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(54) Titre : COMPOSES THERAPEUTIQUES
(54) Title: THERAPEUTIC COMPOUNDS

(57) Abrégé/Abstract:
Therapeutic substituted cyclopentane compounds, and compositions, medicaments, and therapeutic methods related thereto are disclosed herein.

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(54) Title: CYCLOPENTANE-DERIVATIVES AND THEIR USE AS OCULAR HYPOTENSIVE AGENTS

(57) Abstract: Therapeutic substituted cyclopentane compounds, and compositions, medicaments, and therapeutic methods related thereto are disclosed herein.

THERAPEUTIC COMPOUNDS

BACKGROUND

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

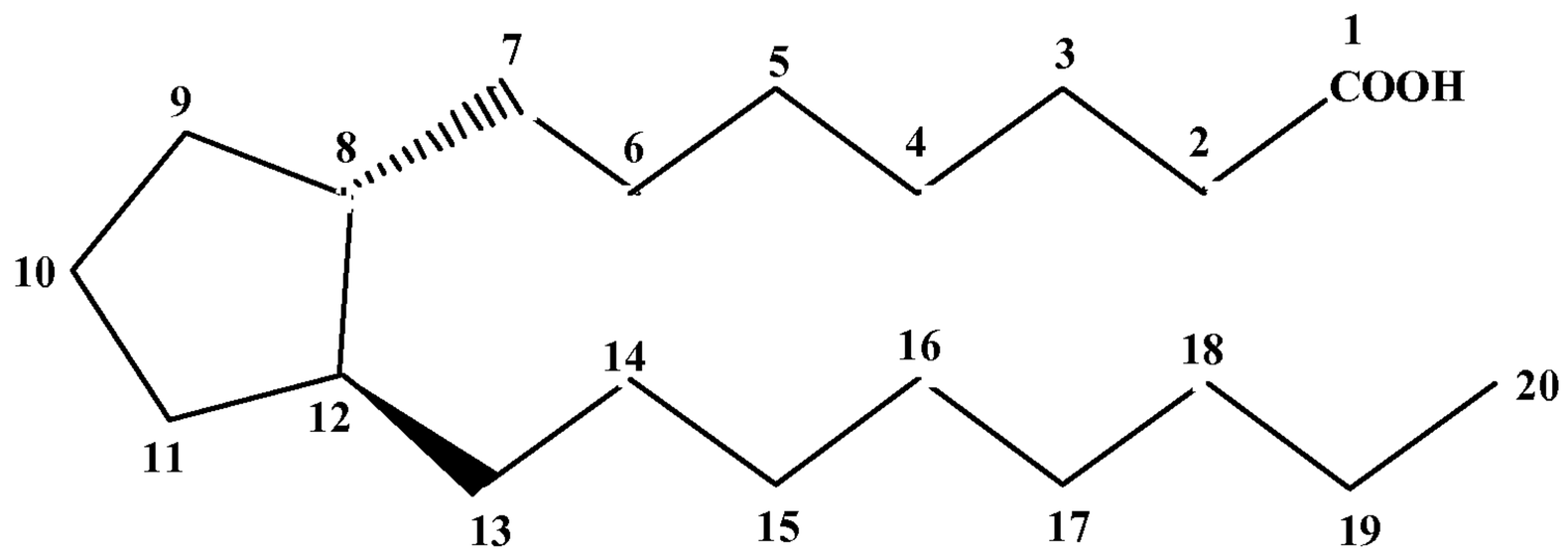
Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical β-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives are currently commercially available for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:

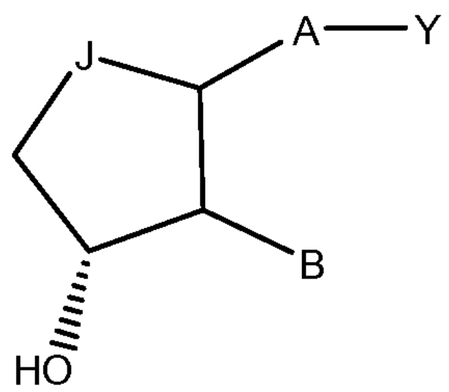


Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by

numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$)].

DESCRIPTION OF THE INVENTION

Disclosed herein is a compound having a structure



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

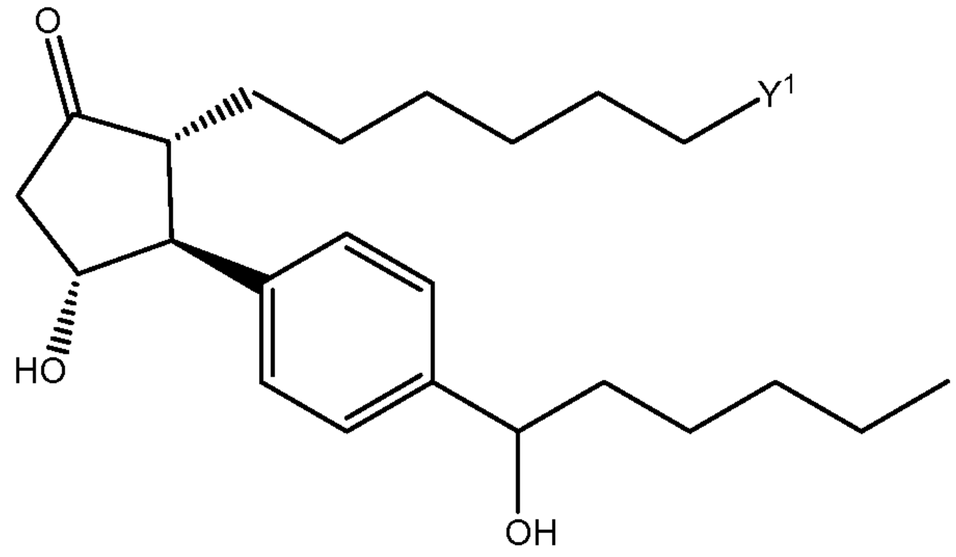
wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 14 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 14 carbon atoms; or Y is a tetrazolyl functional group;

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 one CH_2 may be replaced by S or O;

J is C=O, CHOH, CHF, CHCl, CHBr, CF_2, CCl_2, CBr_2, or CHCN; and

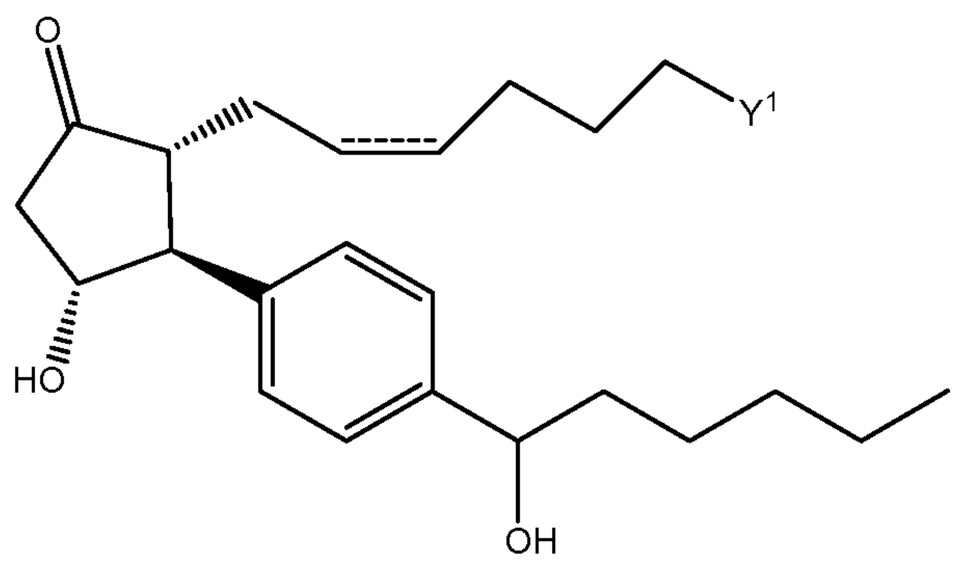
B is substituted aryl or heteroaryl

with the proviso that the compound is not



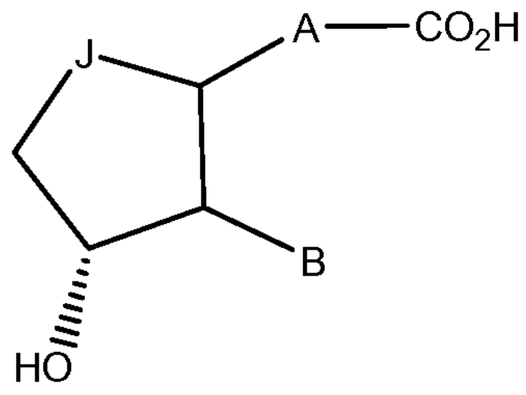
wherein Y^1 is CO_2H or an amide thereof.

In another embodiment, the compound is not



wherein Y^1 is CO_2H or an amide thereof.

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



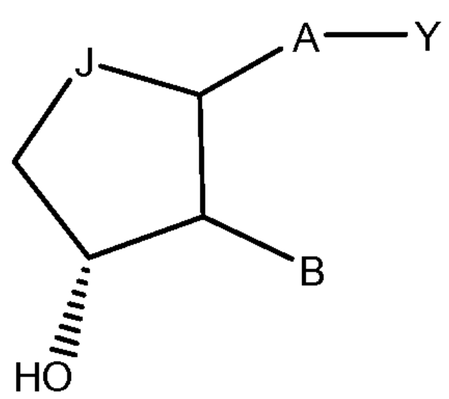
or a pharmaceutically acceptable salt thereof, or a prodrug thereof,;

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 one CH_2 may be replaced by S or O;

J is C=O, CHOH, CHF, CHCl, CHBr, CF_2, CCl_2, CBr_2, or CHCN; and

B is substituted aryl or heteroaryl.

Also disclosed herein is a compound having a structure



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

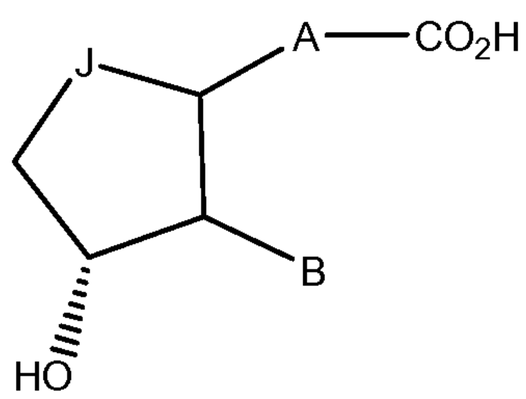
wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 14 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 14 carbon atoms; or Y is a tetrazolyl functional group;

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 one CH_2 may be replaced by S or O;

J is C=O, CHOH, CHF, CHCl, CHBr, CF_2, CCl_2, CBr_2, or CHCN; and

B is $C_{1\text{-}10}$ oxoalkyl substituted aryl or heteroaryl.

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



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 one CH_2 may be replaced by S or O;

J is C=O, CHOH, CHF, CHCl, CHBr, CF_2, CCl_2, CBr_2, or CHCN; and

B is C_{1-10} oxoalkyl substituted aryl or 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, 2nd Edition, Amsterdam: Elsevier Academic Press, 2004, p. 29.

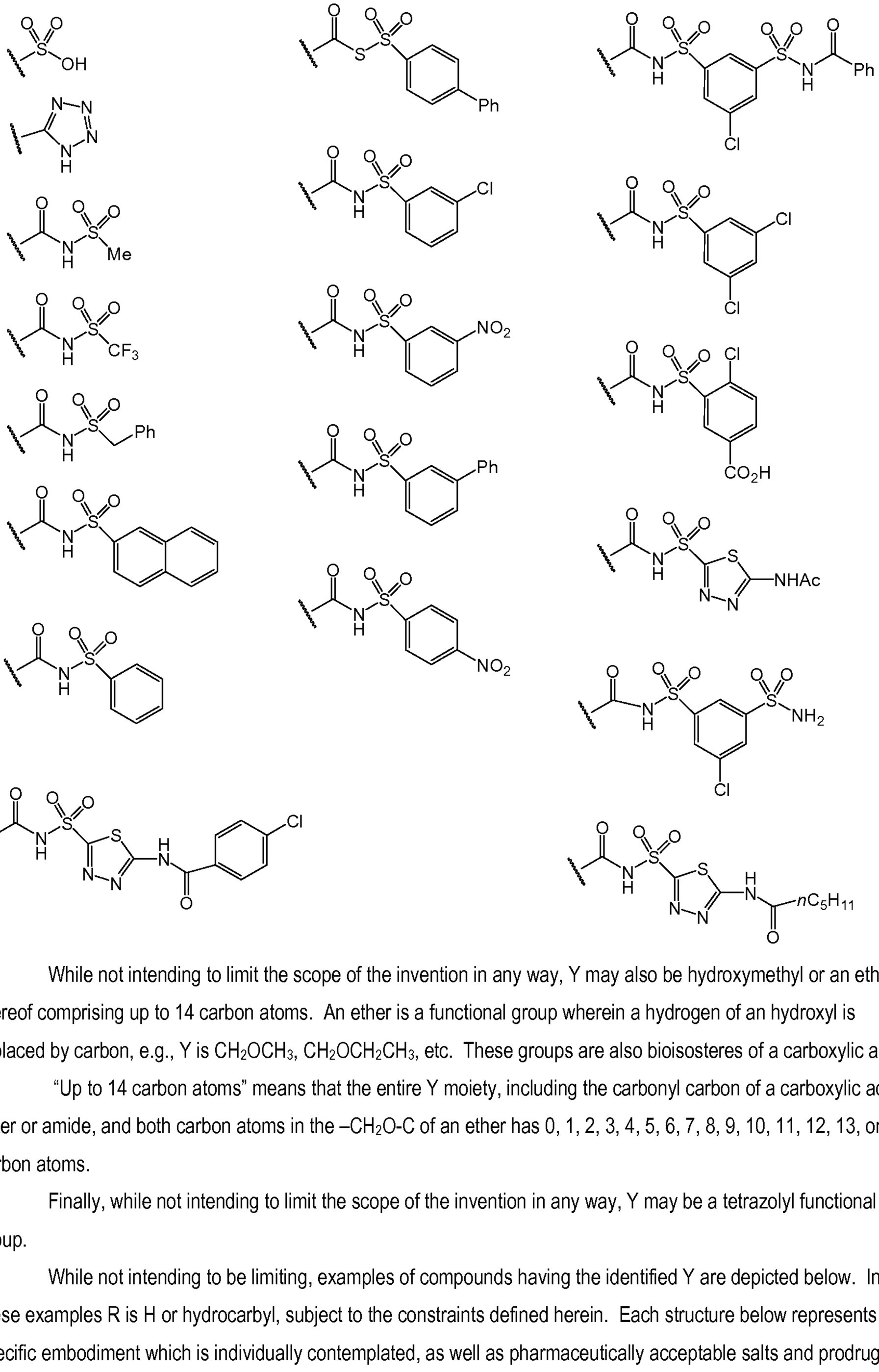
While not intending to be limiting, organic acid functional groups are bioisoteres of carboxylic acids. An organic acid functional group is an acidic functional group on an organic molecule. While not intending to be limiting, organic acid functional groups may comprise an oxide of carbon, sulfur, or 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 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. CO_2Me, CO_2Et, etc.

In an amide, an amine group replaces an OH of the acid. Examples of amides include $CON(R^2)_2$, $CON(OR^2)R^2$, $CON(CH_2CH_2OH)_2$, and $CONH(CH_2CH_2OH)$ where R^2 is independently H, C_1-C_6 alkyl, phenyl, or biphenyl. Moieties such as $CONHSO_2R^2$ are also amides of the carboxylic acid notwithstanding the fact that they may also be considered to be amides of the sulfonic acid R^2-SO_3H. The following amides are also specifically contemplated, $CONSO_2$-biphenyl, $CONSO_2$-phenyl, $CONSO_2$-heteroaryl, and $CONSO_2$-naphthyl. The biphenyl, phenyl, heteroaryl, or naphthyl may be substituted or unsubstituted.

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 CO_2H. Thus, Y could be any group depicted below.

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



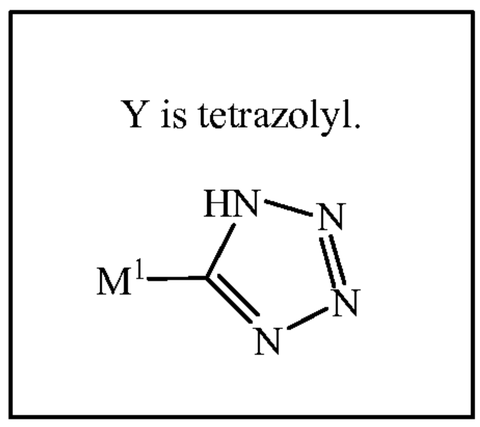
While not intending to limit the scope of the invention in any way, Y may also be hydroxymethyl or an ether thereof comprising up to 14 carbon atoms. An ether is a functional group wherein a hydrogen of an hydroxyl is replaced by carbon, e.g., Y is CH_2OCH_3, $CH_2OCH_2CH_3$, etc. These groups are also bioisosteres of a carboxylic acid.

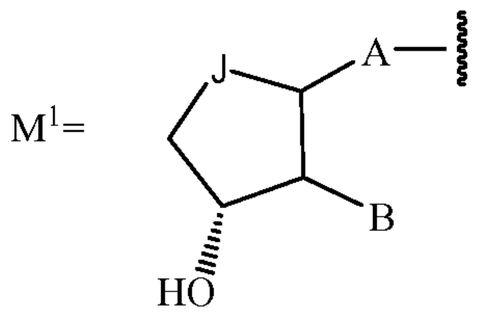
"Up to 14 carbon atoms" means that the entire Y moiety, including the carbonyl carbon of a carboxylic acid ester or amide, and both carbon atoms in the $-CH_2O-C$ of an ether has 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms.

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

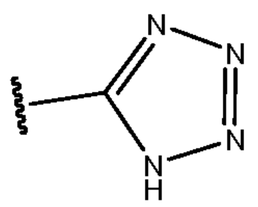
compounds which are represented by the structures. However, other examples are possible which may not fall within the scope of the structures shown below.

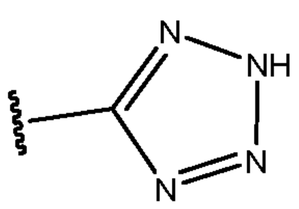




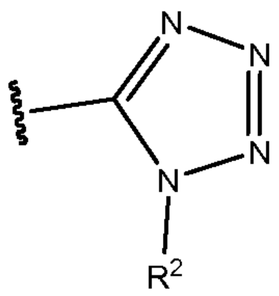
Organic Acids	**Esters**	**Amides**
$M^1—CO_2H$	$M^1—CO_2R$	$M^1—CO_2NR_2$
Carboxylic Acid	Carboxylic Acid Ester	Carboxylic Acid Amide
$M^1—P(O)(OH)_2$	$M^1—P(O)(OH)R$	$M^1—P(O)(OH)NR_2$
Phosponic Acid	Phosphonic Acid Ester	Phosphonic Acid Amide
$M^1—SO_3H$	$M^1—SO_3R$	$M^1—SO_3NR_2$
Sulfonic Acid	Sulfonic Acid Ester	Sulfonic Acid Amide
$M^1—CH_2OH$	$M^1—CH_2OR$	
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.

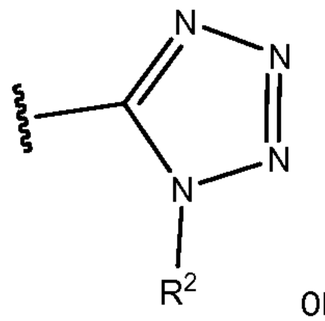
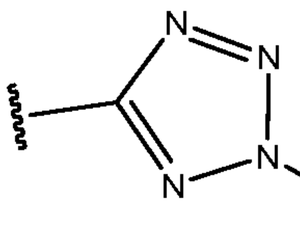




Additionally, if R^2 is C_1-C_6 alkyl, phenyl, or biphenyl, other isomeric forms of the tetrazolyl functional group such as the one shown below are also possible, unsubstituted and hydrocarbyl substituted tetrazolyl up to C_{12} are considered to be within the scope of the term “tetrazolyl.”



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,

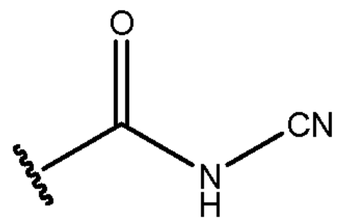
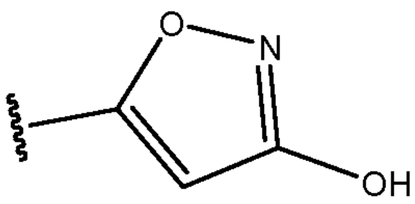
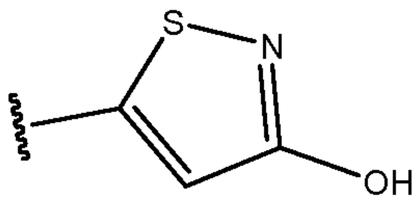



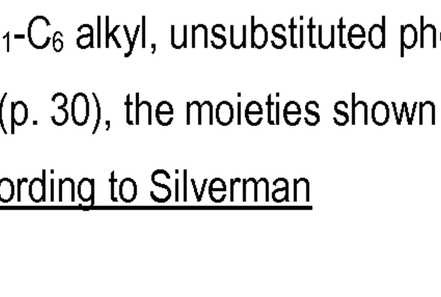
or ;

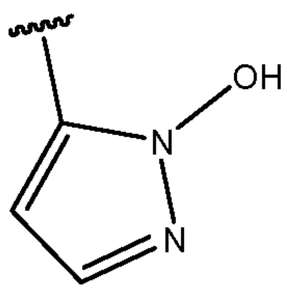
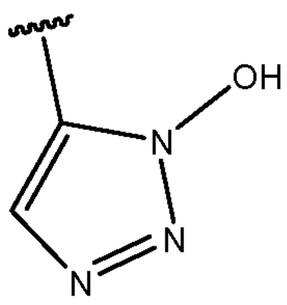
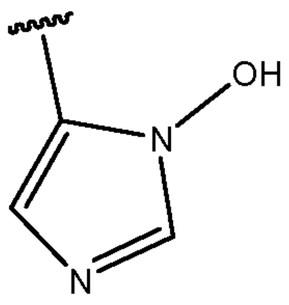
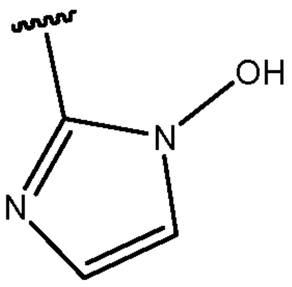
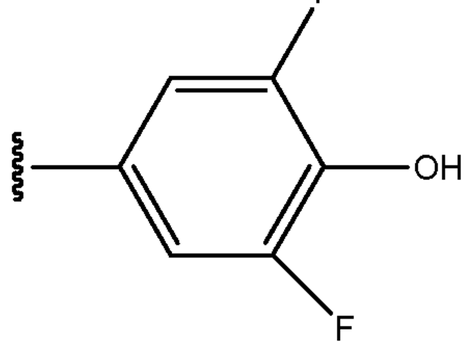
wherein R^2 is independently H, C_1-C_6 alkyl, unsubstituted phenyl, or unsubstituted biphenyl.

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

Carboxylic acid bioisosteres according to Silverman



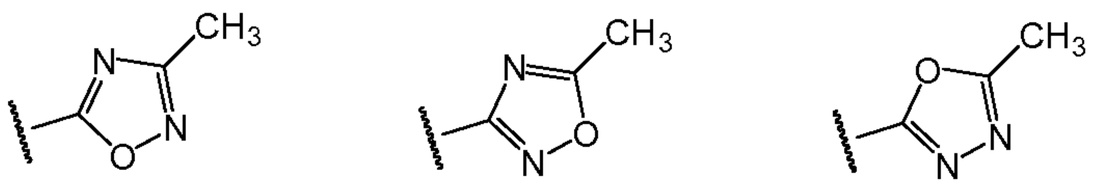






F

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

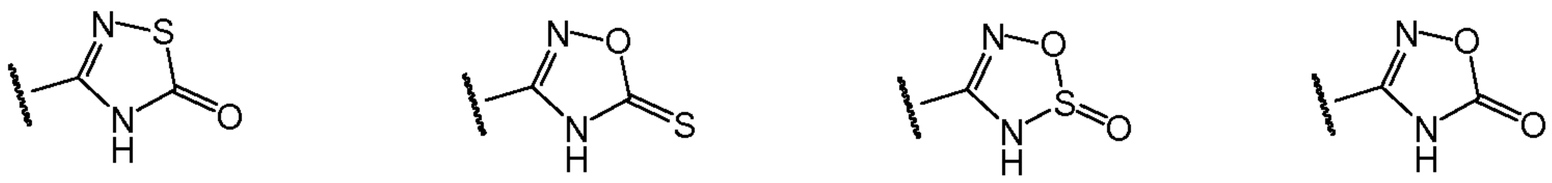
stability. Oxadiazoles were also described by Anderson et al. (Eur. J. Med. Chem. 1996, 31, 417-425) as carboxamide replacements having improved in vivo efficacy at the benzodiazepine receptor.

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



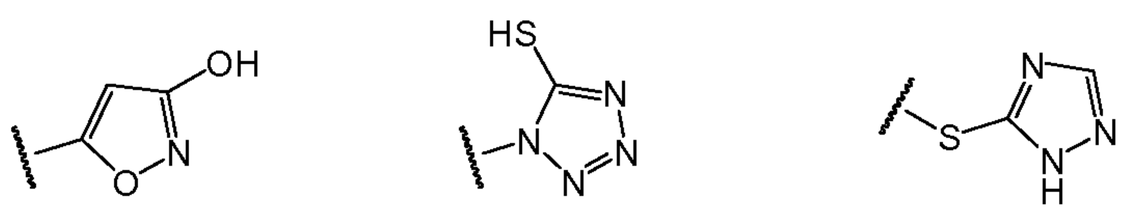
Kohara et al. (*J. Med. Chem.* **1996**, *39*, 5228-5235) described acidic heterocycles as suitable bioisosteres for a tetrazole. These carboxylic acid replacements were shown to be potent angiotensin II receptor antagonists having improved metabolic stability.

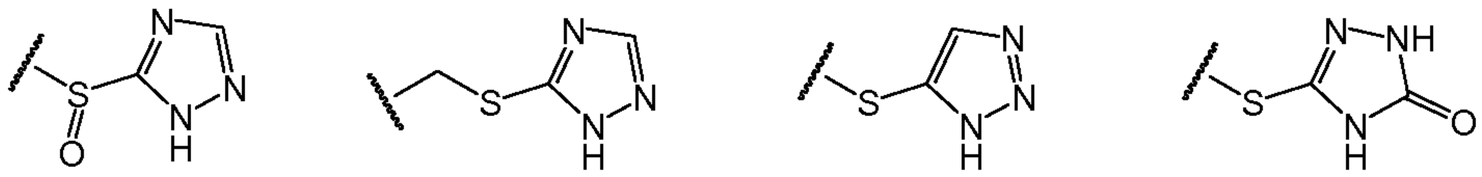
Tetrazole bioisosteres according to Kohara *et. al.*



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.*

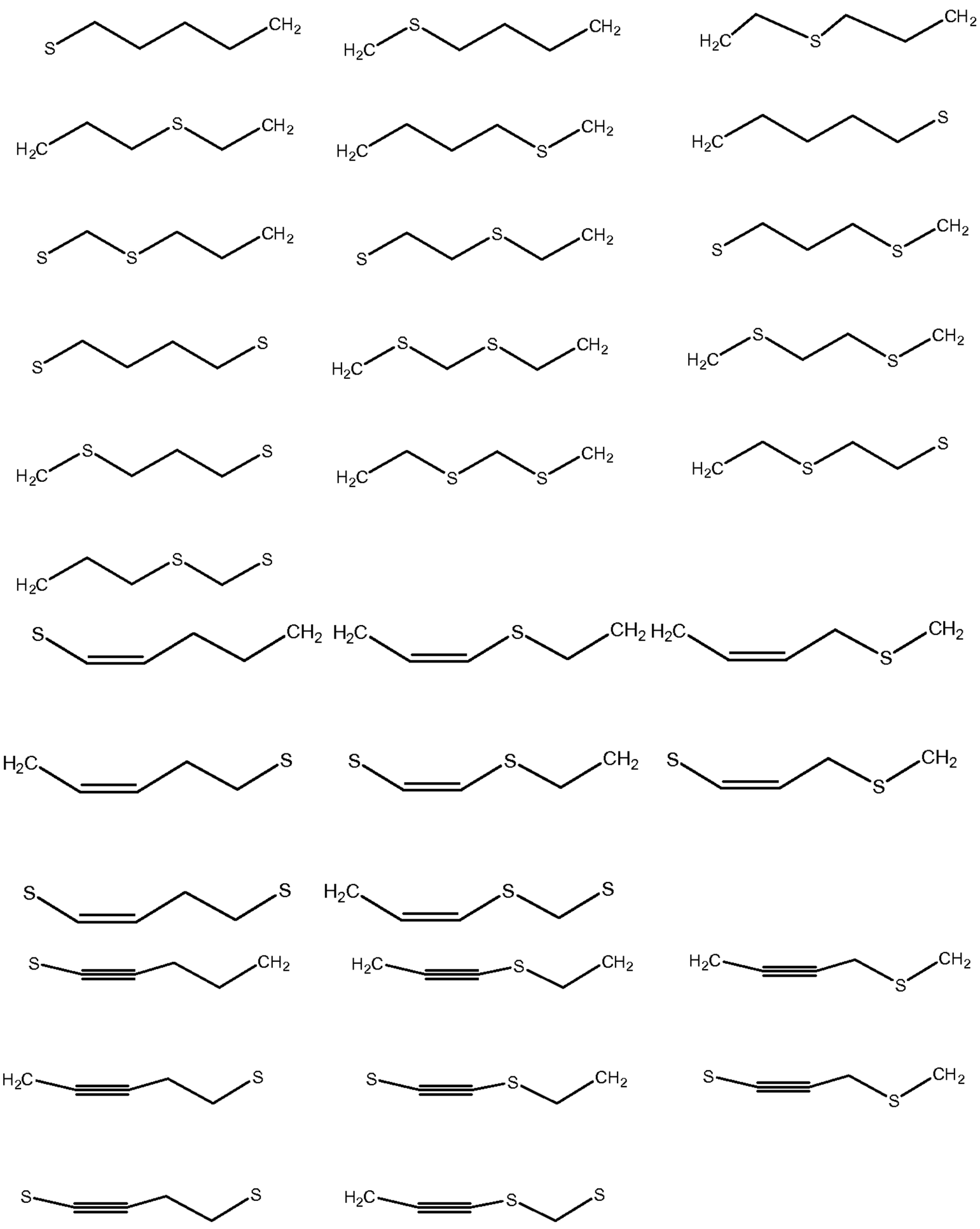




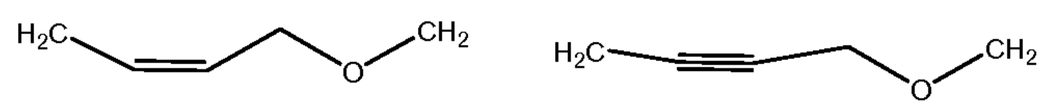
In relation to the identity of A disclosed in the chemical structures presented herein, A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be replaced with S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene,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

While not intending to be limiting, A may be $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$.

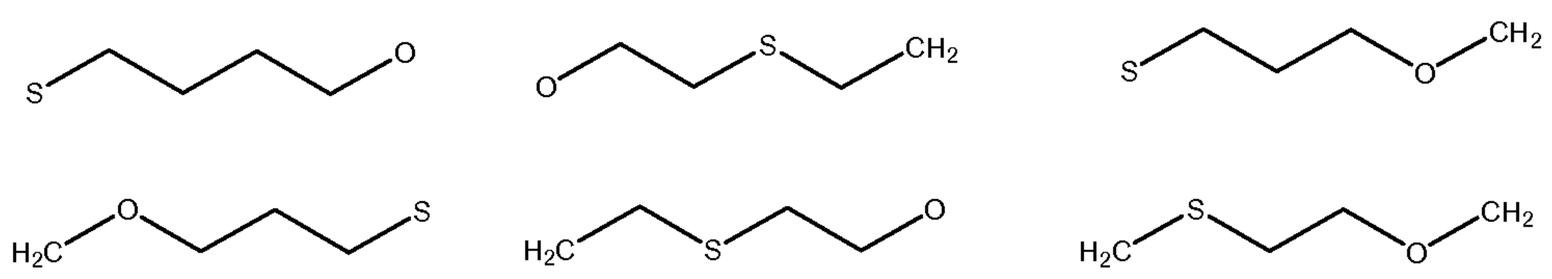
Alternatively, A may be a group which is related to one of these three moieties in that any carbon is replaced with S and/or O. For example, while not intending to limit the scope of the invention in any way, A may be a moiety where S replaces one or two carbon atoms such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, A may be a moiety where O replaces one or two carbon atoms such as one of the following or the like.



Alternatively, while not intending to limit the scope of the invention in any way, 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.



Alternatively, while not intending to limit the scope of the invention in any way, 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 one CH_2 may be replaced with S or O. In other words, while not intending to limit the scope of the invention in any way,

in one embodiment A comprises 1, 2, 3, or 4 CH_2 moieties and Ar, e.g. -CH_2-Ar-, -$(CH_2)_2$-Ar-, -CH_2-Ar-CH_2-, -CH_2Ar-$(CH_2)_2$-, -$(CH_2)_2$-Ar-$(CH_2)_2$-, and the like;

in another embodiment A comprises: O; 0, 1, 2, or 3 CH_2 moieties; and Ar, e.g., -O-Ar-, Ar-CH_2-O-, -O-Ar-$(CH_2)_2$-, -O-CH_2-Ar-, -O-CH_2-Ar-$(CH_2)_2$, and the like; or

in another embodiment A comprises: S; 0, 1, 2, or 3 CH_2 moieties; and Ar, e.g., -S-Ar-, Ar-CH_2-S-, -S-Ar-$(CH_2)_2$-, -S-CH_2-Ar-, -S-CH_2-Ar-$(CH_2)_2$, -$(CH_2)_2$-S-Ar, and the like.

In another embodiment, the sum of m and o is 2, 3, or 4 wherein one CH_2 may be replaced with S or O.

In another embodiment, the sum of m and o is 3 wherein one CH_2 may be replaced with S or O.

In another embodiment, the sum of m and o is 2 wherein one CH_2 may be replaced with S or O.

In another embodiment, the sum of m and o is 4 wherein one CH_2 may be replaced with S or O.

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.

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 $-(CH_2)_2$-Ph-. While not intending to limit scope of the invention in any way, substituents may have 4 or less heavy atoms, wherein the heavy atoms are C, N, O, S, P, F, Cl, Br, and/or I in any stable combination. Any number of hydrogen atoms required for a particular substituent will also be included. A substituent must be stable enough 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 any 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 CO_2H may form a $CO_2^-K^+$ salt. Any cation of the salt is not counted in the "4 or less heavy atoms." Thus, the substituent may be

hydrocarbyl having up to 4 carbon atoms, including alkyl up to C_4, alkenyl, alkynyl, and the like;

hydrocarbyloxy up to C_3;

organic acid such as CO_2H, SO_3H, $P(O)(OH)_2$, and the like, and salts thereof;

CF_3;

halo, such as F, Cl, or Br;

hydroxyl;

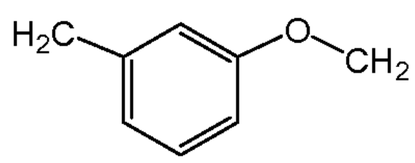
NH_2 and alkylamine functional groups up to C_3;

other N or S containing substituents such as CN, NO_2, and the like;

and the like.

In one embodiment A is $-(CH_2)_m$-Ar-$(CH_2)_o$- wherein Ar is interphenylene, the sum of m and o is 1, 2, or 3, and wherein one CH_2 may be replaced with S or O.

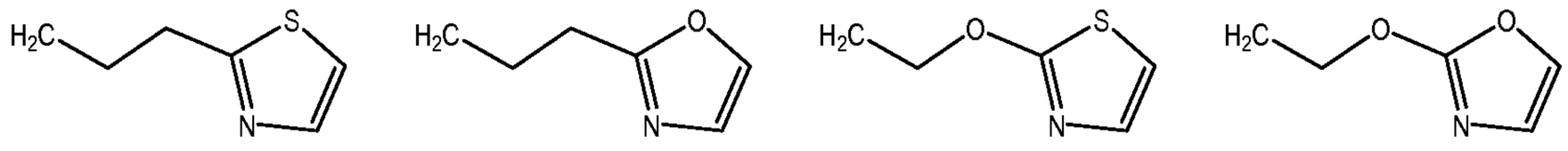
In another embodiment A is -CH_2-Ar-OCH_2-. In another embodiment A is $-CH_2$-Ar-OCH_2- and Ar is interphenylene. In another embodiment, Ar is attached at the 1 and 3 positions, otherwise known as *m*-interphenylene, such as when A has the structure shown below.

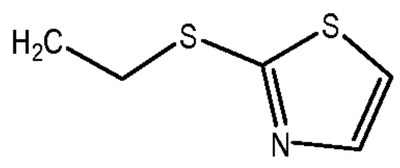
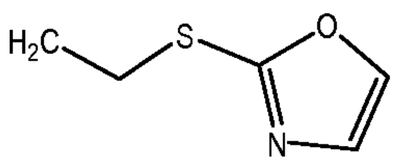
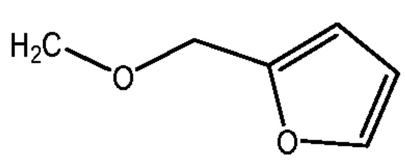
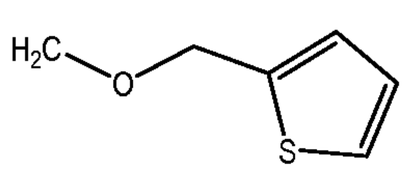
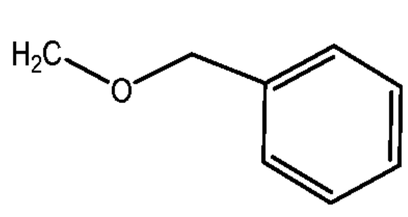
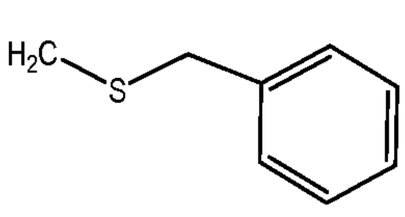
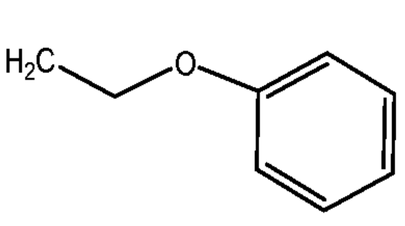
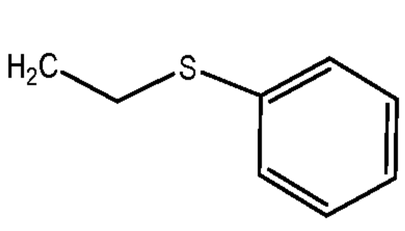


In another embodiment A is $-(CH_2)_6$-, *cis* $-CH_2CH=CH-(CH_2)_3$-, or $-CH_2C\equiv C-(CH_2)_3$-, wherein 1 or 2 carbon atoms may be replaced with S or O; or A is $-(CH_2)_2$-Ph- wherein one CH_2 may be replaced with S or O.

In another embodiment 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 with S or O; or A is $-(CH_2)_2$-Ph-.

In other embodiments, A has one of the following structures, where Y is attached to the aromatic or heteroaromatic ring.



In another embodiment A is -CH_2OCH_2Ar.

In another embodiment A is -CH_2SCH_2Ar.

In another embodiment A is -$(CH_2)_3Ar$.

In another embodiment A is -$CH_2O(CH_2)_4$.

In another embodiment A is -$CH_2S(CH_2)_4$.

In another embodiment A is –$(CH_2)_6$-.

In another embodiment A is *cis* –CH_2CH=CH-$(CH_2)_3$-.

In another embodiment A is –CH_2C≡C-$(CH_2)_3$-.

In another embodiment A is -$S(CH_2)_3S(CH_2)_2$-.

In another embodiment A is -$(CH_2)_4OCH_2$-.

In another embodiment A is *cis* –CH_2CH=CH-CH_2OCH_2-.

In another embodiment A is –CH_2CH≡CH-CH_2OCH_2-.

In another embodiment A is -$(CH_2)_2S(CH_2)_3$-.

In another embodiment A is -CH_2-Ph-OCH_2-, wherein Ph is interphenylene,.

In another embodiment A is -CH_2-mPh-OCH_2-, wherein mPh is *m*-interphenylene.

In another embodiment A is -CH_2-O-$(CH2)_4$-.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interthienylene.

In another embodiment A is -CH_2-O-CH_2-Ar-, wherein Ar is 2,5-interfurylene.

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.

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 .

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

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

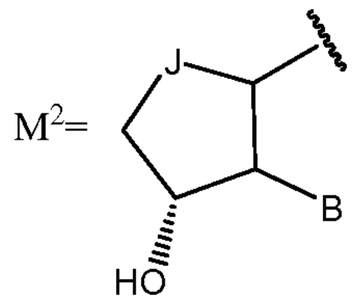
In another embodiment A is 5-(3-propyl)thiophen-2-yl.

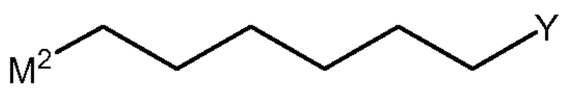
In another embodiment A is 6-hexyl.

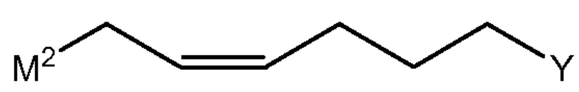
In another embodiment A is (Z)-6-hex-4-enyl.

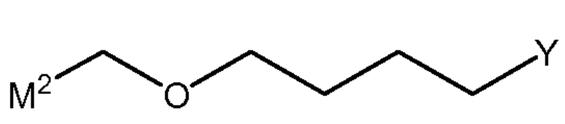
In another embodiment, A is $-(CH_2)_3Ar-$, $-O(CH_2)_2Ar-$, $-CH_2OCH_2Ar-$, $-(CH_2)_2OAr$, $-O(CH_2)_2Ar-$, $-CH_2OCH_2Ar-$, or $-(CH_2)_2OAr-$, wherein Ar is monocyclic interheteroarylene.

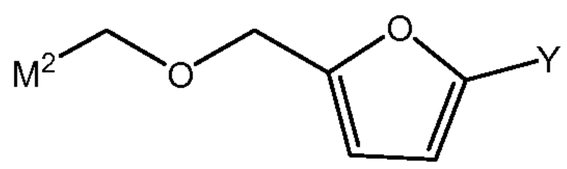
Compounds according to the each of the structures depicted below, and pharmaceutically acceptable salts thereof, and prodrugs thereof, are contemplated as individual embodiments. In other words, each structure represents a different embodiment.

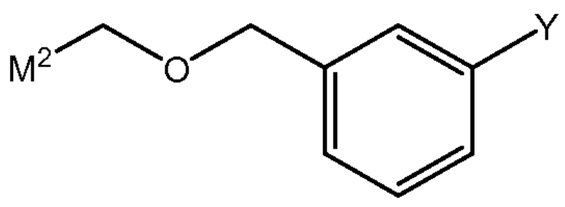

M2=
J
B
HO

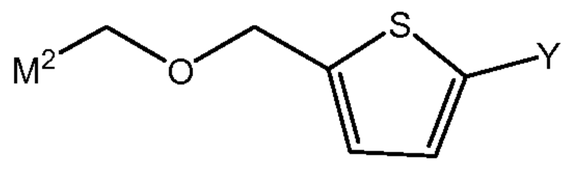

M2
Y

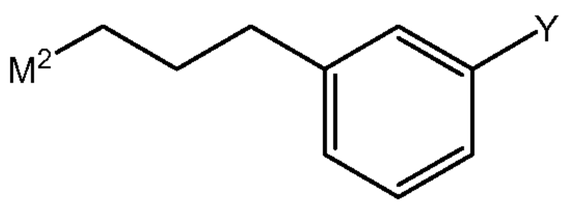

M2
Y

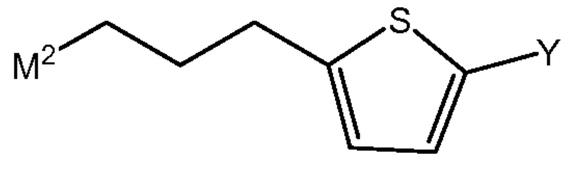

M2
O
Y

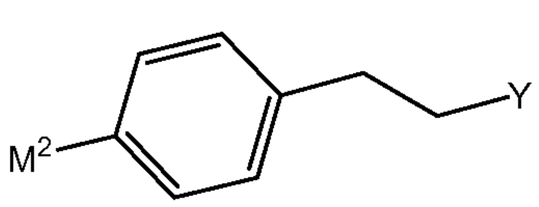

M2
O
O
Y

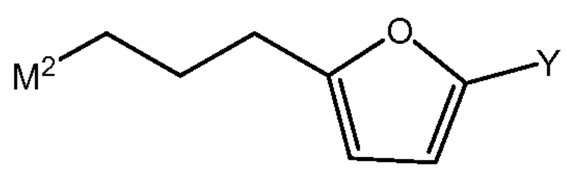

M2
O
Y

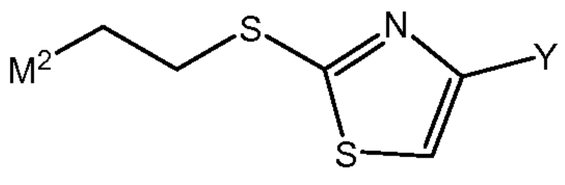

M2
O
S
Y

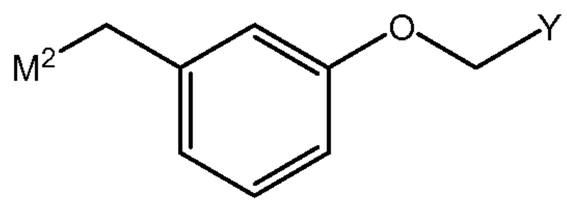

M2
Y

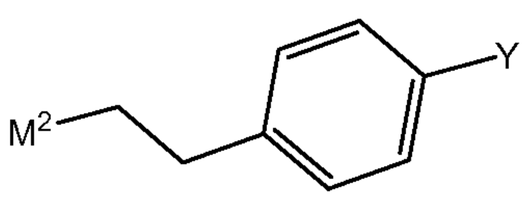

M2
S
Y

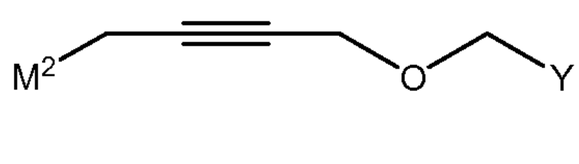

M2
Y

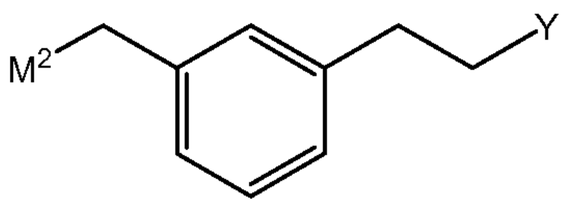

M2
O
Y

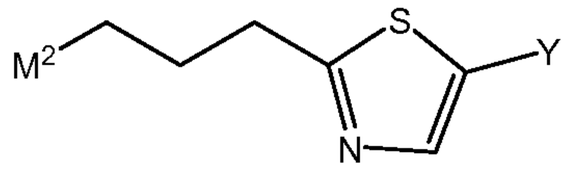

M2
S
N
S
Y


M2
O
Y

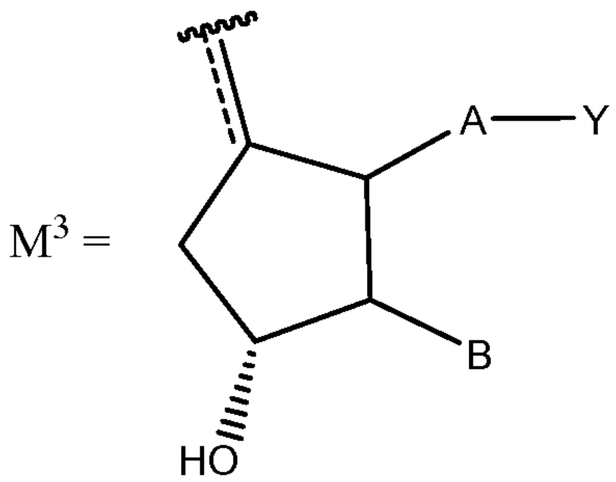

M2
Y

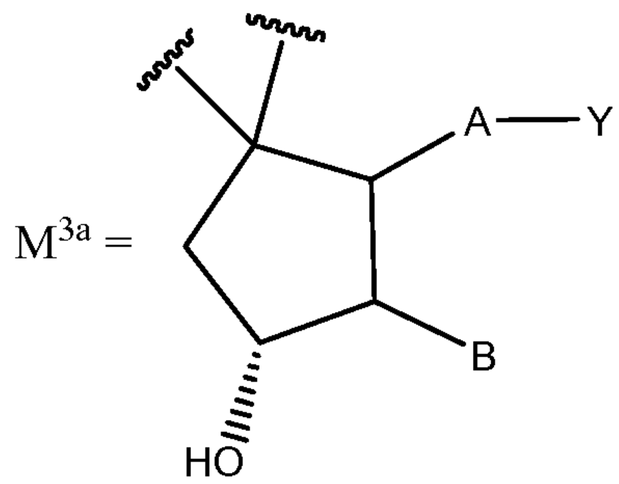

M2
O
Y

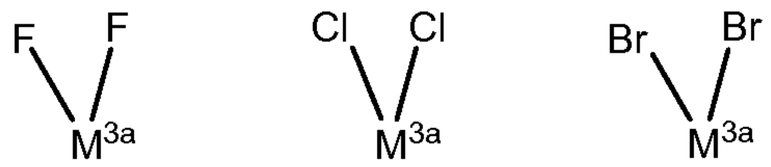

M2
Y


M2
S
Y
N

J is C=O, CHOH, CHF, CHCl, CHBr, CF_2, CCl_2, CBr_2, or CHCN. Thus, each structure depicted below represents a compound embodiment which is individually contemplated. Pharmaceutically acceptable salts and prodrugs of compounds according to the structures below are also contemplated.







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, imidizololyl, 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 CO_2H may form a $CO_2^-K^+$ 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 OCH_3, OCH_2CH_3, O-cyclohexyl, etc, up to 19 carbon atoms;

other ether substituents such as CH_2OCH_3, $(CH_2)_2OCH(CH_3)_2$, and the like;

thioether substituents including S-hydrocarbyl and other thioether substituents;

hydroxyhydrocarbyl, meaning hydrocarbyl-OH such as CH_2OH, $C(CH_3)_2OH$, etc, up to 19 carbon atoms;

nitrogen substituents such as NO_2, CN, and the like, including

amino, such as NH_2, $NH(CH_2CH_3OH)$, $NHCH_3$, and the like up to 19 carbon atoms;

carbonyl substituents, such as CO_2H, ester, amide, and the like;

halogen, such as chloro, fluoro, bromo, and the like

fluorocarbyl, such as CF_3, CF_2CF_3, etc.;

phosphorous substituents, such as PO_3^{2-}, and the like;

sulfur substituents, including S-hydrocarbyl, SH, SO_3H, SO_2-hydrocarbyl, SO_3-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, NO_2, and ethyl; and the like including any conceivable substituent or combination of substituent possible in light of this disclosure.

Subsituted 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, indanolyl, 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.

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.

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

In another embodiment B is 3-(hydroxy(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.

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.

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

"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.

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

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.

Arylalkyl is alkyl which is substituted with aryl. In other words alkyl connects aryl to the remaining part of the molecule. Examples are -CH_2-Phenyl, -CH_2-CH_2-Phenyl, and the like. Arylalkyl may or may not be hydrocarbyl, depending upon whether it has substituents with heteroatoms.

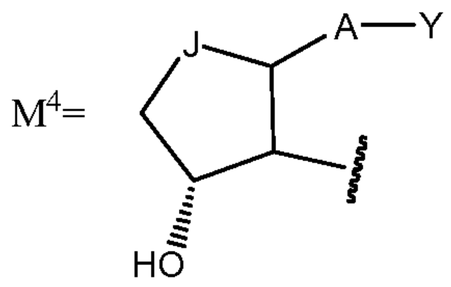
Unconjugated dienes or polyenes have one or more double bonds which are not conjugated. They may be linear, branched, or cyclic, or a combination thereof.

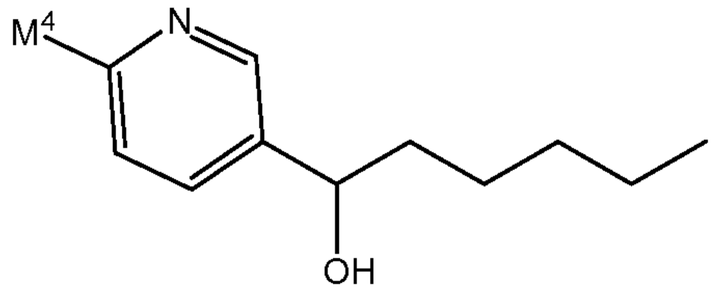
Combinations of the above are also possible.

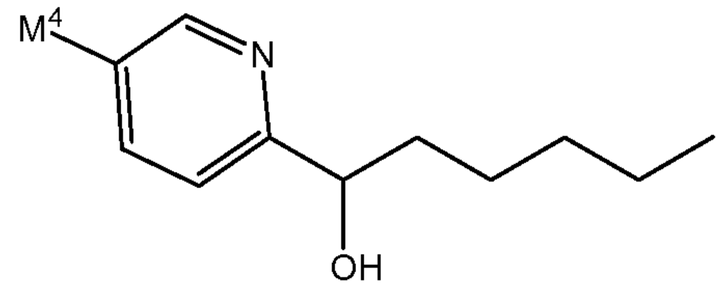
Oxoalkyl is alkyl wherein one carbon atom is C=O. C_{1-10} oxoalkyl is oxoalkyl having 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The oxyalkyl moiety may also form a ring with the aryl or heteroaryl group. Thus, for example, B may be substituted or unsubstituted tetralonyl, indanonyl, or the like.

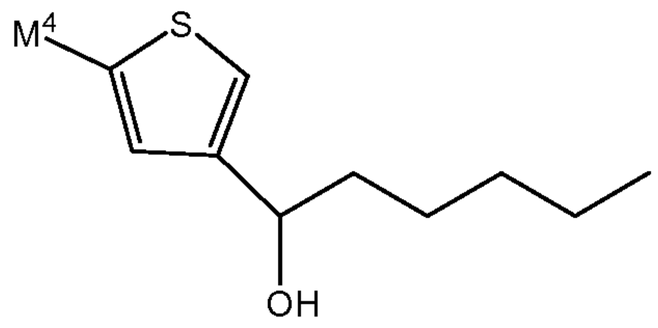
In another embodiment B is C_{1-10} oxoalkyl substituted phenyl.

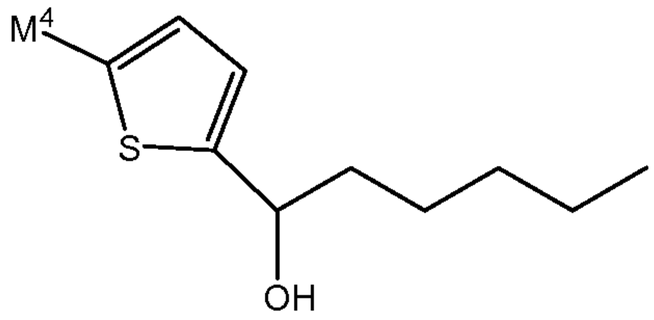
Thus, each of the structures below is contemplated. These structures, or pharmaceutically acceptable salts thereof, or prodrugs thereof, individually represent a compound which is an embodiment contemplated herein. In other words, each structure represents a different embodiment.

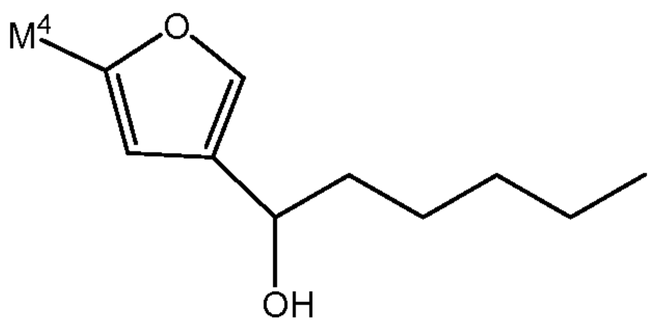

M4=
J
A—Y
HO

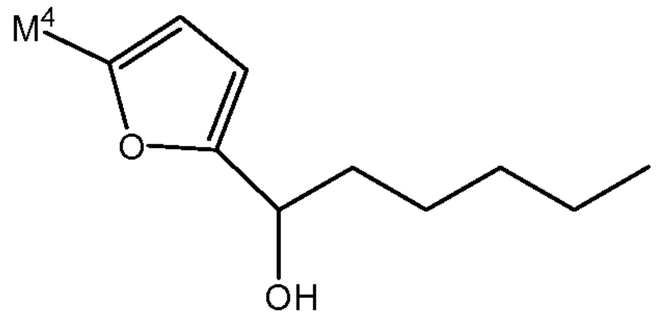

M4
N
OH

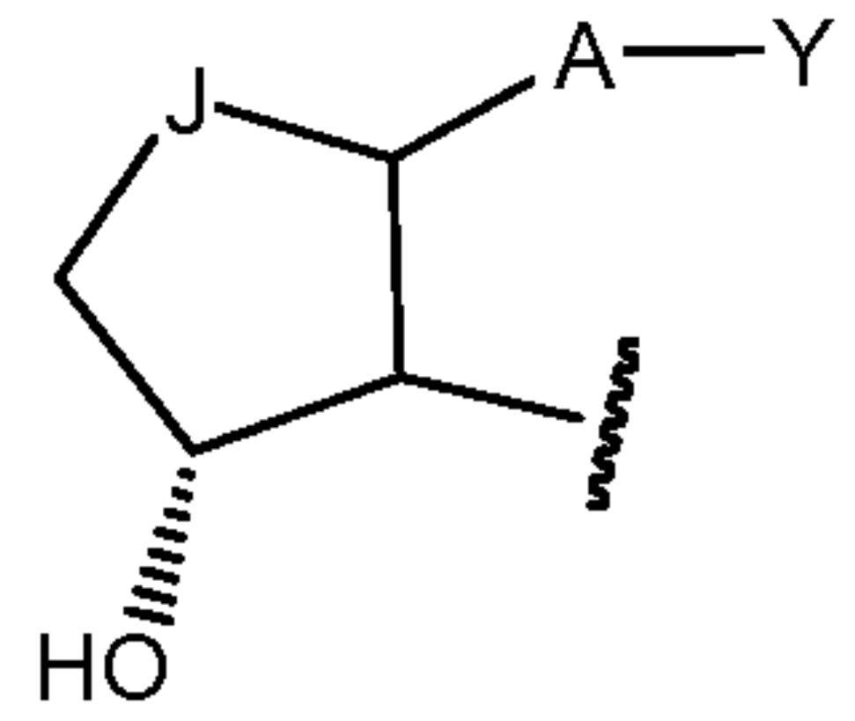

M4
N
OH

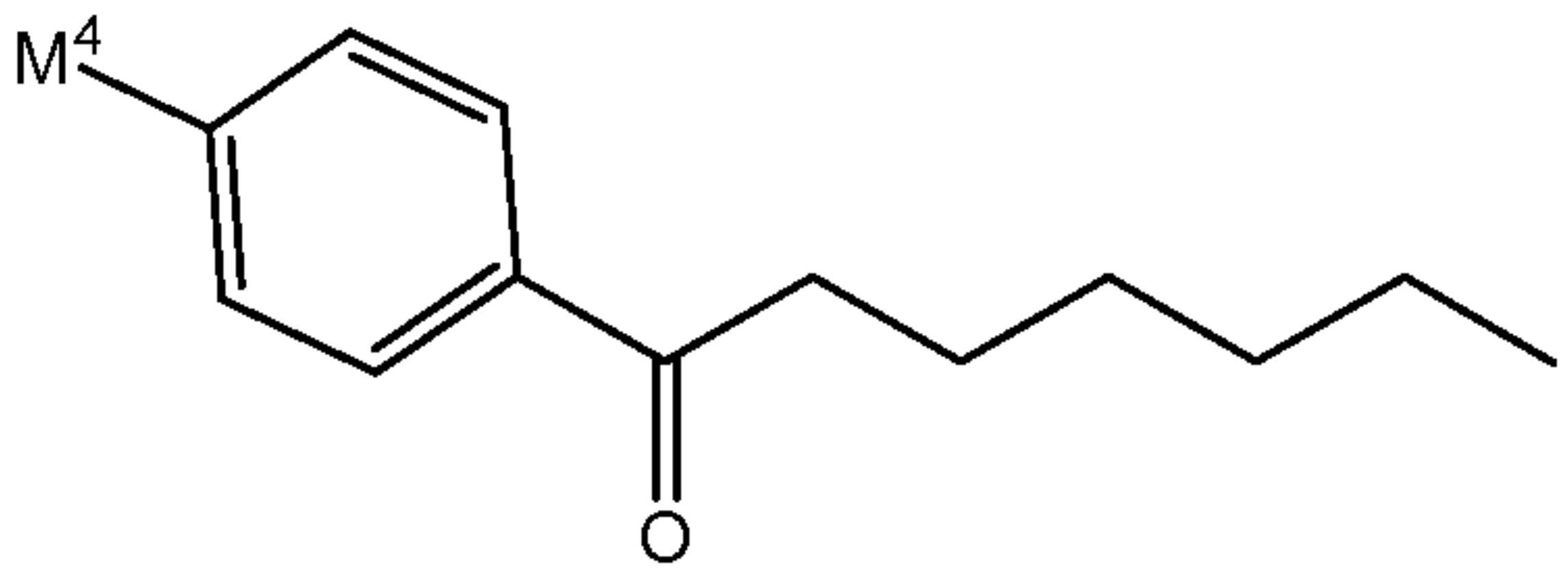

M4
S
OH

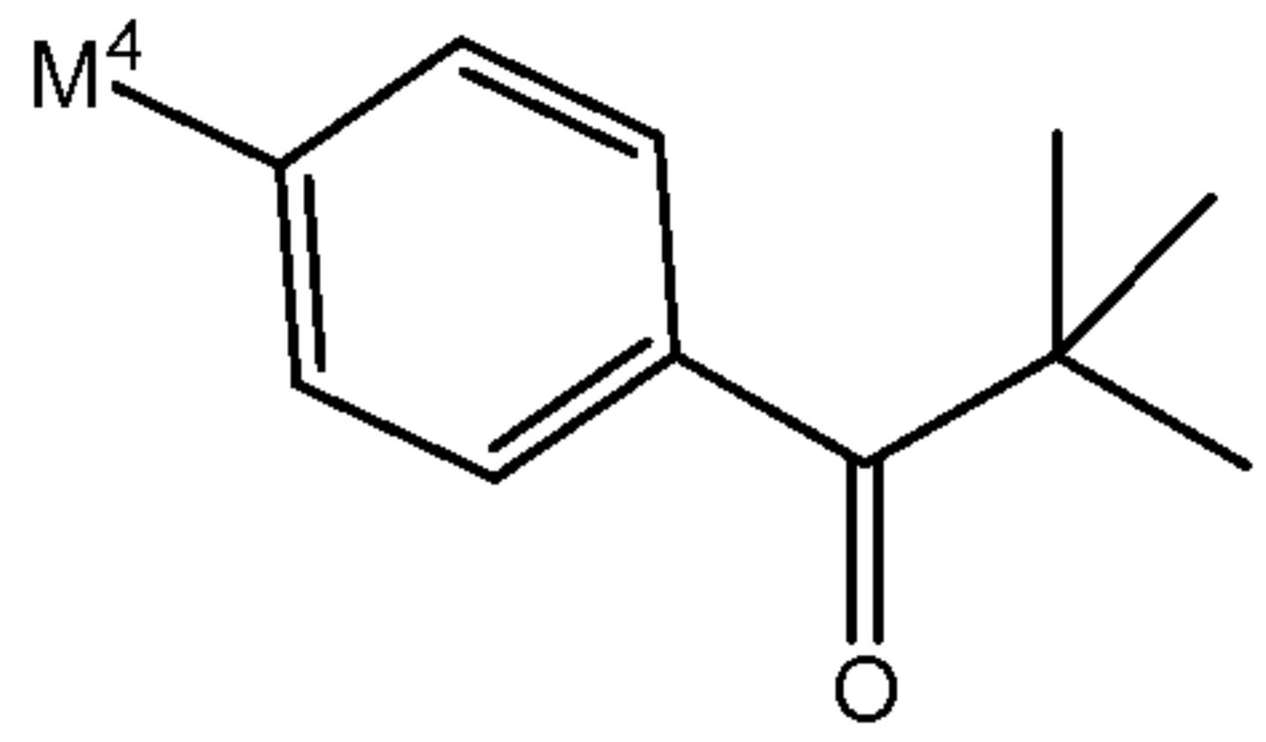

M4
S
OH

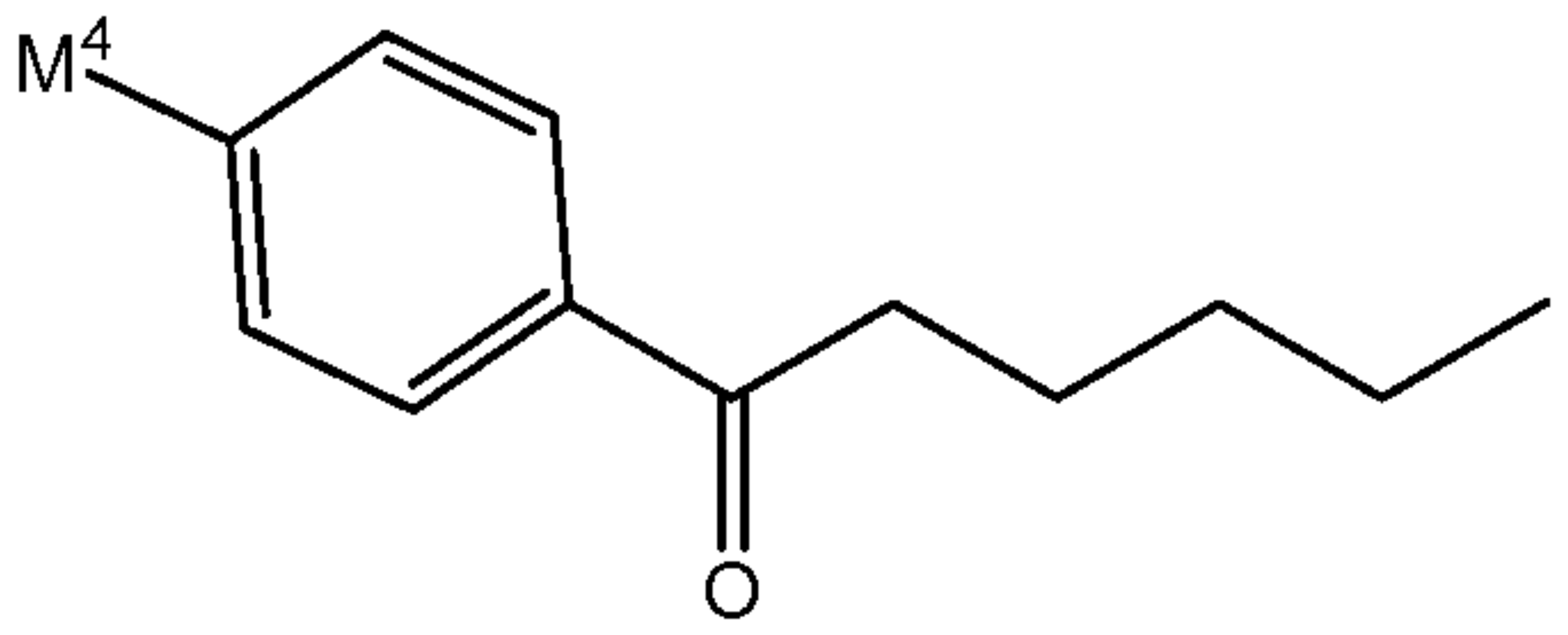

M4
O
OH

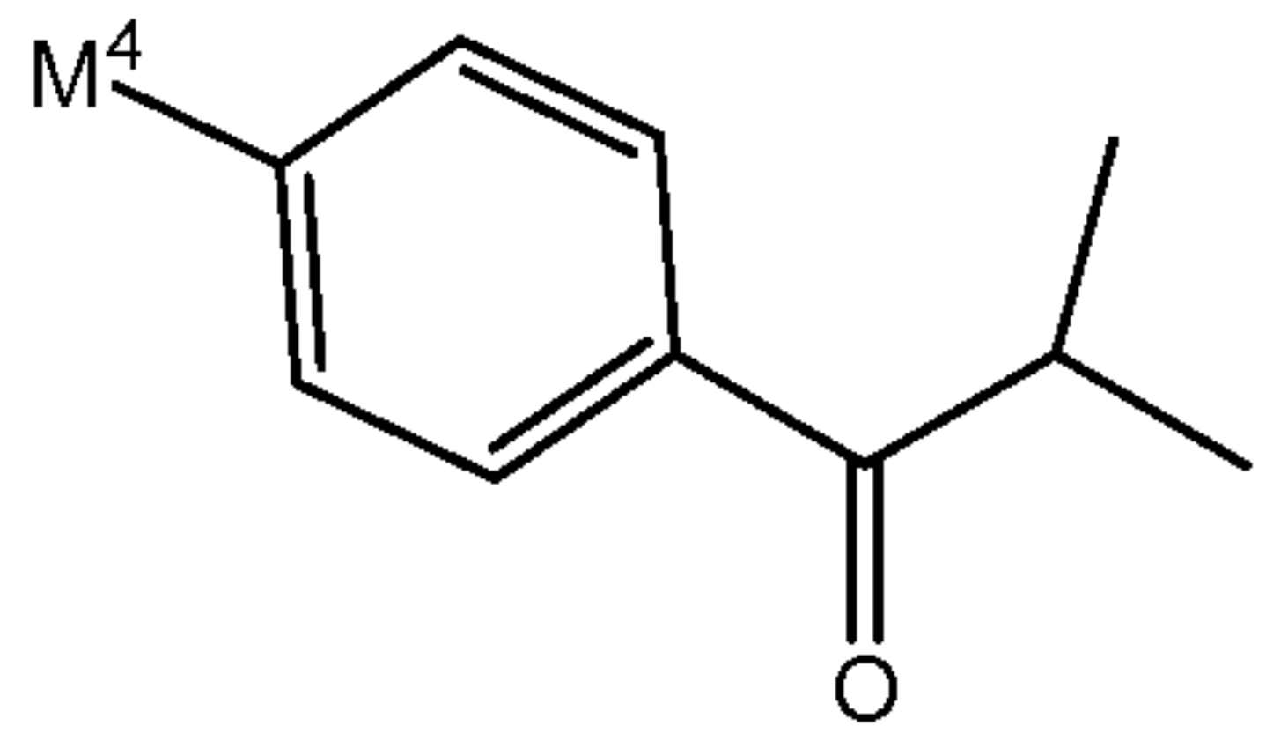

M4
O
OH

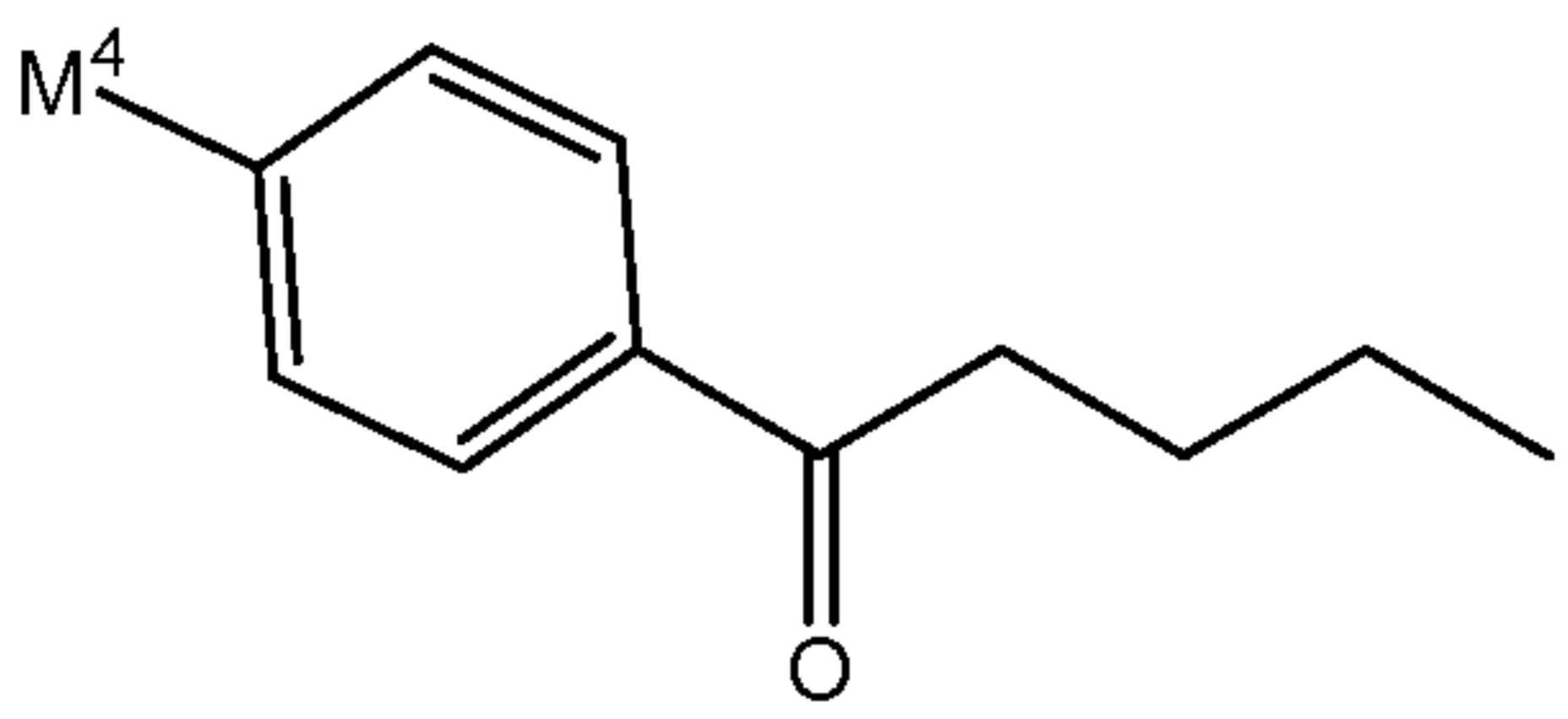
M^4= 

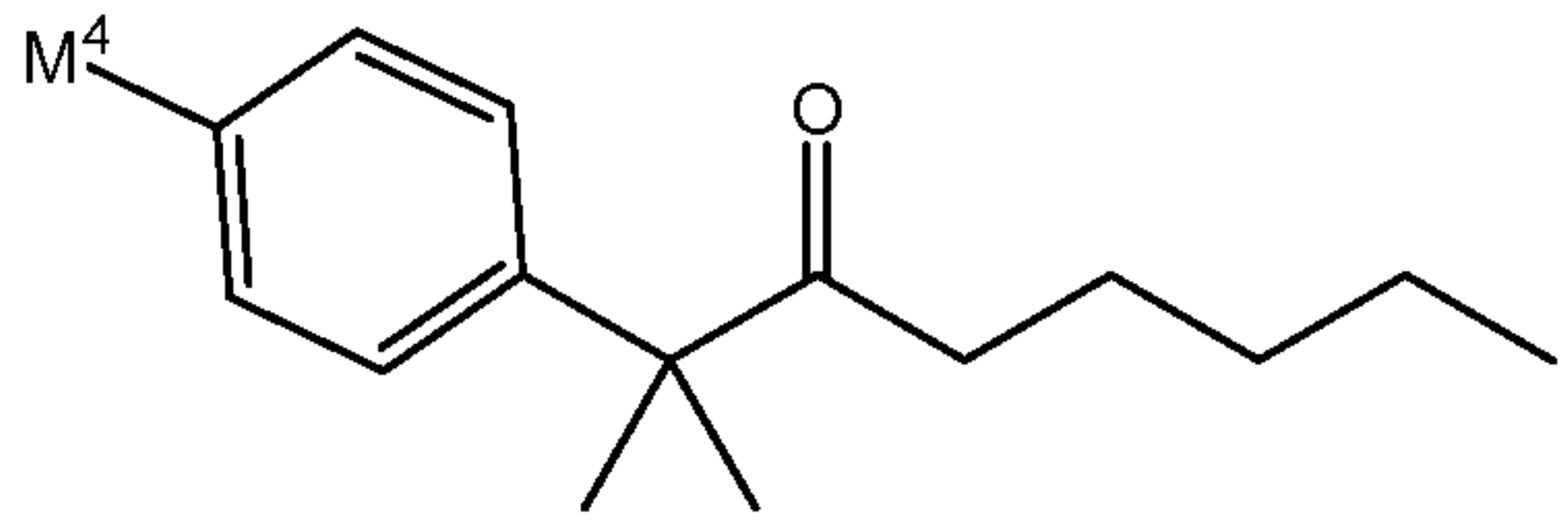


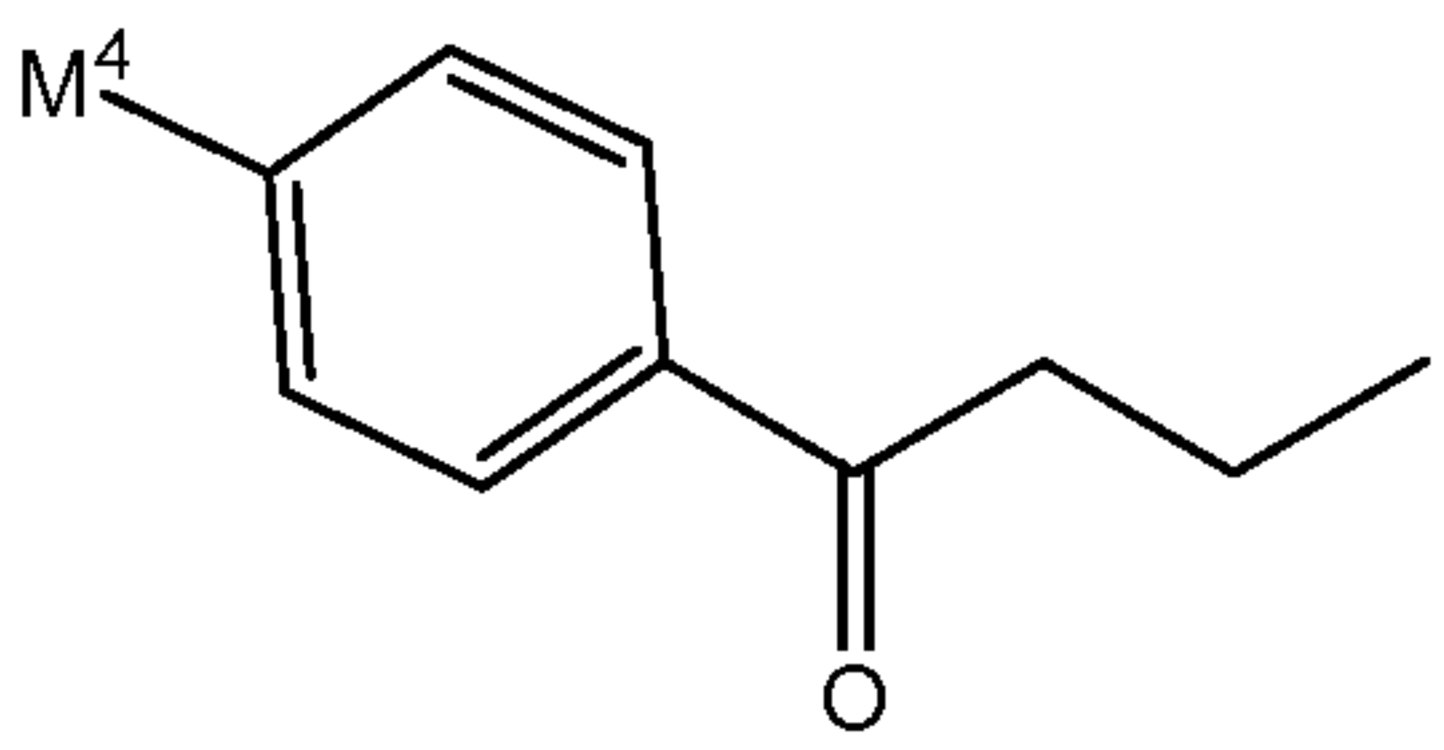


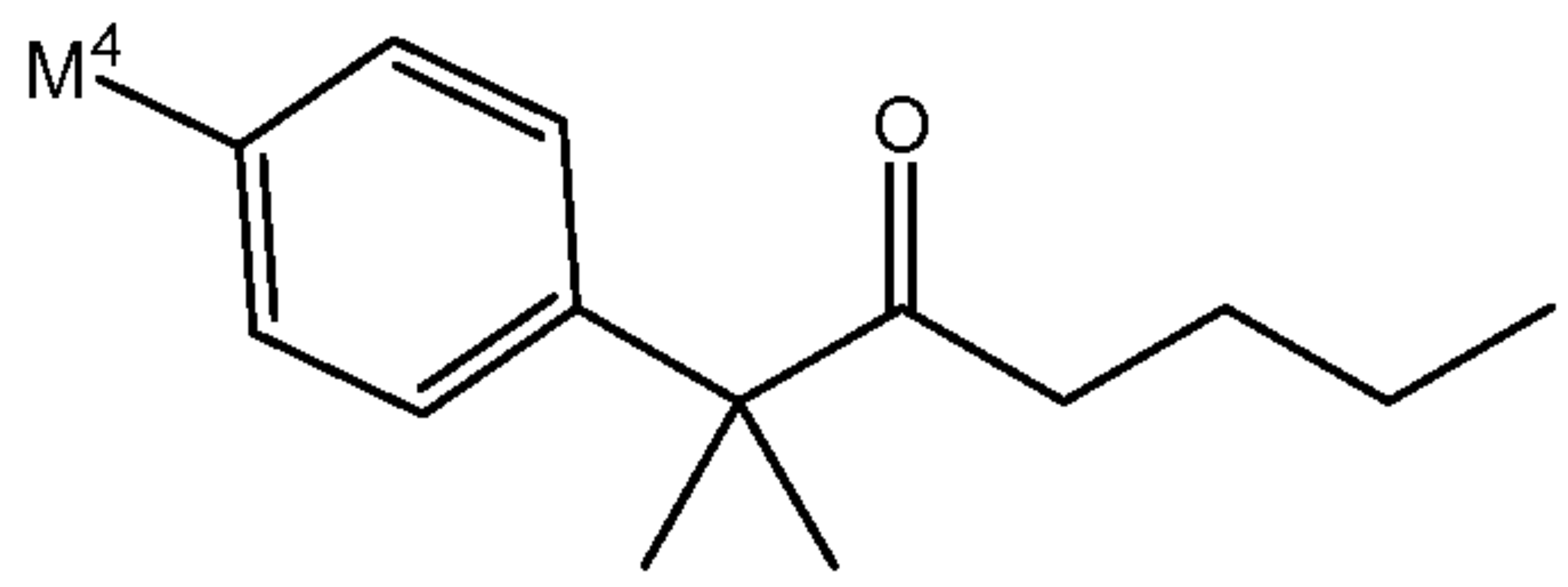


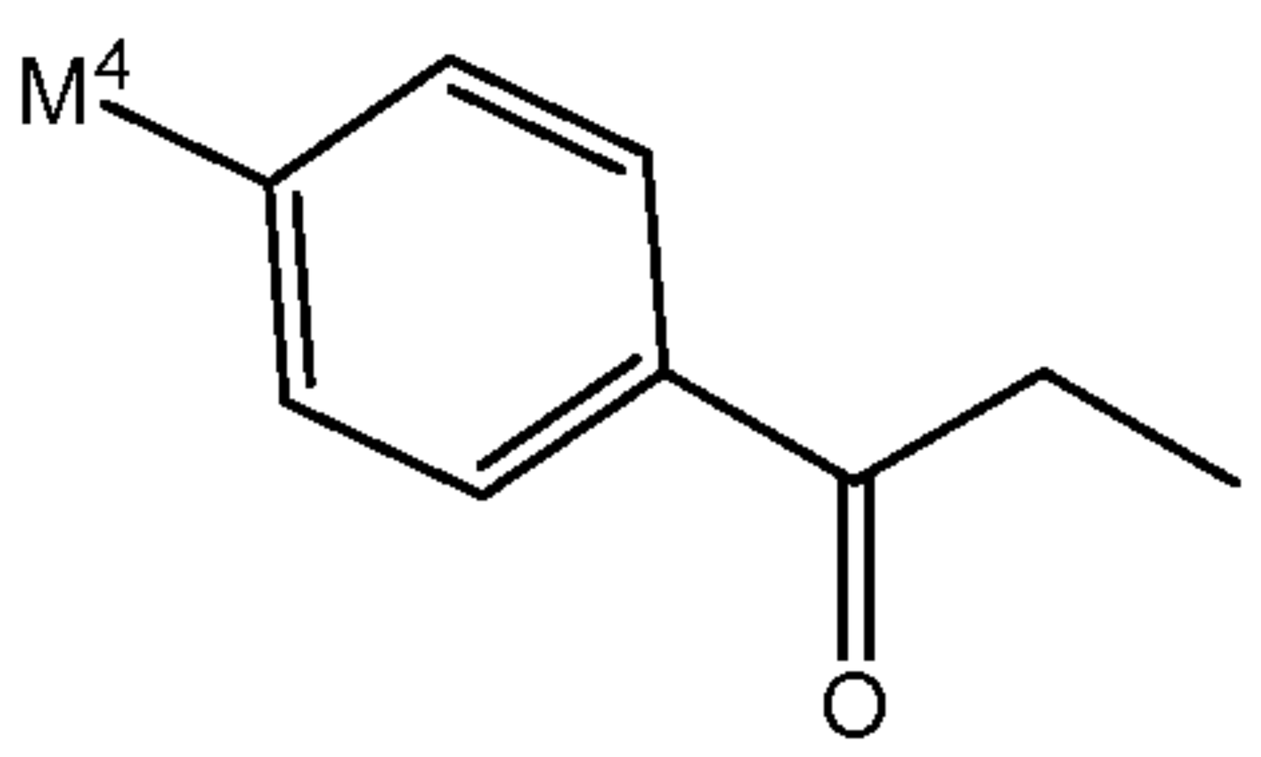


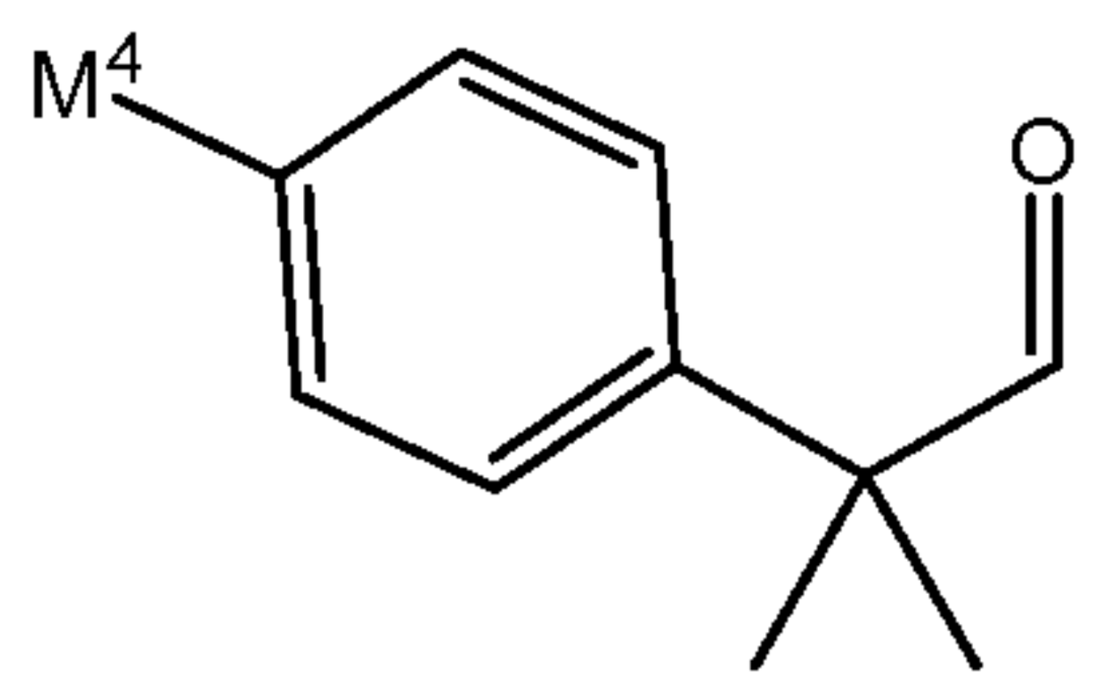


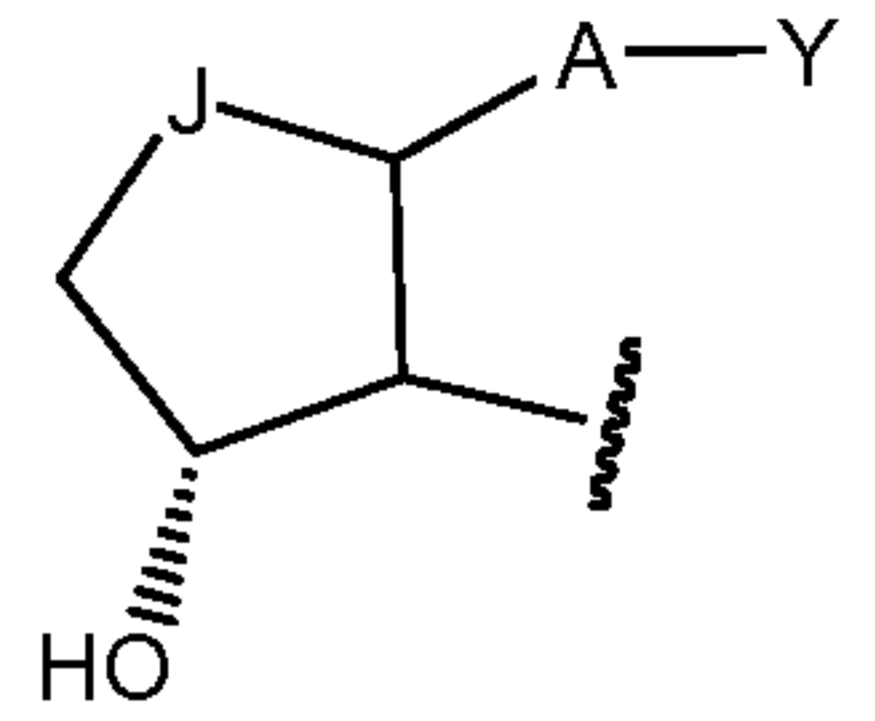


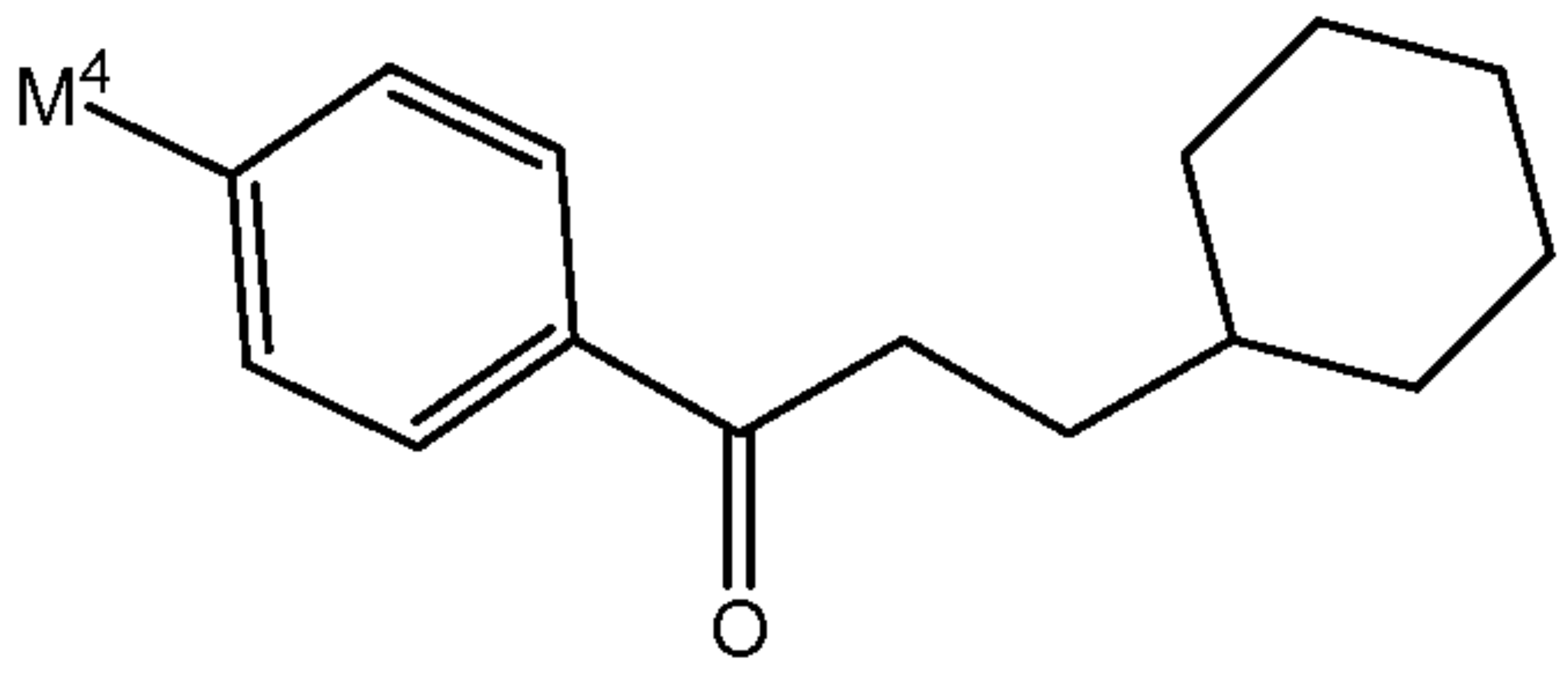


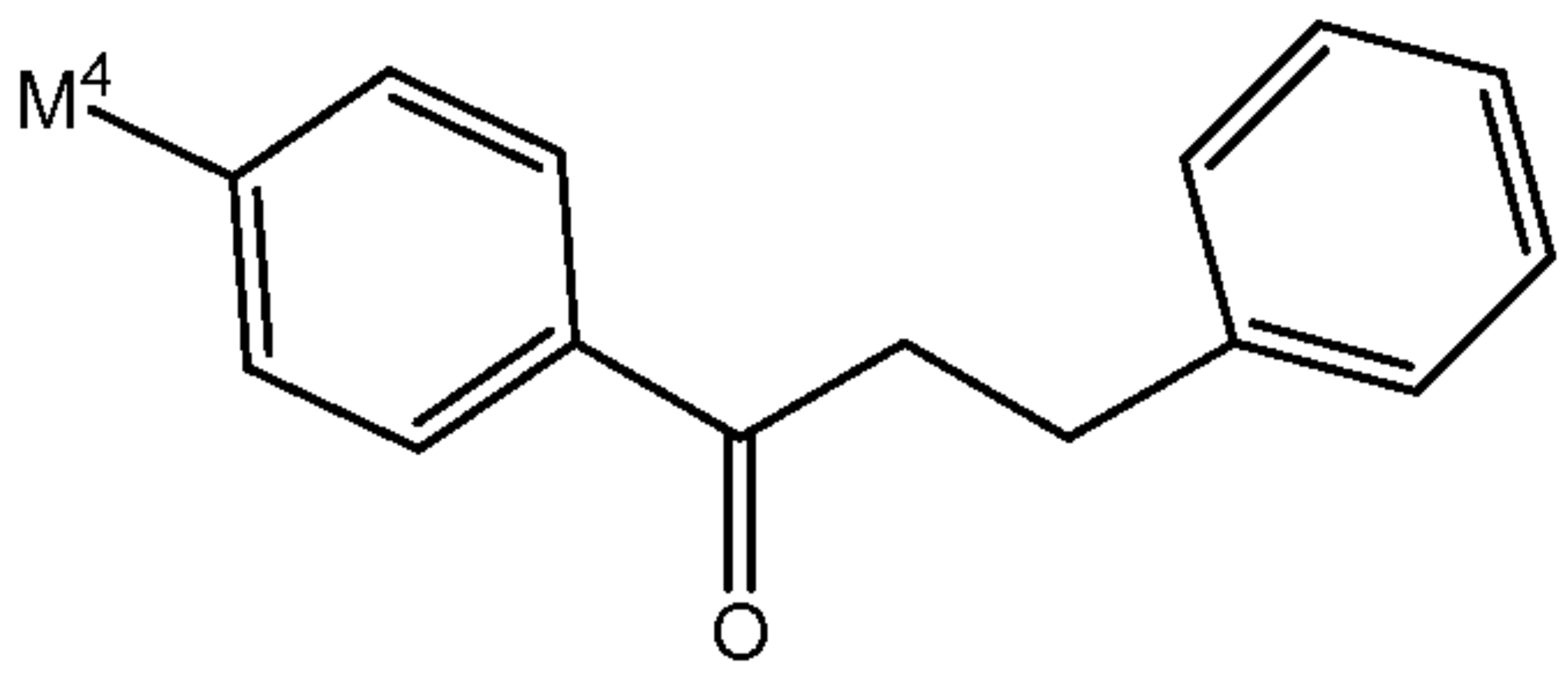


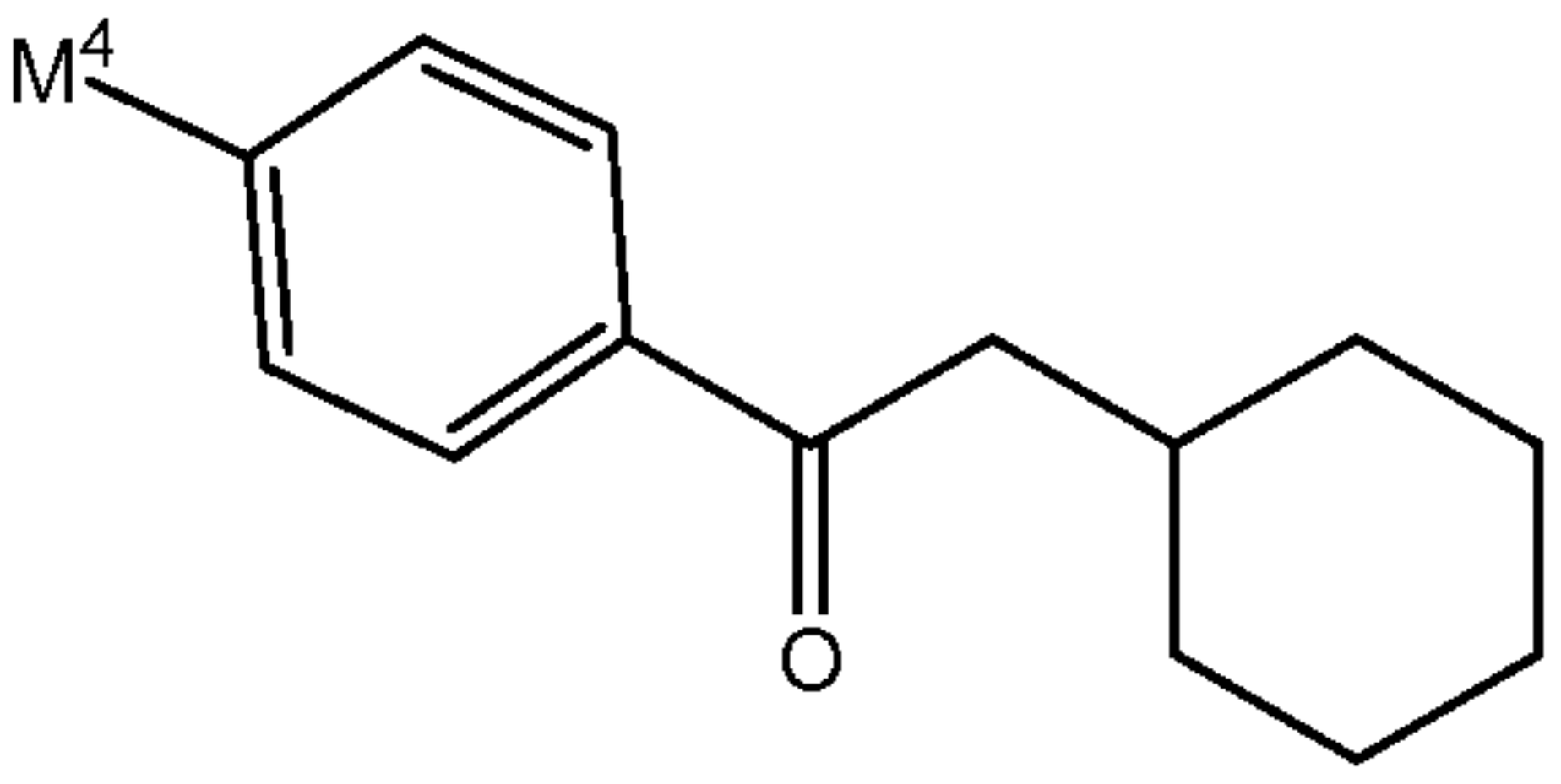


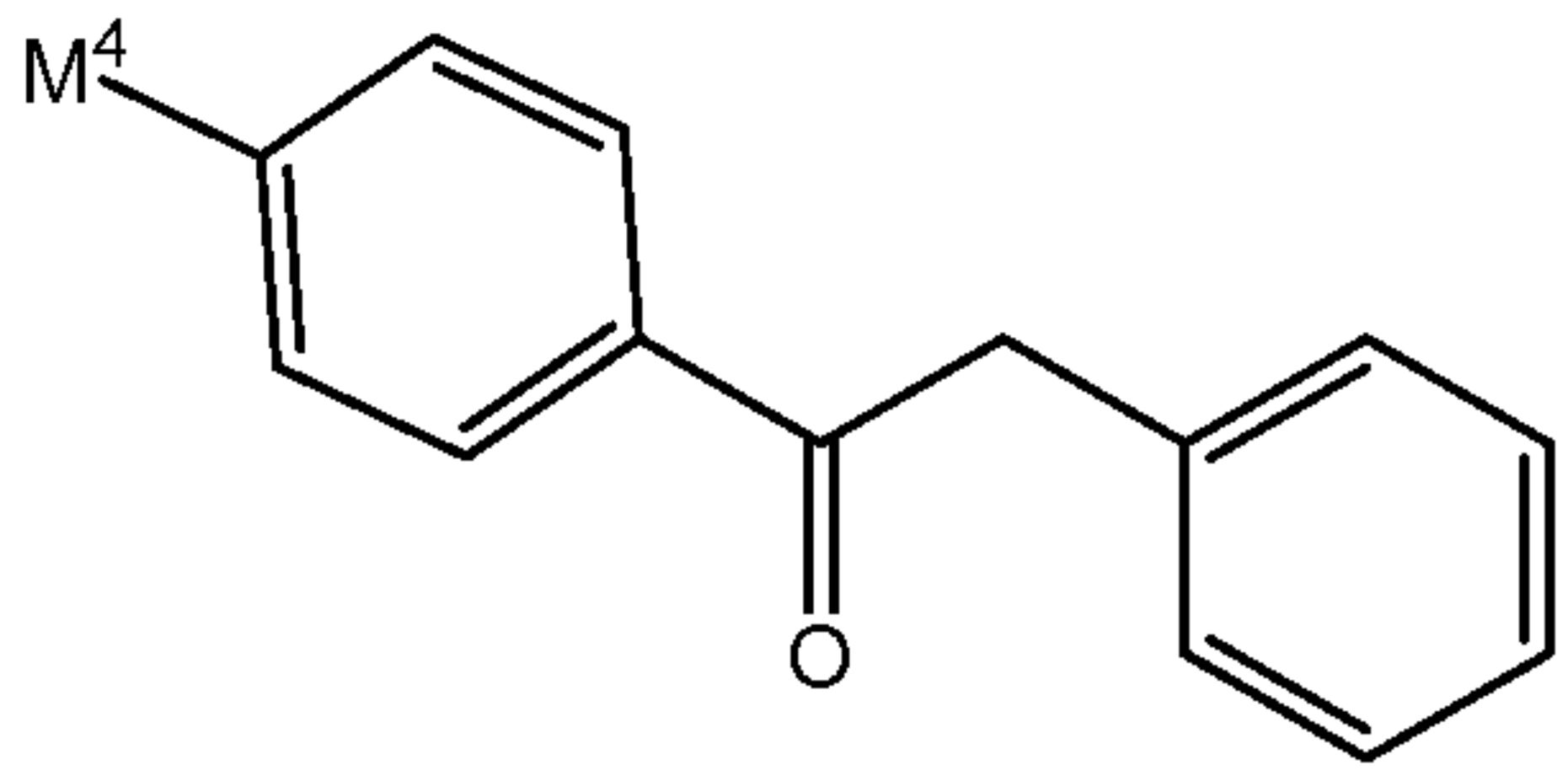


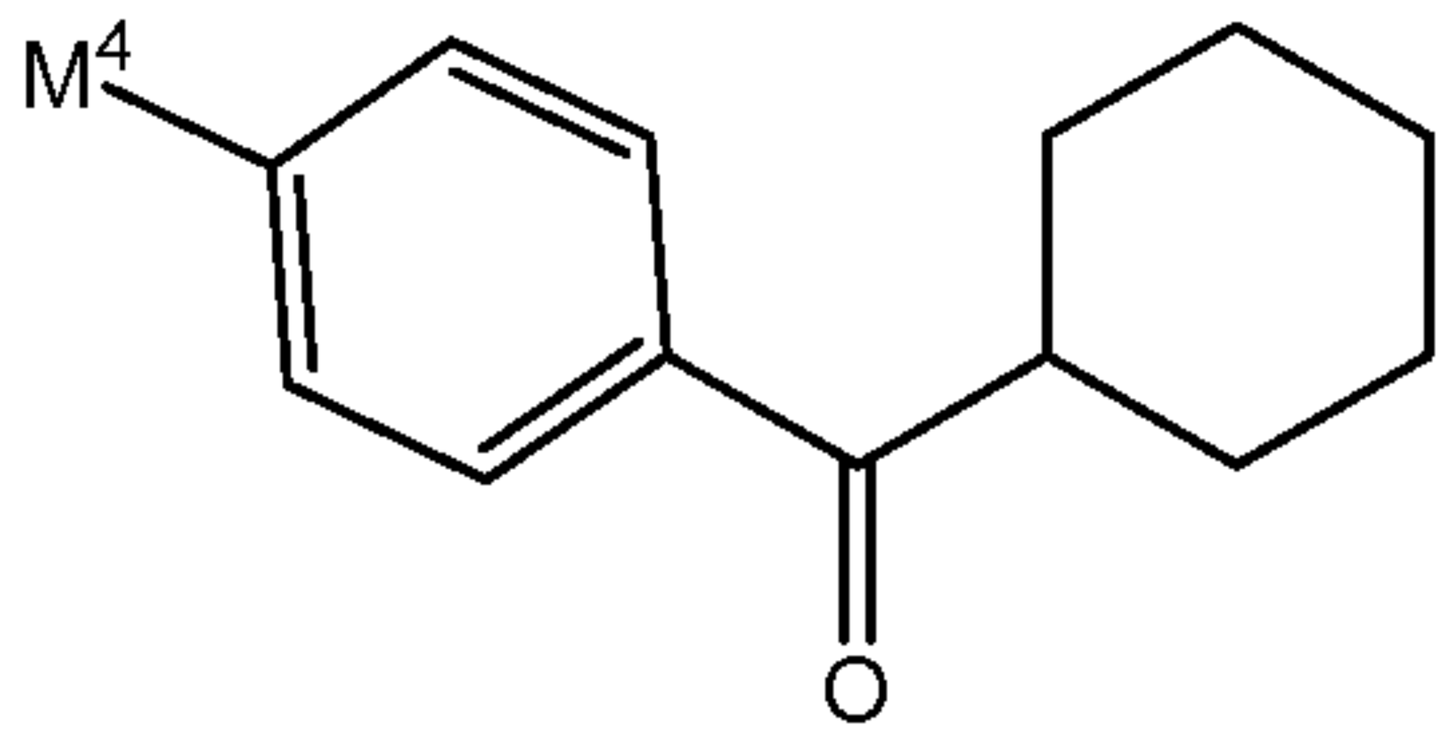
M^4=

J
A
Y
HO

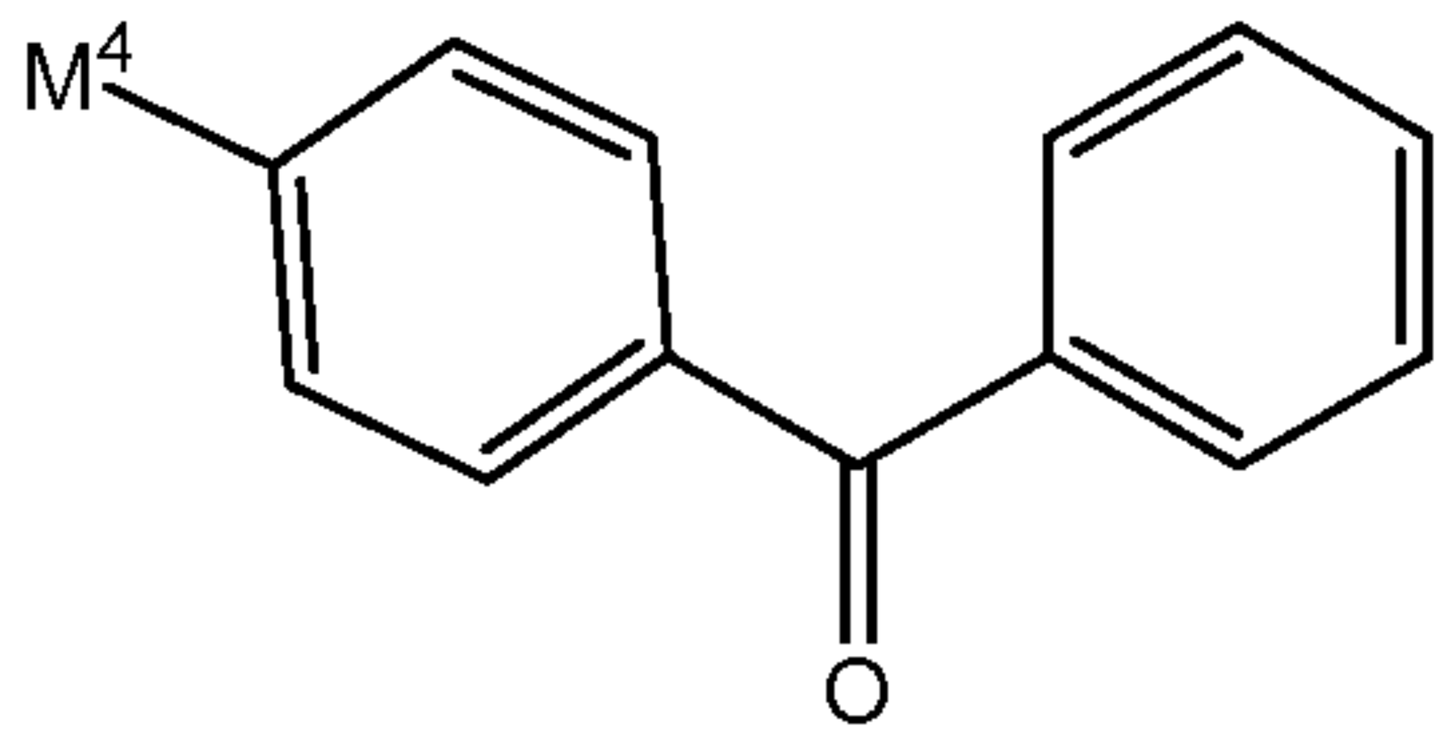

M4
O

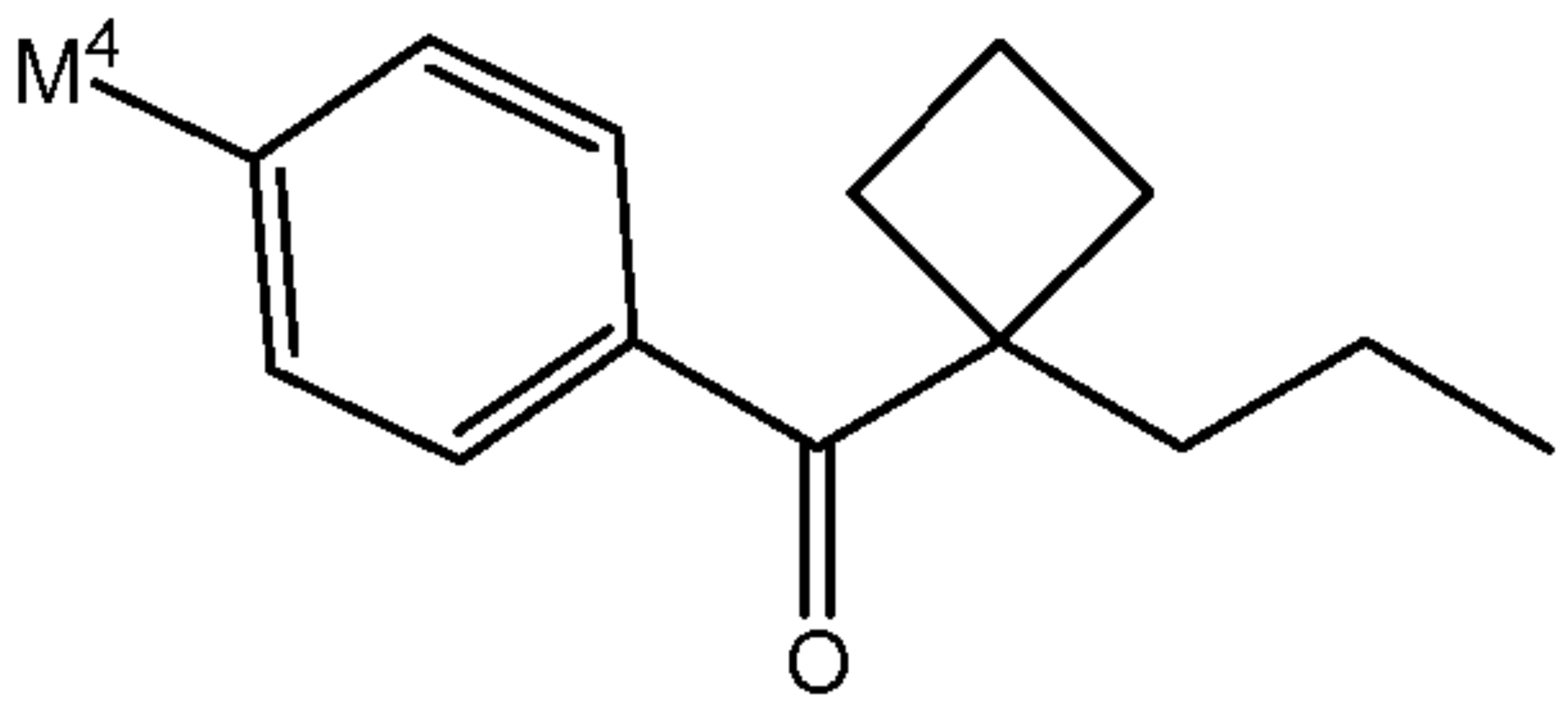

M4
O

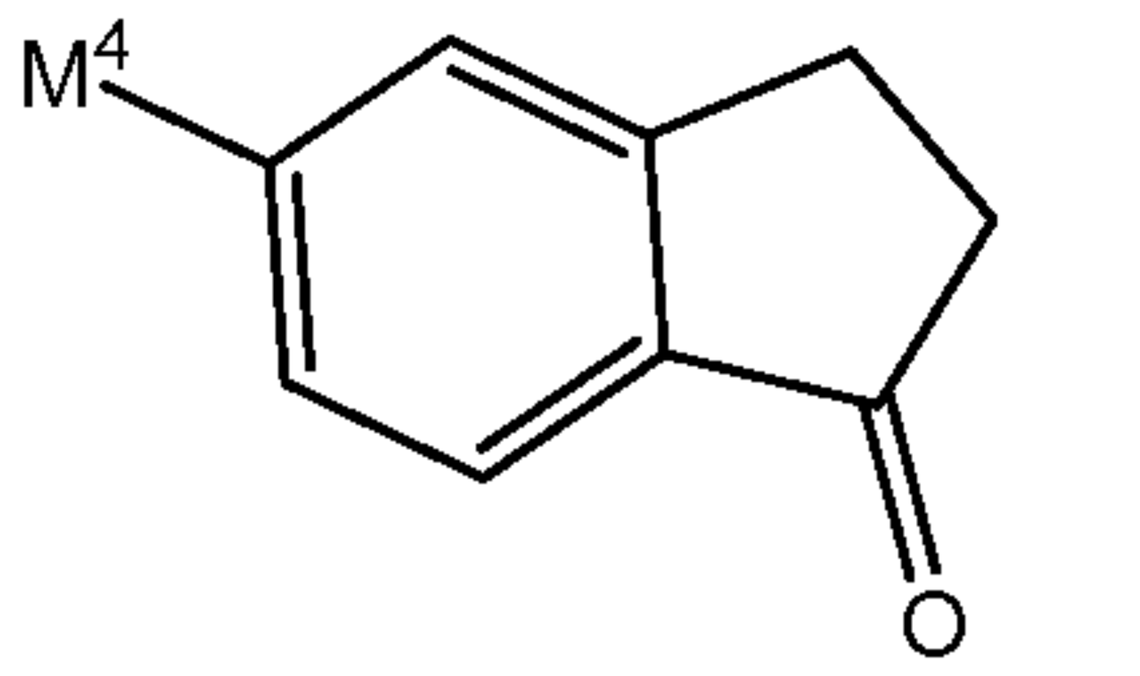

M4
O

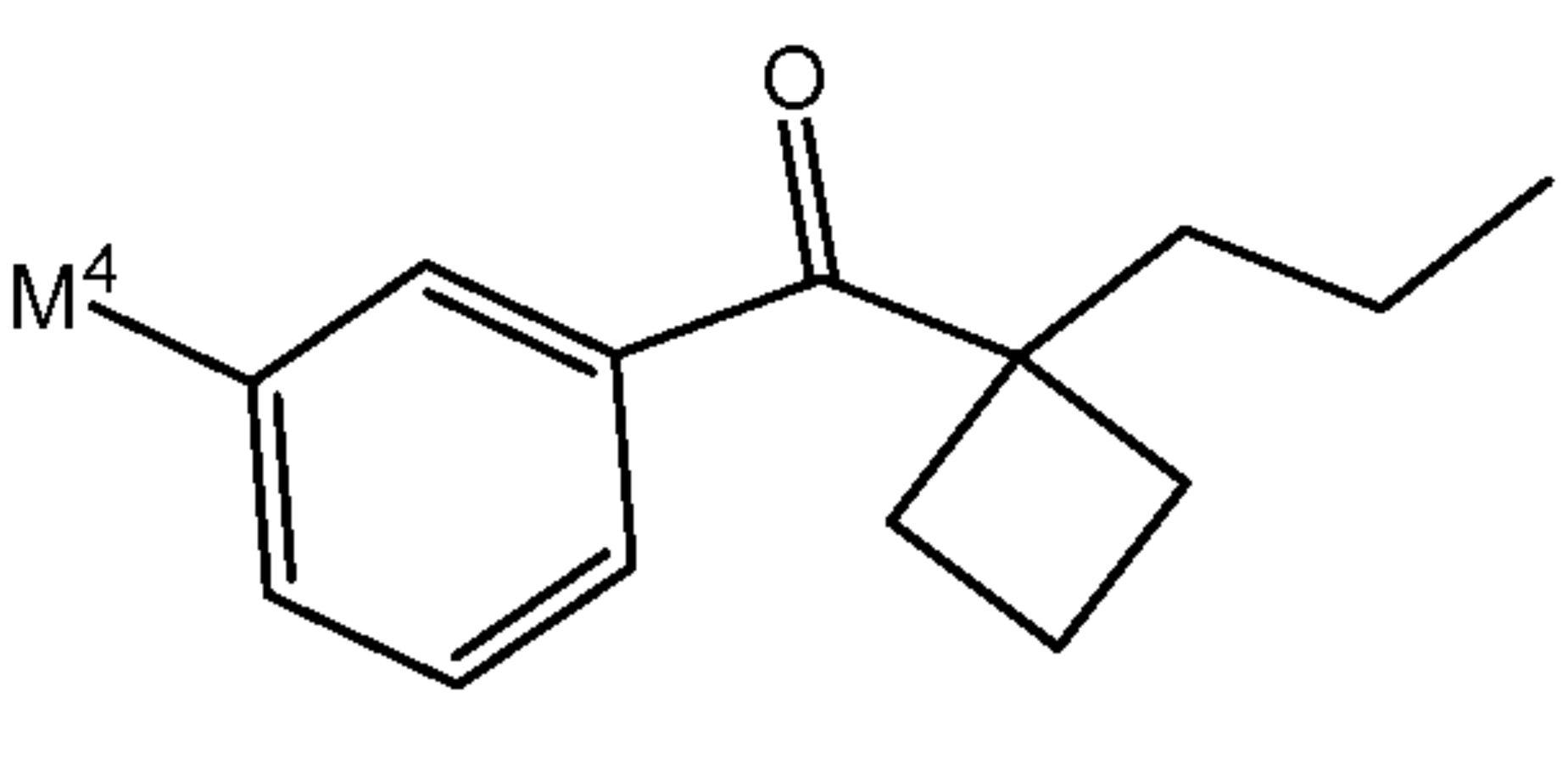

M4
O

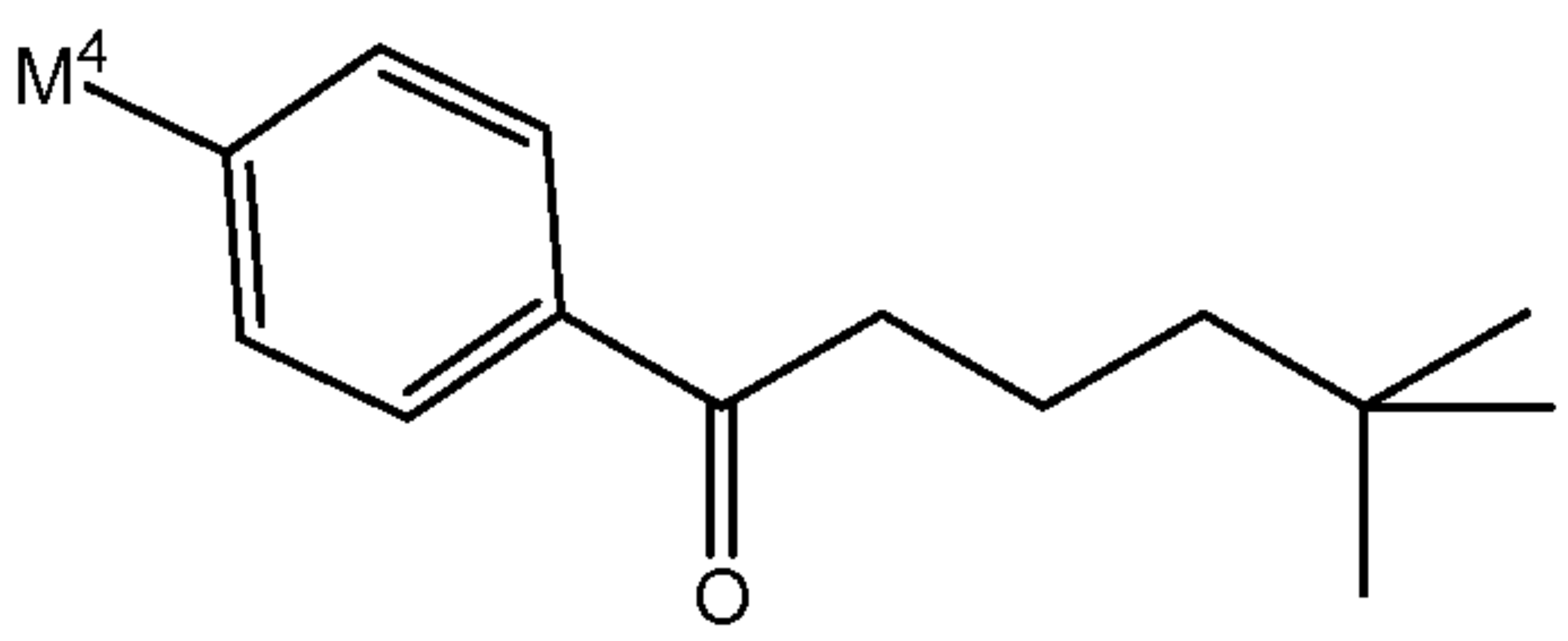

M4
O

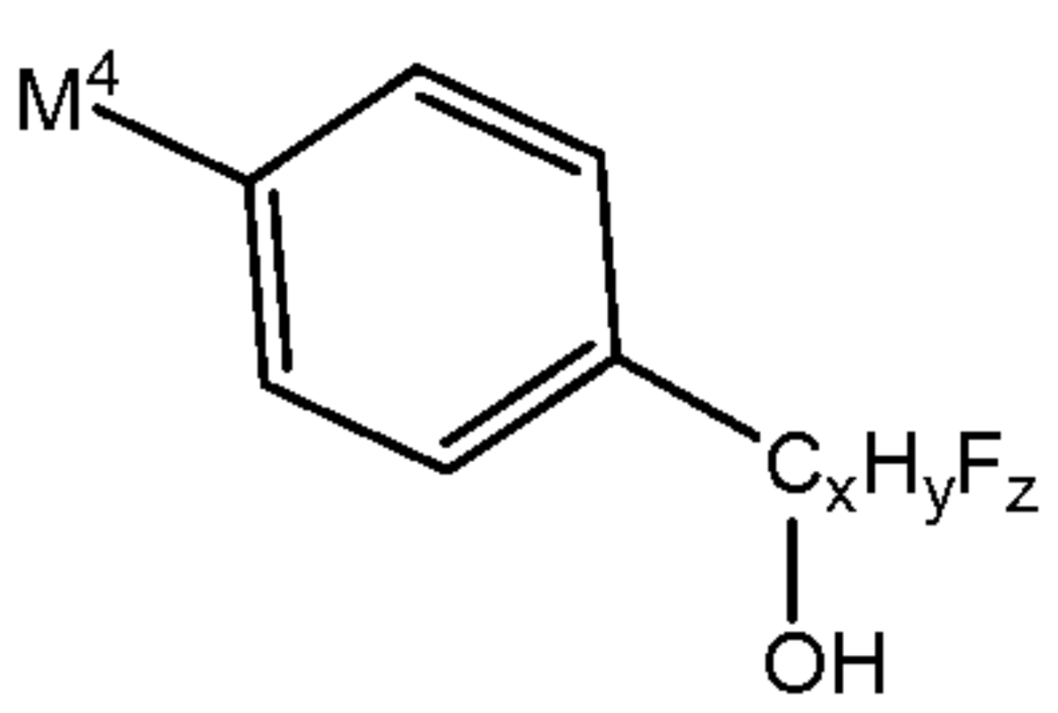

M4
O

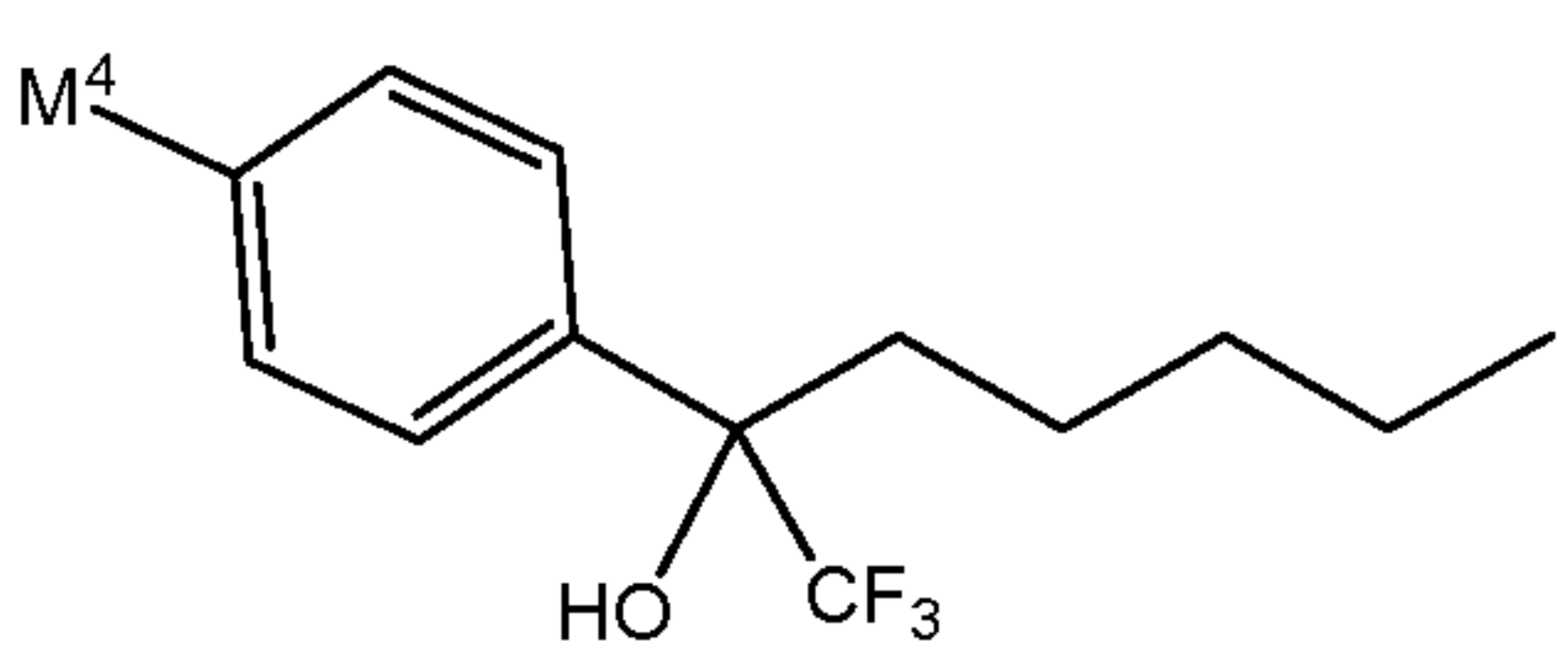

M4
O

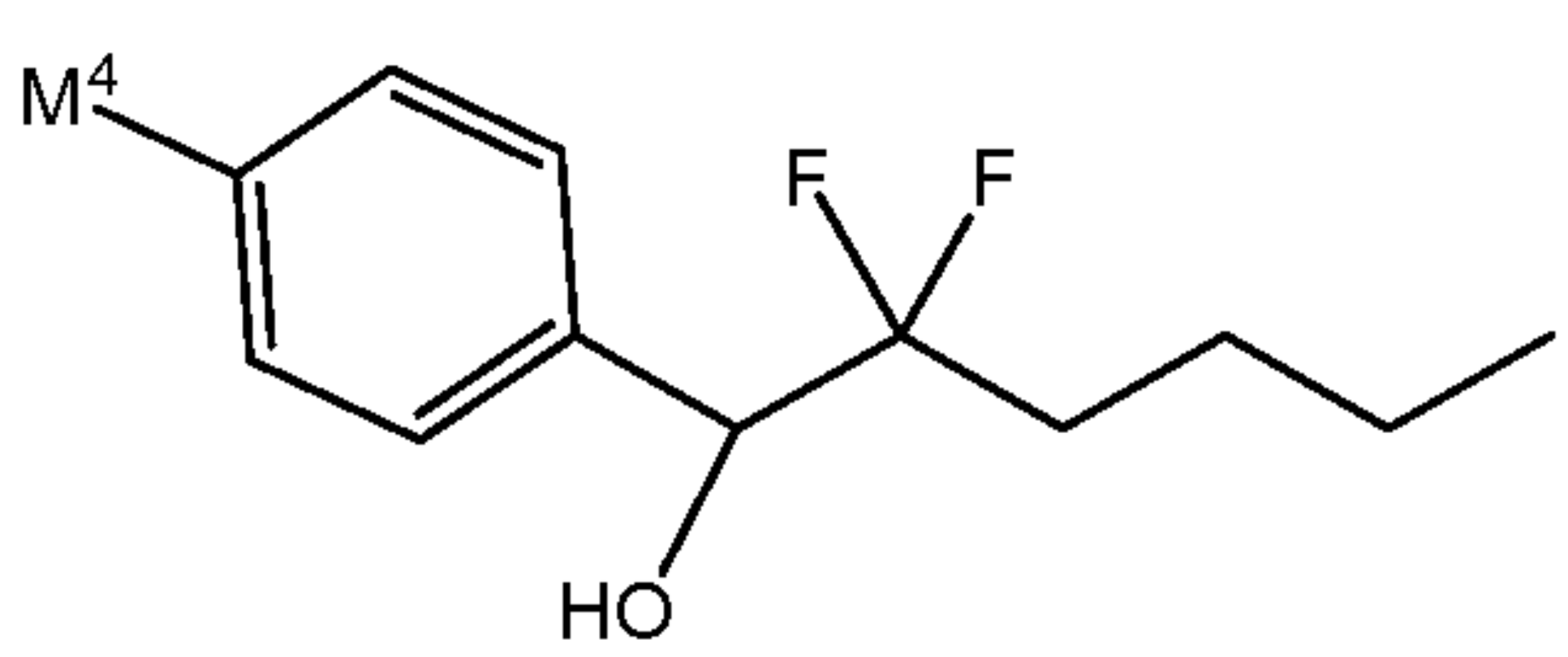

M4
O


M4
O


M4
O


M4
CxHyFz
OH


M4
HO
CF3


M4
F
F
HO

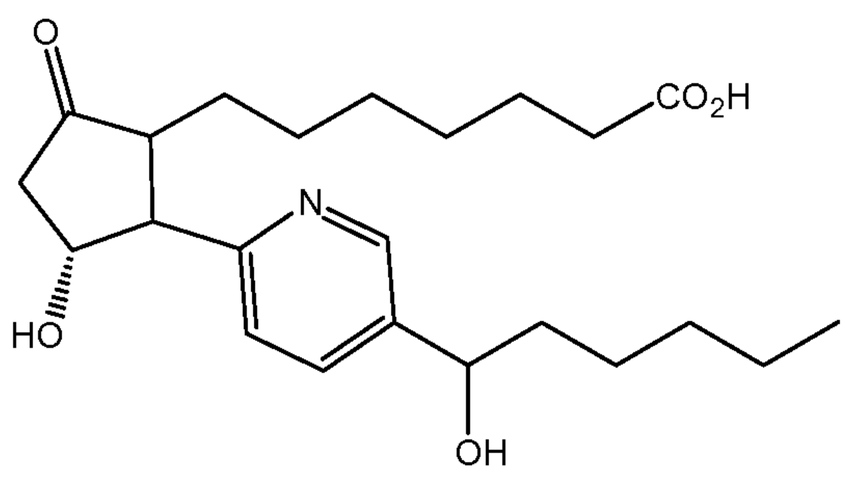
In the above embodiments, x is 5, 6, or 7, and y + z is 2x + 1.

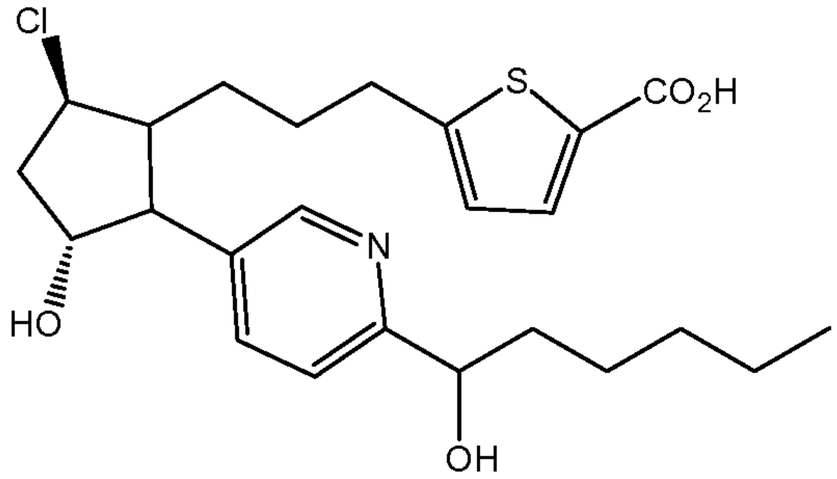
In one embodiment, x is 5 and y + z is 11.

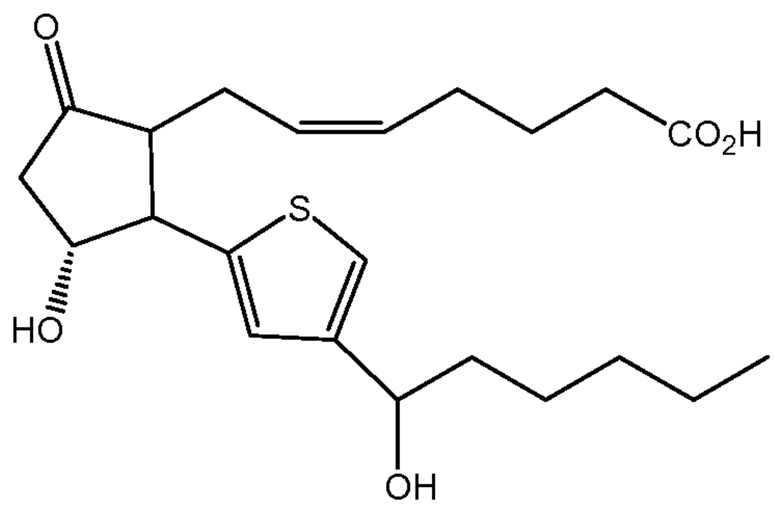
In another embodiment, x is 6 and y + z is 13.

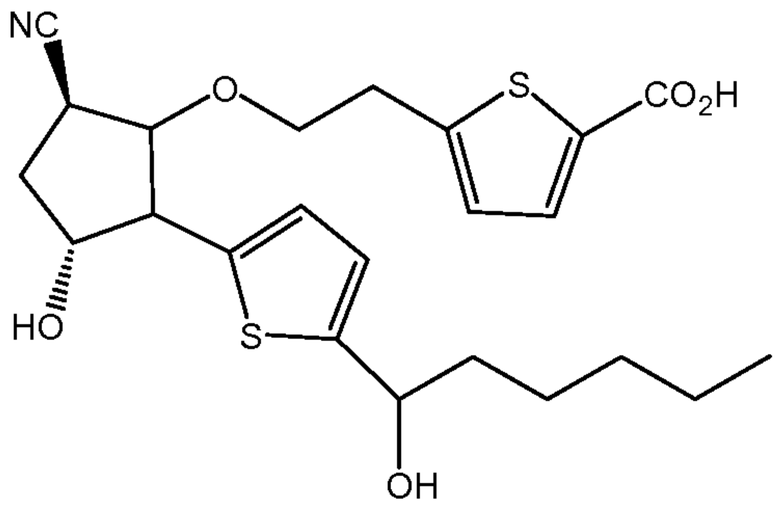
In another embodiment, x is 7 and y + z is 15.

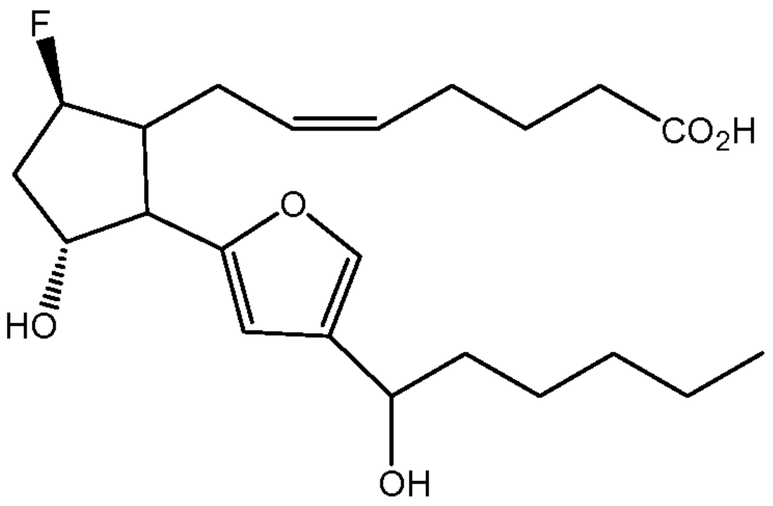
Hypothetical examples of useful compounds are shown below.

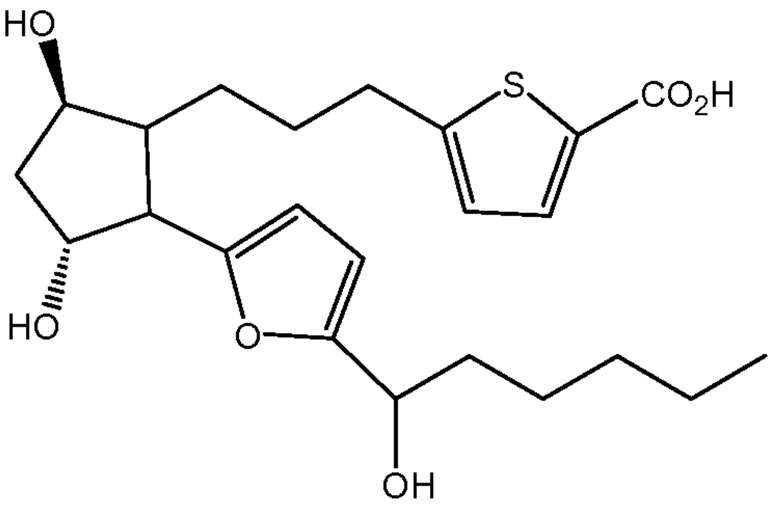


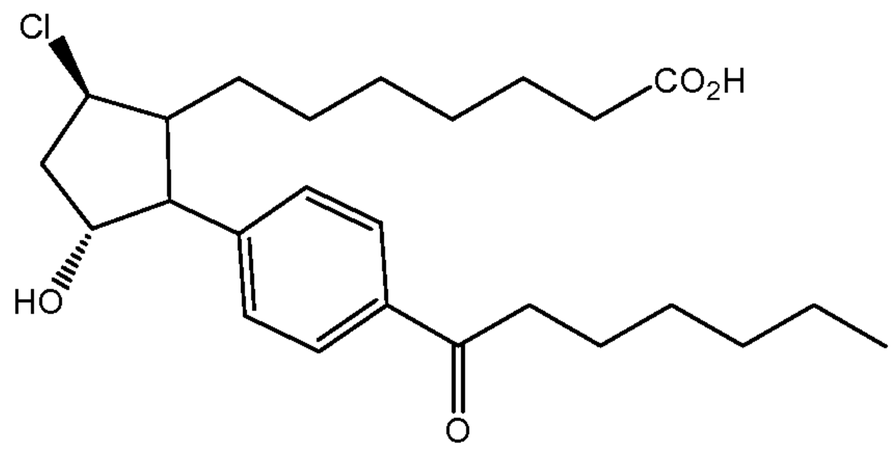


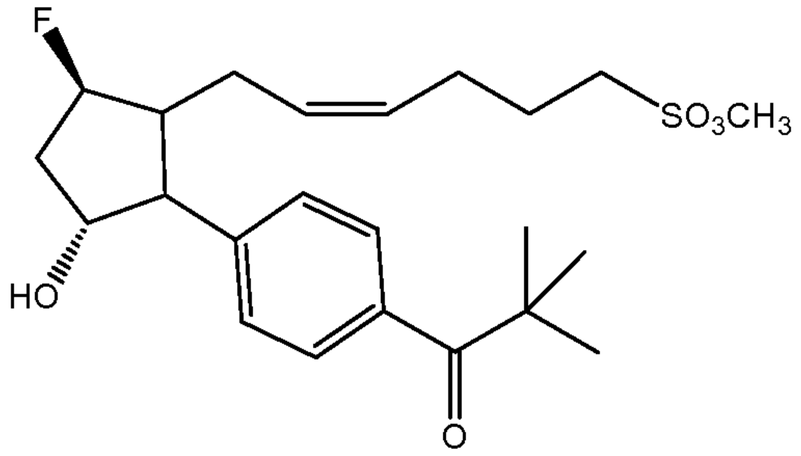


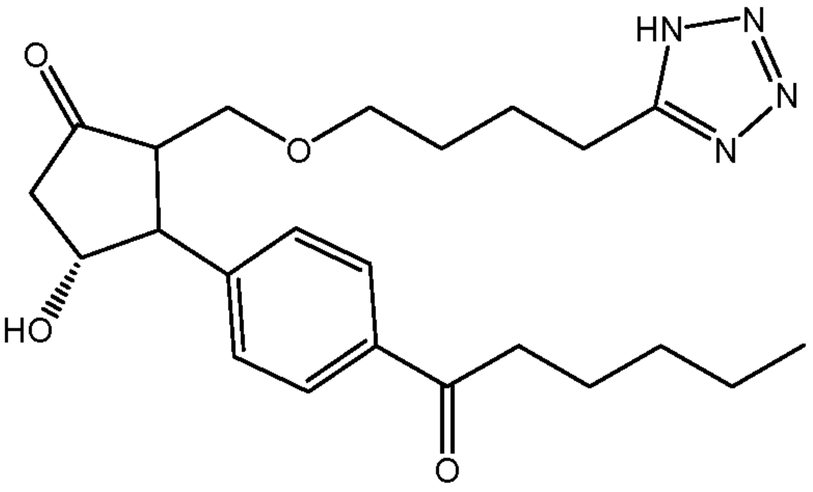


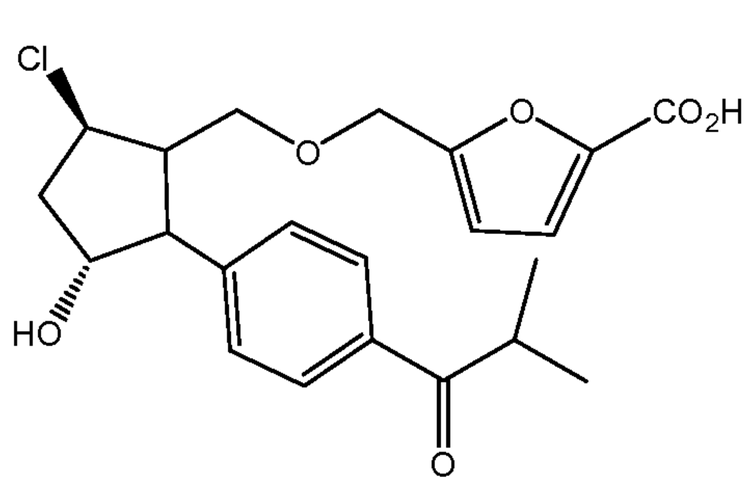


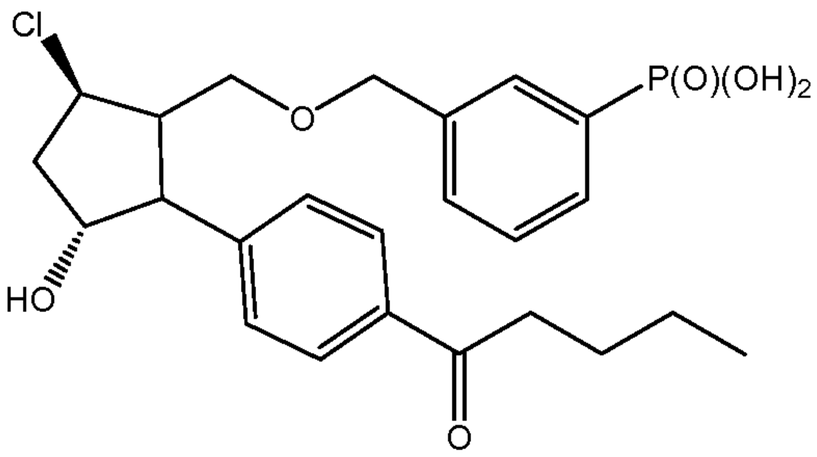


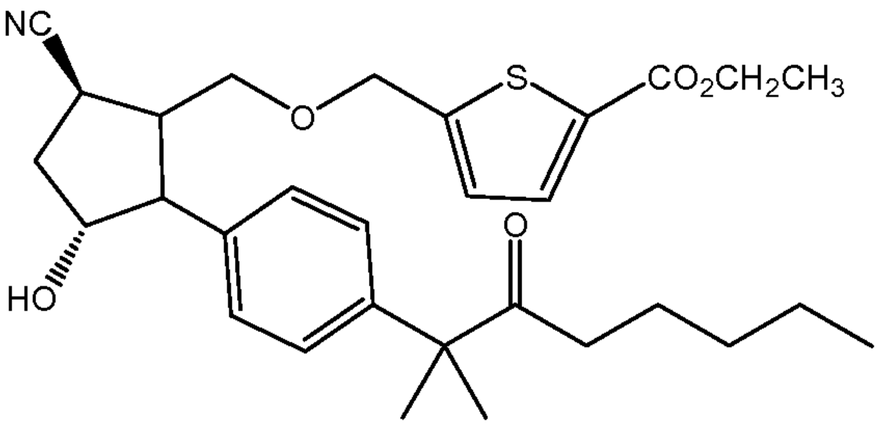


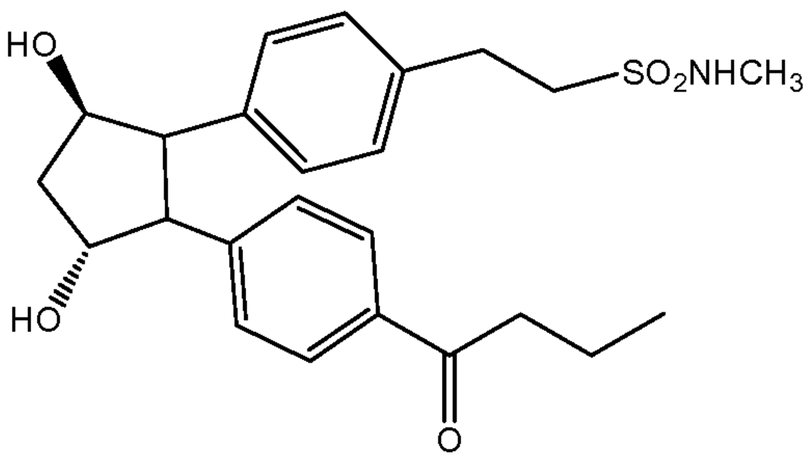


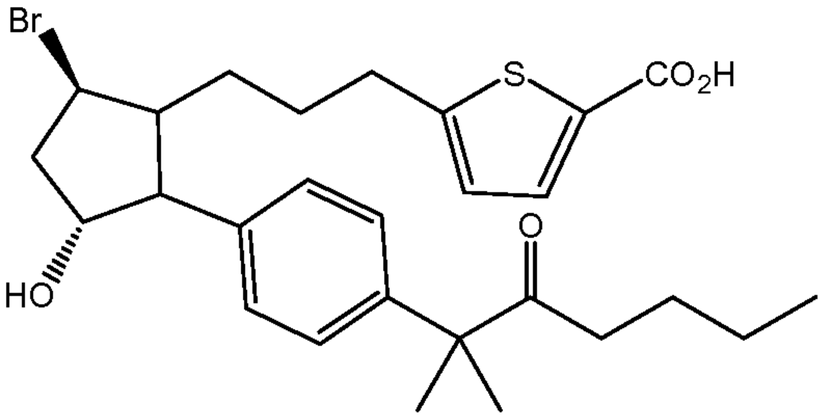


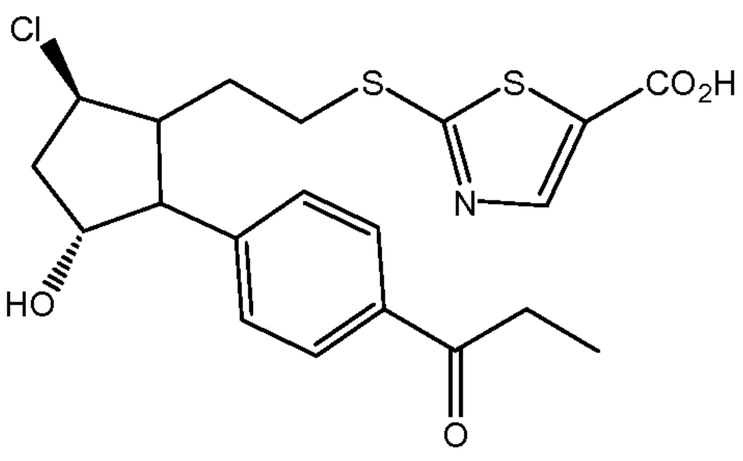


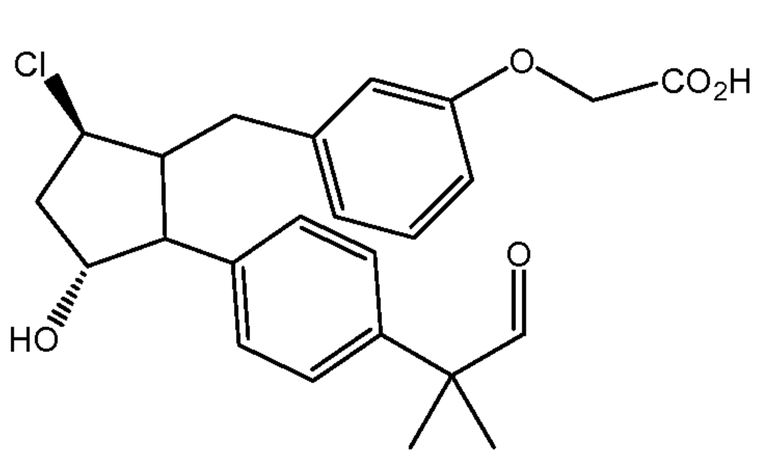


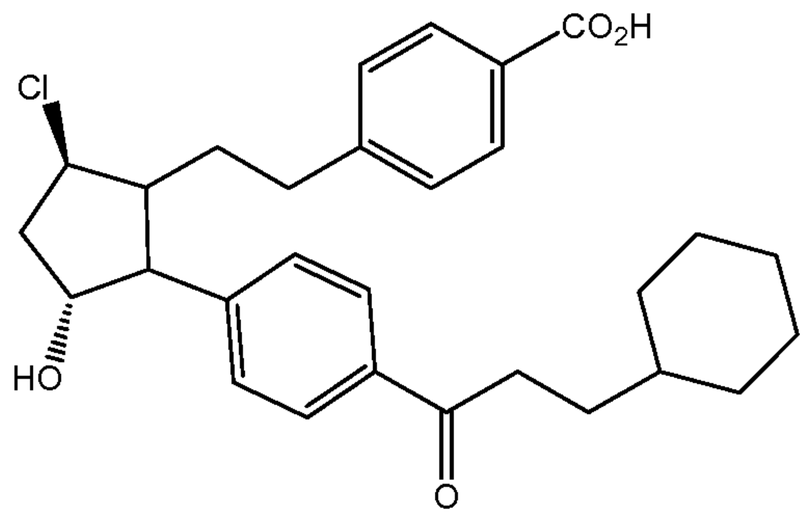


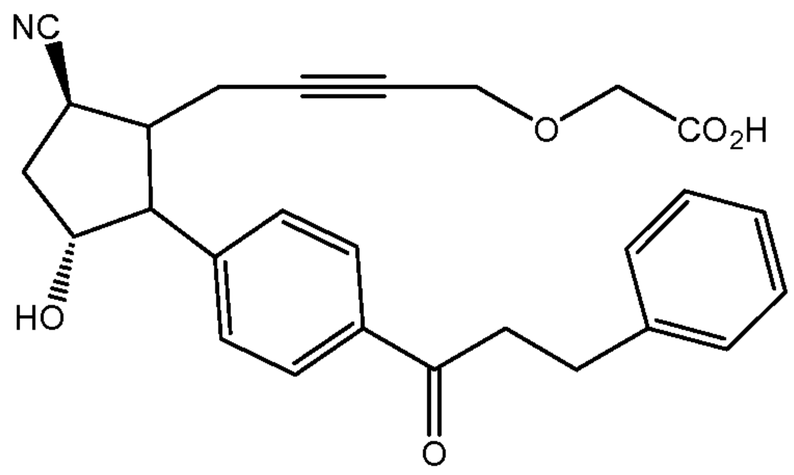


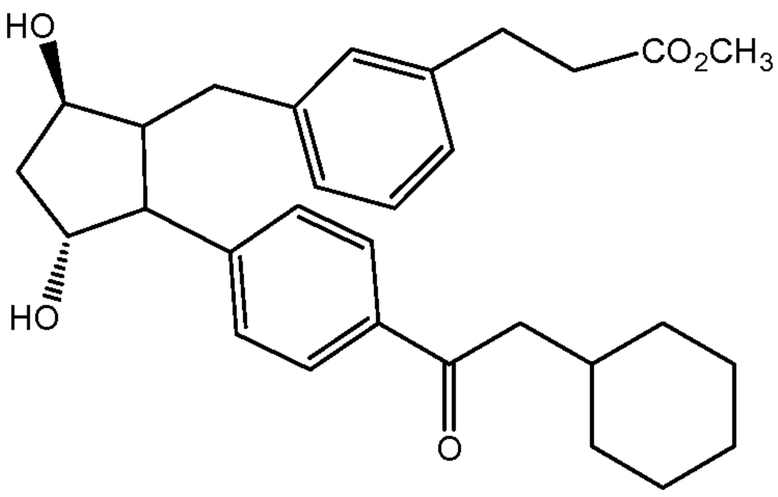


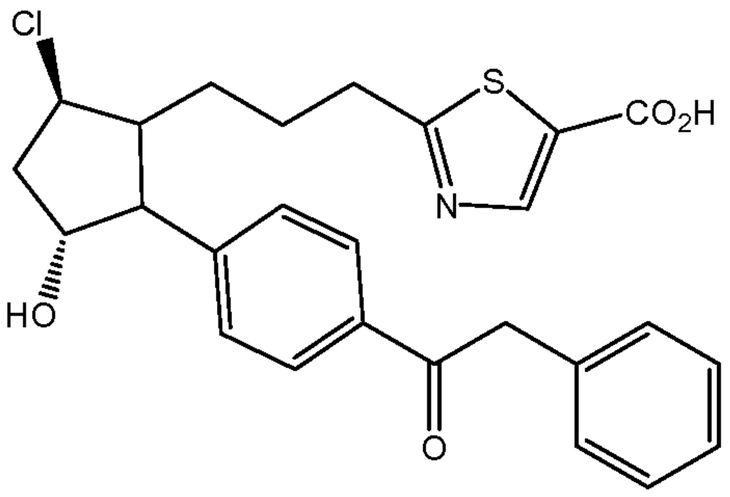


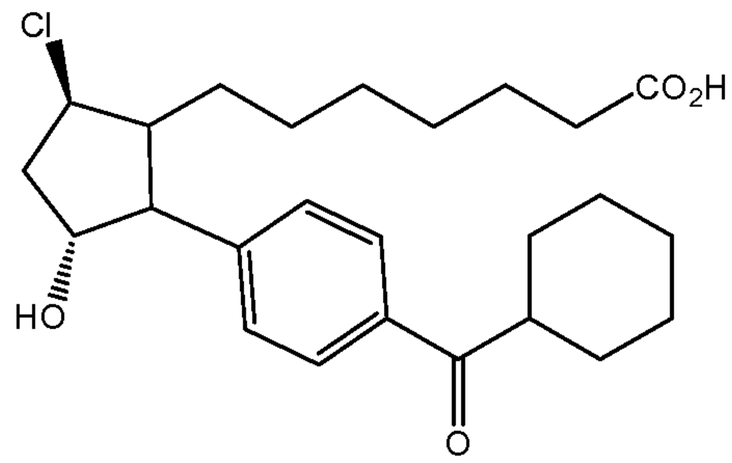


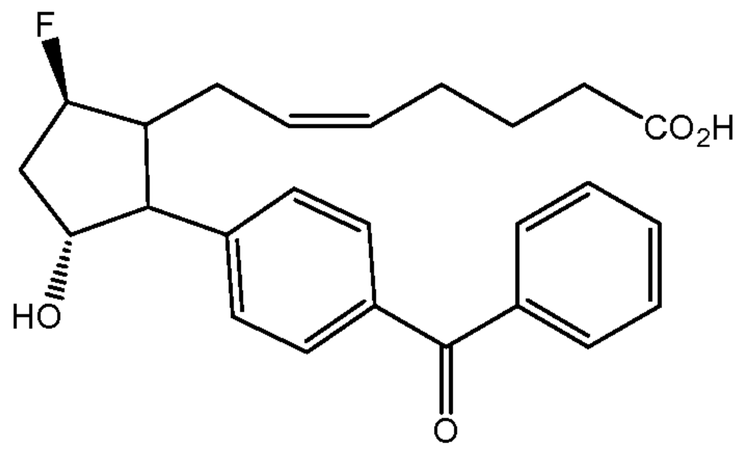


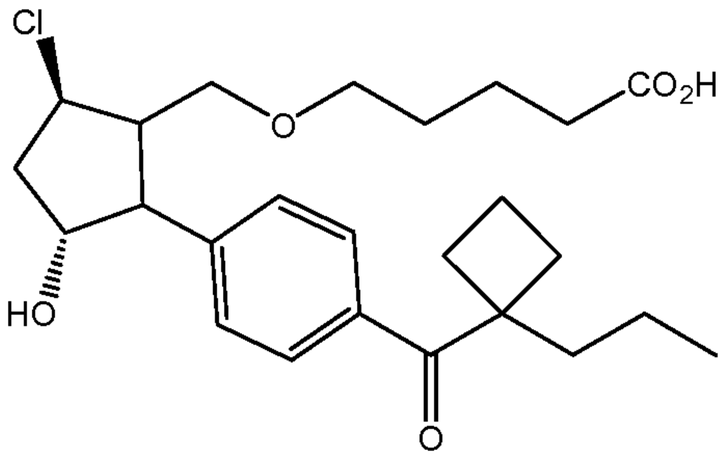


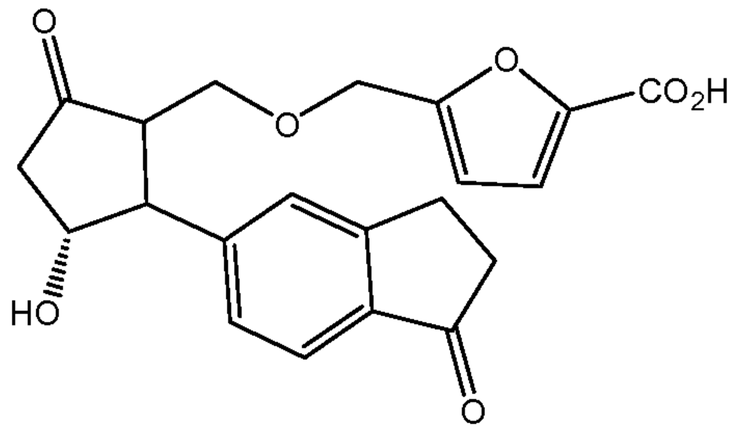


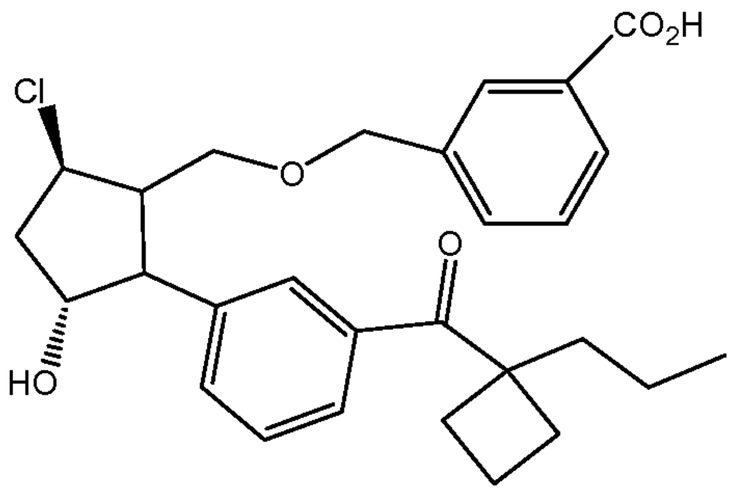


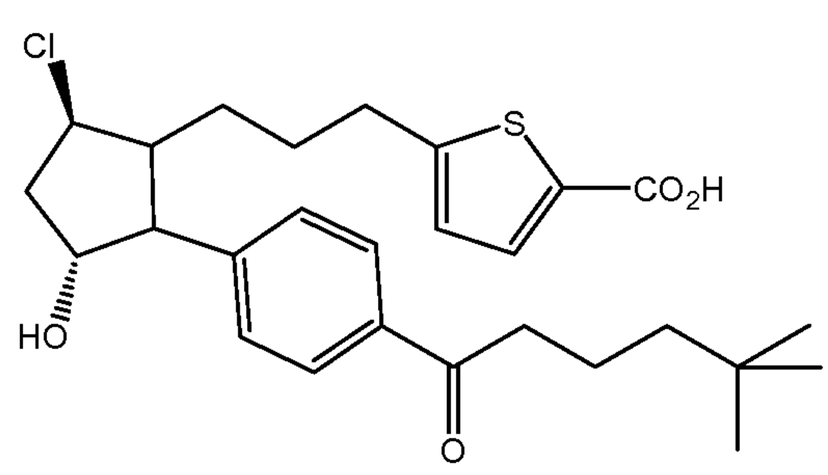












Other useful compounds include:

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester (2);

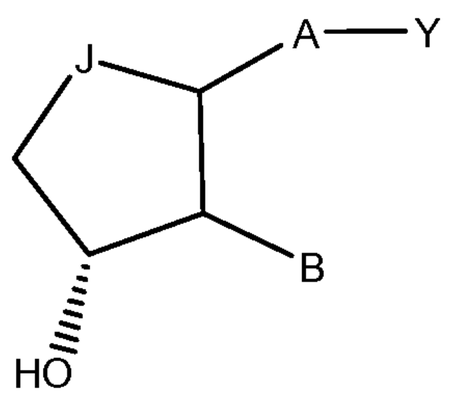
(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid (3); and

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid isopropyl ester (4).

Compound examples:

The following are hypothetical examples of useful compounds:

Compound Example 1. A compound having a structure



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

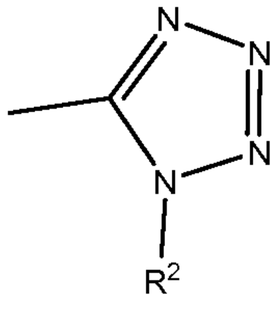
wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 14 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 14 carbon atoms; or Y is a tetrazolyl functional group;

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 one CH_2 may be replaced by S or O;

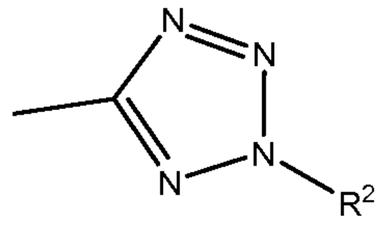
J is C=O, CHOH, CHF, CHCl, CHBr, CF_2, CCl_2, CBr_2, or CHCN; and

B is C_{1-10} oxoalkyl substituted aryl or 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,



and

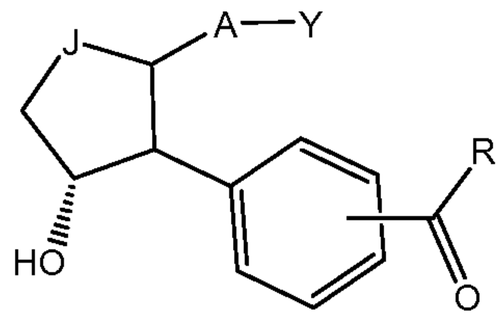


;

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

Compound Example 3. The compound according to any one of compound examples 1 to 8 wherein B is substituted phenyl.

Compound Example 4. The compound according to any one of compound examples 1 to 3 having a structure



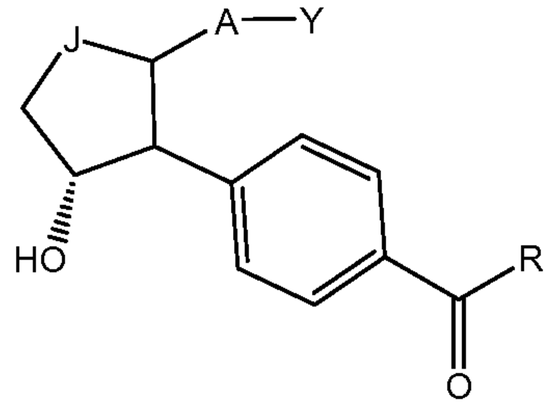
or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

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.

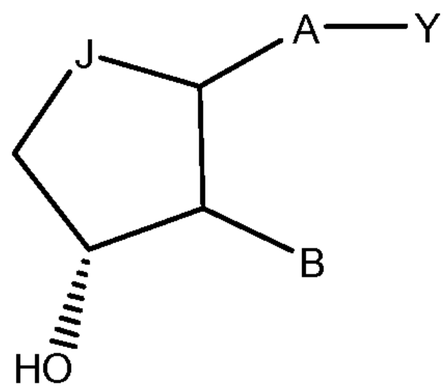
Compound Example 7. The compound according to compound example any one of compound examples 1 to 6 having a structure



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

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

Compound Example 8. A compound having a structure



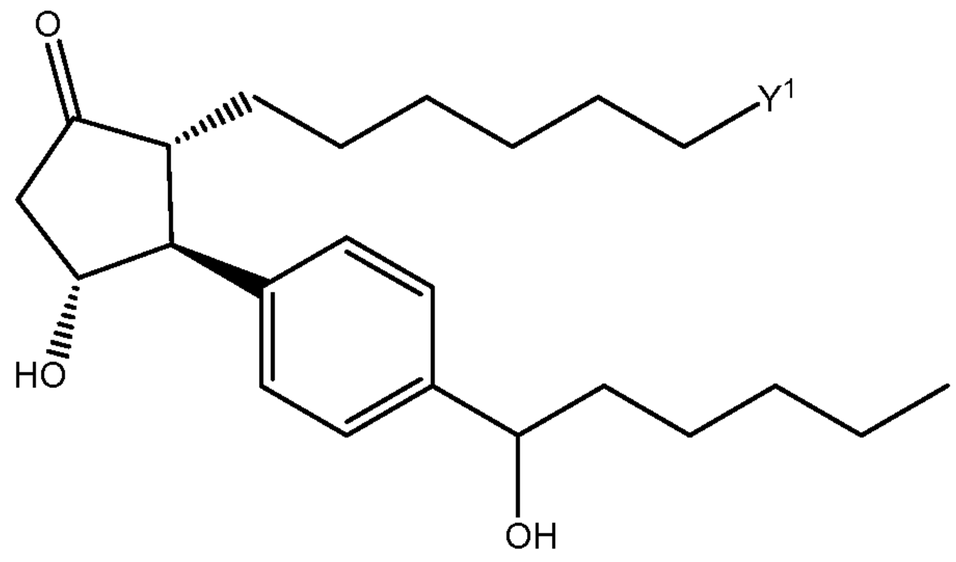
or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

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;

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 one CH_2 may be replaced by S or O;

J is C=O, CHOH, CHF, CHCl, CHBr, CF_2, CCl_2, CBr_2, or CHCN; and

B is substituted aryl or heteroaryl with the proviso that the compound is not



wherein Y^1 is CO_2H or an amide or a carboxylic acid.

The compound according to any one of compound examples 1 to 8 wherein A is (3-methylphenoxy)methyl.

Compound Example 9. The compound according to any one of compound examples 1 to 8 wherein A is (4-but-2-ynyloxy)methyl.

Compound Example 10. The compound according to any one of compound examples 1 to 8 wherein A is 2-(2-ethylthio)thiazol-4-yl.

Compound Example 11. The compound according to any one of compound examples 1 to 8 wherein A is 2-(3-propyl)thiazol-5-yl.

Compound Example 12. The compound according to any one of compound examples 1 to 8 wherein A is 3-methoxymethyl)phenyl.

Compound Example 13. The compound according to any one of compound examples 1 to 8 wherein A is 3-(3-propylphenyl.

Compound Example 14. The compound according to any one of compound examples 1 to 8 wherein A is 3-methylphenethyl.

Compound Example 15. The compound according to any one of compound examples 1 to 8 wherein A is 4-(2-ethyl)phenyl.

Compound Example 16. The compound according to any one of compound examples 1 to 8 wherein A is 4-phenethyl.

Compound Example 17. The compound according to any one of compound examples 1 to 8 wherein A is 4-methoxybutyl.

Compound Example 18. The compound according to any one of compound examples 1 to 8 wherein A is 5-(methoxymethyl)furan-2-yl .

Compound Example 19. The compound according to any one of compound examples 1 to 8 wherein A is 5-(methoxymethyl)thiophen-2-yl.

Compound Example 20. The compound according to any one of compound examples 1 to 8 wherein A is 5-(3-propyl)furan-2-yl.

Compound Example 21. The compound according to any one of compound examples 1 to 8 wherein A is 5-(3-propyl)thiophen-2-yl.

Compound Example 22. The compound according to any one of compound examples 1 to 8 wherein A is 6-hexyl.

Compound Example 23. The compound according to any one of compound examples 1 to 8 wherein A is (Z)-6-hex-4-enyl.

Compound Example 24. The compound according to any one of compound examples 8 to 24 wherein B is 3-(1-hydroxyhexyl)thiophen-2-yl.

Compound Example 25. The compound according to any one of compound examples 8 to 24 wherein B is 3-(1-hydroxyhexyl)thiophen-3-yl.

Compound Example 26. The compound according to any one of compound examples 8 to 24 wherein B is 3-(1-hydroxyhexyl)furan-2-yl.

Compound Example 27. The compound according to any one of compound examples 8 to 24 wherein B is 3-(1-hydroxyhexyl)furan-3-yl.

Compound Example 28. The compound according to any one of compound examples 8 to 24 wherein B is 3-(1-hydroxyhexyl)pyridin-2-yl.

Compound Example 29. The compound according to any one of compound examples 8 to 24 wherein B is 3-(1-hydroxyhexyl)pyridin-3-yl.

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

Composition Example:

A composition comprising a compound according to any one of compound examples 1 to 30, 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 30 in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension in a mammal.

A medicament comprising a compound according to any one of compound examples 1 to 30, 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 23 to a mammal for the treatment of glaucoma or ocular hypertension.

Kit Example:

A kit comprising a composition comprising compound according to any one of compound examples 1 to 23, a container, and instructions for administration of said composition to a mammal for the treatment of glaucoma or ocular hypertension.

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.

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 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 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. C_{1-6} 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.

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 confected 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.

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 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 adjutants 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 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 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 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:

Ingredient	**Amount (% w/v)**
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
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 synthetic methods disclosed in United States Patent Application Serial Number 11/009,298, filed December 10, 2004, and United States Provisional Patent Application No. 60/742,779, filed December 6, 2005, both of which are expressly incorporated by reference herein, may be readily adapted by one of ordinary skill in the art to obtain the compounds disclosed herein.

Compounds wherein J is CN compounds may be prepared by adapting the procedure disclosed in United States Provisional Patent Application No. 60/747835, filed May 22, 2006.

Compounds wherein J is CHF may be prepared by adapting the procedures disclosed in United States Patent Application Serial Number 11/009,298 and United States Provisional Patent Application No. 60/742,779.

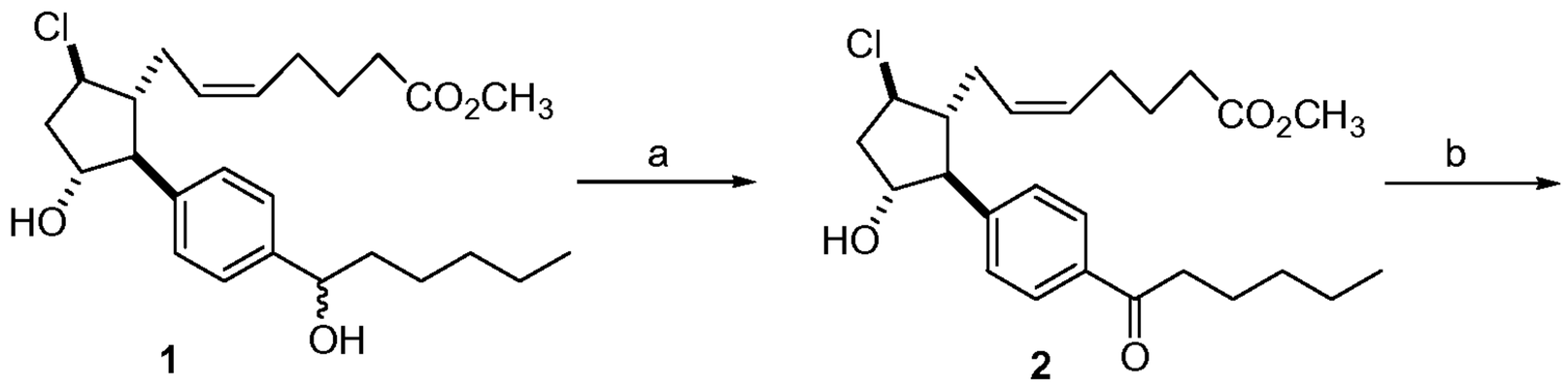
Compounds wherein J is CHBr may be prepared by adapting the procedures disclosed in Tani, K. et.al. (ONO) *Bioorganic and Medicinal Chemistry* **2002**, *10*, 1883.

Compounds wherein J is CCl_2 or CBr_2 may be prepared by adapting the procedures disclosed in cite United States Provisional Patent Application No. 60746275, filed on May 3, 2006, which is expressly incorporated herein by reference.

Compounds wherein J is CF_2 be made from the corresponding compounds where J is C=O in a similar procedure to making compounds wherein J is CHF according to Lal et.al. *J.Org.Chem*. 1999,*64*, 7048.

Synthetic Examples

Scheme 1



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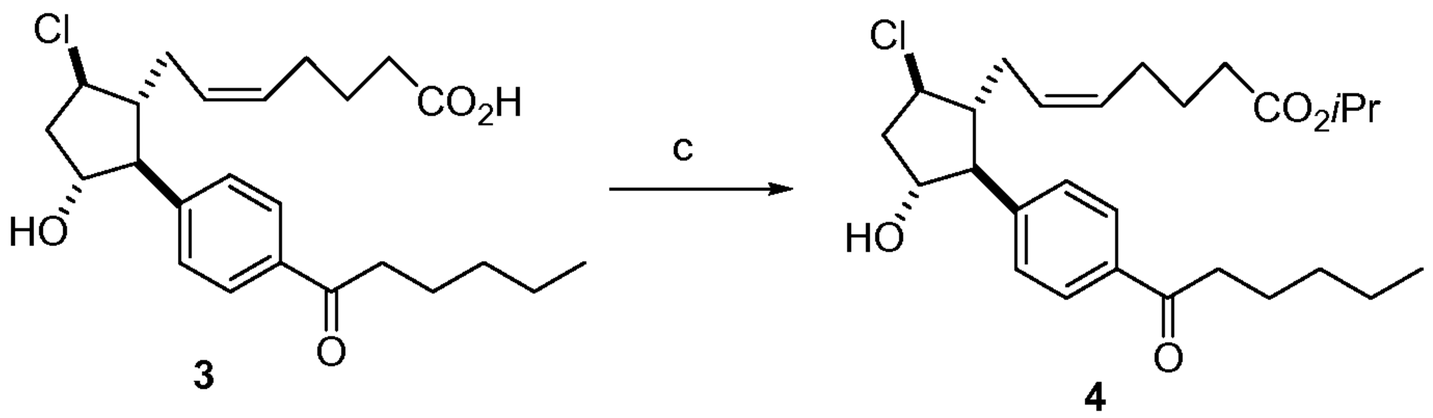


3 4

(a)DDQ, CH_2Cl_2, H_2O; (b) HF-pyridine 0 °C; (c) 1 M LiOH, THF; (d) 2-iodopropane, DBU, acetone.

(Z)-7-{(1R,2S,3R,5R)-5-Chloro-3-hydroxy-2-[4-(1-hydroxy-hexyl)-phenyl]-cyclopentyl}-hept-5-enoic acid methyl ester (1). Compound 1 was synthesized as described in United States Provisional Patent Application No. 60/742,779.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester (2). DDQ (13 mg, 0.056 mmol) was added to a solution of **1** (23 mg, 0.052 mmol) in dichloromethane (1 mL)/ H_2O (50 μL). After 6 h, more DDQ (16 mg) and dichloromethane (1 mL)/ H_2O (50 μL) were added. The resulting mixture was allowed to stir overnight and then 5 mL saturated $NaHCO_3$ solution was added. The mixture was extracted with dichloromethane (3 x 30 mL) and the combined dichloromethane solution was dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography on silica gel (20% ethyl acetate/hexanes) gave the title compound (13 mg, 57%).

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid (3). The LiOH hydrolysis procedure described in United States Patent Application Serial No. 11/009,298.

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid isopropyl ester (4). The DBU/*i*PrI procedure described in United States Patent Application Serial No. 11/009,298.

Biology Examples

Binding Data

Ki

Competition binding experiments were performed in a medium containing Hank's balanced salt solution, Hepes 20 mM, pH 7.3, membranes (~60 μg protein) or $2x10^5$ cells from HEK 293 cells stably expressing human EP2 receptors, [^{3}H]PGE2 (10 nM) and various concentrations of test compounds in a total volume of 300 μl. Reaction mixtures were incubated at 23 °C for 60 min, and were filtered over Whatman GF/B filters under vacuum. Filters were washed three times with 5 ml ice-cold buffer containing 50 mM Tris/HCl (pH 7.3). Non-specific binding was estimated

in the presence of excess unlabeled PGE2 (10 μM). Binding data fitted to the binding model for a single class of binding sites, using nonlinear regression analysis. IC_{50} values thus obtained were converted to Ki using the equation of $Ki=(IC_{50}/(1+[L]/K_D)$ where [L] represents PGE2 concentration (10 nM) and K_D the dissociation constant for [^{3}H]PGE2 at human EP2 receptors (40 nM).

Radioligand Binding

Cells Stably Expressing EP_1, EP_2, EP_4 and FP Receptors

HEK-293 cells stably expressing the human or feline FP receptor, or EP_1, EP_2, or EP_4 receptors were washed with TME buffer, scraped from the bottom of the flasks, and homogenized for 30 sec using a Brinkman PT 10/35 polytron. TME buffer was added to achieve a final 40 ml volume in the centrifuge tubes (the composition of TME is 100 mM TRIS base, 20 mM $MgCl_2$, 2M EDTA; 10N HCl is added to achieve a pH of 7.4).

The cell homogenate was centrifuged at 19000 r.p.m. for 20 min at 4° C using a Beckman Ti-60 rotor. The resultant pellet was resuspended in TME buffer to give a final 1 mg/ml protein concentration, as determined by Biorad assay. Radioligand binding competition assays vs. [^{3}H-]17 –phenyl $PGF_{2\alpha}$ (5 nM) were performed in a 100μl volume for 60 min. Binding reactions were started by adding plasma membrane fraction. The reaction was terminated by the addition of 4 ml ice-cold TRIS-HCl buffer and rapid filtration through glass fiber GF/B filters using a Brandel cell harvester. The filters were washed 3 times with ice-cold buffer and oven dried for one hour.

[^{3}H-] PGE_2 (specific activity 180 Ci mmol) was used as the radioligand for EP receptors. [^{3}H] 17-phenyl $PGF_{2\alpha}$ was employed for FP receptor binding studies. Binding studies employing EP_1, EP_2, EP_4 and FP receptors were performed in duplicate in at least three separate experiments. A 200μl assay volume was used. Incubations were for 60 min at 25°C and were terminated by the addition of 4 ml of ice-cold 50 mM TRIS-HCl, followed by rapid filtration through Whatman GF/B filters and three additional 4 ml washes in a cell harvester (Brandel). Competition studies were performed using a final concentration of 5 nM [^{3}H]-PGE_2, or 5 nM [^{3}H] 17-phenyl $PGF_{2\alpha}$ and non-specific binding determined with 10^{-5}M of unlabeled PGE_2, or 17-phenyl $PGF_{2\alpha}$, according to receptor subtype studied.

METHODS FOR FLIPR™ STUDIES

(a) CELL CULTURE

HEK-293(EBNA) cells, stably expressing one type or subtype of recombinant human prostaglandin receptors (prostaglandin receptors expressed: hDP/Gqs5; hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5; hFP; hIP; hTP), were cultured in 100 mm culture dishes in high-glucose DMEM medium containing 10% fetal bovine serum, 2 mM l-glutamine, 250 μg/ml geneticin (G418) and 200 μg/ml hygromycin B as selection markers, and 100 units/ml penicillin G, 100 μg/ml streptomycin and 0.25 μg/ml amphotericin B.

(b) CALCIUM SIGNAL STUDIES ON THE FLIPR™

Cells were seeded at a density of $5x10^4$ cells per well in Biocoat® Poly-D-lysine-coated black-wall, clear-bottom 96-well plates (Becton-Dickinson) and allowed to attach overnight in an incubator at 37 ºC. Cells were then washed two times with HBSS-HEPES buffer (Hanks Balanced Salt Solution without bicarbonate and phenol red, 20 mM HEPES, pH 7.4) using a Denley Cellwash plate washer (Labsystems). After 45 minutes of dye-loading in the dark, using the calcium-sensitive dye Fluo-4 AM at a final concentration of 2 μM, plates were washed four times with

HBSS-HEPES buffer to remove excess dye leaving 100 μl in each well. Plates were re-equilibrated to 37 °C for a few minutes.

Cells were excited with an Argon laser at 488 nm, and emission was measured through a 510-570 nm bandwidth emission filter (FLIPR™, Molecular Devices, Sunnyvale, CA). Drug solution was added in a 50 μl volume to each well to give the desired final concentration. The peak increase in fluorescence intensity was recorded for each well. On each plate, four wells each served as negative (HBSS-HEPES buffer) and positive controls (standard agonists: BW245C (hDP); PGE_2 (hEP_1; hEP_2/Gqs5; hEP_{3A}/Gqi5; hEP_4/Gqs5); $PGF_{2\alpha}$ (hFP); carbacyclin (hIP); U-46619 (hTP), depending on receptor). The peak fluorescence change in each drug-containing well was then expressed relative to the controls.

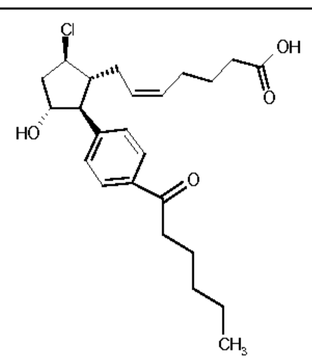
Compounds were tested in a high-throughput (HTS) or concentration-response (CoRe) format. In the HTS format, forty-four compounds per plate were examined in duplicates at a concentration of 10^{-5} M. To generate concentration-response curves, four compounds per plate were tested in duplicates in a concentration range between 10^{-5} and 10^{-11} M. The duplicate values were averaged. In either, HTS or CoRe format each compound was tested on at least 3 separate plates using cells from different passages to give an $n \geq 3$.

<u>cAMP assay</u>

A 384-well drug plate was prepared to contain 6 test compounds, PGE2 and cAMP in 16 serial dilutions in triplicate, using a Biomek station. HEK-EBNA cells expressing a target PG receptor subtype (EP2 or EP4) were suspended in a stimulation buffer (HBSS, 0.1 % BSA, 0.5 mM IBMX and 5 mM HEPES, pH 7.4) in a density of 10^4 cells/5μl. The reaction was initiated by mixing 5 μL drug dilutions with 5 μl of HEK-EBNA cells in a well, carried out for 30 min at room temperature, and followed by the addition of 5 μl anti-cAMP acceptor beads in the control buffer with Tween-20 (25 mM NaCl, 0.03 % Tween-20, 5 mM HEPES, pH7.4). After 30 min in the dark at room temperature, the mixtures were incubated with 15 μl biotinylated-cAMP/strepavidin donor beads in Lysis/Detection buffer (0.1 % BSA, 0.3 % Tween-20 and 5 mM HEPES, pH7.4) for 45 min at the room temperature. Fluorescence changes were read using a Fusion-alpha HT microplate reader.

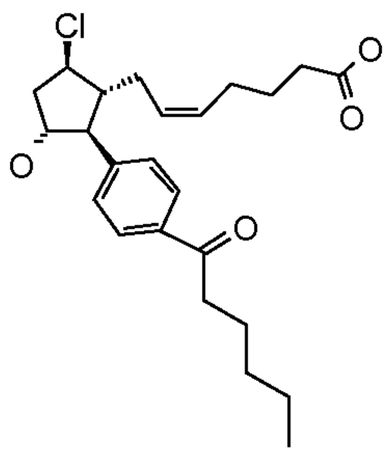
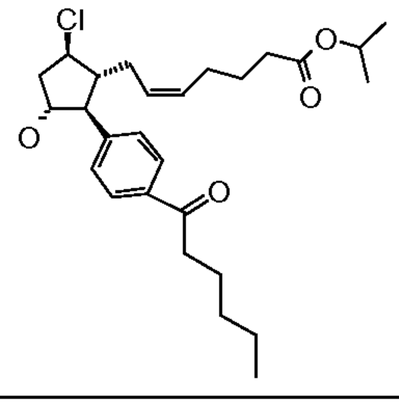
The results of the binding and activity studies, presented in Table 1 below, demonstrate that the compounds disclosed herein are selective prostaglandin EP_2 agonists, and are thus useful for the treatment of glaucoma, ocular hypertension, and other diseases or conditions.

Table 1

	EP2			**EP4**			**OTHER RECEPTORS**
STRUCTURE	cAMP EC50 (nM)	Ki (nM)	Ca2+ EC50 (nM)	cAMP EC50 (nM)	Ki EC50 (nM)	Ca2+ EC50 (nM)	Ca2+ EC50 (nM)
	9	111	31		2809	NA	NA: EP1,EP3,DP, FP,IP,TP

In vivo testing done as described in United States Patent Application Serial Number 11/009,298 gave the results in Table 2 below.

Table 2

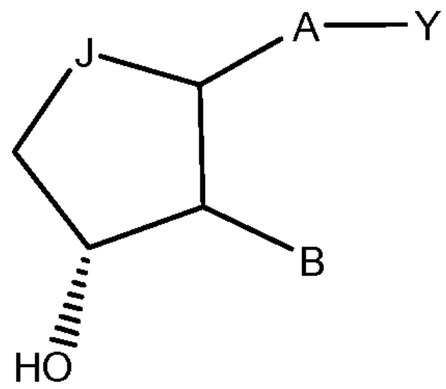
ENTRY	STRUCTURE		DOG		MONKEY	RABBIT
		Conc. (g/100 mL)	Max. IOP (%)	Max. hyperemia	Max. IOP (%)	Max. hyperemia
1		0.1%	-50	2.0	31	
2		0.1%	-37	0.8	20	0

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."

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, 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;

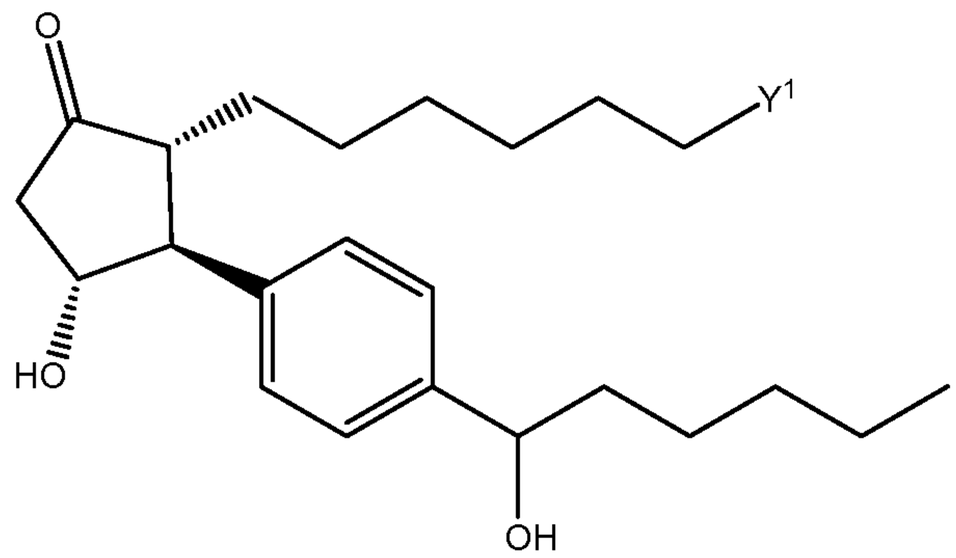
wherein Y is an organic acid functional group, or an amide or ester thereof comprising up to 14 carbon atoms; or Y is hydroxymethyl or an ether thereof comprising up to 14 carbon atoms; or Y is a tetrazolyl functional group;

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 one CH_2 may be replaced by S or O;

J is C=O, CHOH, CHF, CHCl, CHBr, CF_2, CCl_2, CBr_2, or CHCN; and

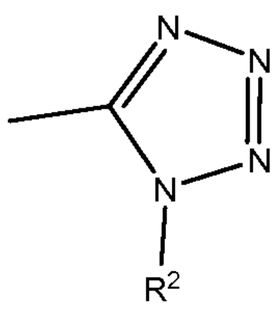
B is substituted aryl or heteroaryl

with the proviso that the compound is not

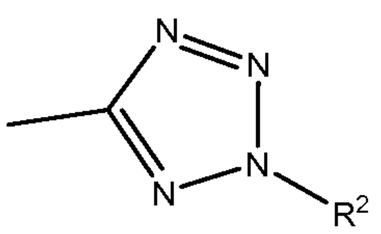


wherein Y^1 is CO_2H, or an amide thereof.

2. 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,



and

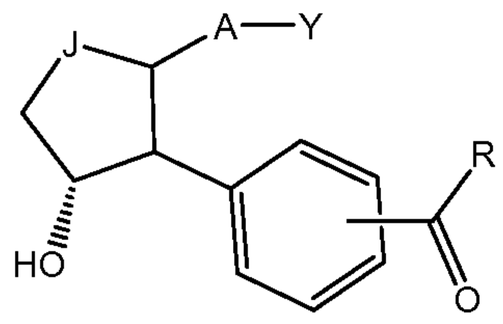


;

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

3. The compound of claim 1 or 2 wherein B is substituted phenyl.

4. The compound of claim 1 or 2 having a structure

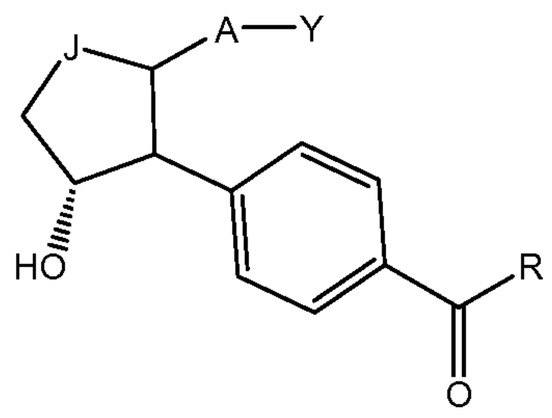


or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

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

5. The compound of claim 4 wherein R is alkyl.

6. The compound according to claim any one of claims 1 to 6 having a structure



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

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

7. The compound of any one of claims 1 to 7 wherein J is C=O.

8. The compound of any one of claims 1 to 7 wherein J is CHOH

9. The compound of any one of claims 1 to 7 wherein J isCHF.

10. The compound of any one of claims 1 to 7 wherein J is CHCl.

11. The compound of any one of claims 1 to 7 wherein J is CHBr.

12. The compound of any one of claims 1 to 7 wherein J is CF_2.

13. The compound of any one of claims 1 to 7 wherein J is CCl_2.

14. The compound of any one of claims 1 to 7 wherein J isCBr_2.

15. The compound of any one of claims 1 to 7 wherein J is CHCN

16. The compound of any one of claims 1 to 15 wherein A is $–(CH_2)_3Ar$-, $-O(CH_2)_2Ar$-, $-CH_2OCH_2Ar$-, $-(CH_2)_2OAr$, $-O(CH_2)_2Ar$-, $-CH_2OCH_2Ar$-, or $-(CH_2)_2OAr$, wherein Ar is monocyclic interheteroarylene.

17. The compound of claim 16 wherein Ar is interthienylene.

18. The compound of claim 16 wherein Ar is interthiazolylene.

19. The compound of claim 16 wherein Ar is interoxazolylene.

20. Use of a compound according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension in a mammal.

21. A method comprising administering a compound according to any one of claims 1 to 19 to a mammal for the treatment of glaucoma or ocular hypertension.

22. A kit comprising a composition comprising compound according to any one of claims 1 to 19, a container, and instructions for administration of said composition to a mammal for the treatment of glaucoma or ocular hypertension.

23. A composition comprising a compound according to any one of claims 1 to 19, wherein said composition is a liquid which is ophthalmically acceptable.

24. A compound according to claim 1 selected from

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid methyl ester;

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid; and

(Z)-7-[(1R,2S,3R,5R)-5-Chloro-2-(4-hexanoyl-phenyl)-3-hydroxy-cyclopentyl]-hept-5-enoic acid isopropyl ester.