# MAGL INHIBITORS

## CROSS-REFERENCE

**[0001]** This application claims benefit of U.S. Provisional Application No. 62/423,099, filed on November 16, 2016, which is herein incorporated by reference in its entirety.

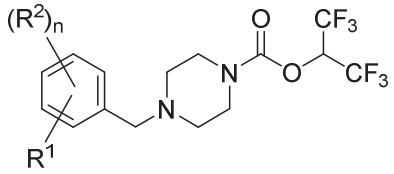
## BACKGROUND

**[0002]** Monoacylglycerol lipase (MAGL) is an enzyme responsible for hydrolyzing endocannabinoids such as 2-AG (2-arachidonoylglycerol), an arachidonate based lipid, in the nervous system.

## BRIEF SUMMARY

**[0003]** This disclosure provides, for example, compounds and compositions which are modulators of MAGL, and their use as medicinal agents, processes for their preparation, and pharmaceutical compositions that include disclosed compounds as at least one active ingredient. The disclosure also provides for the use of disclosed compounds as medicaments and/or in the manufacture of medicaments for the inhibition of MAGL activity in warm-blooded animals such as humans.

**[0003a]** In one aspect, provided herein is a compound having the structure of Formula (I):



Formula (I);

wherein:

$R^1$ is $-R^{14}$, $-OR^3$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)(R^5)$, $-NH(R^{4'})$, or $-C\equiv C-(CR^6R^7)-R^8$;

each $R^2$ is independently selected from $C_{1-6}$alkyl, halogen, -CN, $C_{1-6}$haloalkyl, $-C_{1-6}$alkyl(heterocycloalkyl), $-OR^{17}$, and $-C(O)NR^{18}R^{19}$;

$R^3$ is $-(CR^6R^7)_m-R^8$, $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$, or $-(CR^6R^7)_t-C_{3-6}$cycloalkyl-$R^8$;

$R^4$ is $-(CR^6R^7)_m-R^{8'}$, $-(CR^6R^7)_v-C(O)OH$, or $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$; $R^{4'}$ is $-(CR^6R^7)_m-R^{8'}$, $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$, $-C_{4-6}$alkyl-C(O)OH, $-C_{3-6}$cycloalkyl-C(O)OH, or $-C_{1-6}$alkyl-$C_{3-6}$cycloalkyl-C(O)OH;

Y is -O- or $-N(R^{22})-$;

$R^5$ is $C_{1-6}$alkyl or $-CH_2$-phenyl optionally substituted with one, two, or three groups independently selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$haloalkyl, and $C_{1-6}$alkoxy;

each $R^6$ and $R^7$ is each independently selected from H, F, and $C_{1-6}$alkyl; or $R^6$ and $R^7$, together with the carbon to which they are attached, form a $C_{3-6}$cycloalkyl ring;

$R^8$ is -C(O)$OR^9$, -C(O)$R^{10}$, or -C(O)O-($CR^{12}R^{13}$)-OC(O)$R^{11}$;

$R^{8'}$ is -C(O)$OR^{9'}$, -C(O)$R^{10'}$, or -C(O)O-($CR^{12}R^{13}$)-OC(O)$R^{11}$;

$R^9$ is H or $C_{1-6}$alkyl;

$R^{9'}$ is $C_{1-6}$alkyl;

$R^{10}$ is $C_{1-6}$alkyl or -$NHSO_2R^{21}$;

$R^{10'}$ is $C_{2-6}$alkyl or -$NHSO_2R^{21}$;

$R^{11}$ is $C_{1-6}$alkyl or $C_{1-6}$alkoxy;

$R^{12}$ and $R^{13}$ is each independently H or $C_{1-6}$alkyl;

$R^{14}$ is -$(CR^{15}R^{16})_m$-$R^8$ or -$(CR^6R^7)_p$-Y-$(CR^6R^7)_q$-$R^8$;

each $R^{15}$ and $R^{16}$ is each independently selected from H, F, and $C_{1-6}$alkyl;

each $R^{17}$ is independently selected from H, $C_{1-6}$alkyl, $C_{1-6}$haloalkyl, and $C_{3-6}$cycloalkyl;

each $R^{18}$ and $R^{19}$ is each independently selected from H, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, aryl, and heteroaryl; or $R^{18}$ and $R^{19}$, together with the nitrogen to which they are attached, form a heterocycloalkyl ring optionally substituted with one, two, or three $R^{20}$;

each $R^{20}$ is independently selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$haloalkyl, oxo, -CN, and $C_{3-6}$cycloalkyl;

$R^{21}$ is $C_{1-6}$alkyl or $C_{3-6}$cycloalkyl;

$R^{22}$ is H, $C_{1-6}$alkyl, or -$SO_2R^{23}$;

$R^{23}$ is $C_{1-6}$alkyl;

m is 1, 2, 3 or 4;

n is 1;

p is 2, 3, or 4;

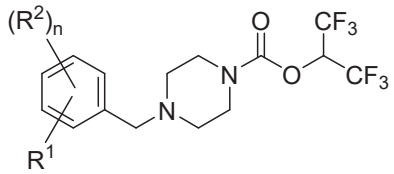
q is 1, 2, or 3;

t is 0, 1, or 2; and

v is 3 or 4;

or a pharmaceutically acceptable salt or solvate thereof.

**[0004]** In one aspect is a compound of Formula (I):




Formula (I);

wherein:

$R^1$ is $-R^{14}$, $-OR^3$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)(R^5)$, $-NH(R^{4'})$, or $-C\equiv C-(CR^6R^7)-R^8$;

each $R^2$ is independently selected from $C_{1-6}$alkyl, halogen, -CN, $C_{1-6}$haloalkyl, $-C_{1-6}$alkyl(heterocycloalkyl), $-OR^{17}$, and $-C(O)NR^{18}R^{19}$;

$R^3$ is $-(CR^6R^7)_m-R^8$, $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$, or $-(CR^6R^7)_t-C_{3-6}$cycloalkyl$-R^8$;

$R^4$ is $-(CR^6R^7)_m-R^{8'}$, $-(CR^6R^7)_v-C(O)OH$, or $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$;

$R^{4'}$ is $-(CR^6R^7)_m-R^{8'}$, $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$, $-C_{4-6}$alkyl-C(O)OH, $-C_{3-6}$cycloalkyl-C(O)OH, or $-C_{1-6}$alkyl$-C_{3-6}$cycloalkyl-C(O)OH;

Y is -O- or $-N(R^{22})-$;

$R^5$ is $C_{1-6}$alkyl or $-CH_2$-phenyl optionally substituted with one, two, or three groups independently selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$haloalkyl, and $C_{1-6}$alkoxy;

other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, $C_1$-$C_5$ alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, $C_1$-$C_4$ alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, $C_1$-$C_3$ alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, $C_1$-$C_2$ alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, $C_1$ alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, $C_5$-$C_{15}$ alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, $C_5$-$C_8$ alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, $C_2$-$C_5$ alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, $C_3$-$C_5$ alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl, and each $R^f$ is independently alkyl, fluoroalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl.

**[0025]** "Alkoxy" refers to a radical bonded through an oxygen atom of the formula -O-alkyl, where alkyl is an alkyl chain as defined above.

**[0026]** "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^f$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl, and each $R^f$ is independently alkyl, fluoroalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl.

**[0027]** "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^f$, $-OC(O)-NR^aR^f$, $-N(R^a)C(O)R^f$, $-N(R^a)S(O)_tR^f$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^f$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl, and each $R^f$ is independently alkyl, fluoroalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl.

**[0028]** "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from six to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that may be optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl, each $R^b$ is independently a direct bond or a straight or branched alkylene or alkenylene chain, and $R^c$ is a straight or branched alkylene or alkenylene chain.

**[0029]** "Aryloxy" refers to a radical bonded through an oxygen atom of the formula –O-aryl, where aryl is as defined above.

**[0030]** "Aralkyl" refers to a radical of the formula $-R^c$-aryl where $R^c$ is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl

radical may be optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical may be optionally substituted as described above for an aryl group.

**[0031]** "Aralkyloxy" refers to a radical bonded through an oxygen atom of the formula –O-aralkyl, where aralkyl is as defined above.

**[0032]** "Aralkenyl" refers to a radical of the formula $-R^d$-aryl where $R^d$ is an alkenylene chain as defined above. The aryl part of the aralkenyl radical may be optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical may be optionally substituted as defined above for an alkenylene group.

**[0033]** "Aralkynyl" refers to a radical of the formula $-R^e$-aryl, where $R^e$ is an alkynylene chain as defined above. The aryl part of the aralkynyl radical may be optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical may be optionally substituted as defined above for an alkynylene chain.

**[0034]** "Cycloalkyl " refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a cycloalkyl comprises three to ten carbon atoms. In other embodiments, a cycloalkyl comprises five to seven carbon atoms. The cycloalkyl is attached to the rest of the molecule by a single bond. Cycloalkyls are saturated, (*i.e.*, containing single C-C bonds only) or partially unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In certain embodiments, a cycloalkyl comprises three to eight carbon atoms (*e.g.*, $C_3$-$C_8$ cycloalkyl). In other embodiments, a cycloalkyl comprises three to seven carbon atoms (*e.g.*, $C_3$-$C_7$ cycloalkyl). In other embodiments, a cycloalkyl comprises three to six carbon atoms (*e.g.*, $C_3$-$C_6$ cycloalkyl). In other embodiments, a cycloalkyl comprises three to five carbon atoms (*e.g.*, $C_3$-$C_5$ cycloalkyl). In other embodiments, a cycloalkyl comprises three to four carbon atoms (*e.g.*, $C_3$-$C_4$ cycloalkyl). A partially unsaturated cycloalkyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals that may be optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, $-R^b$-$OR^a$, $-R^b$-$OC(O)$-$R^a$, $-R^b$-$OC(O)$-$OR^a$, $-R^b$-$OC(O)$-$N(R^a)_2$, $-R^b$-$N(R^a)_2$, $-R^b$-$C(O)R^a$, $-R^b$-$C(O)OR^a$, $-R^b$-$C(O)N(R^a)_2$, $-R^b$-$O$-$R^c$-$C(O)N(R^a)_2$, $-R^b$-$N(R^a)C(O)OR^a$, $-R^b$-$N(R^a)C(O)R^a$, -R

$^{b}$-N($R^a$)S(O)$_t$$R^a$ (where t is 1 or 2), -$R^b$-S(O)$_t$O$R^a$ (where t is 1 or 2), -$R^b$-S(O)$_t$$R^a$ (where t is 1 or 2) and -$R^b$-S(O)$_t$N($R^a$)$_2$ (where t is 1 or 2), where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl, each $R^b$ is independently a direct bond or a straight or branched alkylene or alkenylene chain, and $R^c$ is a straight or branched alkylene or alkenylene chain.

**[0035]** "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

**[0036]** "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above.

**[0037]** "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.

**[0038]** "Haloalkoxy" refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above.

**[0039]** "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which include fused, spiro, or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, may be optionally quaternized. The heterocycloalkyl radical may be partially or fully saturated. In some embodiments, the heterocycloalkyl is attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, the term "heterocycloalkyl" is meant to include heterocycloalkyl radicals as defined above that may be optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, -$R^b$-O$R^a$, -$R^b$-OC(O)-$R^a$, -$R^b$-OC(O)-O$R^a$, -$R^b$-OC(O)-N($R^a$)$_2$, -$R^b$-N($R^a$)$_2$, -$R^b$-C(O)$R^a$, -$R^b$-C(O)O$R^a$, -$R^b$-C(O)N($R^a$)$_2$, -$R^b$-O-$R^c$-C(O)N($R^a$)$_2$, -$R^b$-N($R^a$)C(O)O$R^a$, -$R^b$-N($R^a$)C(O)$R^a$, -$R^b$-N($R^a$)S(O)$_t$$R^a$ (where t is 1 or 2), -$R^b$-S(O)$_t$O$R^a$ (where t is 1 or 2), -$R^b$-S(O)$_t$$R^a$ (where t is 1 or 2)

and -$R^b$-$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl, each $R^b$ is independently a direct bond or a straight or branched alkylene or alkenylene chain, and $R^c$ is a straight or branched alkylene or alkenylene chain.

**[0040]** "Heteroaryl" refers to a radical derived from a 5- to 18-membered aromatic ring radical that comprises one to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical may be optionally oxidized. One or more nitrogen atoms, if present, may be optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above that may be optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, haloalkyl, oxo, thioxo, cyano, nitro, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, -$R^b$-$OR^a$, -$R^b$-OC(O)-$R^a$, -$R^b$-OC(O)-$OR^a$, -$R^b$-OC(O)-$N(R^a)_2$, -$R^b$-$N(R^a)_2$, -$R^b$-C(O)$R^a$, -$R^b$-C(O)$OR^a$, -$R^b$-C(O)$N(R^a)_2$, -$R^b$-O-$R^c$-C(O)$N(R^a)_2$, -$R^b$-$N(R^a)$C(O)$OR^a$, -$R^b$-$N(R^a)$C(O)$R^a$, -$R^b$-$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$R^b$-$S(O)_tOR^a$ (where t is 1 or 2), -$R^b$-$S(O)_tR^a$ (where t is 1 or 2) and -$R^b$-$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl, each $R^b$ is independently a direct bond or a straight or branched alkylene or alkenylene chain, and $R^c$ is a straight or branched alkylene or alkenylene chain.

**[0041]** "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical may be optionally substituted as described above for heteroaryl radicals.

**[0042]** "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical may be optionally substituted as described above for heteroaryl radicals.

**[0043]** "Heteroaryloxy" refers to radical bonded through an oxygen atom of the formula -O-heteroaryl, where heteroaryl is as defined above.

**[0044]** "Heteroarylalkyl" refers to a radical of the formula –$R^c$-heteroaryl, where $R^c$ is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be

optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical may be optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical may be optionally substituted as defined above for a heteroaryl group.

**[0045]** "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula -O-$R^c$-heteroaryl, where $R^c$ is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical may be optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical may be optionally substituted as defined above for a heteroaryl group.

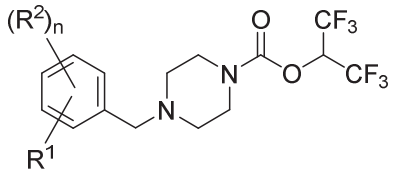
**[0046]** In some embodiments, the compounds disclosed herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and Z geometric isomers (*e.g., cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or Z geometric isomers (*e.g., cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho*-, *meta*-, and *para*- isomers around a benzene ring.

**[0047]** A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. In certain embodiments, the compounds presented herein exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:

## CLAIMS

We Claim:

1. A compound having the structure of Formula (I):



Formula (I);

wherein:

$R^1$ is $-R^{14}$, $-OR^3$, $-SR^4$, $-S(O)_2R^4$, $-N(R^4)(R^5)$, $-NH(R^{4'})$, or $-C\equiv C-(CR^6R^7)-R^8$;

each $R^2$ is independently selected from $C_{1-6}$alkyl, halogen, -CN, $C_{1-6}$haloalkyl, $-C_{1-6}$alkyl(heterocycloalkyl), $-OR^{17}$, and $-C(O)NR^{18}R^{19}$;

$R^3$ is $-(CR^6R^7)_m-R^8$, $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$, or $-(CR^6R^7)_t-C_{3-6}$cycloalkyl-$R^8$;

$R^4$ is $-(CR^6R^7)_m-R^{8'}$, $-(CR^6R^7)_v-C(O)OH$, or $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$; $R^{4'}$ is $-(CR^6R^7)_m-R^{8'}$, $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$, $-C_{4-6}$alkyl-C(O)OH, $-C_{3-6}$cycloalkyl-C(O)OH, or $-C_{1-6}$alkyl-$C_{3-6}$cycloalkyl-C(O)OH;

Y is -O- or $-N(R^{22})-$;

$R^5$ is $C_{1-6}$alkyl or $-CH_2$-phenyl optionally substituted with one, two, or three groups independently selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$haloalkyl, and $C_{1-6}$alkoxy;

each $R^6$ and $R^7$ is each independently selected from H, F, and $C_{1-6}$alkyl; or $R^6$ and $R^7$, together with the carbon to which they are attached, form a $C_{3-6}$cycloalkyl ring;

$R^8$ is $-C(O)OR^9$, $-C(O)R^{10}$, or $-C(O)O-(CR^{12}R^{13})-OC(O)R^{11}$;

$R^{8'}$ is $-C(O)OR^{9'}$, $-C(O)R^{10'}$, or $-C(O)O-(CR^{12}R^{13})-OC(O)R^{11}$;

$R^9$ is H or $C_{1-6}$alkyl;

$R^{9'}$ is $C_{1-6}$alkyl;

$R^{10}$ is $C_{1-6}$alkyl or $-NHSO_2R^{21}$;

$R^{10'}$ is $C_{2-6}$alkyl or $-NHSO_2R^{21}$;

$R^{11}$ is $C_{1-6}$alkyl or $C_{1-6}$alkoxy;

$R^{12}$ and $R^{13}$ is each independently H or $C_{1-6}$alkyl;

$R^{14}$ is $-(CR^{15}R^{16})_m-R^8$ or $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$;

each $R^{15}$ and $R^{16}$ is each independently selected from H, F, and $C_{1-6}$alkyl;

each $R^{17}$ is independently selected from H, $C_{1-6}$alkyl, $C_{1-6}$haloalkyl, and $C_{3-6}$cycloalkyl;

each $R^{18}$ and $R^{19}$ is each independently selected from H, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, aryl, and heteroaryl; or $R^{18}$ and $R^{19}$, together with the nitrogen to which they are attached, form a heterocycloalkyl ring optionally substituted with one, two, or three $R^{20}$;

each $R^{20}$ is independently selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$haloalkyl, oxo, -CN, and $C_{3-6}$cycloalkyl;

$R^{21}$ is $C_{1-6}$alkyl or $C_{3-6}$cycloalkyl;

$R^{22}$ is H, $C_{1-6}$alkyl, or $-SO_2R^{23}$;

$R^{23}$ is $C_{1-6}$alkyl;

m is 1, 2, 3 or 4;

n is 1;

p is 2, 3, or 4;

q is 1, 2, or 3;

t is 0, 1, or 2; and

v is 3 or 4;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^1$ is $-OR^3$.
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^3$ is $-(CR^6R^7)_m-R^8$.
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1, 2, or 3.
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1.
6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 2.
7. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 3.
8. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^3$ is $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$.
9. The compound of claim 8, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -O-.
10. The compound of claim 8, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is $-N(R^{22})-$.

11. The compound of claim 10, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{22}$ is $-SO_2R^{23}$.
12. The compound of any one of claims 8-11, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1.
13. The compound of any one of claims 8-12, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 2.
14. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^1$ is $-C\equiv C-(CR^6R^7)-R^8$.
15. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^3$ is $-(CR^6R^7)_t-C_{3-6}$cycloalkyl$-R^8$.
16. The compound of claim 15, or a pharmaceutically acceptable salt or solvate thereof, wherein t is 1.
17. The compound of claim 15, or a pharmaceutically acceptable salt or solvate thereof, wherein t is 0.
18. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt or solvate thereof, wherein each $R^6$ and $R^7$ is each independently selected from H and $C_{1-6}$alkyl.
19. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt or solvate thereof, wherein each $R^6$ and $R^7$ is H.
20. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^6$ and $R^7$, together with the carbon to which they are attached, form a $C_{3-6}$cycloalkyl ring.
21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)OR^9$.
22. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^9$ is H.
23. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^9$ is $C_{1-6}$alkyl.
24. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)R^{10}$.
25. The compound of claim 24, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{10}$ is $-NHSO_2R^{21}$.
26. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)O-(CR^{12}R^{13})-OC(O)R^{11}$.

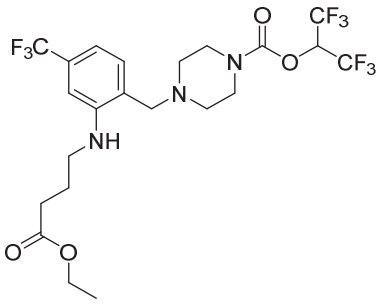
27. The compound of claim 26, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1-6}$alkyl.
28. The compound of claim 26, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1-6}$alkoxy.
29. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^1$ is $-N(R^4)(R^5)$.
30. The compound of claim 29, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^5$ is $-CH_3$.
31. The compound of claim 29, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^5$ is $-CH_2$-phenyl optionally substituted with one, two, or three groups independently selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$haloalkyl, and $C_{1-6}$alkoxy.
32. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^1$ is $-SR^4$.
33. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^1$ is $-S(O)_2R^4$.
34. The compound of any one of claims 29-33, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^4$ is $-(CR^6R^7)_v$-C(O)OH.
35. The compound of claim 34, or a pharmaceutically acceptable salt or solvate thereof, wherein v is 3.
36. The compound of claim 34, or a pharmaceutically acceptable salt or solvate thereof, wherein v is 4.
37. The compound of any one of claims 29-33, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^4$ is $-(CR^6R^7)_m$-$R^{8'}$.
38. The compound of claim 37, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1, 2, or 3.
39. The compound of claim 37, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1.
40. The compound of claim 37, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 2.
41. The compound of claim 37, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 3.
42. The compound of any one of claims 37-41, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{8'}$ is $-C(O)OR^{9'}$.

43. The compound of any one of claims 37-41, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{8'}$ is $-C(O)R^{10'}$.
44. The compound of claim 43, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{10'}$ is $-NHSO_2R^{21}$.
45. The compound of any one of claims 37-41, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{8'}$ is $-C(O)O-(CR^{12}R^{13})-OC(O)R^{11}$.
46. The compound of claim 45, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1-6}$alkyl.
47. The compound of claim 45, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1-6}$alkoxy.
48. The compound of any one of claims 29-33, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^4$ is $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$.
49. The compound of claim 48, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -O-.
50. The compound of claim 48, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is $-N(R^{22})-$.
51. The compound of claim 50, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{22}$ is $-SO_2R^{23}$.
52. The compound of any one of claims 48-51, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1.
53. The compound of any one of claims 48-52, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 2.
54. The compound of any one of claims 48-53, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)OR^9$.
55. The compound of claim 54, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^9$ is H.
56. The compound of claim 54, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^9$ is $C_{1-6}$alkyl.
57. The compound of any one of claims 48-53, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)R^{10}$.
58. The compound of claim 57, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{10}$ is $-NHSO_2R^{21}$.
59. The compound of any one of claims 48-53, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)O-(CR^{12}R^{13})-OC(O)R^{11}$.

60. The compound of claim 59, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1\text{-}6}$alkyl.
61. The compound of claim 59, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1\text{-}6}$alkoxy.
62. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^1$ is $-NH(R^{4'})$.
63. The compound of claim 62, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{4'}$ is $-(CR^6R^7)_m-R^{8'}$.
64. The compound of claim 63, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1, 2, or 3.
65. The compound of claim 63, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1.
66. The compound of claim 63, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 2.
67. The compound of claim 63, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 3.
68. The compound of any one of claims 63-67, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{8'}$ is $-C(O)OR^{9'}$.
69. The compound of any one of claims 63-67, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{8'}$ is $-C(O)R^{10'}$.
70. The compound of claim 69, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{10'}$ is $-NHSO_2R^{21}$.
71. The compound of any one of claims 63-67, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{8'}$ is $-C(O)O-(CR^{12}R^{13})-OC(O)R^{11}$.
72. The compound of claim 71, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1\text{-}6}$alkyl.
73. The compound of claim 71, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1\text{-}6}$alkoxy.
74. The compound of claim 62, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{4'}$ is $-(CR^6R^7)_p-Y-(CR^6R^7)_q-R^8$.
75. The compound of claim 74, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -O-.
76. The compound of claim 74, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is $-N(R^{22})-$.

77. The compound of claim 76, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{22}$ is $-SO_2R^{23}$.
78. The compound of any one of claims 74-77, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1.
79. The compound of any one of claims 74-78, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 2.
80. The compound of any one of claims 74-79, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)OR^9$.
81. The compound of claim 80, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^9$ is H.
82. The compound of claim 80, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^9$ is $C_{1-6}$alkyl.
83. The compound of any one of claims 74-79, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)R^{10}$.
84. The compound of claim 83, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{10}$ is $-NHSO_2R^{21}$.
85. The compound of any one of claims 74-79, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is $-C(O)O-(CR^{12}R^{13})-OC(O)R^{11}$.
86. The compound of claim 85, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1-6}$alkyl.
87. The compound of claim 85, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{11}$ is $C_{1-6}$alkoxy.
88. The compound of any one of claims 34-87, or a pharmaceutically acceptable salt or solvate thereof, wherein each $R^6$ and $R^7$ is each independently selected from H and $C_{1-6}$alkyl.
89. The compound of any one of claims 34-87, or a pharmaceutically acceptable salt or solvate thereof, wherein each $R^6$ and $R^7$ is H.
90. The compound of any one of claims 34-87, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^6$ and $R^7$, together with the carbon to which they are attached, form a $C_{3-6}$cycloalkyl ring.
91. The compound of claim 62, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{4'}$ is $-C_{4-6}$alkyl-C(O)OH.
92. The compound of claim 62, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{4'}$ is $-C_{3-6}$cycloalkyl-C(O)OH.

93. The compound of claim 62, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{4'}$ is -$C_{1-6}$alkyl-$C_{3-6}$cycloalkyl-C(O)OH.
94. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^1$ is -$R^{14}$.
95. The compound of claim 94, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{14}$ is -$(CR^{15}R^{16})_m$-$R^8$.
96. The compound of claim 95, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1.
97. The compound of claim 95, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 2.
98. The compound of claim 95, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 3.
99. The compound of claim 95, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 4.
100. The compound of any one of claims 95-99, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^8$ is -C(O)$OR^9$.
101. The compound of claim 100, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^9$ is H.
102. The compound of claim 100, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^9$ is $C_{1-6}$alkyl.
103. The compound of any one of claims 1-102, or a pharmaceutically acceptable salt or solvate thereof, wherein each $R^2$ is independently selected from $C_{1-6}$alkyl, halogen, -CN, and $C_{1-6}$haloalkyl.
104. The compound of any one of claims 1-103, or a pharmaceutically acceptable salt or solvate thereof, wherein each $R^2$ is independently selected from $C_{1-6}$alkyl, halogen, and $C_{1-6}$haloalkyl.
105. The compound of claim 104, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^2$ is -Cl.
106. The compound of claim 104, or a pharmaceutically acceptable salt or solvate thereof, wherein $R^2$ is -$CF_3$.
107. A compound having the structure selected from: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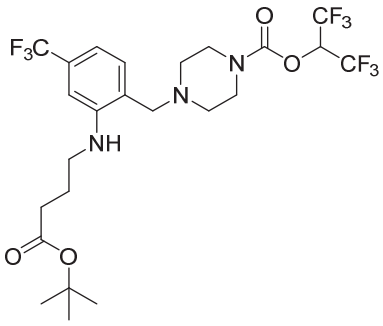
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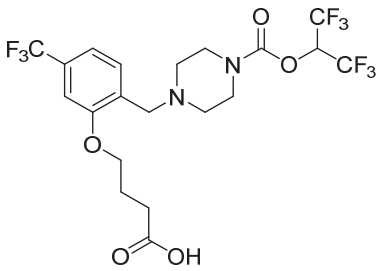
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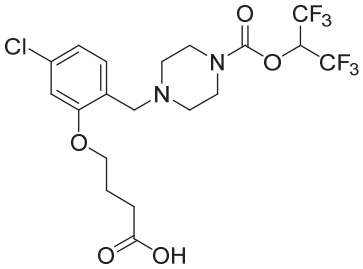
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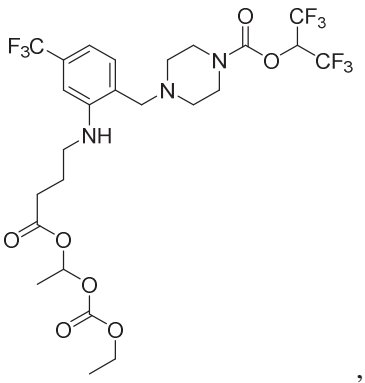
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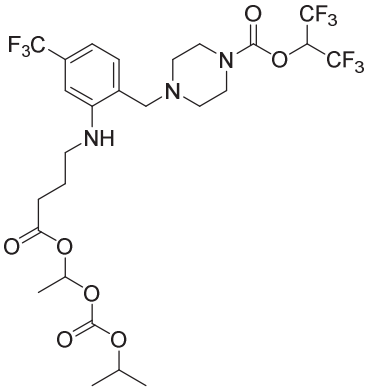
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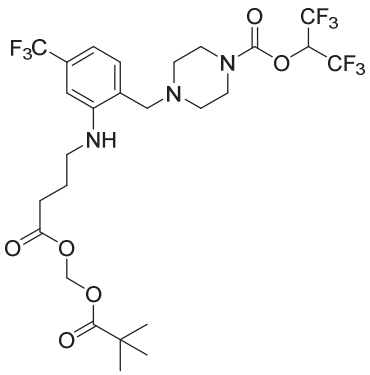
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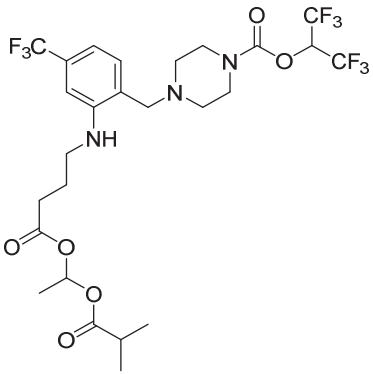
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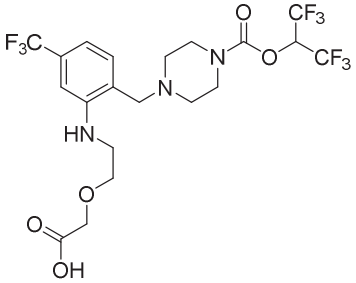
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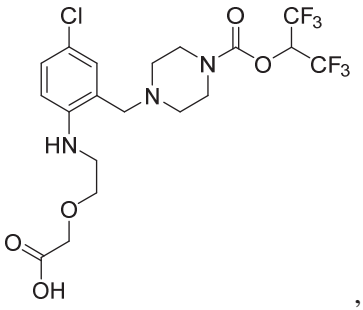
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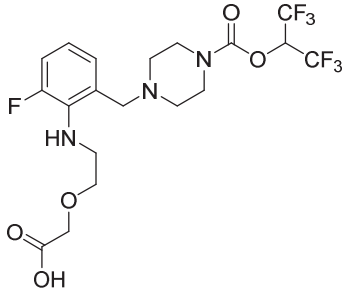
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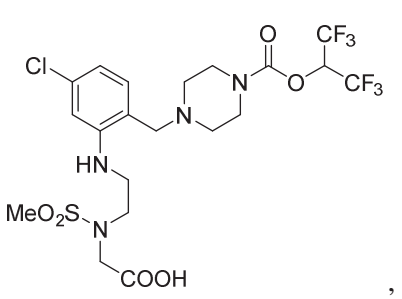
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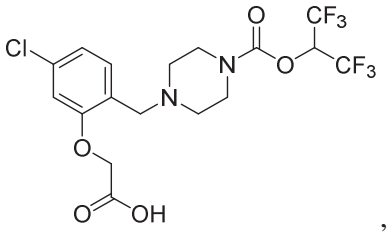
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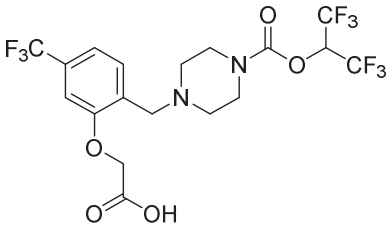
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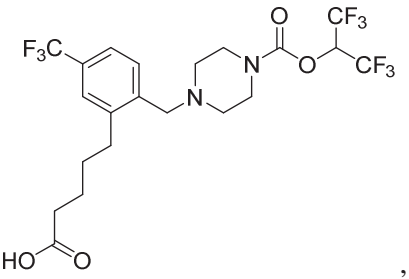
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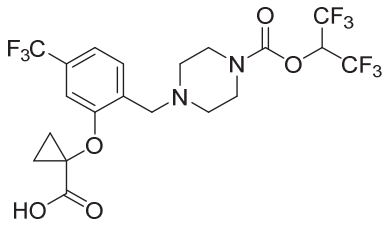
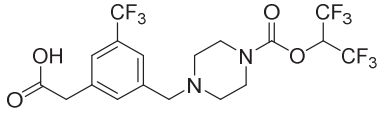

and ;

or a pharmaceutically acceptable salt or solvate thereof.

108. A compound having the structure selected from: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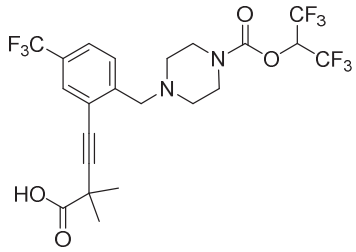
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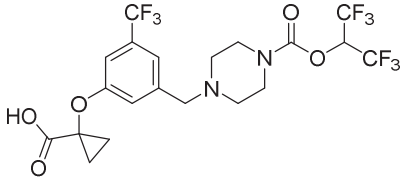
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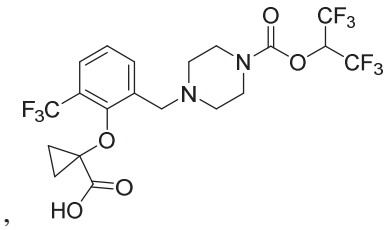
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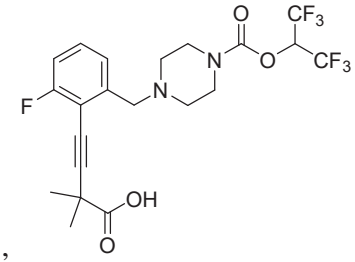
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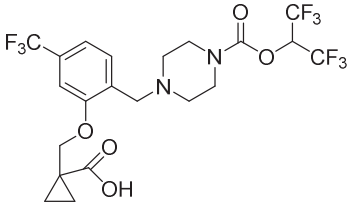
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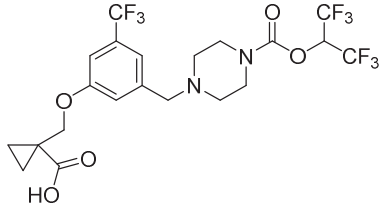
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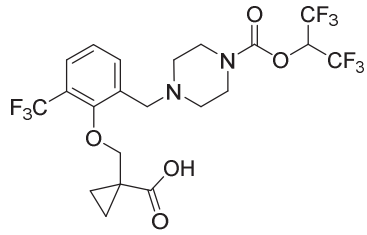
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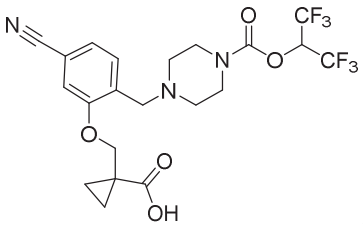
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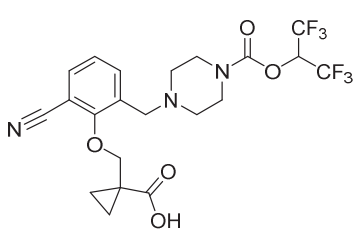
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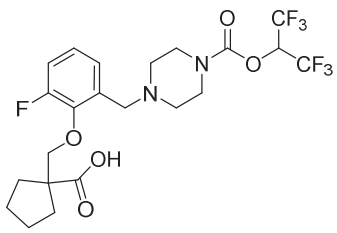
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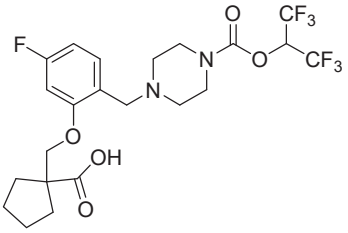
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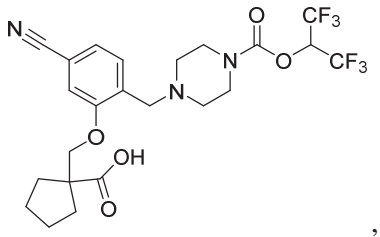
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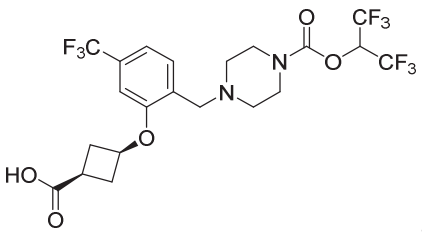
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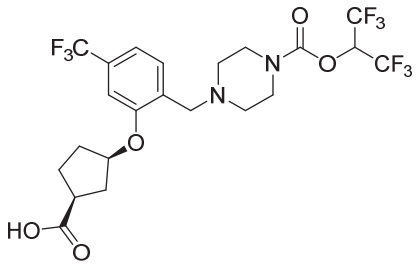
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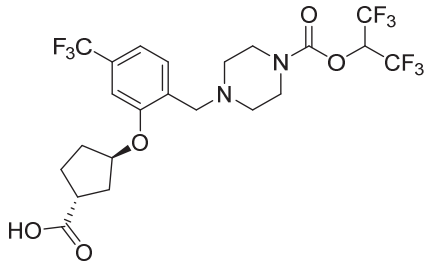
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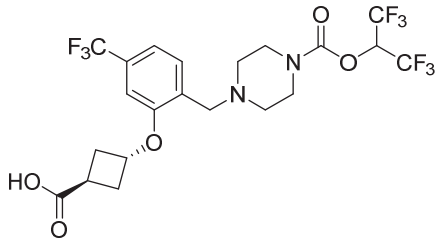
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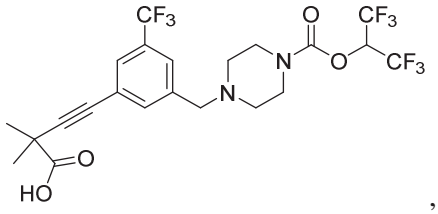
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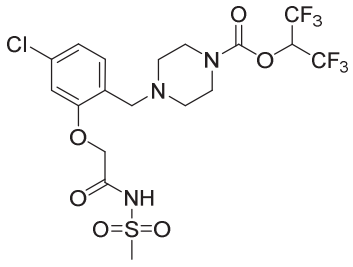
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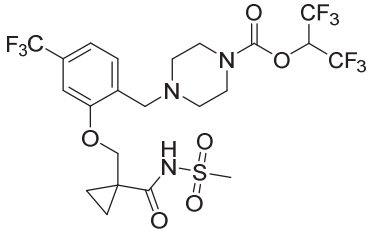
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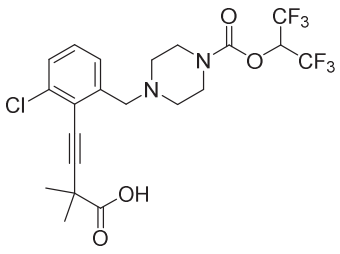
;

or a pharmaceutically acceptable salt or solvate thereof.

109. A pharmaceutical composition comprising a compound of any one of claims 1-108, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

110. The compound of any one of claims 1-108, or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

111. Use of a compound of any one of claims 1-108, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating pain in a patient.

112. The use of claim 111, wherein the pain is neuropathic pain.

113. The use of claim 111, wherein the pain is inflammatory pain.

114. Use of a compound of any one of claims 1-108, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a disease or disorder in a patient, wherein the disease or disorder is selected from the group consisting of epilepsy/seizure

disorder, multiple sclerosis, neuromyelitis optica (NMO), Tourette syndrome, Alzheimer's disease, and abdominal pain associated with irritable bowel syndrome.

115. The use of claim 114, wherein the disease or disorder is multiple sclerosis.

116. The use of claim 114, wherein the disease or disorder is Tourette syndrome.

117. The use of claim 114, wherein the disease or disorder is Alzheimer's disease.

118. The use of claim 114, wherein the disease or disorder is abdominal pain associated with irritable bowel syndrome.

119. Use of a compound of any one of claims 1-108, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating attention deficit and hyperactivity disorder (ADHD) in a patient.