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[Continued on next page]

(54) Title: THERAPEUTIC AMIDES AND RELATED COMPOUNDS

(57) Abstract: Disclosed herein is a compound having a structure: Therapeutic methods, compositions, and medications relating thereto are also disclosed.



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GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

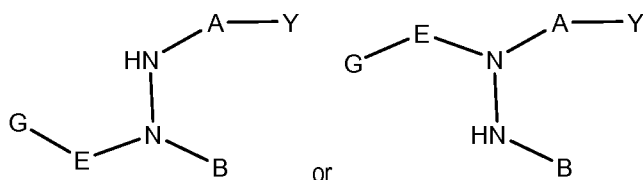
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THERAPEUTIC AMIDES AND RELATED COMPOUNDS

DESCRIPTION OF THE INVENTION

Disclosed herein is a compound having a structure



5 or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 14 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 14 carbon atoms; or Y is a tetrazolyl functional group;

A is $-(\text{CH}_2)_6-$, *cis* $-\text{CH}_2\text{CH}=\text{CH}-(\text{CH}_2)_3-$, or $-\text{CH}_2\text{C}\equiv\text{C}-(\text{CH}_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(\text{CH}_2)_m-\text{Ar}-(\text{CH}_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and

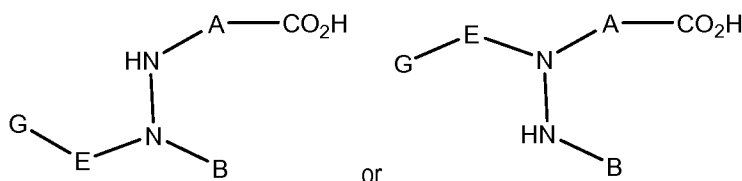
10 wherein 1 $-\text{CH}_2-$ may be replaced by S or O, and 1 $-\text{CH}_2-\text{CH}_2-$ may be replaced by $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

E is SO_2 , CO, or CS;

G is alkyl, aryl or heteroaryl having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms; and

B is substituted aryl or substituted heteroaryl.

Also disclosed herein is a carboxylic acid or a bioisostere thereof, said carboxylic acid having a structure



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or a pharmaceutically acceptable salt thereof, or a prodrug thereof,;

wherein A is $-(\text{CH}_2)_6-$, *cis* $-\text{CH}_2\text{CH}=\text{CH}-(\text{CH}_2)_3-$, or $-\text{CH}_2\text{C}\equiv\text{C}-(\text{CH}_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(\text{CH}_2)_m-\text{Ar}-(\text{CH}_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-\text{CH}_2-$ may be replaced by S or O, and 1 $-\text{CH}_2-\text{CH}_2-$ may be replaced by $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

20 E is SO_2 , CO, or CS;

G is alkyl, aryl or heteroaryl having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms; and

B is substituted aryl or substituted heteroaryl.

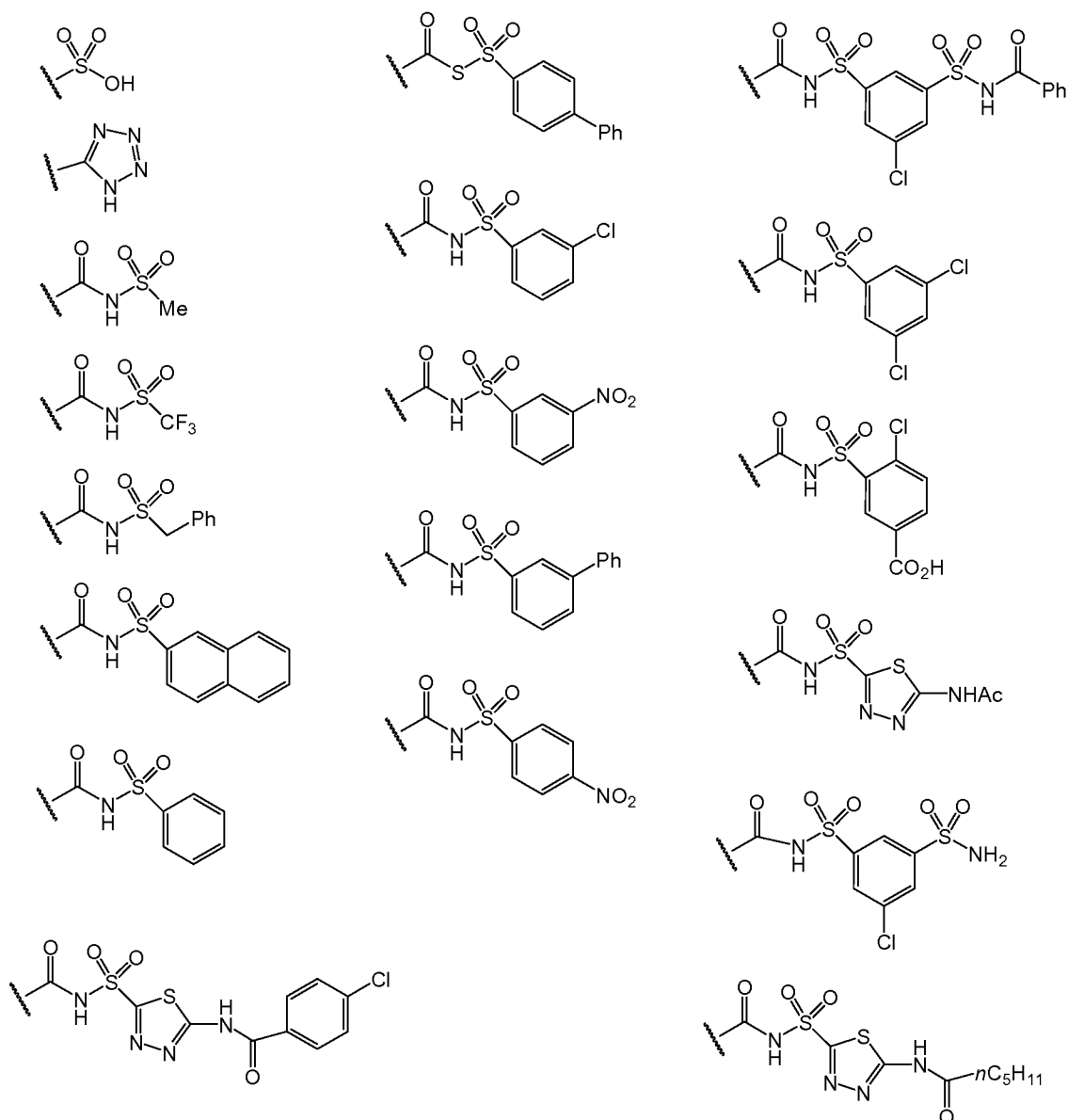
"Bioisosteres are substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties." Silverman, Richard B., The Organic Chemistry of Drug Design and Drug Action,
25 2nd Edition, Amsterdam: Elsevier Academic Press, 2004, p. 29.

While not intending to be limiting, organic acid functional groups are bioisosteres of carboxylic acids. An organic acid functional group is an acidic functional group on an organic molecule. While not intending to be limiting, organic acid functional groups may comprise an oxide of carbon, sulfur, or phosphorous. Thus, while not intending to limit the scope of the invention in any way, in certain compounds Y is a carboxylic acid, sulfonic acid, or phosphonic
30 acid functional group.

Additionally, an amide or ester of one of the organic acids shown above comprising up to 14 carbon atoms is also contemplated. In an ester, a hydrocarbyl moiety replaces a hydrogen atom of an acid such as in a carboxylic acid ester, e.g. CO₂Me, CO₂Et, etc.

In an amide, an amine group replaces an OH of the acid. Examples of amides include CON(R²)₂,
5 CON(OR²)R², CON(CH₂CH₂OH)₂, and CONH(CH₂CH₂OH) where R² is independently H, C₁-C₆ alkyl, phenyl, or biphenyl. Moieties such as CONHSO₂R² are also amides of the carboxylic acid notwithstanding the fact that they may also be considered to be amides of the sulfonic acid R²-SO₃H. The following amides are also specifically contemplated, CONSO₂-biphenyl, CONSO₂-phenyl, CONSO₂-heteroaryl, and CONSO₂-naphthyl. The biphenyl, phenyl, heteroaryl, or naphthyl may be substituted or unsubstituted.

10 Han *et. al.* (Biorganic & Medicinal Chemistry Letters 15 (2005) 3487-3490) has recently shown that the groups shown below are suitable bioisosteres for a carboxylic acid. The activity of compounds with these groups in inhibiting HCV NS3 protease was comparable to or superior to similar compounds where the group is replaced by CO₂H. Thus, Y could be any group depicted below.

Carboxylic acid bioisosteres according to Han *et. al.*

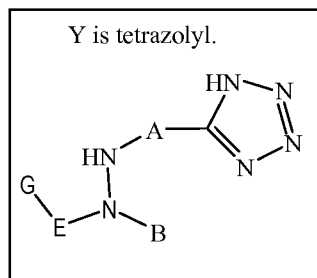
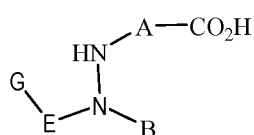
While not intending to limit the scope of the invention in any way, Y may also be hydroxymethyl or an ether thereof comprising up to 14 carbon atoms. An ether is a functional group wherein a hydrogen of an hydroxyl is replaced by carbon, e.g., Y is CH₂OCH₃, CH₂OCH₂CH₃, etc. These groups are also bioisosteres of a carboxylic acid.

“Up to 14 carbon atoms” means that the entire Y moiety, including the carbonyl carbon of a carboxylic acid ester or amide, and both carbon atoms in the -CH₂O-C of an ether has 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms.

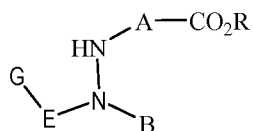
Finally, while not intending to limit the scope of the invention in any way, Y may be a tetrazolyl functional group.

While not intending to be limiting, examples of compounds having the identified Y are depicted below. In these examples R is H or hydrocarbyl, subject to the constraints defined herein. Each structure below represents a specific embodiment which is individually contemplated, as well as pharmaceutically acceptable salts and prodrugs of

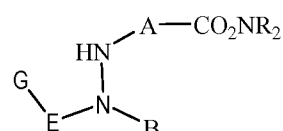
compounds which are represented by the structures. However, other examples are possible which may not fall within the scope of the structures shown below.

**Organic Acids**

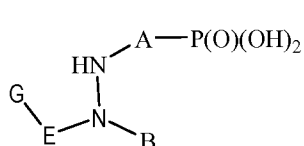
Carboxylic Acid

Esters

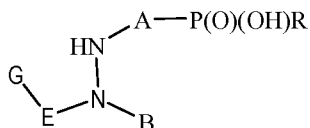
Carboxylic Acid Ester

Amides

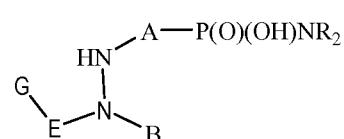
Carboxylic Acid Amide



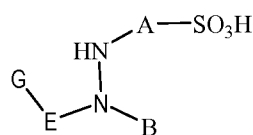
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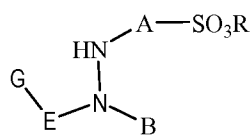
Phosphonic Acid Ester



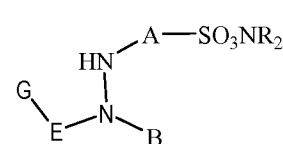
Phosphonic Acid Amide



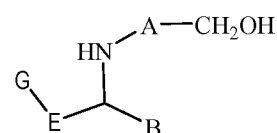
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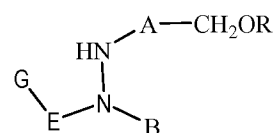
Sulfonic Acid Ester



Sulfonic Acid Amide

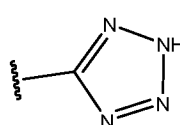
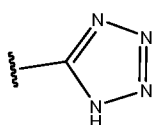


Y is hydroxymethyl

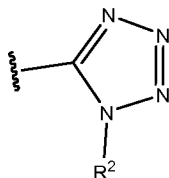


Ether

A tetrazolyl functional group is another bioisostere of a carboxylic acid. An unsubstituted tetrazolyl functional group has two tautomeric forms, which can rapidly interconvert in aqueous or biological media, and are thus equivalent to one another. These tautomers are shown below.

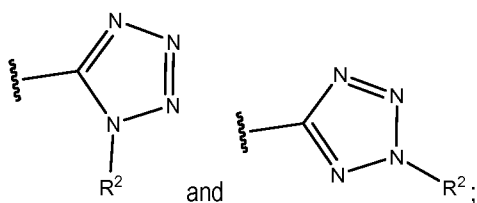


Additionally, if R^2 is C_1 - C_6 alkyl, phenyl, or biphenyl, other isomeric forms of the tetrazolyl functional group such as the one shown below are also possible, unsubstituted and hydrocarbyl substituted tetrazolyl up to C_{12} are considered to be within the scope of the term "tetrazolyl."



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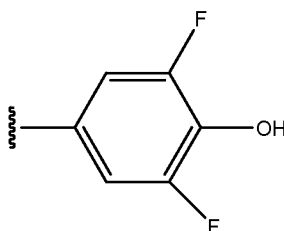
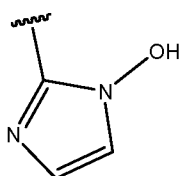
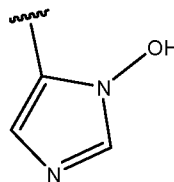
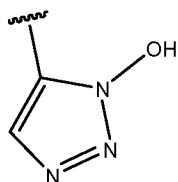
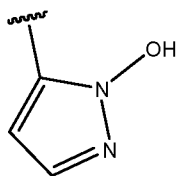
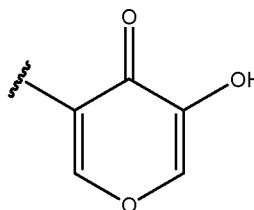
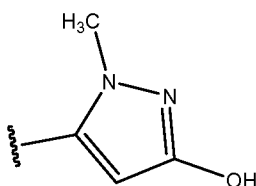
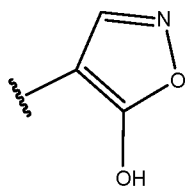
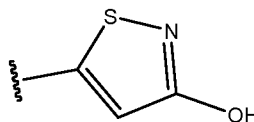
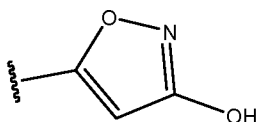
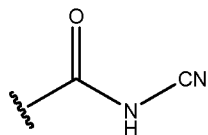
While not intending to limit the scope of the invention in any way, in one embodiment, Y is CO_2R^2 , $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH , $P(O)(OH)_2$, $CONHSO_2R^2$, $SO_2N(R^2)_2$, SO_2NHR^2 ,



10 wherein R^2 is independently H, C_1 - C_6 alkyl, unsubstituted phenyl, or unsubstituted biphenyl.

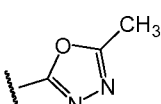
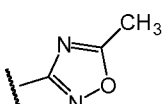
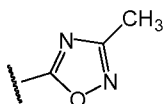
According to Silverman (p. 30), the moieties shown below are also bioisosteres of a carboxylic acid.

Carboxylic acid bioisosteres according to Silverman



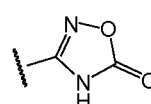
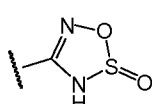
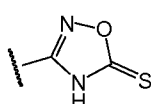
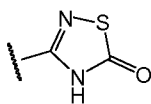
Orlek et al. (*J. Med. Chem.* **1991**, 34, 2726-2735) described oxadiazoles as suitable bioisosteres for a carboxylic acid. These ester replacements were shown to be potent muscarinic agonists having improved metabolic stability. Oxadiazoles were also described by Anderson et al. (*Eur. J. Med. Chem.* 1996, 31, 417-425) as carboxamide replacements having improved in vivo efficacy at the benzodiazepine receptor.

Carboxylic acid bioisosteres according to Orlek et. al.



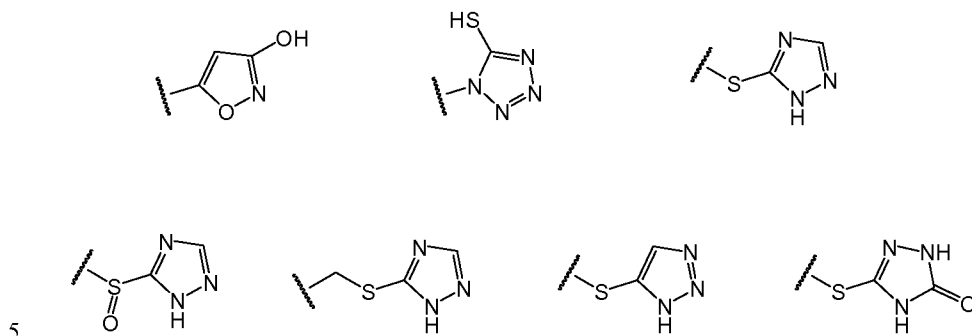
Kohara et al. (*J. Med. Chem.* **1996**, 39, 5228-5235) described acidic heterocycles as suitable bioisosteres for a tetrazole. These carboxylic acid replacements were shown to be potent angiotensin II receptor antagonists having improved metabolic stability.

Tetrazole bioisosteres according to Kohara et. al.



Drysdale et al. (*J. Med. Chem.* **1992**, 35, 2573-2581) have described carboxylic acid mimics of non-peptide CCK-B receptor antagonists. The binding affinities of many of the bioisosteres are similar to the parent carboxylic acid.

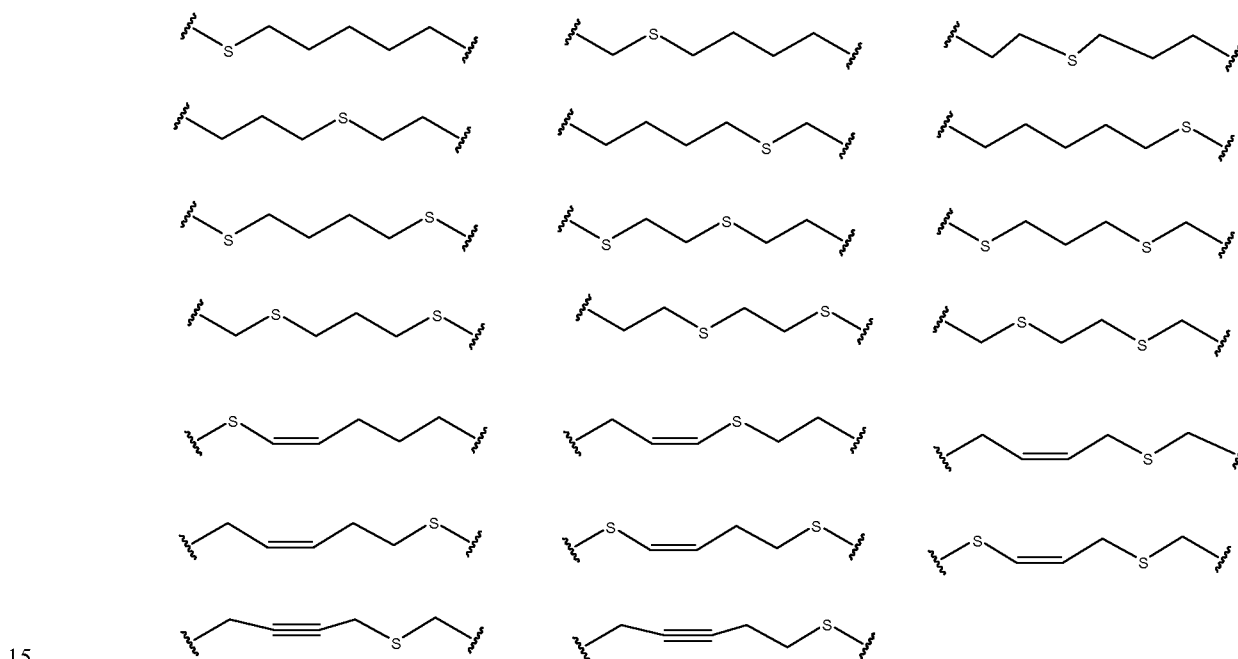
Carboxylic acid bioisosteres according to Drysdale et. al.



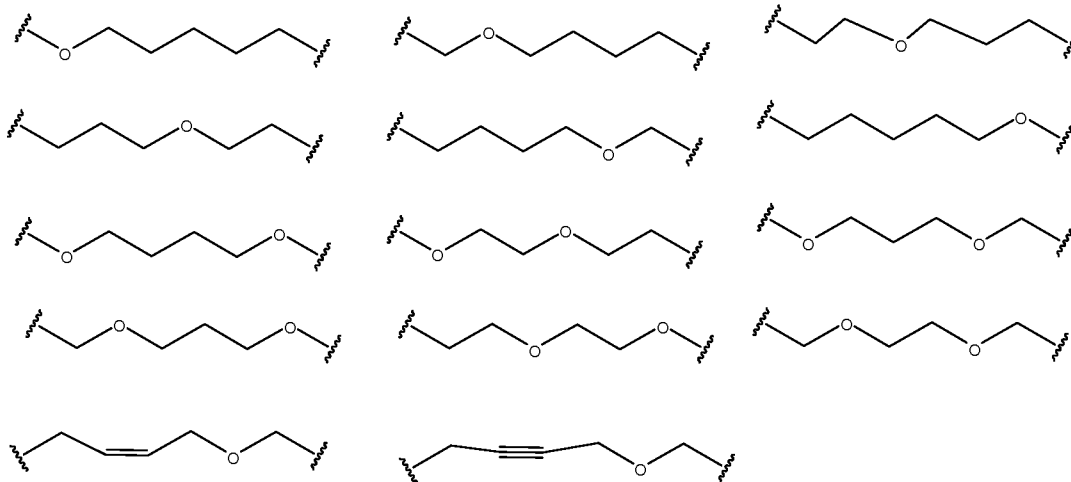
In relation to the identity of A disclosed in the chemical structures presented herein, A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(CH_2)_m-$ Ar $-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-CH_2-$ may be replaced by S or O, and 1 $-CH_2-CH_2-$ may be replaced by $-CH=CH-$ or $-C\equiv C-$.

10 Thus, A may be $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$.

Alternatively, A may be a group which is related to one of these three moieties in that any carbon is replaced with S or O. For example, A may be a moiety where S replaces one or two carbon atoms such as one of the following or the like.

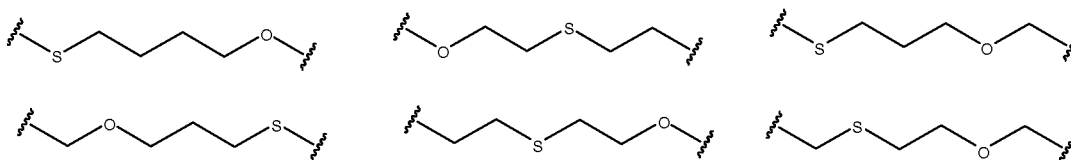


Alternatively, A may be a moiety where O replaces one or two carbon atoms such as one of the following or the like.



Alternatively, A may have an O replacing one carbon atom and an S replacing another carbon atom, such as one of the following or the like.

5



Alternatively, in certain embodiments A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-CH_2-$ may be replaced by S or O, and 1 $-CH_2-CH_2-$ may be replaced by $-CH=CH-$ or $-C\equiv C-$. In other words,

10

in one embodiment A comprises:

- a) 1, 2, 3, or 4 $-CH_2-$ moieties, or
 - b) 0, 1 or 2 $-CH_2-$ moieties and $-CH=CH-$ or $-C\equiv C-$; and
- Ar;

e.g. $-CH_2-Ar-$, $-(CH_2)_2-Ar-$, $-CH=CH-Ar-$, $-C\equiv C-Ar-$, $-CH_2-Ar-CH_2-$, $-CH_2Ar-(CH_2)_2-$, $-CH_2Ar-CH=CH-$,

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$-CH_2Ar-C\equiv C-$, $-(CH_2)_2-Ar-(CH_2)_2-$, and the like;

in another embodiment A comprises:

- a) O; and 0, 1, 2, or 3 $-CH_2-$ moieties; or
 - b) O; and 0 or 1 $-CH_2-$ moieties and $-CH=CH-$ or $-C\equiv C-$; and
- Ar;

20

e.g., $-O-Ar-$, $-Ar-CH_2-O-$, $-O-Ar-(CH_2)_2-$, $-OAr-CH=CH-$, $-O-Ar-C\equiv C-$, $-O-CH_2-Ar-$, $-O-CH_2-Ar-(CH_2)_2-$, $-O-CH_2Ar-CH=CH-$, $-O-CH_2Ar-C\equiv C-$, and the like; or

in another embodiment A comprises:

- a) S; and 0, 1, 2, or 3 $-CH_2-$ moieties; or
- b) S; and 0 or 1 $-CH_2-$ moieties and $-CH=CH-$ or $-C\equiv C-$; and

25

Ar;

e.g., -S-Ar-, -Ar-CH₂-S-, -S-Ar-(CH₂)₂-, -SAr-CH=CH-, -S-Ar-C≡C-, -S-CH₂-Ar-, -S-CH₂-Ar-(CH₂)₂-, -S-CH₂-Ar-CH=CH-, -S-CH₂-Ar-C≡C-, and the like.

In another embodiment, the sum of m and o is 2, 3, or 4 wherein one CH₂ may be replaced with S or O and 1 -CH₂-CH₂- may be replaced by -CH=CH- or -C≡C-.

5 In another embodiment, the sum of m and o is 3 wherein one CH₂ may be replaced with S or O and 1 -CH₂-CH₂- may be replaced by -CH=CH- or -C≡C-.

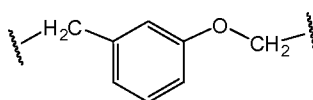
In another embodiment, the sum of m and o is 2 wherein one CH₂ may be replaced with S or O or 1 -CH₂-CH₂- may be replaced by -CH=CH- or -C≡C-.

10 In another embodiment, the sum of m and o is 4 wherein one CH₂ may be replaced with S or O and 1 -CH₂-CH₂- may be replaced by -CH=CH- or -C≡C-.

Interarylene or heterointerarylene refers to an aryl ring or ring system or a heteroaryl ring or ring system which connects two other parts of a molecule, i.e. the two parts are bonded to the ring in two distinct ring positions. Interarylene or heterointerarylene may be substituted or unsubstituted. Unsubstituted interarylene or heterointerarylene has no substituents other than the two parts of the molecule it connects. Substituted interarylene or heterointerarylene has substituents in addition to the two parts of the molecule it connects.

15 In one embodiment, Ar is substituted or unsubstituted interphenylene, interthienylene, interfurylene, interpyridinylene, interoxazolylene, and interthiazolylene. In another embodiment Ar is interphenylene (Ph). In another embodiment A is -(CH₂)₂-Ph-. Substituents of Ar each have from 0 to 4 carbon atoms, from 0 to 3 oxygen atoms, from 0 to 2 sulfur atoms, from 0 to 2 nitrogen atoms, from 0 to 3 fluorine atoms, from 0 to 1 chlorine atoms, from 0 to 1 bromine atoms, from 0 to 1 iodine atoms, and from 0 to 10 hydrogen atoms.

In another embodiment A is -CH₂-Ar-OCH₂-. In another embodiment A is -CH₂-Ph-OCH₂-. In another embodiment, Ph is attached at the 1 and 3 positions, otherwise known as *m*-interphenylene, such as when A has the structure shown below.



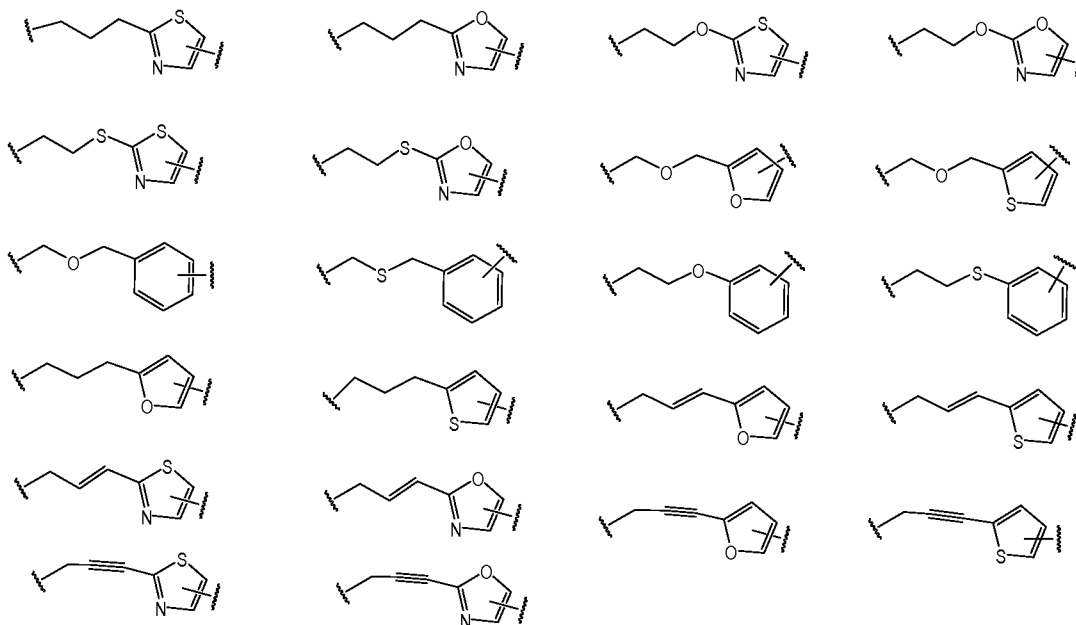
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In another embodiment A is -(CH₂)₆-, *cis* -CH₂CH=CH-(CH₂)₃-, or -CH₂C≡C-(CH₂)₃-, wherein 1 or 2 carbon atoms may be replaced with S or O; or A is -(CH₂)₂-Ph- wherein one -CH₂- may be replaced with S or O.

30 In another embodiment A is -(CH₂)₆-, *cis* -CH₂CH=CH-(CH₂)₃-, or -CH₂C≡C-(CH₂)₃-, wherein 1 or 2 carbon atoms may be replaced with S or O; or A is -(CH₂)₂-Ph-.

In one embodiment, Ar is thienyl.

In other embodiments, A has one of the following structures.



In another embodiment A is $-\text{CH}_2\text{OCH}_2\text{Ar}-$.

In another embodiment A is $-\text{CH}_2\text{SCH}_2\text{Ar}-$.

In another embodiment A is $-(\text{CH}_2)_3\text{Ar}-$.

5 In another embodiment A is $-\text{CH}_2\text{O}(\text{CH}_2)_4-$.

In another embodiment A is $-\text{CH}_2\text{S}(\text{CH}_2)_4-$.

In another embodiment A is $-(\text{CH}_2)_6-$.

In another embodiment A is *cis* $-\text{CH}_2\text{CH}=\text{CH}-(\text{CH}_2)_3-$.

In another embodiment A is $-\text{CH}_2\text{C}\equiv\text{C}-(\text{CH}_2)_3-$.

10 In another embodiment A is $-\text{S}(\text{CH}_2)_3\text{S}(\text{CH}_2)_2-$.

In another embodiment A is $-(\text{CH}_2)_4\text{OCH}_2-$.

In another embodiment A is *cis* $-\text{CH}_2\text{CH}=\text{CH}-\text{CH}_2\text{OCH}_2-$.

In another embodiment A is $-\text{CH}_2\text{CH}\equiv\text{CH}-\text{CH}_2\text{OCH}_2-$.

In another embodiment A is $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_3-$.

15 In another embodiment A is $-\text{CH}_2-\text{Ph}-\text{OCH}_2-$, wherein Ph is interphenylene,.

In another embodiment A is $-\text{CH}_2-\text{mPh}-\text{OCH}_2-$, wherein mPh is *m*-interphenylene.

In another embodiment A is $-\text{CH}_2-\text{O}-(\text{CH}_2)_4-$.

In another embodiment A is $-\text{CH}_2-\text{O}-\text{CH}_2-\text{Ar}-$, wherein Ar is 2,5-interthienylene.

In another embodiment A is $-\text{CH}_2-\text{O}-\text{CH}_2-\text{Ar}-$, wherein Ar is 2,5-interfurylene.

20 In another embodiment A is (3-methylphenoxy)methyl.

In another embodiment A is (4-but-2-ynyloxy)methyl.

In another embodiment A is 2-(2-ethylthio)thiazol-4-yl.

In another embodiment A is 2-(3-propyl)thiazol-5-yl.

In another embodiment A is 3-(methoxymethyl)phenyl.

25 In another embodiment A is 3-(3-propylphenyl).

In another embodiment A is 3-methylphenethyl.

In another embodiment A is 4-(2-ethyl)phenyl.

In another embodiment A is 4-phenethyl.

In another embodiment A is 4-methoxybutyl.

In another embodiment A is 5-(methoxymethyl)furan-2-yl .

5 In another embodiment A is 5-(methoxymethyl)thiophen-2-yl.

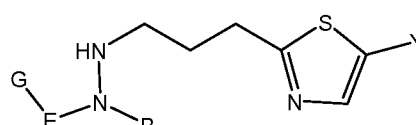
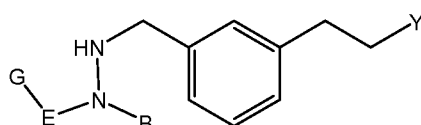
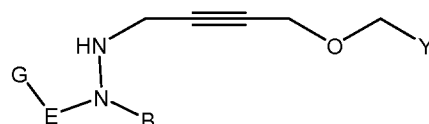
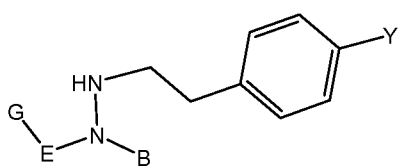
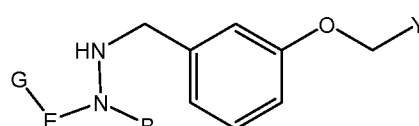
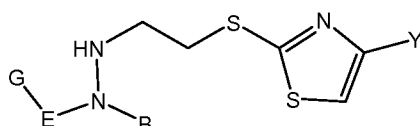
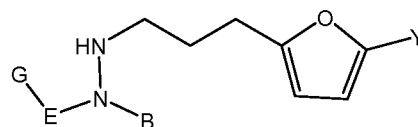
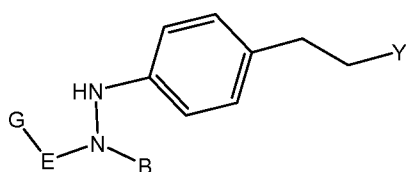
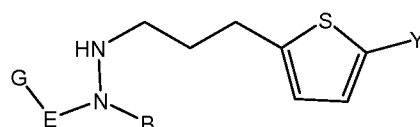
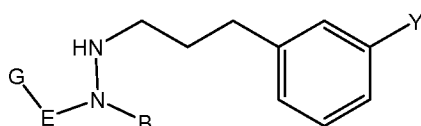
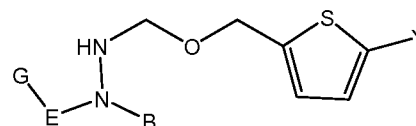
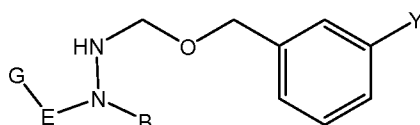
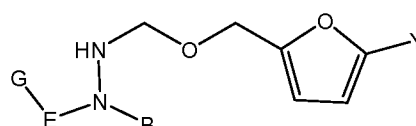
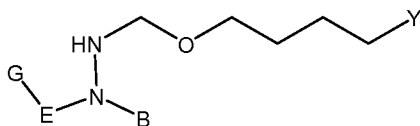
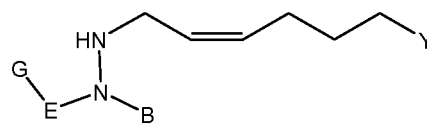
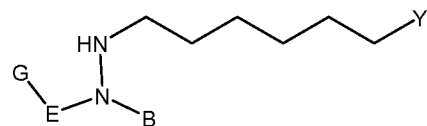
In another embodiment A is 5-(3-propyl)furan-2-yl.

In another embodiment A is 5-(3-propyl)thiophen-2-yl.

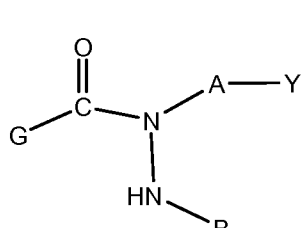
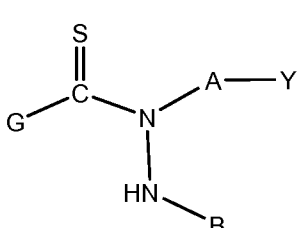
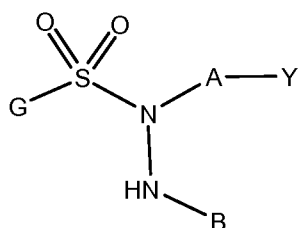
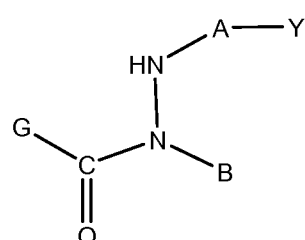
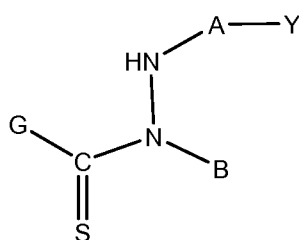
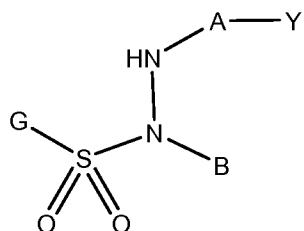
In another embodiment A is 6-hexyl.

In another embodiment A is (Z)-6-hex-4-enyl.

10 Compounds according to the each of the structures depicted below, and pharmaceutically acceptable salts thereof, and prodrugs thereof, are contemplated as individual embodiments. In other words, each structure represents a different embodiment.

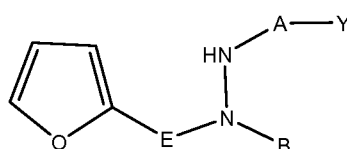
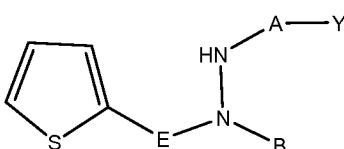
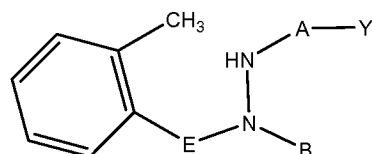
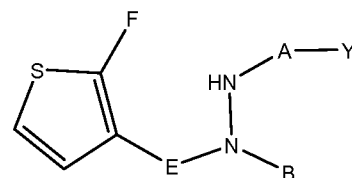
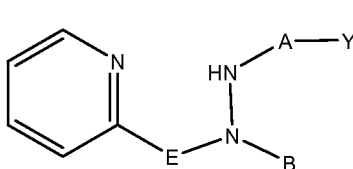
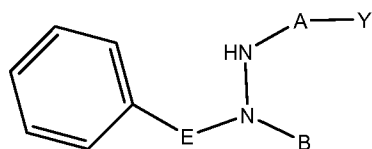
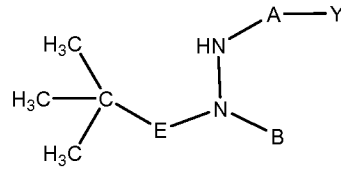
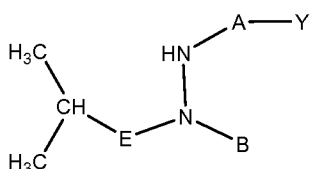
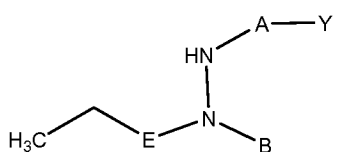
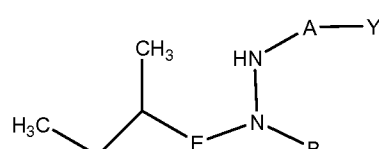
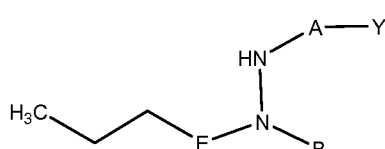
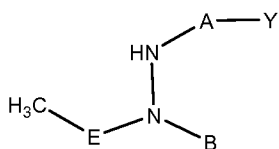


E is SO₂, CO, or CS. Thus, each of the structures below is contemplated. These structures, or pharmaceutically acceptable salts thereof, or prodrugs thereof, individually represent a compound which is an embodiment contemplated herein. In other words, each structure represents a different embodiment.



G is alkyl, aryl or heteroaryl having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. Thus, each of the structures below is contemplated. These structures, or pharmaceutically acceptable salts thereof, or prodrugs thereof, individually represent a compound which is an embodiment contemplated herein. In other words, each structure represents a different embodiment.

5



Aryl is an aromatic ring or ring system such as phenyl, naphthyl, biphenyl, and the like.

Heteroaryl is aryl having one or more N, O, or S atoms in the ring, i.e. one or more ring carbons are substituted by N, O, and/or S. While not intending to be limiting, examples of heteroaryl include thienyl, pyridinyl, furyl, benzothienyl, benzofuryl, imidazolyl, indolyl, and the like.

A substituent of aryl or heteroaryl may have up to 20 non-hydrogen atoms each in any stable combination and as many hydrogen atoms as necessary, wherein the non-hydrogen atoms are C, N, O, S, P, F, Cl, Br, and/or I in any stable combination. However, the total number of non-hydrogen atoms on all of the substituents combined must also be 20 or less. A substituent must be sufficiently stable for the compound to be useful as described herein. In addition to the atoms listed above, a substituent may also have a metal cation or other stable cation having an atom not listed above if the substituent is acidic and the salt form is stable. For example, -OH may form an -O⁻Na⁺ salt or CO₂H may form a CO₂⁻K⁺ salt. Thus, while not intending to limit the scope of the invention in any way, a substituent may be:

hydrocarbyl, i.e. a moiety consisting of only carbon and hydrogen such as alkyl, alkenyl, alkynyl, and the like, including linear, branched or cyclic hydrocarbyl, and combinations thereof;
hydrocarbyloxy, meaning O-hydrocarbyl such as OCH₃, OCH₂CH₃, O-cyclohexyl, etc, up to 19 carbon atoms;
other ether substituents such as CH₂OCH₃, (CH₂)₂OCH(CH₃)₂, and the like;
thioether substituents including S-hydrocarbyl and other thioether substituents;
hydroxyhydrocarbyl, meaning hydrocarbyl-OH such as CH₂OH, C(CH₃)₂OH, etc, up to 19 carbon atoms;
nitrogen substituents such as NO₂, CN, and the like, including
amino, such as NH₂, NH(CH₂CH₃OH), NHCH₃, and the like up to 19 carbon atoms;
carbonyl substituents, such as CO₂H, ester, amide, and the like;
halogen, such as chloro, fluoro, bromo, and the like
fluorocarbyl, such as CF₃, CF₂CF₃, etc.;
phosphorous substituents, such as PO₃²⁻, and the like;
sulfur substituents, including S-hydrocarbyl, SH, SO₃H, SO₂-hydrocarbyl, SO₃-hydrocarbyl, and the like.

Substituted aryl or heteroaryl may have as many substituents as the ring or ring system will bear, and the substituents may be the same or different. Thus, for example, an aryl ring or a heteroaryl ring may be substituted with chloro and methyl; methyl, OH, and F; CN, NO₂, and ethyl; and the like including any conceivable substituent or combination of substituent possible in light of this disclosure.

Substituted aryl or substituted heteroaryl also includes a bicyclic or polycyclic ring system wherein one or more rings are aromatic and one or more rings are not. For example, indanonyl, indanyl, indanoly, tetralonyl, and the like are substituted aryl. For this type of polycyclic ring system, an aromatic or heteroaromatic ring, not a non-aromatic ring, must be attached to the remainder of the molecule. In other words, in any structure depicting -B herein, where - is a bond, the bond is a direct bond to an aromatic ring.

In one embodiment, B is substituted aryl or heteroaryl.

In another embodiment B is substituted phenyl.

In another embodiment B has no halogen atoms.

In another embodiment B is 4-(1-hydroxy-2,2-dimethylpropyl)phenyl.

In another embodiment B is 4-(1-hydroxy-2-methylpropan-2-yl)phenyl.

In another embodiment B is 4-(1-hydroxy-2-methylpropyl)phenyl.

In another embodiment B is 4-(1-hydroxybutyl)phenyl.

In another embodiment B is 4-(1-hydroxyheptyl)phenyl.

In another embodiment B is 4-(1-hydroxyhexyl)phenyl.

5 In another embodiment B is 4-(1-hydroxypentyl)phenyl.

In another embodiment B is 4-(1-hydroxypropyl)phenyl.

In another embodiment B is 4-(3-hydroxy-2-methylheptan-2-yl)phenyl.

In another embodiment B is 4-(3-hydroxy-2-methyloctan-2-yl)phenyl.

In another embodiment B is 1-hydroxy-2,3-dihydro-1H-inden-5-yl.

10 In another embodiment B is 2,3-dihydro-1H-inden-5-yl.

In another embodiment B is 3-(hydroxyl(1-propylcyclobutyl)methyl)phenyl.

In another embodiment B is 4-(1-hydroxy-5,5-dimethylhexyl)phenyl.

In another embodiment B is 4-(hydroxy(1-propylcyclobutyl)methyl)phenyl.

In another embodiment B is 4-tert-butylphenyl.

15 In another embodiment B is 4-hexylphenyl.

In another embodiment B is 4-(1-hydroxy-2-phenylethyl)phenyl.

In another embodiment B is 4-(1-hydroxy-3-phenylpropyl)phenyl.

In another embodiment B is 4-(1-hydroxycyclobutyl)phenyl.

In another embodiment B is 4-(2-cyclohexyl-1-hydroxyethyl)phenyl.

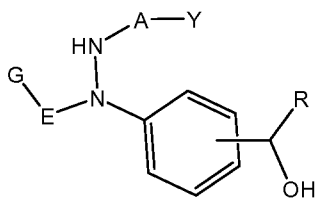
20 In another embodiment B is 4-(3-cyclohexyl-1-hydroxypropyl)phenyl.

In another embodiment B is 4-(cyclohexyl(hydroxy)methyl)phenyl.

In another embodiment B is 4-(cyclohexylmethyl)phenyl.

In another embodiment B is 4-(hydroxy(phenyl)methyl)phenyl.

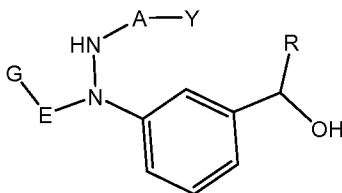
Another embodiment is a compound according to the structure



or a pharmaceutical salt thereof, or a prodrug thereof,

wherein R is hydrogen or C₁₋₁₀ hydrocarbyl.

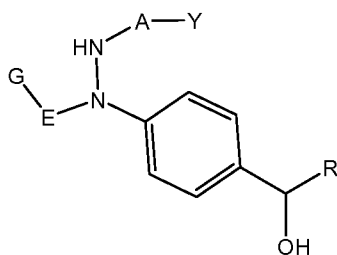
Another embodiment is a compound according to the structure



or a pharmaceutical salt thereof, or a prodrug thereof,

wherein R is hydrogen or C₁₋₁₀ hydrocarbyl.

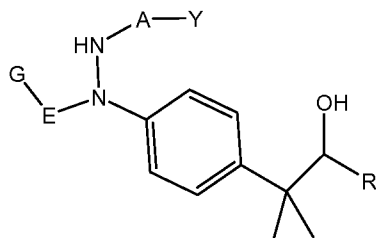
Another embodiment is a compound according to the structure



or a pharmaceutical salt thereof, or a prodrug thereof,

wherein R is hydrogen or C₁₋₁₀ hydrocarbyl.

Another embodiment is a compound according to the structure



"C1-10" hydrocarbyl is hydrocarbyl having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms.

Hydrocarbyl is a moiety consisting of only carbon and hydrogen, and includes, but is not limited to alkyl, alkenyl, alkynyl, and the like, and in some cases aryl, and combinations thereof.

5 Alkyl is hydrocarbyl having no double or triple bonds including:

linear alkyl such as methyl, ethyl, propyl, n-butyl, n-pentyl, n-hexyl, and the like;

branched alkyl such as isopropyl, branched butyl isomers (i.e. sec-butyl, tert-butyl, etc), branched pentyl isomers (i.e. isopentyl, etc), branched hexyl isomers, and higher branched alkyl fragments;

cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.; and alkyl fragments consisting of both cyclic and noncyclic components, whether linear or branched, which may be attached to the remainder of the molecule at any available position including terminal, internal, or ring carbon atoms.

Alkenyl is hydrocarbyl having one or more double bonds including

- 5 linear alkenyl, branched alkenyl, cyclic alkenyl, and combinations thereof in analogy to alkyl.

Alkynyl is hydrocarbyl having one or more triple bonds including linear alkynyl, branched alkynyl, cyclic alkynyl and combinations thereof in analogy to alkyl.

Aryl is an unsubstituted or substituted aromatic ring or ring system such as phenyl, naphthyl, biphenyl, and the like.

Aryl may or may not be hydrocarbyl, depending upon whether it has substituents with heteroatoms.

- 10 Arylalkyl is alkyl which is substituted with aryl. In other words alkyl connects aryl to the remaining part of the molecule. Examples are -CH₂-Phenyl, -CH₂-CH₂-Phenyl, and the like. Arylalkyl may or may not be hydrocarbyl, depending upon whether it has substituents with heteroatoms.

Unconjugated dienes or polyenes have one or more double bonds which are not conjugated. They may be linear, branched, or cyclic, or a combination thereof.

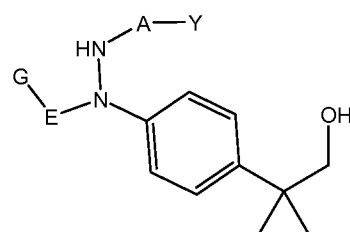
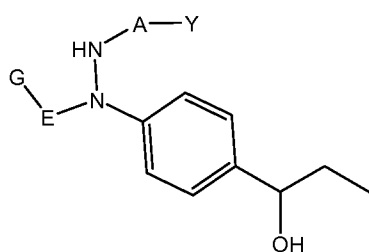
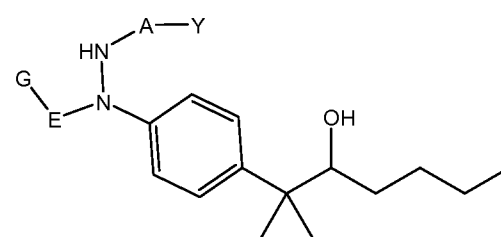
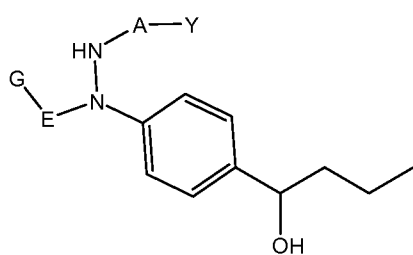
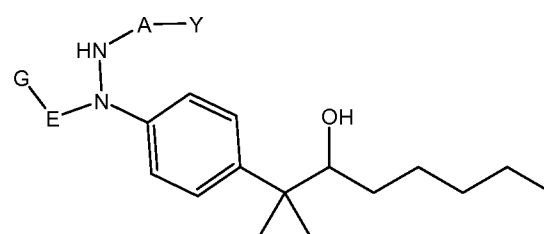
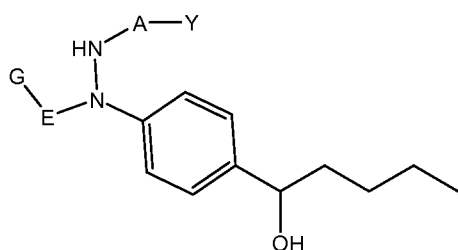
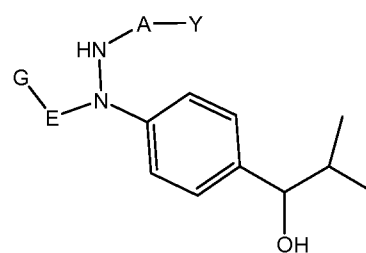
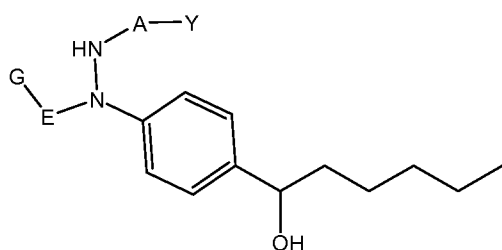
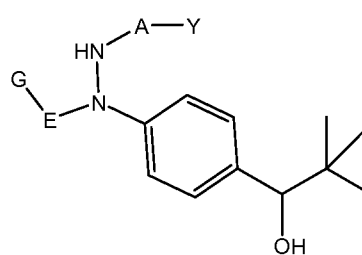
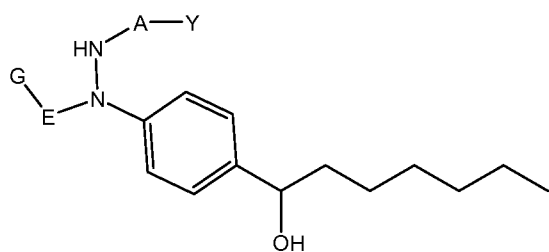
- 15 Combinations of the above are also possible.

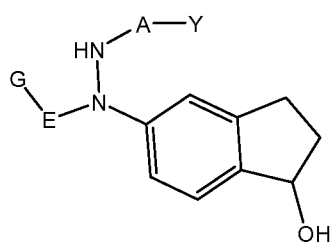
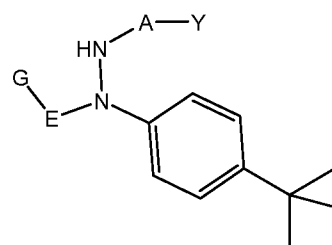
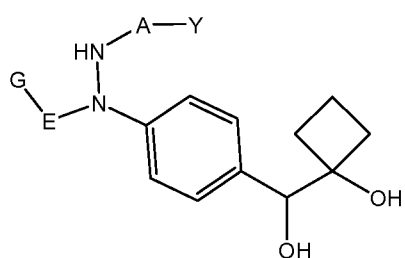
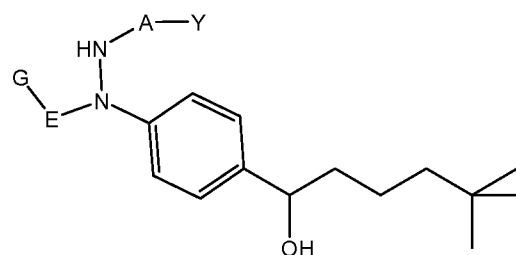
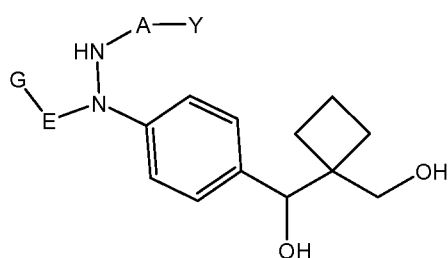
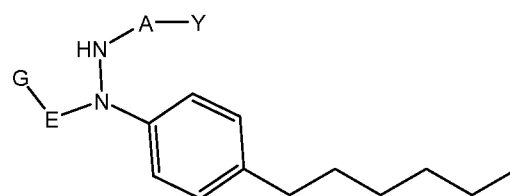
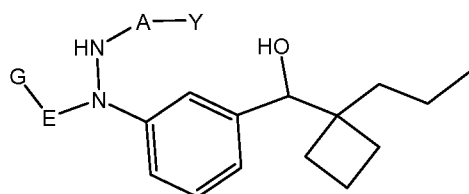
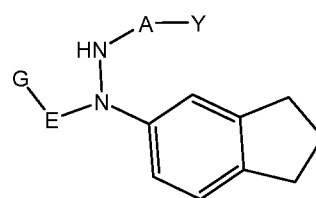
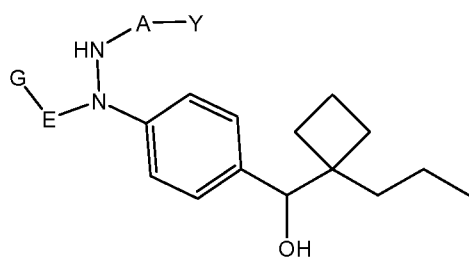
Hydroxyalkylaryl is aryl, including phenyl, heteroaryl and the like, which is substituted with hydroxyalkyl.

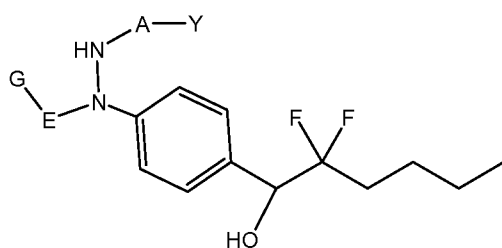
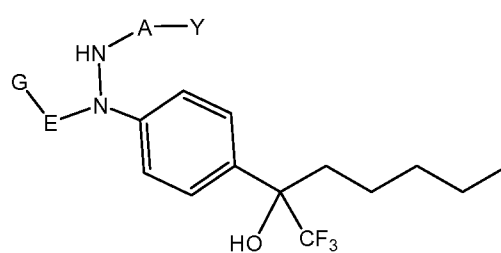
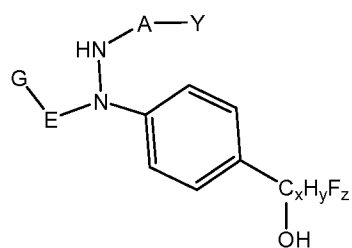
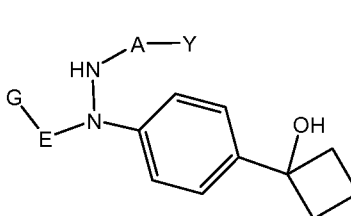
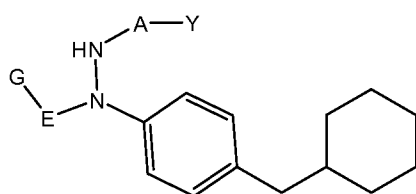
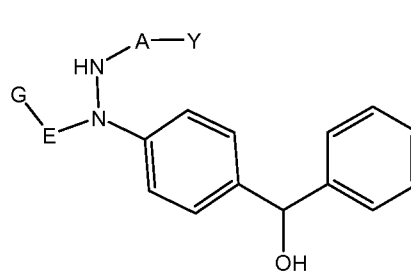
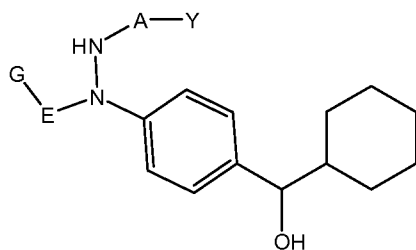
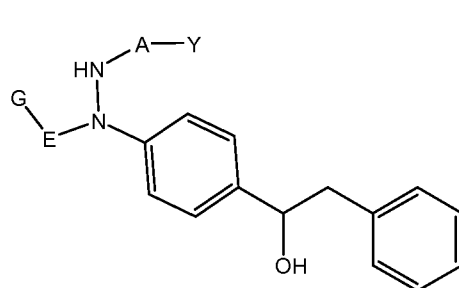
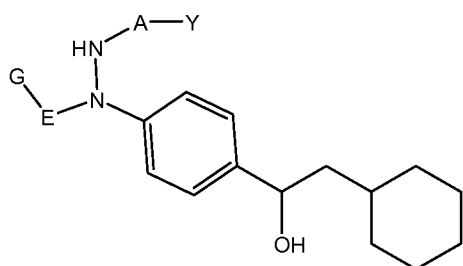
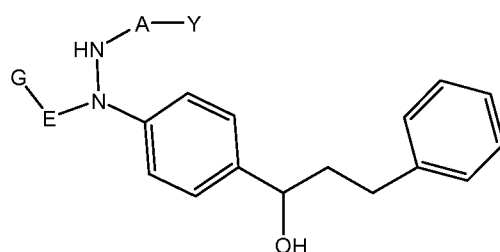
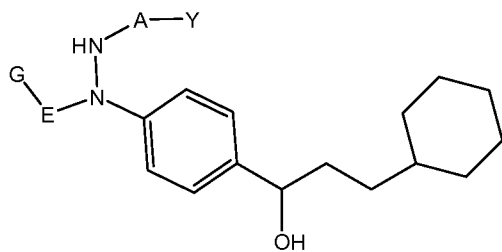
Hydroxyalkyl is alkyl, whether linear, branched, cyclic, or a combination thereof, which has a hydroxyl substituent.

For example, CHOH(CH₂)₄CH₃ is hydroxyalkyl, and phenyl-CHOH(CH₂)₄CH₃, is hydroxyalkylaryl.

- 20 Thus, each of the structures below is contemplated. These structures, or pharmaceutically acceptable salts thereof, or prodrugs thereof, individually represent a compound which is an embodiment contemplated herein. In other words, each structure represents a different embodiment.







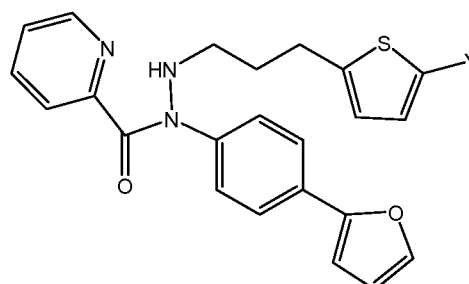
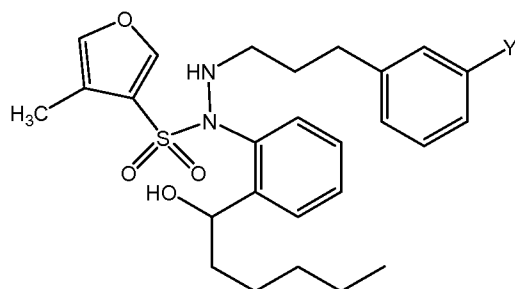
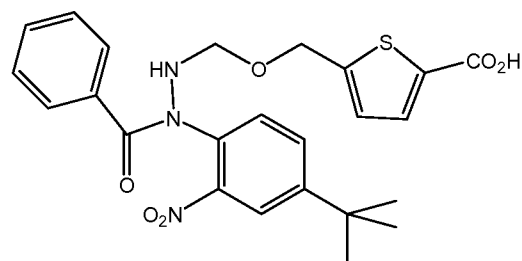
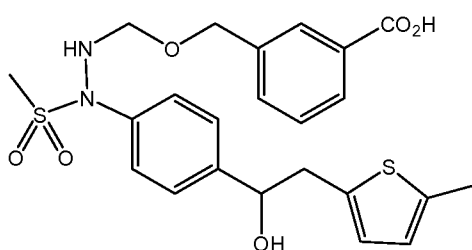
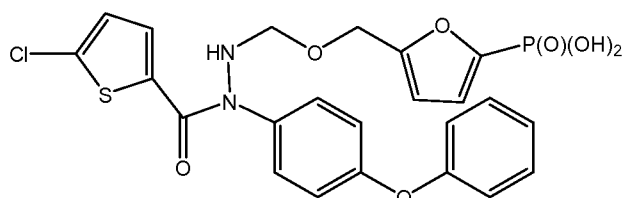
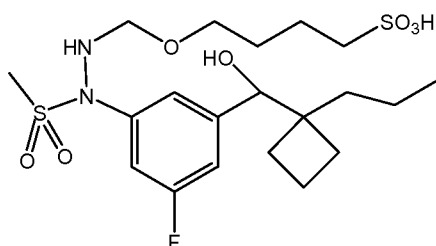
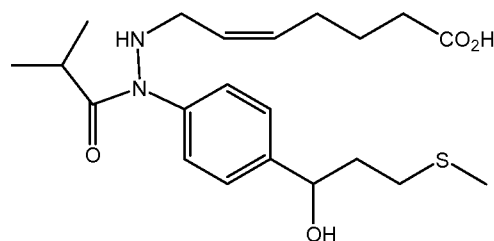
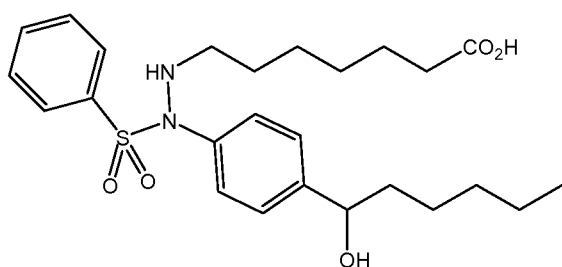
In the above embodiments, x is 5, 6, or 7, and y + z is $2x + 1$.

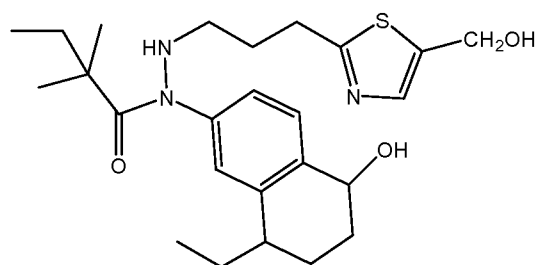
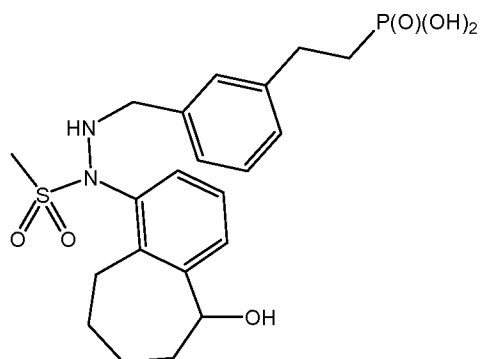
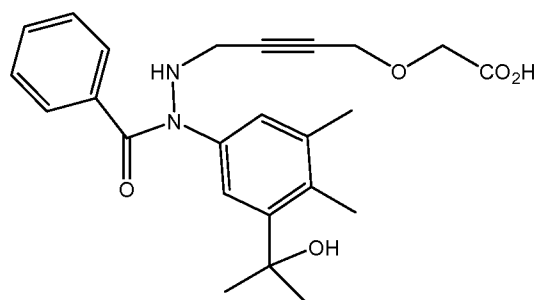
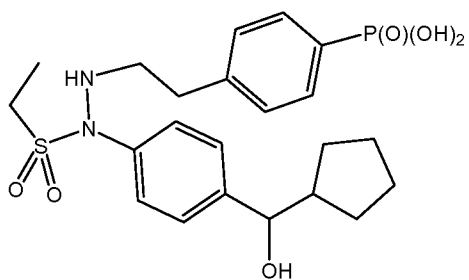
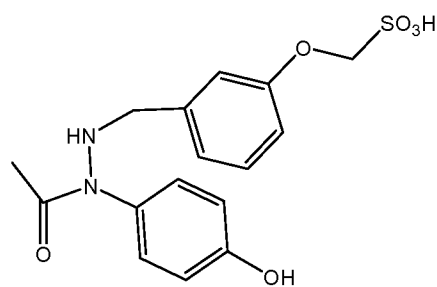
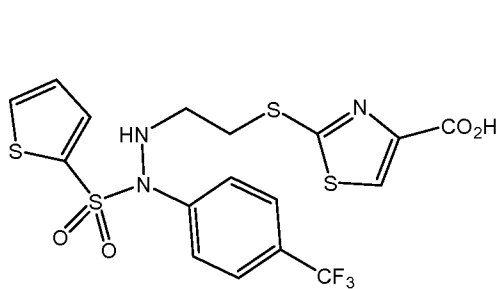
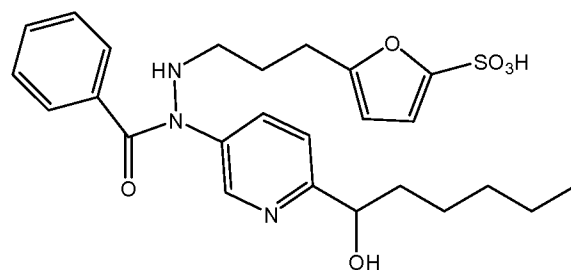
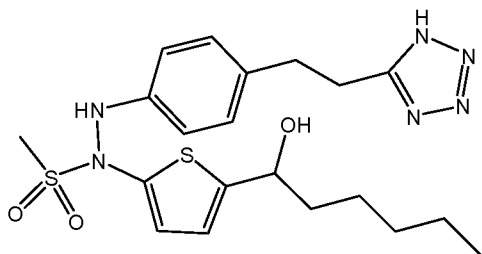
In one embodiment, x is 5 and y + z is 11.

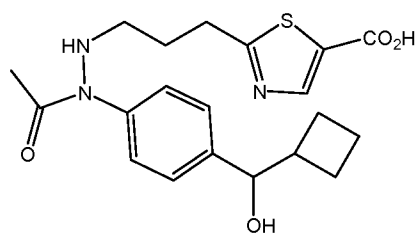
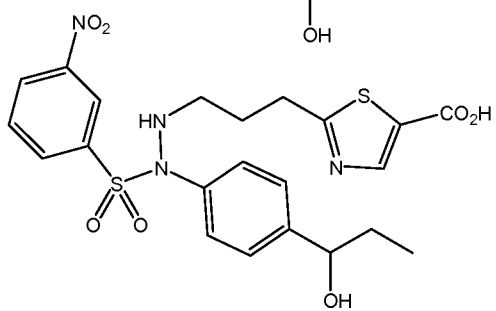
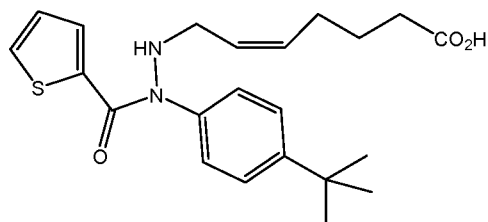
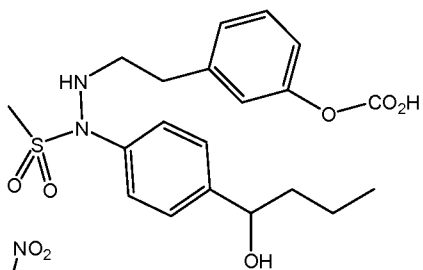
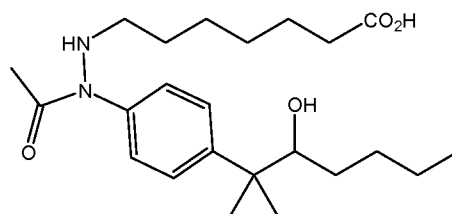
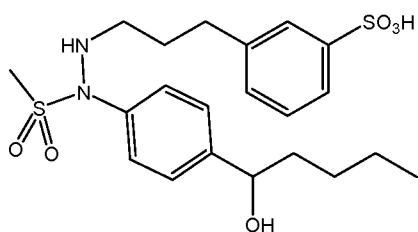
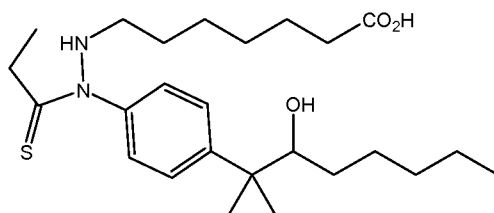
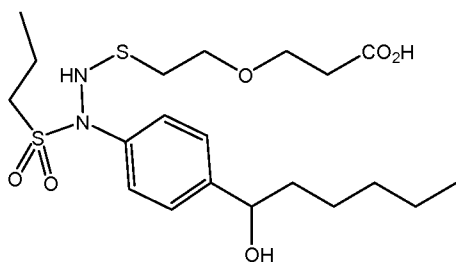
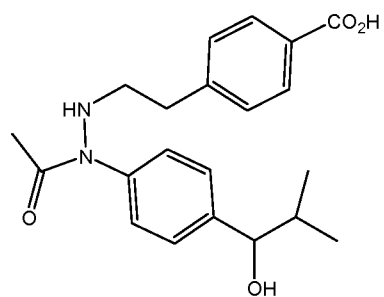
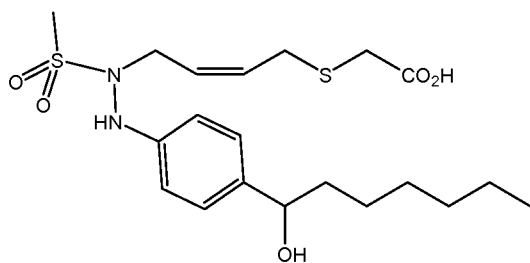
5 In another embodiment, x is 6 and y + z is 13.

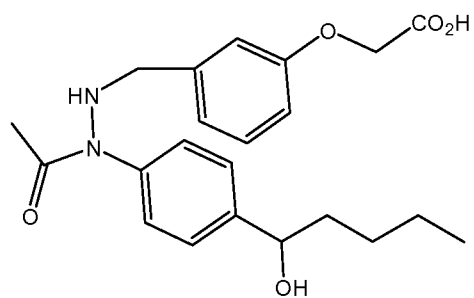
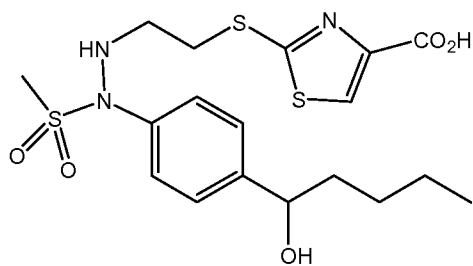
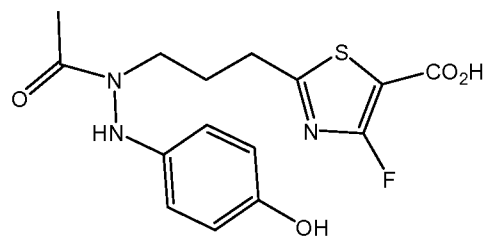
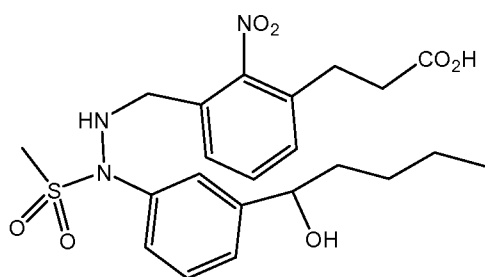
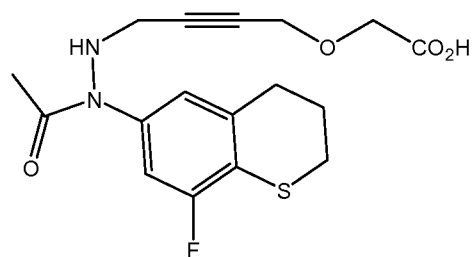
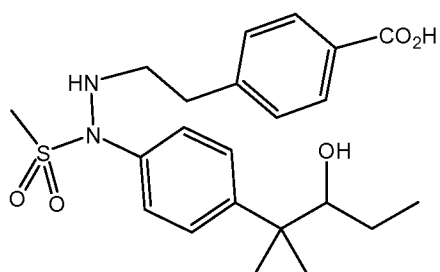
In another embodiment, x is 7 and y + z is 15.

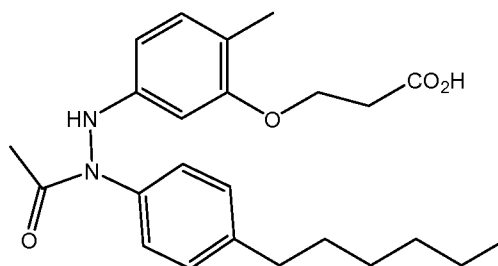
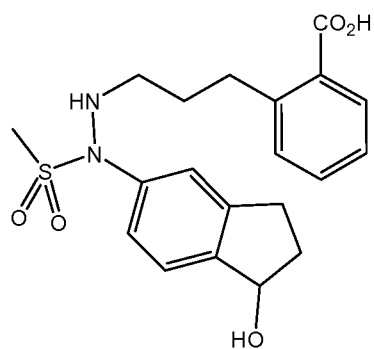
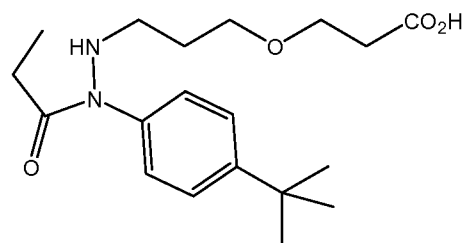
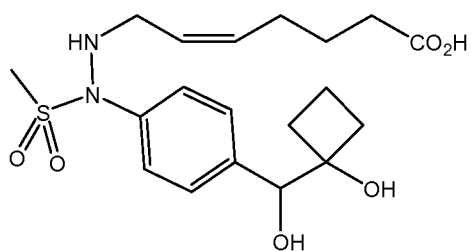
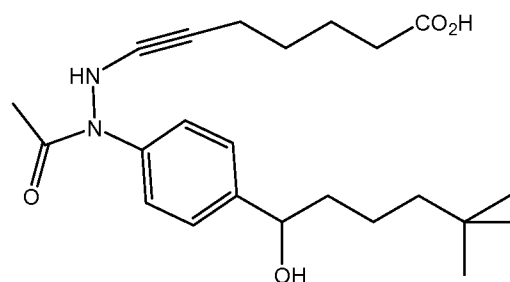
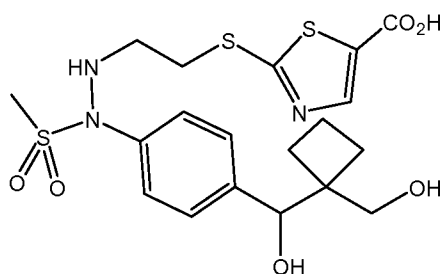
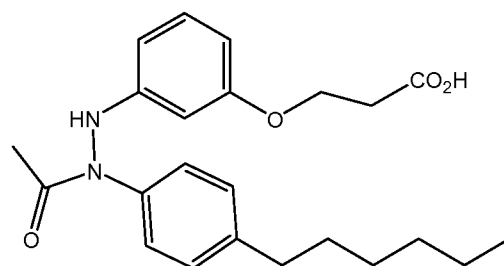
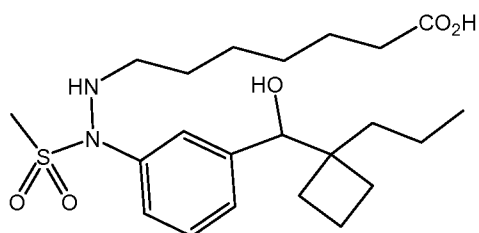
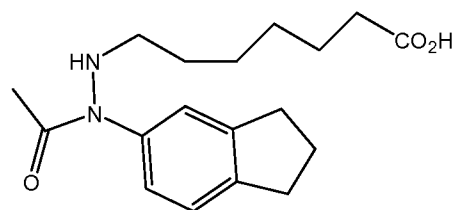
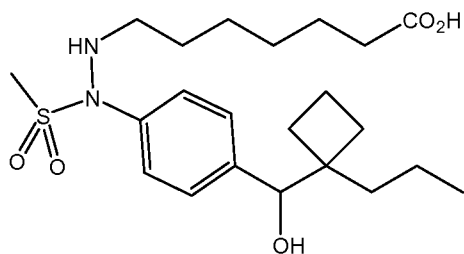
Hypothetical examples of useful compounds are shown below.

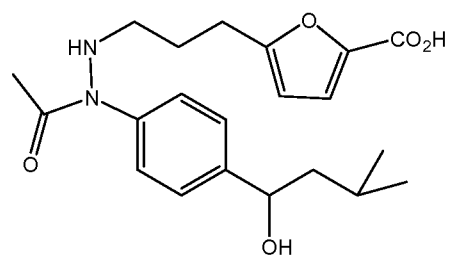
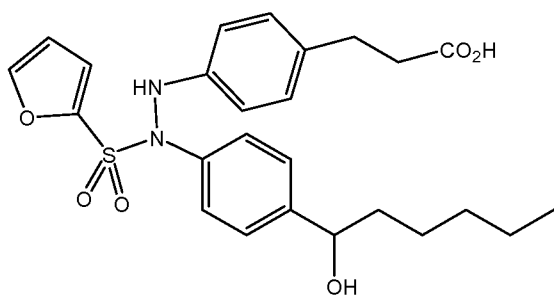
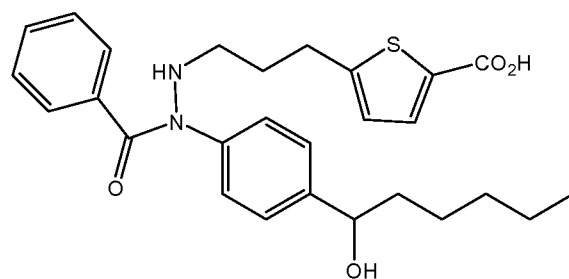
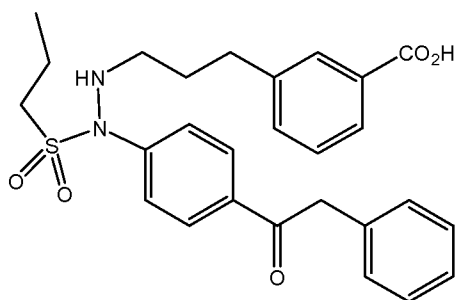
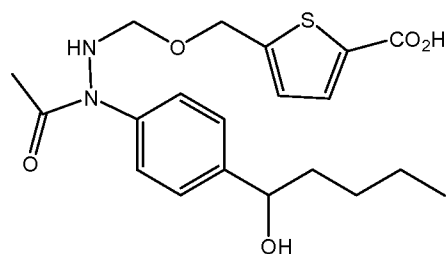
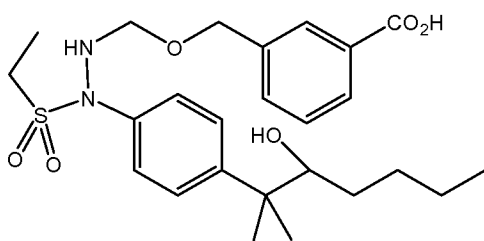
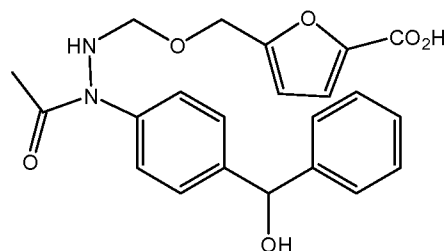
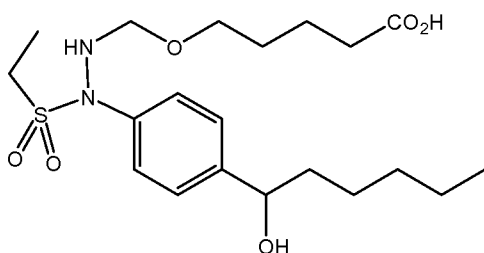
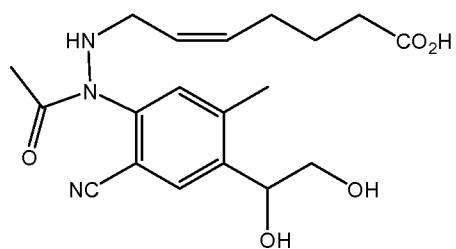
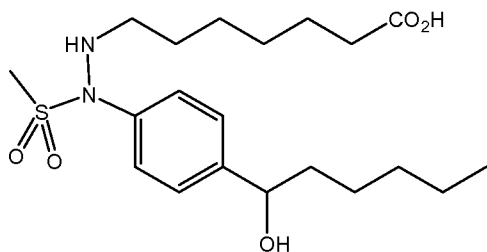






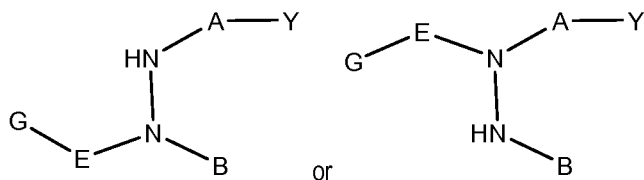




**Compound examples:**

The following are hypothetical examples of useful compounds:

- 5 **Compound Example 1.** A compound having a structure



or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 14 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 14 carbon atoms; or Y is a tetrazolyl functional group;

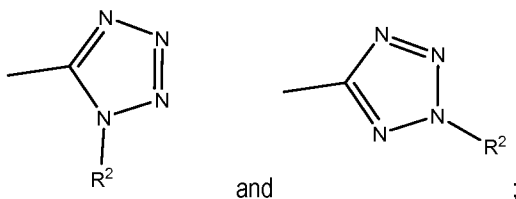
- 5 A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-CH_2-$ may be replaced by S or O, and 1 $-CH_2-CH_2-$ may be replaced by $-CH=CH-$ or $-C\equiv C-$;

E is SO_2 , CO, or CS;

G is alkyl, aryl or heteroaryl having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms; and

- 10 B is substituted aryl or substituted heteroaryl.

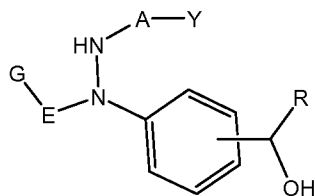
Compound Example 2. The compound according to compound example 1 wherein Y is selected from CO_2R^2 , $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH , $P(O)(OH)_2$, $CONHSO_2R^2$, $SO_2N(R^2)_2$, SO_2NHR^2 ,



- 15 wherein R^2 is independently H, C_1-C_6 alkyl, unsubstituted phenyl, or unsubstituted biphenyl.

Compound Example 3. The compound according to compound example 1 or 2 wherein B is substituted phenyl.

Compound Example 4. The compound according to compound example 1 or 2 having a structure



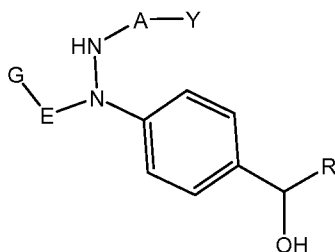
or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

- 20 R is hydrogen or C_{1-10} hydrocarbyl.

Compound Example 5. The compound according to compound example 4 wherein R is alkyl.

Compound Example 6. The compound according to compound example 4 wherein R is arylalkyl.

Compound Example 7. The compound according to compound example any one of compound examples 1 to 6 having a structure



or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

R is hydrogen or C₁₋₁₀ hydrocarbonyl.

Compound Example 8. The compound according to compound example 1 or 2 wherein A is (3-methylphenoxy)methyl.

Compound Example 9. The compound according to compound example 1 or 2 wherein A is (4-but-2-ynoxy)methyl.

Compound Example 10. The compound according to compound example 1 or 2 wherein A is 2-(2-ethylthio)thiazol-4-yl.

Compound Example 11. The compound according to compound example 1 or 2 wherein A is 2-(3-propyl)thiazol-5-yl.

Compound Example 12. The compound according to compound example 1 or 2 wherein A is 3-methoxymethyl)phenyl.

Compound Example 13. The compound according to compound example 1 or 2 wherein A is 3-(3-propylphenyl.

Compound Example 14. The compound according to compound example 1 or 2 wherein A is 3-methylphenethyl.

Compound Example 15. The compound according to compound example 1 or 2 wherein A is 4-(2-ethyl)phenyl.

Compound Example 16. The compound according to compound example 1 or 2 wherein A is 4-phenethyl.

Compound Example 17. The compound according to compound example 1 or 2 wherein A is 4-methoxybutyl.

Compound Example 18. The compound according to compound example 1 or 2 wherein A is 5-(methoxymethyl)furan-2-yl.

Compound Example 19. The compound according to compound example 1 or 2 wherein A is 5-(methoxymethyl)thiophen-2-yl.

Compound Example 20. The compound according to compound example 1 or 2 wherein A is 5-(3-propyl)furan-2-yl.

Compound Example 21. The compound according to compound example 1 or 2 wherein A is 5-(3-propyl)thiophen-2-yl.

Compound Example 22. The compound according to compound example 1 or 2 wherein A is 6-hexyl.

Compound Example 23. The compound according to compound example 1 or 2 wherein A is (Z)-6-hex-4-enyl.

Compound Example 24. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-2,2-dimethylpropyl)phenyl.

Compound Example 25. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-2-methylpropan-2-yl)phenyl.

Compound Example 26. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-2-methylpropyl)phenyl.

Compound Example 27. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxybutyl)phenyl.

Compound Example 28. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxyheptyl)phenyl.

5 **Compound Example 29.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxyhexyl)phenyl.

Compound Example 30. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxypentyl)phenyl.

10 **Compound Example 31.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxypropyl)phenyl.

Compound Example 32. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(3-hydroxy-2-methylheptan-2-yl)phenyl.

Compound Example 33. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(3-hydroxy-2-methyloctan-2-yl)phenyl.

15 **Compound Example 34.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 1-hydroxy-2,3-dihydro-1H-inden-5-yl.

Compound Example 35. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 2,3-dihydro-1H-inden-5-yl.

20 **Compound Example 36.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 3-(hydroxy(1-propylcyclobutyl)methyl)phenyl.

Compound Example 37. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-5,5-dimethylhexyl)phenyl.

Compound Example 38. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(hydroxy(1-propylcyclobutyl)methyl)phenyl.

25 **Compound Example 39.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-tert-butylphenyl.

Compound Example 40. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-hexylphenyl.

30 **Compound Example 41.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-2-phenylethyl)phenyl.

Compound Example 42. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-3-phenylpropyl)phenyl.

Compound Example 43. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxycyclobutyl)phenyl.

35 **Compound Example 44.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(2-cyclohexyl-1-hydroxyethyl)phenyl.

Compound Example 45. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(3-cyclohexyl-1-hydroxypropyl)phenyl.

Compound Example 46. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(cyclohexyl(hydroxy)methyl)phenyl.

Compound Example 47. The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(cyclohexylmethyl)phenyl.

5 **Compound Example 48.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(hydroxy(phenyl)methyl)phenyl.

The following are hypothetical examples of compositions, kits, methods, uses, and medicaments employing the hypothetical compound examples.

Composition Example:

10 A composition comprising a compound according to any one of compound examples 1 to 48, wherein said composition is a liquid which is ophthalmically acceptable.

Medicament Examples:

Use of a compound according to any one of compound examples 1 to 48 in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension in a mammal.

15 A medicament comprising a compound according to any one of compound examples 1 to 48, wherein said composition is a liquid which is ophthalmically acceptable.

Method Example:

A method comprising administering a compound according to any one of compound examples 1 to 48 to a mammal for the treatment of glaucoma or ocular hypertension.

20 **Kit Example:**

A kit comprising a composition comprising compound according to any one of compound examples 1 to 48, a container, and instructions for administration of said composition to a mammal for the treatment of glaucoma or ocular hypertension.

25 A "pharmaceutically acceptable salt" is any salt that retains the activity of the parent compound and does not impart any additional deleterious or untoward effects on the subject to which it is administered and in the context in which it is administered compared to the parent compound. A pharmaceutically acceptable salt also refers to any salt which may form in vivo as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt.

30 Pharmaceutically acceptable salts of acidic functional groups may be derived from organic or inorganic bases. The salt may comprise a mono or polyvalent ion. Of particular interest are the inorganic ions lithium, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Hydrochloric acid or some other pharmaceutically acceptable acid may form a salt with a compound that
35 includes a basic group, such as an amine or a pyridine ring.

A "prodrug" is a compound which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly herein as is generally understood in the art. While not intending to limit the scope of the invention, conversion may occur by hydrolysis of an ester group or some other biologically labile group.

Generally, but not necessarily, a prodrug is inactive or less active than the therapeutically active compound to which it is converted. Ester prodrugs of the compounds disclosed herein are specifically contemplated. An ester may be derived from a carboxylic acid of C1 (i.e. the terminal carboxylic acid of a natural prostaglandin), or an ester may be derived from a carboxylic acid functional group on another part of the molecule, such as on a phenyl ring. While not
5 intending to be limiting, an ester may be an alkyl ester, an aryl ester, or a heteroaryl ester. The term alkyl has the meaning generally understood by those skilled in the art and refers to linear, branched, or cyclic alkyl moieties. C₁₋₆ alkyl esters are particularly useful, where alkyl part of the ester has from 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl isomers, hexyl isomers, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and combinations thereof having from 1-6 carbon atoms, etc.

10 Those skilled in the art will readily understand that for administration or the manufacture of medicaments the compounds disclosed herein can be admixed with pharmaceutically acceptable excipients which per se are well known in the art. Specifically, a drug to be administered systemically, it may be confectioned as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

15 For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or
20 glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjuncts in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical
25 composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's
30 Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for
35 example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

The amount of the presently useful compound or compounds administered is dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgment of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds may be in the range of about 0.5 or about 1 to about 100 mg/kg/day.

A liquid which is ophthalmically acceptable is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

<u>Ingredient</u>	<u>Amount (% w/v)</u>
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40

	tonicity adjustor	1-10
	buffer	0.01-10
	pH adjustor	q.s. pH 4.5-7.5
	antioxidant	as needed
5	surfactant	as needed
	purified water	as needed to make 100%

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The compounds disclosed herein are also useful in combination with other drugs useful for the treatment of glaucoma or other conditions.

For the treatment of glaucoma, combination treatment with the following classes of drugs are contemplated: β -Blockers (or β -adrenergic antagonists) including carteolol, levobunolol, metipranolol, timolol hemihydrate, timolol maleate, β 1-selective antagonists such as betaxolol, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Adrenergic Agonists including

non-selective adrenergic agonists such as epinephrine borate, epinephrine hydrochloride, and dipivefrin, and the like, or pharmaceutically acceptable salts or prodrugs thereof; and

α 2-selective adrenergic agonists such as apraclonidine, brimonidine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Carbonic Anhydrase Inhibitors including acetazolamide, dichlorphenamide, methazolamide, brinzolamide, dorzolamide, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Cholinergic Agonists including

direct acting cholinergic agonists such as carbachol, pilocarpine hydrochloride, pilocarpine nitrate, pilocarpine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

cholinesterase inhibitors such as demecarium, echothiophate, physostigmine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Glutamate Antagonists and other neuroprotective agents such as Ca^{2+} channel blockers such as memantine, amantadine, rimantadine, nitroglycerin, dextrophan, detromethorphan, CGS-19755, dihydropyridines, verapamil, emopamil, benzothiazepines, bepridil, diphenylbutylpiperidines, diphenylpiperazines, HOE 166 and related drugs, fluspirilene, eliprodil, ifenprodil, CP-101,606, tibalosine, 2309BT, and 840S, flunarizine, nicardipine, nifedipine, nimodipine, barnidipine, verapamil, lidoflazine, prenylamine lactate, amiloride, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Prostanamides such as bimatoprost, or pharmaceutically acceptable salts or prodrugs thereof; and

Prostaglandins including travoprost, UFO-21, chloprostenol, fluprostenol, 13,14-dihydro-chloprostenol, isopropyl unoprostone, latanoprost and the like.

Cannabinoids including CB1 agonists such as WIN-55212-2 and CP-55940 and the like, or pharmaceutically acceptable salts or prodrugs thereof.

5 For treatment of diseases affecting the eye including glaucoma, these compounds can be administered topically, periorcularly, intraocularly, or by any other effective means known in the art.

In addition to the treatment of glaucoma, prostaglandin EP₂ selective agonists are believed to have several medical uses. For example, U.S. Patent No. 6,437,146 teaches the use of prostaglandin EP₂ selective agonists "for treating or preventing inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis, 10 osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Crohn's disease, atrophic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, pain and 15 tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodosa, rheumatic fever, Sjögren's syndrome, Behçet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic neuropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimer's disease, 20 kidney dysfunction (nephritis, nephritic syndrome, etc.), liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel disease, etc.) shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hypercalcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially, 25 urolithiasis), solid carcinoma, mesangial proliferative glomerulonephritis, edema (e.g. cardiac edema, cerebral edema, etc.), hypertension such as malignant hypertension or the like, premenstrual tension, urinary calculus, oliguria such as the one caused by acute or chronic failure, hyperphosphaturia, or the like."

United State Patent No 6,710,072 teaches the use of EP₂ agonists for the treatment or prevention of "osteoporosis, constipation, renal disorders, sexual dysfunction, baldness, diabetes, cancer and in disorder of 30 immune regulation...various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris."

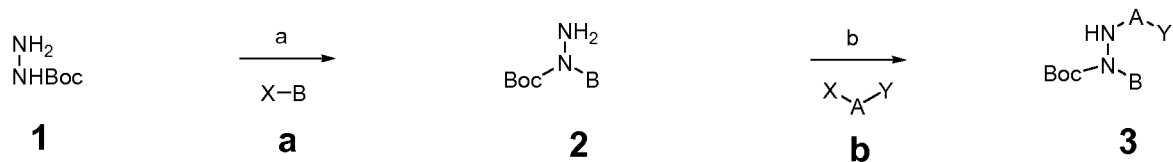
These compounds can also be used to treat or prevent conditions affecting the posterior part of the eye including maculopathies/ retinal degeneration such as non-exudative age related macular degeneration (ARMD), exudative age related macular degeneration (ARMD), choroidal neovascularization, diabetic retinopathy, acute 35 macular neuroretinopathy, central serous chorioretinopathy, cystoid macular edema, and diabetic macular edema; uveitis/ retinitis/ choroiditis such as acute multifocal placoid pigment epitheliopathy, Behçet's disease, birdshot retinochoroidopathy, infectious (syphilis, Lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (mewds), ocular sarcoidosis, posterior scleritis,

serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-and Harada syndrome; vascular diseases/ exudative diseases such as retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angioid streaks, familial exudative vitreoretinopathy, and Eales disease; traumatic/ surgical conditions such as sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, conditions caused by laser, conditions caused by photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation retinopathy, and bone marrow transplant retinopathy; proliferative disorders such as proliferative vitreal retinopathy and epiretinal membranes, and proliferative diabetic retinopathy; infectious disorders such as ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associate with HIV infection, uveitic disease associate with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis; genetic disorders such as retinitis pigmentosa, systemic disorders with associated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, and pseudoxanthoma elasticum; retinal tears/ holes such as retinal detachment, macular hole, and giant retinal tear; tumors such as retinal disease associated with tumors, congenital hypertrophy of the retinal pigmented epithelium, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma, and intraocular lymphoid tumors; and miscellaneous other diseases affecting the posterior part of the eye such as punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, and acute retinal pigment epitheliitis. Preferably, the disease or condition is retinitis pigmentosa, proliferative vitreal retinopathy (PVR), age-related macular degeneration (ARMD), diabetic retinopathy, diabetic macular edema, retinal detachment, retinal tear, uveitis, or cytomegalovirus retinitis.

These compounds are also useful in treating asthma.

Synthetic Methods

Scheme 1

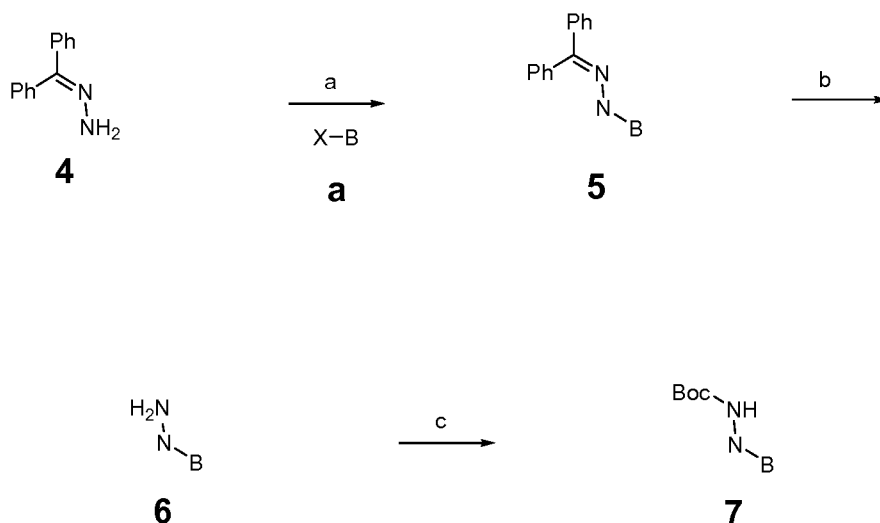


(a) **a**, CuI, MeN(H)CH₂CH₂N(H)Me, K₂CO₃, MeCN; (b) NaH, **b**, DMF

While there are many ways the compounds disclosed herein, one exemplary synthesis may begin with commercially available N-Boc hydrazine (**1**, also known as *t*-butyl carbazate, Aldrich Chemical Company, see Scheme 1). N-arylation occurs to give **2** according to Buchwald's copper-catalyzed procedure (*Org. Lett.* **2001**, 3, 3803-3805) using a wide variety of substituted bromophenyl and other bromoaryl compounds **a**. The haloarenes **a** are either available commercially or may be made according to published literature procedures. For example, United States Patent Application No. 11/009,298, filed on December 10, 2004 and United States Provisional Patent Application 60/742,779 filed on December 6, 2005, both of which are expressly incorporated by reference herein, disclose methods of making a number of useful substituted bromophenyl compounds. These procedures may also be readily adapted to other bromoaryl compounds such as substituted bromothieryl, substituted bromofuryl, substituted bromopyridinyl, substituted bromonaphthyl, substituted bromobenzothieryl, and the like. Intermediate **2** is then alkylated on N' using electrophiles **b** to provide intermediate **3**.

Examples of **b** include ethyl 7-bromoheptanoate (commercially available from Aldrich Chemical Company) and methyl 7-bromohept-5-ynoate (*Org. Synth.* **1993**, Collect. Vol. VIII, 415-420). Examples of **b** also include electrophiles bearing aryl and heteroaryl groups (e.g. methyl 4-(2-bromoethyl)benzoate [available in one step from commercially available 4-(2-bromoethyl)benzoic acid] and methyl 5-(3-bromopropyl)-thiophene-2-carboxylate [see WO 2004/037786, incorporated by reference herein]). Other methods for preparing **b** are readily ascertained by those of ordinary skill in the art based upon this disclosure.

Scheme 2



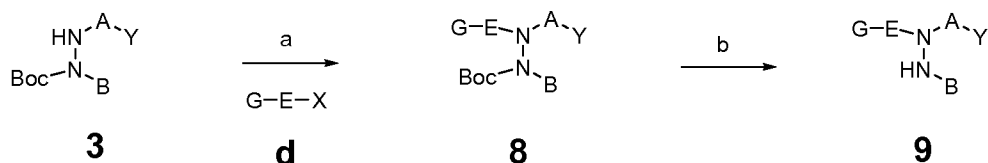
(a) **a**, Pd(OAc)₂, BINAP, NaOt-Bu, toluene; (b) TsOH, H₂O, EtOH; (c) BOC₂O, CH₂Cl₂.

In another hypothetical example, benzophenone hydrazone (**4**, Aldrich chemical company) serves as the starting material (see Scheme 2). In this case, N'-arylation occurs to give **5** according to Buchwald's palladium-catalyzed procedure (*J. Am. Chem. Soc.* **1998**, 120, 6621-6622) using a wide variety of substituted bromophenyl and

other bromoaryl compounds **a**. Deprotection reveals the aryl hydrazine **6** which is protected to give N-Boc-N'-aryl hydrazine **7**. A large variety of substituted aryl hydrazines such as **6** are commercially available.

Intermediates **2** and **7** are regioisomers. In certain cases, the copper chemistry used to arrive at **2** will also afford compound **7** (see Buchwald, above, and Buchwald, *J. Am. Chem. Soc.* **2001**, 123, 7727-7729). Palladium-catalyzed arylation may also afford mixtures of regioisomers (Wang, et al., *Tetrahedron Lett.* **1999**, 40, 3543-3546), mainly favoring isomer **2**. This represents an alternative approach to compound **7**.

Scheme 3

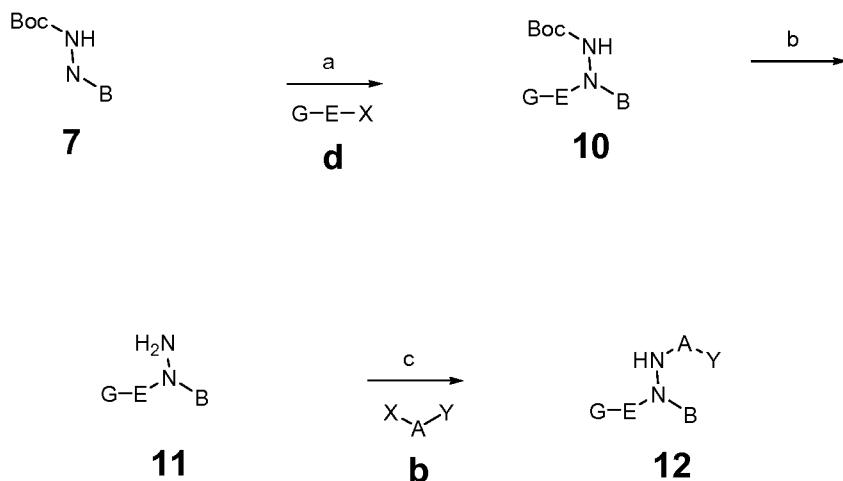


(a) **d**, Et₃N, DMAP, CH₂Cl₂; (b) TFA, CH₂Cl₂.

Intermediate **3** may be acylated or sulfonylated using an appropriate acyl or sulfonyl halide **d** to afford intermediate **8**. Removal of the Boc protecting group then affords compound **9** (Scheme 3).

In another hypothetical example, intermediate **7** may be acylated or sulfonylated using an appropriate acyl or sulfonyl halide **d** to afford intermediate **10**. Removal of the Boc protecting group and alkylation of the resulting amine **11** then affords compound **12** (Scheme 4). Compounds **9** and **12** may be the target compounds, or may require deprotection(s) and/or functionalization (depending on the nature of B and Y) to arrive at the target compounds.

Scheme 4



(a) **d**, Et₃N, DMAP, CH₂Cl₂; (b) TFA, CH₂Cl₂. (c) NaH, **b**, DMF.

Based upon this disclosure, numerous other ways of preparing the compounds disclosed herein will be apparent to a person of ordinary skill in the art.

A person of ordinary skill in the art understands the meaning of the stereochemistry associated with the hatched wedge/solid wedge structural features. For example, an introductory organic chemistry textbook (Francis A. Carey, Organic Chemistry, New York: McGraw-Hill Book Company 1987, p. 63) states "a wedge indicates a bond coming from the plane of the paper toward the viewer" and the hatched wedge, indicated as a "dashed line", "represents a bond receding from the viewer."

Treatment of inflammatory bowel disease may be accomplished by the administration of the compounds described herein to the suffering mammal. Inflammatory bowel disease describes a variety of diseases characterized by inflammation of the bowels including, but not limited to, ulcerative colitis and Crohn's disease. Treatment may be accomplished by oral administration, by suppository, or parenteral administration, or some other suitable method.

While not intending to limit the scope of the invention in any way, delivery of the compounds disclosed herein to the colon via oral dosage forms may be accomplished by any of a number of methods known in the art. For example, reviews by Chourasia and Jain in J Pharm Pharmaceut Sci 6 (1): 33-66, 2003 and Shareef et. al (AAPS PharmSci 2003; 5 (2) Article 17) describe a number of useful methods. While not intending to limit the scope of the invention in any way these methods include 1) administration of a prodrug, including an azo or a carbohydrate based prodrug; 2) coating the drug with, or encapsulating or impregnating the drug into a polymer designed for delivery to the colon, 3) time released delivery of the drug, 4) use of a bioadhesive system; and the like.

While not intending to be bound in any way by theory, it is believed that intestinal microflora are capable of reductive cleavage of an azo bond leaving the two nitrogen atoms as amine functional groups. While not intending to limit the scope of the invention in any way, the azo prodrug approach has been used to deliver 5-aminosalicylic acid to the colons of humans in clinical trials for the treatment of inflammatory bowel disease. It is also believed that bacteria of the lower GI also have enzymes which can digest glycosides, glucuronides, cyclodextrins, dextrans, and other carbohydrates, and ester prodrugs formed from these carbohydrates have been shown to deliver the parent active drugs selectively to the colon. For example, in vivo and in vitro studies on rats and guinea pigs with prodrugs of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone, suggest that glycoside conjugates may be useful for the delivery of steroids to the human colon. Other in vivo studies have suggested that glucouronide, cyclodextrin, and dextran prodrugs of steroids or non-steroidal anti-inflammatory drugs are useful for delivery of these drugs to the lower GI tract. An amide of salicylic acid and glutamic acid has been shown to be useful for the delivery of salicylic acid to the colon of rabbit and dog.

While not intending to limit the scope of the invention in any way, carbohydrate polymers such as amylase, arabinogalactan, chitosan, chondroitin sulfate, dextran, guar gum, pectin, xylan, and the like, or azo-group containing polymers can be used to coat a drug compound, or a drug may be impregnated or encapsulated in the polymer. It is believed that after oral administration, the polymers remain stable in the upper GI tract, but are digested by the microflora of the lower GI thus releasing the drug for treatment.

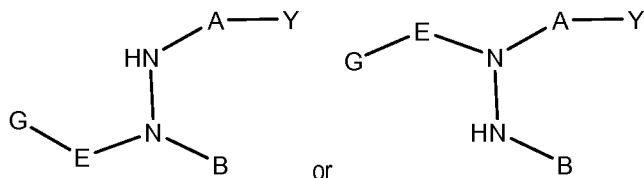
Polymers which are sensitive to pH may also be used since the colon has a higher pH than the upper GI tract. Such polymers are commercially available. For example, Rohm Pharmaceuticals, Darmstadt, Germany, commercially provides pH dependent methacrylate based polymers and copolymers which have varying solubilities

over different pH ranges based upon the number of free carboxylate groups in the polymer under the tradename Eudragit®. Several Eudragit® dosage forms are currently used to deliver salsalazine for the treatment of ulcerative colitis and Crohn's disease. Time release systems, bioadhesive systems, and other delivery systems have also been studied.

5 The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus,
10 however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the claims.

What is claimed is:

1. A compound having a structure



or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

5 wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 14 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 14 carbon atoms; or Y is a tetrazolyl functional group;

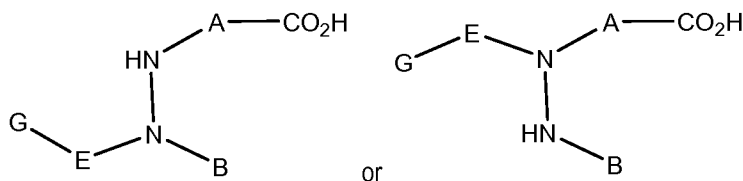
A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-CH_2-$ may be replaced by S or O, and 1 $-CH_2-CH_2-$ may be replaced by $-CH=CH-$ or $-C\equiv C-$;

10 E is SO_2 , CO, or CS;

G is alkyl, aryl or heteroaryl having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms; and

B is substituted aryl or substituted heteroaryl.

2. A compound which is a carboxylic acid or a bioisostere thereof, said carboxylic acid having a structure



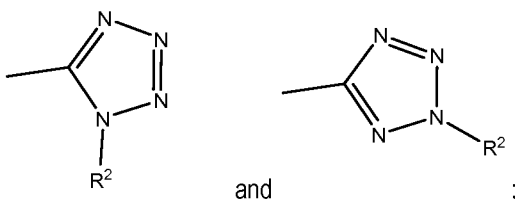
15 or a pharmaceutically acceptable salt thereof, or a prodrug thereof,;

wherein A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-CH_2-$ may be replaced by S or O, and 1 $-CH_2-CH_2-$ may be replaced by $-CH=CH-$ or $-C\equiv C-$;

G is alkyl, aryl or heteroaryl having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms; and

20 B is substituted aryl or substituted heteroaryl.

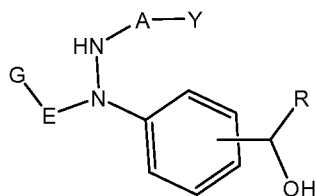
3. The compound of claim 1 wherein Y is selected from CO_2R^2 , $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, $CONH(CH_2CH_2OH)$, CH_2OH , $P(O)(OH)_2$, $CONHSO_2R^2$, $SO_2N(R^2)_2$, SO_2NHR^2 ,



wherein R^2 is independently H, C_1-C_6 alkyl, unsubstituted phenyl, or unsubstituted biphenyl.

25 4. The compound according to any one of claims 1-3, wherein B is substituted phenyl.

5. The compound of claim 4 having a structure

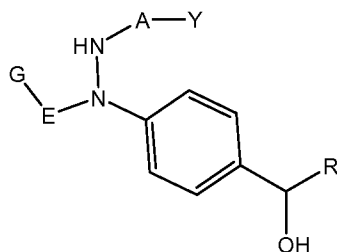


or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

R is hydrogen or C₁₋₁₀ hydrocarbyl.

6. The compound of claim 5 wherein R is alkyl.

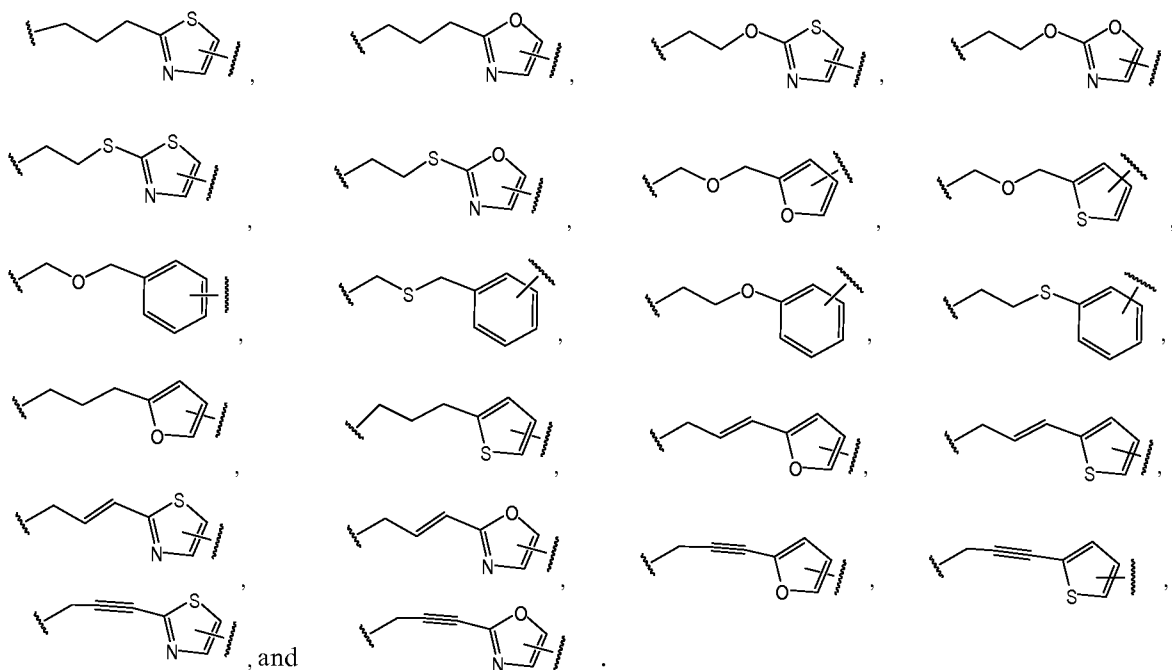
5 7. The compound of claim 5 having a structure



or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

R is hydrogen or C₁₋₁₀ hydrocarbyl.

8. The compound according to any one of claims 1-7 wherein A has a structure selected from:

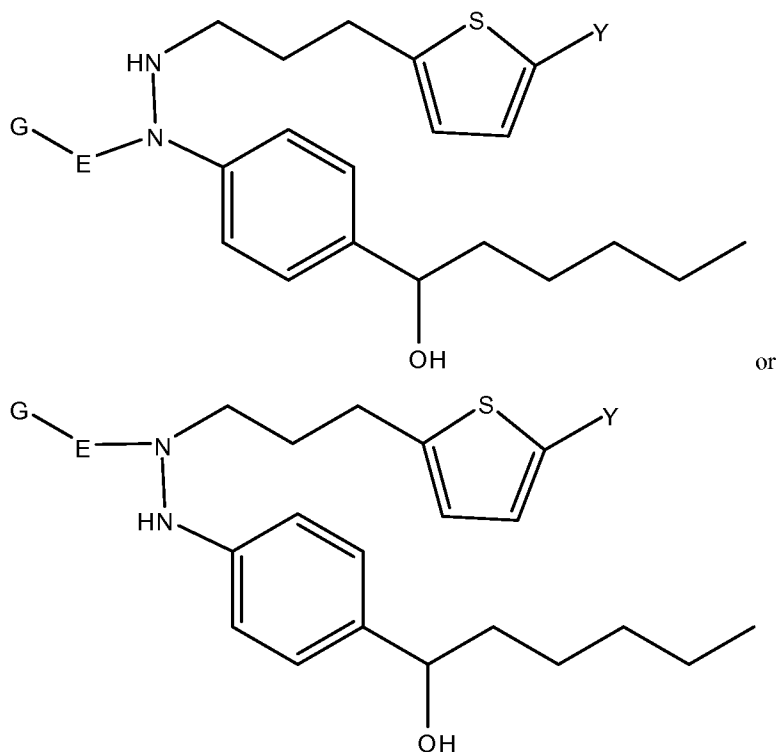


9. The compound according to any one of claims 1-7 wherein A is 6-hexyl.

10. The compound according to any one of claims 1-7 wherein A is (Z)-6-hex-4-enyl.

11. The compound according to claim 7 wherein B is 4-(1-hydroxyhexyl)phenyl.

15 12. The compound of claim 11 having a structure:



13. The compound of claim 12 wherein Y is $-\text{CO}_2\text{H}$ or $-\text{CO}_2\text{R}^3$, wherein R^3 is C_{1-6} alkyl.

14. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment
5 of glaucoma or ocular hypertension in a mammal.

15. A method comprising administering a compound according to any one of claims 1 to 13 to a mammal for the reduction of intraocular pressure.

16. A composition comprising a compound according to any one of claims 1 to 13, wherein said composition is a liquid which is ophthalmically acceptable.

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