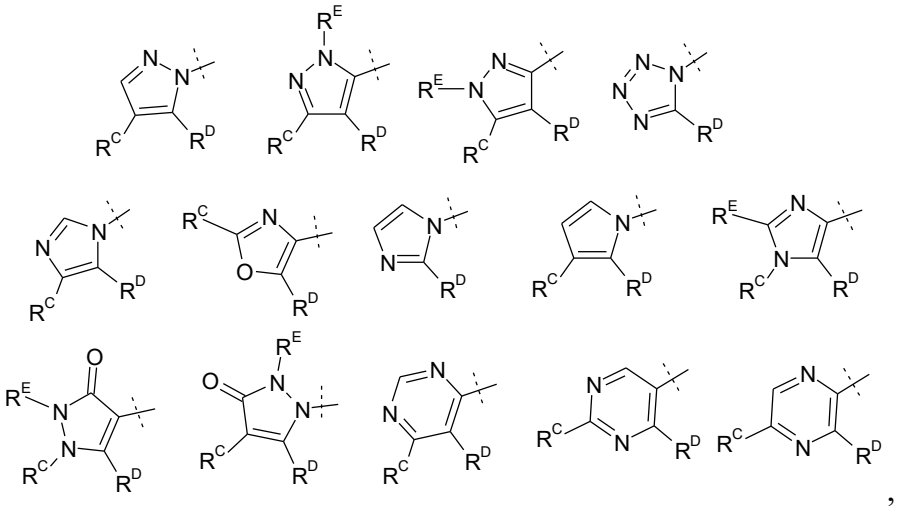
[28] Ring C is absent or optionally substituted C_3-C_{10} cycloalkylene, optionally substituted C_2-C_{10} heterocycloalkylene, optionally substituted arylene, or optionally substituted heteroarylene, where if ring C is substituted then ring C is substituted with 1, 2, or 3 independently selected R^H, wherein R^H is as previously defined;

[29] wherein when Ring B is substituted or unsubstituted arylene, Ring C is absent, L^2 is absent, L^1 is -UV-Z-, wherein -UV- is -N(R^J)-C(=O) -, wherein R^F is -H, R^D is -N(R^F)-C(=O)XCH(R^G)-CY, wherein X is -O-, R^G is -CH_3 and R^F is -H, and R^C is -H, -CH_3 or -CF_3,

[30] or when Ring B is optionally substituted arylene and Ring C is substituted or unsubstituted arylene or is substituted or unsubstituted C_3-C_{10} cycloalkylene, or Ring B is substituted or unsubstituted C_3-C_{10} cycloalkylene and Ring C is substituted or unsubstituted arylene, L^2 is absent, L^1 is C_1-C_6 alkylene,

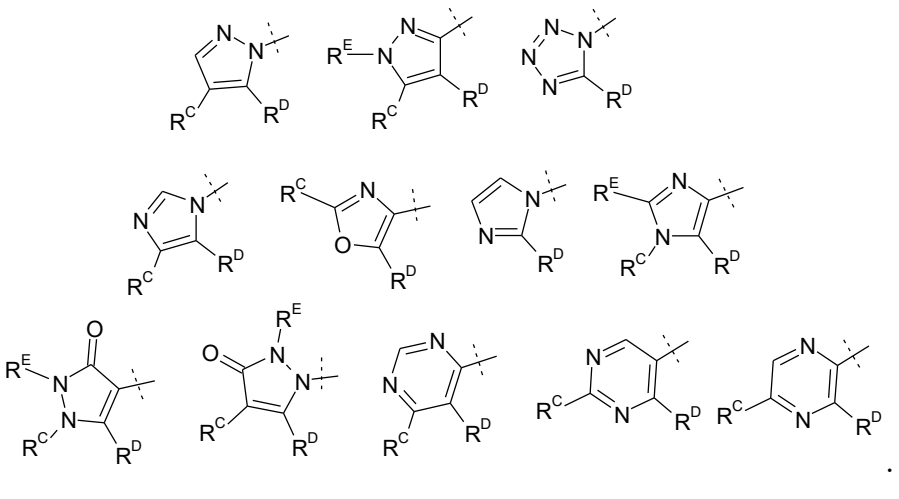
[31] and R^C is -H or -CH_3 and R^A is -CO_2H or -CO_2R^B,

[32] then Ring A has the structure of one of:



[33] ,

[34] and when Ring B is C_2-C_{10} heterocycloalkylene, Ring C is substituted or unsubstituted arylene, L^2 is absent, L^1 is C_1-C_6 alkylene, R^C is -CH_3 and R^A is -CO_2H or -CO_2R^B, then Ring A has the structure of one of:



[35] .

herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[41] "Membered ring" as used herein means any cyclic structure. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, by way of example and not limitation, those membered rings include cyclohexyl, pyridinyl, pyranyl and thiopyranyl, which are 6-membered rings and cyclopentyl, pyrrolyl, furanyl, and thienyl, which are 5-membered rings.

[42] "Moiety" as used herein means a specific segment, fragment or functional group of a molecule or compound. Chemical moieties are sometimes indicated as chemical entities that are embedded in or appended (i.e., a substituent or variable group) to a molecule or compound.

[43] "Alkyl" as used herein is a collection of carbon atoms that are covalently linked together in normal, secondary, tertiary or cyclic arrangements, i.e., in a linear, branched, cyclic arrangement or some combination thereof. An alkyl substituent to a structure is that chain of carbon atoms that is covalently attached to the structure through a sp^3 carbon of the substituent. The alkyl substituents, as used herein, contains one or more saturated moieties or groups and may additionally contain unsaturated alkyl moieties or groups, i.e., the substituent may comprise one, two, three or more independently selected double bonds or triple bonds of a combination thereof, typically one double or one triple bond if such unsaturated alkyl moieties or groups are present.

[44] Unsaturated alkyl moieties or groups include moieties or groups as described below for alkenyl, alkynyl, cycloalkyl, and aryl moieties. Saturated alkyl moieties contain saturated carbon atoms (sp^3) and no aromatic, sp^2 or sp carbon atoms. The number of carbon atoms in an alkyl moiety or group can vary and typically is 1 to about 50, e.g., about 1-30 or about 1-20, unless otherwise specified, e.g., $C_{1\text{-}8}$ alkyl or C1-C8 alkyl means an alkyl moiety containing 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms and $C_{1\text{-}6}$ alkyl or C1-C6 means an alkyl moiety containing 1, 2, 3, 4, 5 or 6 carbon atoms.

[45] When an alkyl substituent, moiety or group is specified, species may include methyl, ethyl, 1-propyl (*n*-propyl), 2-propyl (*iso*-propyl, $-CH(CH_3)_2$), 1-butyl (*n*-butyl), 2-methyl-1-propyl (*iso*-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (*sec*-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*t*-butyl, $-C(CH_3)_3$), amyl, isoamyl, *sec*-amyl and other linear, cyclic and branch chain alkyl moieties. Unless otherwise specified, alkyl groups can contain species and groups described below for cycloalkyl, alkenyl, alkynyl groups, aryl groups, arylalkyl groups, alkylaryl groups and the like.

substituted alkyl) or -O-C(=O)N(optionally substituted alkyl)$_2$- structure (i.e., carbamate functional group) where R^{PR} and optionally substituted alkyl are independently selected and R^{PR} are independently -H, a protecting group or an organic moiety as described for ester, alkyl or optionally substituted alkyl. Typically, carbamate groups as used here comprise or consist of an organic moiety containing about 1-50 carbon atoms, 1-20 carbon atoms or 1-8 carbon atoms and 0 to 10 independently selected heteroatoms (e.g., O, S, N, P, Si), typically 0-2, bonded through the -O-C(=O)-NR^{PR}- structure, e.g., organic moiety-O-C(=O)-NR^{PR}- or -O-C(=O)-NR^{PR}-organic moiety. When carbamate is used as a Markush group (i.e., a substituent) the singly bonded oxygen (O-linked) or nitrogen (N-linked) of the carbamate functional group is attached to a Markush formula with which it is associated. The linkage of the carbamate substituent is either explicitly stated (N- or O-linked) or implicit in the context to which this substituent is referred.

[85] For any substituent group or moiety described by a given range of carbon atoms, the designated range means that any individual number of carbon atoms is described. Thus, reference to, e.g., "C1-C4 optionally substituted alkyl", "C2-6 alkenyl optionally substituted alkenyl", "C3-C8 optionally substituted heterocycle" specifically means that a 1, 2, 3 or 4 carbon optionally substituted alkyl moiety as defined herein is present, or a 2, 3, 4, 5 or 6 carbon alkenyl, or a 3, 4, 5, 6, 7 or 8 carbon moiety comprising a heterocycle or optionally substituted alkenyl moiety as defined herein is present. All such designations are expressly intended to disclose all of the individual carbon atom groups and thus "C1-C4 optionally substituted alkyl" includes, e.g., 3 carbon alkyl, 4 carbon substituted alkyl and 4 carbon alkyl, including all positional isomers and the like are disclosed and can be expressly referred to or named. For esters, carbonates and carbamates defined by a given range of carbon atoms, the designated range includes the carbonyl carbon of the respective functional group. Thus a C1 ester refers to a formate ester and a C2 ester refers to an acetate ester. The organic substitutents, moieties and groups described herein, and for other any other moieties described herein, usually will exclude unstable moieties except where such unstable moieties are transient species that one can use to make a compound with sufficient chemical stability for the one or more of the uses described herein. Substituents, moieties or groups by operation of the definitions herein that results in those having a pentavalent carbon are specifically excluded.

[86] "LPA-dependent", "LPA-mediated" or like terms as used herein means a disease or condition whose etiology, progression or persistence is effected by in whole or in part by signaling through one or more lysophosphatidic acid receptor subtypes, including by way of example and not limitation lysophosphatidic acid receptor subtypes 1-6 (LPARs).

activity towards an “intent to treat” disease or condition. Typically, the “intent to treat” disease or condition is a lysophosphatidic acid receptor-mediated condition or disease. More typically the disease or condition to be treated or prevented is a lysophosphatidic acid lysophosphatidic acid type 1 receptor-mediated disease or condition. A pharmaceutically acceptable formulation that is suitable for administration to an animal does not necessarily require a biological activity for treating or preventing a disease or condition, and may be administered to the animal in order to evaluate a potential pharmacological or biological activity of a Formula I-XII compound. Those formulations must therefore be suitable for treating or preventing a disease or condition disclosed herein in an animal in need thereof or is suitable for evaluating a pharmacological or biological activity of a Formula I-XII compound. Compositions that are suitable only for use in vitro assays or which contain a vehicle, component or excipient in an amount not permitted in a drug product are specifically excluded from the definition of a pharmaceutically acceptable formulation.

[89] The pharmaceutically acceptable formulation may be comprised of, or be prepared from, one, two or more Formula I-XII compounds, typically one or two, and one or more pharmaceutically acceptable excipients. More typically, the formulations will consist essentially of or consist of a single Formula I-XII compound and one or more pharmaceutically acceptable excipients. Other formulations may be comprised of, consist essentially of, or consist of one, two or more Formula I-XII compounds and one two or more compounds in current use for treating lysophosphatidic acid lysophosphatidic acid type 1 receptor-mediated disease or condition disclosed herein and one or more pharmaceutically acceptable excipients. Typically those formulations will consist essentially of or consist of a single Formula I-XII compound, a single compound in current use for treating a lysophosphatidic acid lysophosphatidic acid type 1 receptor-mediated disease or condition and one or more pharmaceutically acceptable excipients.

[90] "Solid formulation" as used herein refers to a pharmaceutically acceptable formulation comprising at least one Formula I-XII compound and one or more pharmaceutically acceptable excipients in solid form(s) wherein the formulation is in a unit dosage form suitable for administration of a solid. The dosage units include tablets, capsules, caplets, gelcaps, suspensions and other dosage units typically associated with parenteral or enteral (oral) administration of a solid.

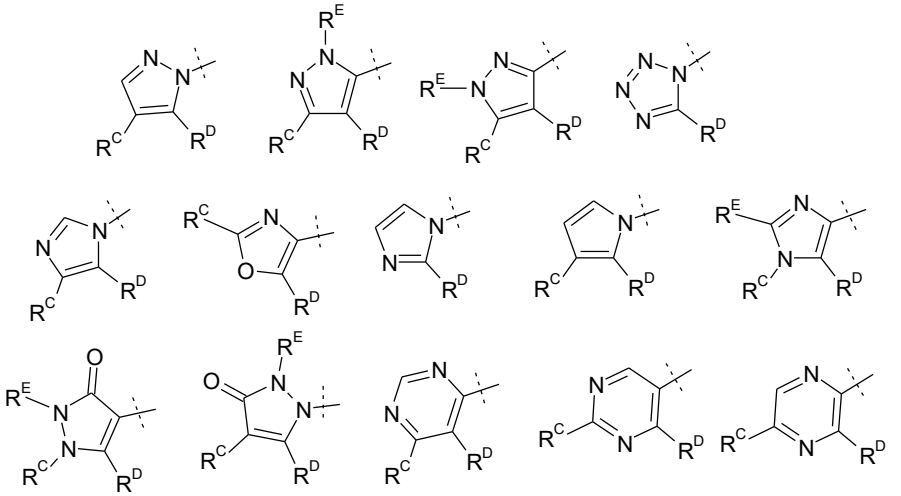
[91] "Liquid formulation" as used herein refers to a pharmaceutically acceptable formulation wherein at least one Formula I-XII compound has been admixed or contacted with one or more pharmaceutically acceptable excipients, wherein at least one of the excipients is in liquid form in proportions required for a liquid formulation, i.e.,

[117] wherein when Ring B is substituted or unsubstituted arylene, Ring C is absent, L^2 is absent, L^1 is -UV-Z, wherein -UV- is -N(R^J)-C(=O) -, wherein R^F is -H, R^D is -N(R^F)C(=O)XCH(R^G)-CY, wherein X is -O-, R^G is $-CH_3$ and R^F is -H, and R^C is -H, $-CH_3$ or $-CF_3$,

[118] or when Ring B is substituted or unsubstituted arylene and Ring C is substituted or unsubstituted arylene or is substituted or unsubstituted C_3-C_{10} cycloalkylene, or Ring B is substituted or unsubstituted C_3-C_{10} cycloalkylene and Ring C is substituted or unsubstituted arylene, L^2 is absent, L^1 is C_1-C_6 alkylene,

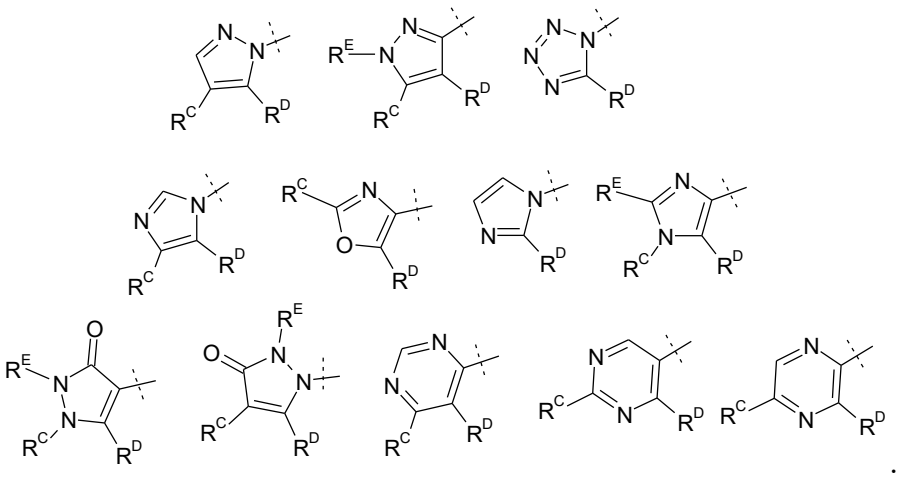
[119] and R^C is -H or $-CH_3$ and R^A is $-CO_2H$ or $-CO_2R^B$,

[120] then Ring A has the structure of one of:

[121] ,

[122] and when Ring B is C_2-C_{10} heterocycloalkylene, Ring C is substituted or unsubstituted arylene, L^2 is absent, L^1 is C_1-C_6 alkylene, R^C is $-CH_3$ and R^A is $-CO_2H$ or $-CO_2R^B$,

[123] then Ring A has the structure of one of:

[124] .

[125] In some embodiments 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 and R^D is -N(R^F)-C(=O)XCH(R^G)-CY, -N(R^F)-

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

[184] wherein each R^H is independently selected -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, or C_1-C_4 heteroalkyl, and

[185] wherein R^J is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 fluoroalkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C_1-C_4 alkylene-(optionally substituted C_3-C_6 cycloalkyl), -C_1-C_4 alkylene-(optionally substituted heterocycloalkyl), -C_1-C_4 alkylene-(substituted or unsubstituted aryl), or -C_1-C_4 alkylene-(optionally substituted heteroaryl), and

[186] each R^L is independently -H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 fluoroalkyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C_1-C_4 alkylene-(optionally substituted C_3-C_6 cycloalkyl), -C_1-C_4 alkylene-(optionally substituted heterocycloalkyl), -C_1-C_4 alkylene-(optionally substituted aryl), or -C_1-C_4 alkylene-(optionally substituted heteroaryl), or

[187] 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 an optionally substituted heterocycle,

[188] or when W 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;

[189] wherein when Ring B is substituted or unsubstituted arylene, Ring C is absent, L^1 is -UV-Z, wherein -UV- is -$N(R^J)$-C(=O) -, wherein R^J is -H, R^D is -$N(R^F)C(=O)XCH(R^G)$-CY, wherein X is -O-, R^G is -CH_3 and R^F is -H, and R^C is -H, -CH_3 or -CF_3, or when Ring B is substituted or unsubstituted arylene and Ring C is substituted or unsubstituted arylene or is substituted or unsubstituted C_3-C_{10} cycloalkylene, or Ring B is substituted or unsubstituted C_3-C_{10} cycloalkylene and Ring C is substituted or unsubstituted arylene and L^1 is C_1-C_6 alkylene,

[190] and R^C is -H or -CH_3 and R^A is -CO_2H or -CO_2R^B,

or unsubstituted carbocycle or a substituted or unsubstituted heterocycle and the other R^G, if present, is as defined for R^E;,

[212] A^1, A^2 and A^3 are independently =NH-, -N=, =CH- or -CH=;,

[213] Ring C is absent or substituted or unsubstituted C_3-C_{10} cycloalkylene, substituted or unsubstituted C_2-C_{10} heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene, wherein if ring C is substituted then ring C is substituted with 1, 2, or 3 independently selected R^H;

[214] 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 R^H;

[215] wherein each R^H is independently -H, halogen, -CN, -NO_2, -OH, -OR^J, -SR^J, -$S(=O)R^J$, -$S(=O)_2R^J$, -$N(R^J)S(=O)_2R^J$, -$S(=O)_2N(R^L)_2$, -$C(=O)R^J$, -$OC(=O)R^J$, -$C(=O)OR^J$, -$OC(=O)OR^J$, -$N(R^L)_2$, -$C(=O)N(R^L)_2$, -$OC(=O)N(R^L)_2$, $N(R^J)C(=O)N(R^L)_2$, -$N(R^J)C(=O)R^J$, -$NR^JC(=O)OR^J$, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, C_1-C_4 alkoxy, or C_1-C_4 heteroalkyl;

[216] 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);

[217] 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 cycloalkyl, a 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

[218] 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

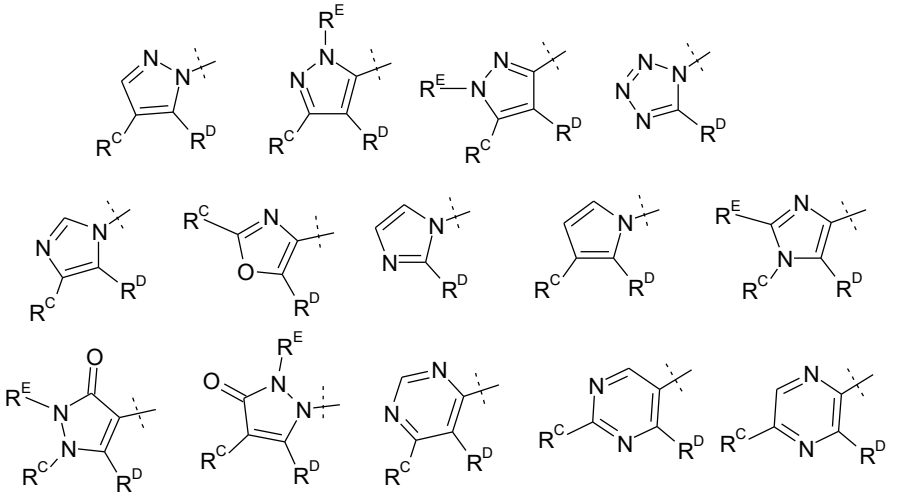
[219] when W or Z is -$C(R^L)_2$-, each R^L is independently -H or C_1-C_6 alkyl, or the R^L groups independently are C_1-C_6 alkyl which are taken together with the carbon atom to which they are attached to define a carbocycle;

[220] wherein when A^1, A^2 and A^3 are =CH- or -CH=, Ring C is absent, L^1 is -UV-Z, wherein -UV- is $-N(R^J)C(=O)-$, wherein R^J is -H, R^D is $-N(R^F)C(=O)XCH(R^G)-CY$, wherein X is -O-, R^G is $-CH_3$ and R^F is -H, and R^C is -H, $-CH_3$ or $-CF_3$,

[221] or when Ring C is substituted or unsubstituted arylene or substituted or unsubstituted C_3-C_{10} cycloalkylene

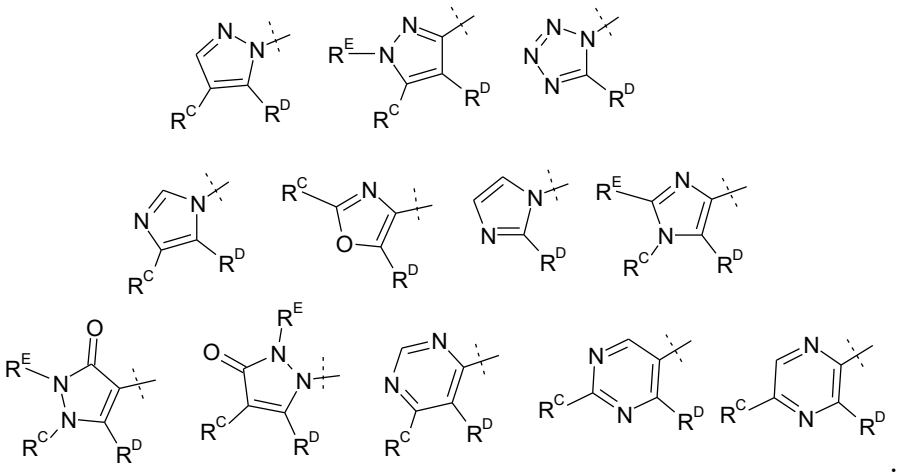
[222] and R^C is -H or $-CH_3$ and R^A is $-CO_2H$ or $-CO_2R^B$,

[223] then Ring A has the structure of one of:

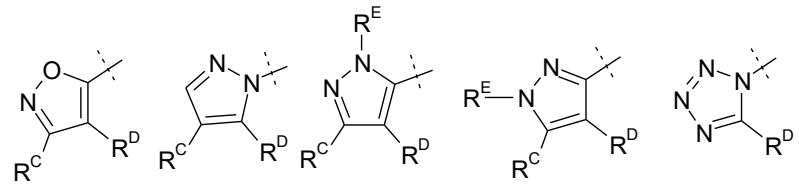
[224] ,

[225] and when Ring C is substituted or unsubstituted arylene, L^1 is C_1-C_6 alkylene, R^C is $-CH_3$ and R^A is $-CO_2H$ or $-CO_2R^B$,

[226] then Ring A has the structure of one of:

[227] .

[228] In preferred embodiments Ring A has the structure of one of:

[229] .

[249] or when W 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,

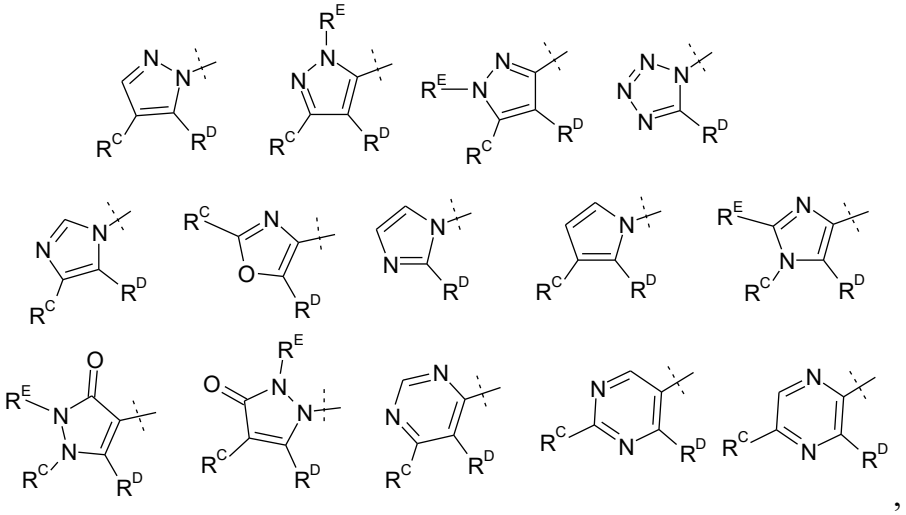
[250] or when R^H is -S(=O)$_2$N(R^L)$_2$, -N(R^L)$_2$, -C(=O)N(R^L)$_2$, -OC(=O)N(R^L)$_2$ or -N(R^J)C(=O)N(R^L)$_2$, each R^L is independently is -H or C_1-C_6 alkyl, or the R^L groups independently are C_1-C_6 alkyl which are taken together with the N atom to which they are attached to define a substituted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

[251] or when W is -C(R^L)$_2$-, each R^L is independently -H, 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;

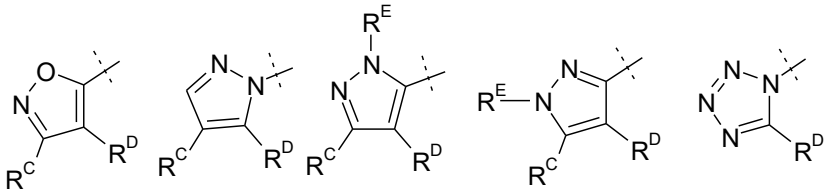
[252] wherein A^1 is =CH-, L^1 is -UV-Z, wherein -UV- is -N(R^J)-C(=O) -, wherein R^J is -H, R^D is -N(R^F)-C(=O)XCH(R^G)-CY, wherein X is -O-, R^G is -CH_3 and R^F is -H, and R^C is -H, -CH_3 or -CF_3,

[253] and R^C is -H or -CH_3 and R^A is -CO_2H or CO_2R^B,

[254] then Ring A has the structure of one of:

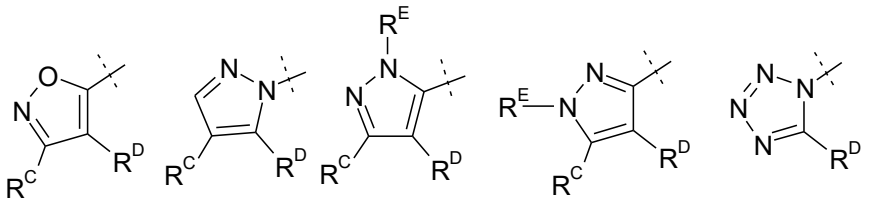
[255] ,

[256] In preferred embodiments Ring A has the structure of one of:

[257] 

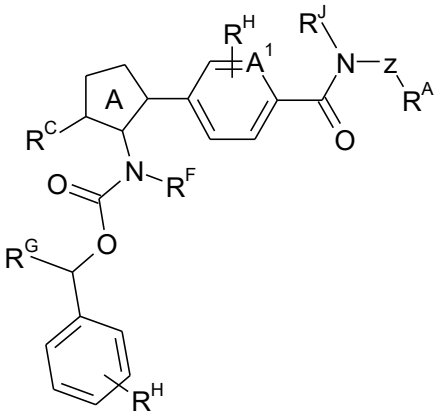
[258] Particularly preferred Formula IV compounds have L^1 defined as -UV-Z-, wherein -UV -is defined by -WO-, -WN(R^J)-, or -C(=O)N(R^J)-, wherein W is -CH_2-, Z is substituted or unsubstituted C_1-C_6 alkylene, R^A is -CO_2H, and R^D is -N(R^F)C(=O)OCH(R^G)-CY.

[259] 17. A compound of Formula V having the structure:

[300]  .

[301] Particularly preferred Formula VI compounds have L^1 as -UV-Z- wherein -UV- is -C(=O)NH-, $-CH_2O-$ or $-CH_2NH-$, Z is substituted -CH-, and R^A is $-CO_2H$.

[302] 19. A compound of Formula VII having the structure of:



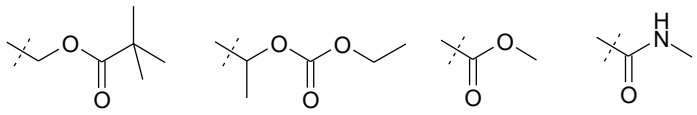
Formula VII

,

[303] or a pharmaceutically acceptable salt or prodrug thereof,

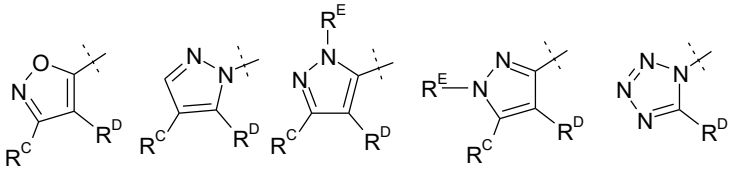
[304] wherein R^A is $-CO_2H$, $-CO_2R^B$, -CN, tetrazolyl, $-C(=O)NH_2$, $-C(=O)NHR^B$, $-C(=O)NHSO_2R^B$ or $-C(=O)NHCH_2CH_2SO_3H$ or a carboxylic acid isostere;

[305] R^B is optionally substituted C_1-C_4 alkyl or has the structure of one of:

[306] 

[307] A^1 is independently =N- or =CH-;

[308] Ring A has the structure of one of:

[309] 

[310] 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;

[311] 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;

[312] R^E, R^F and R^G independently are -H or C_1-C_4 alkyl;

[313] Z is $-C(R^L)_2-$;

[314] R^H is independently -H, halogen, -CN, $-NO_2$, -OH,$-OR^J$, $-SR^J$, $-S(=O)R^J$, $-S(=O)_2R^J$, $-N(R^J)S(=O)_2R^J$, $-S(=O)_2N(R^L)_2$, $-C(=O)R^J$, $-OC(=O)R^J$, $-CO_2R^J$, $-OCO_2R^J$, -

[422] 26. A compound of Formula I-XII or a pharmaceutically acceptable salt or prodrug thereof wherein the binding affinity of the compound to lysophosphatidic acid receptor-1 (LPA1R) is between about 10 μM and 1 pM or less

[423] 27. The compound of embodiment 19 wherein the compound is a selective lysophosphatidic acid receptor-1 (LPA1R) compound.

[424] 28. A compound of Formula I-XII or a pharmaceutically acceptable salt, or prodrug thereof wherein the compound is a selective lysophosphatidic acid receptor-1 (LPA1R) compound.

[425] 29. The compound of embodiment 20, 21 or 22 wherein the compound is a selective lysophosphatidic acid receptor-1 (LPA1R) compound wherein the binding affinity (i.e., K_D) of the LPA1R compound is between about 1 μM and 1 pM or less. In preferred embodiments the K_D is 100 nM or less, more preferably 10 nM or less.

[426] 30. A compound of Table 1.

[427] 31. The compound of embodiment 30 wherein the compound is 1-(4-{4-[1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-cyclopropane-carboxylic 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)-ethoxy-carbonylamino]-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, 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)-phenylethoxycarbonyl-amino)isoxazol-5-yl]benzoyl]amino]-3-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, (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)-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)-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-

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;

[561] Ring B is substituted or unsubstituted C_3-C_{10} cycloalkylene, substituted or unsubstituted C_2-C_{10} heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene, where if ring B is substituted then ring B is substituted with 1, 2, or 3 independently selected R^H, wherein R^H is as previously defined;

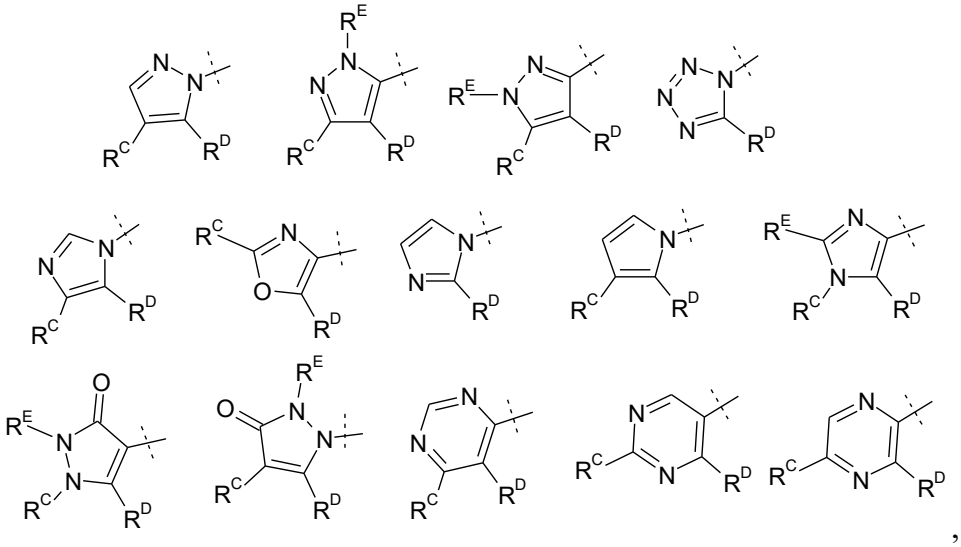
[562] Ring C is absent or substituted or unsubstituted C_3-C_{10} cycloalkylene, substituted or unsubstituted C_2-C_{10} heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene, where if ring C is substituted then ring C is substituted with 1, 2, or 3 independently selected R^H, wherein R^H is as previously defined,

[563] wherein when Ring B is substituted or unsubstituted arylene, Ring C is absent, L^2 is absent, L^1 is -UV-Z-, wherein -UV- is -N(R^J)-C(=O) -, wherein R^J is -H, R^D is -N(R^F)-C(=O)XCH(R^G)-CY, wherein X is -O-, R^G is $-CH_3$ and R^F is -H, and R^C is -H, $-CH_3$ or $-CF_3$,

[564] or when Ring B is substituted or unsubstituted arylene and Ring C is substituted or unsubstituted arylene or is substituted or unsubstituted C_3-C_{10} cycloalkylene, or Ring B is substituted or unsubstituted C_3-C_{10} cycloalkylene and Ring C is substituted or unsubstituted arylene, L^2 is absent, L^1 is C_1-C_6 alkylene,

[565] and R^C is -H or $-CH_3$ and R^A is $-CO_2H$ or CO_2R^B,

[566] then Ring A has the structure of one of::

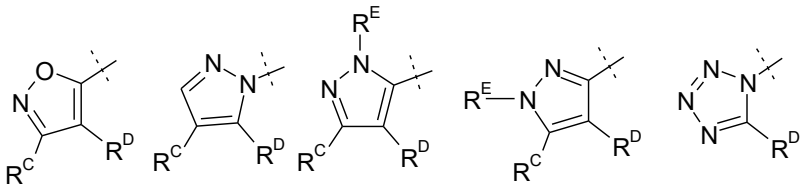
[567] ,

[568] and when Ring B is C_2-C_{10} heterocycloalkylene, Ring C is substituted or unsubstituted arylene, L^2 is absent, L^1 is C_1-C_6 alkylene, R^C is $-CH_3$ and R^A is $-CO_2H$ or CO_2R^B, then Ring A has the structure of one of:

[586] 13A. The compound of embodiment 2A wherein L^1 is absent or a substituted or unsubstituted substituted C_1-C_4 alkylene or a substituted or unsubstituted C_3 cycloalkylene (i.e., cyclopropyl-di-yl).

[587] 14A. The compound of embodiment 2 wherein L^1 is $-CH_2-$,  or $-C(CH_3)_2-$.

[588] 15A. The compound of embodiment 2 wherein Ring A has the structure of one of:

[589] ,

[590] wherein R^C is -H, -CN, $-CH_3$, 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 $-C(=O)N(R^J)$-.

[591] 16A. The compound of embodiment 15A wherein R^C is -H, $-CH_3$ or $-CF_3$ and R^D is $-N(R^F)C(=O)XCH(R^G)$-CY.

[592] 17A. The compound of embodiment 15A 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 $-CH_3$.

[593] 18A. The compound of embodiment 17A wherein R^G is $-CH_3$, in the *R* or *S* configuration, and CY is substituted or unsubstituted phenyl or substituted or unsubstituted heteroaryl.

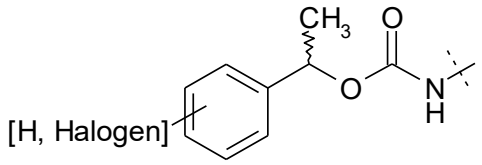
[594] 19A. The compound of embodiment 17A wherein R^D is $-N(R^F)C(=O)OCH(R^G)$-CY, wherein CY is unsubstituted or substituted phenyl, wherein substituted phenyl is phenyl that is substituted with one or two of independently selected R^J.

[595] 20A. The compound of embodiment 17A, wherein R^D is $-N(R^F)C(=O)OCH(CH_3)$-CY, wherein R^F is -H, and wherein CY is unsubstituted phenyl.

[596] 21A. The compound of embodiment 17A, 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^J, wherein R^J are halogens.

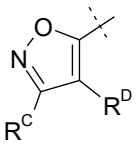
[597] 22A. The compound of embodiment 21A, wherein R^D is $-NH$-$C(=O)OCH(CH_3)$-CY wherein CY is substituted phenyl, wherein substituted phenyl is phenyl that is substituted with one R^H, wherein R^J is -F, -Cl or -Br.

[598] 23A. The compound of embodiment 21A, 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^H, wherein R^J is -Cl.

[599] 24A. The compound of embodiment 19A, wherein R^D is -NH-C(=O)OCH(CH_3)-CY having the structure of 

.

[600] 25A. The compound of claim 19A wherein R^D is -NH-C(=O)OCH(CH_3)-CY wherein the methyl group in R^D is in the *R* configuration.

[601] 26A. The compound of any one of embodiments 5-25 wherein Ring A has the structure of: 

, wherein L^2 is absent and Ring B is substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene,

[602] provided that when Ring C is not absent and L^1 is C_1-C_6 alkylene, or Ring C is absent and L^1 is -UV-Z, wherein -UV- is -N(R^J)-C(=O) -, and R^D has the structure of -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 R^A is -CO_2H, then R^C is other than -H, -CH_3 and -CF_3.

[603] 27A. The compound of embodiment 26A 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.

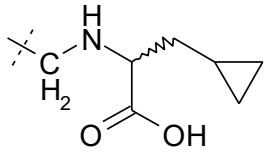
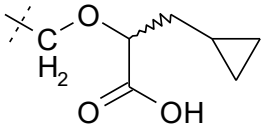
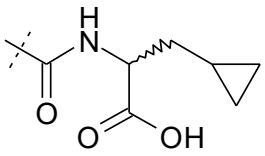
[604] 28A. The compound of embodiment 26A wherein L^2 and Ring C are absent, Ring B is substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene, and L^1 is -UV-Z-, wherein -UV-, is defined by -WO-, -WN(R^J)- or -C(=O)N(R^J)-.

[605] 29A. The compound of embodiment 26A wherein L^2 and Ring C are absent, Ring B is substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene, and L^1 is -UV-Z-, wherein -UV-, is defined by -WN(R^J)- or -C(=O)N(R^J)-, wherein R^J is -H or -CH_3.

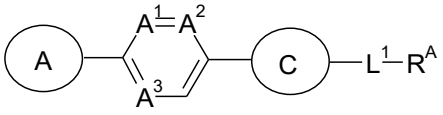
[606] 30A. The compound of embodiment 29A wherein L^1 is -UV-Z-, wherein -UV- is defined by -C(=O)NH-, and wherein Z is substituted or unsubstituted C_1-C_6 alkylene.

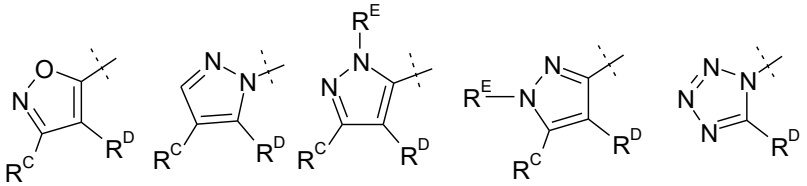
[607] 31A. The compound of embodiment 29A wherein L^1 is -UV-Z-, wherein -UV- is defined by -WO-, wherein W is substituted or unsubstituted C_1-C_3 alkylene, and wherein Z is substituted or unsubstituted C_1-C_6 alkylene.

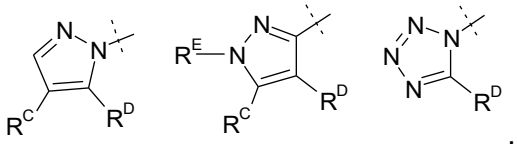
by -C(=O)NH-, -WO- or -W-NH-, wherein -W- is -CH_2 -, and Z is -CH(CH_2-cyclopropyl)-, having the structure of

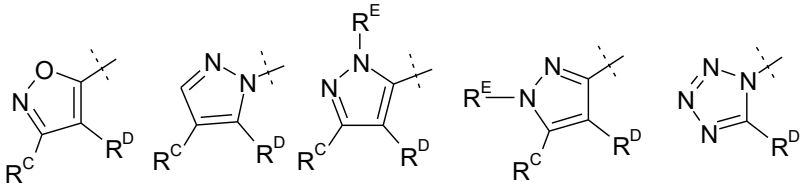




[618] 41A. The compound of embodiment 1A, 2A, 3A, or 4A, wherein the compound has the structure of Formula V

[619]  Formula III , wherein A^1, A^2 and A^3 are independently -N=, =N-, =CH- or -CH=.

[620] 42A. The compound of embodiment 41A wherein Ring A wherein Ring A has the structure of one of: , wherein when L^1 is C_1-C_6 alkylene, R^D is -N(R^F)-C(=O)XCH(R^G)-CY, -N(R^F)-C(=O)XC(R^G)$_2$-CY, wherein R^F is -H, R^G is -H or -CH_3; R^A is -CO_2H or CO_2R^B, and R^C is -H or -CH_3, then Ring A has the structure of one of:

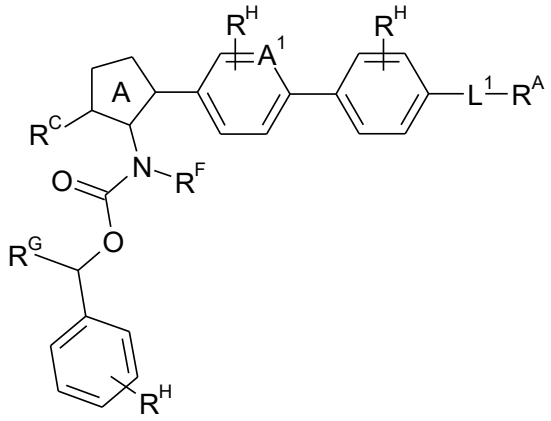

.

[621] 43A. The compound of embodiment 41A, wherein Ring A wherein Ring A has the structure of one of: ,

[622] wherein Ring C is a substituted or unsubstituted arylene or heteroarylene, L^1 is C_1-C_6 alkylene, R^A is -CO_2H or CO_2R^B, R^D is -N(R^F)-C(=O)XCH(R^G)-CY, -N(R^F)-C(=O)XC(R^G)$_2$-CY, wherein R^F is -H, R^G is -CH_3 and CY is substituted phenyl and R^C is - is -CN, -F, -Cl, -Br, -I, -OC_1-C_4 alkyl, -C_2-C_4 alkyl, -C_3-C_6 cycloalkyl, or -C_2-C_4 fluoroalkyl.

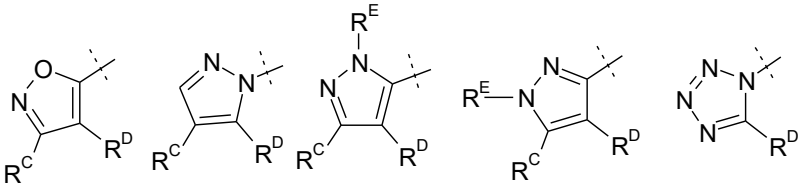
[623] 44A. The compound of embodiment 41A, wherein Ring A has the structure of one of:

[634] 50A. The compound of embodiment 2A wherein the compound has the structure



Formula XII

of Formula XII ,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 independently are -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.

[635] 51A The compound of embodiment 2A wherein the compound is selected from Table 1.

[636] 52A. The compound of embodiment 51A 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, 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-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-[2,5-dimethyl-4-((R)-1-

	piperidyl)cyclopropyl]acetic acid

EXAMPLES

[640] HPLC Methods

[641] HPLC traces for examples synthesized were recorded using a HPLC consisting of Agilent HPLC pumps, degasser and UV detector, equipped with an Agilent 1100 series auto-sampler. A MS detector (APCI) PE Sciex API 150 EX was incorporated for purposes of recording mass spectral data. HPLC/mass traces were obtained using one of three chromatographic methods:

[642] **Method 1:** Column Zorbax C18, size 4.6 mm X 7.5 cm; Solvent A: 0.05 % TFA in water, Solvent B: 0.05 % TFA in acetonitrile; Flow rate – 0.7 mL/min; Gradient: 5 % B to 100 % B in 9 min, hold at 100 % B for 4 min and 100 % B to 5 % B in 0.5 min; UV detector – channel 1 = 220 nm, channel 2 = 254 nm.

[643] **Method 2:** Column Zorbax C18, size 4.6 mm X 7.5 cm;
Solvent A: 0.05 % TFA in water, Solvent B: 0.05 % TFA in acetonitrile;
Flow rate – 0.7 mL/min; Gradient: 5 % B to 100 % B in 5 min, hold at 100 % B for 2 min and 100 % B to 5 % B in 0.5 min; UV detector – channel 1 = 220 nm, channel 2 = 254 nm.

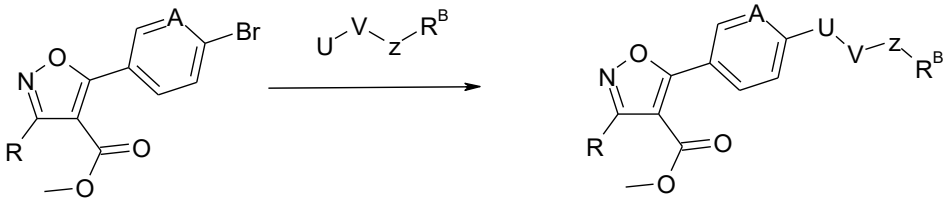
[644] **Method 3**: Column SunFire™ (Waters) C18, size 2.1 mm X 50 mm;
Solvent A: 0.05 % TFA in water, Solvent B: 0.05 % TFA in acetonitrile;
Flow rate – 0.8 mL/min; Gradient: 10 % B to 90 % B in 2.4 min, hold at 90 % B for 1.25 min and 90 % B to 10 % B in 0.25 min, hold at 10 % B for 1.5 min.; UV detector – channel 1 = 220 nm, channel 2 = 254 nm.

[645] **Example 1**: 1-(4-{4-[1-(2-Chloro-phenyl)-ethoxycarbonylamino]-3-methyl-isoxazol-5-yl}-benzoylamino)-cyclopropanecarboxylic acid

[646] **Step 1:** 2-(4-carboxymethyl-benzoyl)-3-oxo-butyric acid t-butyl ester
t-Butyl acetoacetate (15.1mL, 89.0 mmol) was added to a suspension of magnesium chloride (8.48g, 89.0 mmol) in dichloromethane (88mL) that had been cooled to 0°C. To the mixture was added pyridine (13.8mL, 171mmol) and stirring continued for an additional 15 minutes. 4-(Chlorocarbonyl)benzoic acid methyl ester (17.0g, 85.6 mmol) in dichloromethane (88mL) was then added dropwise to the reaction. This mixture was stirred at 0°C for 90minutes and then at room temperature for 90 minutes. At this time the mixture was treated with 0.2M hydrochloric acid solution (10mL). The organic layer was diluted with dichloromethane (70mL), washed with 0,2M hydrochloric acid solution (30mL), separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. A yellow oil was obtained that was used directly in the next step (17.1g, 68%).

[937] Alternatively the bromides (4) may be directly coupled to alcohols or amines (UV-Z-R^B) whereby U is -OH or –NH2 by thermal or metal catalyzed halide displacement as in scheme 4. All key intermediates (10-12) may be further modified to produce final products as described in scheme 1 using acid hydrolysis, Curtius rearrangement followed by acid deprotection

Scheme 4



4 12

[938]

[939] Example 57. Receptor Binding Assays

[940] Binding affinity of compounds of Formula I-XII were determined based on their ability to displace tritiated lysophosphatidic acid ([^{3}H]-LPA) from CHO cells expressing LPA1R in a protocol similar to that described in reference 17. In a 96 well format, CHO cells expressing human LPA1R [Cerep] were treated with [^{3}H]-LPA (2nM). Test compounds were added in increasing concentration to each well and incubated at room temperature for 90 minutes. At this time the plates were washed and the wells counted for radioactivity. Results were compared to a control in which cells were treated with [^{3}H]-LPA in the presence of 10μM unlabeled LPA. The specific ligand binding to the receptors was defined as the difference between the total binding and the nonspecific binding determined in the presence of an excess of unlabelled ligand. The results were expressed as a percent of control specific binding ((measured specific binding/control specific binding) x 100) and as a percent inhibition of control specific binding (100-((measured specific binding/control specific binding) x 100)) obtained in the presence of the test compounds. The IC_{50} value (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficient (nH) were determined by non-linear regression analysis of the competition curve generated with mean replicate values using Hill equation curve fitting (Y = D + [(A – D)/(1 + (C/C50)nH)], where Y = specific binding, D = minimum specific binding, A = maximum specific binding, C = compound concentration, C50 = IC50, and nH = slope factor). This analysis was performed using a software developed at Cerep (Hill software) and validated by comparison with data generated by the commercial software SigmaPlot® 4.0 for Windows® (© 1997 by SPSS Inc.). The inhibition constant (Ki) was calculated using the Cheng Prusoff equation (Ki = IC50/(1+(L/KD)), where L = concentration of radioligand in the assay, and KD = affinity of the radioligand for the receptor). A scatchard plot was used to determine the Kd.

[941] Example 58. Calcium Flux Assay

0.3 μM and less than 1 μM; C = greater than 1 μM and less than 50 μM; D = greater than 50 μM

CITATIONS

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[3] 3) Takagi M., Nakamura T., Matsuda I., Kiguchi T., Ogawa N., Ozeki H. US2009/36450 A1, 2009

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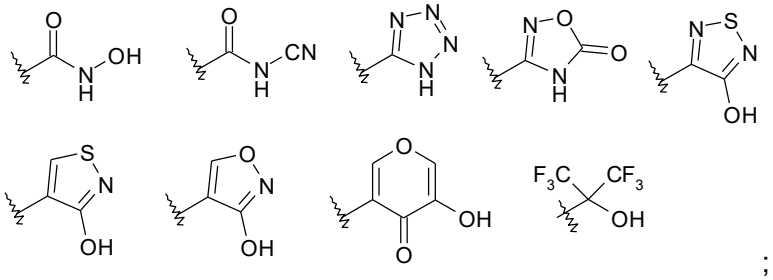
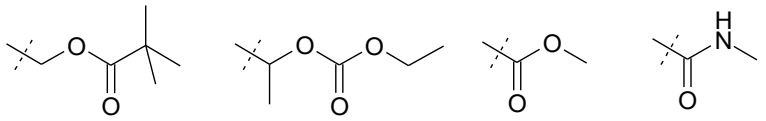
L^2 is absent;

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 -Hor $-C_1$-C_4 alkyl, or has the structure of one of:



;

and when -UV- is defined by $-WN(R^J)-$, or $-C(=O)N(R^J)-$, R^B further includes $-C_1$-C_4 alkyl,

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, wherein X is -O-, -NH- or $-CH_2-$, or X is absent;

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,

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 that includes pruritus, cancer, psoriasis, nephropathy, pneumonia, inflammatory bowel disease, age-related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy (PVR), cicatricial pemphigoid, glaucoma filtration surgery scarring, uveitis, acute hepatitis, chronic hepatitis, liver fibrosis, liver cirrhosis, cholestatic pruritus, portal hypertension, regenerative failure, nonalcoholic steatohepatitis (NASH), liver hypofunction, hepatic blood flow disorder, chronic kidney disease, end stage renal disease, uremic pruritus, scleroderma, skin scarring and atopic dermatitis.

41. Use of a compound of any one of claims 1-39 in the manufacture of a medicament for the treatment of a LPA-dependent disease or condition that is diabetic nephropathy or nonalcoholic steatohepatitis (NASH).