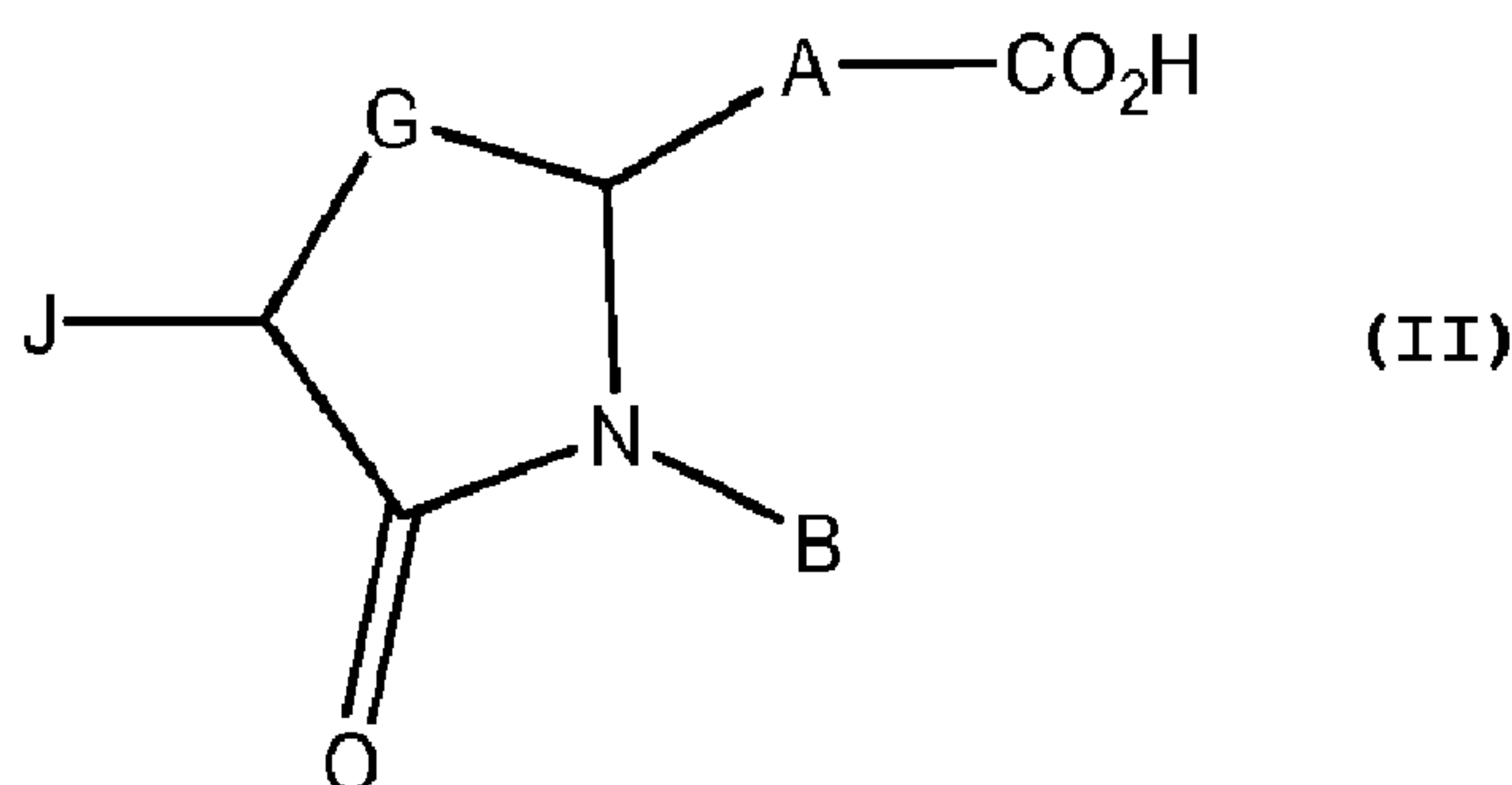
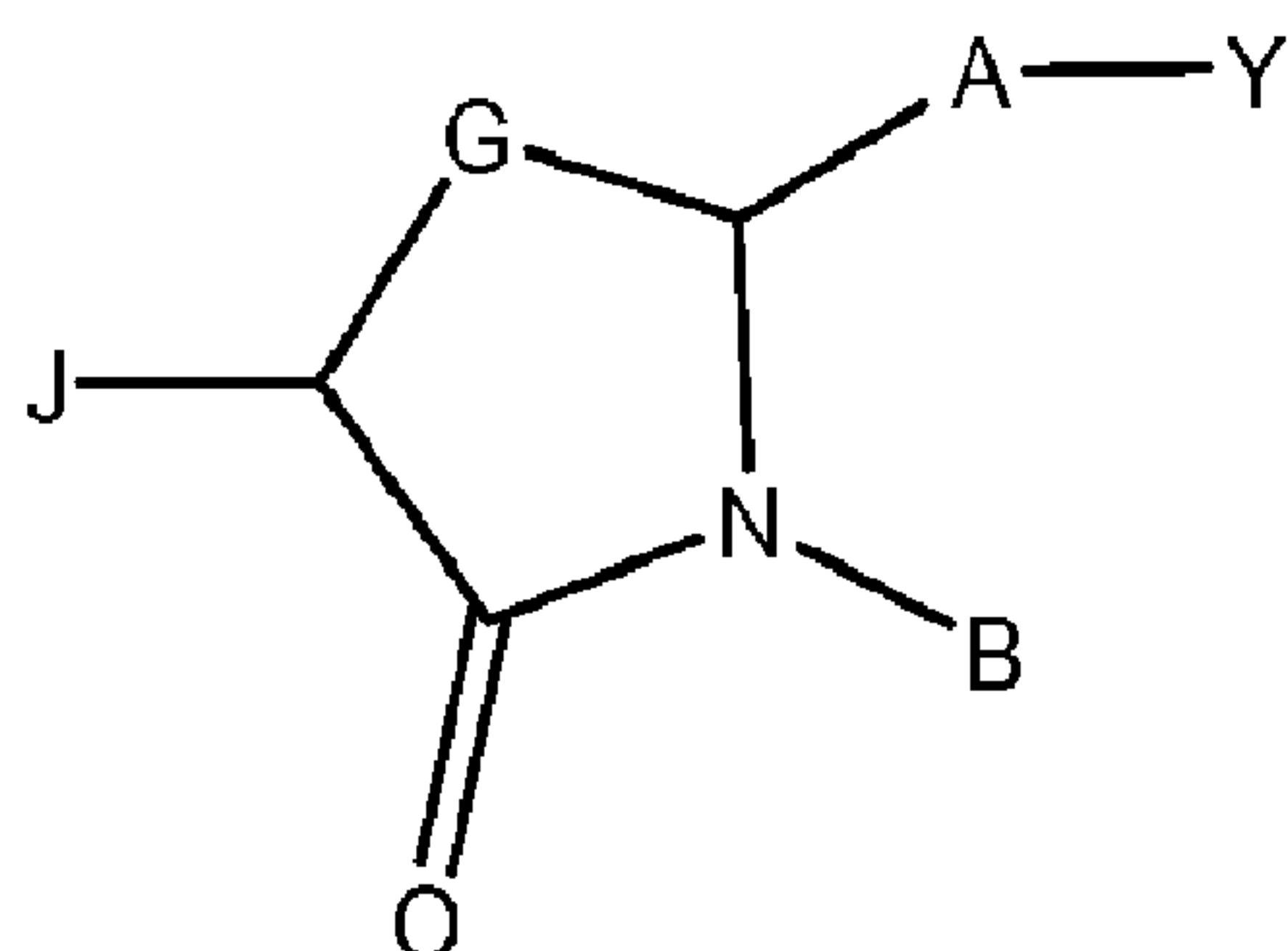




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(54) Title: THERAPEUTIC SUBSTITUTED THIAZOLIDINONES, OXAZOLIDINONES, AND RELATED COMPOUNDS



(57) Abrégé/Abstract:

A compound having a structure (I) or (II) is disclosed herein. Therapeutic methods, compositions, and medicaments related thereto are also disclosed.



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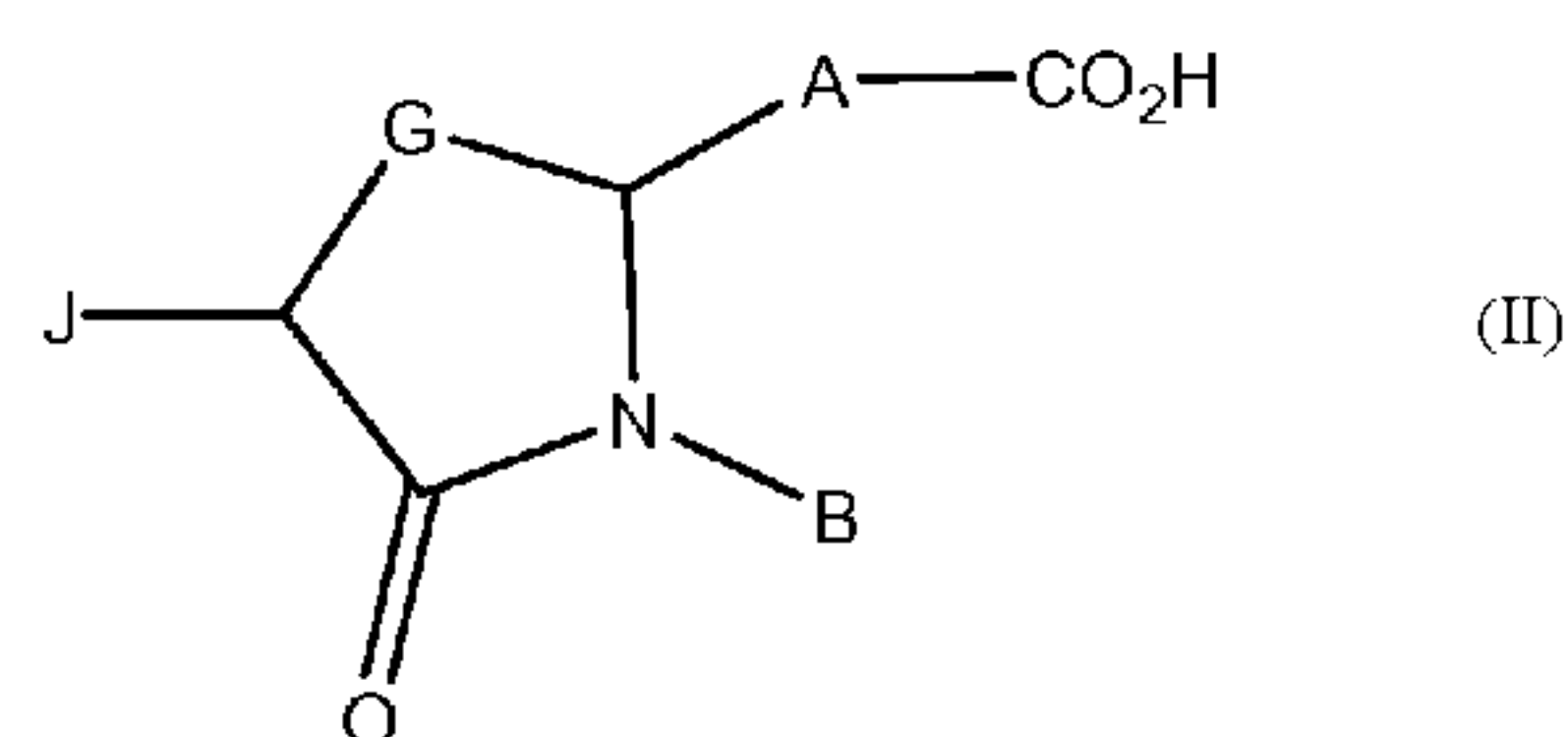
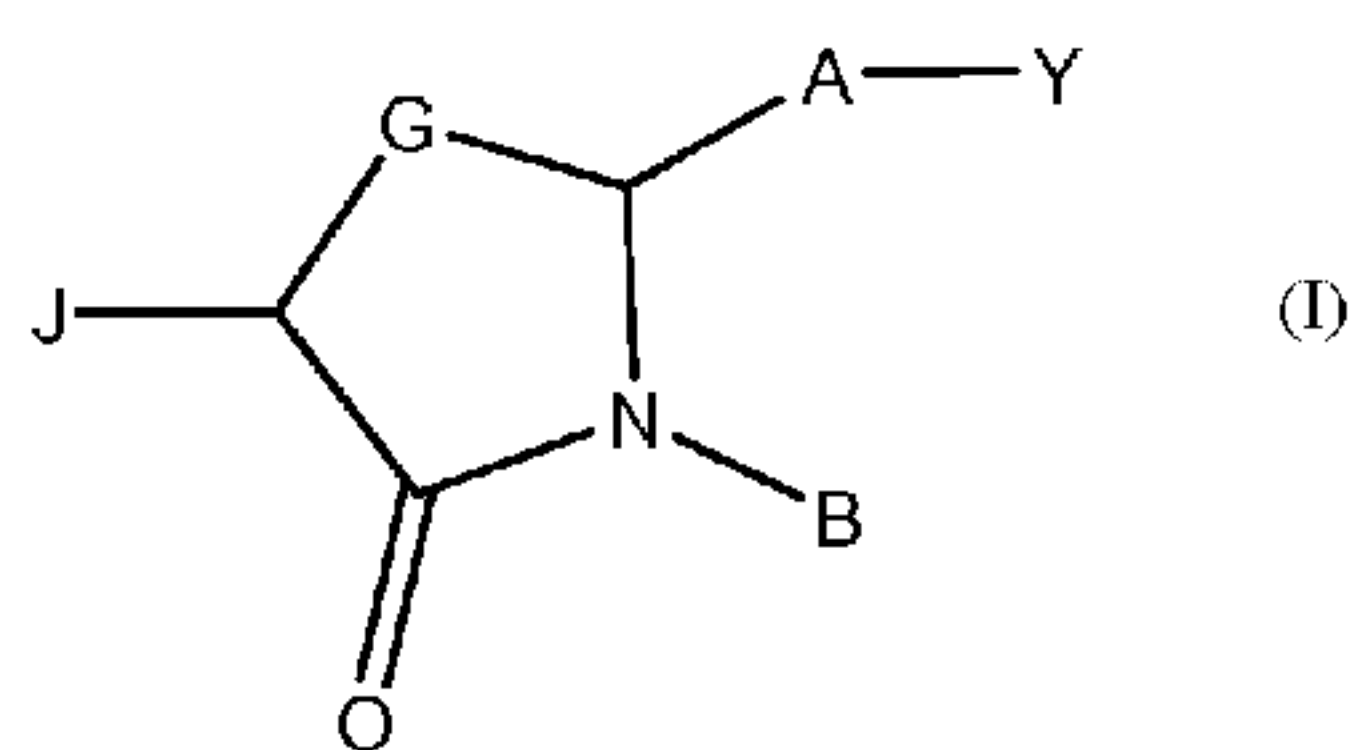
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(57) Abstract: A compound having a structure (I) or (II) is disclosed herein. Therapeutic methods, compositions, and medicaments related thereto are also disclosed.

THERAPEUTIC SUBSTITUTED THIAZOLIDINONES, OXAZOLIDINONES, AND RELATED COMPOUNDS

by Inventor

David W. Old

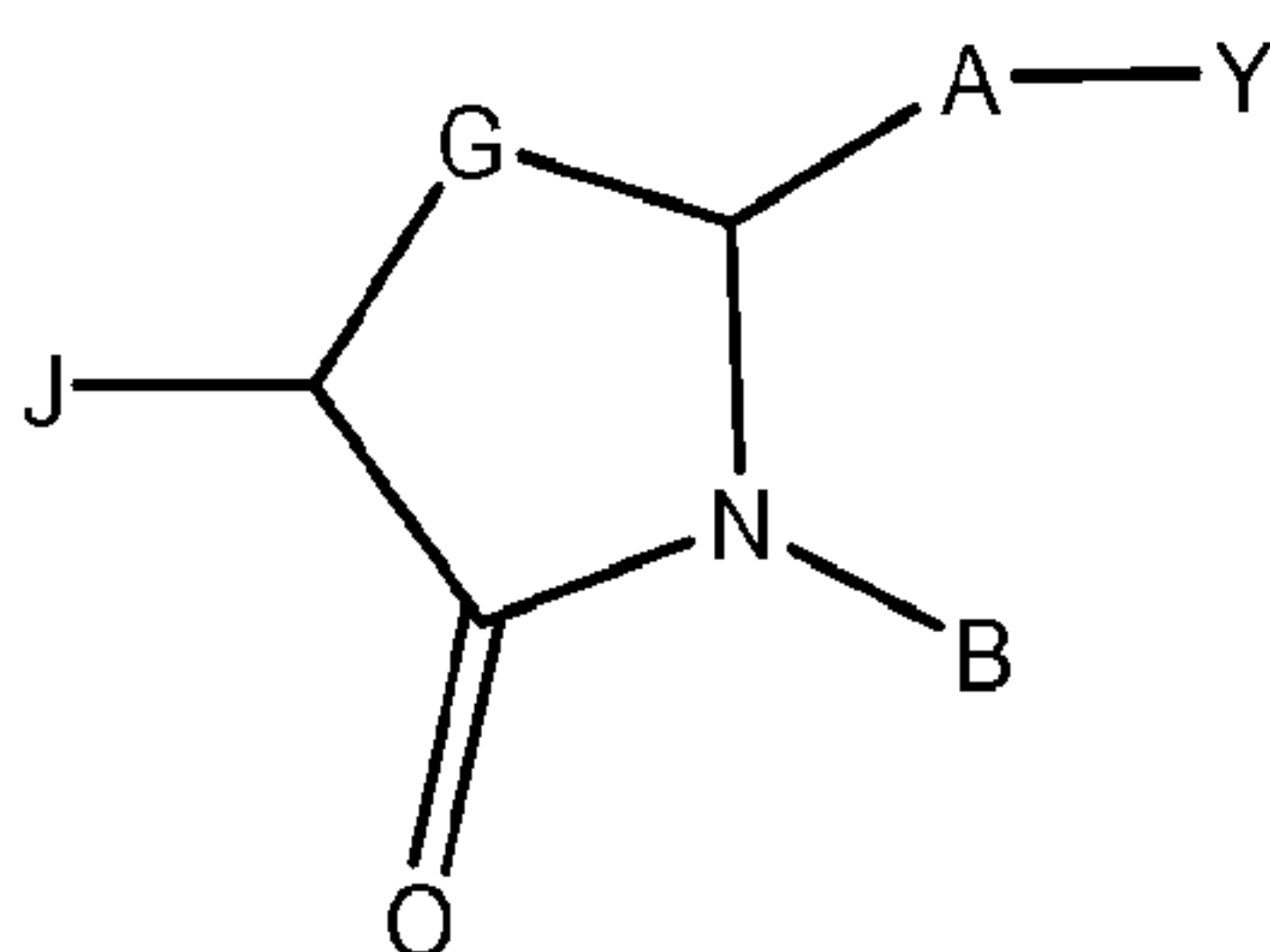
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DESCRIPTION OF THE INVENTION

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. Prostaglandin agonists have been shown to be useful as ocular hypotensive agents.

10 The compounds disclosed herein are ocular hypotensive agents.

Disclosed herein is a compound having a structure



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

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;

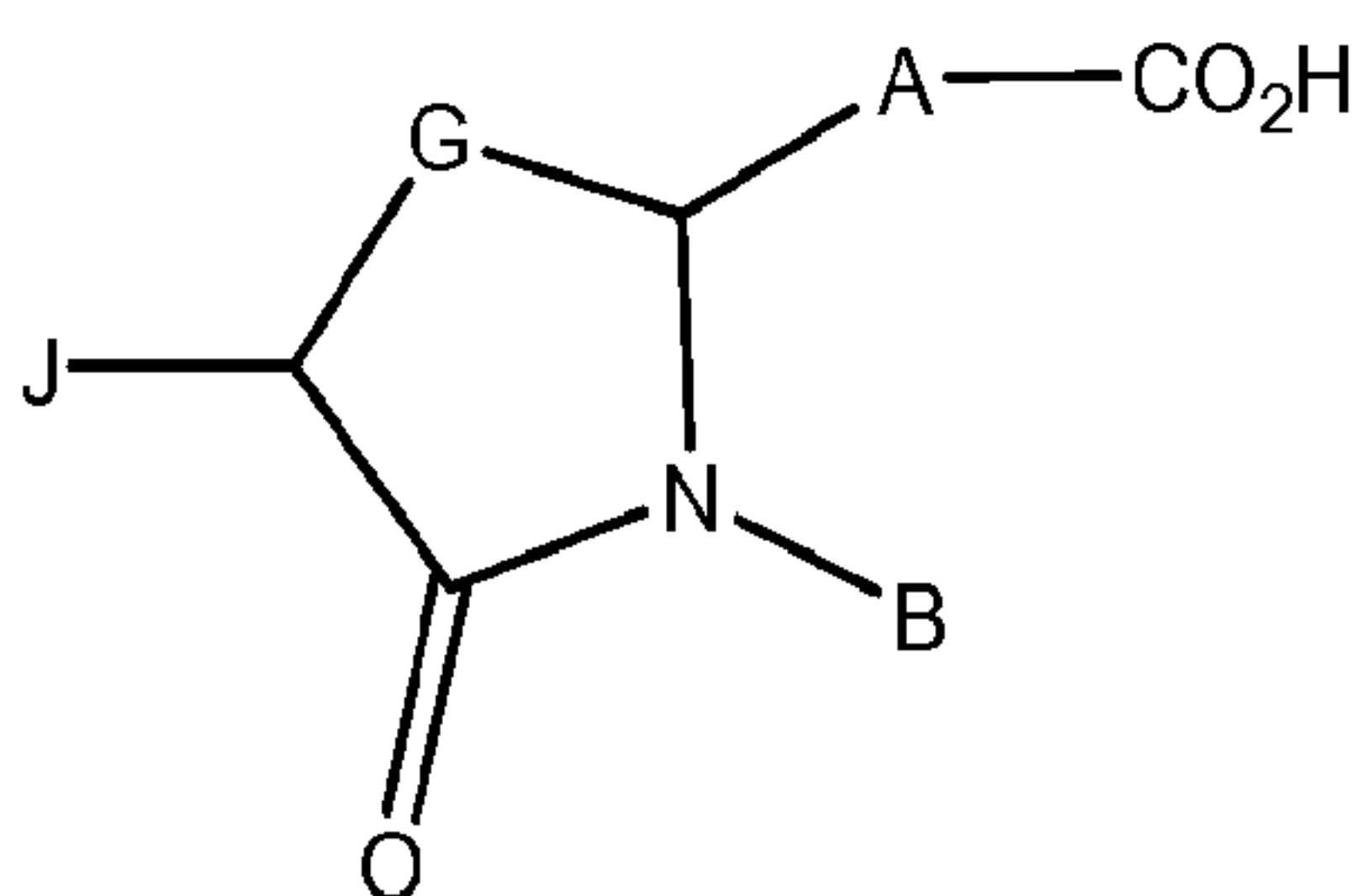
15 A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein one CH_2 may be replaced by S or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

G is O, S, S=O, or $S(=O)_2$;

20 J is H, halogen, CF_3 ; or C_{1-6} alkyl; and

B is 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,;

25 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;

G is O, S, S=O, or $S(=O)_2$;

J is H, halogen, CF_3 ; or C_{1-6} alkyl; and

30 B is aryl or heteroaryl.

In one embodiment, if B is unsubstituted aryl or heteroaryl and J^1 is H, J^2 is not H.

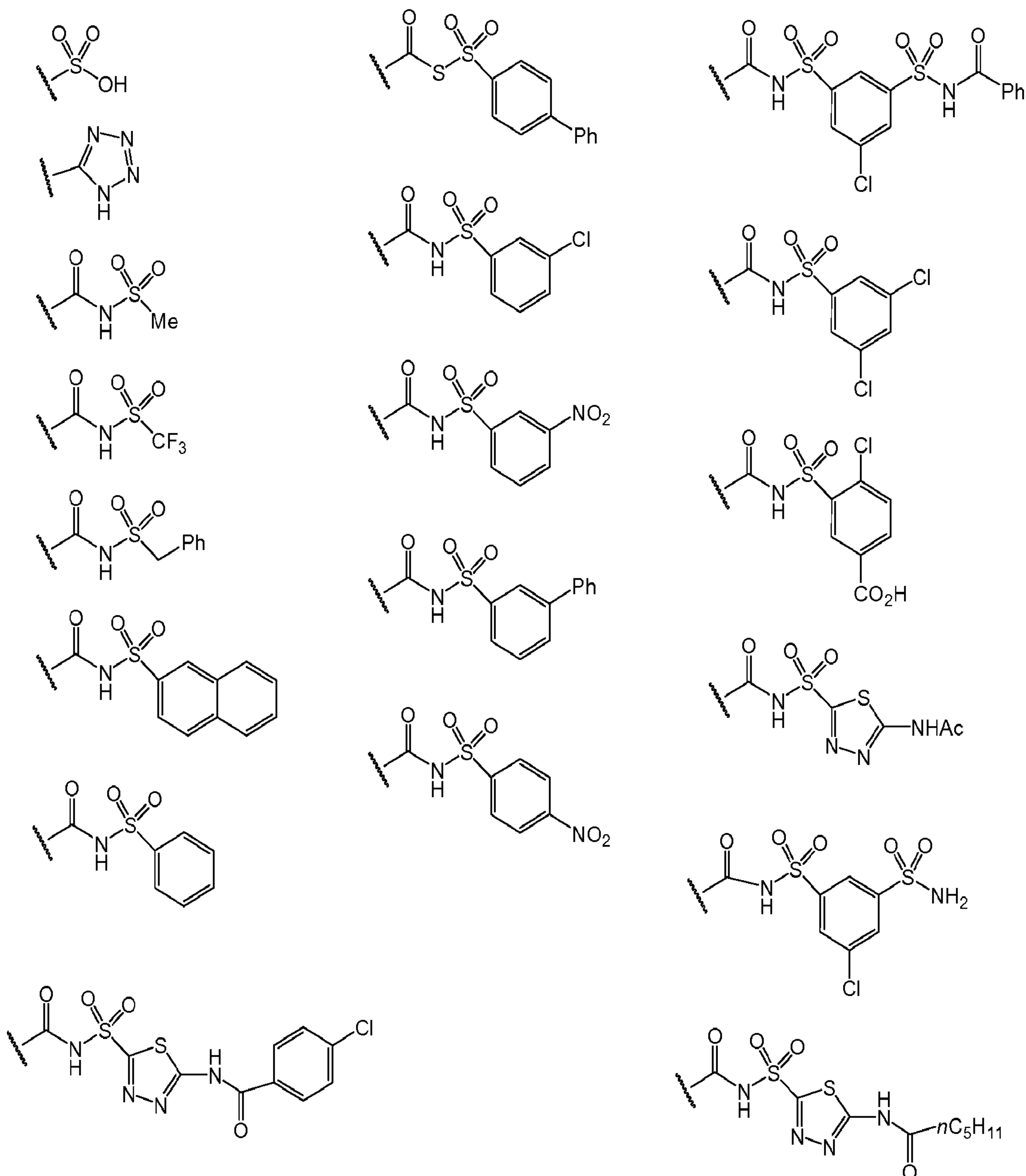
"Bioisosteres are substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties." Silverman, Richard B., The Organic Chemistry of Drug Design and Drug Action, 2nd Edition, Amsterdam: Elsevier Academic Press, 2004, p. 29.

5 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.

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

In an amide, an amine group replaces an OH of the acid. Examples of amides include CON(R²)₂, CON(OR²)R², CON(CH₂CH₂OH)₂, and CONH(CH₂CH₂OH) where R² is independently H, C₁-C₆ alkyl, phenyl, or biphenyl. Moieties such as CONHSO₂R² are also amides of the carboxylic acid notwithstanding the fact that they may also be considered to be amides of the sulfonic acid R²-SO₃H. The following amides are also specifically contemplated, CONSO₂-biphenyl, CONSO₂-phenyl,
15 CONSO₂-heteroaryl, and CONSO₂-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 CO₂H. Thus, Y could be any group depicted below.

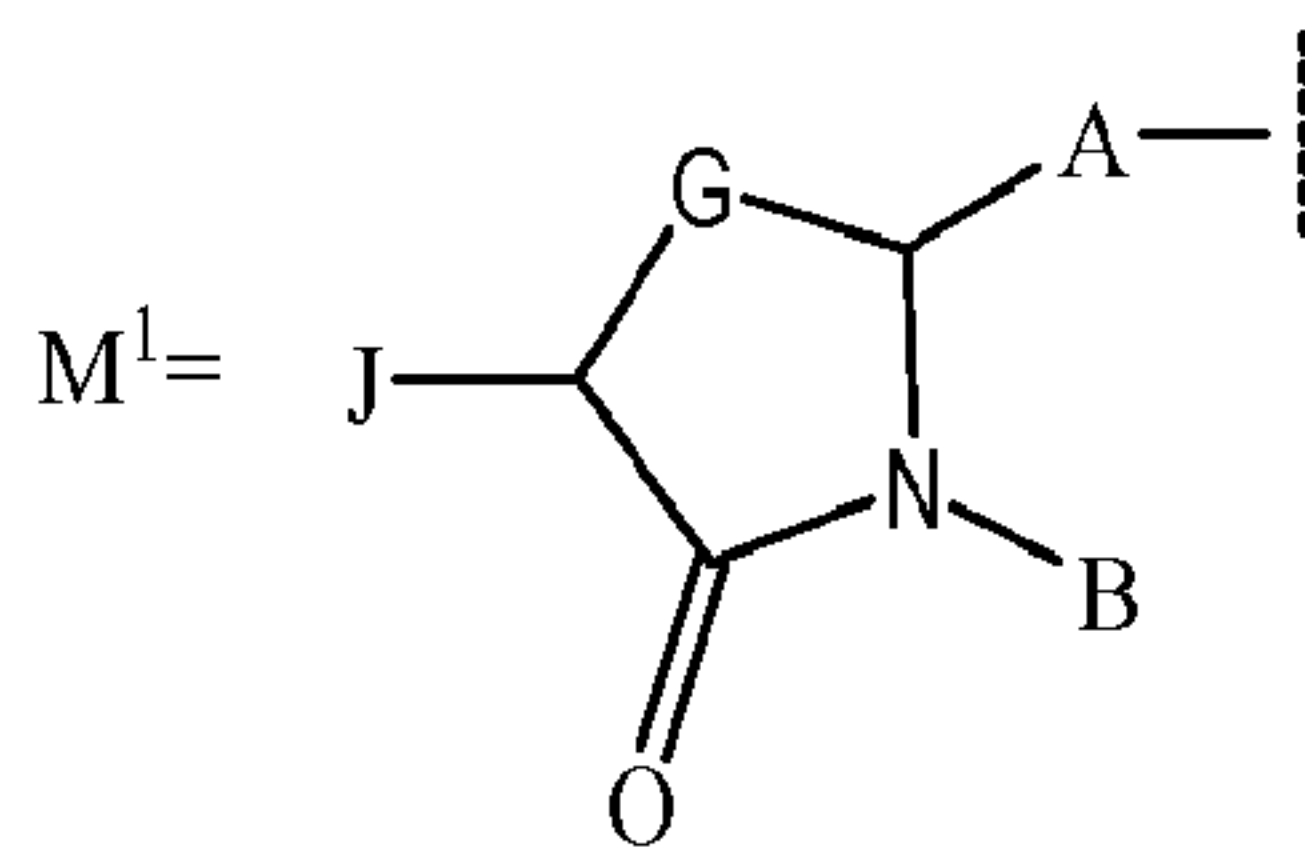
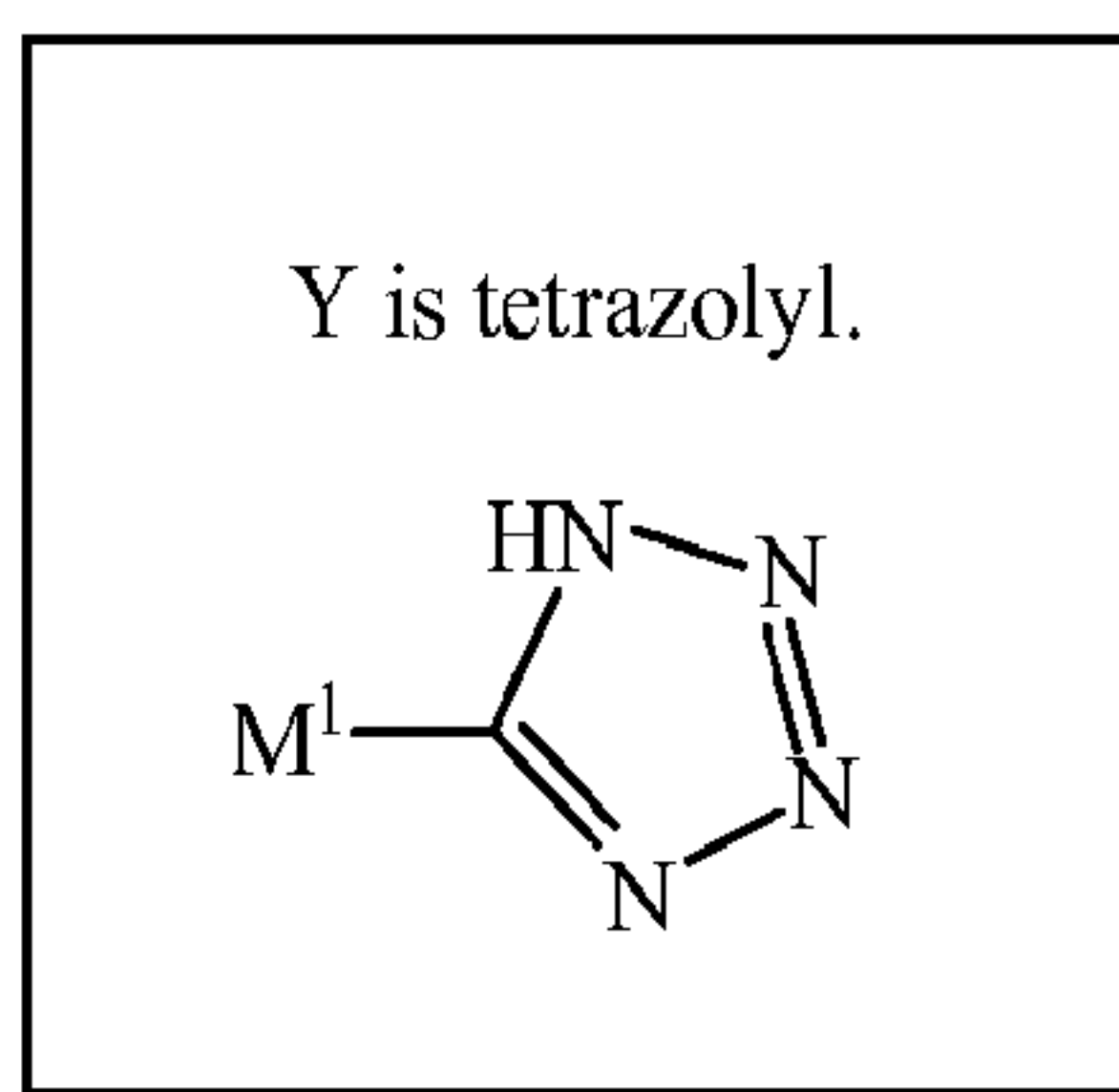
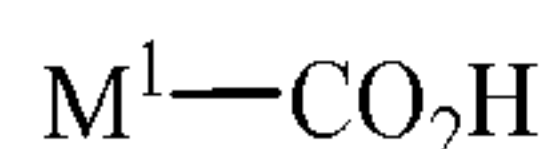
Carboxylic acid bioisosteres according to Han *et. al.*

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

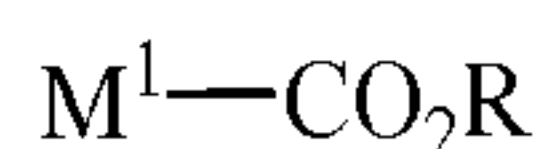
“Up to 14 carbon atoms” means that the entire Y moiety, including the carbonyl carbon of a carboxylic acid ester or amide, and both carbon atoms in the -CH₂O-C of an ether has 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms.

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

While not intending to be limiting, examples of compounds having the identified Y are depicted below. In these
 10 examples R is H or hydrocarbonyl, subject to the constraints defined herein. Each structure below represents a specific embodiment which is individually contemplated, as well as pharmaceutically acceptable salts and prodrugs of compounds which are represented by the structures. However, other examples are possible which may not fall within the scope of the structures shown below.

**Organic Acids**

Carboxylic Acid

Esters

Carboxylic Acid Ester

Amides

Carboxylic Acid Amide



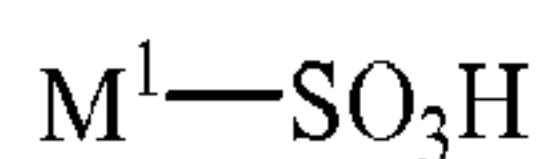
Phosponic Acid



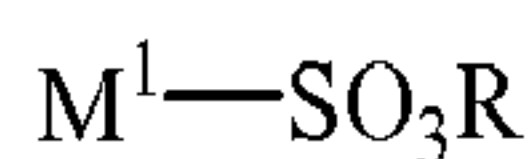
Phosphonic Acid Ester



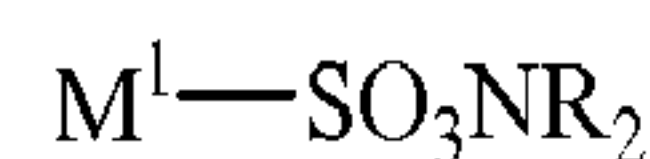
Phosphonic Acid Amide



Sulfonic Acid



Sulfonic Acid Ester



Sulfonic Acid Amide

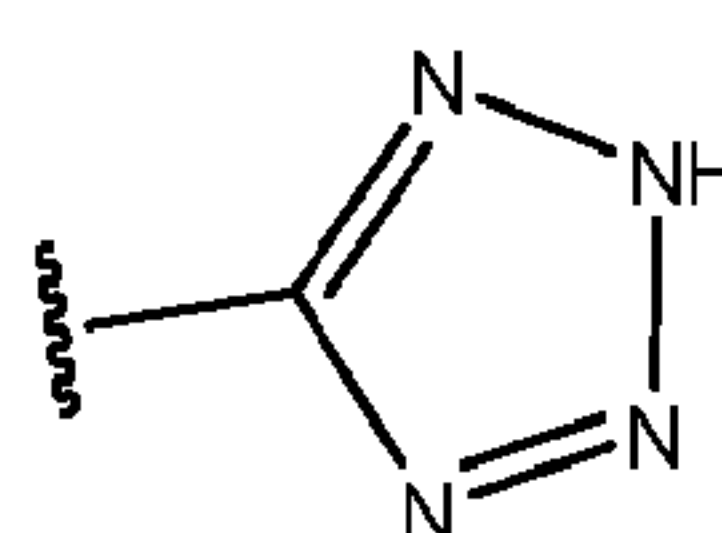
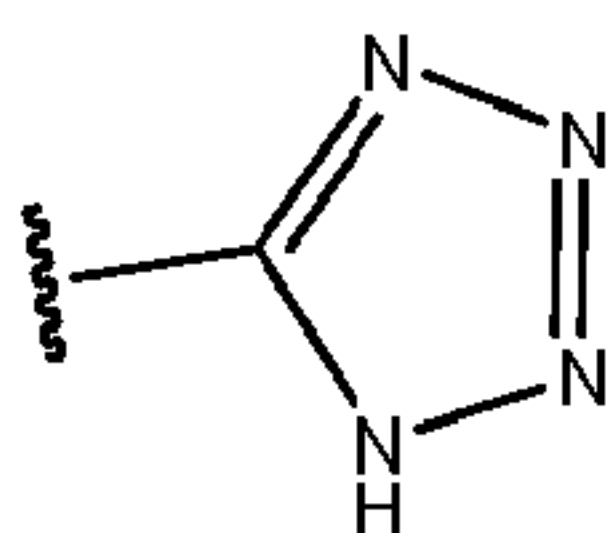


Y is hydroxymethyl

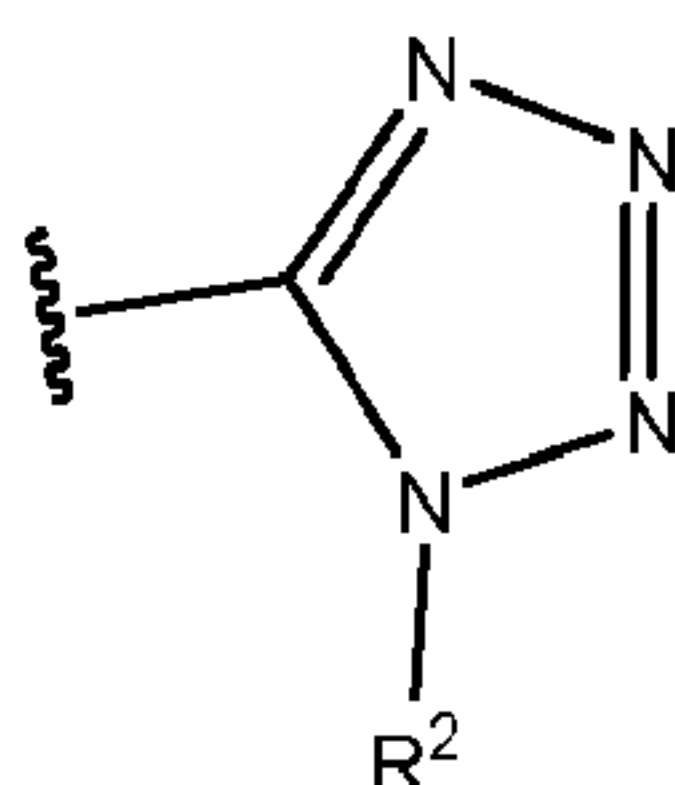


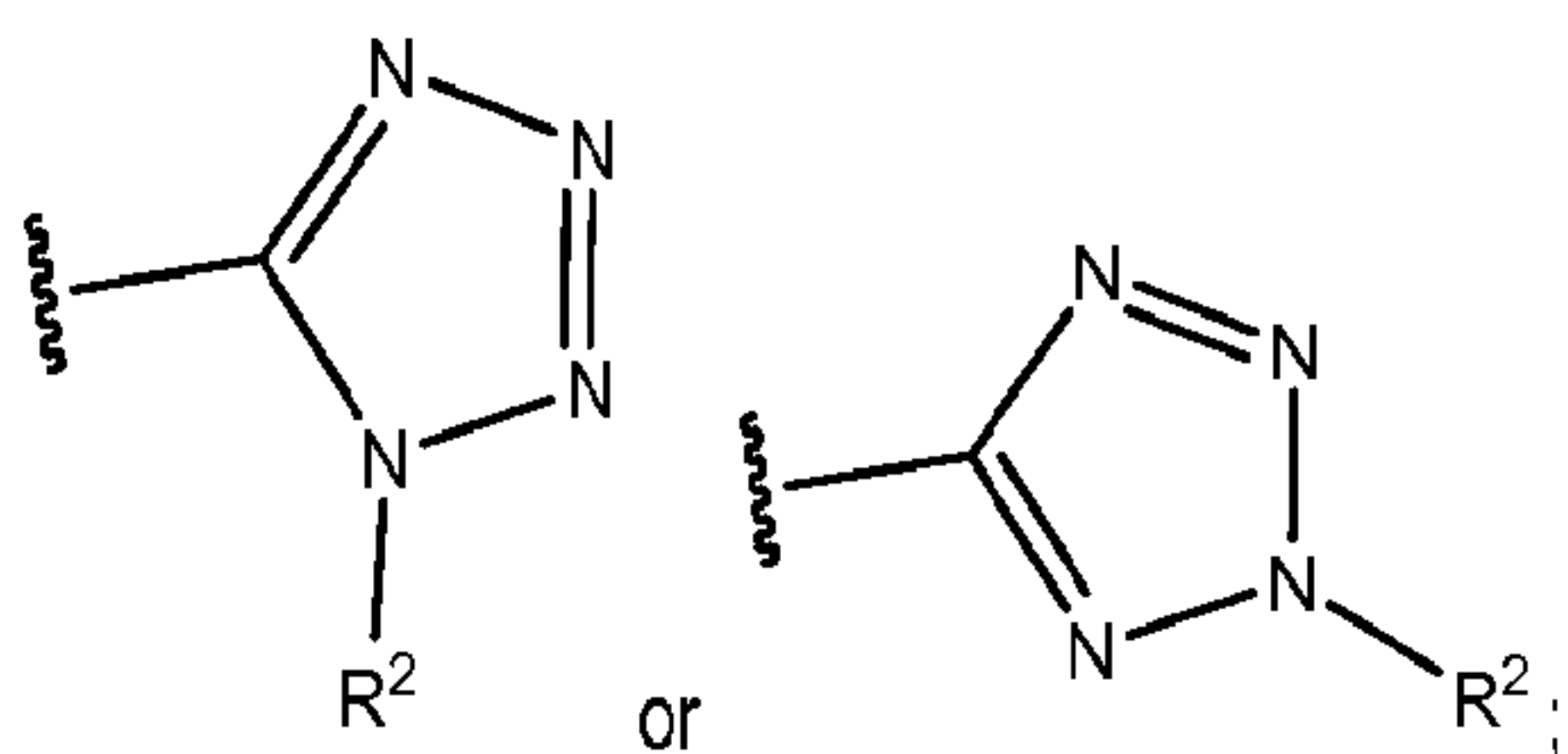
Ether

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



Additionally, if R² is C₁-C₆ 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 C₁₂ are considered to be within the scope of the term "tetrazolyl."

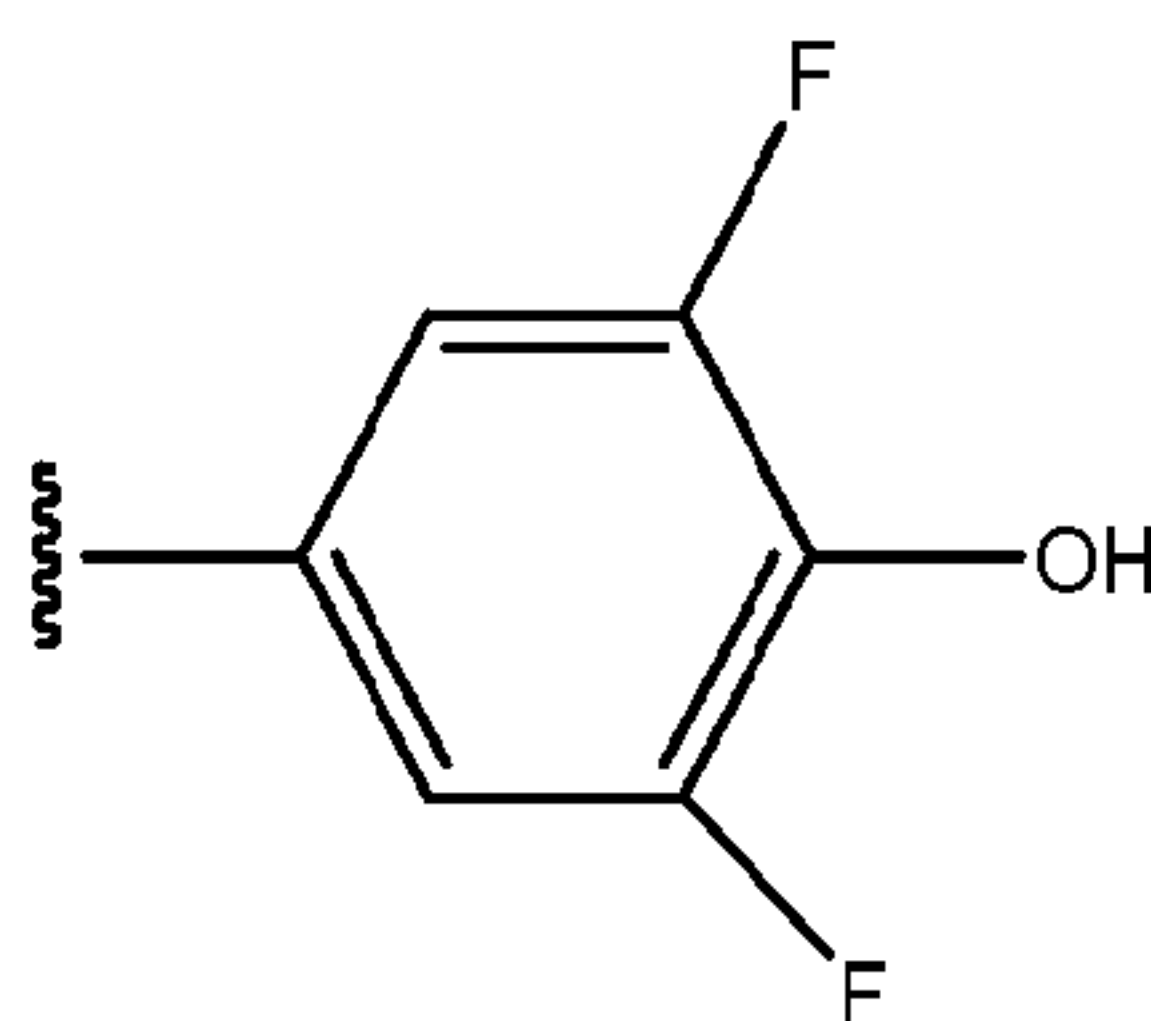
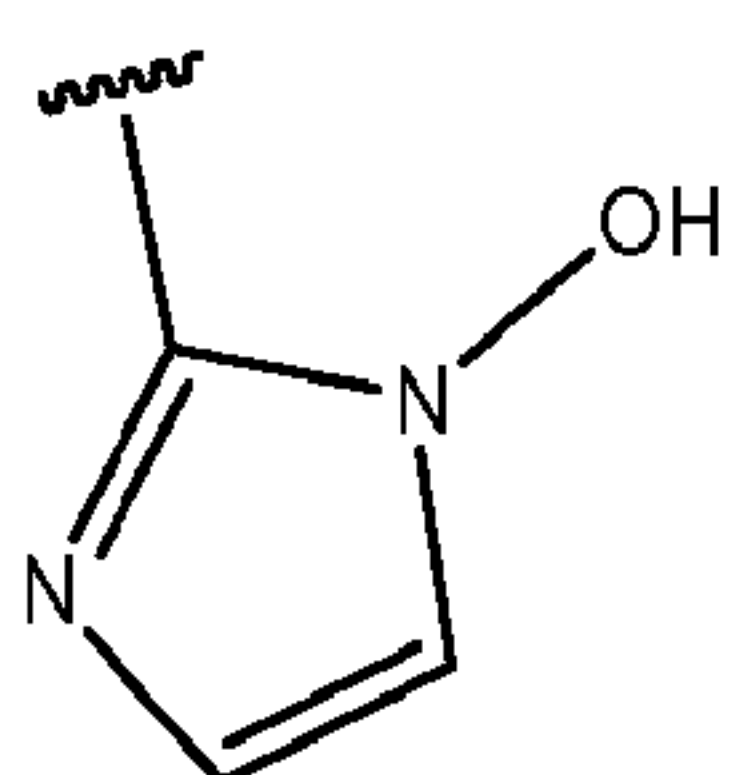
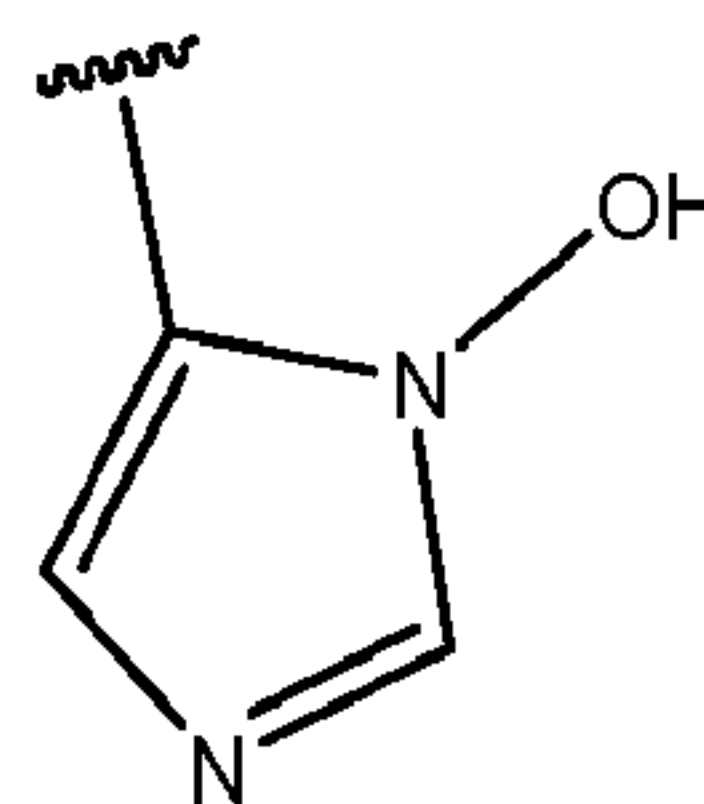
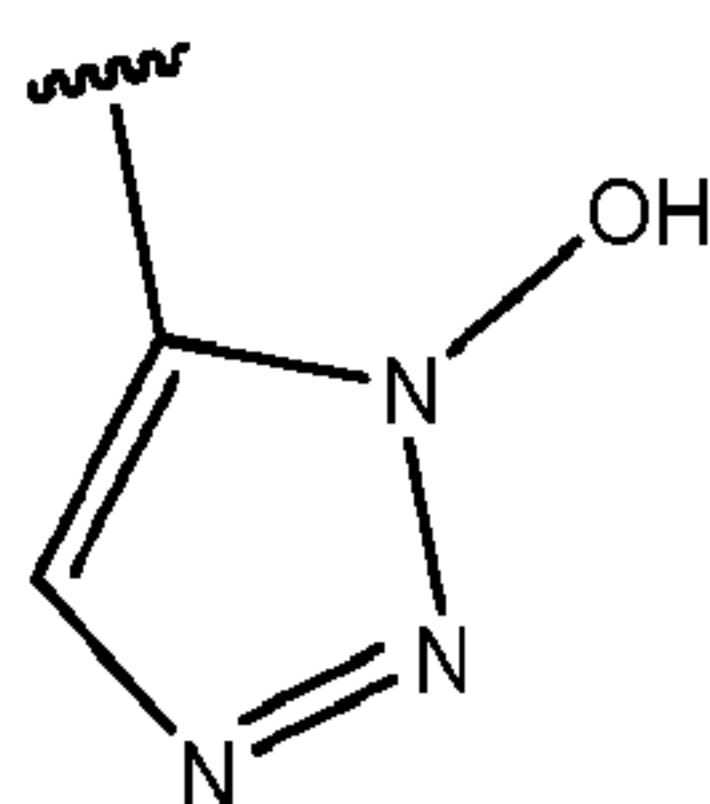
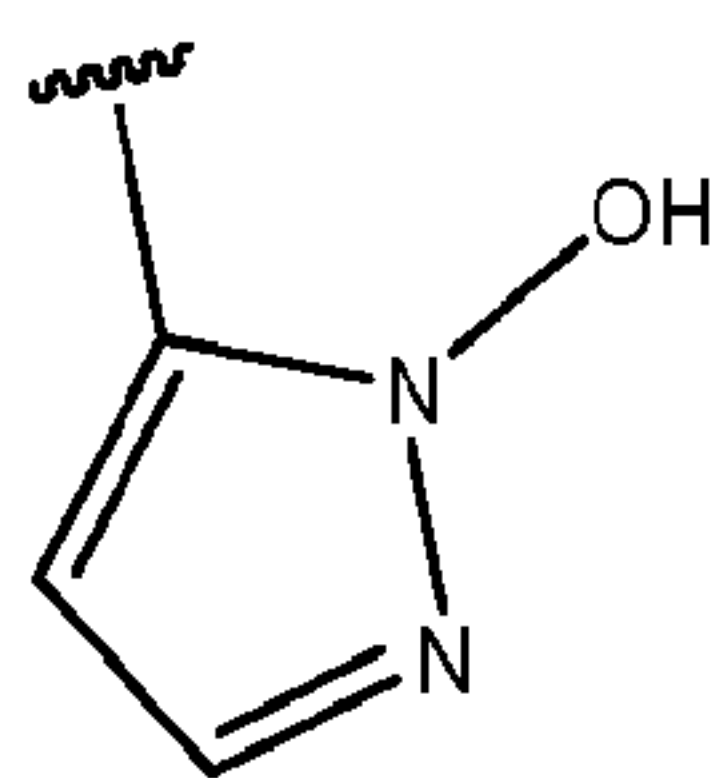
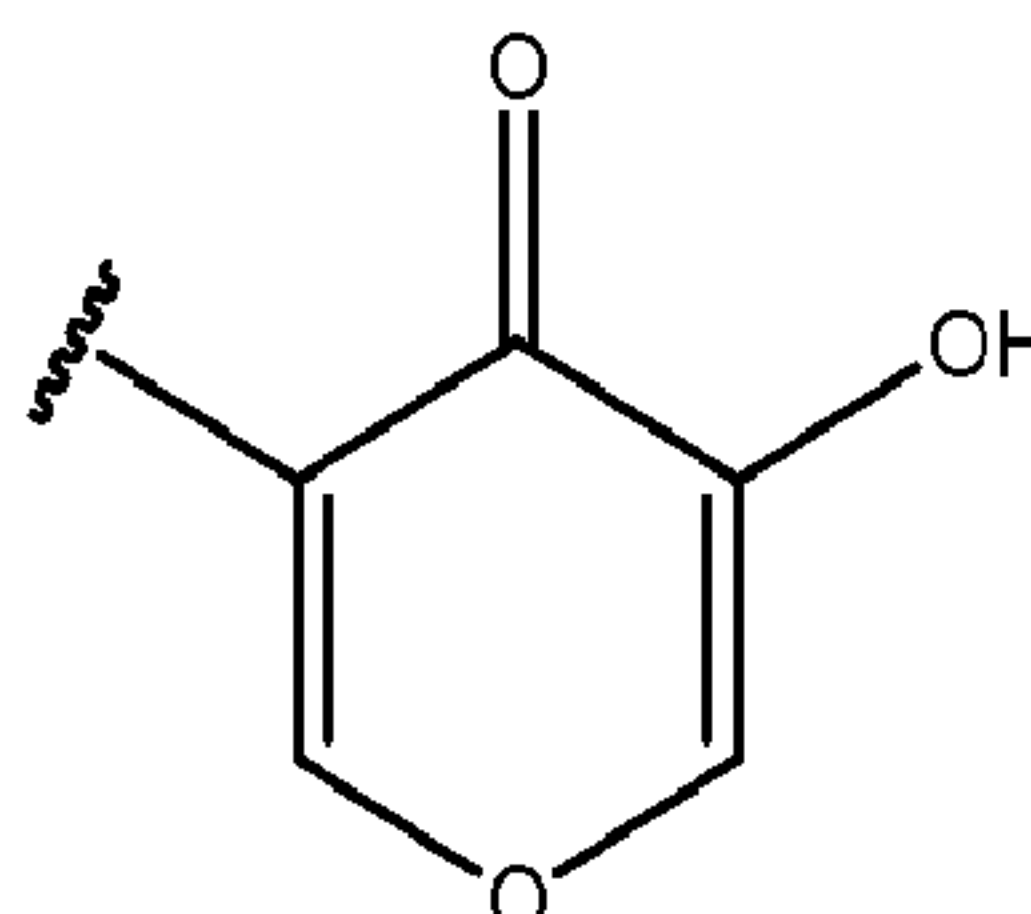
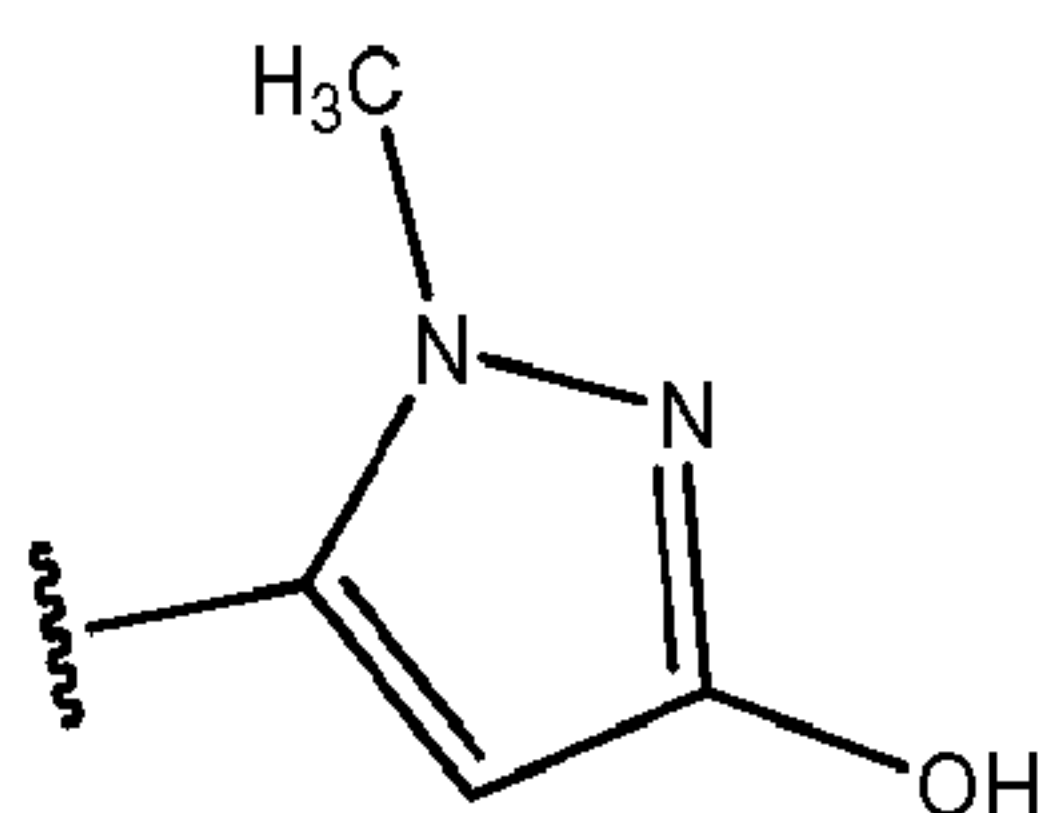
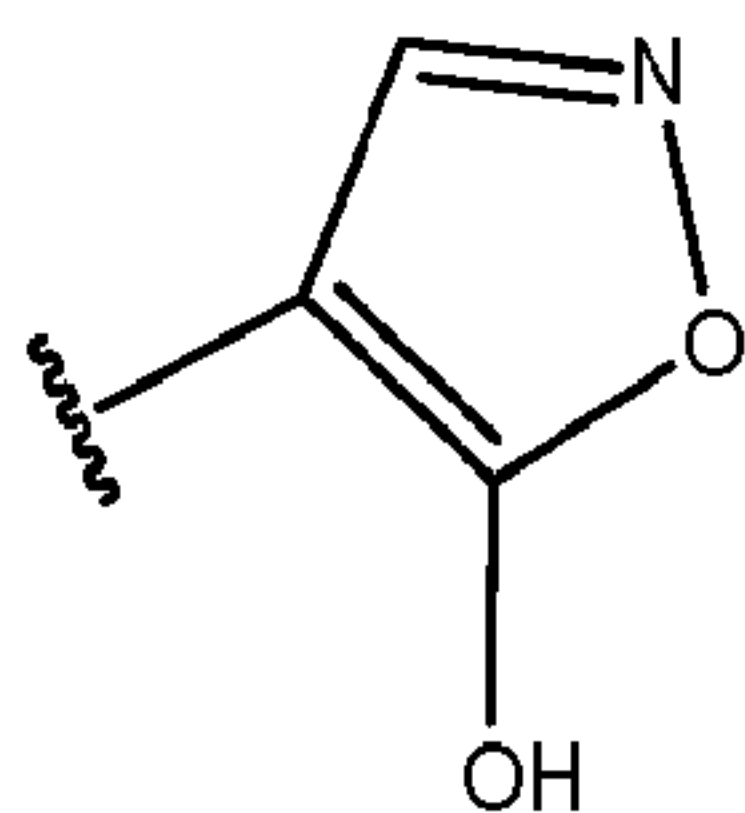
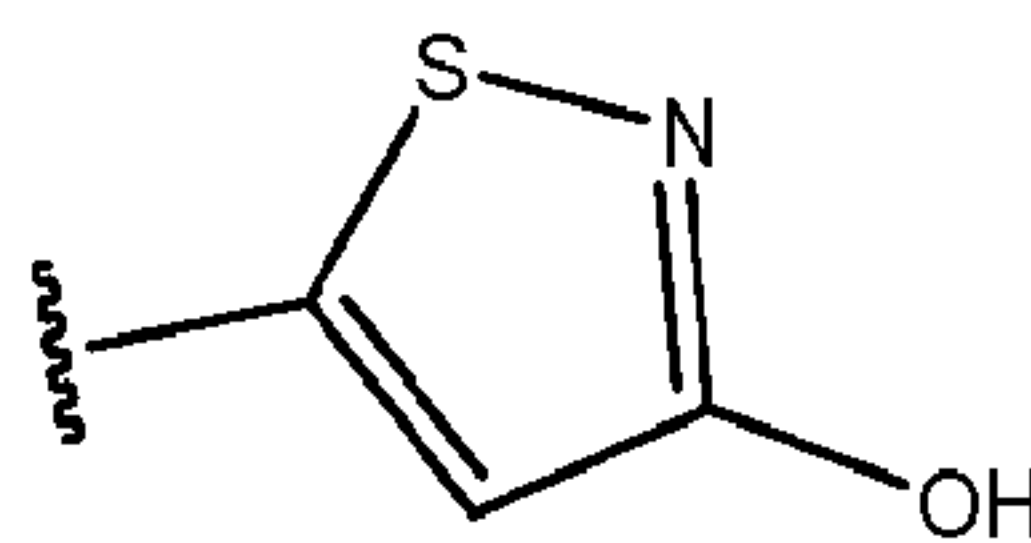
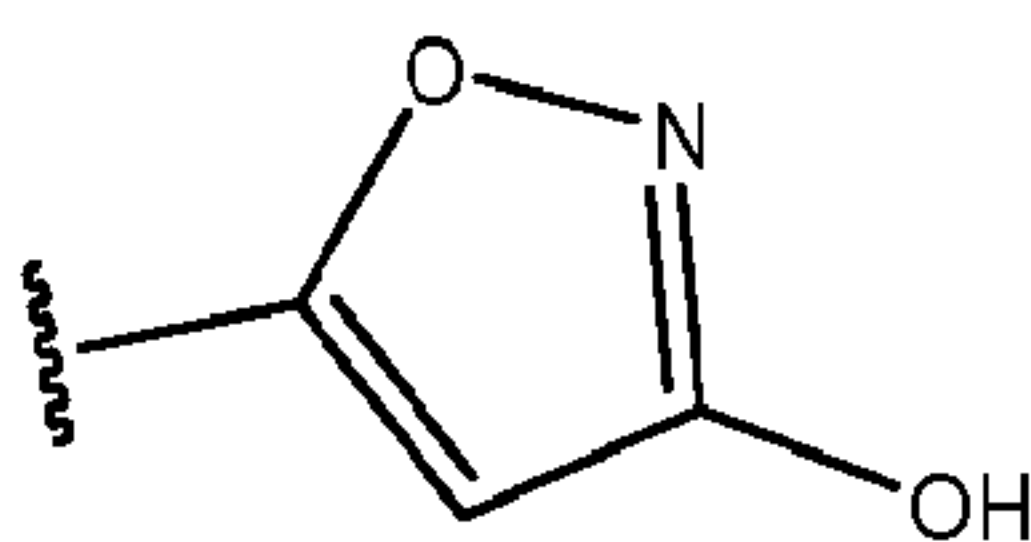
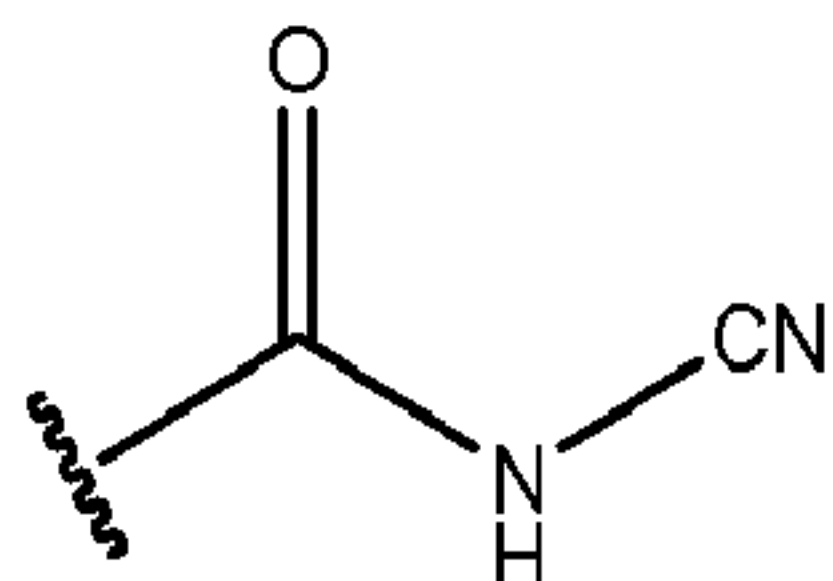




wherein R² is independently H, C₁-C₆ alkyl, unsubstituted phenyl, or unsubstituted biphenyl.

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

Carboxylic acid bioisosteres according to Silverman



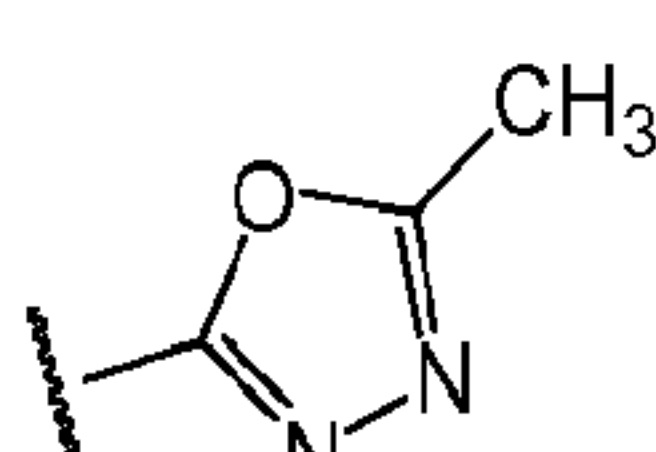
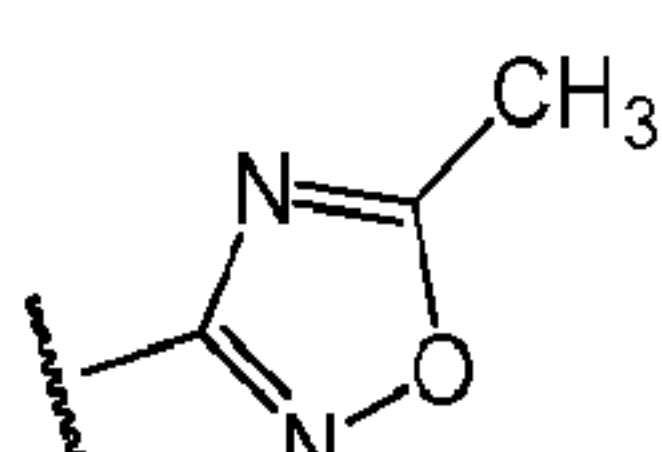
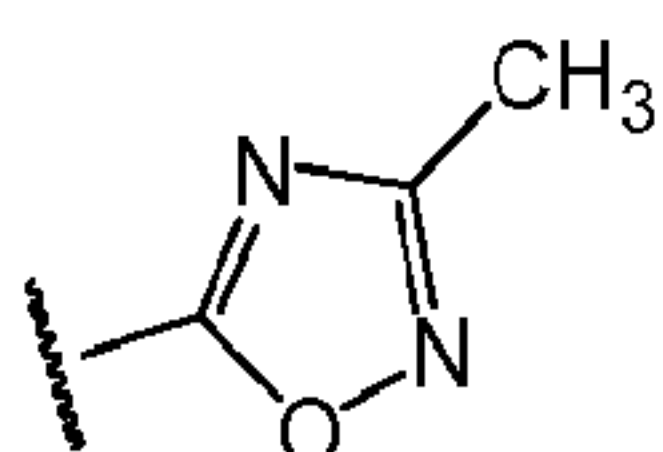
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Orlek et al. (*J. Med. Chem.* **1991**, 34, 2726-2735) described oxadiazoles as suitable bioisosteres for a carboxylic acid.

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.

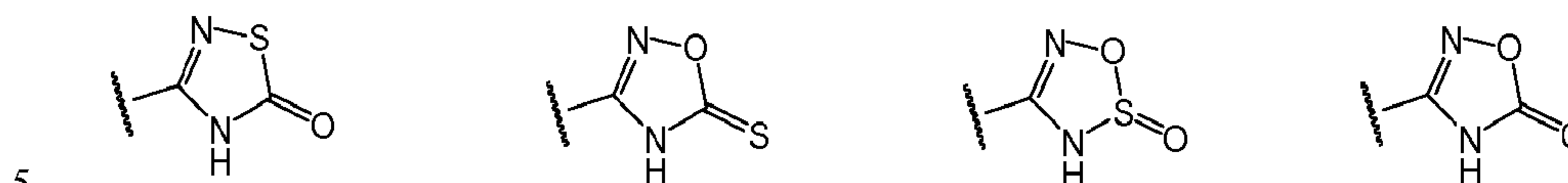
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Carboxylic acid bioisosteres according to Orlek et. al.



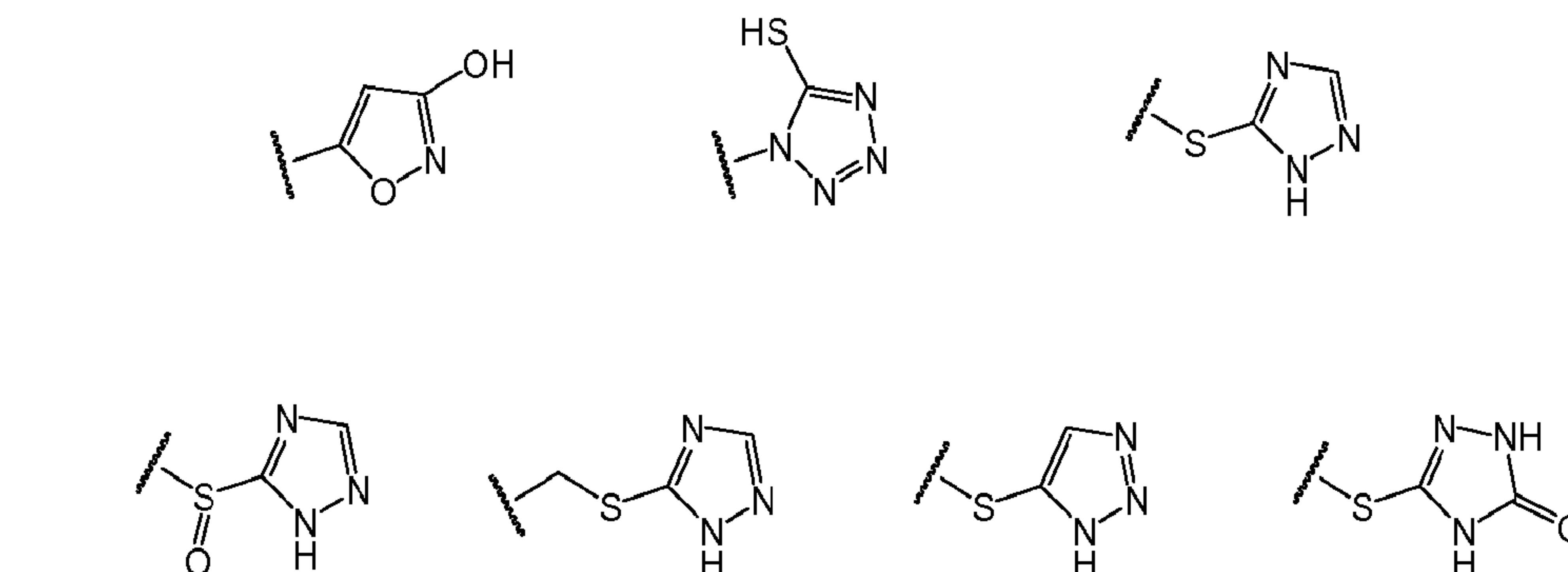
Kohara et al. (*J. Med. Chem.* **1996**, 39, 5228-5235) described acidic heterocycles as suitable bioisosteres for a tetrazole. These carboxylic acid replacements were shown to be potent angiotensin II receptor antagonists having improved metabolic stability.

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.

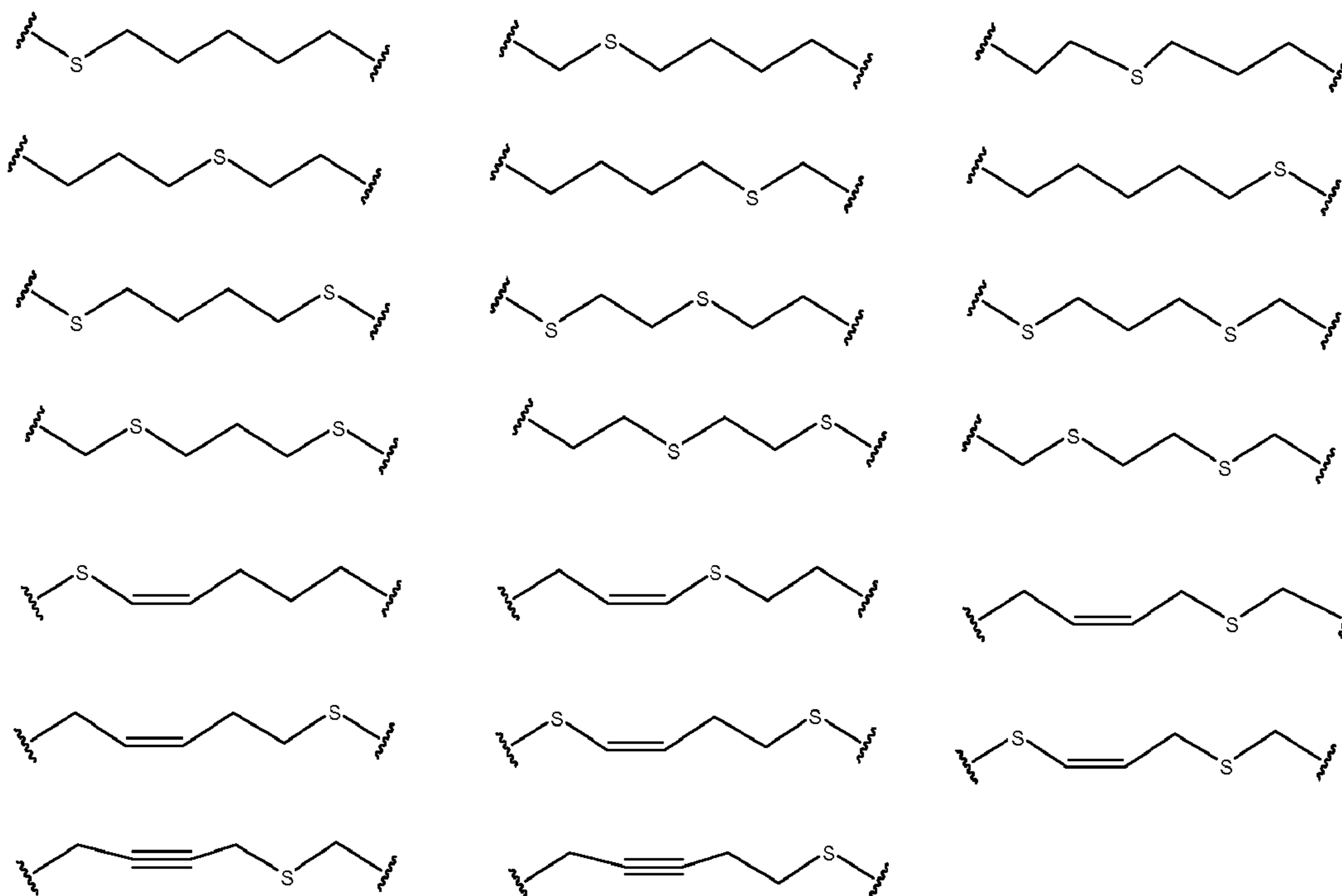
Carboxylic acid bioisosteres according to Drysdale et. al.



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

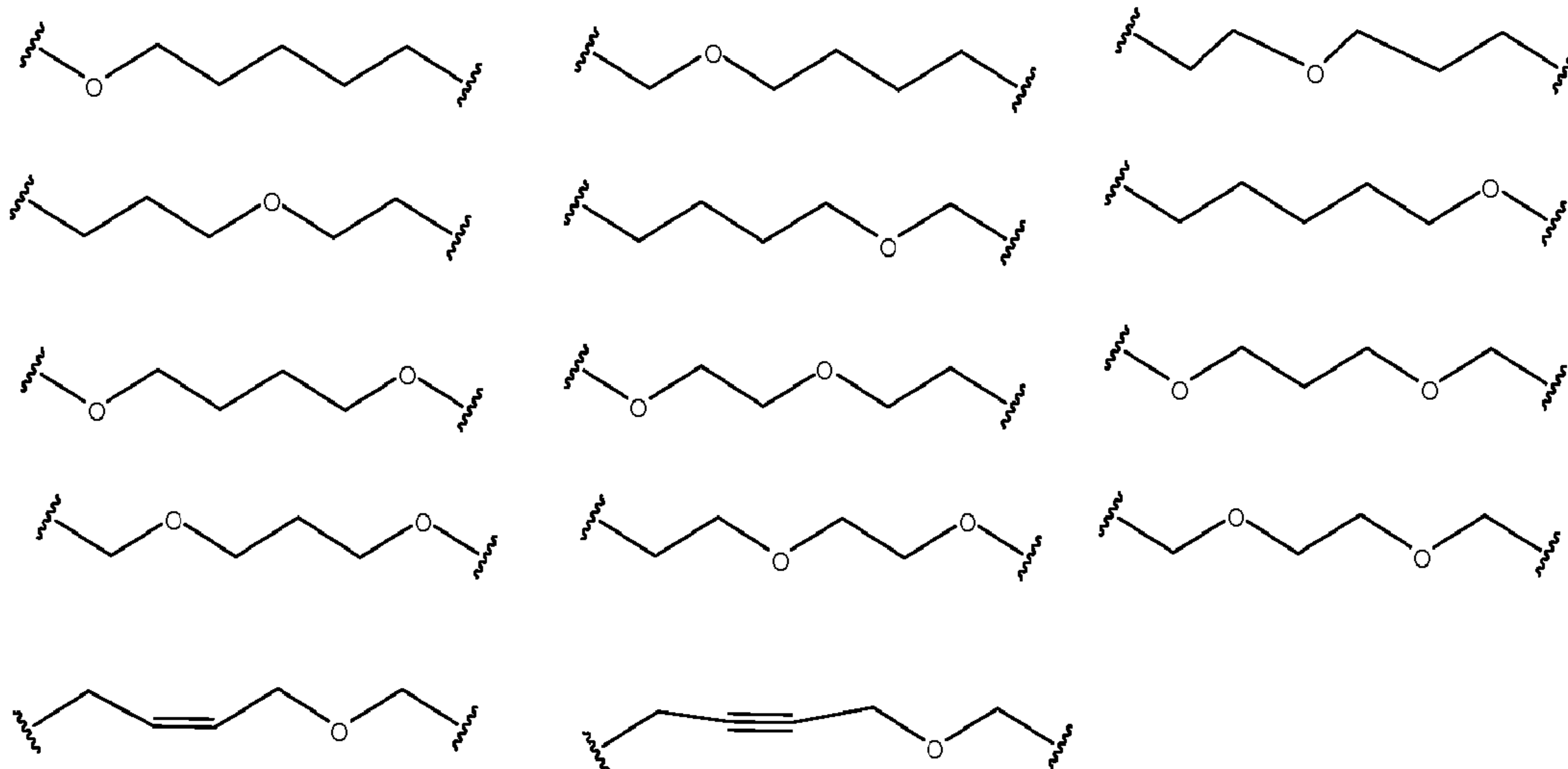
Thus, A may be $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$.

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



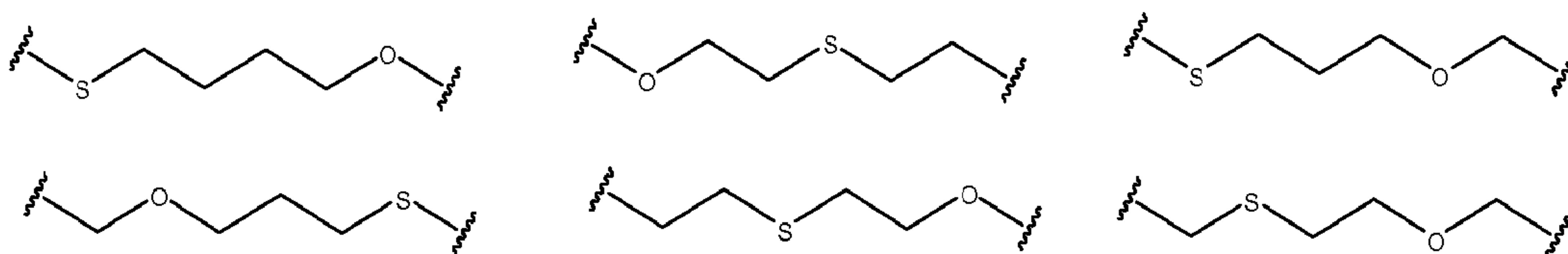
Alternatively, A may be a moiety where O replaces one or two carbon atoms such as one of the following or the like.

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

5



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

10 in one embodiment A comprises:

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

e.g. $-CH_2-Ar-$, $-(CH_2)_2-Ar-$, $-CH=CH-Ar-$, $-C\equiv C-Ar-$, $-CH_2-Ar-CH_2-$, $-CH_2Ar-(CH_2)_2-$, $-CH_2Ar-CH=CH-$, $-CH_2Ar-C\equiv C-$, $-(CH_2)_2-$
 15 $Ar-(CH_2)_2-$, and the like;

in another embodiment A comprises:

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

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

in another embodiment A comprises:

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

25

e.g., $-S-Ar-$, $-Ar-CH_2-S-$, $-S-Ar-(CH_2)_2-$, $-SAr-CH=CH-$, $-S-Ar-C\equiv C-$, $-S-CH_2-Ar-$, $-S-CH_2-Ar-(CH_2)_2-$, $-S-CH_2Ar-CH=CH-$, $-S-CH_2Ar-C\equiv C-$, and the like.

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

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

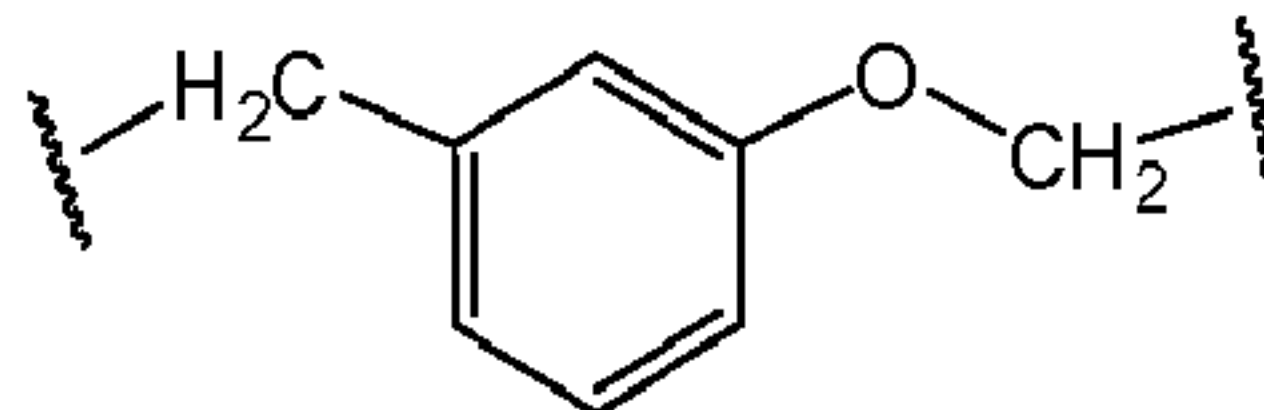
5 In another embodiment, the sum of m and o is 2 wherein one CH₂ may be replaced with S or O or 1 -CH₂-CH₂- may be replaced by -CH=CH- or -C≡C-.

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

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

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

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



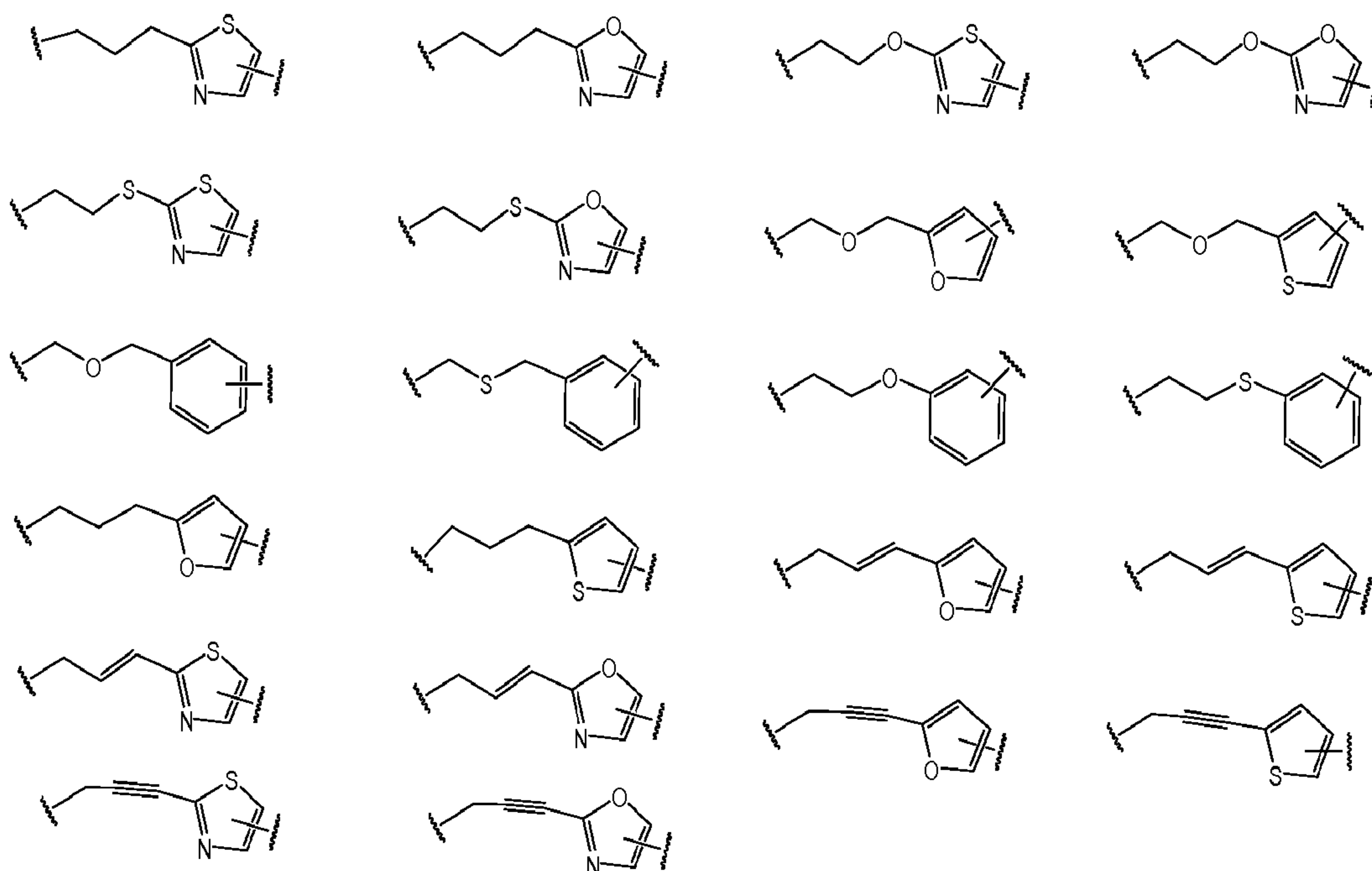
25 In another embodiment A is -(CH₂)₆-, *cis* -CH₂CH=CH-(CH₂)₃-, or -CH₂C≡C-(CH₂)₃-, wherein 1 or 2 carbon atoms may be replaced with S or O; or A is -(CH₂)₂-Ph- wherein one -CH₂- may be replaced with S or O.

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

In one embodiment, Ar is thienyl.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In another embodiment A is 3-methylphenethyl.

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

In another embodiment A is 4-phenethyl.

In another embodiment A is 4-methoxybutyl.

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

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

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

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

In another embodiment A is 6-hexyl.

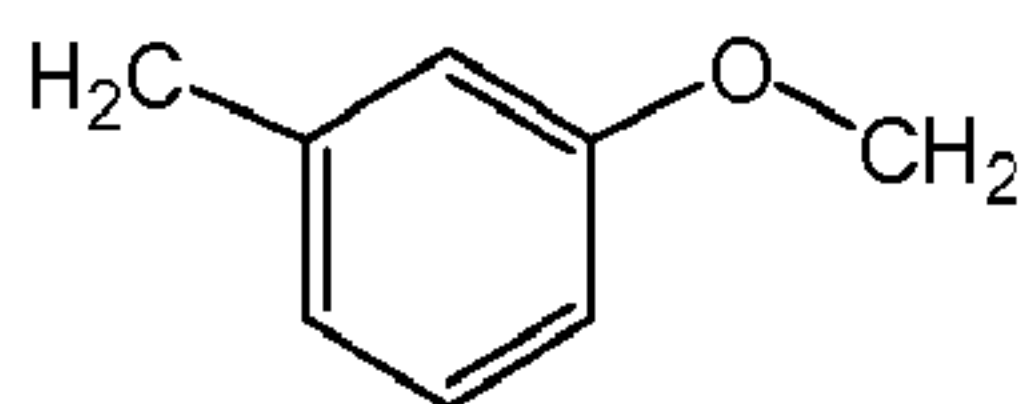
In another embodiment A is (Z)-6-hex-4-enyl.

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
10 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 $-(CH_2)_2-$
15 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
20 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 ;
25 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.

30 In one embodiment A is $-(CH_2)_m-Ph-(CH_2)_o-$ wherein 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 $-CH_2-Ph-OCH_2-$. In another embodiment, Ph is attached at the 1 and 3 positions, otherwise known as *m*-interphenylene, such as when A has the structure shown below.

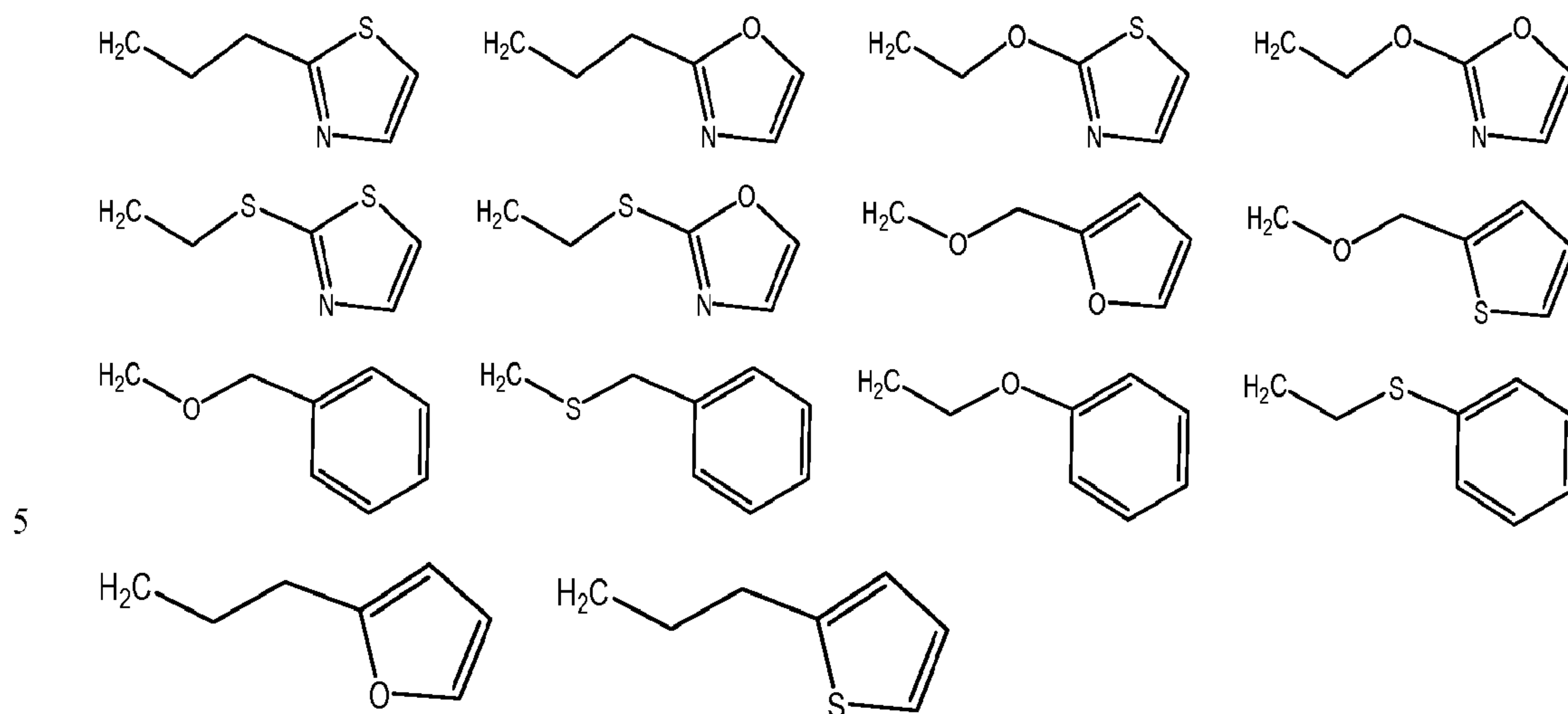


35

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
40 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 $-\text{CH}_2\text{OCH}_2\text{Ar}$.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 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.

30 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.

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

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

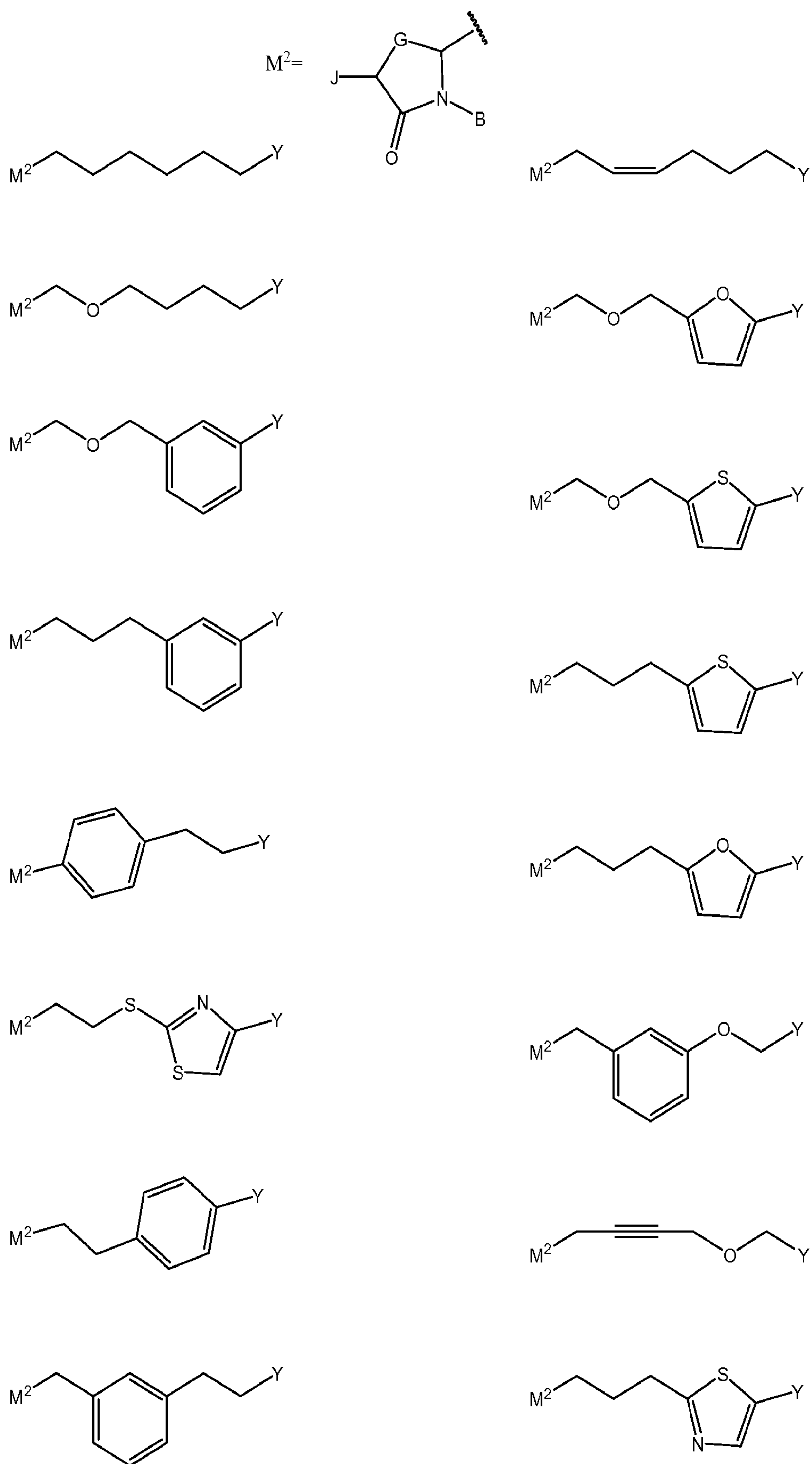
In another embodiment A is 5-(3-propyl)furan-2-yl.

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

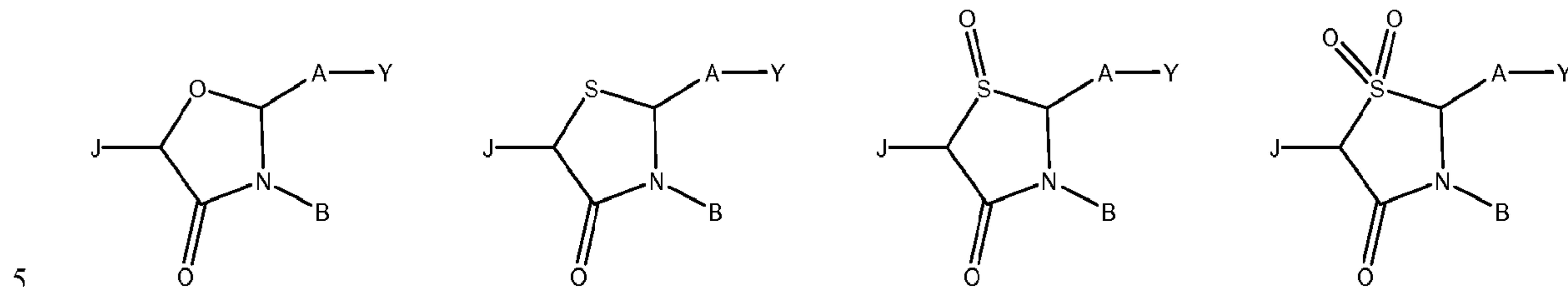
In another embodiment A is 6-hexyl.

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

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.



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.



J is H, halogen, CF₃; or C₁₋₆ alkyl.

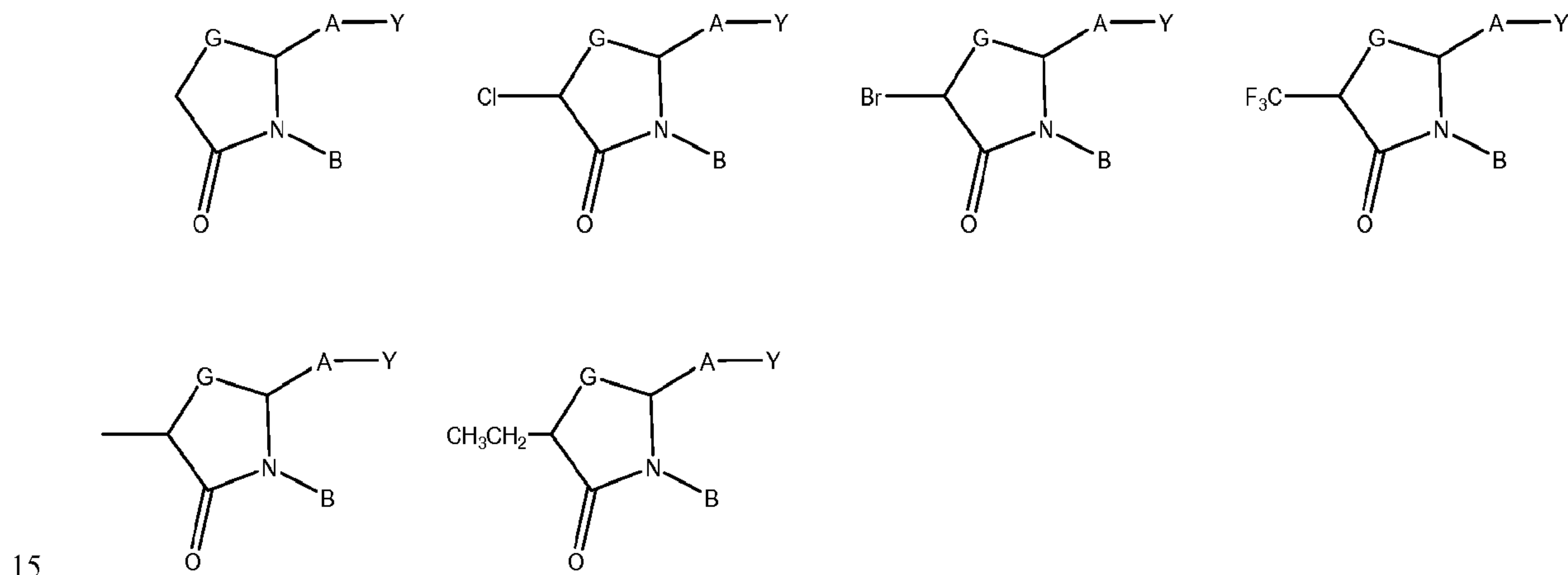
In one embodiment J is H.

In another embodiment J is halogen.

In another embodiment J is CF₃.

10 In another embodiment J is C₁₋₆ alkyl.

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.



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

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

Aryl or heteroaryl may be substituted or unsubstituted. 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, salt, or prodrug to be useful as described herein. In addition to the atoms listed above, a substituent may also have a metal cation or other stable cation having an atom not listed above if the substituent is acidic and the salt form is stable. For example, -OH may form an -O⁻Na⁺ salt or CO₂H may form a CO₂K⁺ salt. Thus, while not intending to limit the scope of the invention in any way, a substituent may be:

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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;

Alkyl is hydrocarbyl having no double or triple bonds;

C₁₋₆ alkyl is alkyl having 1, 2, 3, 4, 5, or 6 carbon atoms;

5 hydrocarbyloxy, meaning O-hydrocarbyl such as OCH₃, OCH₂CH₃, O-cyclohexyl, etc, up to 19 carbon atoms;

alkoxy is O-alkyl;

C₁₋₆ alkoxy is alkoxy having 1, 2, 3, 4, 5, or 6 carbon atoms;

other ether substituents such as CH₂OCH₃, (CH₂)₂OCH(CH₃)₂, and the like;

thioether substituents including S-hydrocarbyl and other thioether substituents;

10 hydroxyhydrocarbyl, meaning hydrocarbyl-OH such as CH₂OH, C(CH₃)₂OH, etc, up to 19 carbon atoms;

nitrogen substituents such as NO₂, CN, and the like, including

amino, such as NH₂, NH(CH₂CH₃OH), NHCH₃, and the like;

C₀₋₆ amino is amino having 0, 1, 2, 3, 4, 5 or 6 carbon atoms;

carbonyl substituents, such as CO₂H, ester, amide, and the like;

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

fluorocarbyl, such as CF₃, CF₂CF₃, etc.;

phosphorous substituents, such as PO₃²⁻, and the like;

sulfur substituents, including S-hydrocarbyl, SH, SO₃H, SO₂-hydrocarbyl, SO₃-hydrocarbyl, and the like.

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

Substituted aryl or substituted heteroaryl also includes a bicyclic or polycyclic ring system wherein one or more rings are aromatic and one or more rings are not. For example, indanonyl, indanyl, indanolyl, tetralonyl, and the like are substituted aryl.

25 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, i.e. the part of the molecule that is not B. 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.

30 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.

35 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.

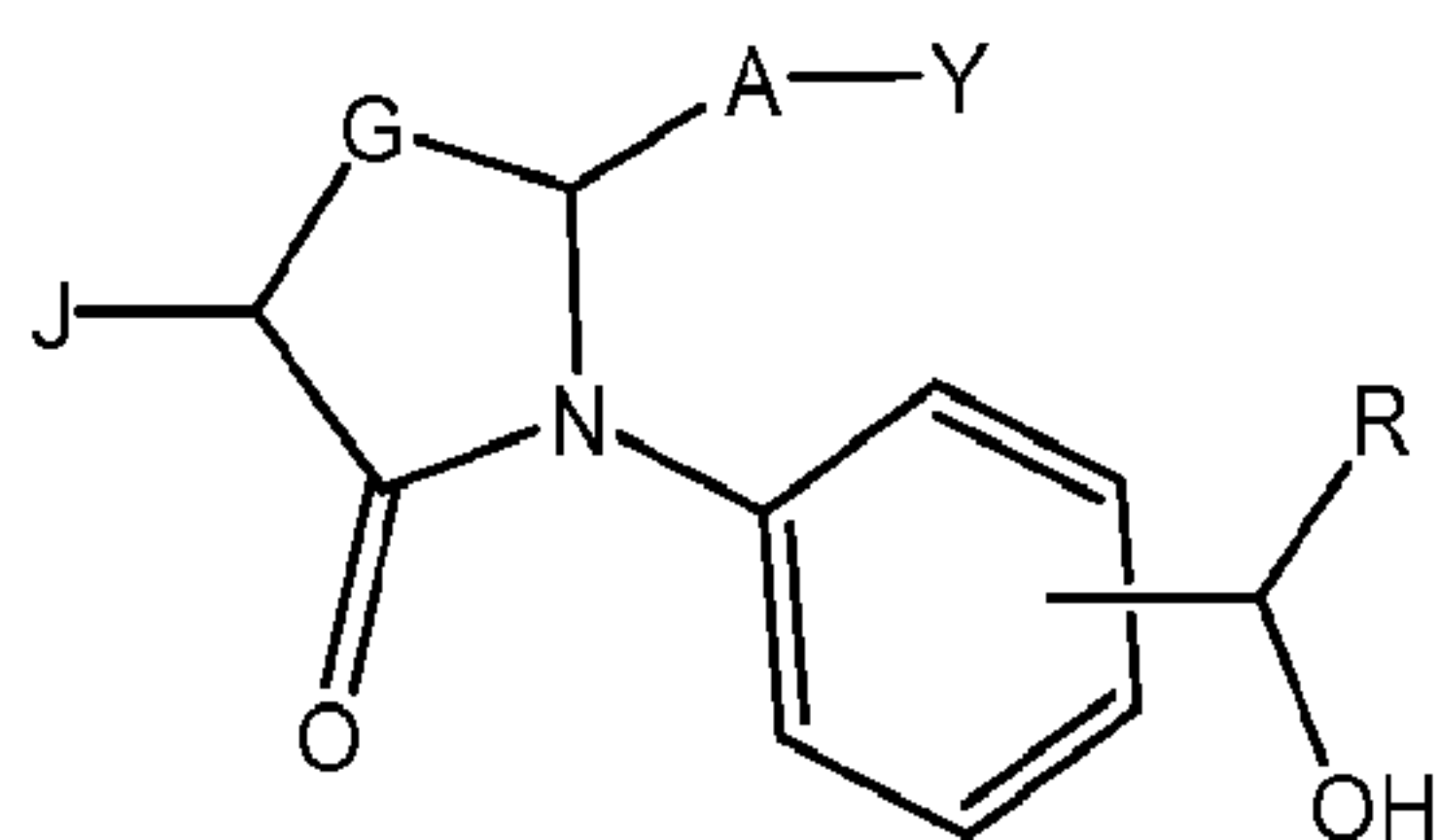
40 In another embodiment B is 4-(3-hydroxy-2-methyloctan-2-yl)phenyl.

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.

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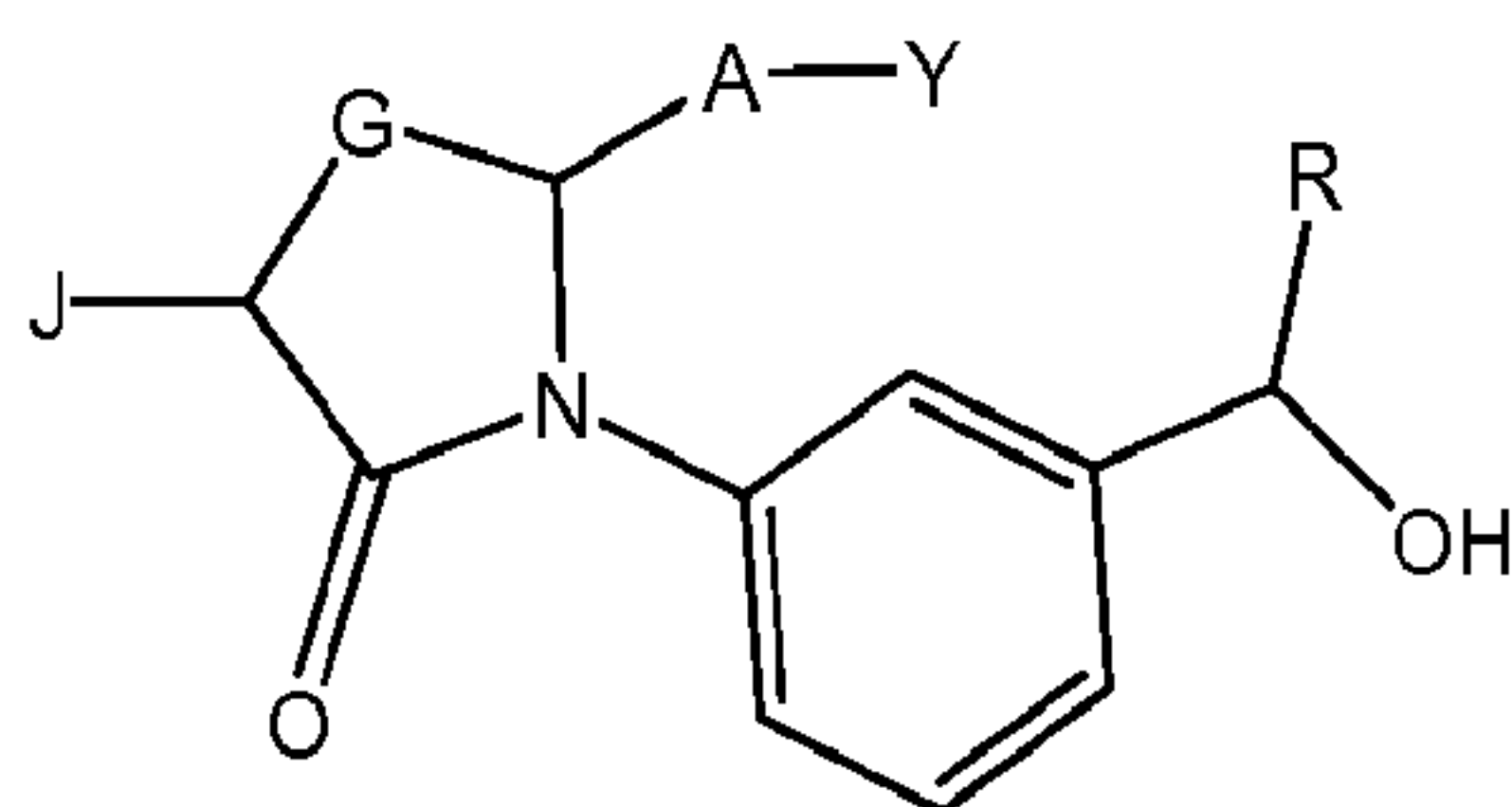
- In another embodiment B is 3-(hydroxy(1-propylcyclobutyl)methyl)phenyl.
- In another embodiment B is 4-(1-hydroxy-5,5-dimethylhexyl)phenyl.
- In another embodiment B is 4-(hydroxy(1-propylcyclobutyl)methyl)phenyl.
- In another embodiment B is 4-tert-butylphenyl.
- 5 In another embodiment B is 4-hexylphenyl.
- 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.
- 10 In another embodiment B is 4-(3-cyclohexyl-1-hydroxypropyl)phenyl.
- In another embodiment B is 4-(cyclohexyl(hydroxy)methyl)phenyl.
- In another embodiment B is 4-(cyclohexylmethyl)phenyl.
- In another embodiment B is 4-(hydroxy(phenyl)methyl)phenyl.
- Another embodiment is a compound according to the structure



or a pharmaceutical salt thereof, or a prodrug thereof,

wherein R is hydrogen or C₁₋₁₀ hydrocarbyl.

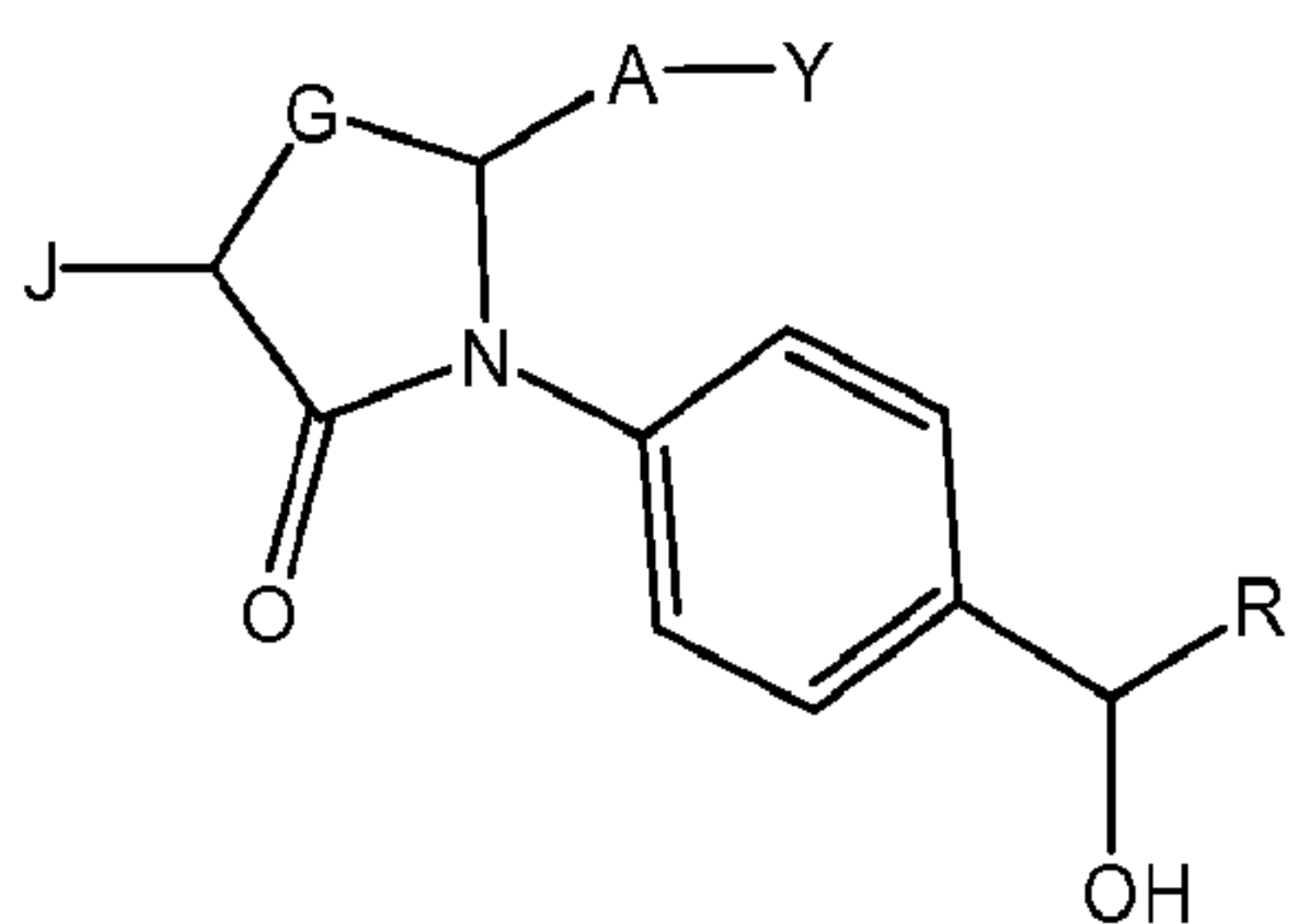
Another embodiment is a compound according to the structure



or a pharmaceutical salt thereof, or a prodrug thereof,

wherein R is hydrogen or C₁₋₁₀ hydrocarbyl.

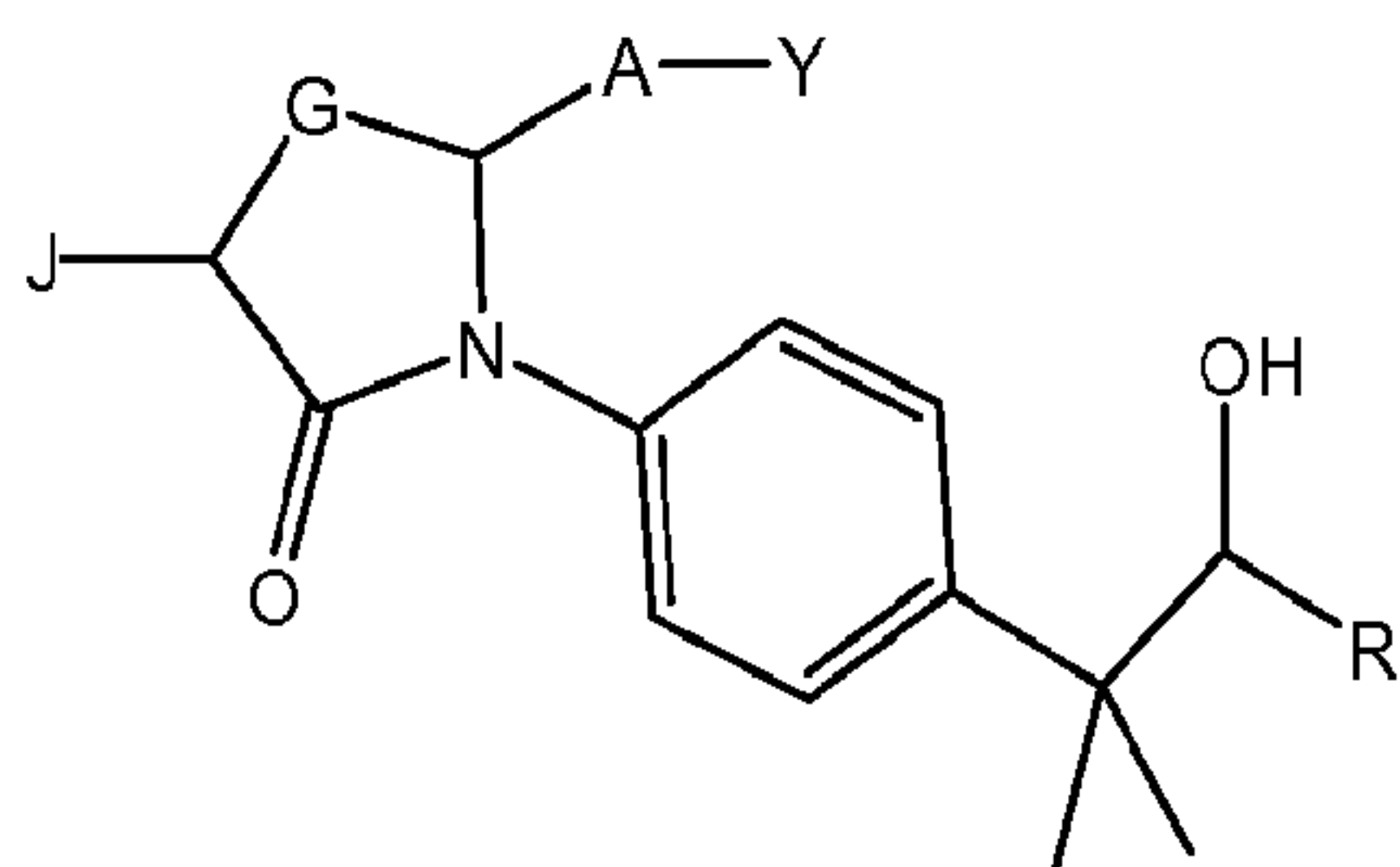
Another embodiment is a compound according to the structure



or a pharmaceutical salt thereof, or a prodrug thereof,

wherein R is hydrogen or C₁₋₁₀ hydrocarbyl.

Another embodiment is a compound according to the structure



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

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

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

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

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

cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.; and

alkyl fragments consisting of both cyclic and noncyclic components, whether linear or branched, which may be attached to the remainder of the molecule at any available position including terminal, internal, or ring carbon atoms.

C₁₋₆ alkyl is alkyl having 1, 2, 3, 4, 5, or 6 carbon atoms.

- 5 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.

- 10 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.

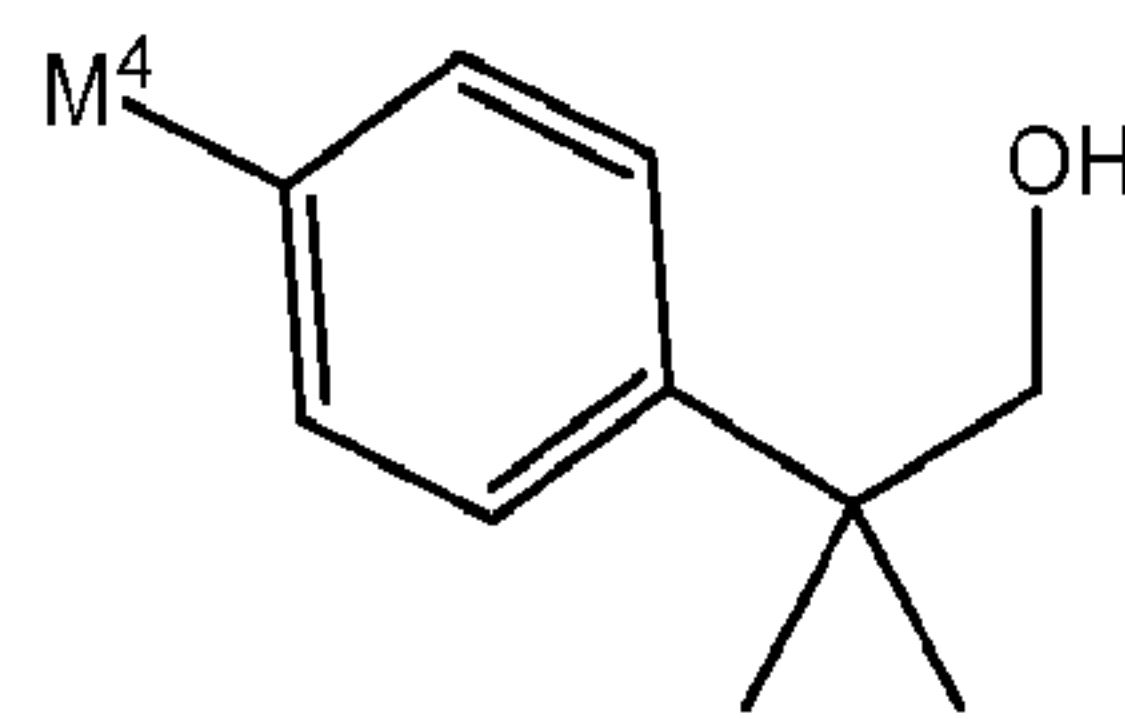
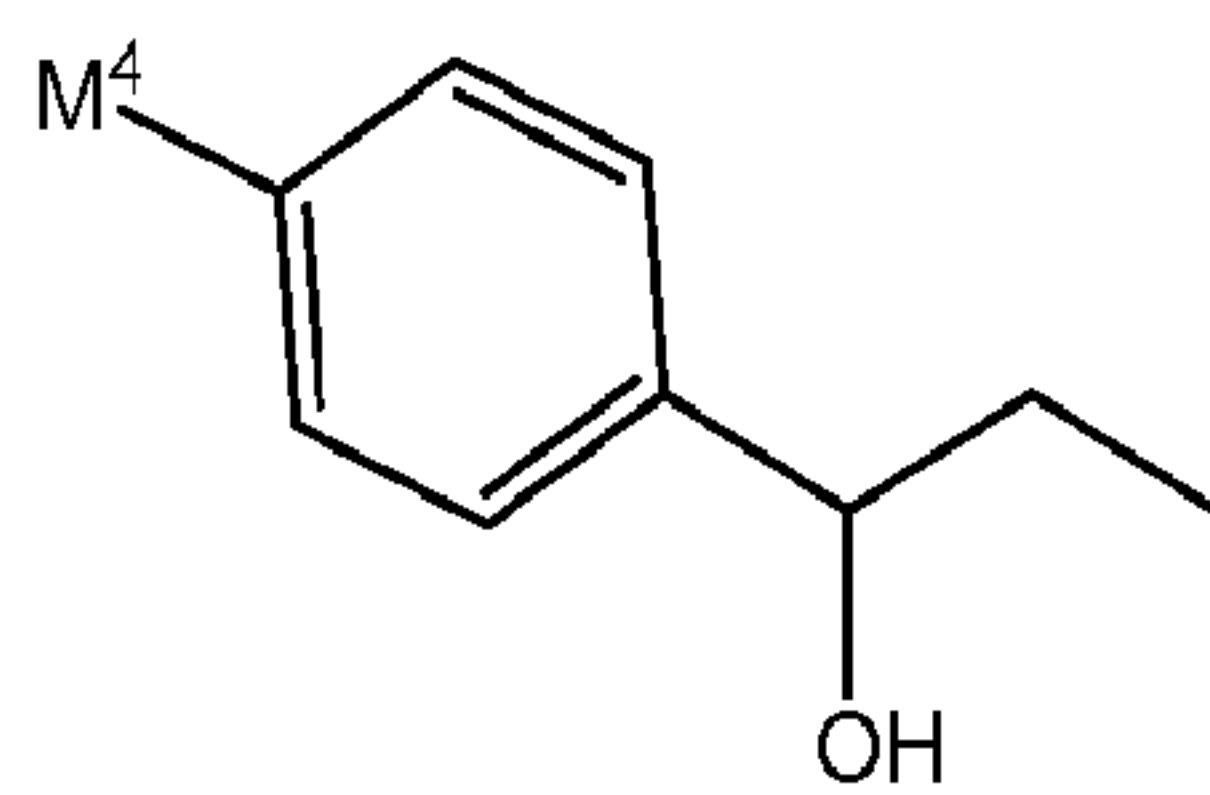
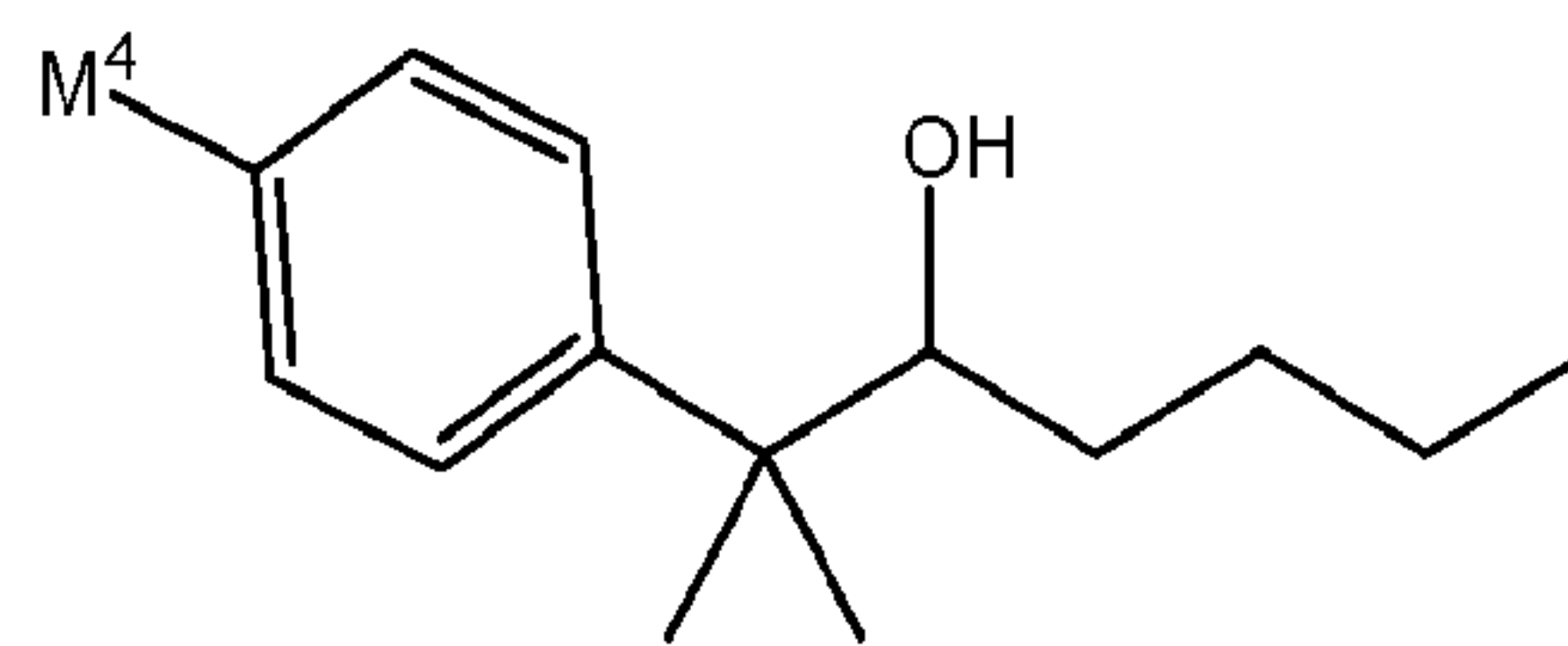
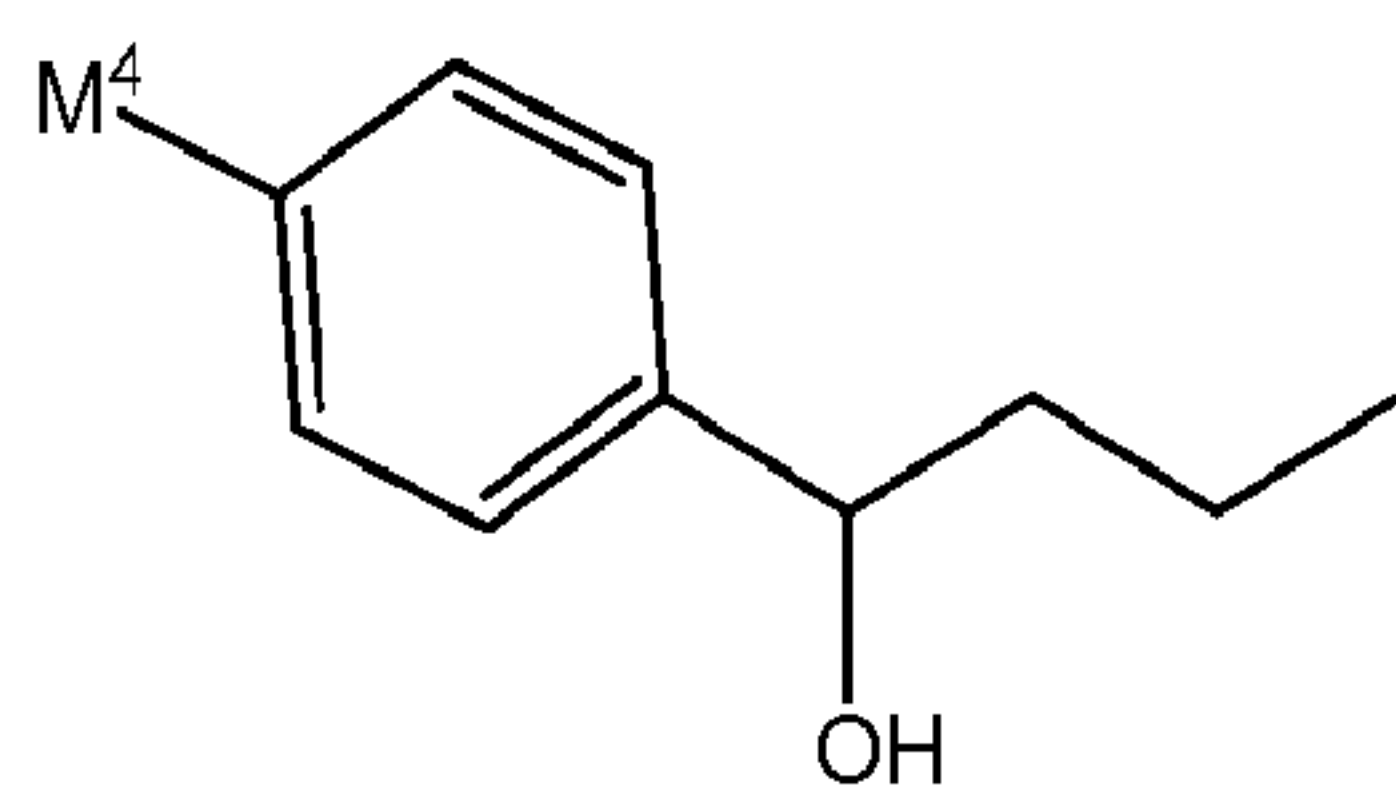
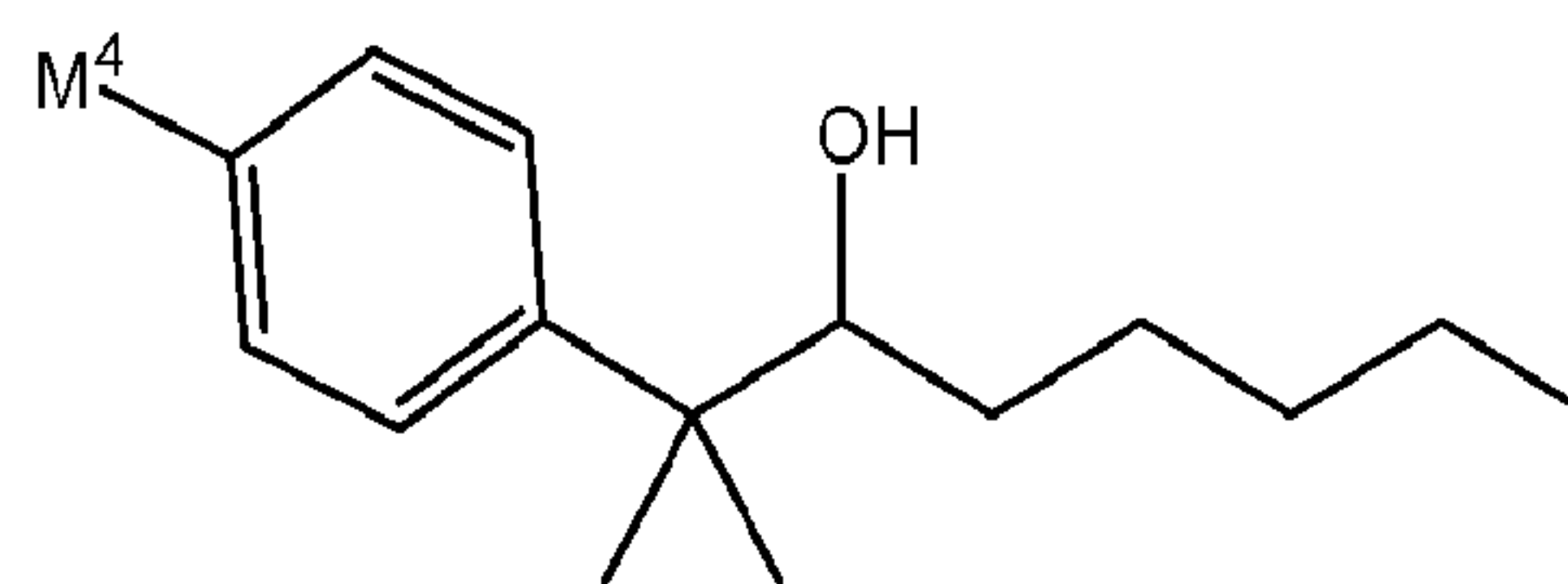
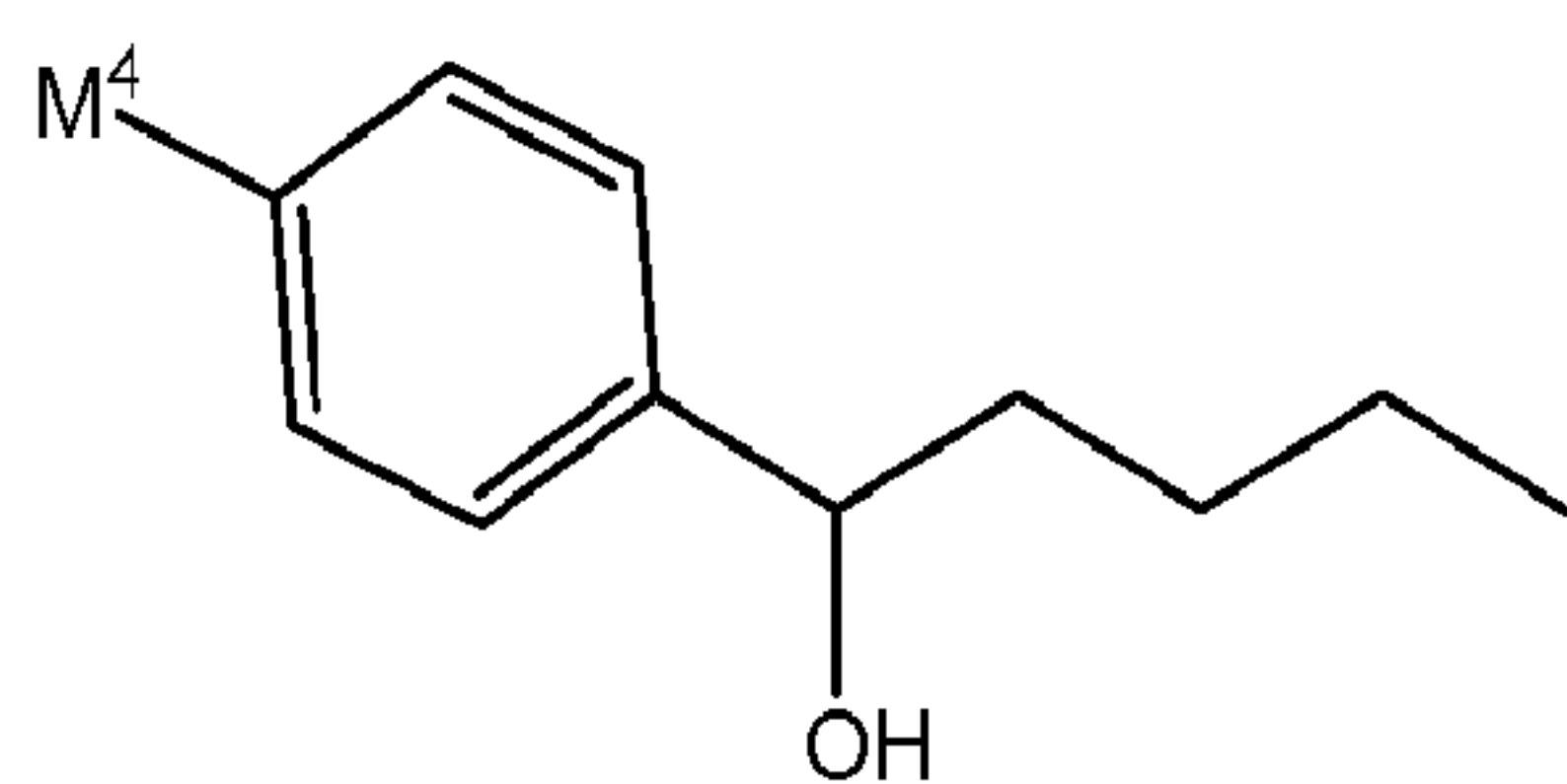
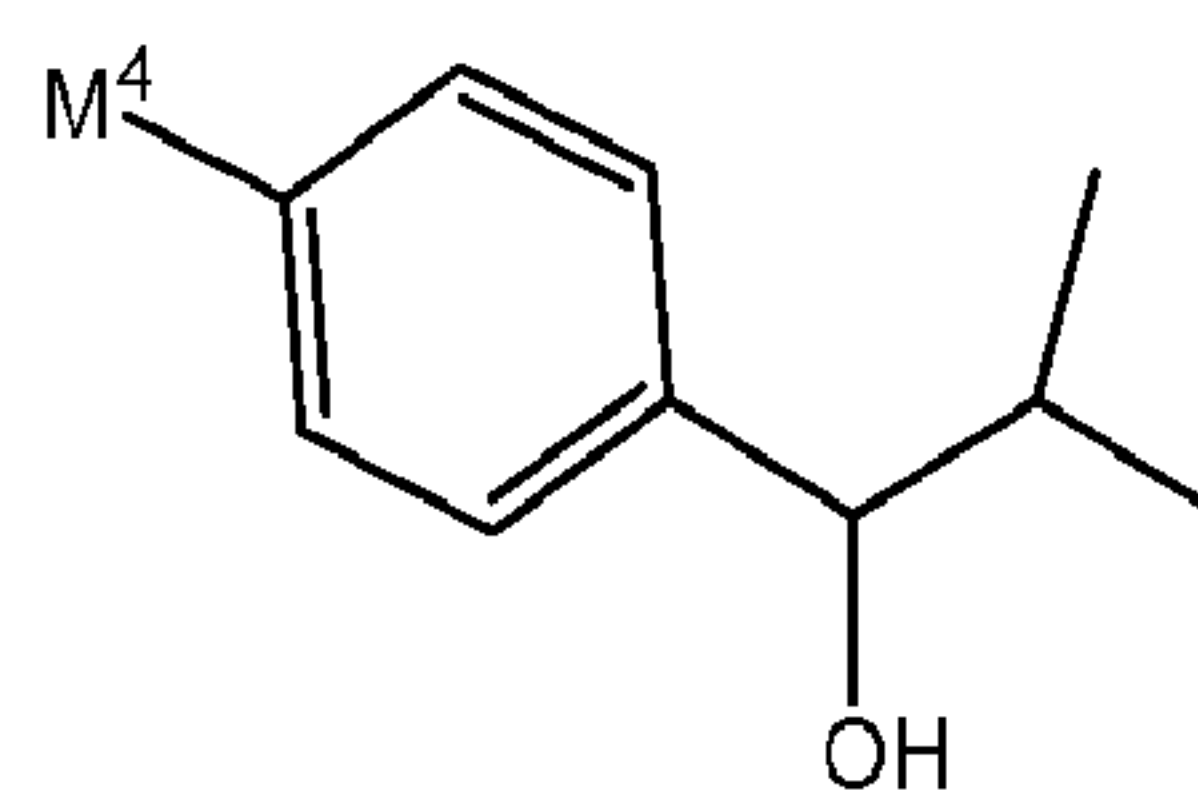
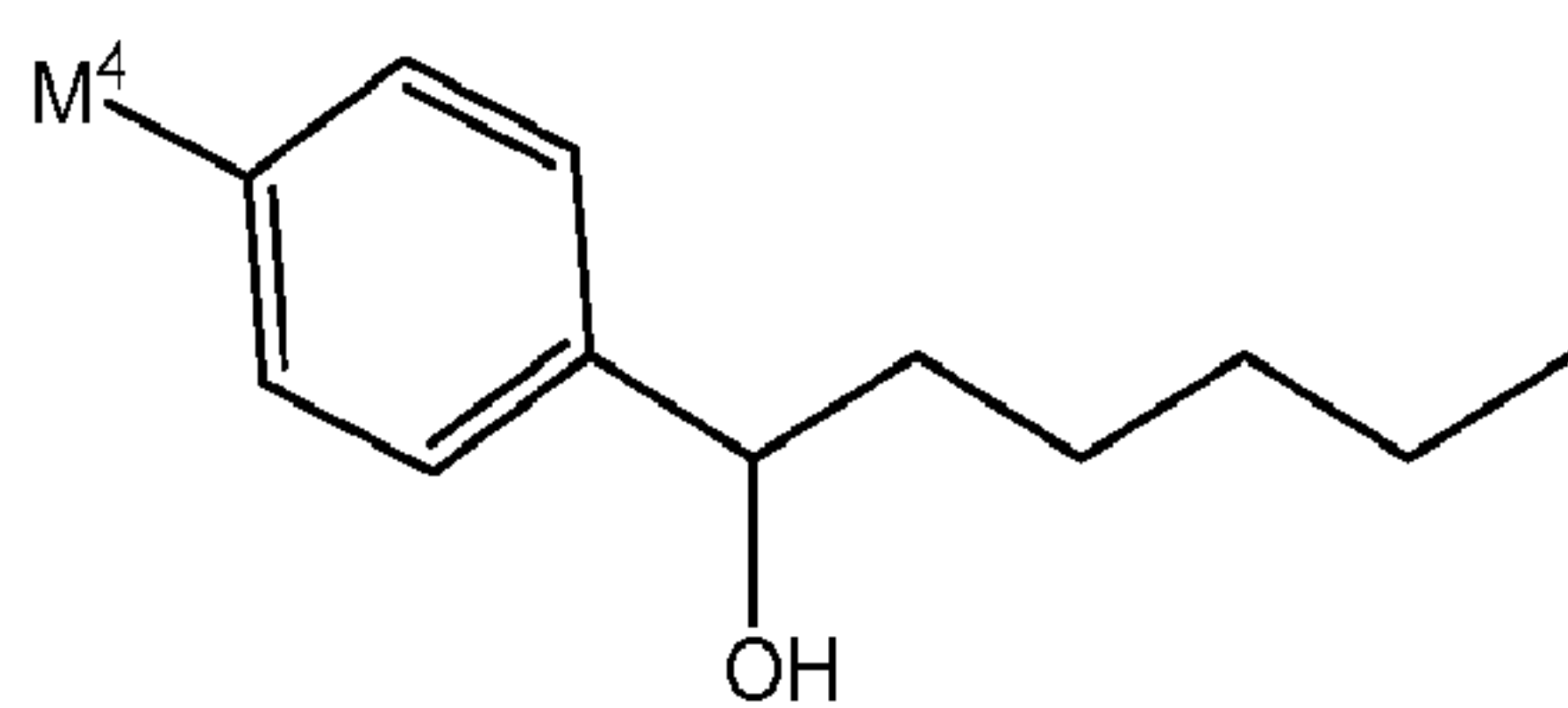
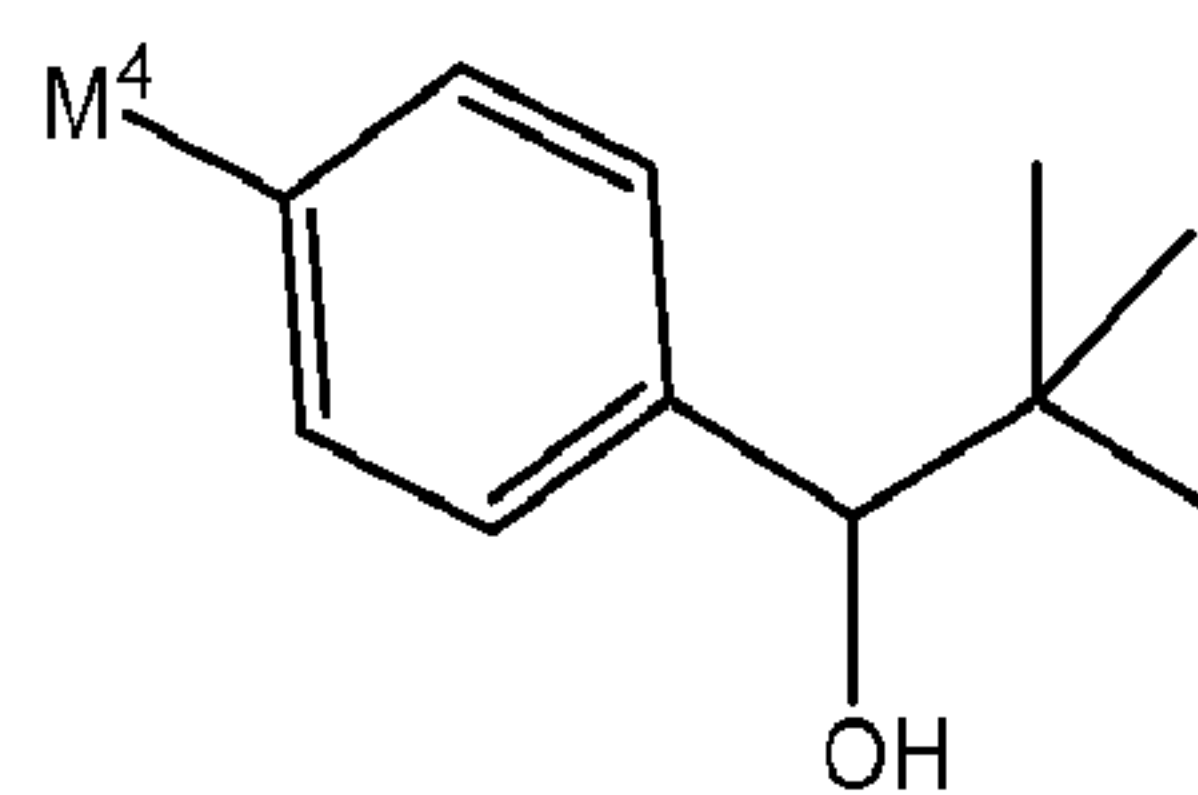
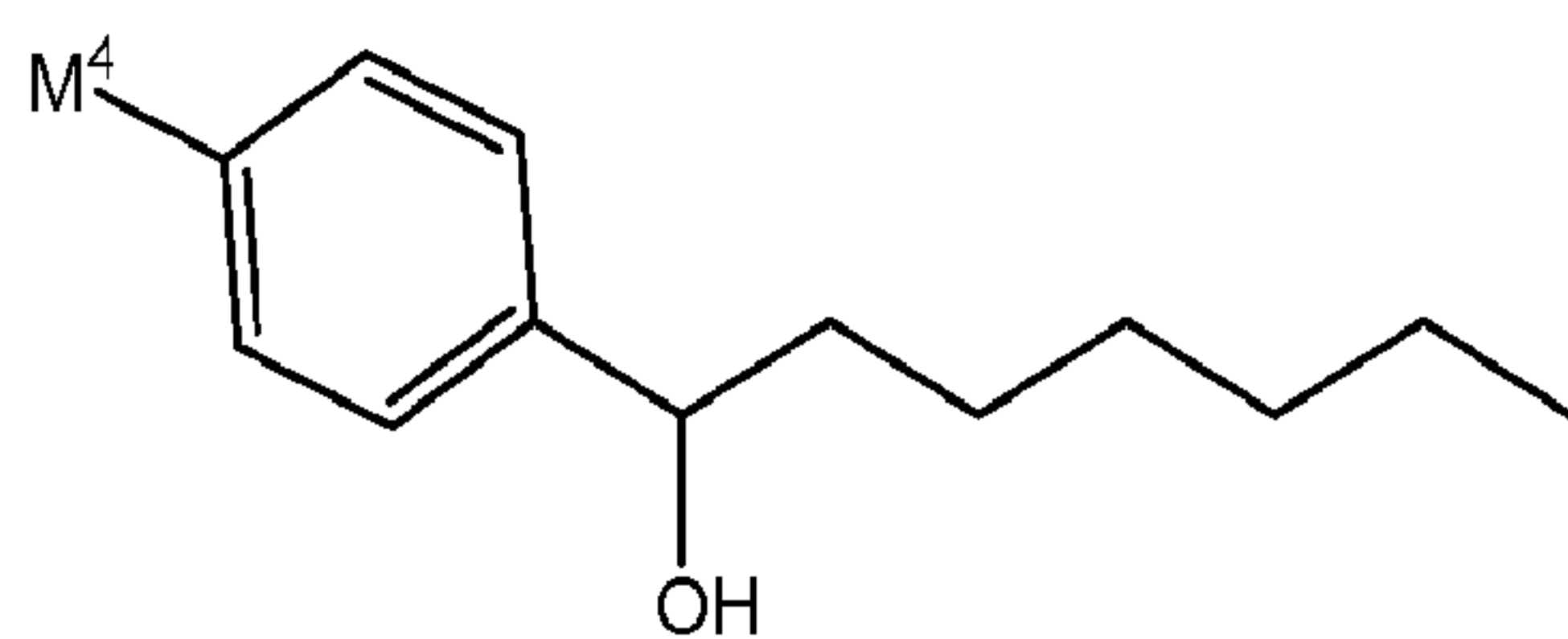
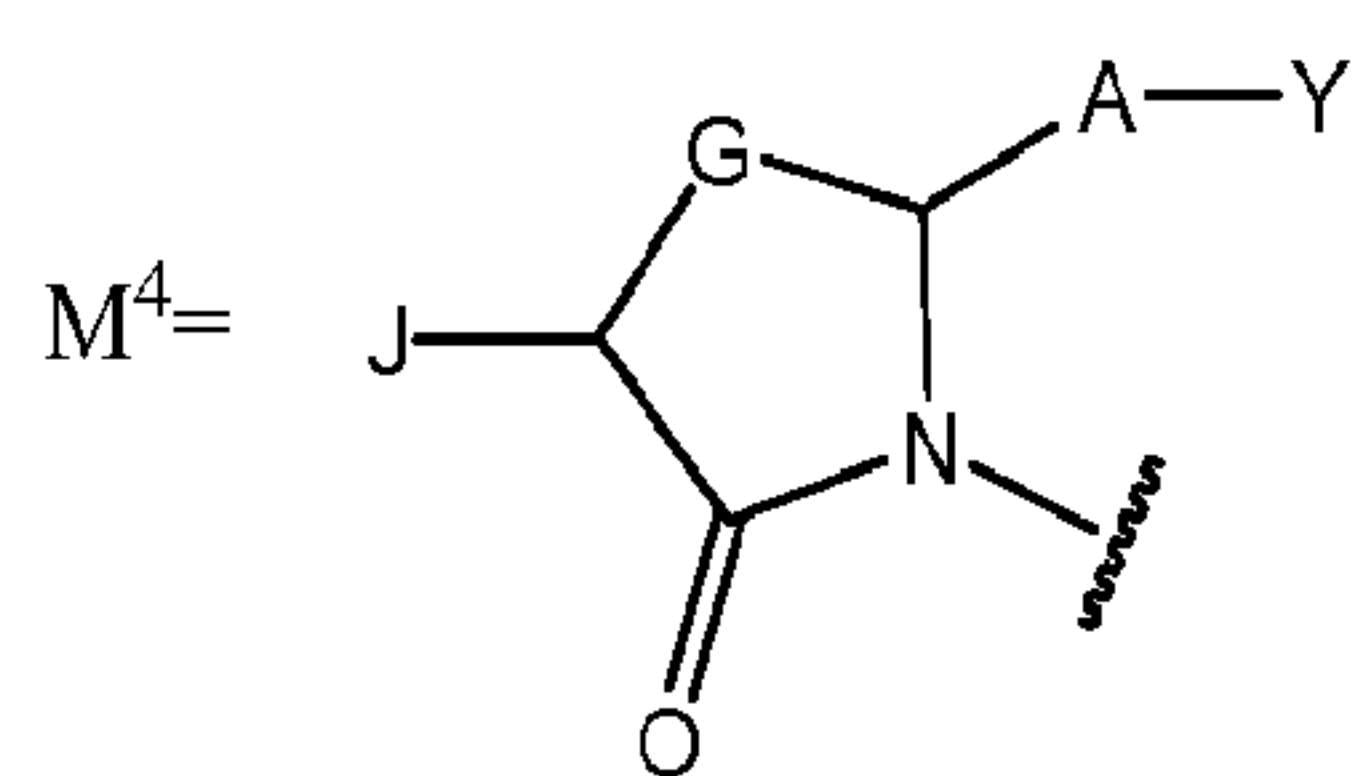
Arylalkyl is alkyl which is substituted with aryl. In other words alkyl connects aryl to the remaining part of the molecule.

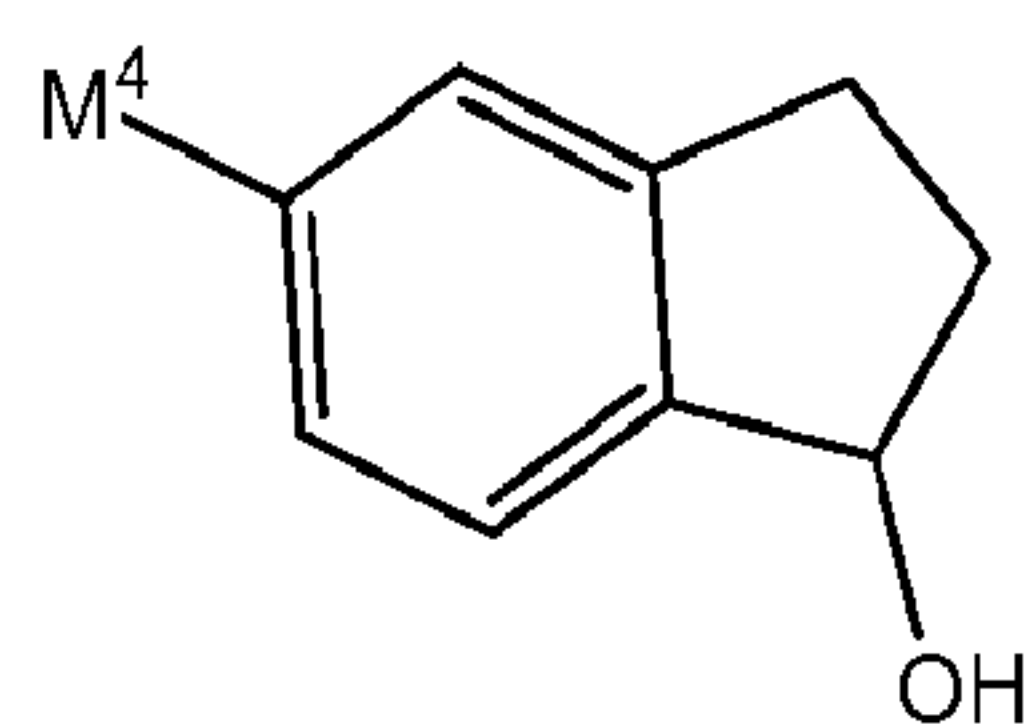
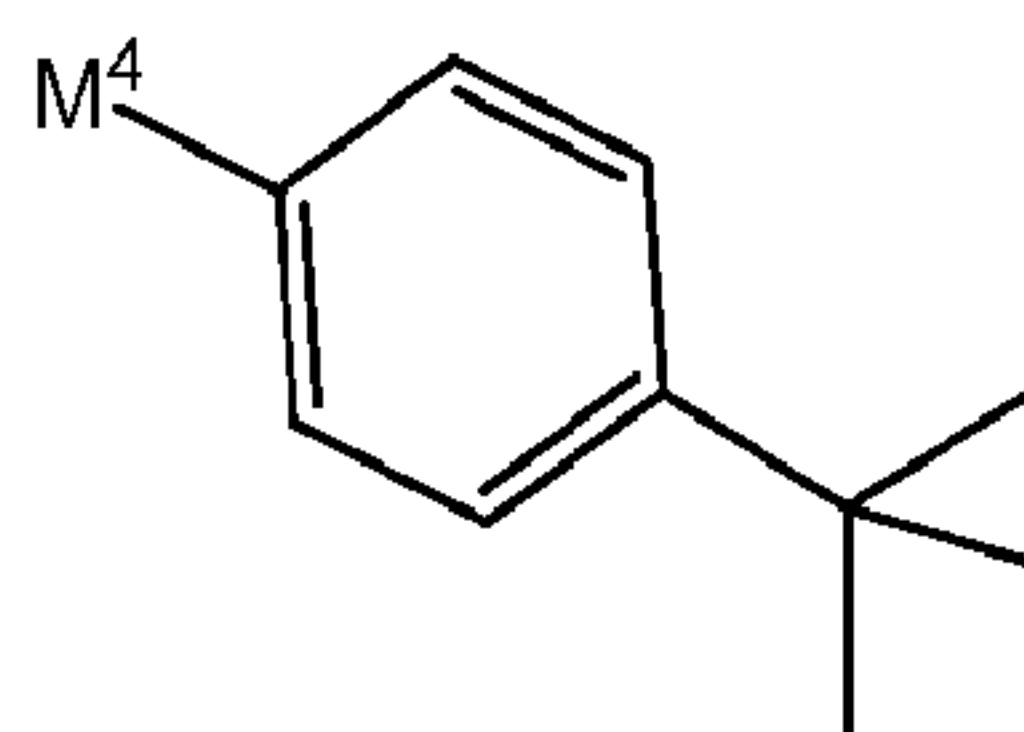
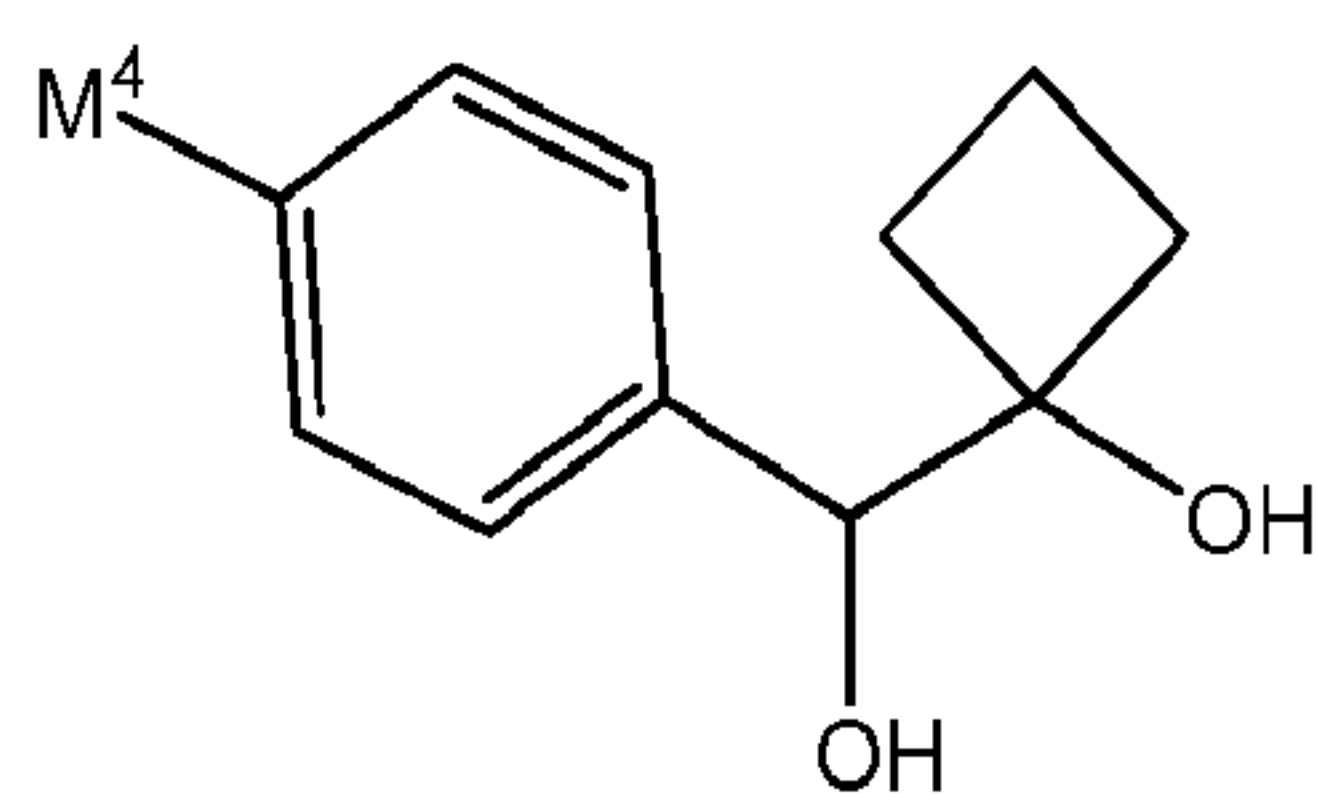
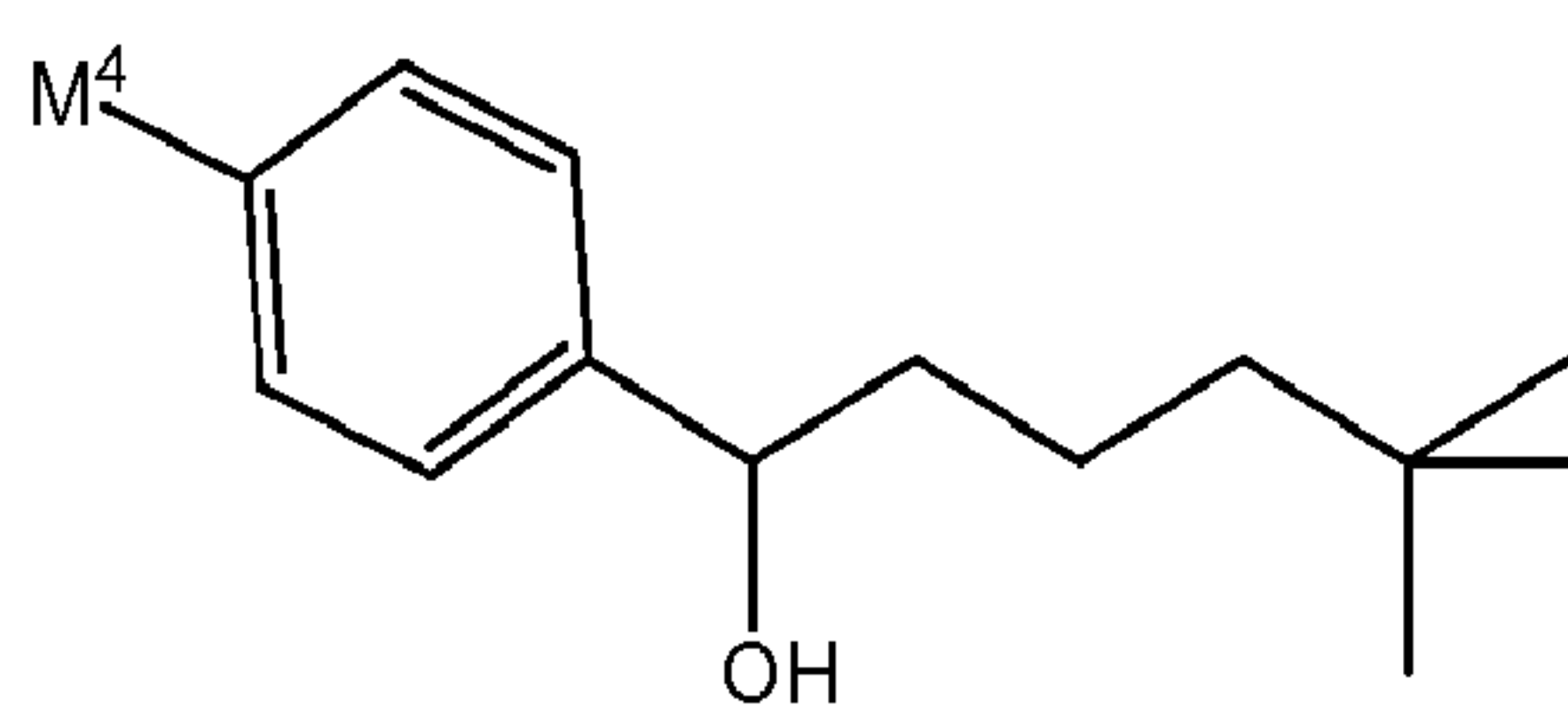
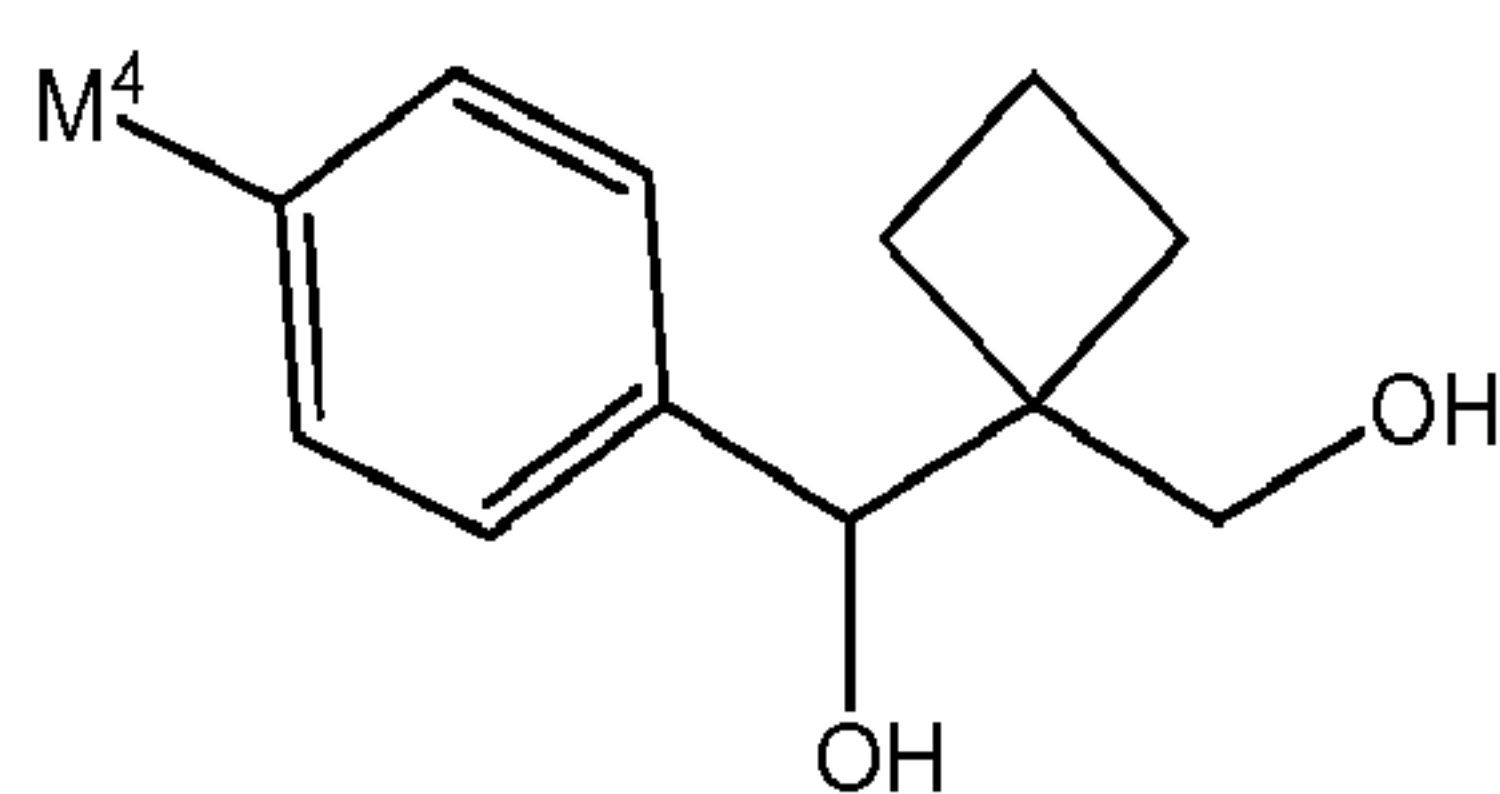
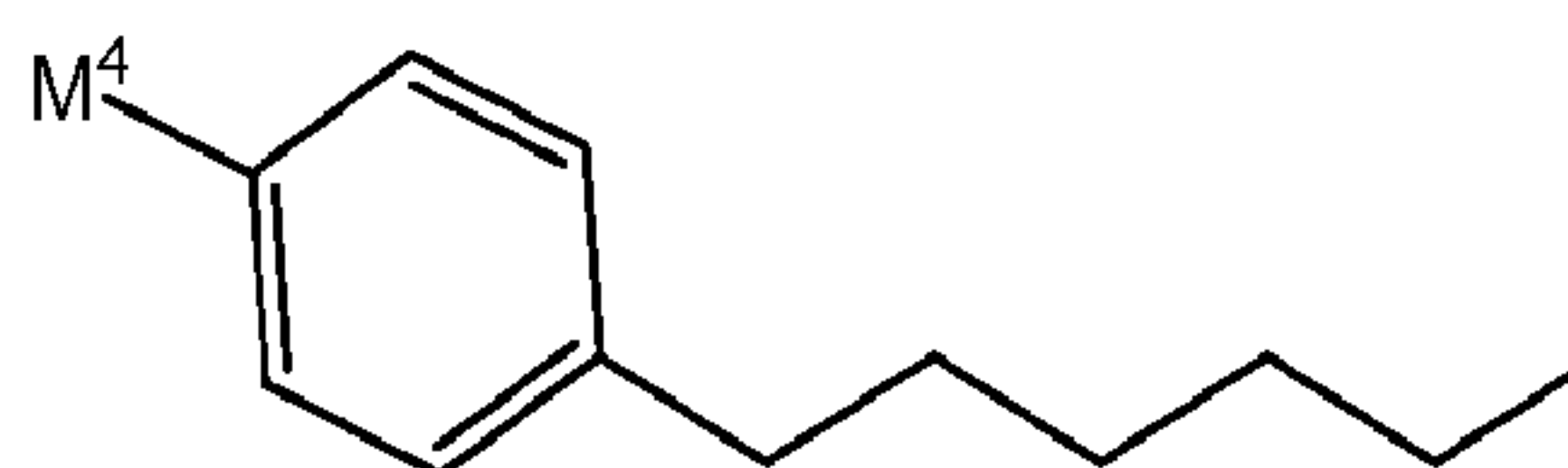
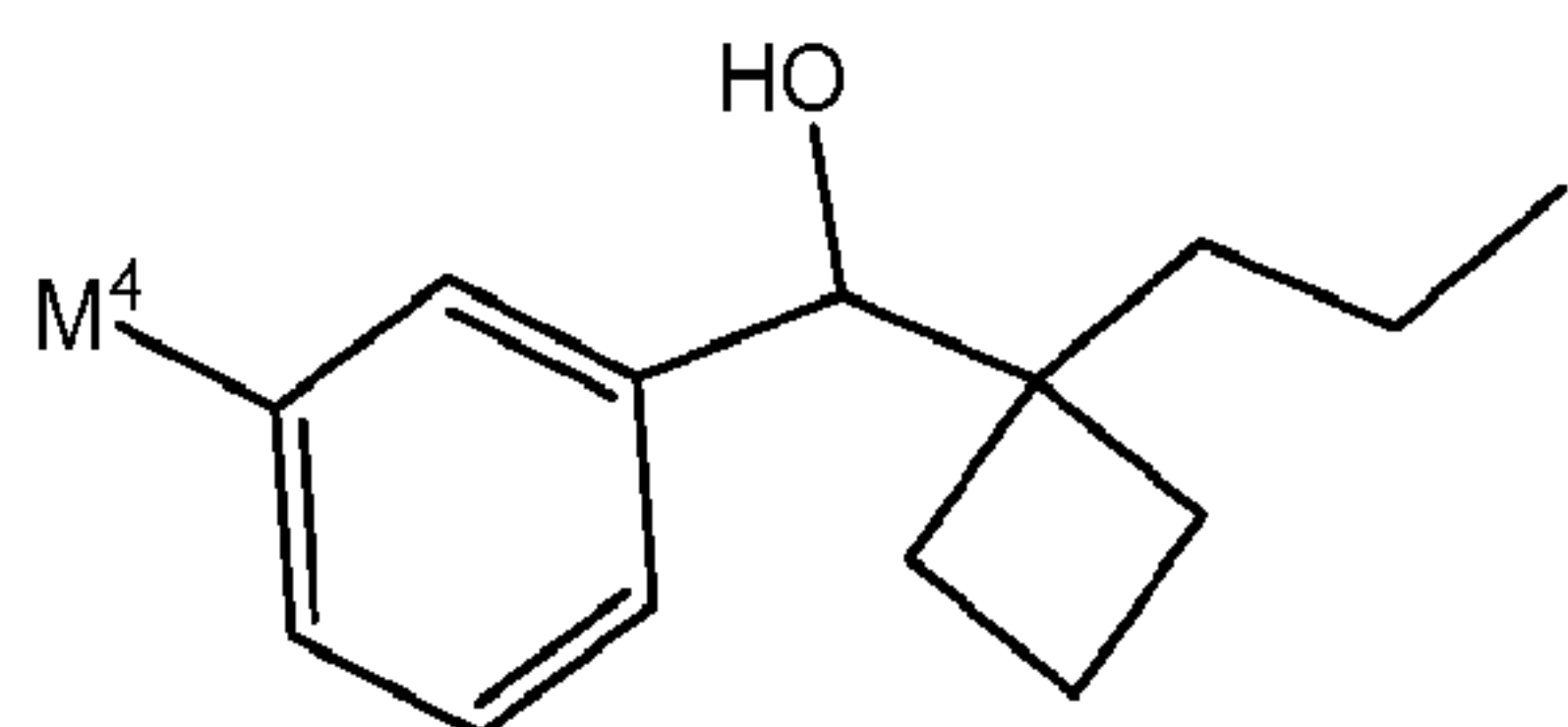
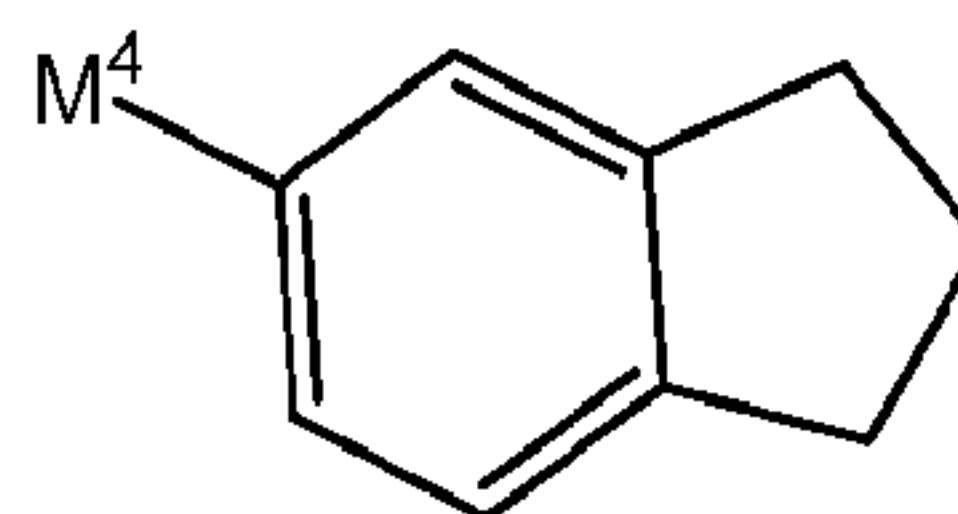
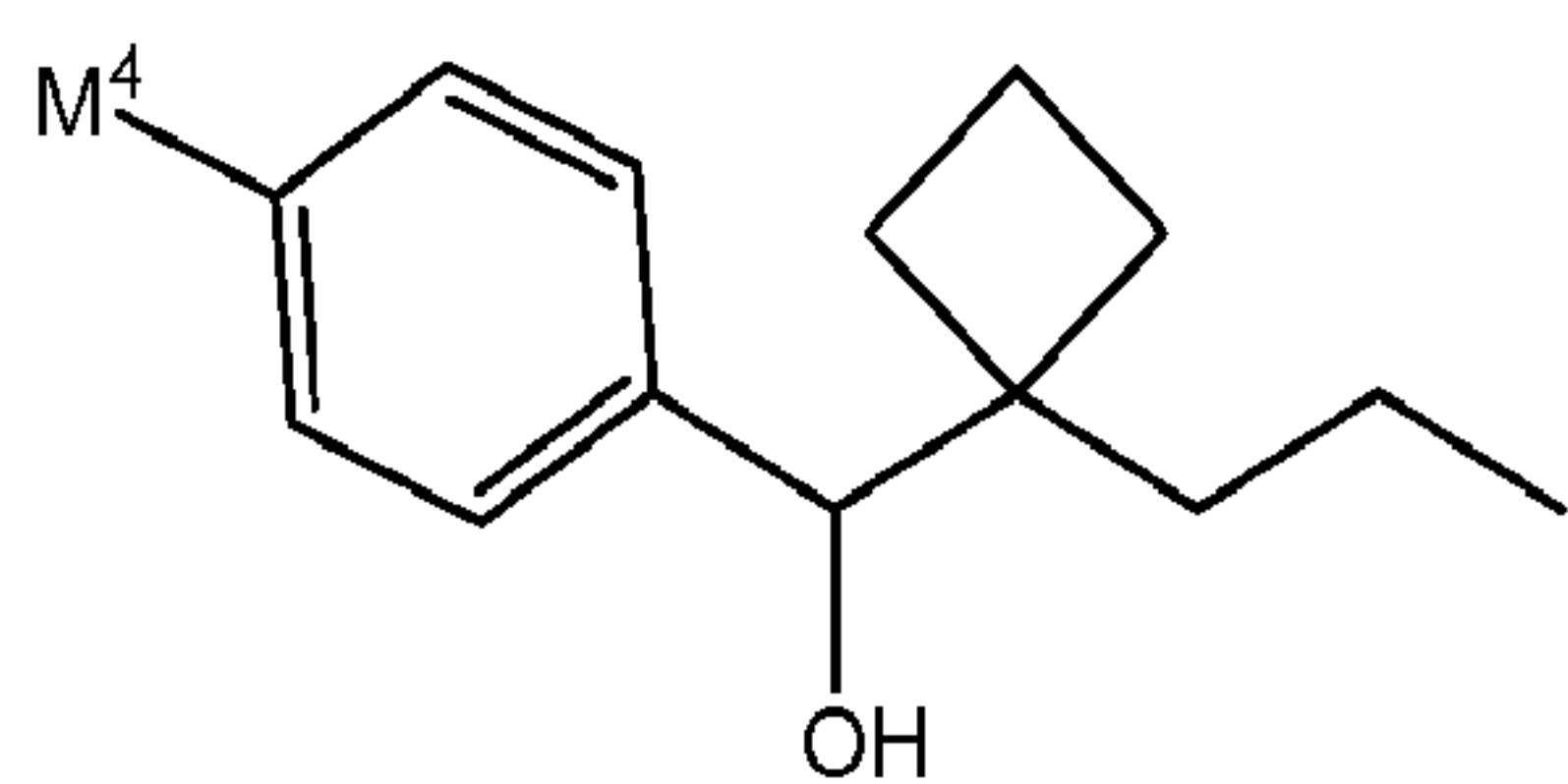
Examples are -CH₂-Phenyl, -CH₂-CH₂-Phenyl, and the like. Arylalkyl may or may not be hydrocarbyl, depending upon whether the aryl portion has substituents with heteroatoms.

- 15 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.

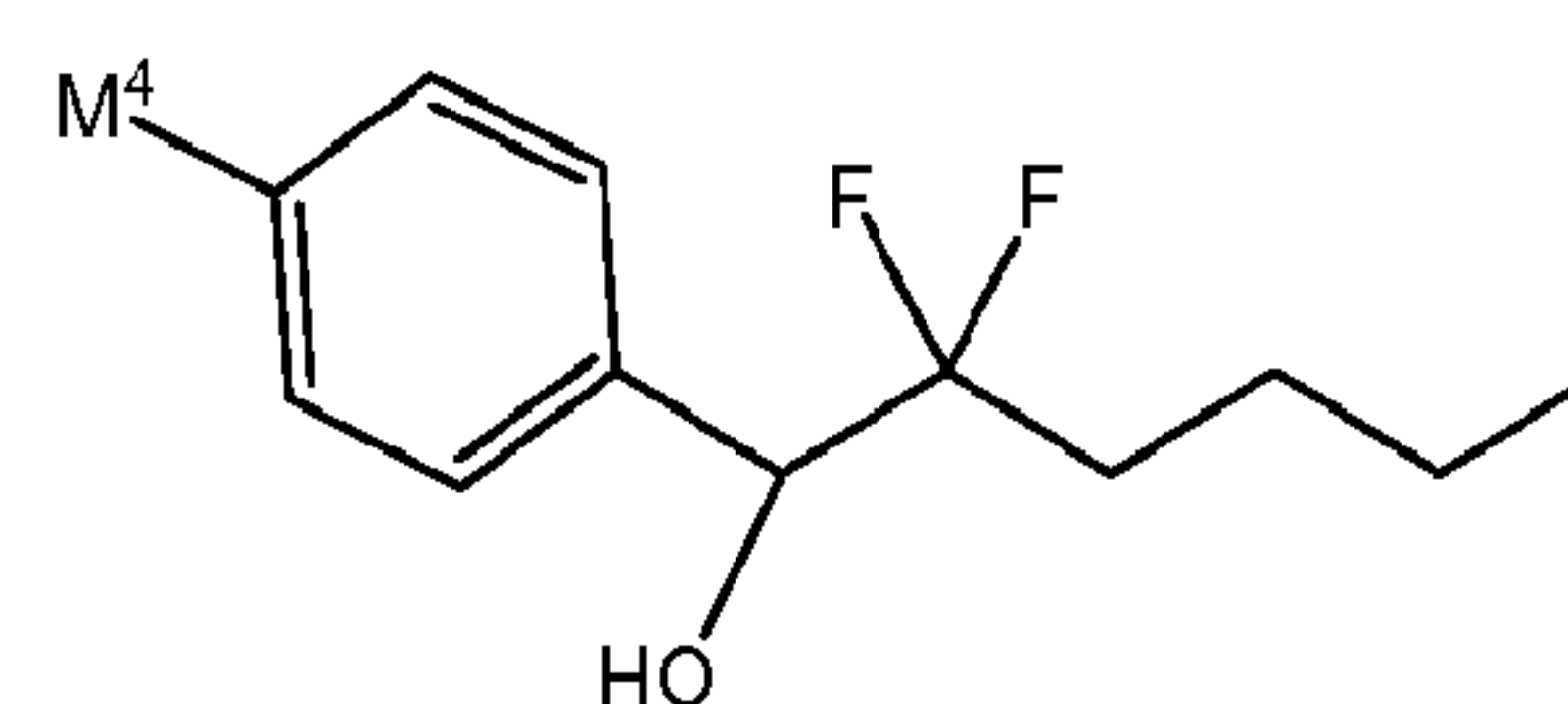
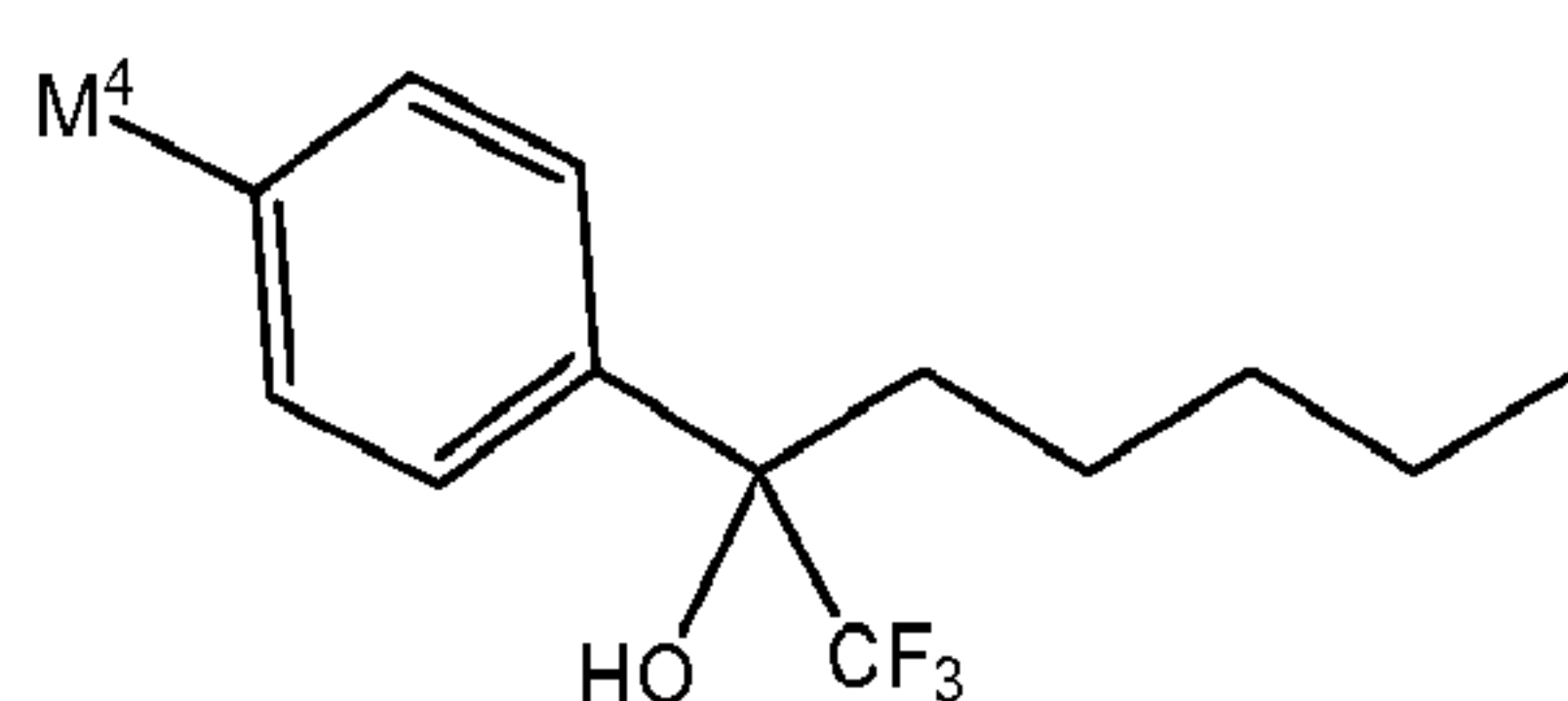
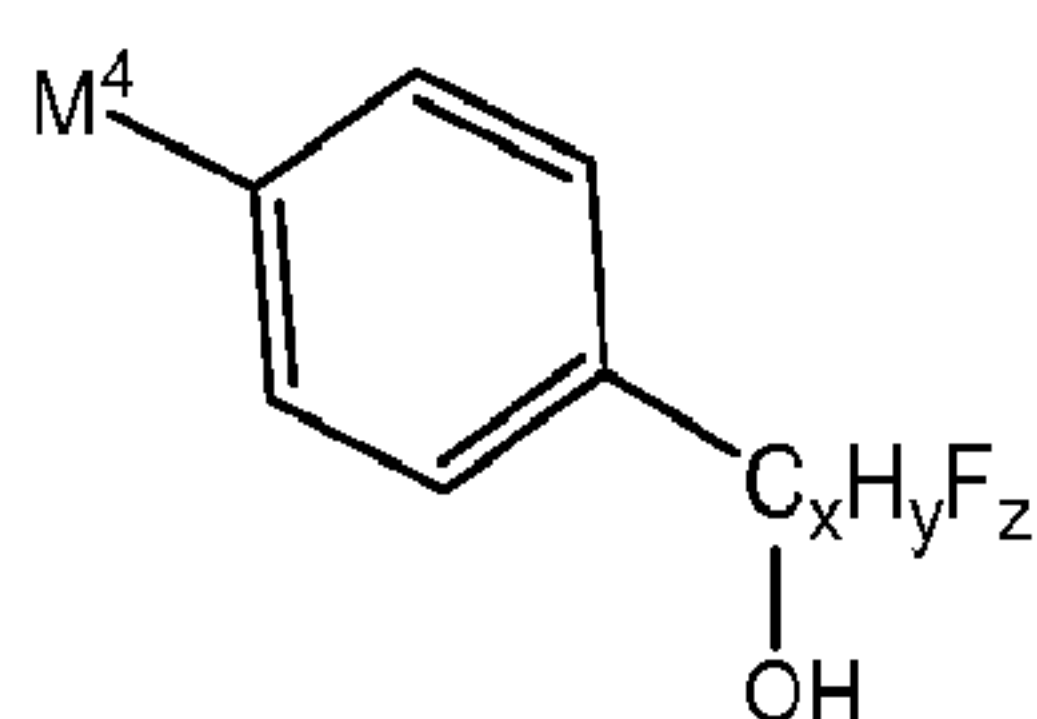
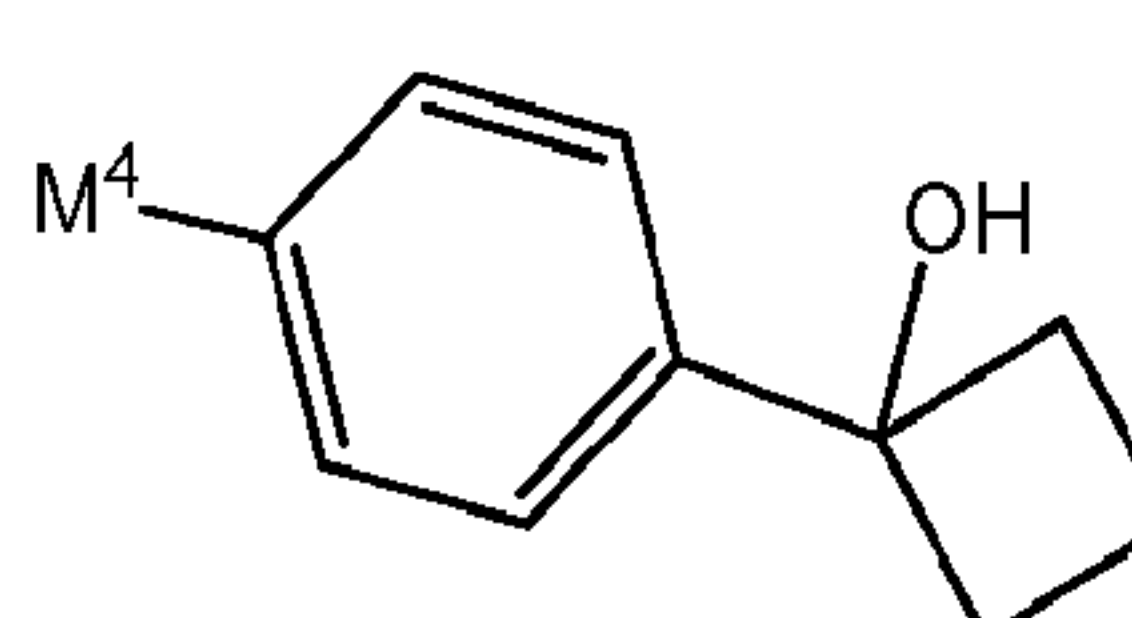
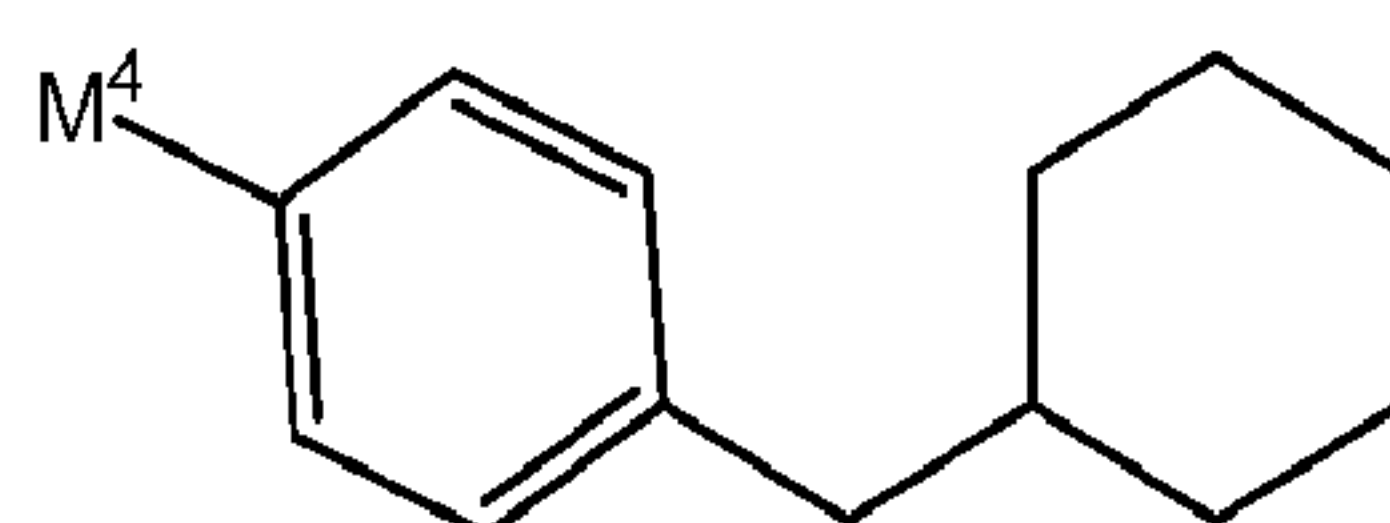
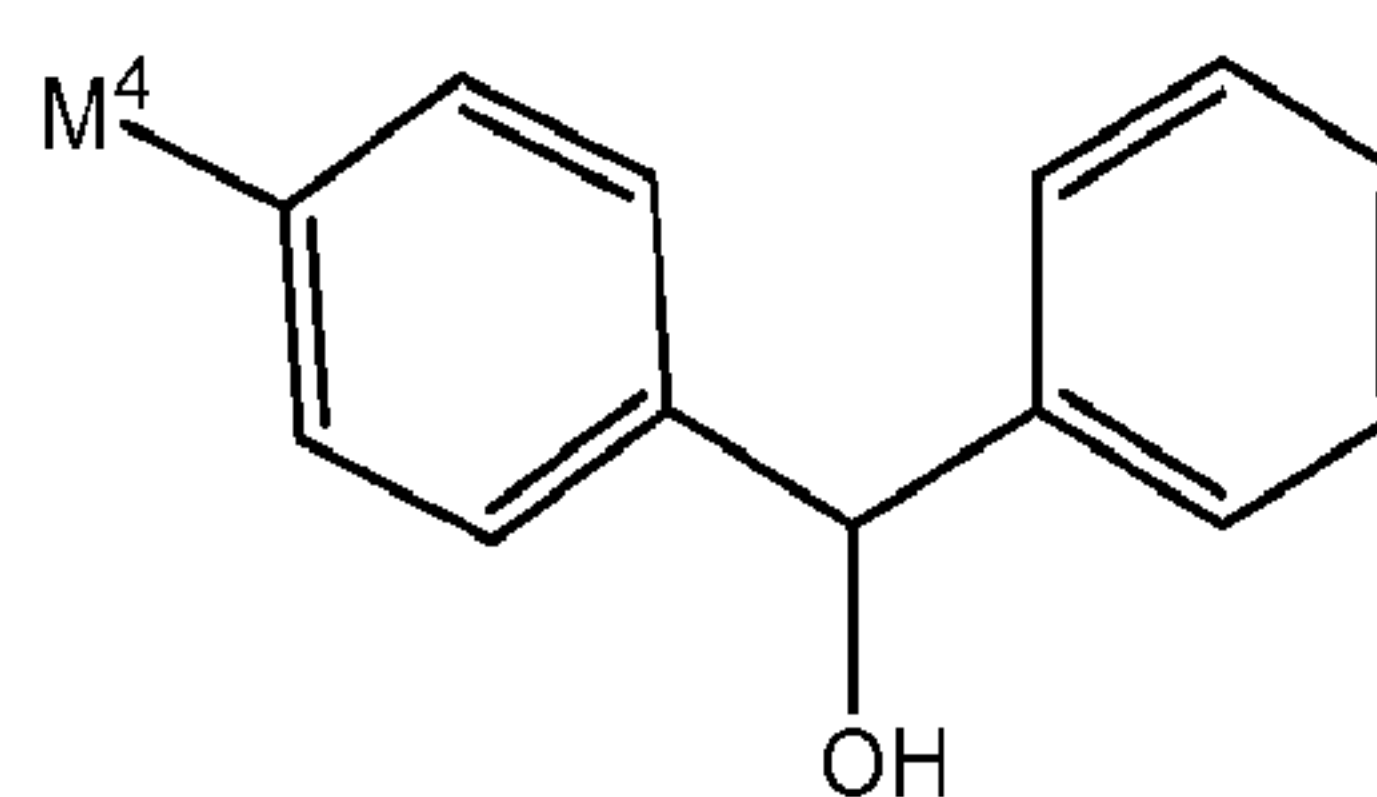
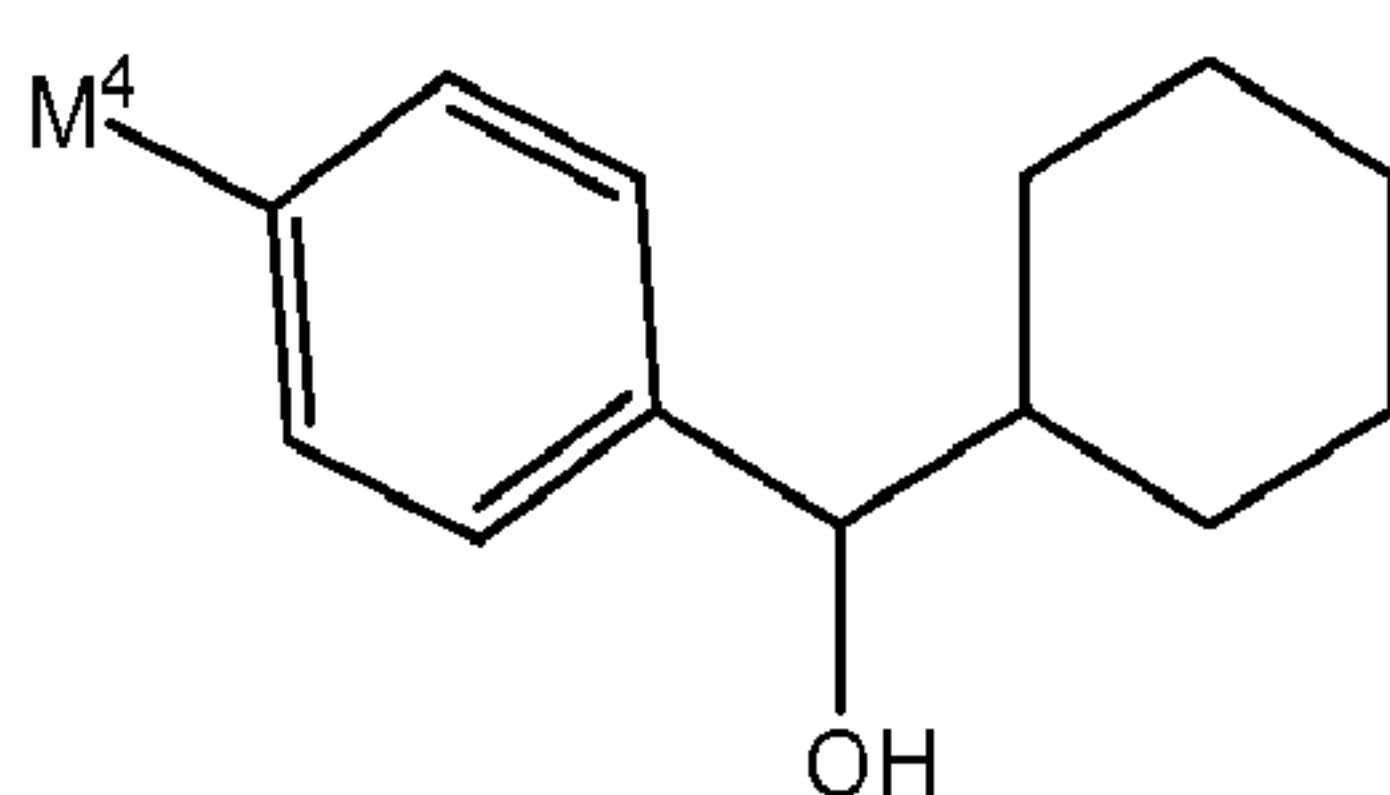
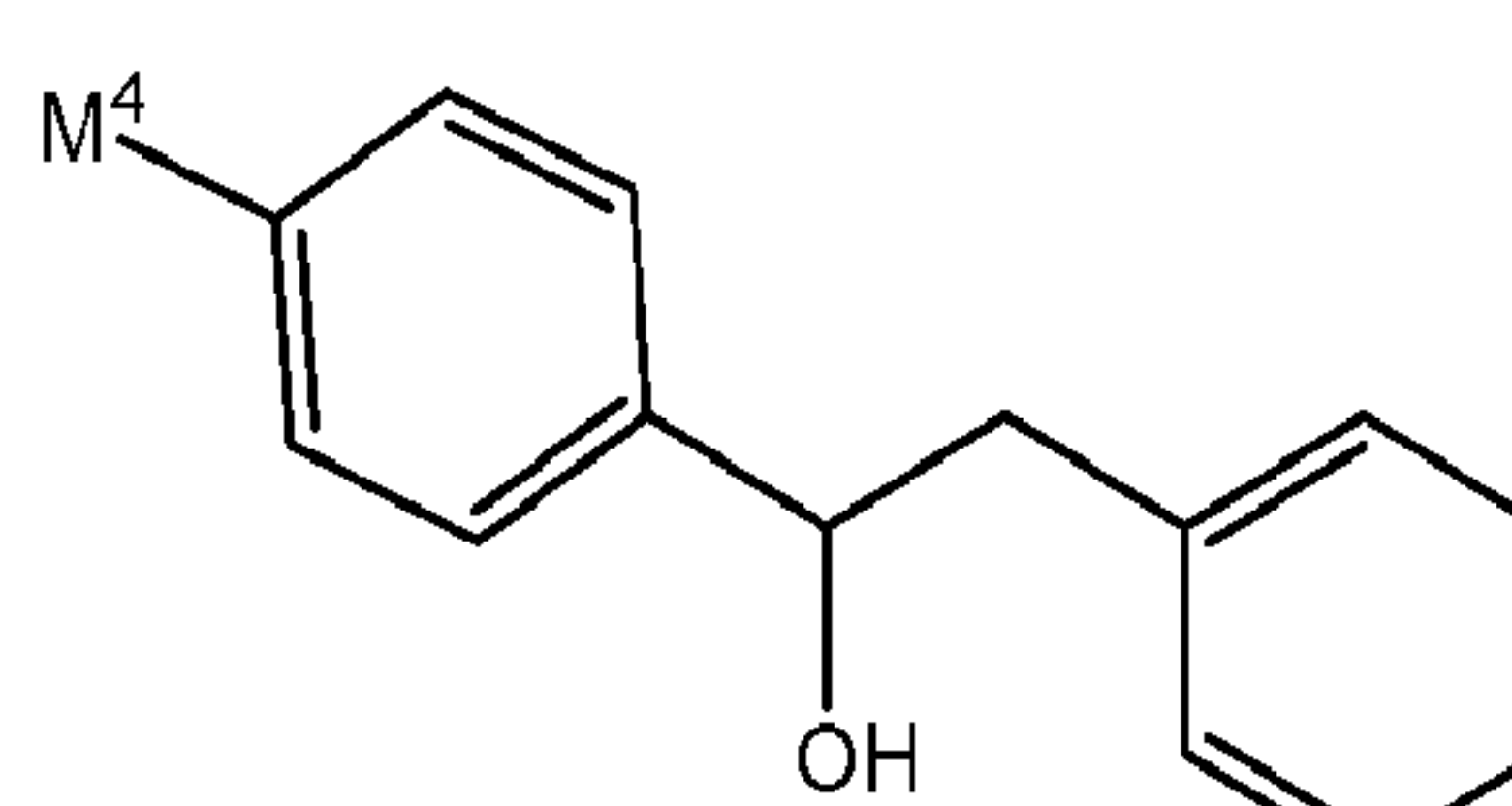
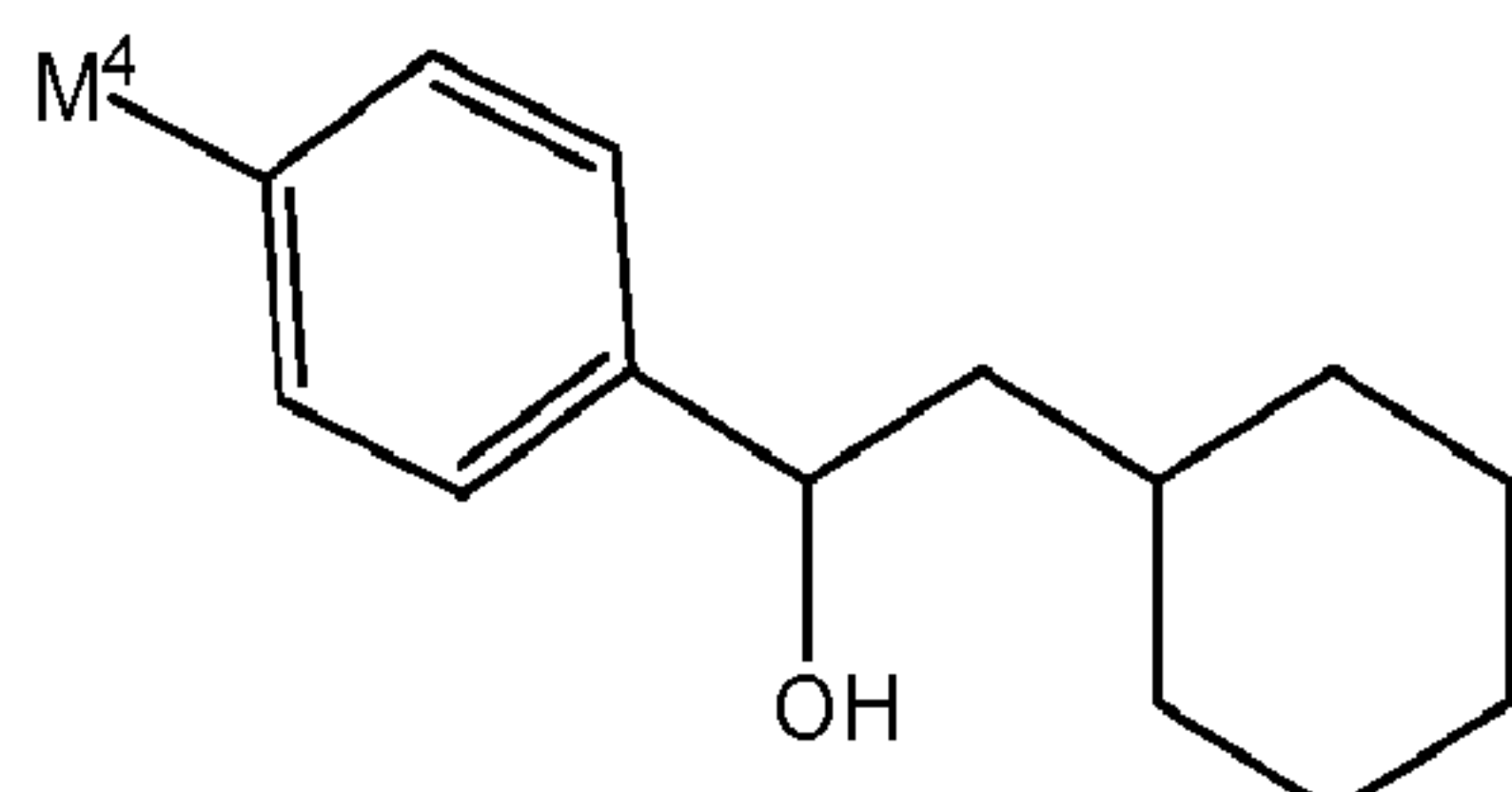
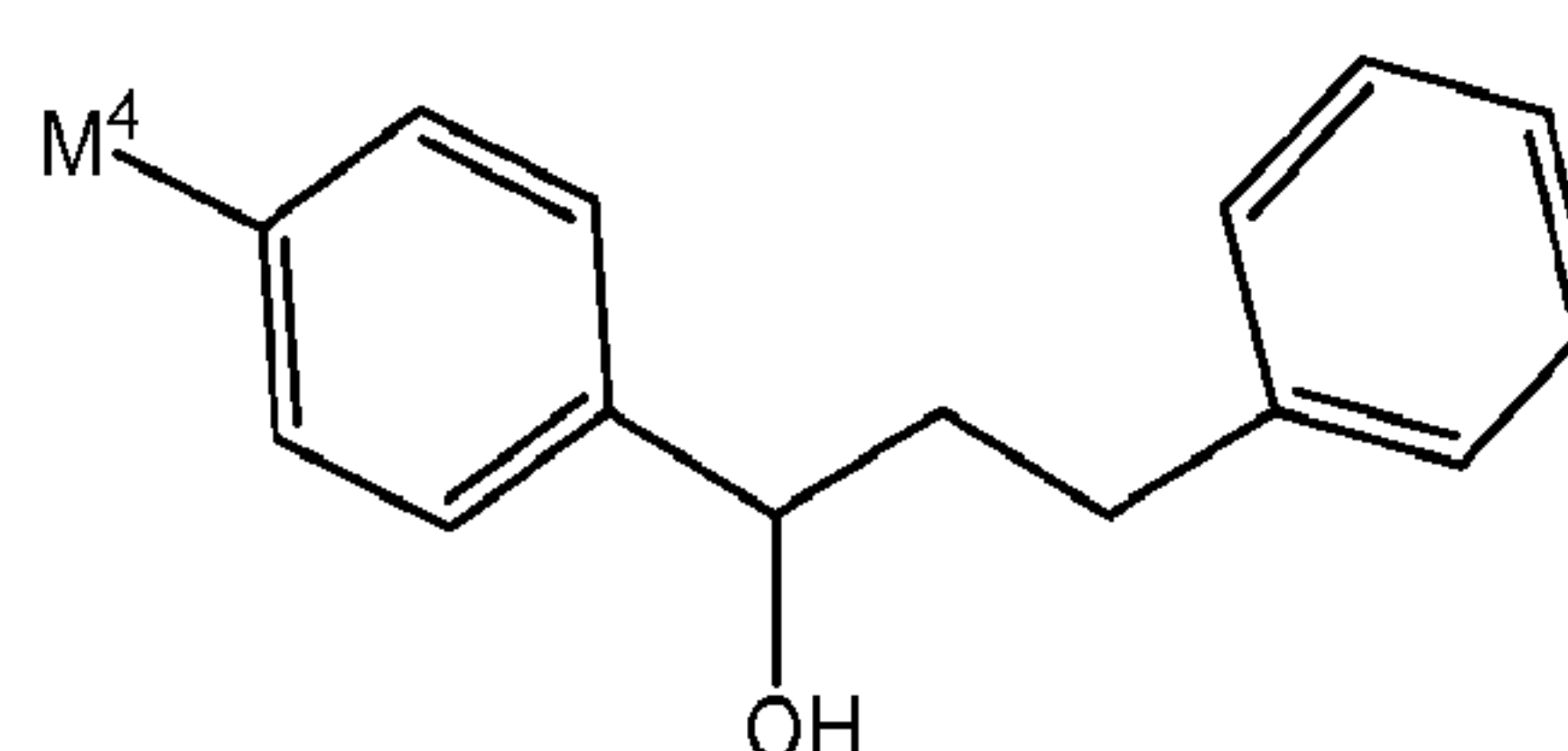
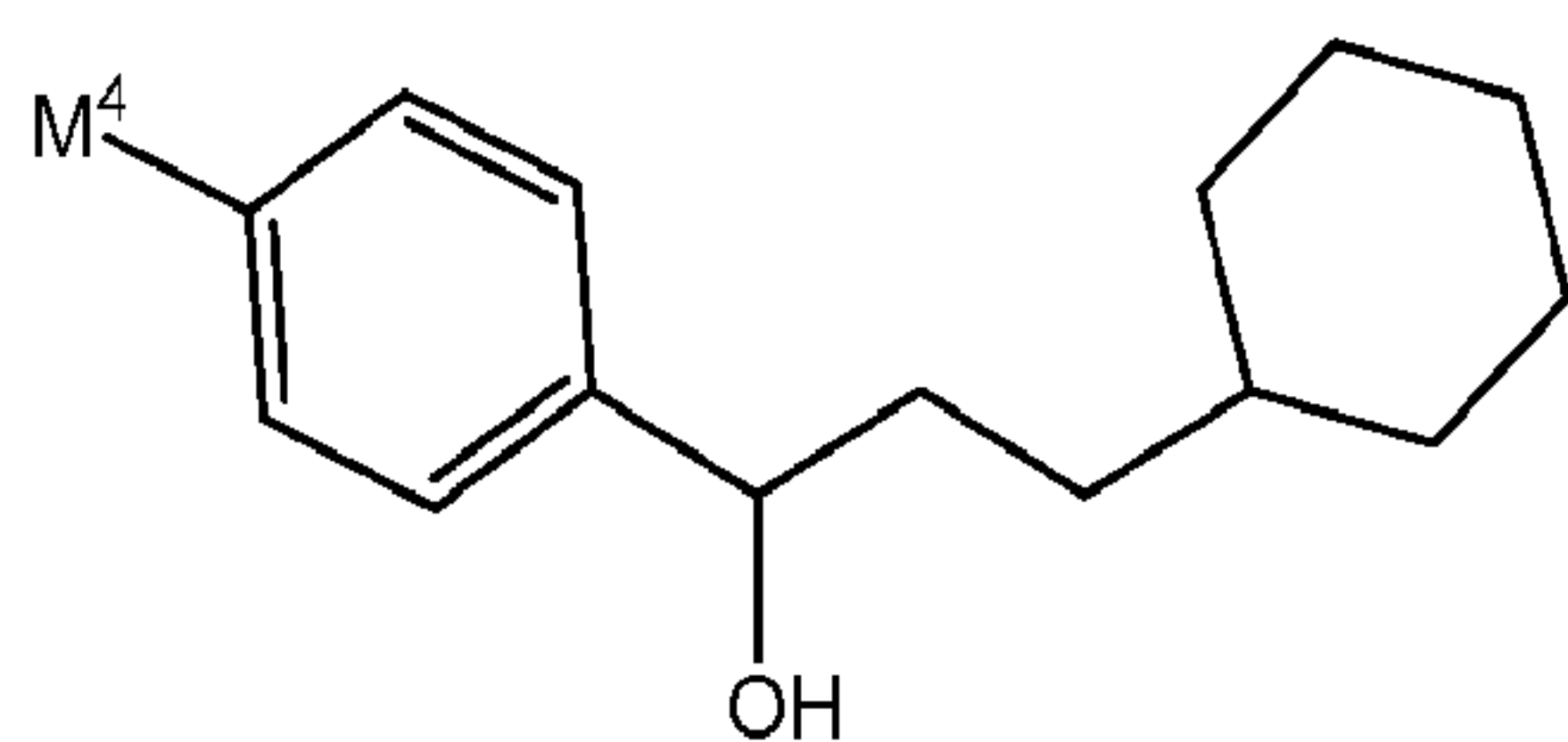
Combinations of the above are also possible.

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.



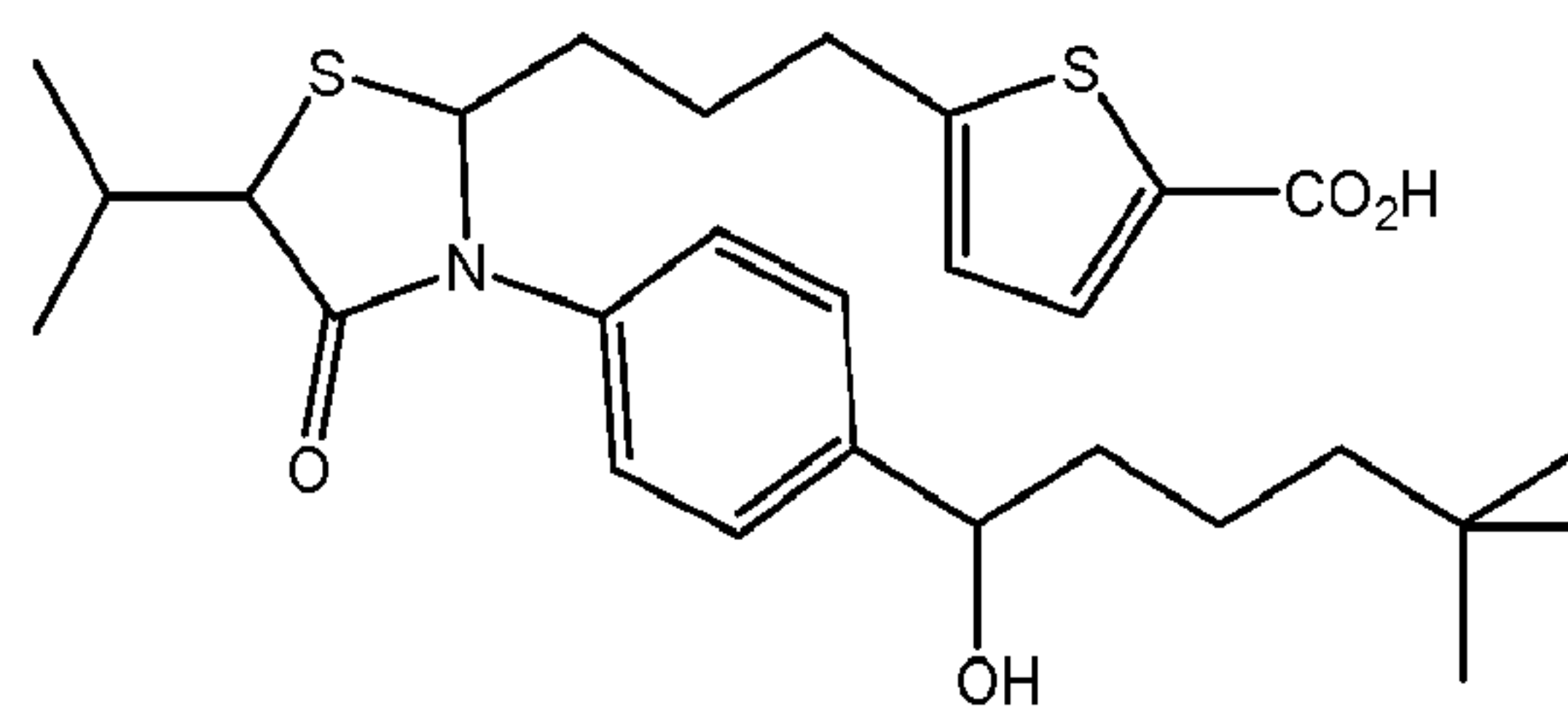
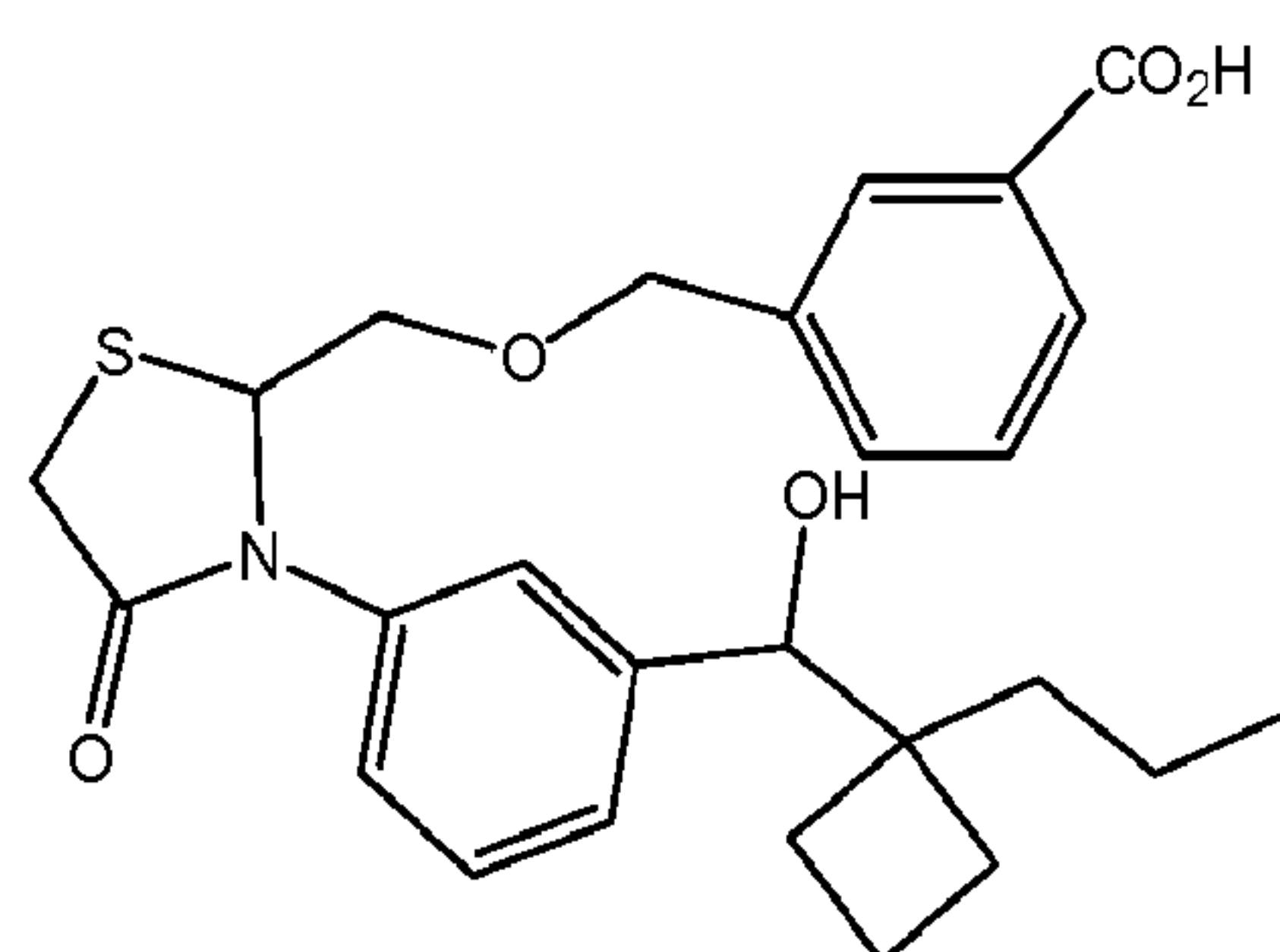
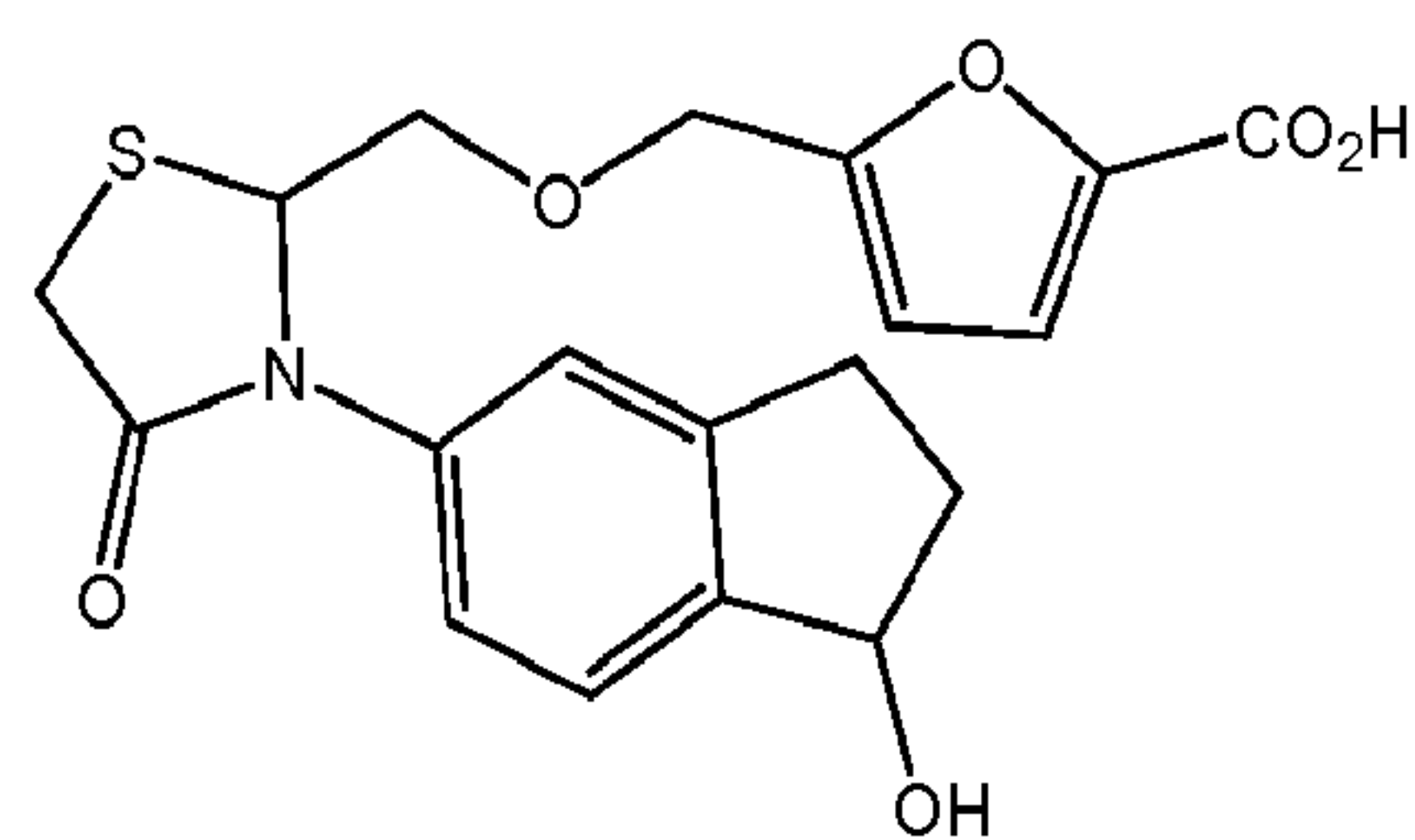
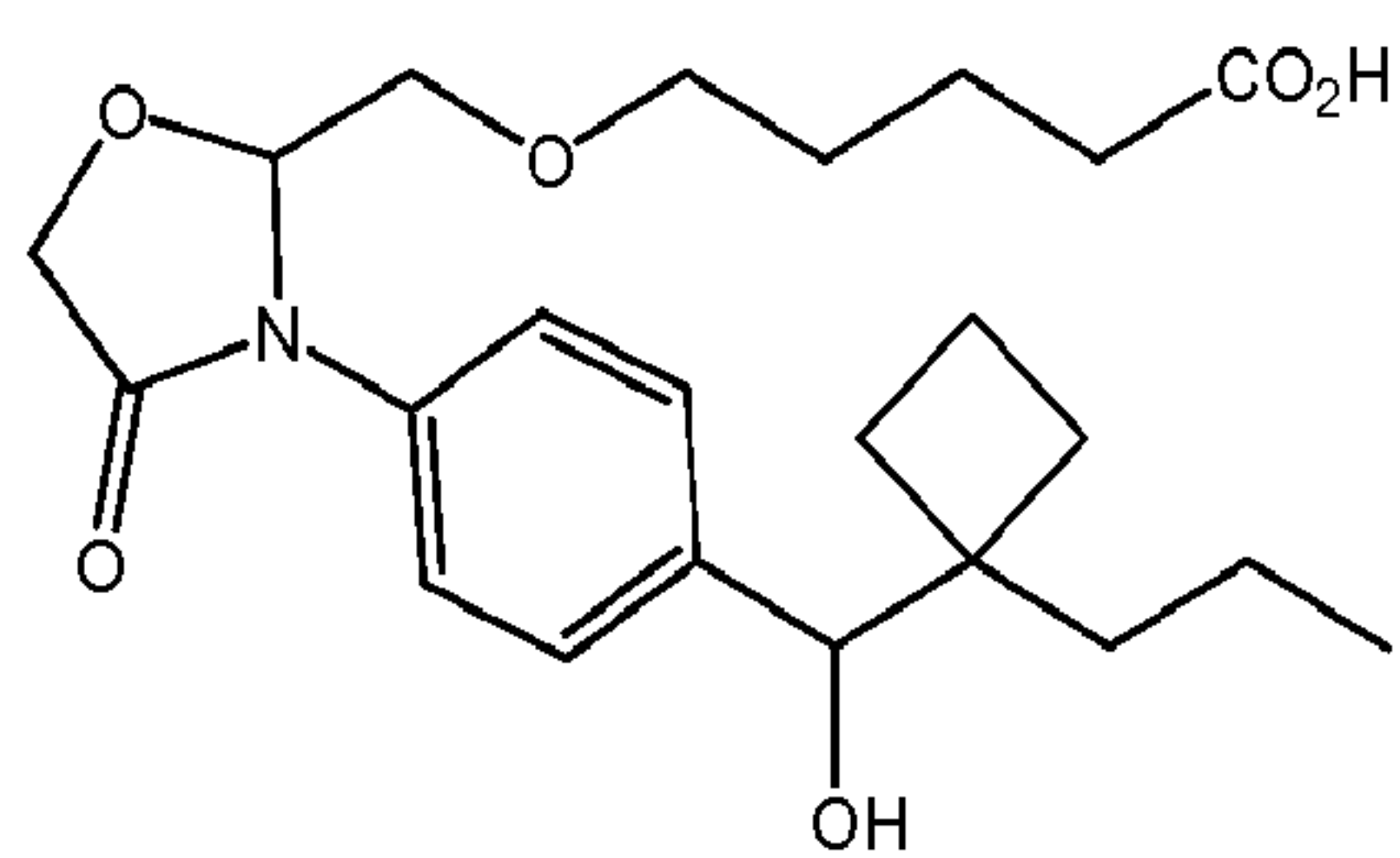
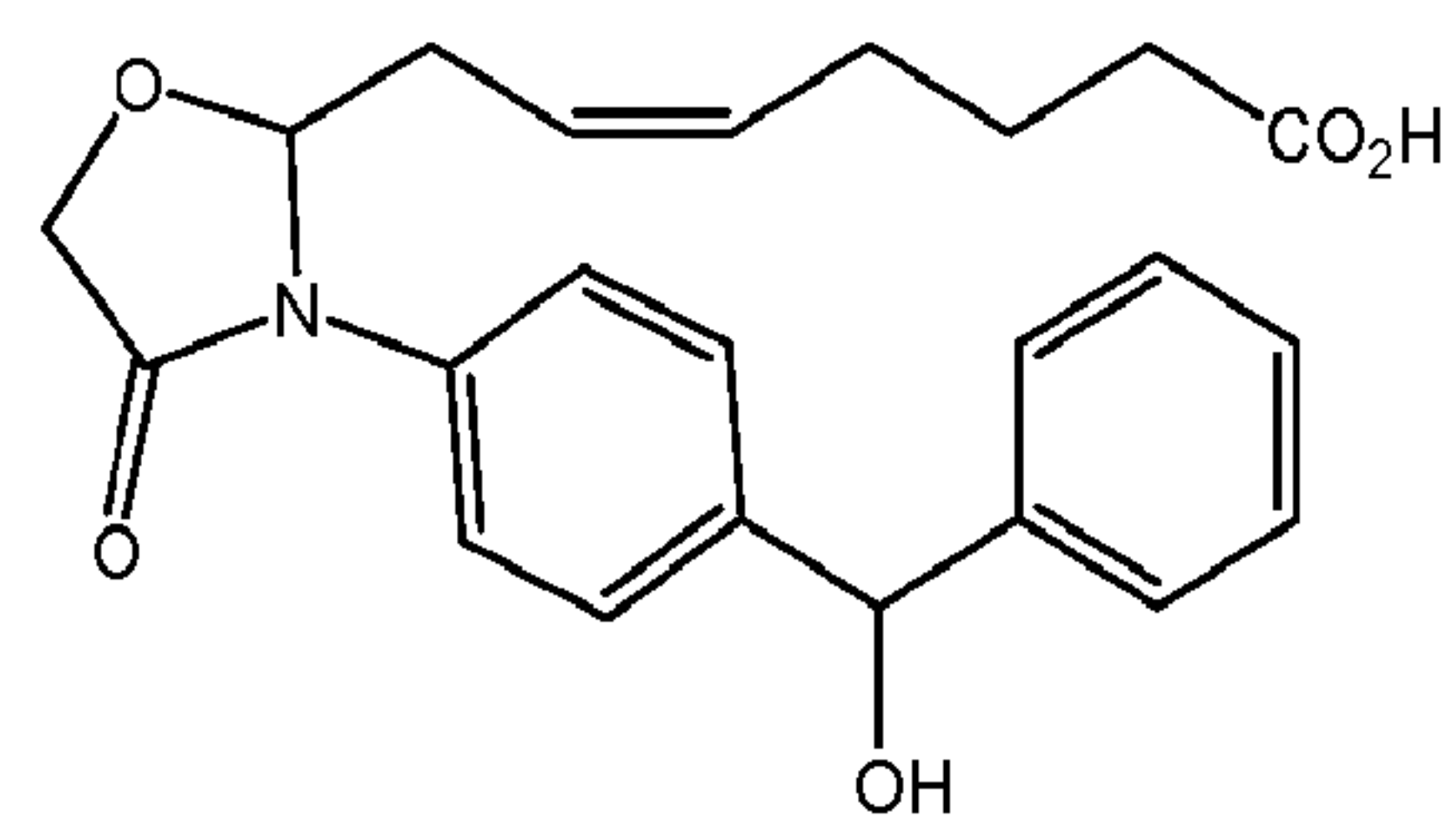
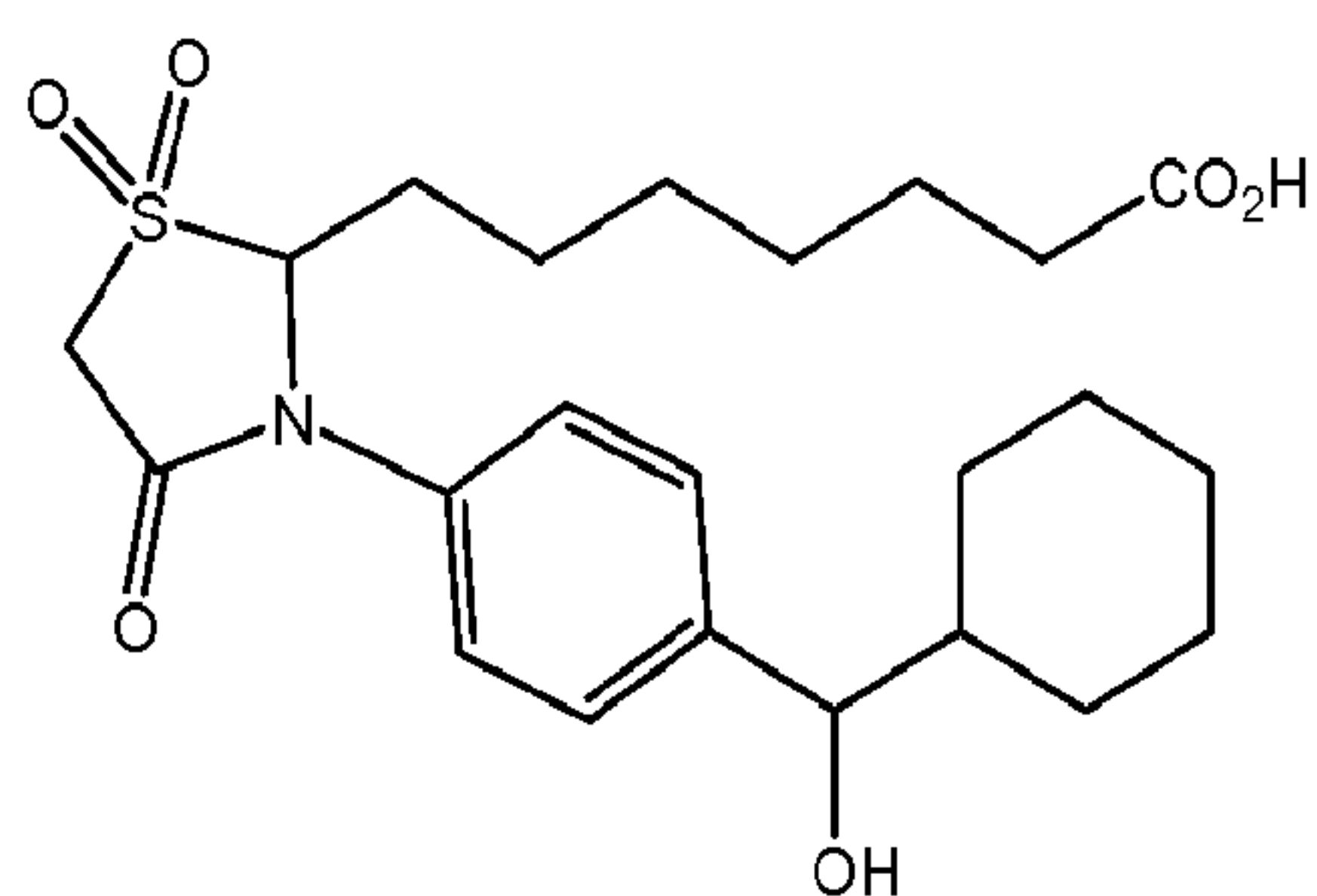
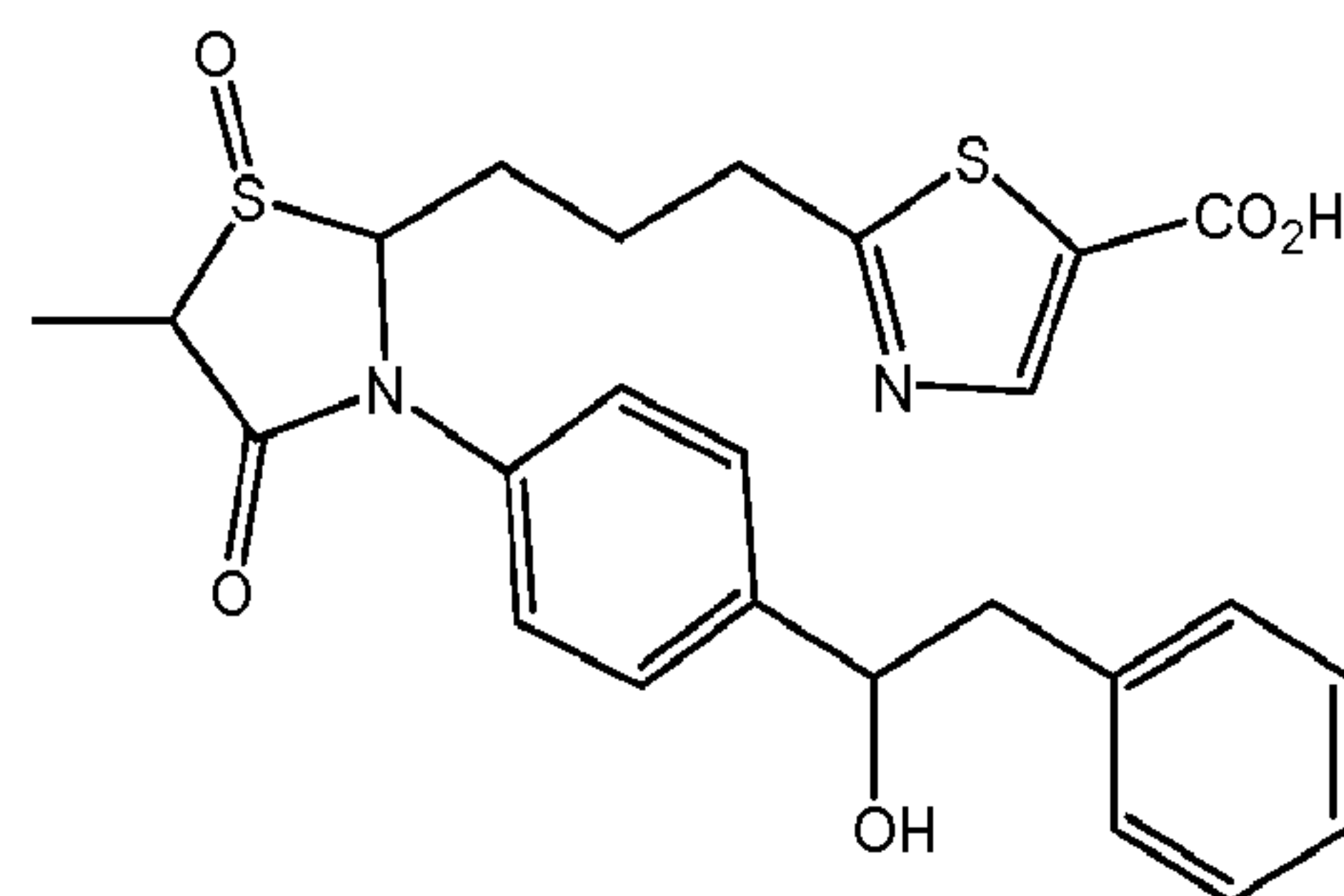
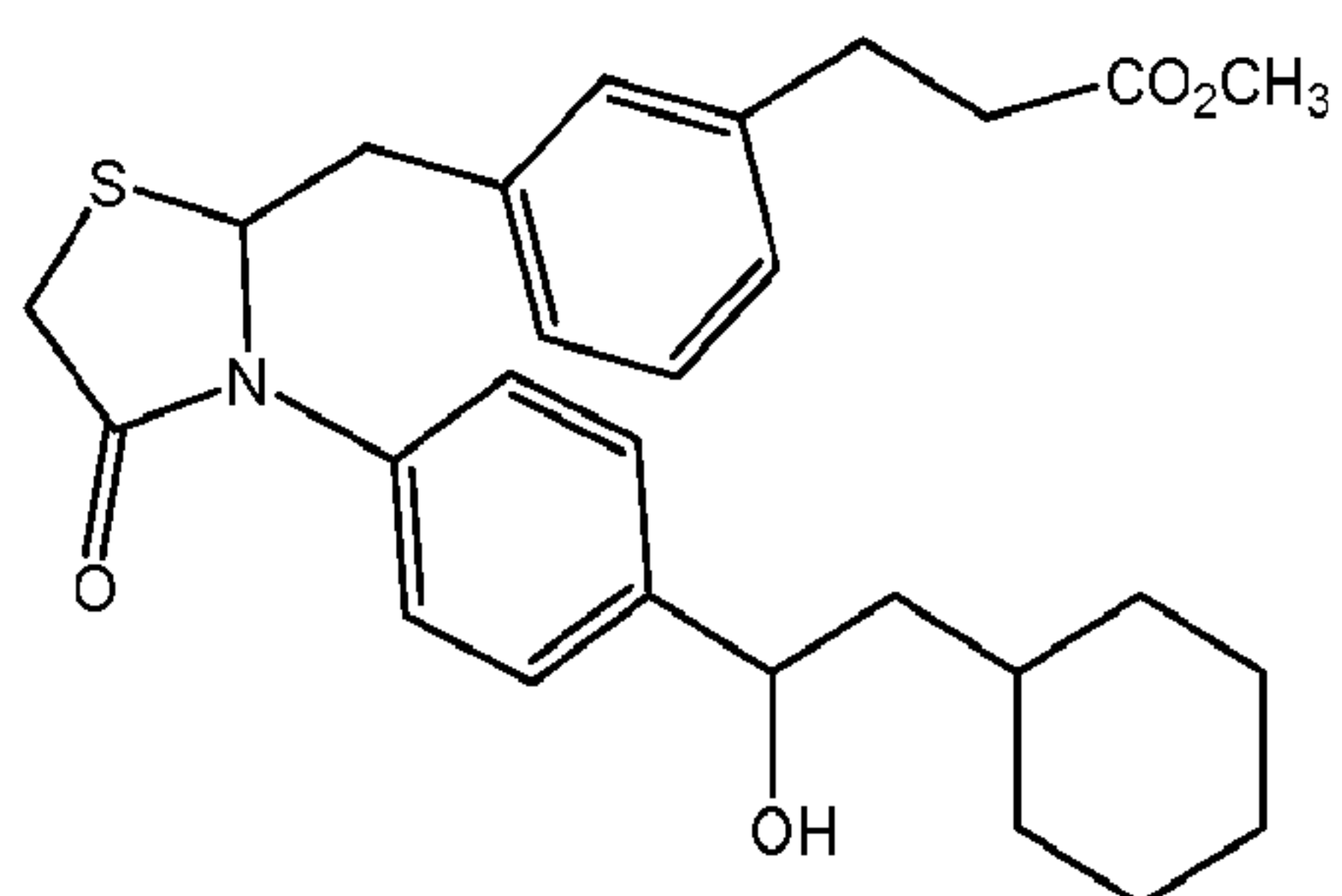
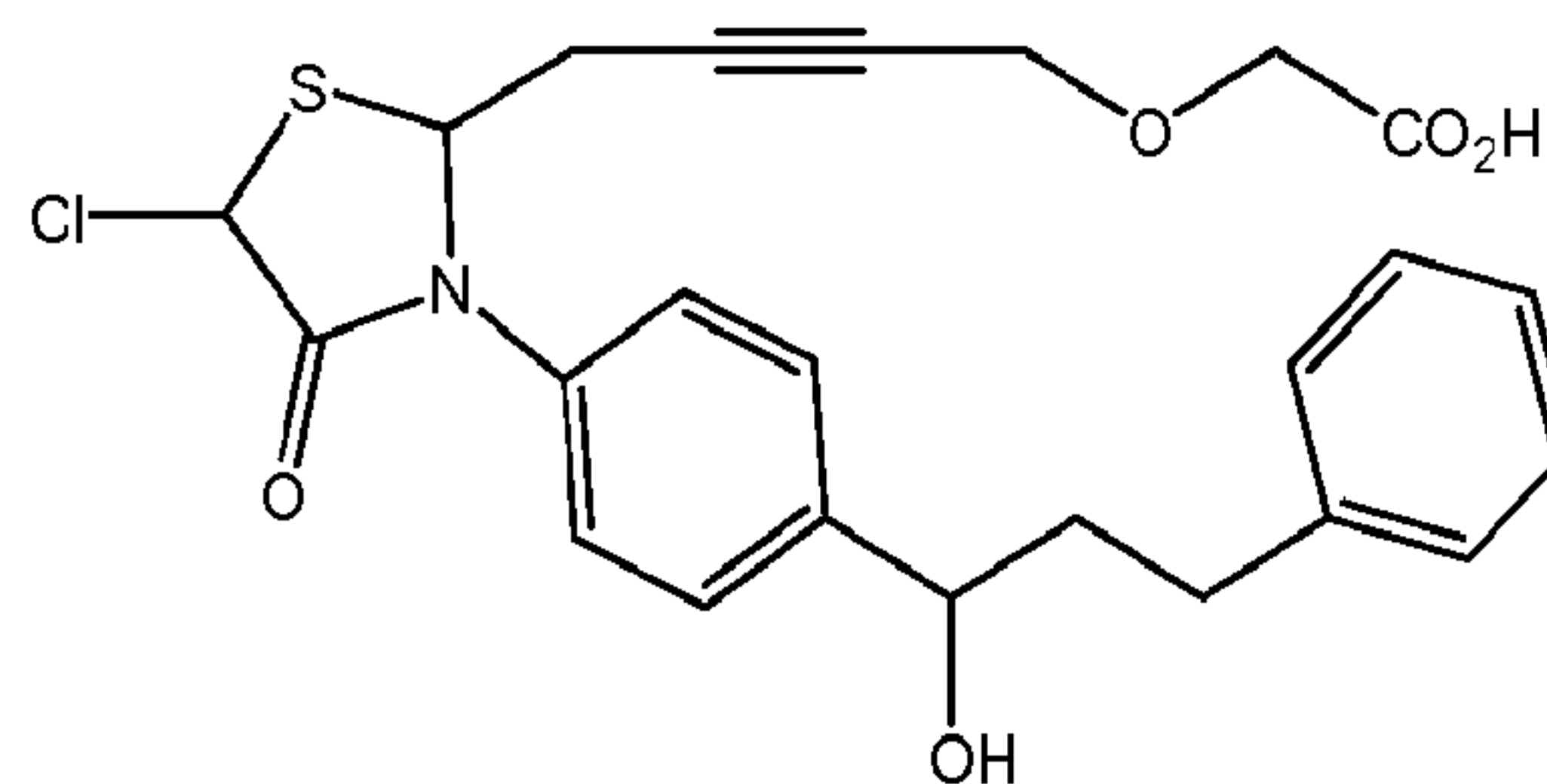
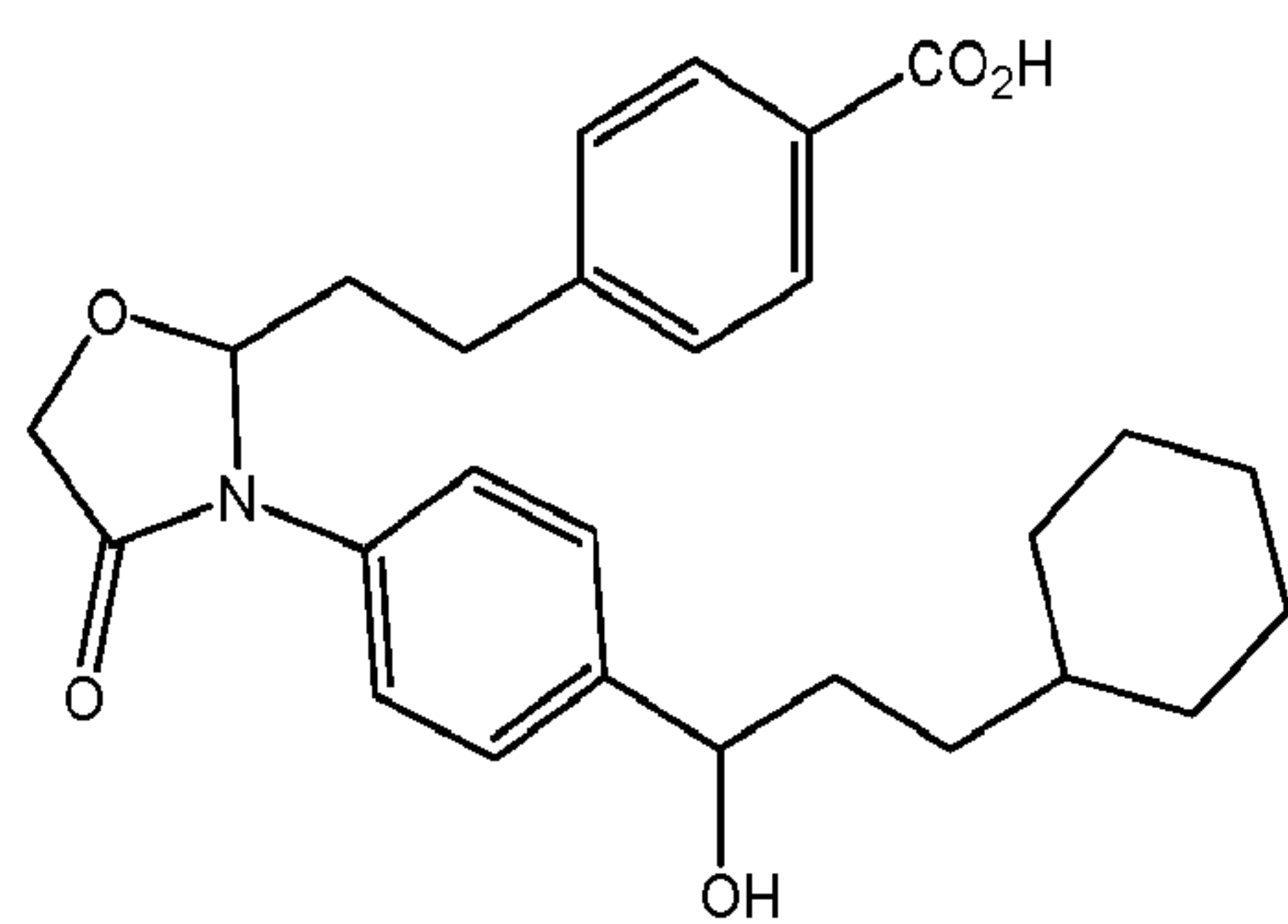


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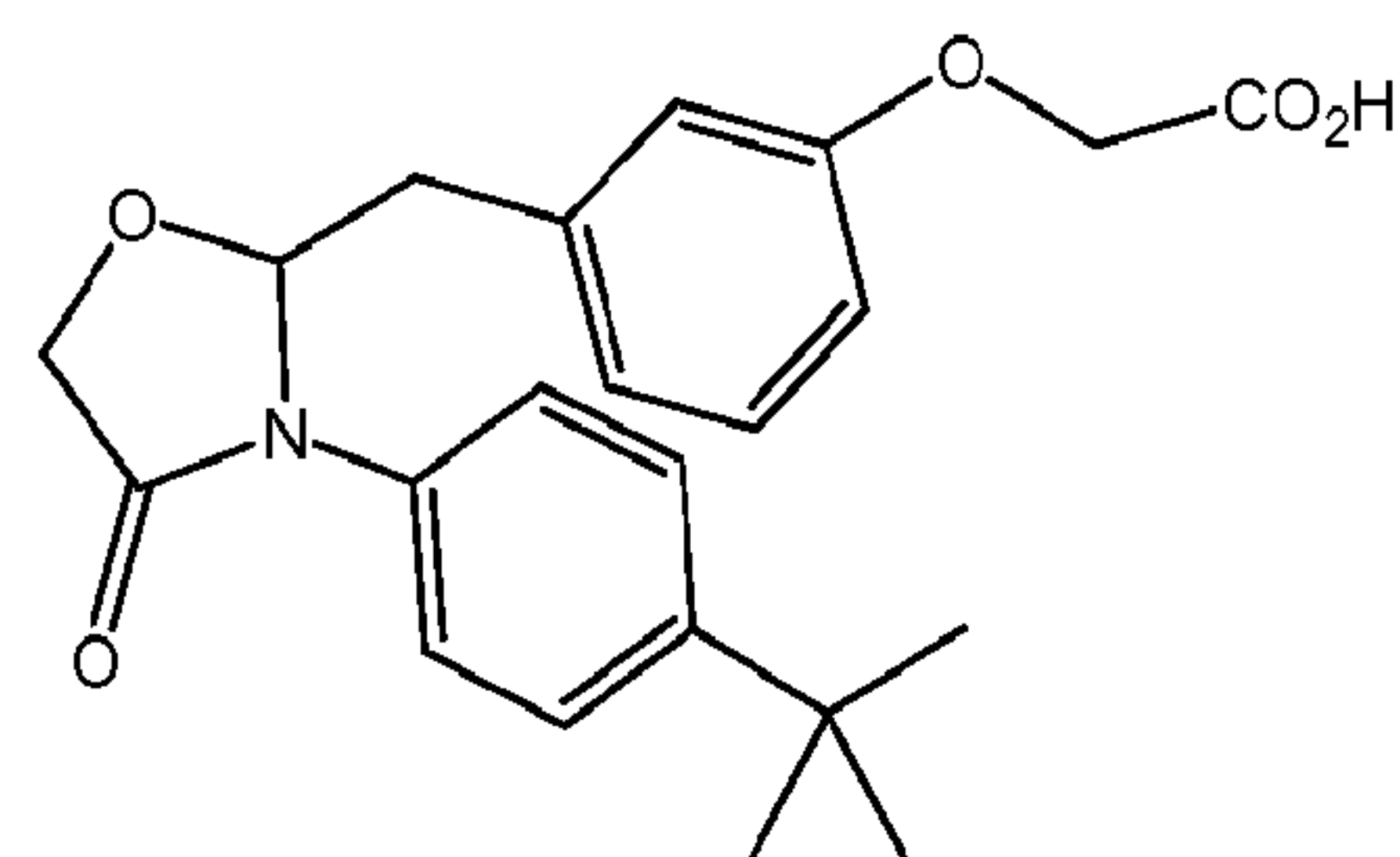
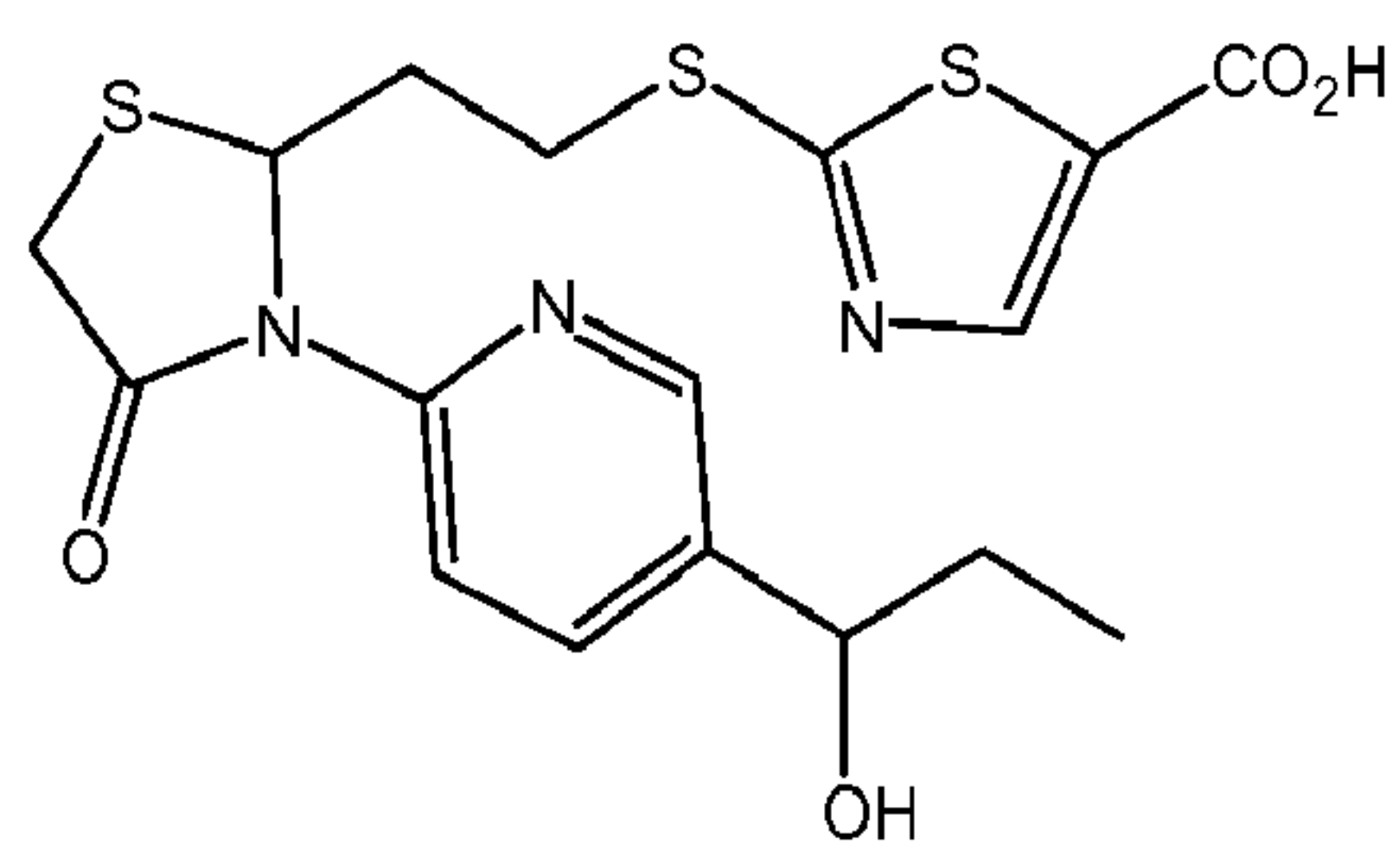
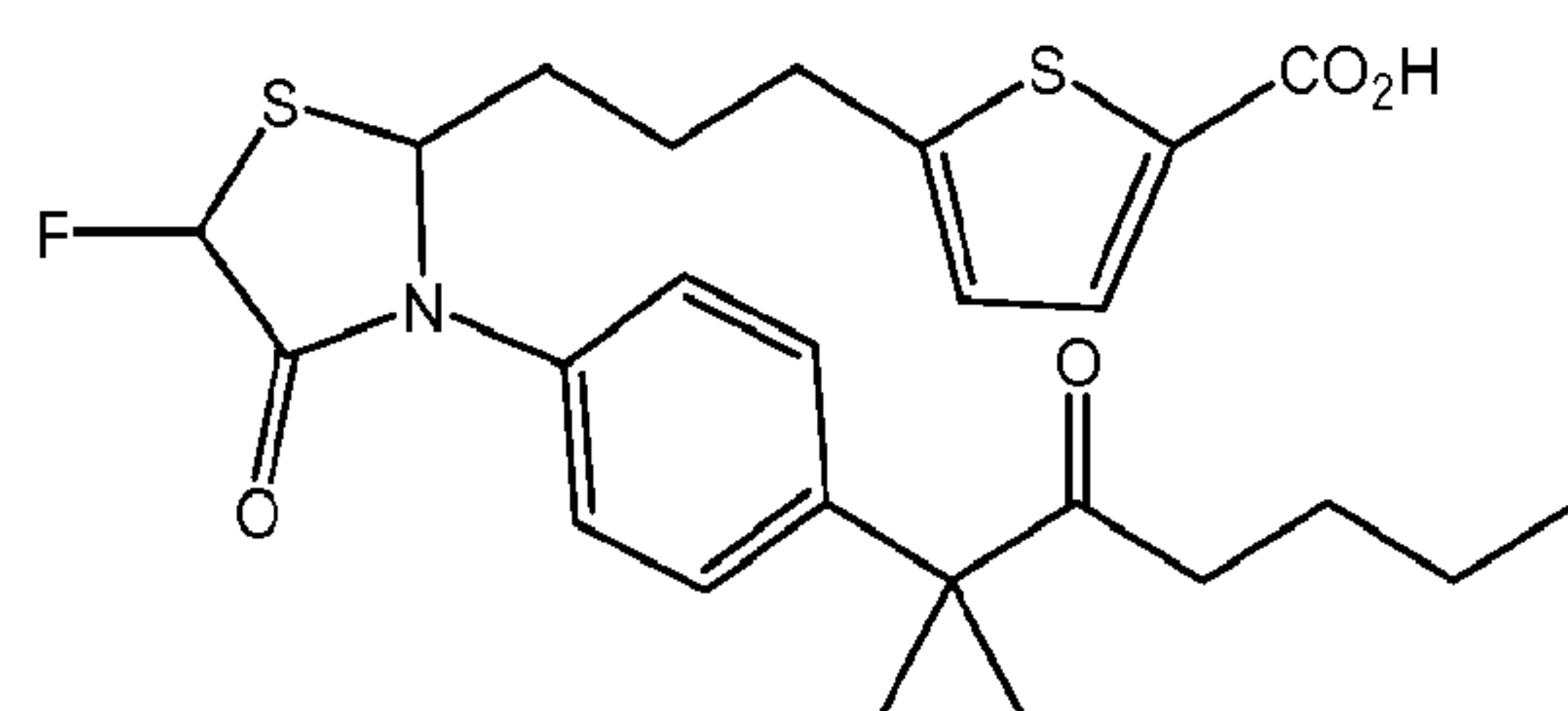
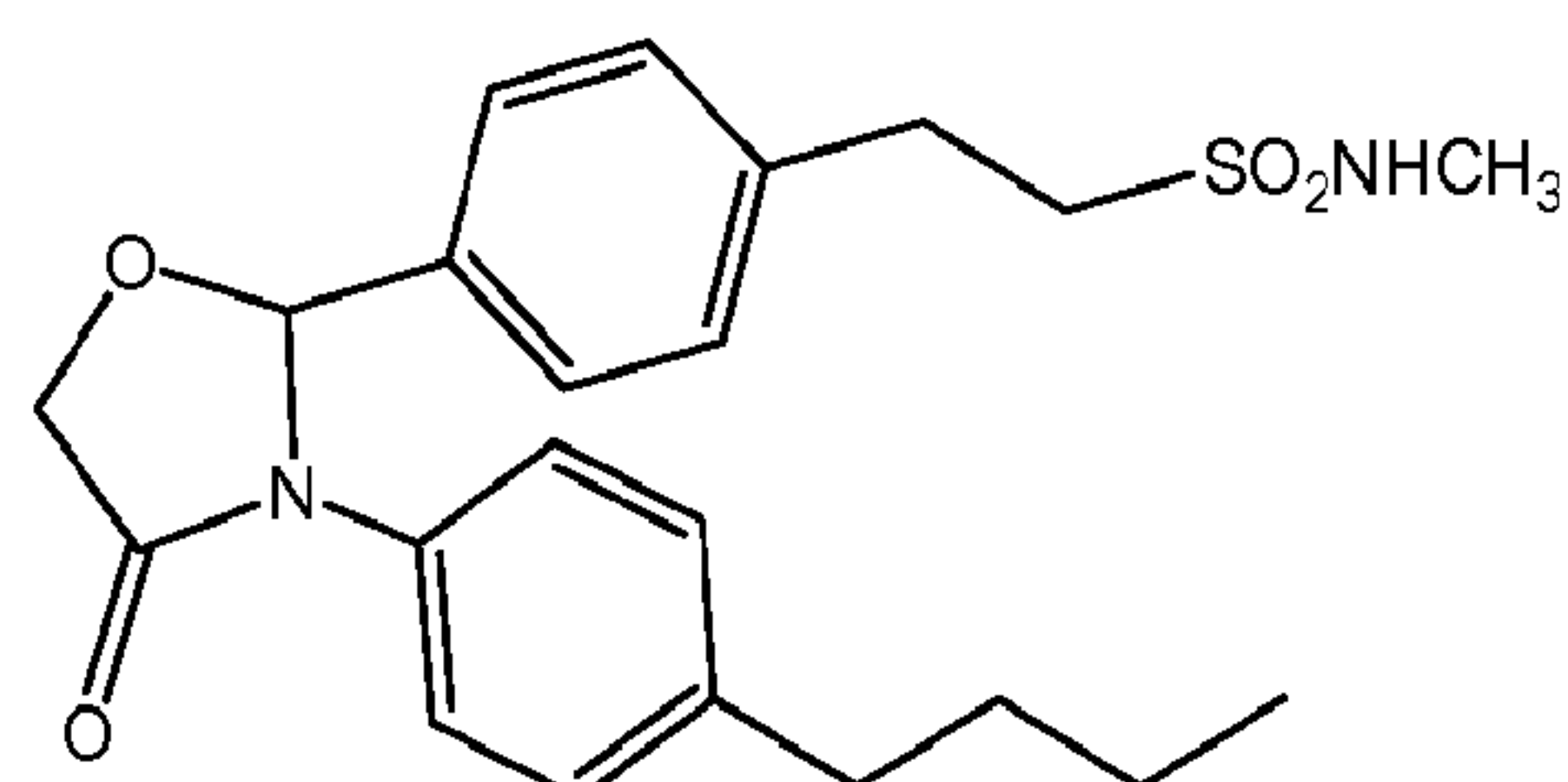
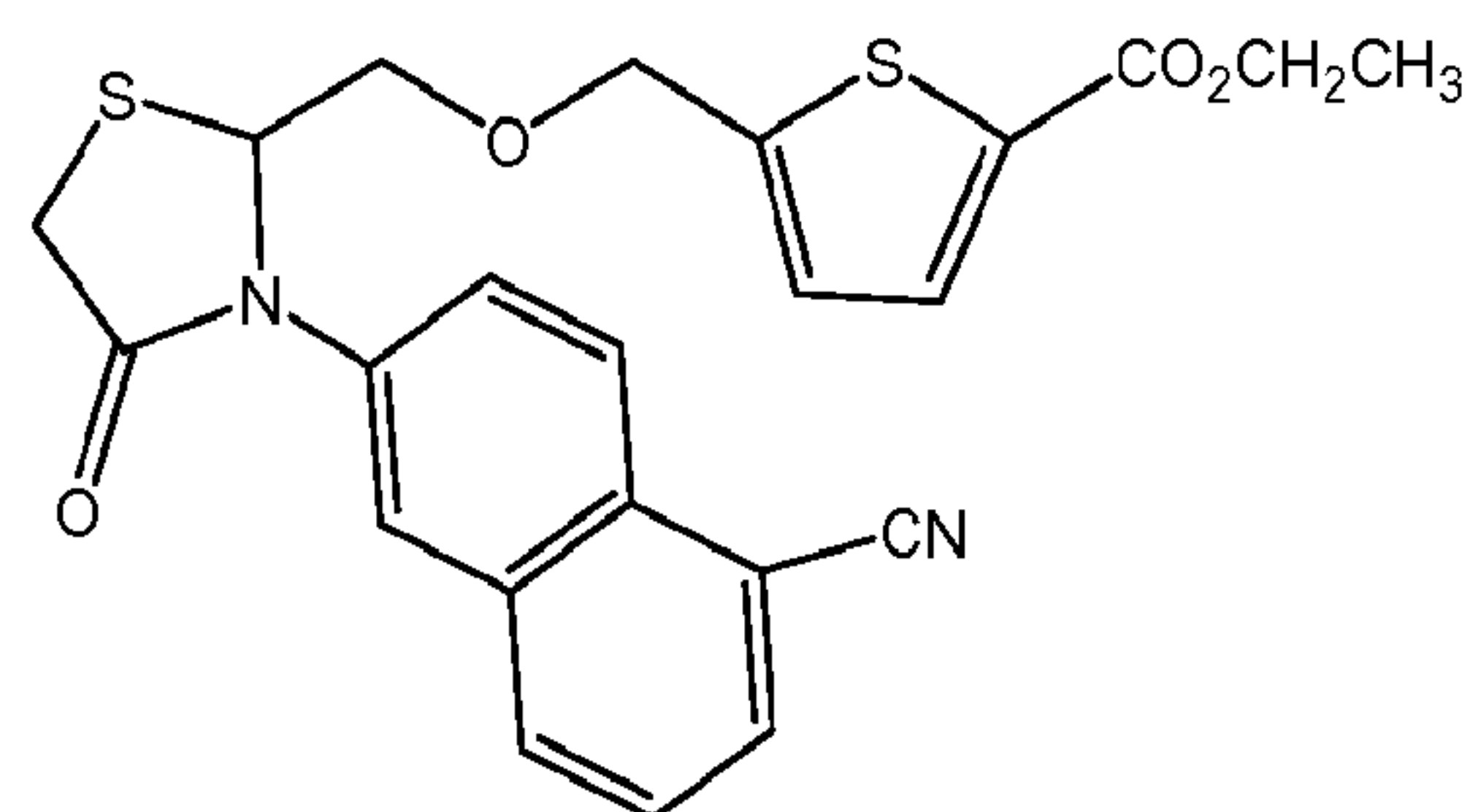
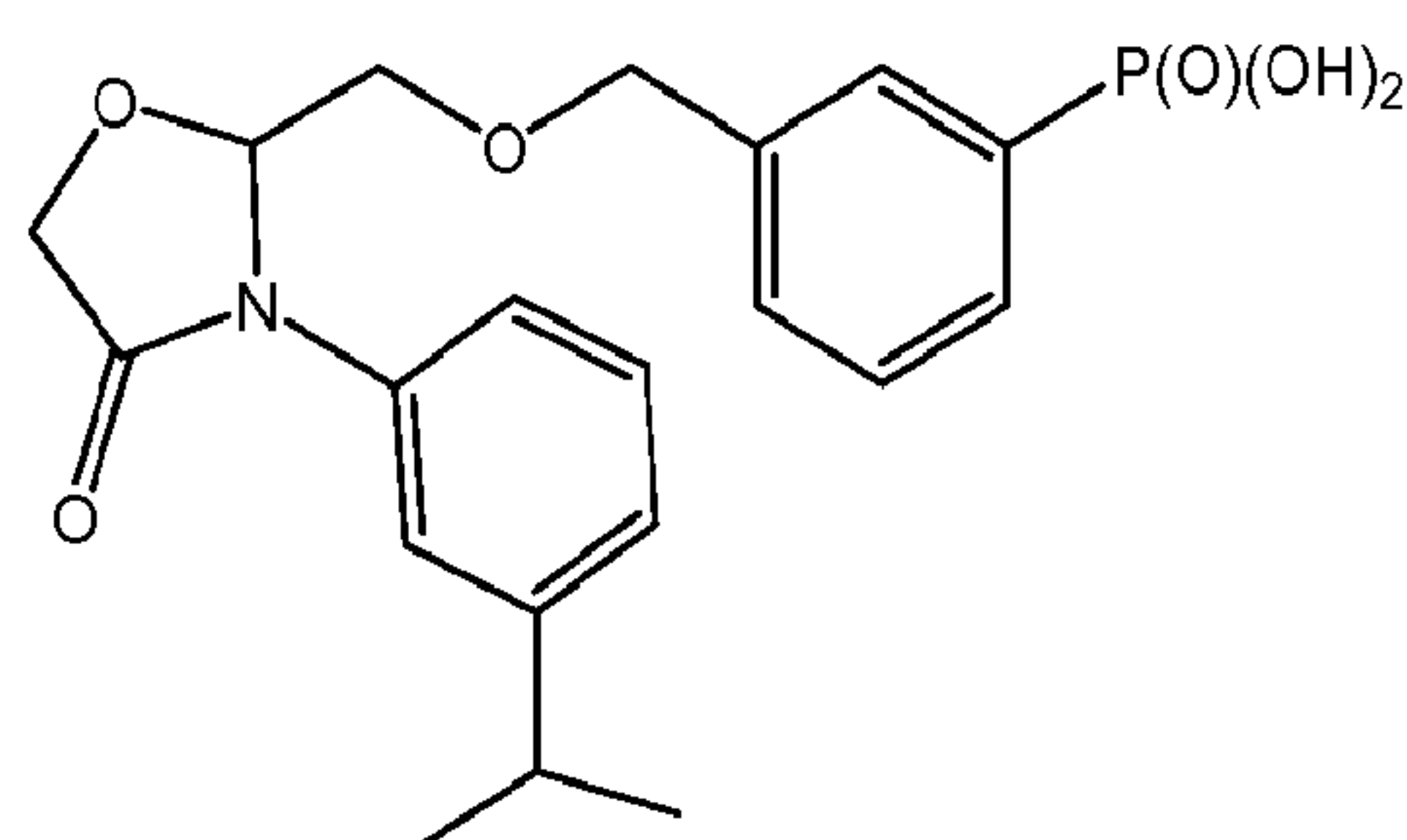
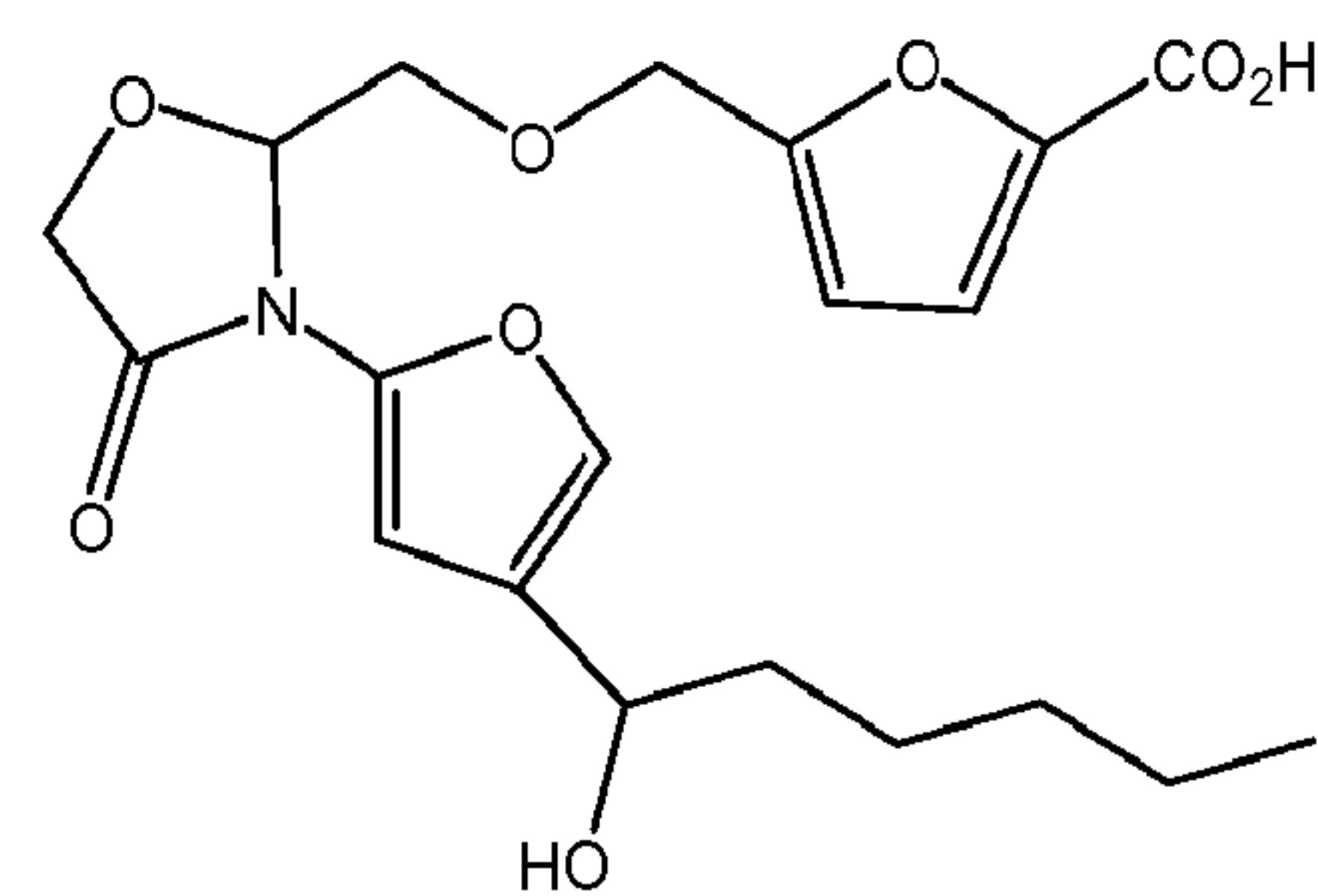
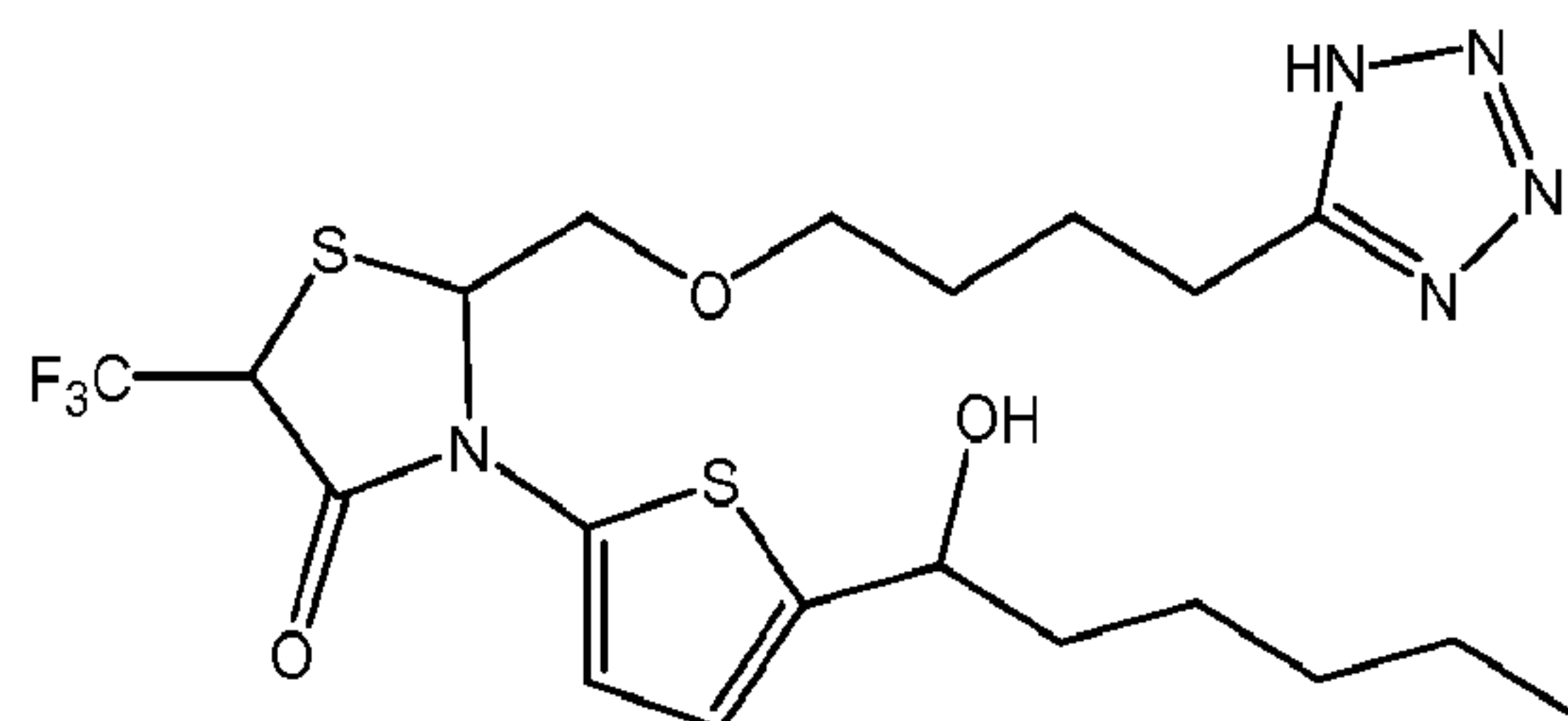
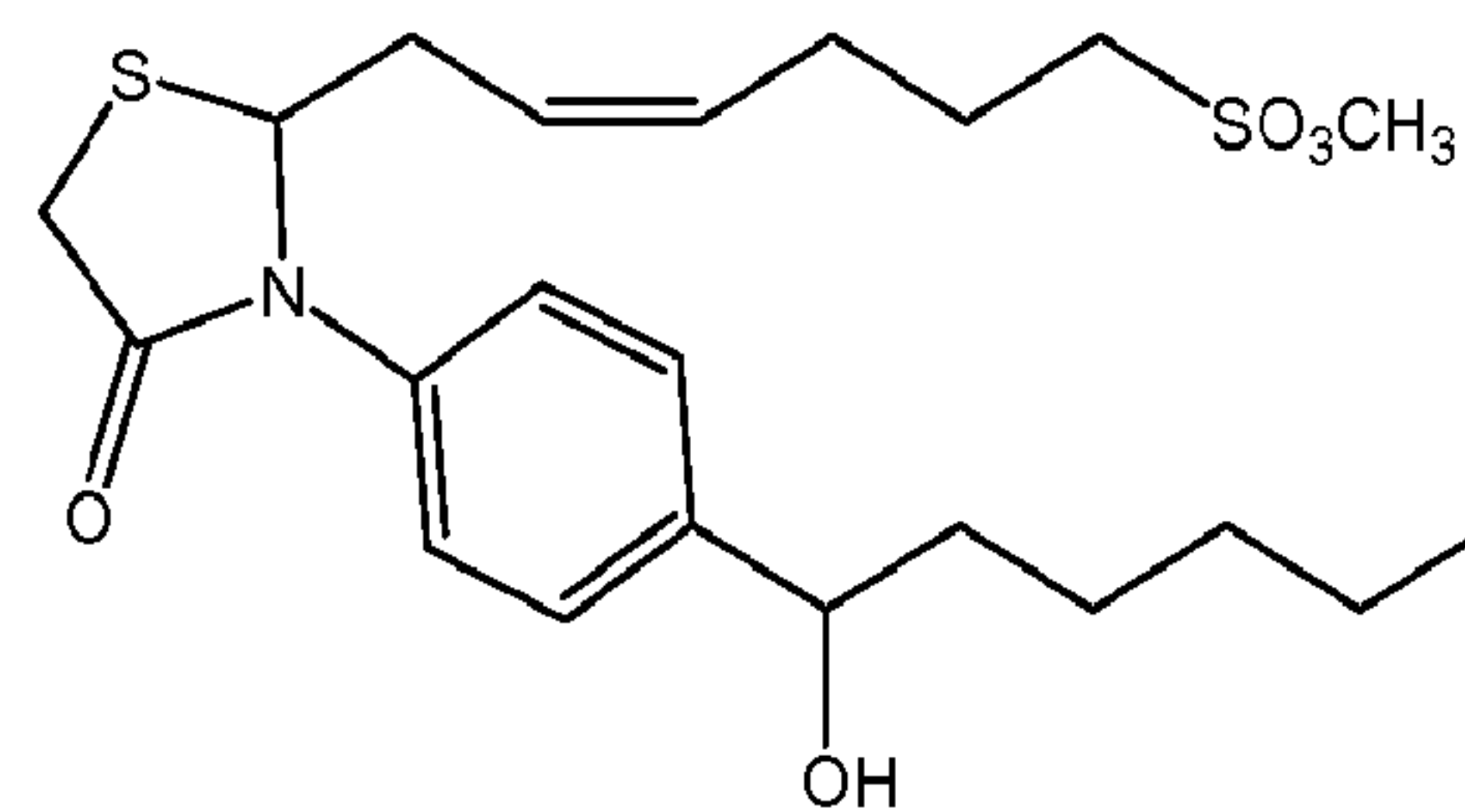
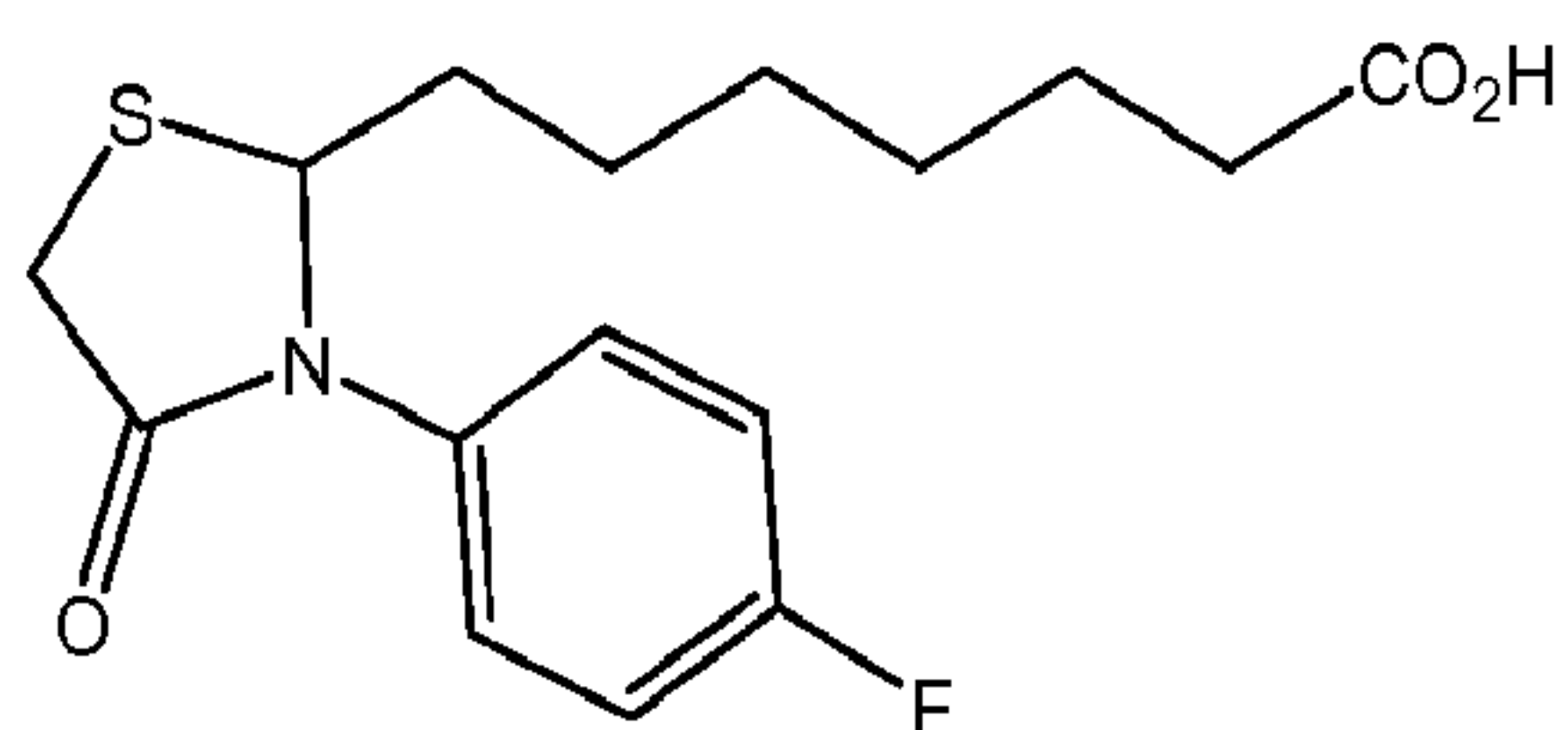
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- 5 In the above embodiments, x is 5, 6, or 7, and y + z is $2x + 1$.
 In one embodiment, x is 5 and y + z is 11.
 In another embodiment, x is 6 and y + z is 13.
 In another embodiment, x is 7 and y + z is 15.

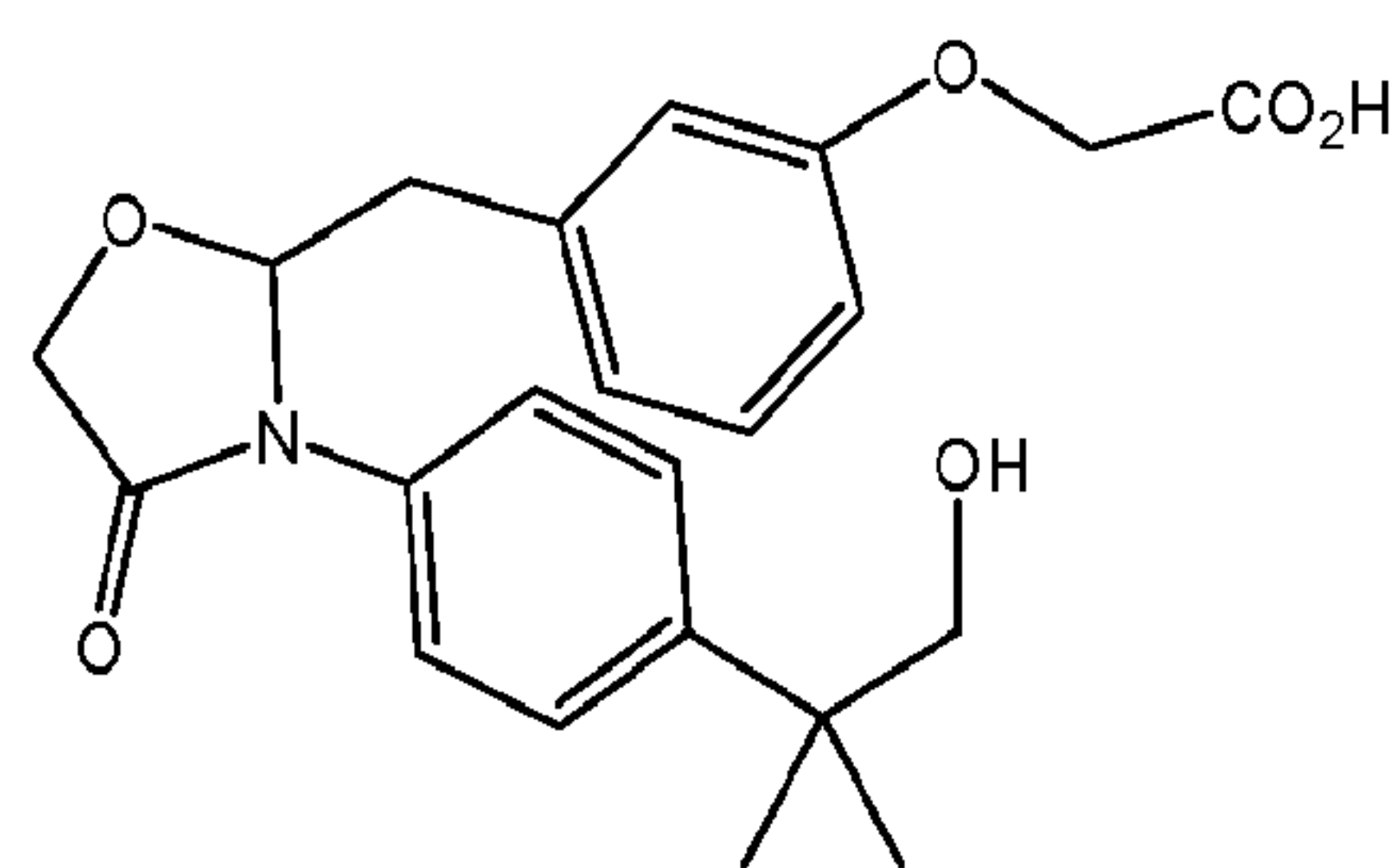
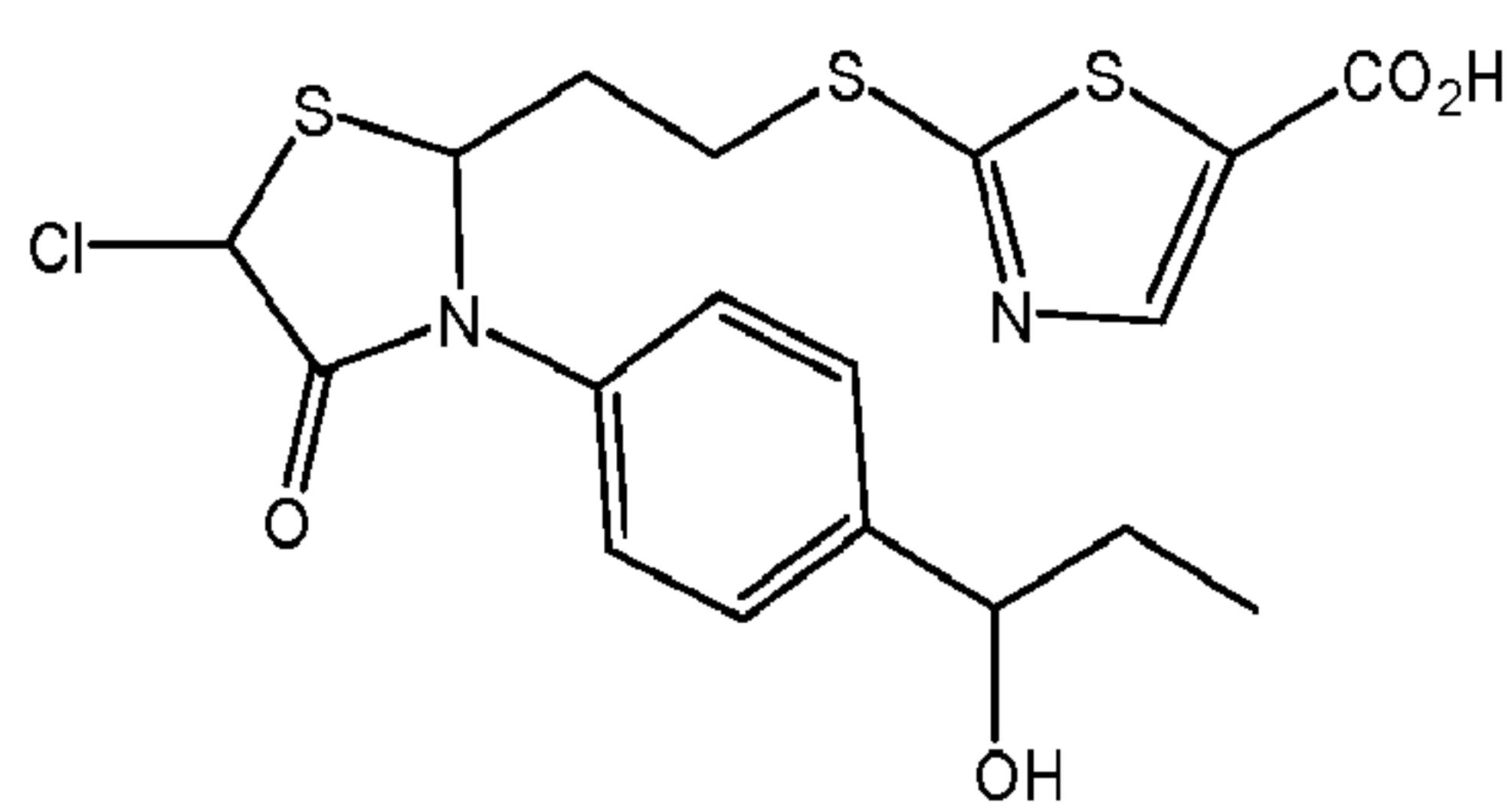
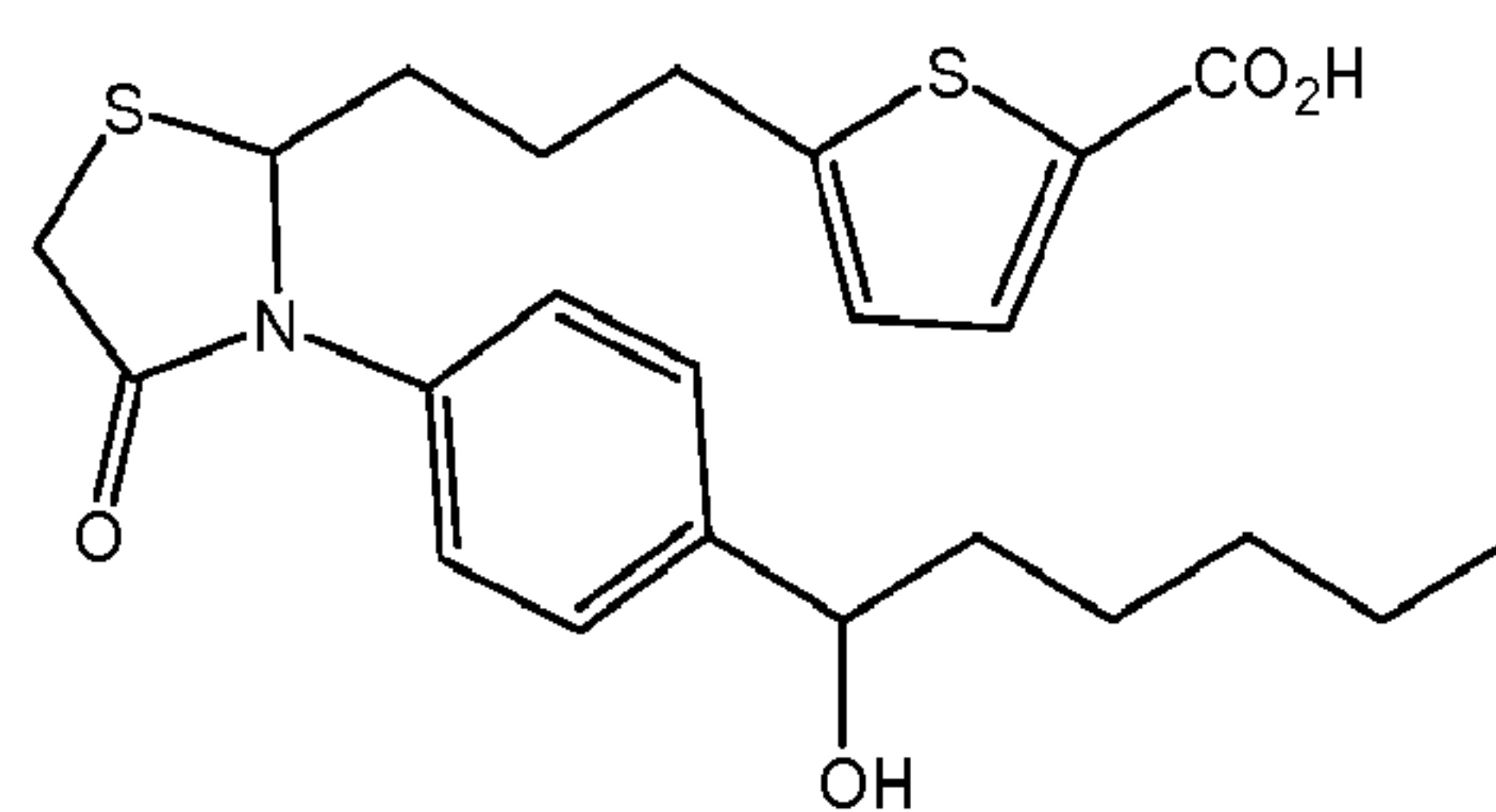
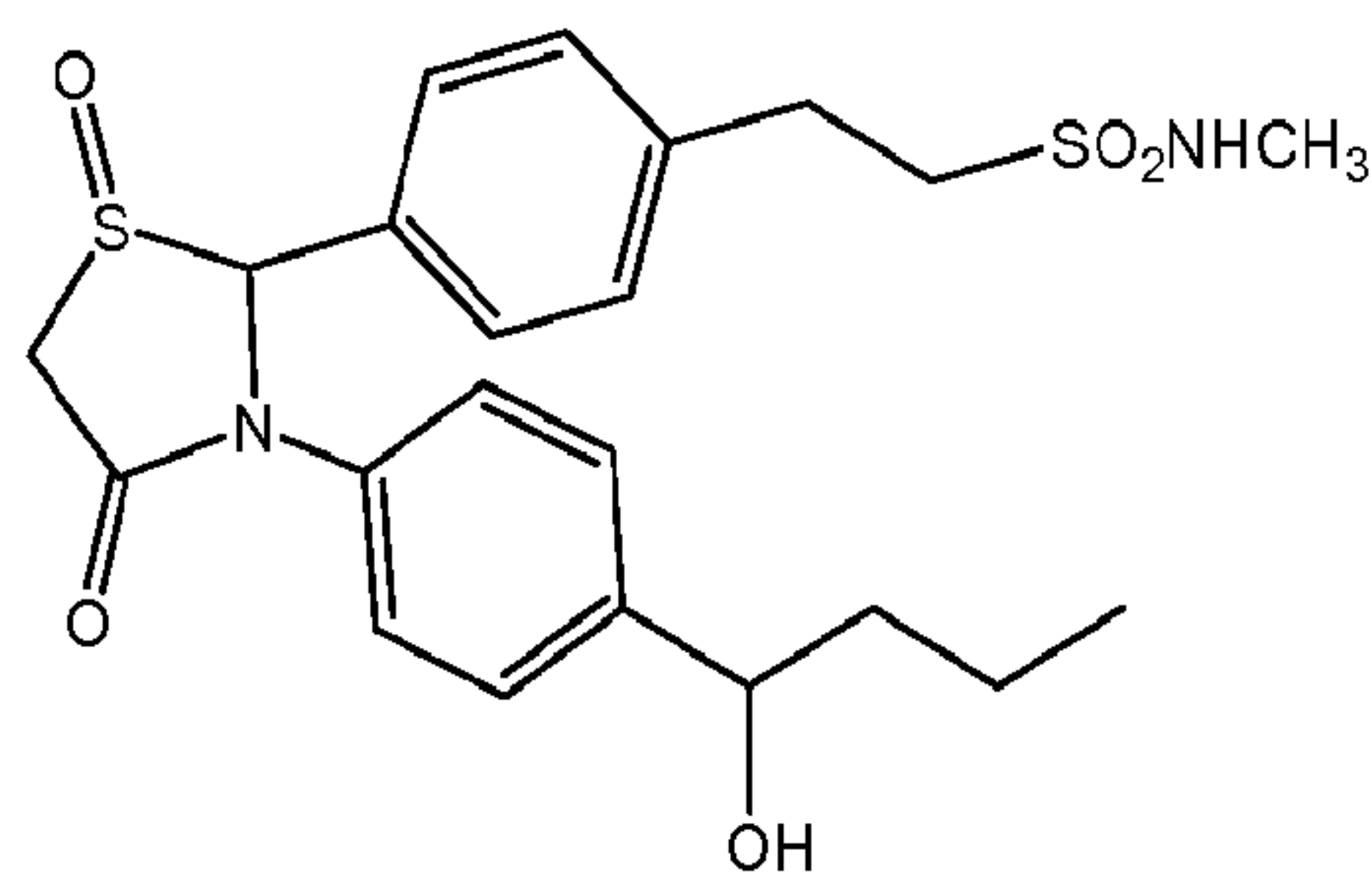
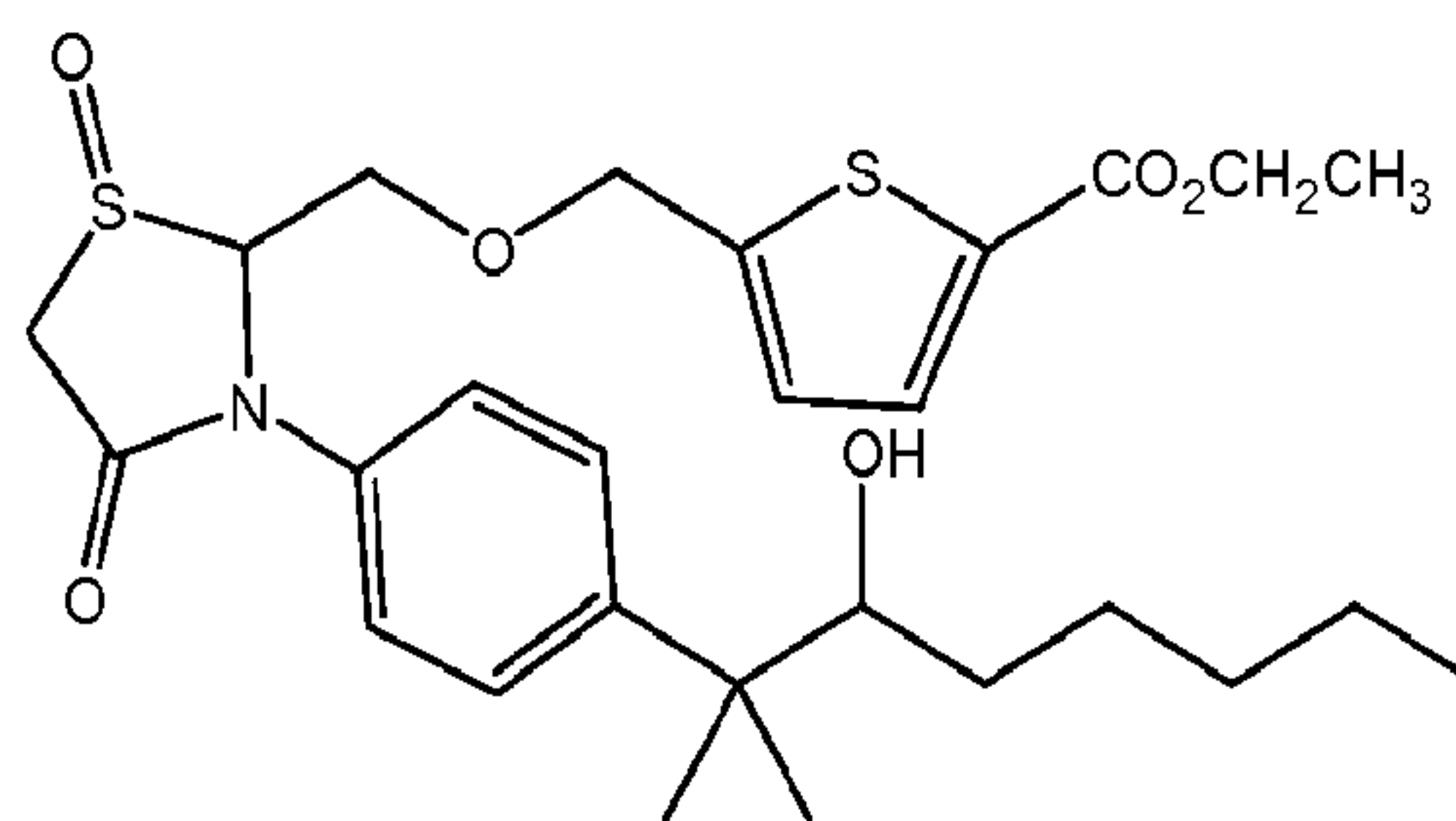
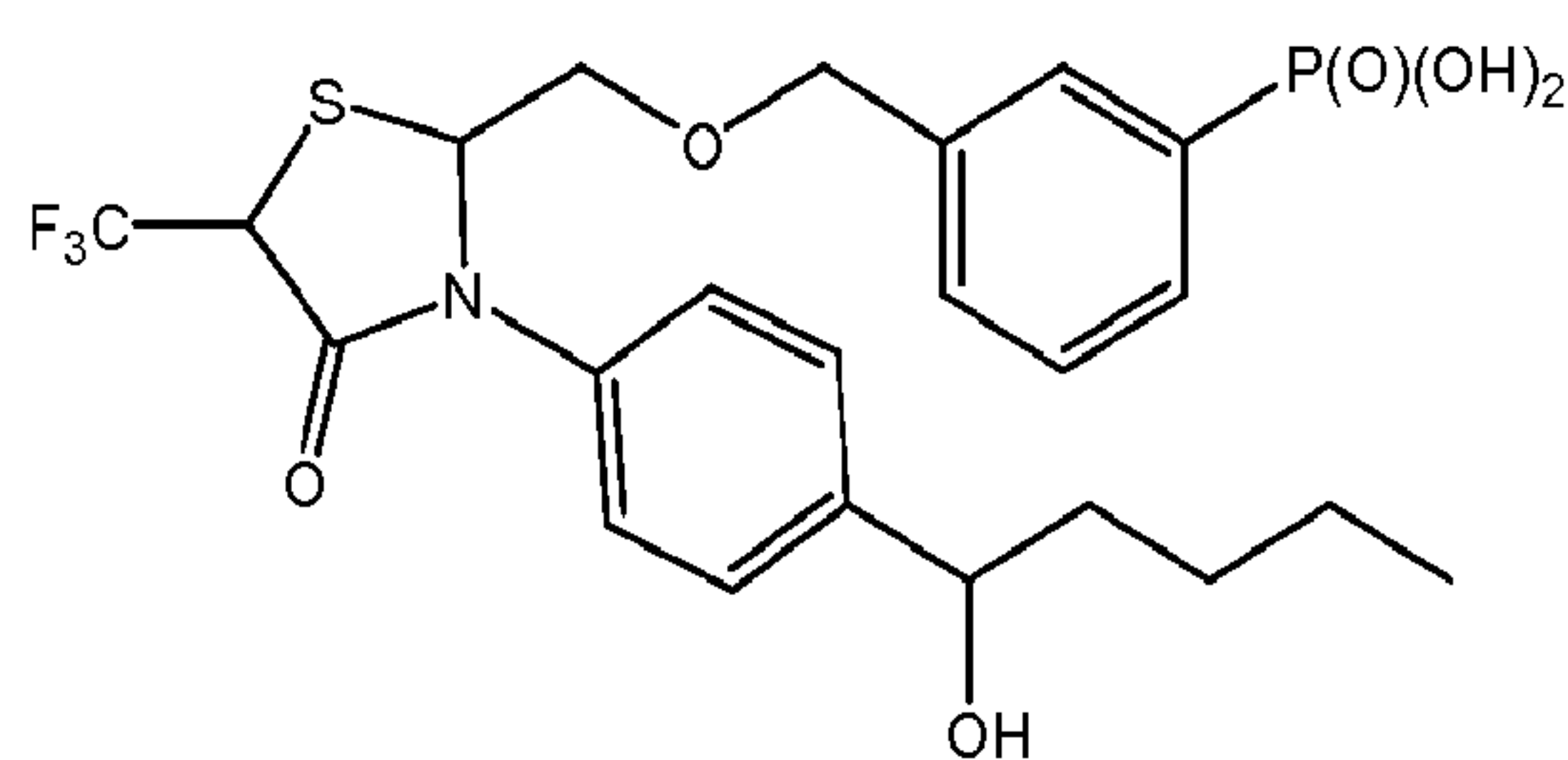
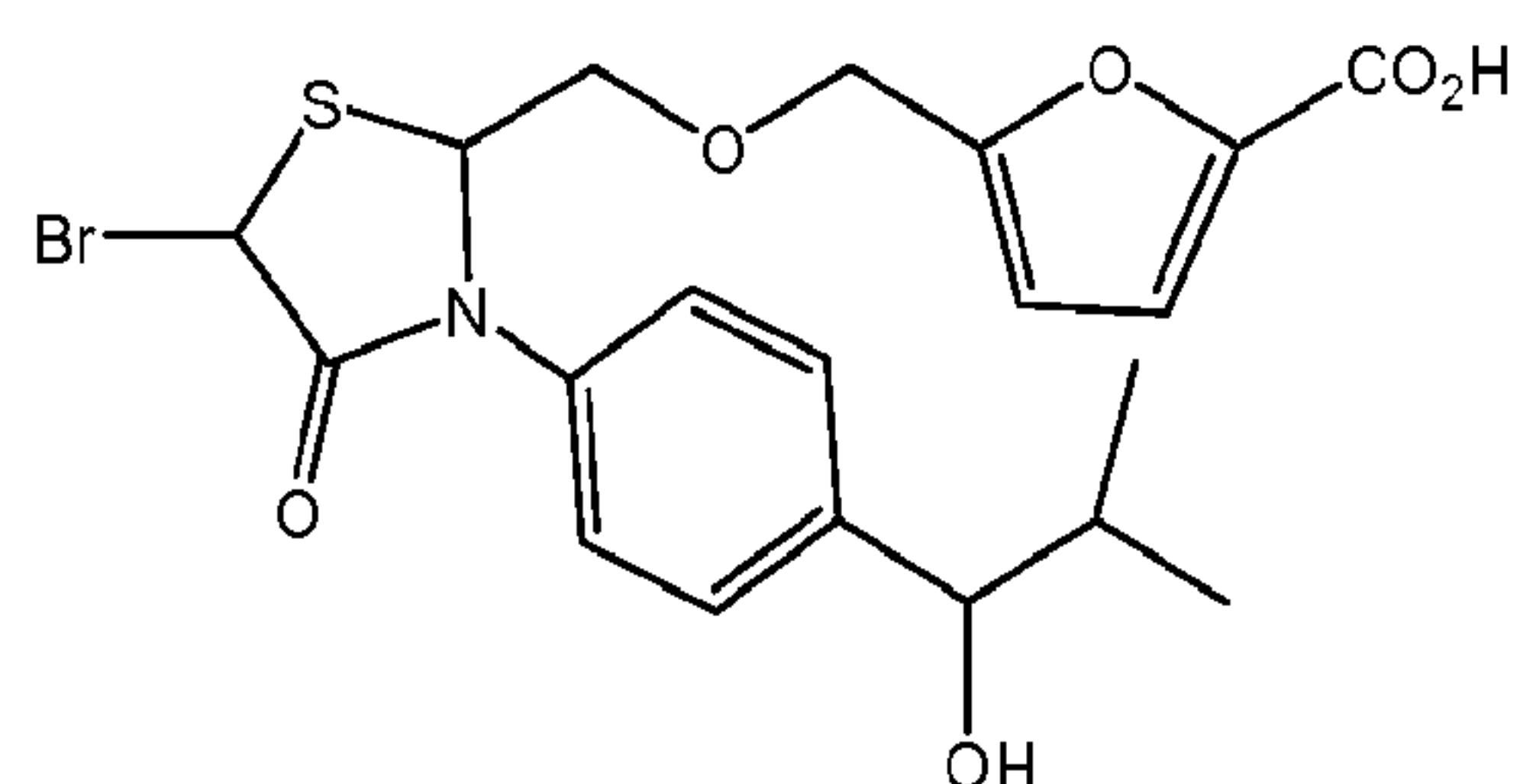
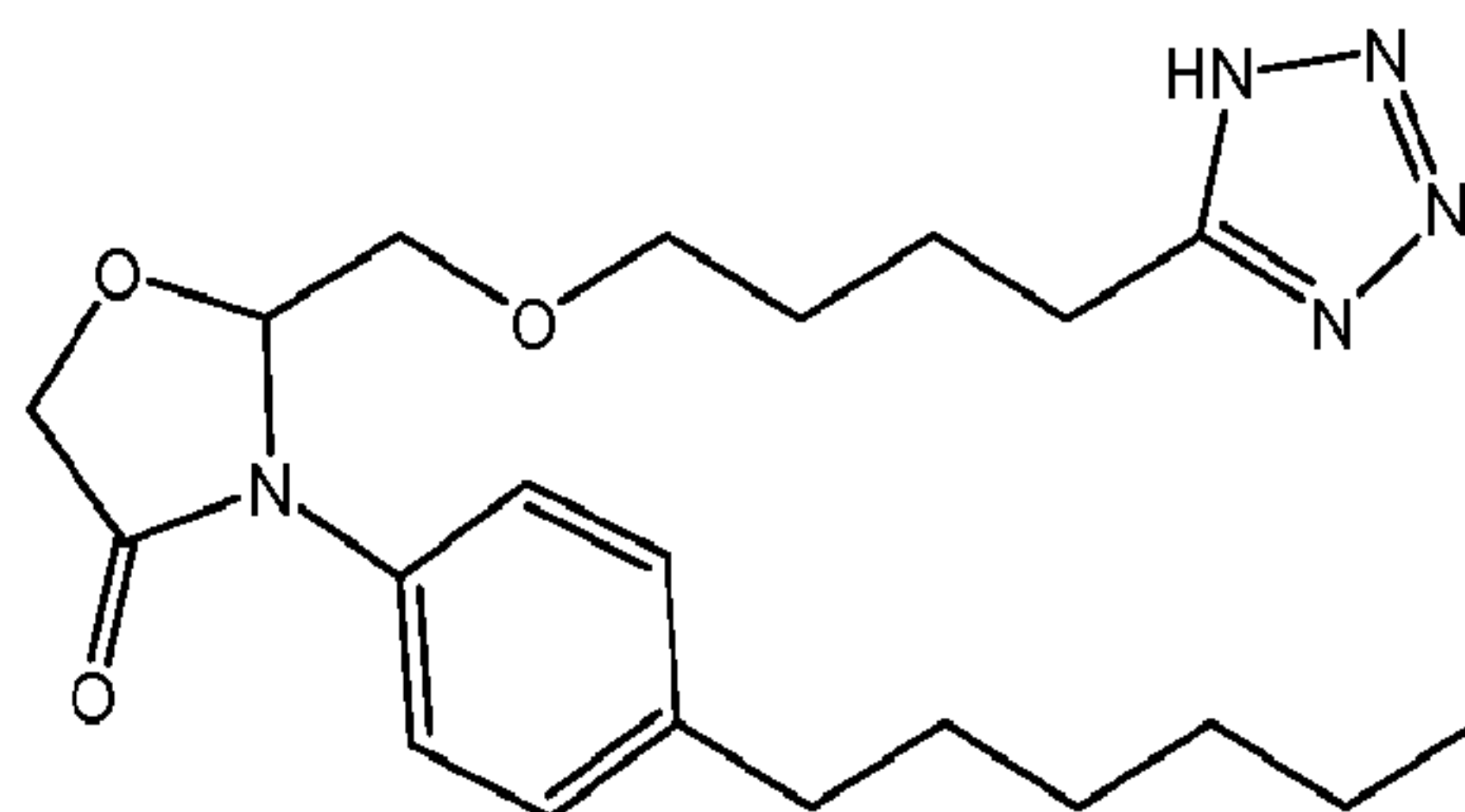
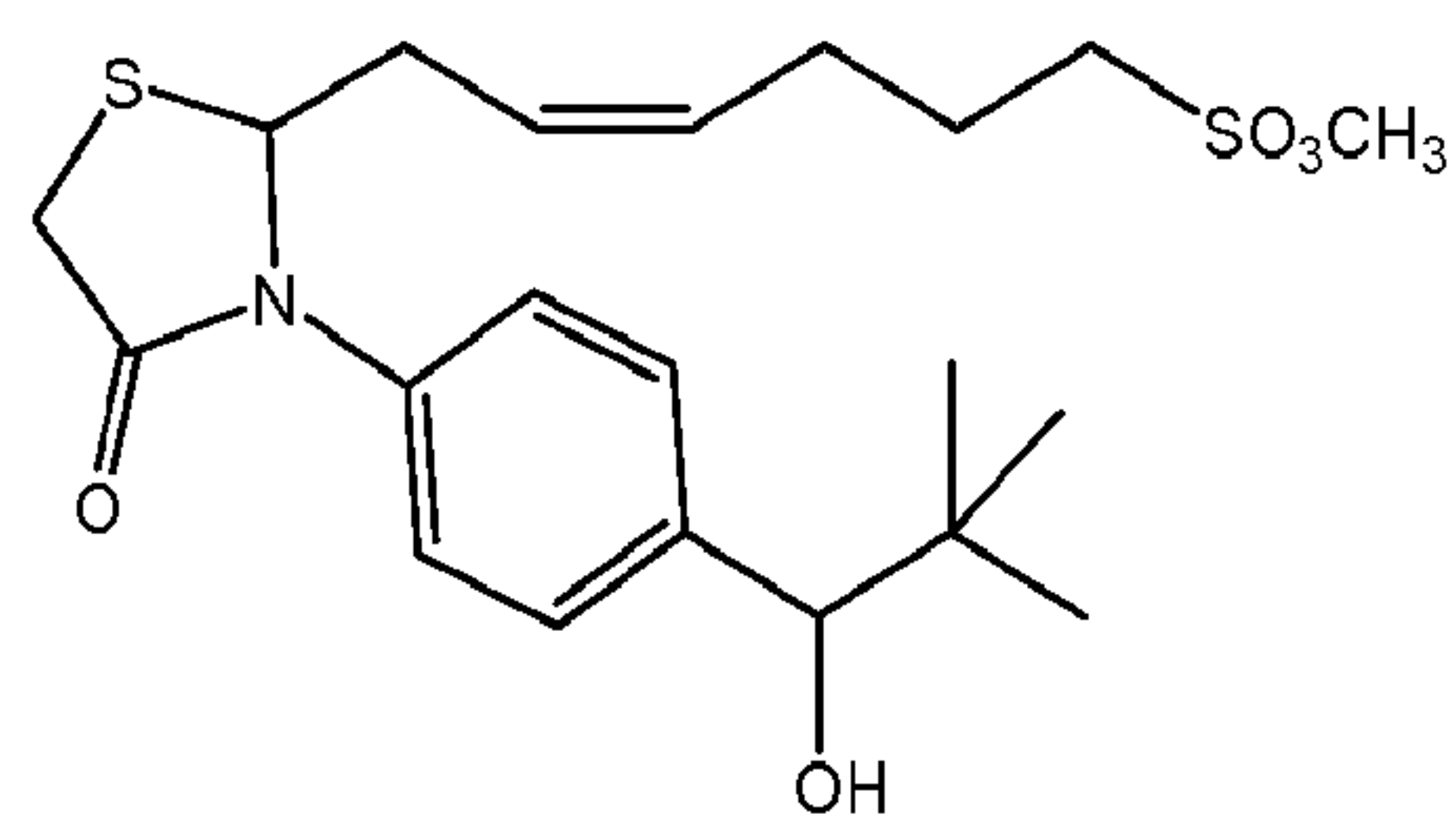
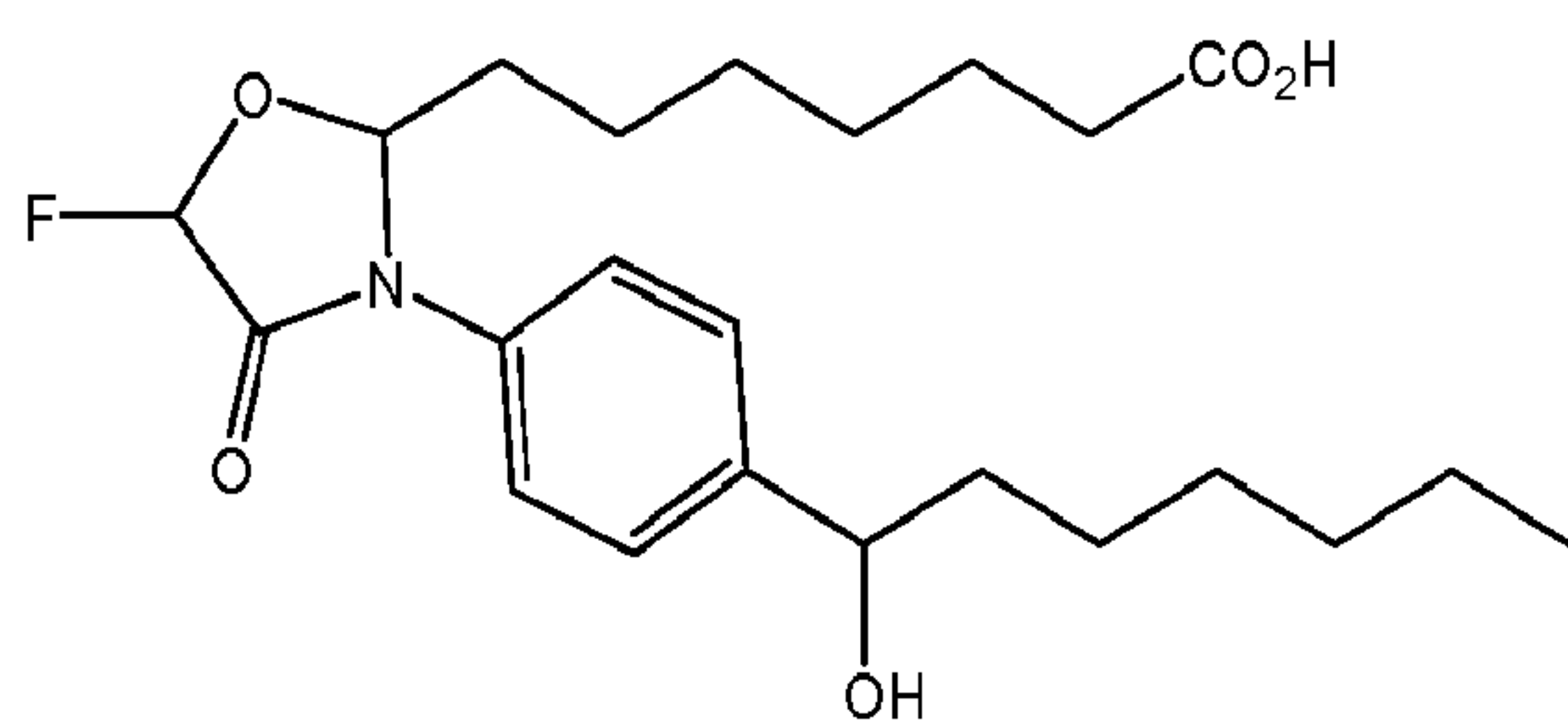
- 10 Hypothetical examples of useful compounds are shown below.



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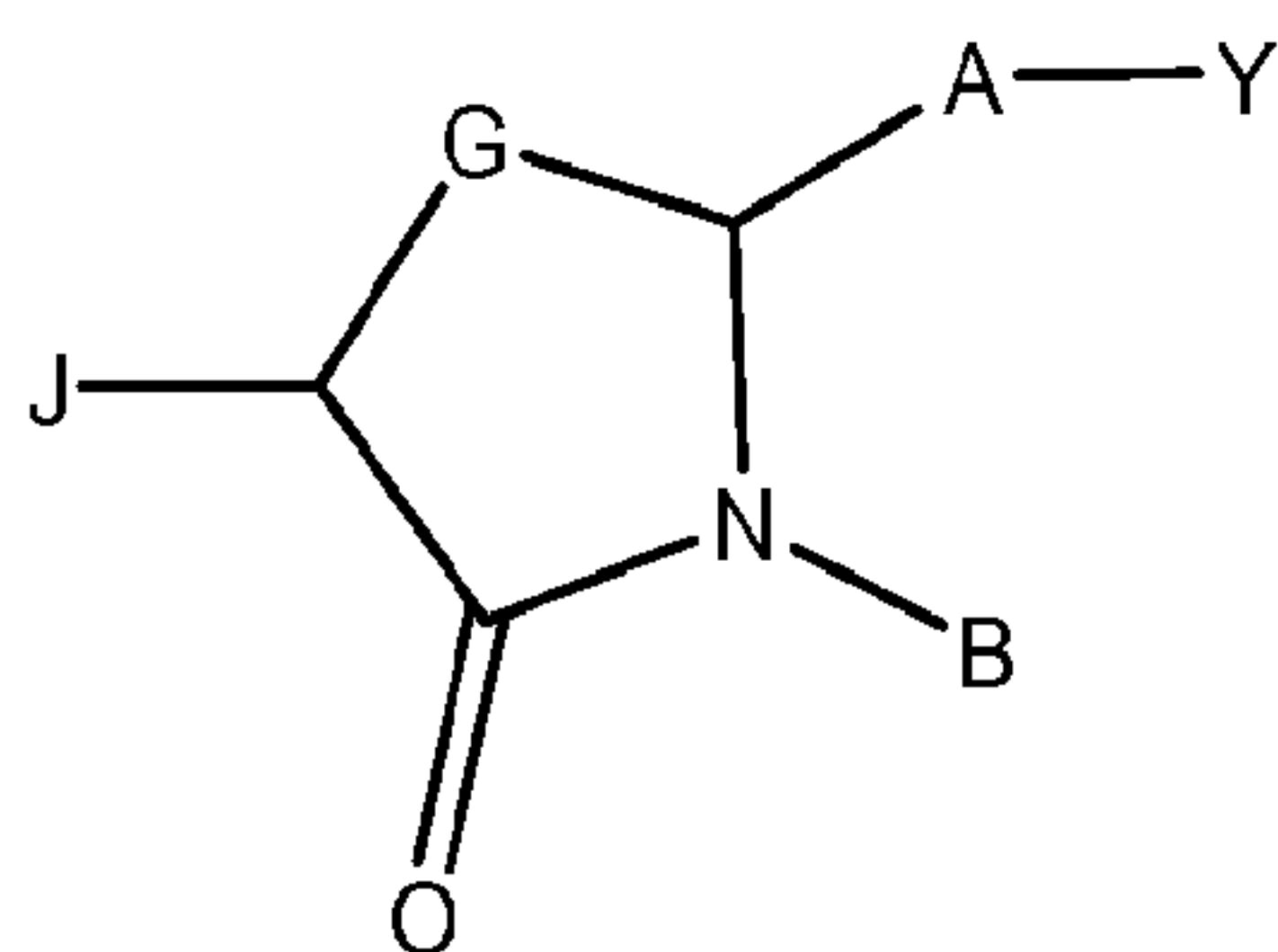
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PCT/US2007/076410^P)**Compound examples:**

5 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;

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

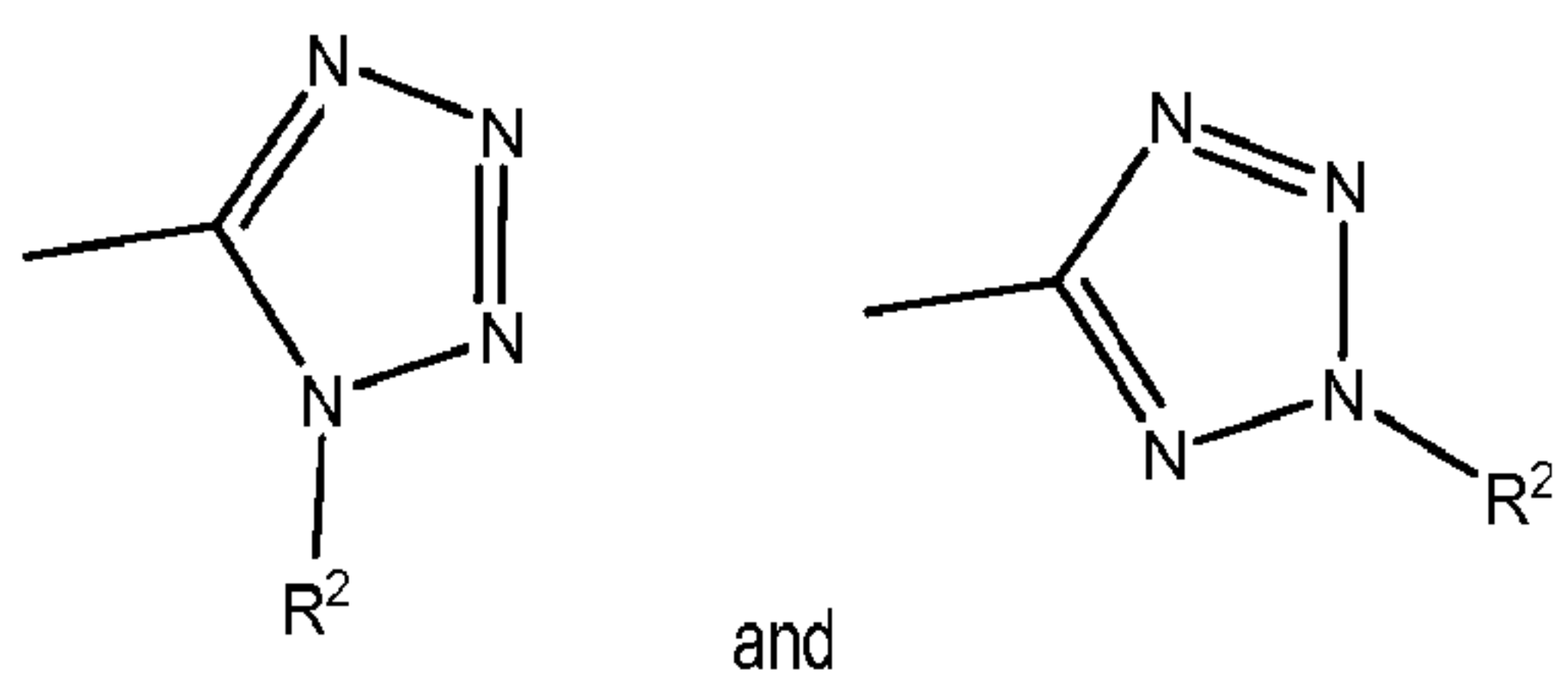
- 5 A is $-(CH_2)_6-$, *cis*- $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-CH_2-$ may be replaced by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

G is O, S, S=O, or S(=O)₂;

J is H, halogen, CF₃; or C₁₋₆ alkyl; and

- 10 B is aryl or heteroaryl.

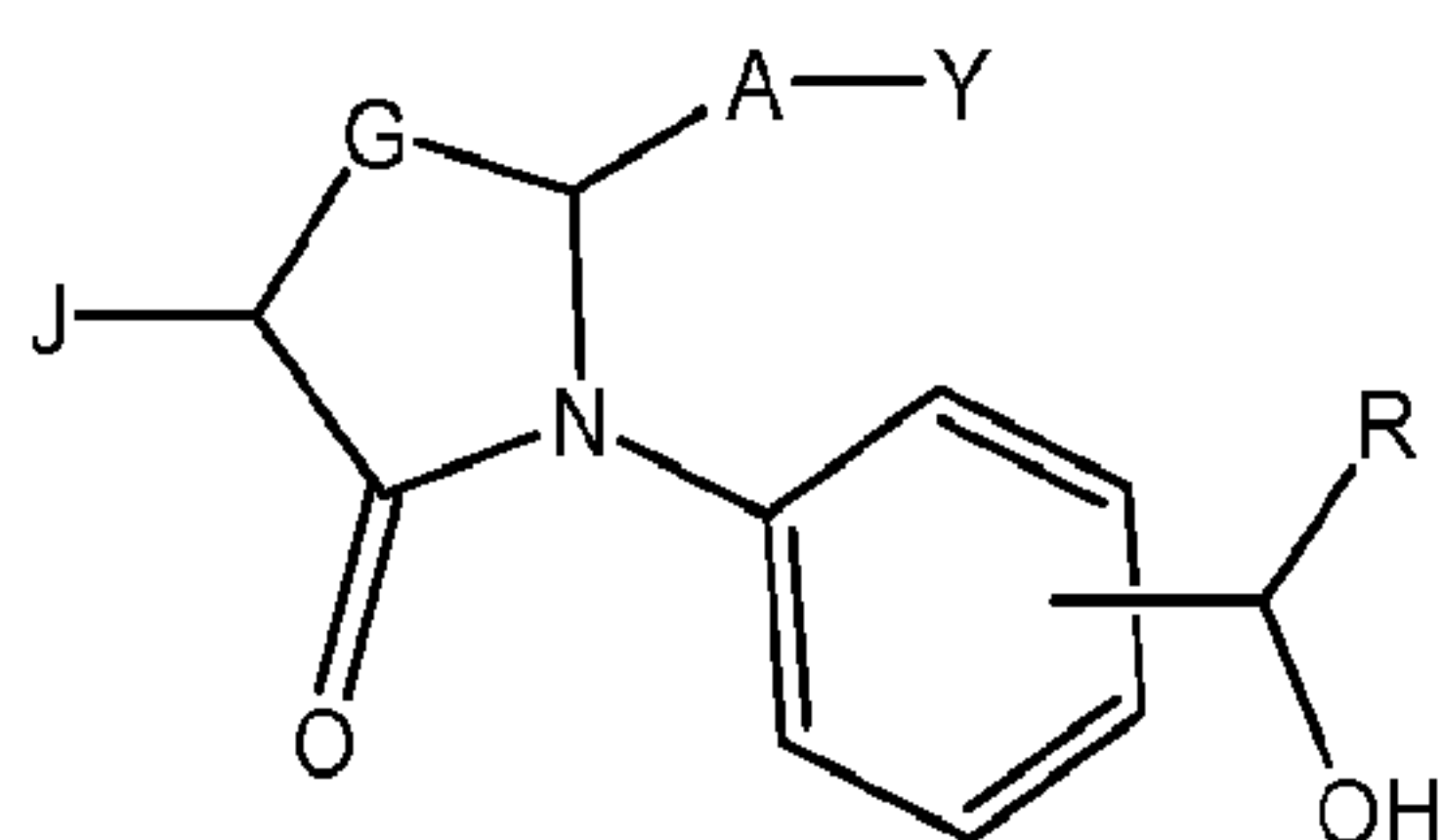
Compound Example 2. The compound according to compound example 1 wherein Y is selected from CO₂R², CON(R²)₂, CON(OR²)R², CON(CH₂CH₂OH)₂, CONH(CH₂CH₂OH), CH₂OH, P(O)(OH)₂, CONHSO₂R², SO₂N(R²)₂, SO₂NHR²,



wherein R² is independently H, C₁-C₆ alkyl, unsubstituted phenyl, or unsubstituted biphenyl.

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

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



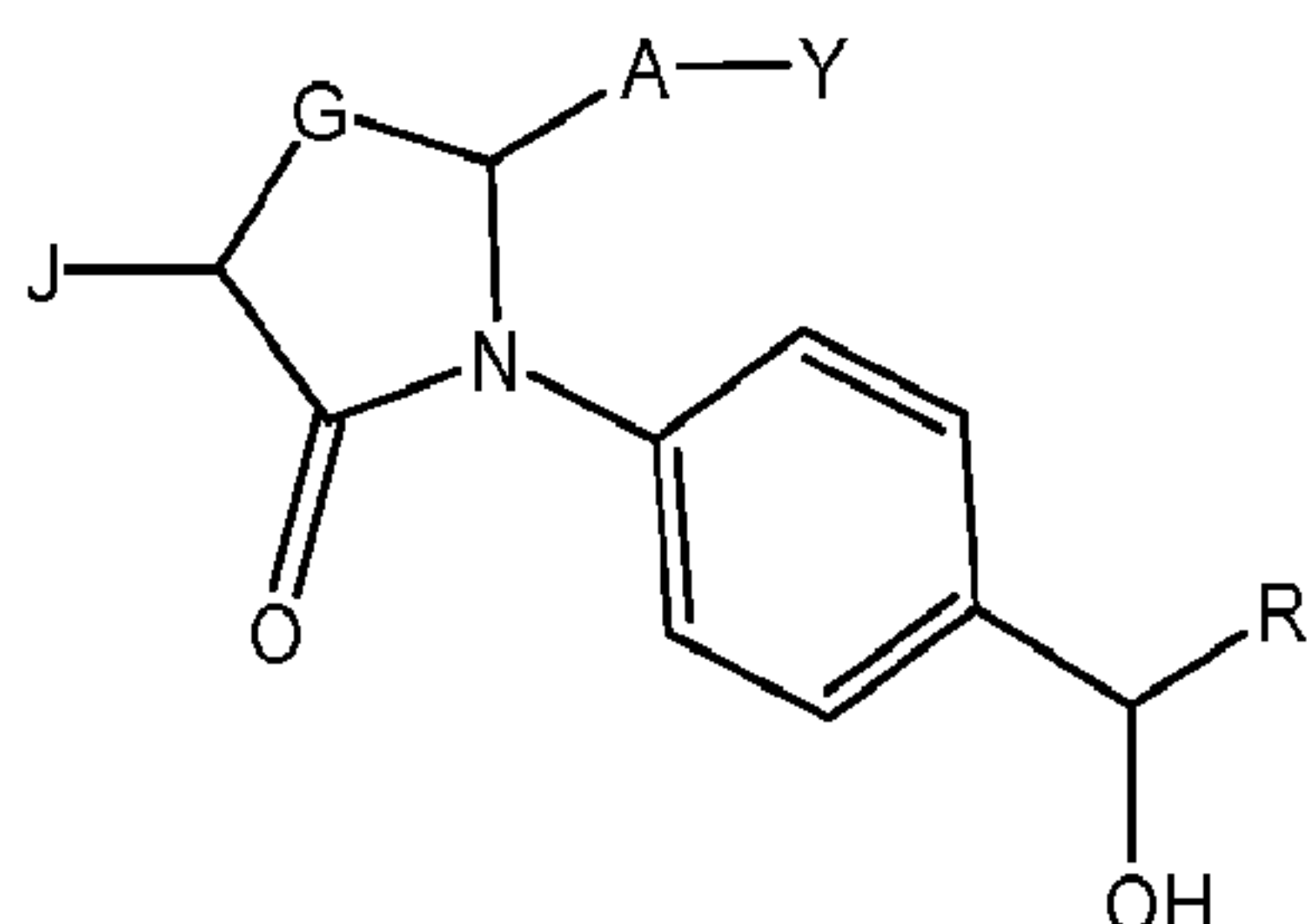
or a pharmaceutically acceptable salt thereof, or a prodrug thereof;

wherein R is hydrogen or C₁₋₁₀ hydrocarbonyl.

- 20 **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;

wherein R is hydrogen or C₁₋₁₀ hydrocarbyl.

- Compound Example 8.** The compound according to compound example 1 or 2 wherein A is (3-methylphenoxy)methyl.
- Compound Example 9.** The compound according to compound example 1 or 2 wherein A is (4-but-2-ynyloxy)methyl.
- 5 **Compound Example 10.** The compound according to compound example 1 or 2 wherein A is 2-(2-ethylthio)thiazol-4-yl.
- Compound Example 11.** The compound according to compound example 1 or 2 wherein A is 2-(3-propyl)thiazol-5-yl.
- Compound Example 12.** The compound according to compound example 1 or 2 wherein A is 3-methoxymethyl)phenyl.
- Compound Example 13.** The compound according to compound example 1 or 2 wherein A is 3-(3-propyl)phenyl.
- Compound Example 14.** The compound according to compound example 1 or 2 wherein A is 3-methylphenethyl.
- 10 **Compound Example 15.** The compound according to compound example 1 or 2 wherein A is 4-(2-ethyl)phenyl.
- Compound Example 16.** The compound according to compound example 1 or 2 wherein A is 4-phenethyl.
- Compound Example 17.** The compound according to compound example 1 or 2 wherein A is 4-methoxybutyl.
- Compound Example 18.** The compound according to compound example 1 or 2 wherein A is 5-(methoxymethyl)furan-2-yl.
- Compound Example 19.** The compound according to compound example 1 or 2 wherein A is 5-(methoxymethyl)thiophen-2-yl.
- 15 **Compound Example 20.** The compound according to compound example 1 or 2 wherein A is 5-(3-propyl)furan-2-yl.
- Compound Example 21.** The compound according to compound example 1 or 2 wherein A is 5-(3-propyl)thiophen-2-yl.
- Compound Example 22.** The compound according to compound example 1 or 2 wherein A is 6-hexyl.
- Compound Example 23.** The compound according to compound example 1 or 2 wherein A is (Z)-6-hex-4-enyl.
- 20 **Compound Example 24.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-2,2-dimethylpropyl)phenyl.
- Compound Example 25.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-2-methylpropan-2-yl)phenyl.
- Compound Example 26.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-2-methylpropyl)phenyl.
- 25 **Compound Example 27.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxybutyl)phenyl.
- Compound Example 28.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxyheptyl)phenyl.
- 30 **Compound Example 29.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxyhexyl)phenyl.
- Compound Example 30.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxypentyl)phenyl.
- Compound Example 31.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxypropyl)phenyl.
- 35 **Compound Example 32.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(3-hydroxy-2-methylheptan-2-yl)phenyl.
- Compound Example 33.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(3-hydroxy-2-methyloctan-2-yl)phenyl.
- 40 **Compound Example 34.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 1-hydroxy-2,3-dihydro-1H-inden-5-yl.

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- Compound Example 35.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 2,3-dihydro-1H-inden-5-yl.
- Compound Example 36.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 3-(hydroxy(1-propylcyclobutyl)methyl)phenyl.
- 5 **Compound Example 37.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-5,5-dimethylhexyl)phenyl.
- Compound Example 38.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(hydroxy(1-propylcyclobutyl)methyl)phenyl.
- Compound Example 39.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-tert-butylphenyl.
- 10 **Compound Example 40.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-hexylphenyl.
- Compound Example 41.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-2-phenylethyl)phenyl.
- 15 **Compound Example 42.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxy-3-phenylpropyl)phenyl.
- Compound Example 43.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(1-hydroxycyclobutyl)phenyl.
- Compound Example 44.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(2-cyclohexyl-1-hydroxyethyl)phenyl.
- 20 **Compound Example 45.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(3-cyclohexyl-1-hydroxypropyl)phenyl.
- Compound Example 46.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(cyclohexyl(hydroxy)methyl)phenyl.
- 25 **Compound Example 47.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(cyclohexylmethyl)phenyl.
- Compound Example 48.** The compound according to any one of compound examples 1, 2, and 8-23 wherein B is 4-(hydroxy(phenyl)methyl)phenyl.
- Compound Example 49.** The compound according to any one of compound examples 1 to 48 wherein G is O.
- 30 **Compound Example 50.** The compound according to any one of compound examples 1 to 48 wherein G is S.
- Compound Example 51.** The compound according to any one of compound examples 1 to 48 wherein G is S=O.
- Compound Example 52.** The compound according to any one of compound examples 1 to 48 wherein G is S(=O)₂.
- Compound Example 53.** The compound according to any one of compound examples 1 to 48 wherein J is hydrogen.
- Compound Example 54.** The compound according to any one of compound examples 1 to 48 wherein J is F.
- 35 **Compound Example 55.** The compound according to any one of compound examples 1 to 48 wherein J is Cl.
- Compound Example 56.** The compound according to any one of compound examples 1 to 48 wherein J is methoxy.
- Compound Example 57.** The compound according to any one of compound examples 1 to 48 wherein J is methyl.
- Compound Example 58.** The compound according to any one of compound examples 1, and 24 to 57 wherein A is -CH₂CH₂A¹- or -CH₂OA¹-, wherein A¹ is linear C₄H₈, C₃H₆O, or C₃C₆S; -CH₂-Ar-; -O-Ar-; -S-Ar-; -Ar-CH₂-; -Ar-O-; -Ar-S-, or Ar; with the proviso that A does not contain -O-O-, -S-O-, or O-S.
- 40

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

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Composition Example:

A composition comprising a compound according to any one of compound examples 1 to 58, wherein said composition is a liquid which is ophthalmically acceptable.

Medicament Examples:

- 5 Use of a compound according to any one of compound examples 1 to 58 in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension in a mammal.

Use of a compound according to any one of compound examples 1 to 58 in the manufacture of a medicament for the treatment of baldness in a person.

- 10 A medicament comprising a compound according to any one of compound examples 1 to 58, 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 58 to a mammal for the treatment of glaucoma or ocular hypertension.

Kit Example:

- 15 A kit comprising a composition comprising compound according to any one of compound examples 1 to 58, a container, and instructions for administration of said composition to a mammal for the treatment of glaucoma or ocular hypertension.

- 20 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."

Unless otherwise indicated, a structure shown herein is intended to include any stereoisomer or mixture thereof of the compounds of the structure.

- 25 For the purposes of this disclosure, "treat," "treating," or "treatment" refer to the use of a compound, composition, therapeutically active agent, or drug in the diagnosis, cure, mitigation, treatment, or prevention of disease or other undesirable condition.

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

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

- 35 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. C₁₋₆ alkyl esters are particularly useful, where alkyl part of the ester has from 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl isomers, hexyl isomers, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and combinations thereof having from 1-6 carbon atoms, etc.

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

For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades
10 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
15 control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjuncts in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical 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,
20 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
25 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
30 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
35 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
40 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.

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

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

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

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

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

The ingredients are usually used in the following amounts:

	<u>Ingredient</u>	<u>Amount (% w/v)</u>
	active ingredient	about 0.001-5
	preservative	0-0.10
20	vehicle	0-40
	tonicity adjustor	1-10
	buffer	0.01-10
	pH adjustor	q.s. pH 4.5-7.5
	antioxidant	as needed
25	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.

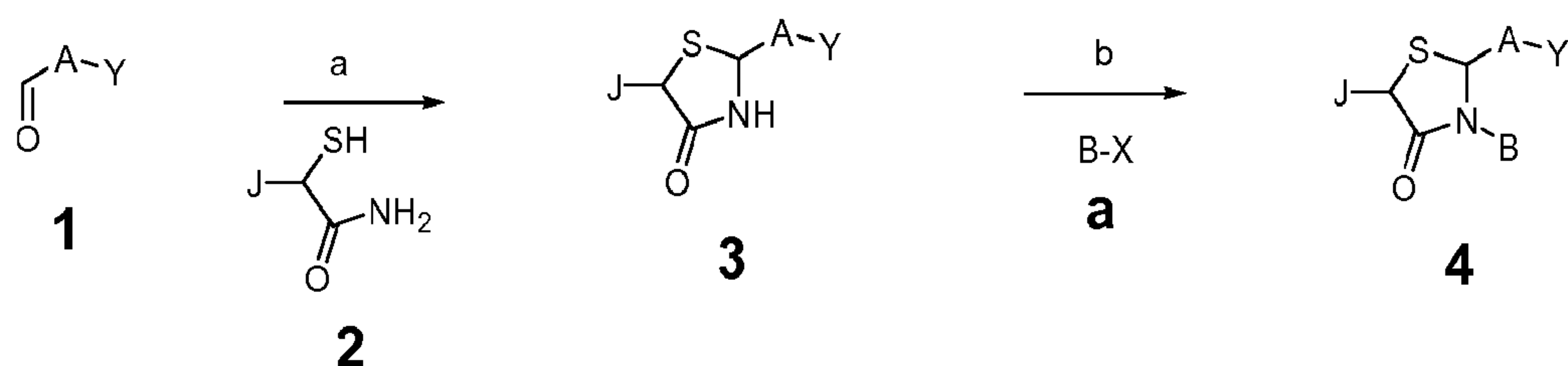
The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

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

Synthetic Methods

Scheme 1

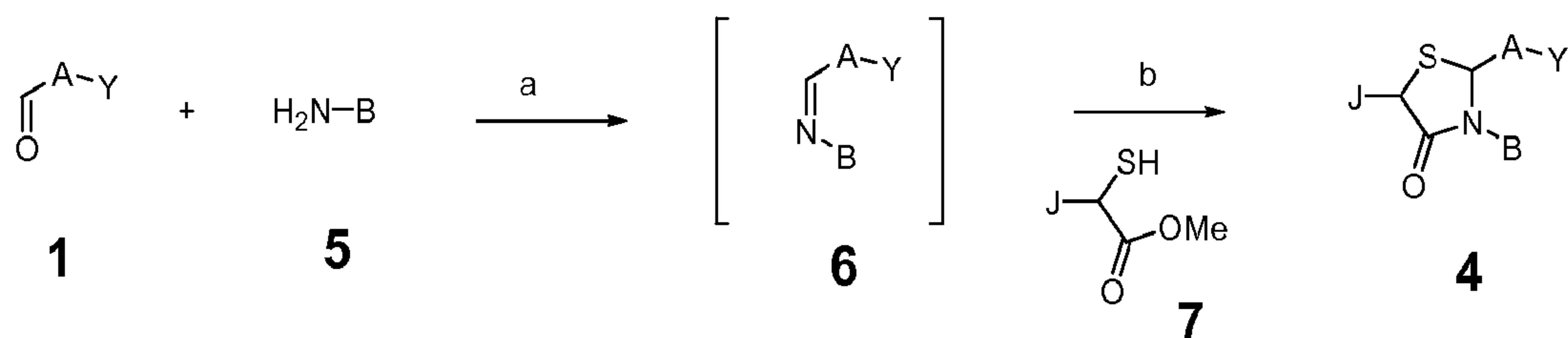
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(a) 2, *p*-TsOH, benzene, reflux; (b) Pd or Cu catalysis, a.

While there are many ways the compounds disclosed herein, one exemplary synthesis may begin with aldehyde 1 (see Scheme 1). Aldehydes such as 1 are commercially available or may be made according to published literature procedures (e.g. methyl 4-(3-oxopropyl)benzoate [commercially available, or by the procedures of Varma and Gordon, US 4,711,900], methyl 5-(4-oxobutyl)thiophene-2-carboxylate [Cragoe, et al. US 4,225,609], and methyl 8-oxooctanoate [Rappoport and Volcheck *J. Am. Chem. Soc.* **1956**, 78, 2451 or by esterification and oxidation of commercially available 8-hydroxyoctanoic acid]). Condensation of 1 with mercaptoacetamide 2 provides thiazolidinone 3 employing the procedure of Bicking et al. (*J. Med. Chem.* **1983**, 26, 342-348). Intermediate 3 is then arylated on nitrogen according to Buchwald's copper-catalyzed procedure (*Org. Lett.* **2000**, 2, 1101-1104) or palladium-catalyzed procedure (*J. Am. Chem. Soc.* **2002**, 124, 7421-7428) using a wide variety of substituted bromophenyl and other bromoaryl compounds a to give compound 4. The haloarenes a are either available commercially or may be made according to published literature procedures. For example, United States Patent Application No. 11/009,298, filed on December 10, 2004 and United States Provisional Patent Application 60/742,779 filed on December 6, 2005, both of which are expressly incorporated by reference herein, disclose methods of making a number of useful substituted bromophenyl compounds. These procedures may also be readily adapted to other bromoaryl compounds such as substituted bromothieryl, substituted bromofuryl, substituted bromopyridinyl, substituted bromonaphthyl, substituted bromobenzothienyl, and the like. Compound 4 may be the target compound, or may require deprotection(s) and/or functionalization (depending on the nature of B and Y) to arrive at the target compound.

Scheme 2



(a) toluene, reflux; (b) 7, Et₃N, toluene, reflux.

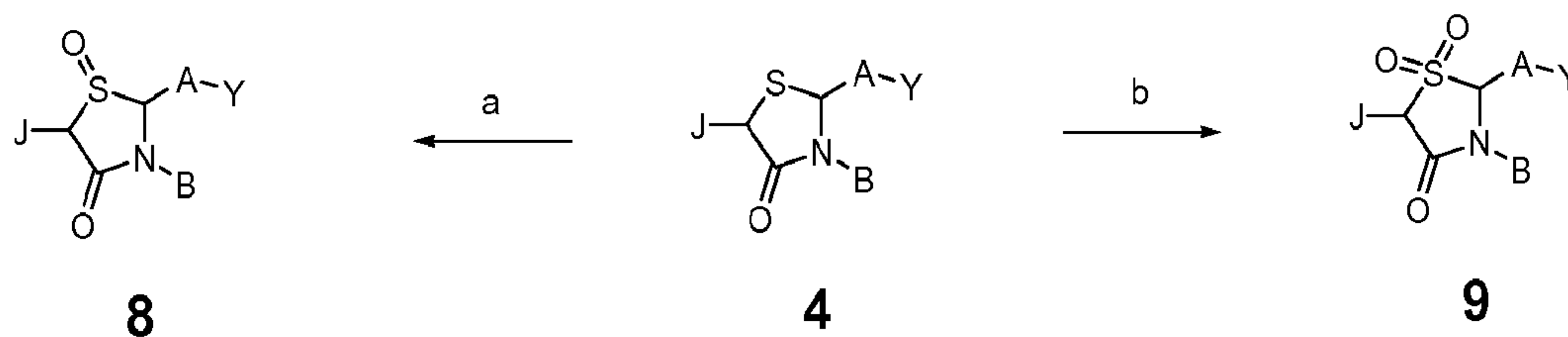
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In another hypothetical route to compound 4, condensation of aldehyde 1 with aniline 5 affords intermediate 6 (see Scheme 2). This intermediate is not isolated, but immediately treated with methyl thioglycolate 7 to afford product 4 by the method of Bicking et al. Anilines such as 5 are either available commercially or may be made according from aryl halides according to published Buchwald-Hartwig amination reactions (for general reviews, see Jiang and Buchwald in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.: de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004, p 699, and Hartwig in *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1051; specifically for primary aniline synthesis, see Shen and Hartwig: *J. Am. Chem. Soc.* **2006**, 128, 10028-10029 and references therein).

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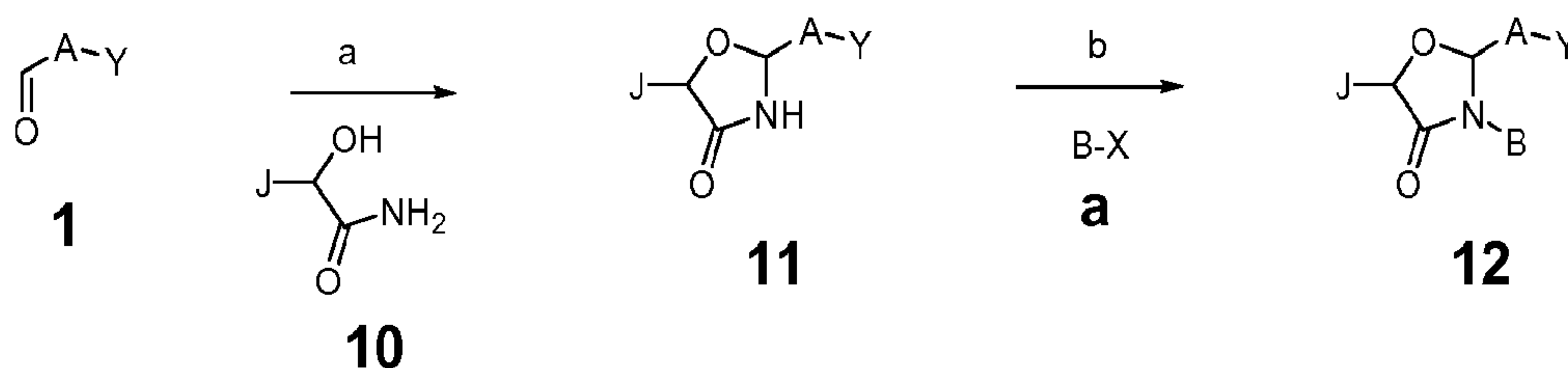
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Scheme 3

(a) NaIO_4 , EtOH, H_2O (b) 30% H_2O_2 , EtOH.

Sulfoxide and sulfone variants of compound **4** are envisioned (see scheme 3). According to the methods of Smith, et al. (US 4,022,794), oxidation of **4** to sulfoxide **8** is accomplished with periodate, and oxidation of **4** (or **8**) to sulfone **9** is accomplished with hydrogen peroxide. Compounds **8** and **9** may be the target compound, or may require deprotection(s) and/or functionalization (depending on the nature of B and Y) to arrive at the target compound.

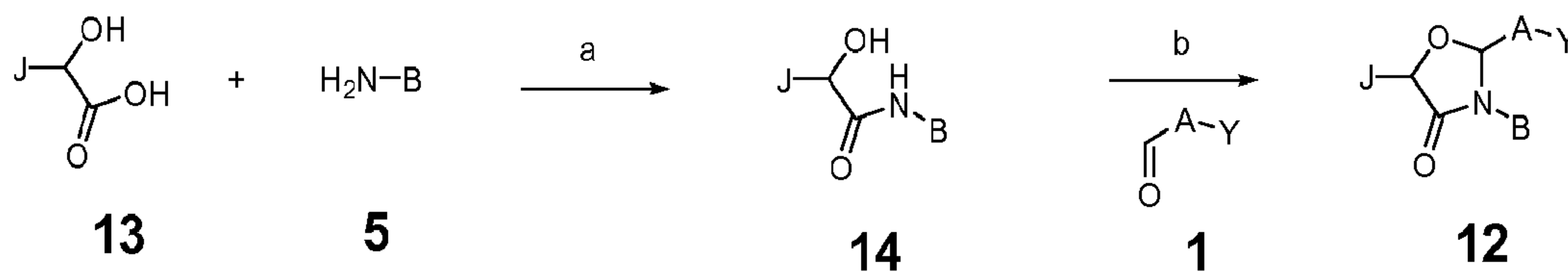
Scheme 4

(a) **10**, *p*-TsOH (cat), benzene, reflux; (b) Pd or Cu catalysis, **a**.

10

Oxazolidinones are also envisioned. Analogous to scheme 1, condensation of aldehyde **1** with hydroxyacetamide **10** affords oxazolidinone **11** (see scheme 4) using the method of Campbell and Jones, US 2,915,527. Arylation as before provides N-aryl oxazolidinone **12**. Compound **12** may be the target compound, or may require deprotection(s) and/or functionalization (depending on the nature of B and Y) to arrive at the target compound. An alternative hypothetical route to compound **12** is shown in scheme 5. Thus, condensation of intermediate aniline **5** with glycolic acid **13** affords amido alcohol **14** using the method of Kametani, et al., *Yakugaku Zasshi* **1981**, 101, 336-344. Cyclization of **14** with aldehyde **1** according to the method of Kametani et al. then provides desired compound **12**.

Scheme 5

(a) neat, high temperature; (b) **1**, *p*-TsOH (cat.), xylene, reflux.

20

The glycolate derivatives described herein (**2**, **7**, **10** and **13**) where J = H are all available from commercial sources. Numerous analogs of **7** and **13** where J = alkyl are also commercially available, and are envisioned to serve as precursors to the other glycolate starting materials by standard techniques known in the art. It is also envisioned that analogs of compounds **4**, **8**, **9** and **12** where J = H may serve as precursors to compounds where J = alkyl or halogen using techniques known in the art

25

The synthetic methods described above must necessarily result in the preparation of racemic mixtures of final products. The individual isomers may be obtained, for instance, by a resolution technique (e.g. see Bicking et al.), or by chiral chromatography techniques.

Reaction scheme showing the synthesis of compounds **4b** and **4c** from **1a** and **2a**.

1a (methyl 2-(4-oxopentyl)thiophene-3-carboxylate) reacts with **2a** (2-aminoethanethiol) under conditions **a** to form intermediate **3a** (methyl 2-(4-((S)-2-oxo-2-(4-oxopentyl)thiophen-3-yl)ethyl)thiophene-3-carboxylate).

Intermediate **3a** reacts with **1b** (1-(4-bromophenyl)pentan-1-one) under conditions **b** to form intermediate **4a** (methyl 2-(4-((S)-2-oxo-2-(4-(4-oxopentyl)phenyl)ethyl)thiophen-3-yl)thiophene-3-carboxylate).

Intermediate **4a** is treated with NaOH under conditions **c** to form **4b** (R=Me) or **4c** (R=H).

Intermediate **4b** (R=Me) is treated with NaOH under conditions **d** to form **4c** (R=H).

Example 1

A mixture of methyl 5-(4-oxobutyl)thiophene-2-carboxylate (**1a**, see Cragoe, et al. US 4,225,609; also prepared by Swern oxidation of the corresponding alcohol prepared as described by Shih, C., et. al. *J. Med. Chem.* **1992**, 35, 1109-1116; 5.3 g, 25.0 mmol) and 2-mercaptoacetamide (**2a**, 6.76 g, 74.2 mmol) in toluene (50 mL) was refluxed in a flask fitted with a Dean-Stark trap. *p*-Toluenesulfonic acid monohydrate (3.8 g, 20.0 mmol) was added portionwise over several hours. After a total of 5 hours at reflux, the mixture was cooled and the toluene layer was decanted. Additional toluene (50 mL) was used to wash the oily remainder and then was decanted. The combined organic phase was washed with water (2x100 mL), saturated aqueous NaHCO₃ (100 mL), water (100 mL) and brine (100 mL) then filtered through filter paper and concentrated in vacuo to afford 1.7 g of crude product. Purification of the residue on silica (hexane → EtOAc, gradient) afforded 1.08 g of thiazolidinone **3a**. This product was recrystallized from hot MeOH (3 mL) to afford 800 mg of **3a** (11%).

Pd₂(dba)₃ (41 mg, 0.045 mmol), Xantphos (77 mg, 0.133 mmol) and Cs₂CO₃ (428 mg, 1.31 mmol) were added sequentially to a solution of **3a** (314 mg, 1.10 mmol) and **a1** (see Borman, et al., United States Patent Application Publication No. 2005/0209336, incorporated by reference herein; 255 mg, 1.00 mmol) in 1,4-dioxane (7.1 mL). The flask was fitted with a reflux condenser, evacuated and refilled with nitrogen (5x) then heated at reflux. After 3 d, the reaction was cooled, diluted with EtOAc (50 mL) and filtered through celite, washing with excess EtOAc. The EtOAc filtrate was concentrated in vacuo. The crude residue was purified on 40 g silica gel (hexanes → EtOAc, gradient) to afford 56 mg (12%) of **4a**.

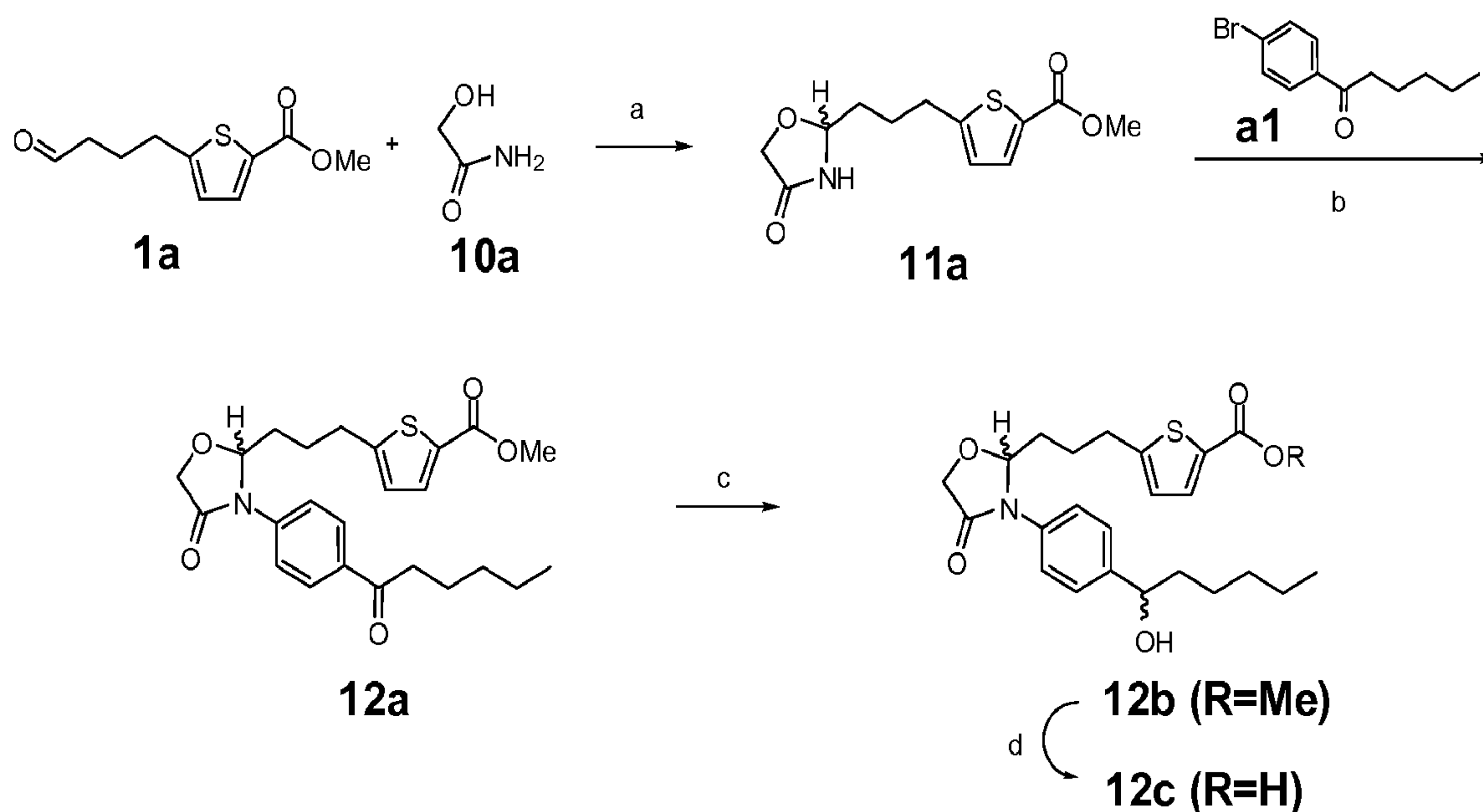
Step 3. Reduction of **4a** to give **4b**

Sodium borohydride (7 mg, 0.19 mmol) was added to a solution of **4a** (55 mg, 0.12 mmol) in MeOH (0.30 mL) and CH₂Cl₂ (0.30 mL). After 18 h at room temperature the reaction was quenched with 1 N HCl (5 mL) and extracted with EtOAc (3x20 mL). The combined organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo. The crude residue was purified on 12 g silica gel (hexanes → EtOAc, gradient) to afford 9 mg (16%) of **4b**.

Step 4. Saponification of **4b** to give **4c**

Lithium hydroxide (0.10 mL of a 1.0 N solution in water, 0.10 mmol) was added to a solution of **4b** (9 mg, 0.019 mmol) in THF (0.19 mL). The reaction mixture was heated at 40 °C. After 24 h at 40 °C, the reaction mixture was cooled to room temperature and the mixture was concentrated under a stream of nitrogen. The residue was diluted with water (0.2 mL), acidified with 1 N HCl (0.5 mL) and extracted with EtOAc (3x2 mL). The combined organic phase was washed with brine (2 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Purification of the crude residue by chromatography on 4 g silica gel (CH₂Cl₂ → 20% MeOH/CH₂Cl₂, gradient) afforded 5 mg (57%) of **4c**.

Scheme 7



(a) *p*-TsOH, toluene, reflux; (b) **a1**, Pd₂(dba)₃, Xantphos, Cs₂CO₃, dioxane, reflux;
(c) NaBH₄, MeOH, CH₂Cl₂; (d) LiOH (aq.), THF.

Example 2

5-(3-(3-(4-(1-hydroxyhexyl)phenyl)-4-oxo-oxazolidin-2-yl)propyl)thiophene-2-carboxylic acid (**12c**)

Step 1. Condensation of **1a** and **10a** to give **11a**

A mixture of **1a** (2.75 g, 13.0 mmol), 2-hydroxyacetamide (**10a**, 2.9 g, 38.6 mmol) and *p*-toluenesulfonic acid monohydrate (250 mg, 1.3 mmol) in toluene (20 mL) was refluxed in a flask fitted with a Dean-Stark trap. After 2 h, the reaction was cooled and partitioned between water (20 mL) and EtOAc (20 mL). The organic phase was separated and washed with water (2x50 mL) and 1 M NH₄OH (50 mL), filtered through filter paper and concentrated in vacuo. Purification of the residue on silica (hexane → EtOAc, gradient) afforded 300 mg of oxazolidinone **11a** (9%).

Step 2. Arylation of **11a** with **a1** to give **12a**

Pd₂(dba)₃ (41 mg, 0.045 mmol), Xantphos (77 mg, 0.133 mmol) and Cs₂CO₃ (428 mg, 1.31 mmol) were added sequentially to a solution of **11a** (297 mg, 1.10 mmol) and **a1** (256 mg, 1.00 mmol) in 1,4-dioxane (7.1 mL). The flask was fitted with a reflux condenser, evacuated and refilled with nitrogen (5x) then heated at reflux. After 18 h, the reaction was cooled, diluted with

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EtOAc (50 mL) and filtered through celite, washing with excess EtOAc. The EtOAc filtrate was concentrated in vacuo. The crude residue was purified on 40 g silica gel (hexanes → 50% EtOAc/hexanes, gradient) to afford 363 mg (82%) of **12a** as a pale yellow solid.

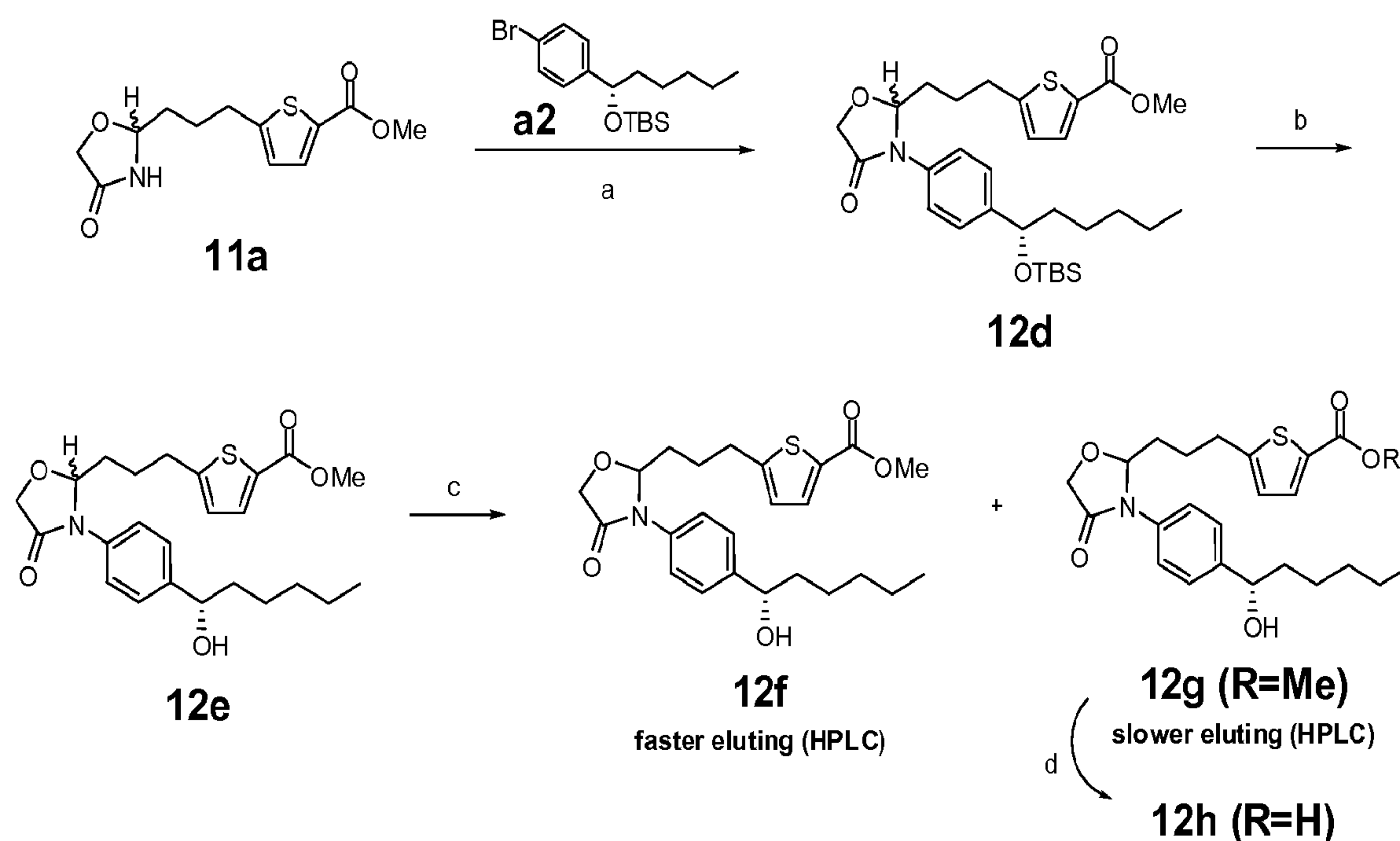
Step 3. Reduction of **12a** to give **12b**

- 5 Sodium borohydride (22 mg, 0.58 mmol) was added to a solution of **12a** (130 mg, 0.29 mmol) in MeOH (0.75 mL) and CH₂Cl₂ (0.75 mL). After 1 h at room temperature the reaction was quenched with 1 N HCl (5 mL) and extracted with EtOAc (3x25 mL). The combined organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo. The crude residue was purified on 12 g silica gel (hexanes → EtOAc, gradient) to afford 130 mg (99%) of **12b**.

Step 4. Saponification of **12b** to give **12c**

- 10 Lithium hydroxide (0.72 mL of a 1.0 N solution in water, 0.72 mmol) was added to a solution of **12b** (64 mg, 0.14 mmol) in THF (0.72 mL). The reaction mixture was heated at 40 °C. After 8 h at 40 °C, the reaction mixture was cooled to room temperature and the mixture was concentrated under a stream of nitrogen. The residue was diluted with water (2 mL), acidified with 1 N HCl (2 mL) and extracted with EtOAc (3x10 mL). The combined organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo. Purification of the crude residue by chromatography on 4 g silica gel (40% EtOAc/hexanes → EtOAc, gradient) afforded
- 15 5 mg (8%) of **12c**.

Scheme 8



(a) CuI, MeN(H)CH₂CH₂N(H)Me, K₂CO₃, MeCN, reflux; (b) HF-pyridine, MeCN; (c) HPLC separation; (d) Rabbit liver esterase, pH 7.2 buffer, MeCN.

20

Example 3

5-(3-(3-(4-((S)-1-hydroxyhexyl)phenyl)-4-oxooxazolidin-2-yl)propyl)thiophene-2-carboxylic acid (**12h**)

Step 1. Arylation of **11a** with **a2** to give **12d**

Potassium carbonate (276 mg, 2.0 mmol), copper(I) iodide (19 mg, 0.10 mmol) and N,N'-dimethylethylene diamine (21.5 μL, 0.2 mmol) were added sequentially to a solution of **11a** (296 mg, 1.10 mmol) and **a2** (see United States Provisional Patent

- 25 Application No. 60/894,369, filed March 12, 2007, incorporated by reference herein, 371 mg, 1.0 mmol) in MeCN (2.5 mL). The

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reaction flask was fitted with a reflux condenser, the mixture was degassed with nitrogen by evac/fill (5x) and then heated at reflux. After 4 d, the mixture was cooled, diluted with EtOAc and filtered through celite, washing with excess EtOAc. The filtrate was concentrated in vacuo. The crude residue was purified on 40 g silica (hexanes → EtOAc, gradient) to afford 33 mg (6%) of **12d**.

5 Step 2. Deprotection of **12d** to give **12e**

HF-pyridine (100 μ L) was added to a solution of **12d** (33 mg, 0.059 mmol) in MeCN (1.2 mL) at 0 °C in a plastic scintillation vial. After 45 min at 0 °C, the reaction was allowed to warm to room temperature. After 1 h at room temperature, the reaction was quenched with saturated aqueous NaHCO₃ (5 mL) and extracted with EtOAc (3x15 mL). The combined organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo. The crude residue was purified on 4 g silica (hexanes → EtOAc, gradient) to afford 14 mg (53%) of **12e**.

10 Step 3. HPLC separation of **12e** to give **12f** and **12g**

The two diastereomers of **12e** (14 mg) were separated on a Waters 600 HPLC instrument employing a Waters 2996 PDA detector and a Phenomenex Luna 10 μ prep silica (2) 1 column, 50 mm x 250 mm (p/no. 00G-4322-V0; s/no. 356757-1). Using a flow rate of 45 mL/min and 50% EtOAc/Hex as the eluent, the first diastereomer (**12f**, 6 mg) eluted at 87-96 min, and the second diastereomer (**12g**, 6 mg) eluted at 97-106 min.

15 Step 4. Saponification of **12g** to give **12h**

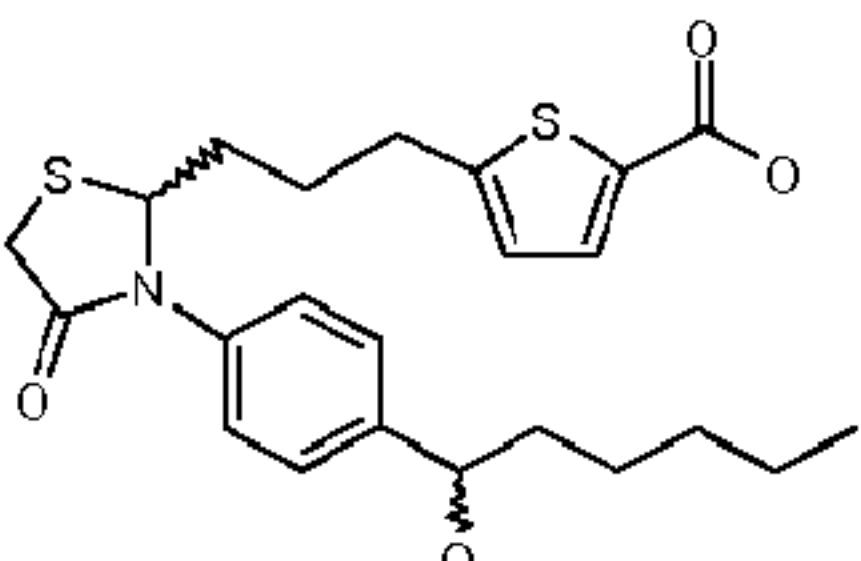
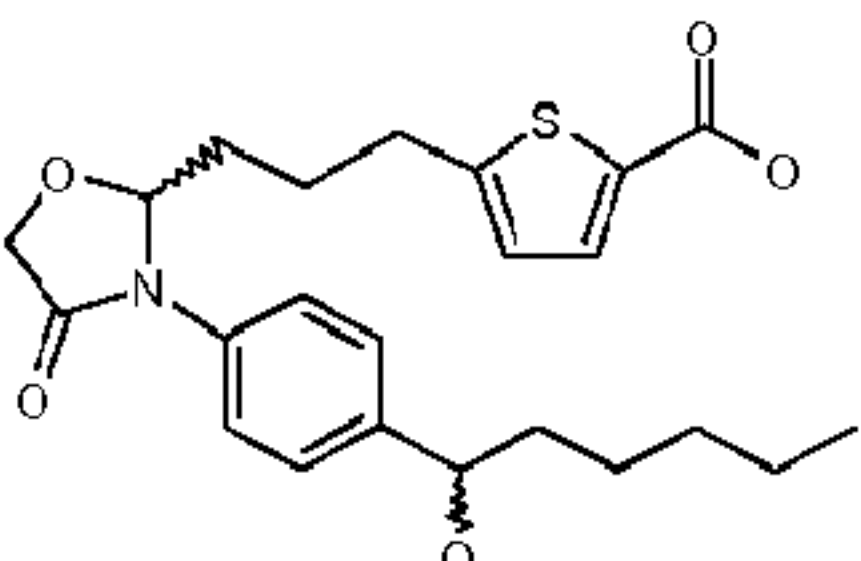
Rabbit liver esterase (5 mg) was added to a mixture of **12g** (6 mg, 0.013 mmol), MeCN (0.1 mL) and pH 7.2 buffer (2.0 mL). The reaction mixture was stirred vigorously for 6 days at room temperature then was concentrated in vacuo. The residue was suspended in CH₂Cl₂ and filtered through celite. The filtrate was concentrated in vacuo to afford 2.5 mg (43%) of **12h**.

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In vitro testing

United States Patent Application Serial No. 11/553,143, filed on October 26, 2006, incorporated by reference herein, describes the methods used to obtain the in vitro data in the table below.

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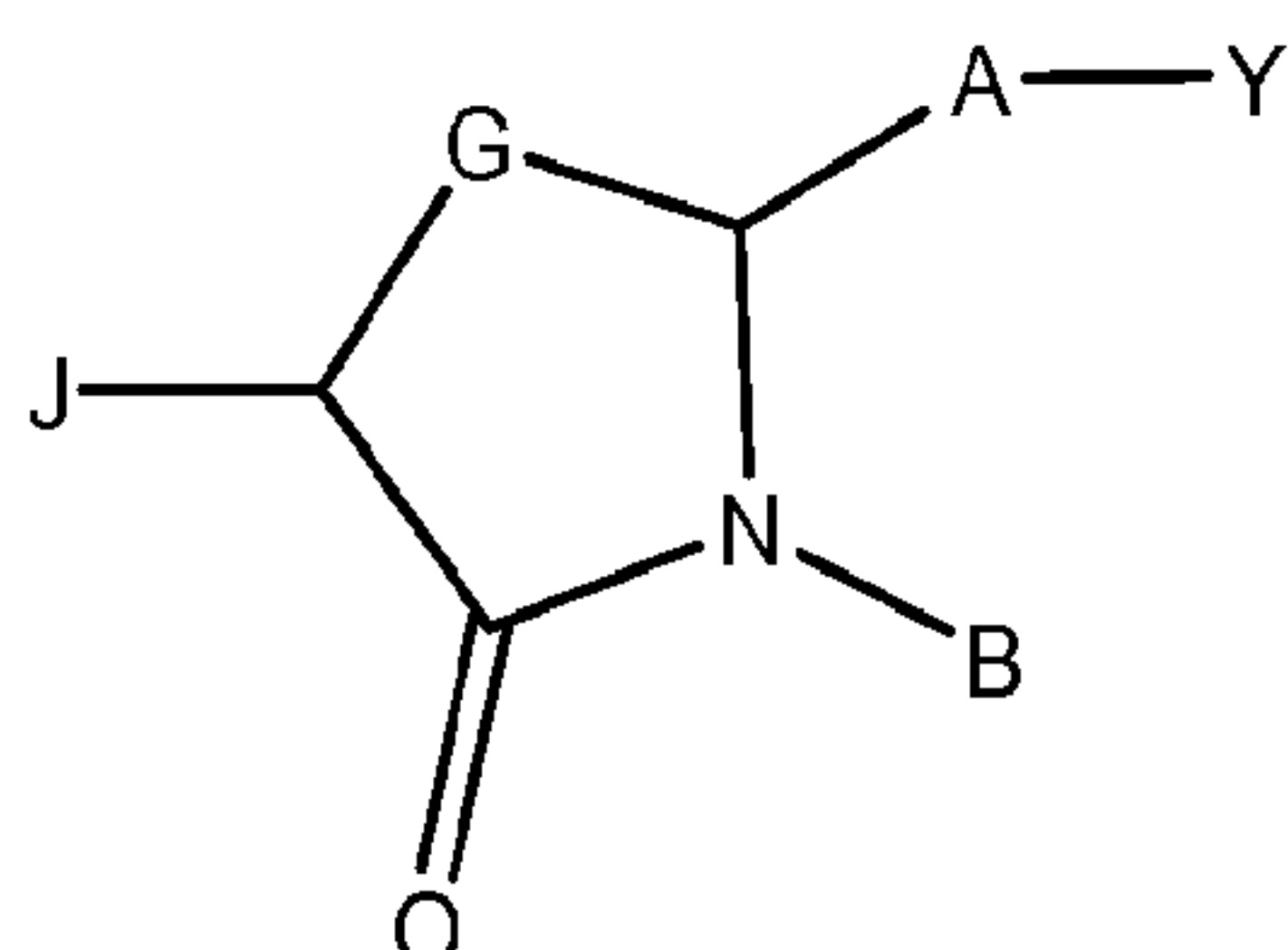
Structure	EP2 data			EP4 data		Other Receptors (EC50 in nM)					
	flpr EC50	cAMP EC50	Ki	flpr EC50	KI	hFP	hEP1	hEP3A	hTP	hIP	hDP
	4400	515	17469	>10000	1461	NA	NA	8324	NA	NA	NA
	8	0.06	14	NT	>10000	NA	NA	11	NA	NA	213

30

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.

CLAIMSWhat is claimed is:

- 5 1. A compound having a structure



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

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;

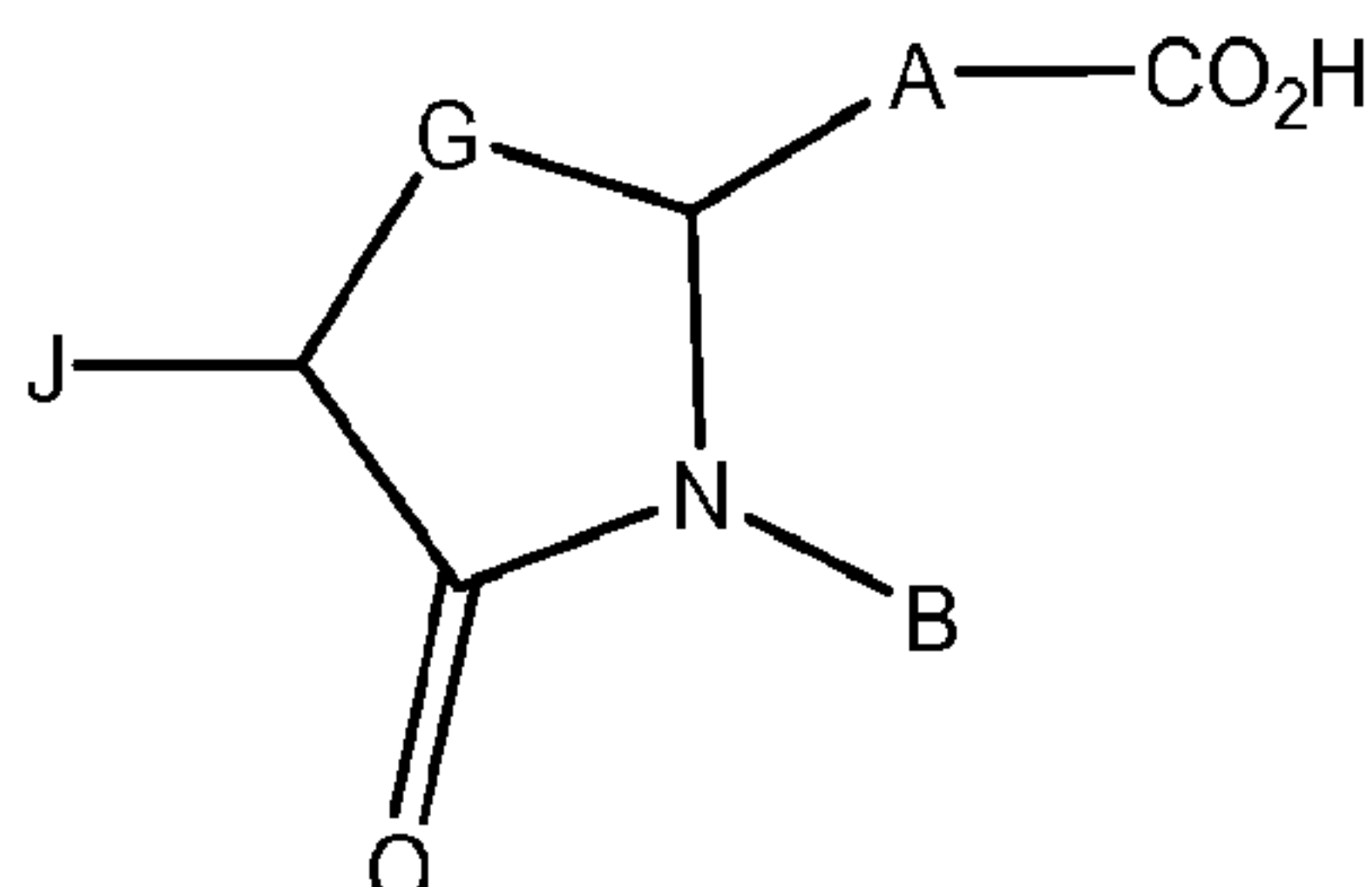
- 10 A is $-(CH_2)_6-$, *cis* $-CH_2CH=CH-(CH_2)_3-$, or $-CH_2C\equiv C-(CH_2)_3-$, wherein 1 or 2 carbon atoms may be replaced by S or O; or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-CH_2-$ may be replaced by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

G is O, S, S=O, or S(=O)₂;

J is H, halogen, CF₃; or C₁₋₆ alkyl; and

- 15 B is aryl or heteroaryl.

2. A compound which 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;

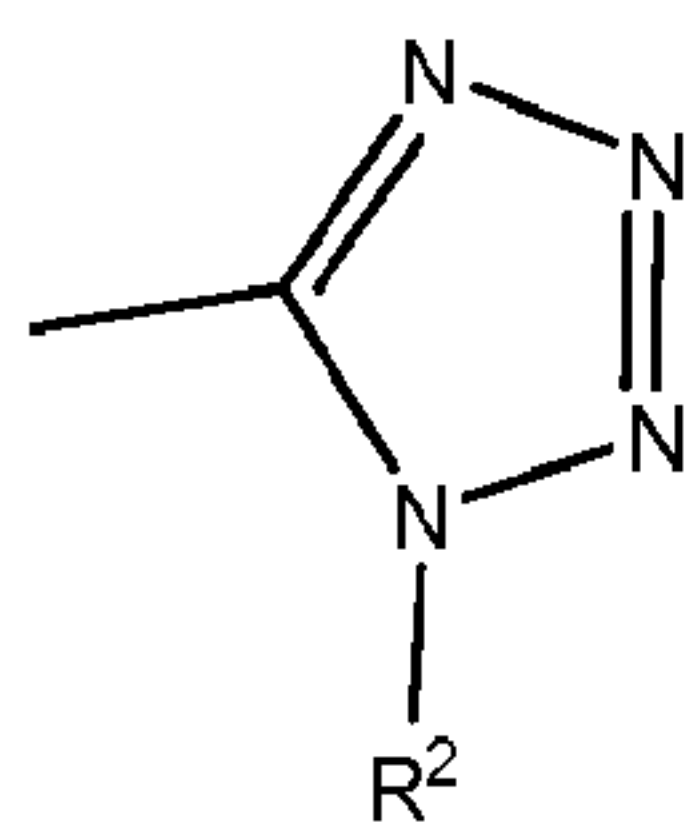
- 20 or A is $-(CH_2)_m-Ar-(CH_2)_o-$ wherein Ar is interarylene or heterointerarylene, the sum of m and o is 1, 2, 3, or 4, and wherein 1 $-CH_2-$ may be replaced by S or O, and 1 $-CH_2-CH_2-$ may be replaced by $-CH=CH-$ or $-C\equiv C-$;

G is O, S, S=O, or S(=O)₂;

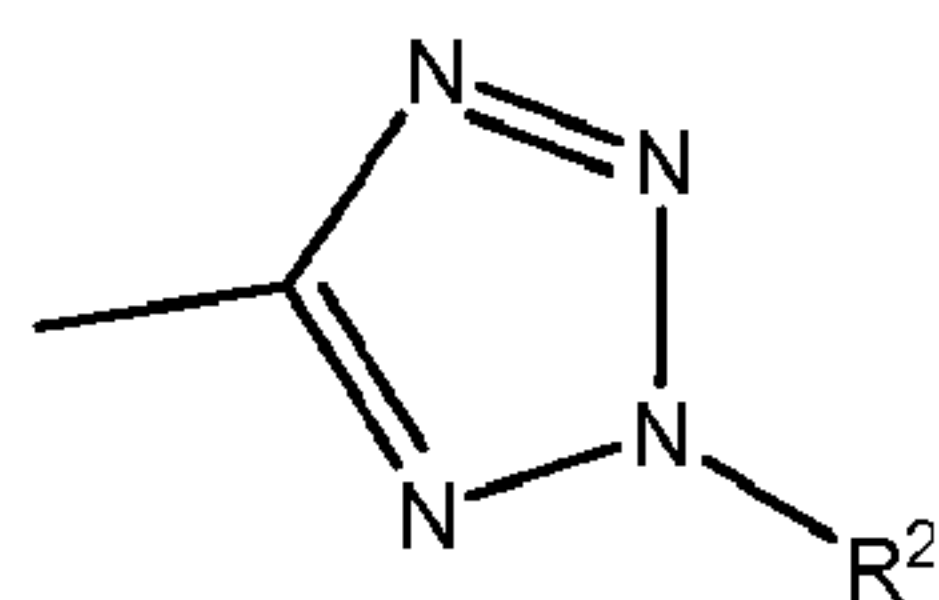
J is H, halogen, CF₃; or C₁₋₆ alkyl; and

B is aryl or heteroaryl.

- 25 3. The compound of claim 1 wherein Y is selected from CO₂R², CON(R²)₂, CON(OR²)R², CON(CH₂CH₂OH)₂, CONH(CH₂CH₂OH), CH₂OH, P(O)(OH)₂, CONHSO₂R², SO₂N(R²)₂, SO₂NHR²,



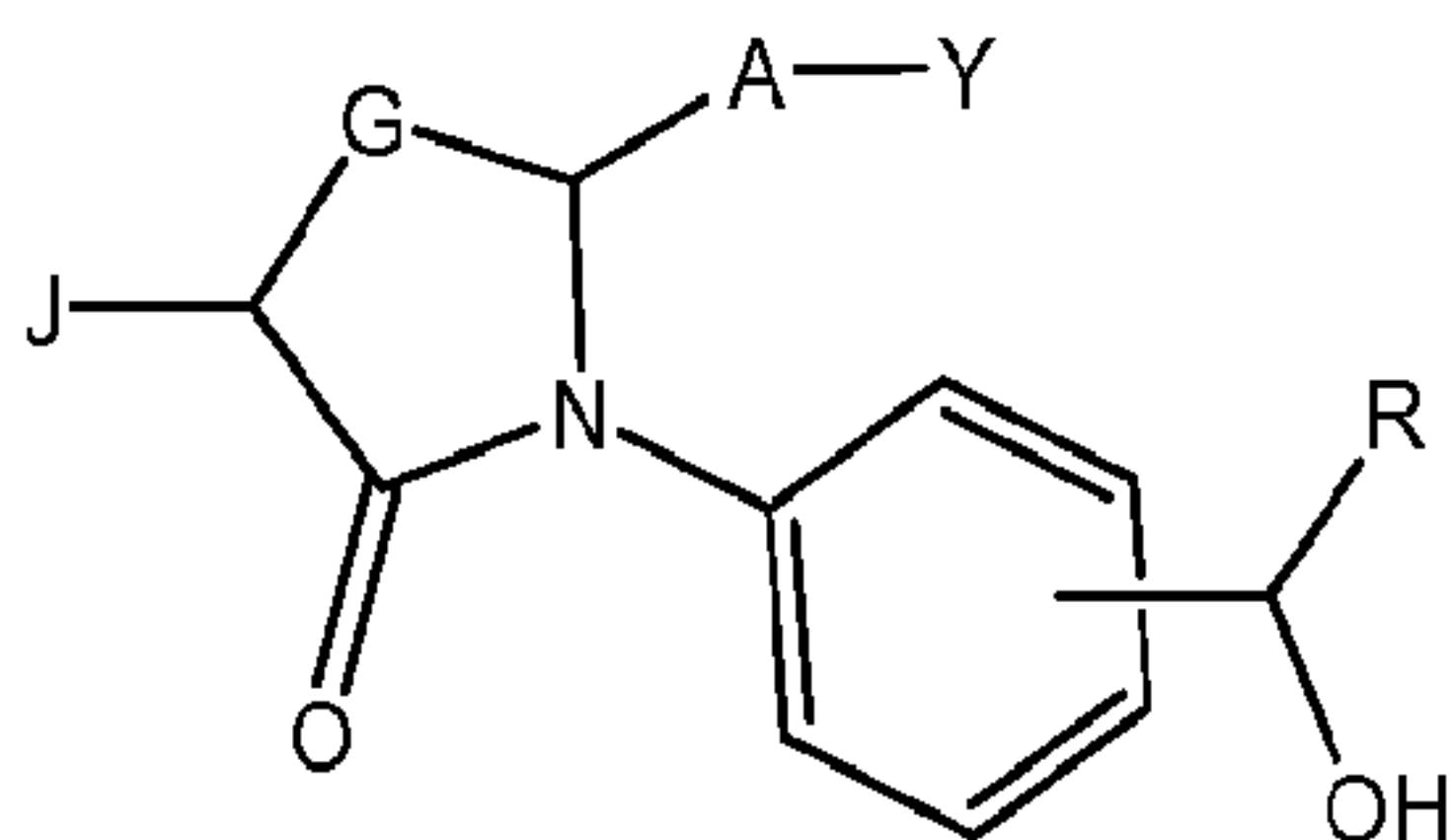
and



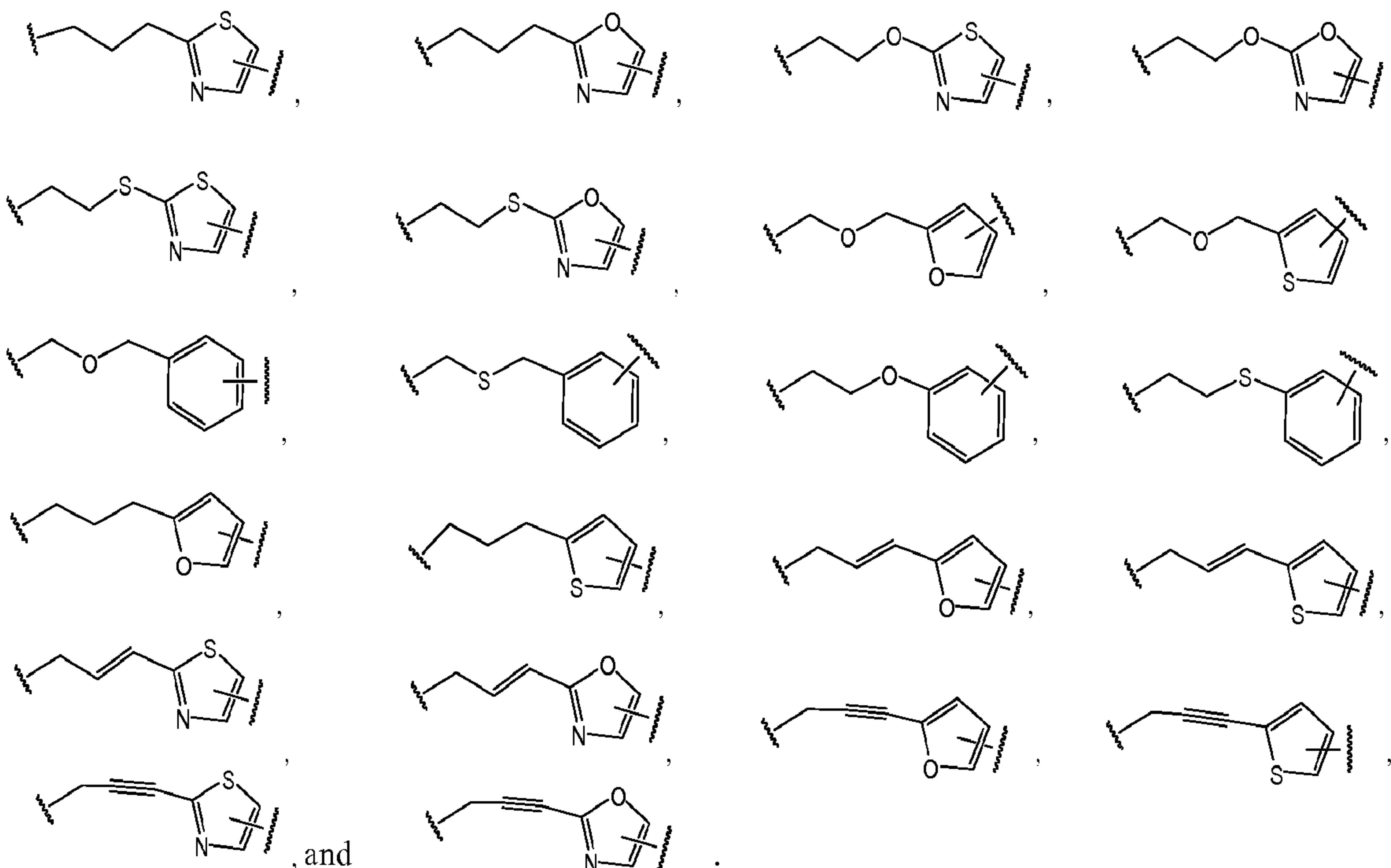
;

wherein R² is independently H, C₁₋₆ alkyl, unsubstituted phenyl, or unsubstituted biphenyl.

4. The compound according to any one of claims 1-3 wherein B is substituted phenyl.
5. The compound of claim 1 wherein J is hydrogen.
6. The compound of claim 4 having a structure

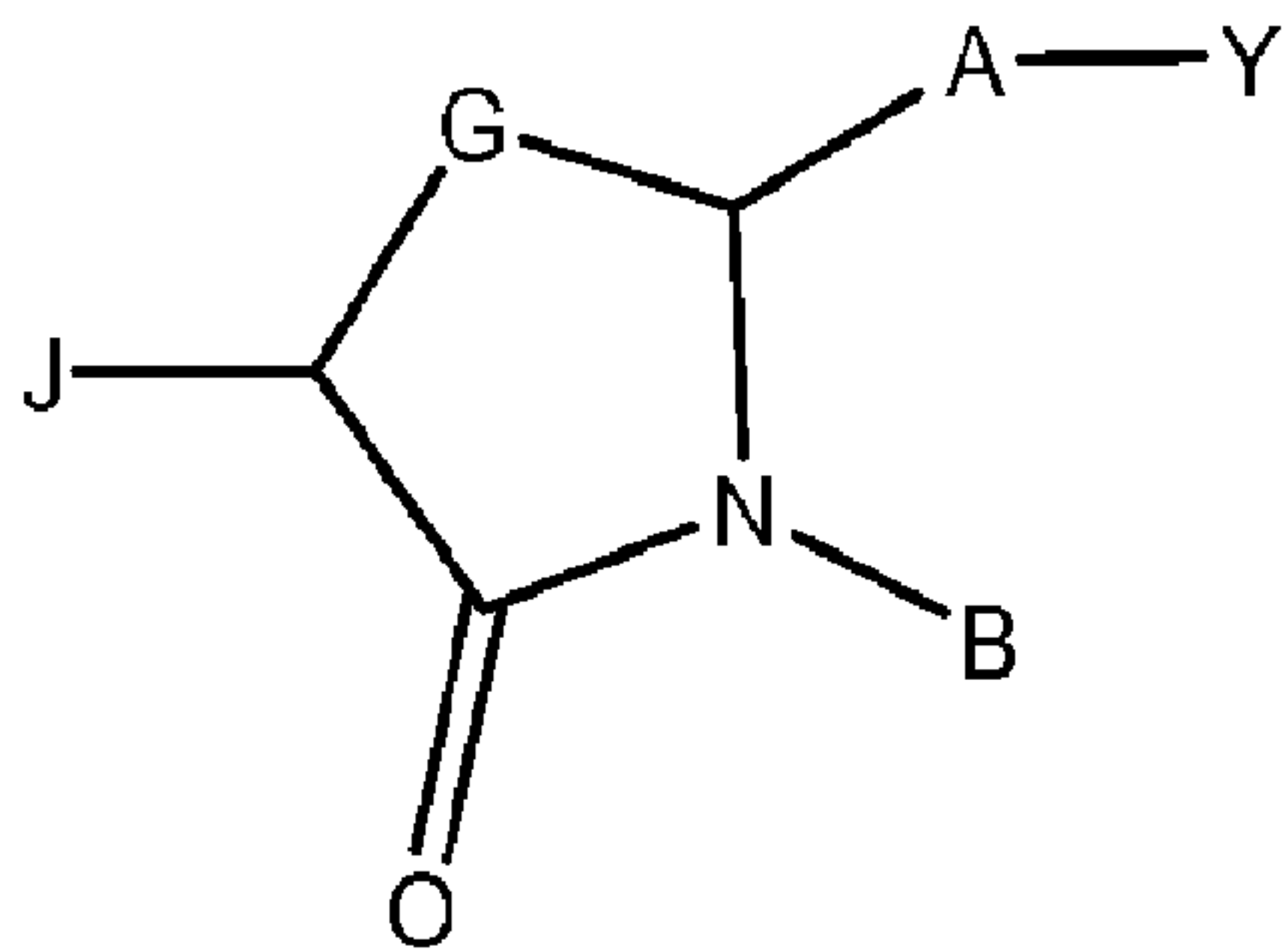


- 5 or a pharmaceutically acceptable salt thereof, or a prodrug thereof;
wherein R is hydrogen or C₁₋₁₀ hydrocarbyl.
7. The compound of claim 6 wherein R is alkyl.
8. The compound according to any one of claims 1-7 wherein A has a structure selected from:

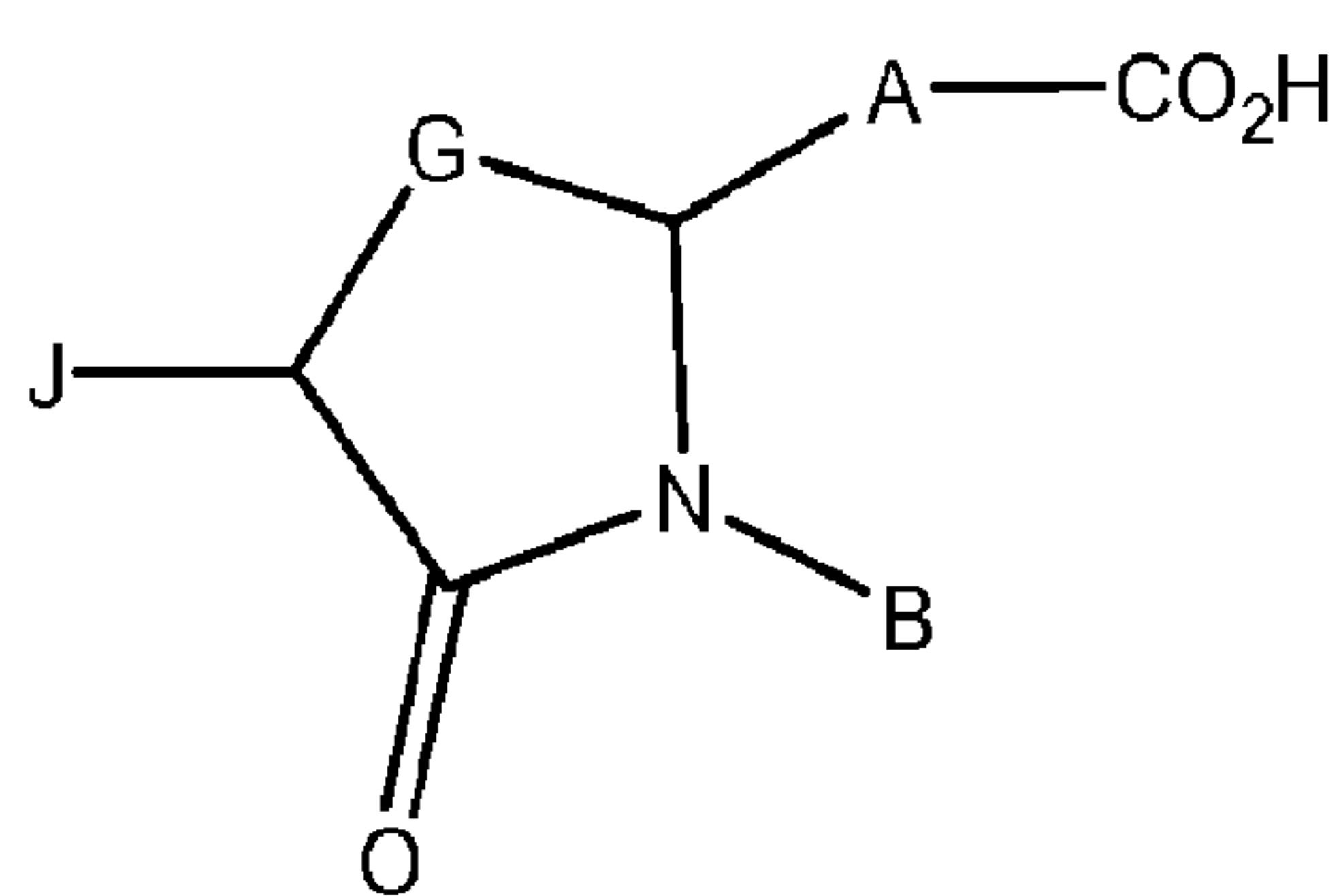


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9. The compound of claim according to any one of claims 1-7 wherein A is 5-(3-propyl)thiophen-2-yl.
10. The compound according to any one of claims 1-9 wherein G is O.
11. The compound according to any one of claims 1-9 wherein G is S.
12. A method of reducing intraocular pressure comprising administering a therapeutically effective amount of a compound
- 15 according to any one of claims 1-11 to a mammal in need thereof.
13. Use of a compound according to any one of claims 1-11 in the manufacture of a medicament for the treatment of glaucoma or ocular hypertension in a mammal.
14. A kit comprising a composition comprising compound according to any one of claims 1-11, a container, and instructions for administration of said composition to a mammal for the treatment of glaucoma or ocular hypertension.
- 20 15. A composition comprising a compound according to any one of claims 1-11, wherein said composition is a liquid which is ophthalmically acceptable.



(I)



(II)