C_4 alkyl or halogen substituent or substituents of the aryl or heteroaryl of -CH(CH_2-aryl) or -CH(CH_2-heteroaryl) are selected from the group consisting of -CH_3, -CF_3, -F, -Cl and -Br.

30. The compound of claim 26, wherein L^1 is -UV-Z- and wherein R^A is -CO_2H to which Z is attached to define -L^1-R^A (i.e., -UV-Z-R^A), wherein -UV- is defined by -C(=O)NH-, -WO- or -W-NH-, wherein -W- is -CH_2-, and Z is -CH(CH_2-aryl), wherein the aryl is substituted or unsubstituted, having the structure of one of:







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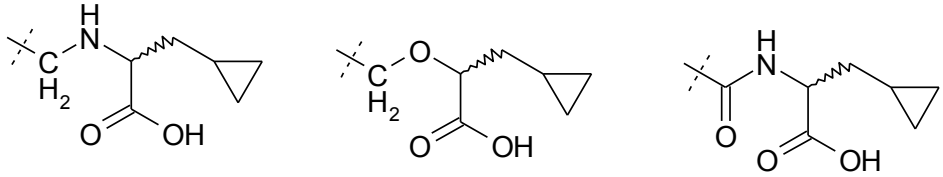
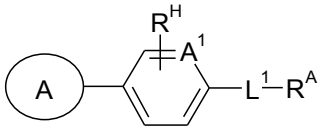
31. The compound of claim 30 wherein the -CH(CH_2-aryl) substituent of Z in -L^1-R^A is in the *R* configuration.

32. The compound of claim 26 wherein L^1 is -UV-Z- and wherein R^A is -CO_2H to which Z is attached to define -L^1-R^A so that –L^1-R^A is -UV-Z-R^A-, wherein -UV- is defined by -C(=O)NH-, -WO- or -W-NH-, wherein -W- is -CH_2 -, and Z is -CH(CH_2-cyclopropyl)-, having the structure of



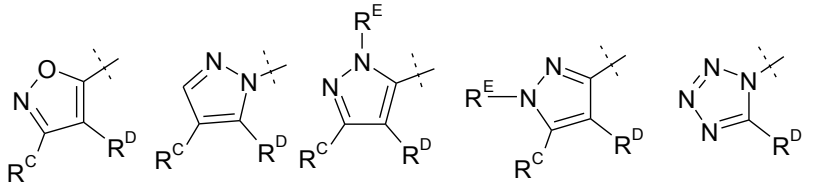
33. The compound of claim 1, wherein the compound has the structure of Formula IV



Formula IV

,

wherein Ring A is a 5-membered heteroarylene having the structure of one of:



,

wherein A^1 is =N- or =C-;

R^D is -$NR^FC(=O)OCH(R^G)$-CY.

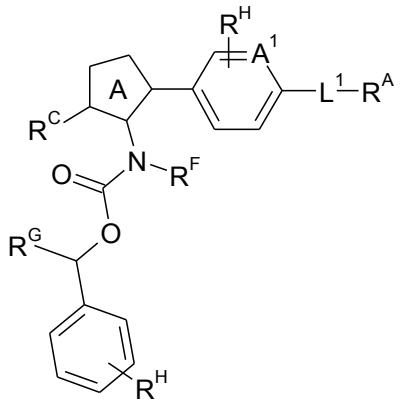
L^1 is -UV-Z-, wherein

UV is -C(=O)N(R^J)-, wherein R^J is -H or -CH_3;

R^F and R^G independently are -H or -CH_3; and

R^A is -CO_2H or -CO_2R^B.

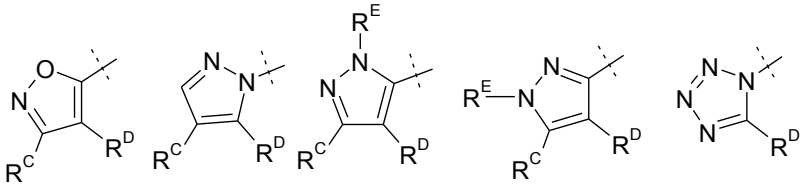
34. The compound of claim 1 wherein the compound has the structure of Formula VI



Formula VI

,

wherein Ring A is a 5-membered heteroarene having one of the structures of:



,

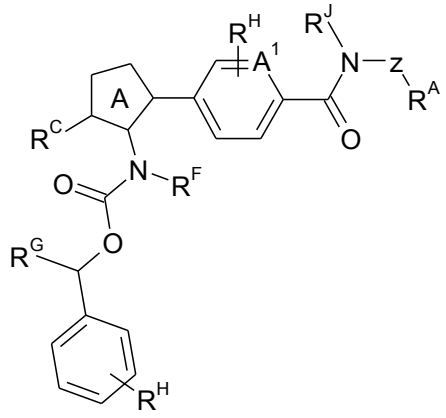
wherein R^D is the -N(R^F)C(=O)CH(R^G)-CY substituent of Formula VI wherein CY is phenyl substituted with one R^H, and R^C is -H, -CH_3, CF_3 or -F.

R^A is -CO_2H or -CO_2R^B; and

R^F and R^G independently are -H or -CH_3; and

R^H independently are -H, halogen, -CH_3 or -CF_3.

35. The compound of claim 1 wherein the compound has the structure of Formula VII

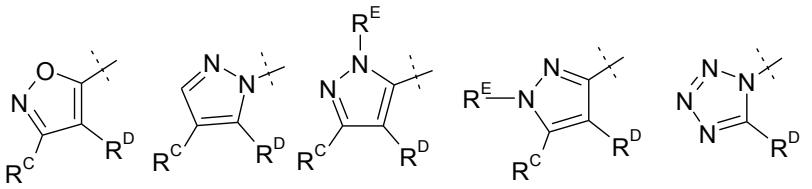


Formula VII

,

wherein A^1 is =CH- or =N-;

Ring A is a 5 membered heteroarene having the structure of one of:



,

wherein R^D is the -N(R^F)C(=O)CH(R^G)-CY substituent of Formula VII wherein CY is phenyl substituted with one R^H; and R^C is -H, -CH_3, -CF_3 or -F;

R^A is -CO_2H or -CO_2R^B;

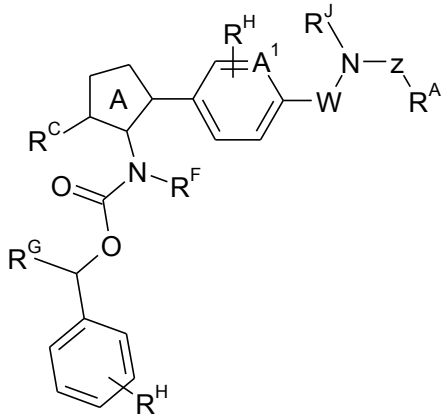
R^E and R^F independently are -H or C_1-C_4 alkyl;

R^G is -H or -CH_3;

R^H is -H, halogen, -CH_3 or -CF_3; and

Z is -C(R^L)$_2$, wherein one R^L is -H and the other R^L is -H or C_1-C_4 alkyl.

36. The compound of claim 1 wherein the compound has the structure of Formula VIII

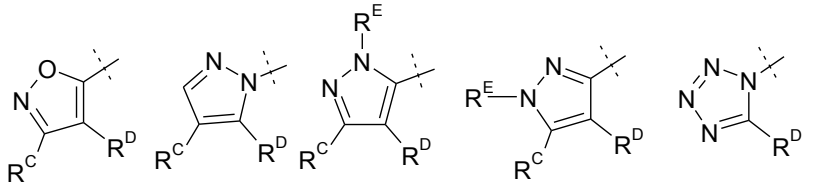


Formula VIII

,

wherein A^1 is =CH- or =N-;

wherein Ring A is a 5 membered heteroarene having the structure of one of:



,

wherein R^D is the -N(R^F)C(=O)CH(R^G)-CY substituent of Formula VIII wherein CY is phenyl substituted with one R^H;

R^A is -CO_2H or -CO_2R^B;

W is -C(R^L)$_2$- or  ;

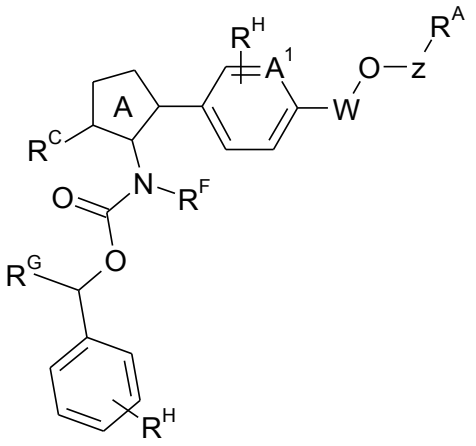
R^E and R^F independently are -H or C_1-C_4 alkyl;

R^G is -H or -CH_3;

R^H is -H, halogen, -CH_3 or -CF_3; and

Z is -C(R^L)$_2$, wherein one R^L is -H and the other R^L is -H or C_1-C_4 alkyl.

37. The compound of claim 1 wherein the compound has the structure of Formula IX

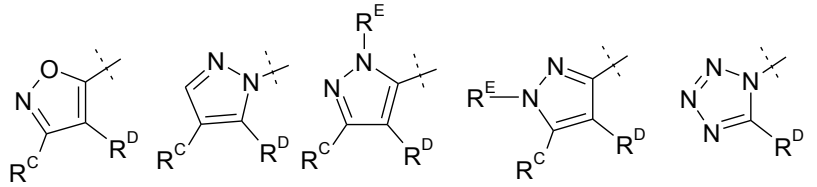


Formula IX

,

wherein A^1 is =CH- or =N-;

wherein Ring A is a 5-membered heteroarene having the structure of one of:



,

wherein R^D is the -N(R^F)C(=O)CH(R^G)-CY substituent of Formula VII wherein CY is phenyl substituted with one R^H;

R^A is -CO_2H or -CO_2R^B;

wherein W is -C(R^L)$_2$- or  ;

R^E and R^F independently are -H or C_1-C_4 alkyl;

R^G is -H or -CH_3;

R^H is -H, halogen, -CH_3 or -CF_3; and

Z is -C(R^L)$_2$, wherein one R^L is -H and the other R^L is -H or C_1-C_4 alkyl.

38 The compound of claim 1 wherein the compound is 1-(4-{4-[1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-cyclopropanecarboxylic acid, 2-(4-{4-[1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-indan-2-carboxylic acid, 2-(S)-(4-{4-[(R,S)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)phenyl acetic acid, 2-(R)-(4-{4-[(R,S)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)phenyl propanoic acid, (R)-2-{4-[3-Methyl-4-((S)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzoylamino}-3-phenyl-propionic

acid, (S)-2-{4-[3-Methyl-4-((S)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzoylamino}-3-phenyl-propionic acid, 2(R)-[[4-[3-methyl-4-((R)-1-phenylethoxycarbonylamino)isoxazol-5-yl]benzoyl]amino]-3-phenyl-propanoic acid, 2(S)-[[4-[3-methyl-4-((R)-1-phenylethoxycarbonylamino)isoxazol-5-yl]benzoyl]amino]-3-phenyl-propanoic acid, (R)-2-[[4-[2,5-dimethyl-4-((R)-1-phenylethoxycarbonylamino)pyrazol-3-yl]benzoyl]amino]-3-(4-fluorophenyl)propanoic acid, (R)-2-[[4-[1,5-dimethyl-4-((R)-1-phenylethoxycarbonylamino)pyrazol-3-yl]benzoyl]amino]-3-(4-fluorophenyl)propanoic acid, (R)-3-(4-bromophenyl)-2-[[4-[2,5-dimethyl-4-((R)-1-phenylethoxycarbonyl-amino)pyrazol-3-yl]benzoyl]amino]propanoic acid, (R)-3-(4-bromophenyl)-2-[[4-[1,5-dimethyl-4-((R)-1-phenylethoxycarbonyl-amino)pyrazol-3-yl]benzoyl]amino]propanoic acid, (R)-3-(4-chlorophenyl)-2-[[4-[2,5-dimethyl-4-((R)-1-phenylethoxycarbonyl-amino)pyrazol-3-yl]benzoyl]amino]propanoic acid, (R)-3-(4-chlorophenyl)-2-[[4-[1,5-dimethyl-4-((R)-1-phenylethoxycarbonyl-amino)pyrazol-3-yl]benzoyl]amino]propanoic acid, (R)-3-(3,4-difluorophenyl)-2-[[4-[2,5-dimethyl-4-((R)-1-phenylethoxycarbonyl-amino)pyrazol-3-yl]benzoyl]amino]propanoic acid, (R)-3-(3,4-difluorophenyl)-2-[[4-[1,5-dimethyl-4-((R)-1-phenylethoxycarbonyl-amino)pyrazol-3-yl]benzoyl]amino]propanoic acid, (R)-2-[[4-[2,5-dimethyl-4-((R)-1-phenylethoxycarbonylamino)pyrazol-3-yl]benzoyl]amino]-3-phenyl-propanoic acid, (R)-2-[[4-[1,5-dimethyl-4-((R)-1-phenylethoxycarbonylamino)pyrazol-3-yl]benzoyl]amino]-3-phenyl-propanoic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-3-phenyl-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-3-(4-fluoro-phenyl)-propionic acid, (R)-3-(4-Chloro-phenyl)-2-(4-{4-[(R)-1-(2-chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-propionic acid, (R)-3-(4-Bromo-phenyl)-2-(4-{4-[(R)-1-(2-chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-3-(2-fluoro-phenyl)-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-3-(4-trifluoromethyl-phenyl)-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-3-(4-cyano-phenyl)-propionic acid, (R)-2-(4-{5-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-4-methyl-pyrazol-1-yl}-benzoylamino)-3-phenyl-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-3-(3,4-difluoro-phenyl)-propionic acid, (R)-3-(2-Chloro-phenyl)-2-(4-{4-[(R)-1-(2-chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-3-p-tolyl-propionic acid, (R)-2-{4-

[3-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzylamino}-3-phenyl-propionic acid, (R)-2-(4-{4-[(R)-1-(2-chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-3-cyclopropyl-propionic acid, (RS)-2-{4-[3-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzyloxy}-3-phenyl-propionic acid, , , (RS)-2-{4-[3-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzyloxy}-3-phenyl-propionic acid, , (RS)-3-(4-Chloro-phenyl)-2-{4-[3-methyl-4-((R)-1-phenyl-ethoxycarbonyloxy)-isoxazol-5-yl]-benzyloxy}-propionic acid, (RS)-3-Cyclopropyl-2-{4-[3-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzyloxy}-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzylamino)-3-phenyl-propionic acid, (R)-2-(4-{4-[(R)—1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzylamino)-3-(2-fluoro-phenyl)-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzylamino)-3-(4-trifluoromethyl-phenyl)-propionic acid, (R)-3-(2-Chloro-phenyl)-2-(4-{4-[(R)-1-(2-chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzylamino)-propionic acid, (R)-3-(2-Fluoro-phenyl)-2-{4-[3-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzylamino}-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzylamino)-3-cyclopropyl-propionic acid, (R)-2-{4-[3-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzylamino}-3-(4-trifluoromethyl-phenyl)-propionic acid, (R)-3-Cyclopropyl-2-{4-[3-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzylamino}-propionic acid, (R)-3-(2-Chloro-phenyl)-2-{4-[3-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzylamino}-propionic acid, or (R)-3-(4-Chloro-phenyl)-2-{4-[3-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzylamino}-propionic acid,

39. The compound of claim 1 wherein the compound is (RS)-3-Cyclopropyl-2-{4-[3-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzyloxy}-propionic acid , 2(R)-[[4-[3-methyl-4-((R)-1-phenylethoxycarbonylamino)isoxazol-5-yl]benzoyl]amino]-3-phenyl-propanoic acid, (R)-2-{4-[3-Methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzylamino}-3-phenyl-propionic acid, (R)-2-(4-{4-[(R)-1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzylamino)-3-phenyl-propionic acid and (R)-3-Cyclopropyl-2-{4-[3-methyl-4-((R)-1-phenyl-ethoxycarbonylamino)-isoxazol-5-yl]-benzylamino}-propionic acid.

40. Use of compound of any one of claims 1-39 in the manufacture of a medicament for the treatment of a LPA-dependent disease or condition.