MAGL INHIBITORS

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/671,985, filed on May 15, 2018, which is herein incorporated by reference in its entirety.

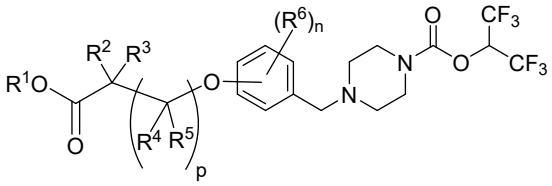
BACKGROUND

[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 ~~OF THE INVENTION~~

[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, the present disclosure refers to a compound having the structure of Formula (I):



Formula (I);

wherein:

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

R^2 is C_{1-6}alkyl;

R^3 is H or C_{1-6}alkyl;

R^4 and R^5 are independently selected from H and C_{1-6}alkyl;

each R^6 is independently selected from C_{1-6}alkyl, halogen, -CN, C_{1-6}haloalkyl, $-OR^7$, $-C(O)NR^8R^9$, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-C_{1-6}$alkyl(C_{2-9}heterocycloalkyl), and C_{2-9}heteroaryl, wherein C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, $-C_{1-6}$alkyl(C_{2-9}heterocycloalkyl), and C_{2-9}heteroaryl are 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^7 is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{3-6}cycloalkyl;

each R^8 and R^9 is each independently selected from H, C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl, and heteroaryl; or R^8 and R^9, together with the nitrogen to which they are attached, form a heterocycloalkyl ring optionally substituted with one, two, or three R^{10};

each R^{10} is independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, oxo, -CN, and C_{3-6}cycloalkyl;

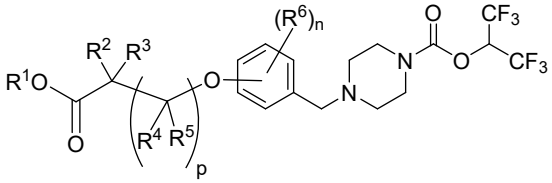
n is 0, 1, 2, 3, or 4; and

p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

~~[0003]~~ **[0003b]** In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

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



Formula (I);

wherein:

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

R^2 is C_{1-6}alkyl;

R^3 is H or C_{1-6}alkyl;

R^4 and R^5 are independently selected from H and C_{1-6}alkyl;

each R^6 is independently selected from C_{1-6}alkyl, halogen, -CN, C_{1-6}haloalkyl, -OR^7, -$C(O)NR^8R^9$, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -C_{1-6}alkyl(C_{2-9}heterocycloalkyl), and C_{2-9}heteroaryl, wherein C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, -C_{1-6}alkyl(C_{2-9}heterocycloalkyl), and C_{2-9}heteroaryl are 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^7 is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{3-6}cycloalkyl;

each R^8 and R^9 is each independently selected from H, C_{1-6}alkyl, C_{3-6}cycloalkyl, aryl, and heteroaryl; or R^8 and R^9, together with the nitrogen to which they are attached, form a heterocycloalkyl ring optionally substituted with one, two, or three R^{10};

each R^{10} is independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, oxo, -CN, and C_{3-6}cycloalkyl;

n is 0, 1, 2, 3, or 4; and

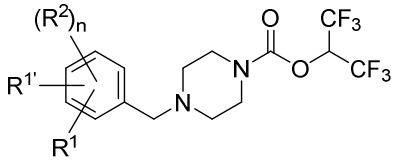
p is 0 or 1;

or a pharmaceutically acceptable salt or solvate thereof.

[0005] In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 0. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^4 and R^5 are H. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is H. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is C_{1-6}alkyl. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-CH_3$. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is $-CH_3$. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^6 is independently selected from C_{1-6}alkyl, halogen, -CN, C_{1-6}haloalkyl, $-OR^7$, C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, and C_{2-9}heteroaryl, wherein C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, and C_{2-9}heteroaryl are optionally substituted with one or two groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^6 is independently selected from C_{1-6}alkyl, halogen, -CN, C_{1-6}haloalkyl, $-OR^7$, and C_{3-6}cycloalkyl. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^7 is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^6 is independently selected from C_{1-6}alkyl, halogen, -CN, and C_{1-6}haloalkyl. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^6 is independently selected from halogen and C_{1-6}haloalkyl. In some ~~embodiments~~examples is a compound of Formula (I), or a

~~[0005]~~ pharmaceutically acceptable salt or solvate thereof, wherein n is 1 or 2. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0. In some ~~embodiments~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is H.

[0006] In another ~~aspect~~example is a compound of Formula (II):



Formula (II);

wherein:

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

$R^{1'}$ is C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, or C_{2-9}heteroaryl, wherein C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, or C_{2-9}heteroaryl are 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^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 0, 1, 2, or 3;

p is 2, 3, or 4;

q is 1, 2, or 3;

t is 0, 1, or 2; and

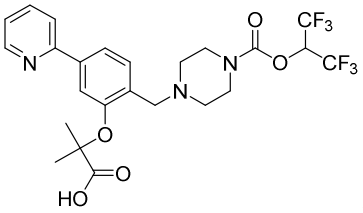
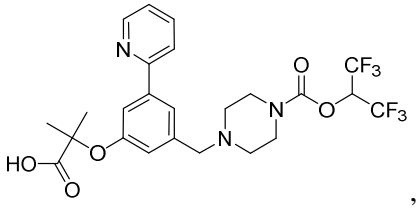
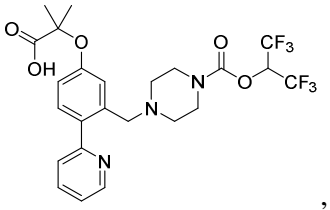
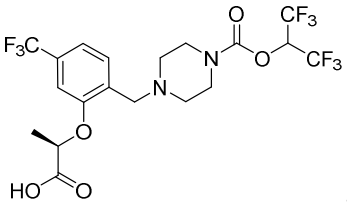
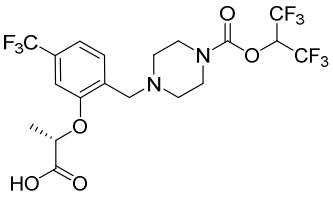
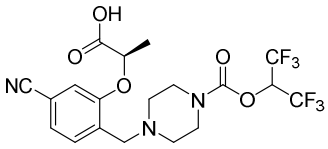
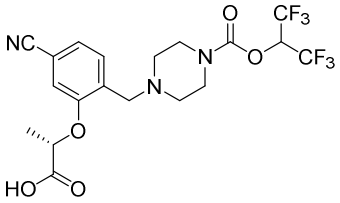
v is 3 or 4;

or a pharmaceutically acceptable salt or solvate thereof.

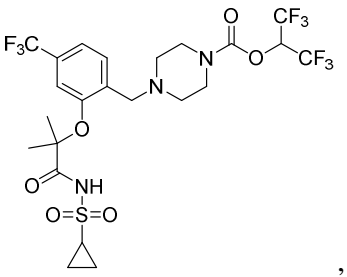
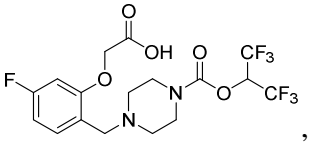
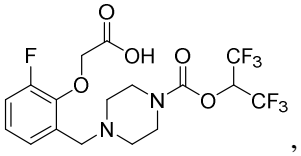
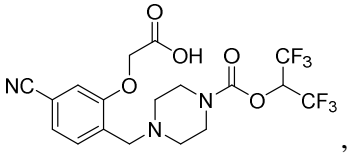
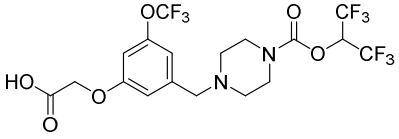
[0007] In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-OR^3$. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-(CR^6R^7)_m-R^8$. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1, 2, or 3. In some ~~embodiments~~examples is a compound of Formula (II), 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; or R^6 and R^7, together with the carbon to which they are attached, form a C_{3-6}cycloalkyl ring. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 is $-C(O)OR^9$. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^9 is H. In some ~~embodiments~~examples is a compound of Formula (II),

or a pharmaceutically acceptable salt or solvate thereof, wherein R^9 is C_{1-6}alkyl. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 is -C(O)R^{10}. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is -$NHSO_2R^{21}$. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{21} is C_{1-6}alkyl. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^{21} is C_{3-6}cycloalkyl. In some ~~embodiments~~examples is a compound of Formula (II), 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. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{1'}$ is C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, or C_{2-9}heteroaryl, wherein C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, or C_{2-9}heteroaryl are optionally substituted with one or two groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{1'}$ is C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, or C_{2-9}heteroaryl, wherein C_{3-6}cycloalkyl, C_{2-9}heterocycloalkyl, or C_{2-9}heteroaryl are unsubstituted. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{1'}$ is unsubstituted C_{3-6}cycloalkyl. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{1'}$ is unsubstituted C_{2-9}heterocycloalkyl. In some ~~embodiments~~examples is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein $R^{1'}$ is unsubstituted C_{2-9}heteroaryl.

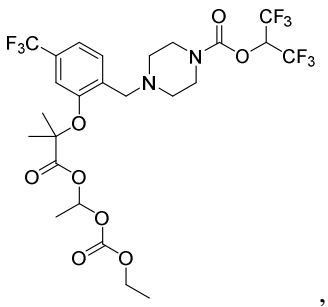
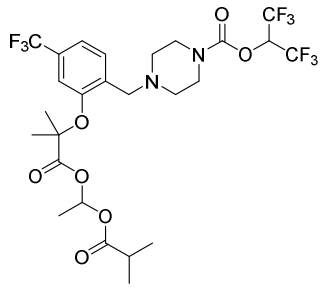
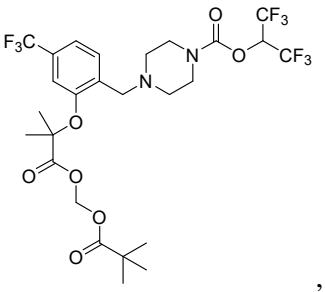
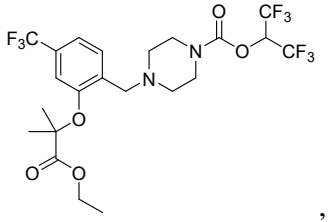
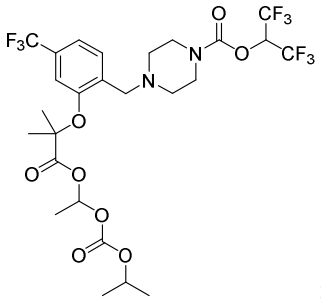
[0008] In another ~~aspect~~example is a compound selected from:


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; or a pharmaceutically acceptable salt or solvate thereof.

[0009] In another ~~aspect~~example is a compound selected from:


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; or a pharmaceutically acceptable salt or solvate thereof.

[0010] In another ~~aspect~~example is a compound selected from:


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; or a pharmaceutically acceptable salt or solvate thereof.

[0011] In another ~~embodiment~~example is a pharmaceutical composition comprising a compound of Formula (I) or (II) described herein, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0012] In another ~~embodiment~~example is a method of treating pain in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or (II) described herein, or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiments~~examples, the pain is neuropathic pain. In some ~~embodiments~~examples, the pain is inflammatory pain.

[0013] In another ~~embodiment~~example is a method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or (II) described herein, or a pharmaceutically acceptable salt or solvate thereof, 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. In some ~~embodiments~~examples, the disease or disorder is epilepsy/seizure disorder. In some ~~embodiments~~examples, the disease or disorder is multiple sclerosis. In some ~~embodiments~~examples, the disease or disorder is neuromyelitis optica (NMO). In some ~~embodiments~~examples, the disease or disorder is Tourette syndrome. In some ~~embodiments~~examples, the disease or disorder is Alzheimer's disease. In some ~~embodiments~~examples, the disease or disorder is abdominal pain associated with irritable bowel syndrome.

[0014] In another ~~embodiment~~example is a method of treating attention deficit and hyperactivity disorder (ADHD) in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or (II) described herein, or a pharmaceutically acceptable salt or solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0015] This disclosure is directed, at least in part, to compounds capable of inhibiting MAGL.

[0016] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range varies between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that which in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

Definitions

[0017] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0018] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. C_1-C_x refers to the number of carbon atoms that make up the moiety to which it designates (excluding optional substituents).

[0019] "Amino" refers to the -NH_2 radical.

[0020] "Cyano" refers to the -CN radical.

[0021] "Nitro" refers to the -NO_2 radical.

[0022] "Oxa" refers to the -O- radical.

[0023] "Oxo" refers to the =O radical.