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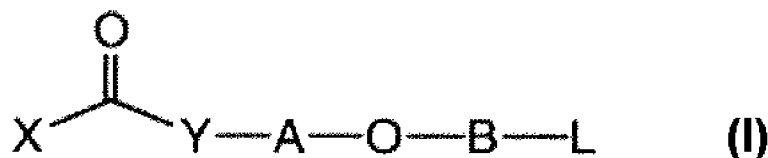
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(54) Title: NOVEL ETHER-BASED COMPOUNDS AND THEIR USE



(57) Abstract: This invention relates to compounds having the structure herein X, Y, A, B, and L are further described herein.



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NOVEL ETHER-BASED COMPOUNDS AND THEIR USE

- 5 This application claims priority of U.S. Provisional Application No. 61/325,197, filed April 16, 2010, the contents of which are hereby incorporated by reference.

Throughout this application, certain publications are referenced in brackets. Full citations for these publications may be found immediately preceding the claims. The disclosures of these
10 publications in their entireties are hereby incorporated by reference into this application in order to describe more fully the state of the art to which this invention relates.

Background of the Invention

Inflammation, a key component of immunity, functions in both defense and
15 pathophysiological events to maintain the homeostasis of tissues, organs and individual cells. Although rheumatological diseases have long been the prototypical inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, autoimmune diseases, and cancer are now appreciated as having inflammation as a unifying component of their pathogenesis.

20 In cancer, chronic inflammation often acts as a tumor promoter, resulting in aggressive cancerous growth and spread. Many of the same inflammatory factors that promote tumor growth also are responsible for cancer cachexia/anorexia, pain, debilitation, and shortened survival. A compelling case has been made even for attacking inflammation at initial diagnosis to improving patient quality of life and survival.

25 Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used anti-inflammatory compounds, with aspirin, the prototypical NSAID, still being one of the oldest and most extensively used medications in the world [1, 2]. NSAIDs have a significant antineoplastic effect, which should be viewed, at least in part, in the context of the increasingly appreciated
30 role of inflammation in cancer. Aspirin is formally documented to be a chemopreventive agent against colon cancer. For other NSAIDs, the evidence on their antineoplastic properties is quite strong but still it is based mainly on epidemiological studies [3-5]. For example, a recent meta-analysis of 91 epidemiological studies showed a significant exponential decline

with increasing intake of NSAIDs in the risk for 7-10 malignancies including the four major types: colon, breast, lung, and prostate cancer [6, 7].

NSAIDs prevent cancer likely through pleiotropic effects. [8, 9] It is, however, clear that
5 conventional NSAIDs do not meet two important criteria for their wide application as chemopreventive agents against cancer, i.e. safety and high efficacy, as NSAIDs are associated with a considerable number of side effects, and their efficacy is rather limited, not exceeding 50% [8].

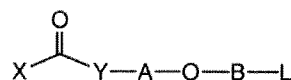
10 Statins, a frequently used class of agents for the treatment of dyslipidemia, have been considered to have anti-cancer properties. Although not uniformly accepted, there is strong evidence that this is the case based on epidemiological and preclinical data. For example, in a large randomized control study (RCT), Alsheikh-Ali et al. reported that there was a significant inverse association between patients treated with statins for LDL-C (low-density
15 lipoprotein cholesterol) and cancer incidence [10]. This evidence was supported by epidemiologic data, which observed an inverse relationship between serum cholesterol levels and cancer incidence [11].

Other meta-analyses of RCTs on statins, however, suggest a neutral relationship between statin treatment and cancer incidence [12-14]. Preclinical data show a favorable cytotoxic
20 effect on cancer cells and strong anticancer effects in animal models of cancer. Nevertheless, the uncertainty on statins' effect on cancer persists, and it may reflect, as in the case of NSAIDs, limited anti-cancer efficacy by statins.

Thus, there is a need to develop compounds with improved efficacy and safety profiles for
25 the treatment of cancer and other inflammation-related diseases, such as neurodegenerative, rheumatological, and cardiovascular diseases.

Summary of the Invention

This invention provides a compound having the structure:



wherein

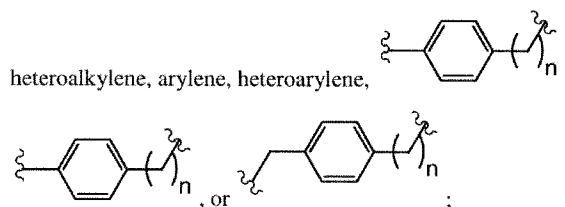
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X is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic;

Y is -O-, -NH-, or -S-;

10

A and B are each, independently, alkylene, alkenylene, alkynylene,



15

L is -ONO₂, -OSO₂R₁, -OSO₂OR₁, -OPO(OR₁)₂, -OB(OR₁)₂, -N₂⁺, -O(R₁)₂⁺, -S(R₁)₂⁺, N(R₁)₃⁺, or halogen,

wherein each instance of R₁ is, independently, H, alkyl, or aryl;

n and m are each, independently, an integer greater than or equal to 1;

20

wherein when A is alkylene and -(CH₂)_n and n is 2, L is -OPO(OR₁)₂, -OB(OR₁)₂, -N₂⁺, -O(R₁)₂⁺, -S(R₁)₂⁺, or halogen;

wherein each instance of alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene, heteroalkylene is branched or unbranched, substituted or unsubstituted; and

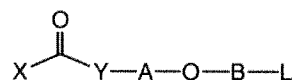
25

wherein each instance of cycloalkyl, aryl, heterocyclic, heteroaryl, and heteroarylene is substituted or unsubstituted;

or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

This invention provides a compound having the structure:



wherein

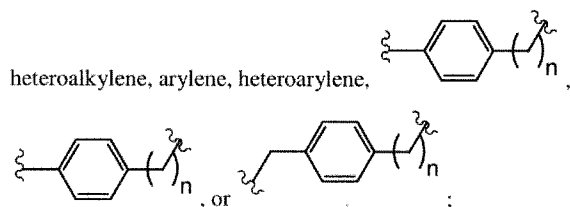
5

X is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic;

Y is -O-, -NH-, or -S-;

10

A and B are each, independently, alkylene, alkenylene, alkynylene,



15

L is -ONO₂, -OSO₂R₁, -OSO₂OR₁, -OPO(OR₁)₂, -OB(OR₁)₂, -N₂⁺, -O(R₁)₂⁺, -S(R₁)₂⁺, N(R₁)₃⁺, or halogen,

wherein each instance of R₁ is, independently, H, alkyl, or aryl;

n and m are each, independently, an integer greater than or equal to 1;

20

wherein when A is alkylene and -(CH₂)_n- and n is 2, L is -OPO(OR₁)₂, -OB(OR₁)₂, -N₂⁺, -O(R₁)₂⁺, -S(R₁)₂⁺, or halogen;

wherein each instance of alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene, heteroalkylene is branched or unbranched, substituted or unsubstituted; and

25

wherein each instance of cycloalkyl, aryl, heterocyclic, heteroaryl, and heteroarylene is substituted or unsubstituted;

or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof.

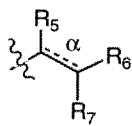
In an embodiment,

5 X is $-(CR_2R_3)_a-R_4$,

wherein

a is an integer from 1 to 10;

each instance of R_2 and R_3 are each, independently, H, OH, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, or aryl substituted with C_1 - C_5 alkyl;



10 R_4 is H or

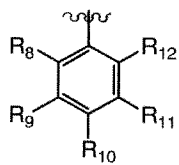
wherein

R_5 is H, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, or C_2 - C_{10} alkynyl;

R_6 and R_7 are each, independently, H, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclic;

15 α is present or absent;

or



wherein

20 R_8 , R_9 , R_{10} , R_{11} , and R_{12} are each, independently, H, OH, halogen, -CN, -NO₂, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, $-(C=O)-R_{13}$, or $-O-(C=O)-R_{13}$,

wherein R_{13} is H, -OH, -OR₁₄, -NR₁₄R₁₅, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, or C_2 - C_{10} alkynyl,

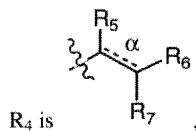
25 wherein R_{14} and R_{15} are, each, independently, H, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, or C_2 - C_{10} alkynyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment,

X is $-(CH_2)-(CHOH)-(CH_2)-(CHOH)-R_4$,

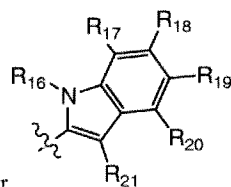
wherein



wherein

R₅ is H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

R₆ and R₇ are each, independently, H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-



C₁₀ alkynyl, or

wherein R₁₆ is H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, or -

(C=O)-R₂₂,

wherein R₂₂ is H, -OH, -OR₂₃, -NR₂₃R₂₄, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl,

wherein R₂₃ and R₂₄ are, each, independently, H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

R₁₇, R₁₈, R₁₉, R₂₀, and R₂₁ are each, independently, H, -OH, halogen, -CN, -NO₂, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, -(C=O)-R₂₅, -O-(C=O)-R₂₅, or aryl substituted by halogen,

wherein R₂₅ is H, -OH, -OR₂₆, -NR₂₆R₂₇, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl,

wherein R₂₆ and R₂₇ are, each, independently, H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

α is present or absent;

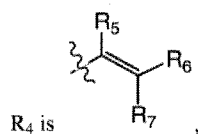
or a pharmaceutically acceptable salt thereof.

In a further embodiment,

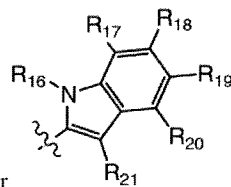
X is $-(CH_2)-(CHOH)-(CH_2)-(CHOH)-R_4$,

wherein

8



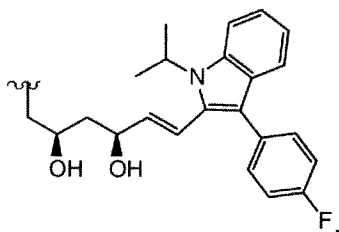
wherein

R₅ is H;R₆ and R₇ are each, independently, H orwherein R₁₆ is C₁-C₁₀ alkyl;R₁₇, R₁₈, R₁₉, R₂₀, and R₂₁ are each, independently, H or aryl substituted with halogen;

or a pharmaceutically acceptable salt thereof.

10 In an embodiment,

X is



or a pharmaceutically acceptable salt thereof.

15 In another embodiment,

X is -CR₂R₃-R₄,

wherein

each instance of R₂ and R₃ are each, independently, C₁-C₁₀ alkyl or aryl substituted with C₁-C₅ alkyl;

20

R₄ is H,

or a pharmaceutically acceptable salt thereof.

In a further embodiment,

X is $-\text{CR}_2\text{R}_3-\text{R}_4$,

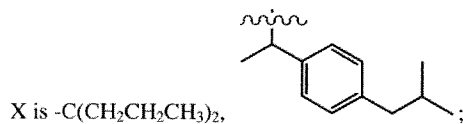
5 wherein

each instance of R_2 and R_3 are each, independently, methyl, propyl, or aryl substituted with isobutyl;

R_4 is H,

10 or a pharmaceutically acceptable salt thereof.

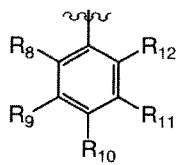
In an embodiment,



15 or a pharmaceutically acceptable salt thereof.

In another embodiment,

X is



20

wherein

R_8 , R_9 , R_{10} , R_{11} , and R_{12} are each, independently, H, OH, halogen, $-\text{CN}$, $-\text{NO}_2$,

C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(\text{C}=\text{O})-\text{R}_{13}$, or $-\text{O}-(\text{C}=\text{O})-\text{R}_{13}$,

wherein R_{13} is H, $-\text{OH}$, $-\text{OR}_{14}$, $-\text{NR}_{14}\text{R}_{15}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl,

25

or C_2-C_{10} alkynyl,

wherein R_{14} and R_{15} are, each, independently, H, C_1-C_{10} alkyl,

C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

or a pharmaceutically acceptable salt thereof.

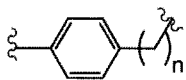
In an embodiment of the compound,

5

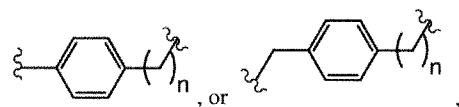
X is a pharmaceutically active agent;

Y is -O-, -NH-, or -S-;

10

A is $-(CH_2)_n-$ or ; and

B is $-(CH_2CH_2O)_mCH_2-$, $-(CH_2CH_2O)_mCH_2CH_2-$, $-(CH_2)_n-$,



wherein

15

n is an integer from 1 to 20,

m is an integer from 1 to 200;

L is $-ONO_2$, $-OSO_2R_1$, $-OSO_2OR_1$, $-OPO(OR_1)_2$, $-OB(OR_1)_2$, $-N_2^+$, $-O(R_1)_2^+$, $-S(R_1)_2^+$, $N(R_1)_3^+$, or halogen,

20

wherein each instance of R_1 is, independently, H, alkyl, or aryl;

wherein when A is $-(CH_2)_n-$ and n is 2, L is $-OPO(OR_1)_2$, $-OB(OR_1)_2$, $-N_2^+$, $-O(R_1)_2^+$, $-S(R_1)_2^+$, or halogen;

25

wherein each instance of alkyl, alkenyl, and alkynyl is branched or unbranched, substituted or unsubstituted; and

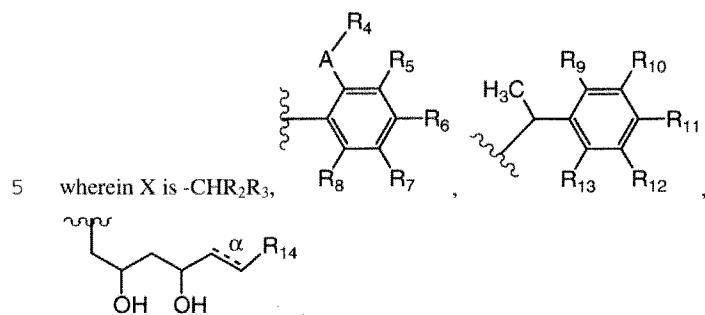
wherein each instance of cycloalkyl, aryl, heterocyclic, and heteroaryl is substituted or unsubstituted;

30

12

or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof.

In an embodiment,



wherein A is $-\text{O}-$ or $-\text{NH}-$,

R_4 is H, $-(\text{C}=\text{O})\text{CH}_3$, or aryl,

R_5 , R_6 , R_7 , and R_8 are each, independently, alkyl or aryl;

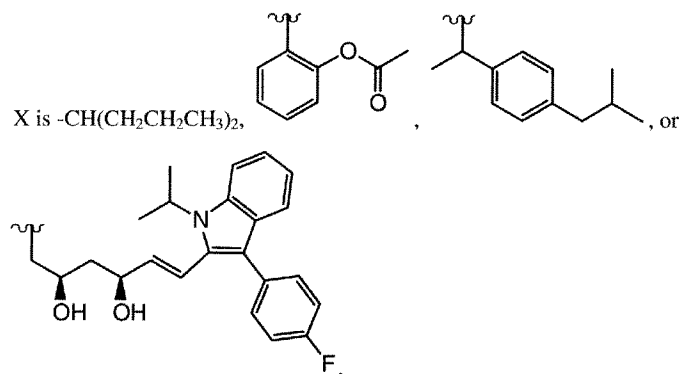
10 R_9 , R_{10} , R_{11} , R_{12} , and R_{13} are each, independently, halogen, alkyl, aryloxy, or heterocyclic;

R_{14} is heteroaryl or cycloalkyl, and

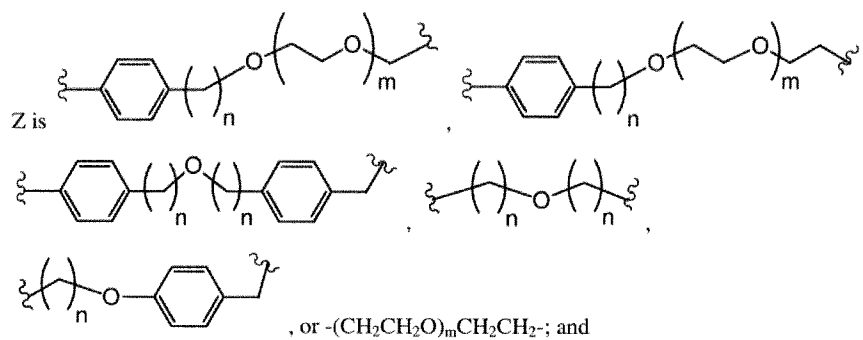
bond α is present or absent;

15 wherein each instance of alkyl is unbranched or branched, substituted or unsubstituted, and each instance of aryl is substituted or unsubstituted.

In another embodiment,



14

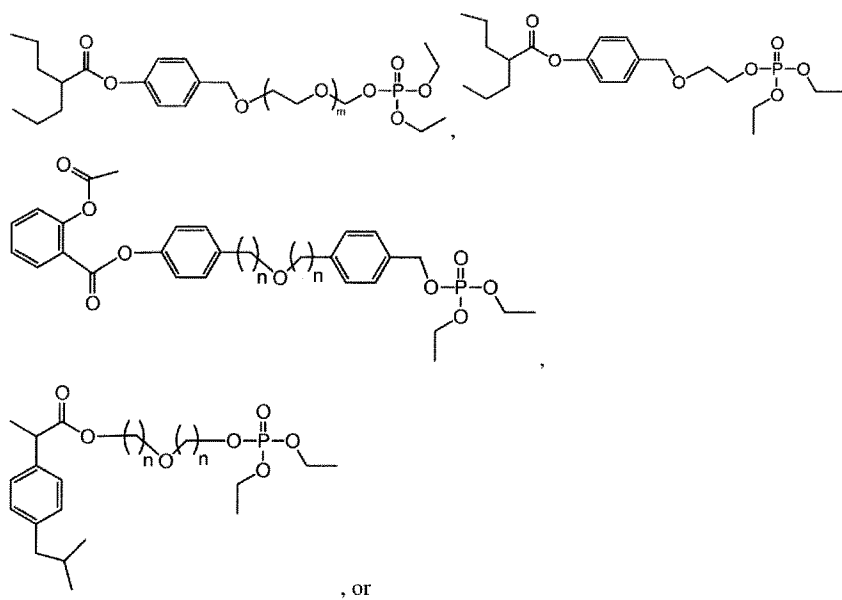


L is $-\text{OPO}(\text{OCH}_2\text{CH}_3)_2$;

5

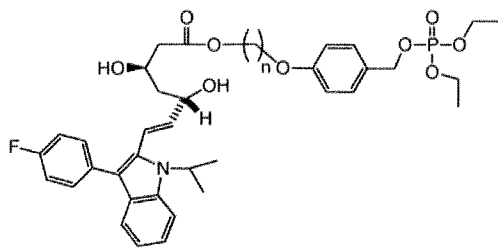
or a pharmaceutically acceptable salt thereof.

In further embodiments, the compound has the structure



10

15



;

or a pharmaceutically acceptable salt thereof.

This invention provides methods of preventing or treating cancer in a subject comprising
 5 administering to the subject compounds and compositions of the present invention so as to prevent or treat cancer in the subject.

This invention further provides methods of treating diseases characterized by inflammation in
 a subject comprising administering to the subject compounds and compositions of the present
 10 invention so as to treat the disease characterized by inflammation in the subject. Diseases characterized by inflammation include, but are not limited to rheumatological disease, neurodegenerative disease, and cardiovascular disease.

This invention further provides methods of treating pain and/or fever in a subject comprising
 15 administering to the subject compounds and compositions of the present invention so as to treat pain and/or fever in the subject.

The compounds of the present invention include hydrates, solvates, and complexes of the
 compounds used by this invention. If a chiral center or another form of an isomeric center is
 20 present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. The compounds described in the present invention
 25 are in racemic form or as individual enantiomers. The enantiomers can be separated using known techniques, such as those described in Pure and Applied Chemistry 69, 1469–1474, (1997) IUPAC. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein

compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

5 When the structure of a compound of this invention includes an asymmetric carbon atom, it is understood that the compound occurs as a racemate, racemic mixture, and isolated single enantiomer. All such isomeric forms of these compounds are expressly included in this invention. Each stereogenic carbon may be of the R or S configuration. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers
10 and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis, such as those described in "Enantiomers, Racemates and Resolutions" by J. Jacques, A. Collet and S. Wilen, Pub. John Wiley & Sons, NY, 1981. For example, the resolution may be carried out by preparative
15 chromatography on a chiral column.

The subject invention is also intended to include all isotopes of atoms occurring on the compounds disclosed herein. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of
20 hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

It will be noted that any notation of a carbon in structures throughout this application, when used without further notation, are intended to represent all isotopes of carbon, such as ^{12}C , ^{13}C , or ^{14}C . Furthermore, any compounds containing ^{13}C or ^{14}C may specifically have the
25 structure of any of the compounds disclosed herein.

It will also be noted that any notation of a hydrogen in structures throughout this application, when used without further notation, are intended to represent all isotopes of hydrogen, such as ^1H , ^2H , or ^3H . Furthermore, any compounds containing ^2H or ^3H may specifically have the
30 structure of any of the compounds disclosed herein.

Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art using appropriate isotopically-labeled reagents in place of the non-labeled reagents employed.

As used herein, "alkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms and may be unsubstituted or substituted. Thus, C_1-C_n as in " C_1-C_n alkyl" is defined to include groups having 1, 2, ..., n-1 or n carbons in a linear or branched arrangement. For example, C_1-C_6 , as in " C_1-C_6 alkyl" is defined to include groups having 1, 2, 3, 4, 5, or 6 carbons in a linear or branched arrangement, and specifically includes methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, pentyl, hexyl, and octyl.

As used herein, "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least 1 carbon to carbon double bond, and up to the maximum possible number of non-aromatic carbon-carbon double bonds may be present, and may be unsubstituted or substituted. For example, " C_2-C_6 alkenyl" means an alkenyl radical having 2, 3, 4, 5, or 6 carbon atoms, and up to 1, 2, 3, 4, or 5 carbon-carbon double bonds respectively. Alkenyl groups include ethenyl, propenyl, and butenyl.

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing at least 1 carbon to carbon triple bond, and up to the maximum possible number of non-aromatic carbon-carbon triple bonds may be present, and may be unsubstituted or substituted. Thus, " C_2-C_6 alkynyl" means an alkynyl radical having 2 or 3 carbon atoms and 1 carbon-carbon triple bond, or having 4 or 5 carbon atoms and up to 2 carbon-carbon triple bonds, or having 6 carbon atoms and up to 3 carbon-carbon triple bonds. Alkynyl groups include ethynyl, propynyl and butynyl.

"Alkylene", "alkenylene" and "alkynylene" shall mean, respectively, a divalent alkane, alkene and alkyne radical, respectively. It is understood that an alkylene, alkenylene, and alkynylene may be straight or branched. An alkylene, alkenylene, and alkynylene may be unsubstituted or substituted.

As used herein, the term "heteroalkyl" refers to a straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at

any interior position of the heteroalkyl group. Examples include $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$.

- 5 Similarly, the term "heteroalkylene" means a divalent radical derived from heteroalkyl, as exemplified by $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$, $-(\text{CH}_2\text{CH}_2\text{O})_m\text{CH}_2-$, and $-(\text{CH}_2\text{CH}_2\text{O})_m\text{CH}_2\text{CH}_2-$, where m is an integer from 1 to 200. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and
- 10 heteroalkylene linking groups, no orientation of the linking group is implied.

As used herein, the term "arylene" refers to divalent aromatic groups having in the range of 6 up to 14 carbon atoms.

- 15 As used herein, the term "heteroarylene" means a divalent radical derived from heteroaryl.

A "heteroalkyl", "heteroalkylene", "arylene", and "heteroarylene" may be unsubstituted or substituted with one or more substituents set forth herein.

- 20 As used herein, the term "cycloalkyl" refers to a monocyclic, bicyclic, or tricyclic ring system, which may be saturated or partially saturated, i.e. possesses one or more double bonds. Monocyclic ring systems are exemplified by a saturated cyclic hydrocarbon group containing from 3 to 8 carbon atoms. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl
- 25 and cyclooctyl. Bicyclic fused ring systems are exemplified by a cycloalkyl ring fused to another cycloalkyl ring. Examples of bicyclic fused ring systems include, but are not limited to, decalin, 1,2,3,7,8,8a-hexahydro-naphthalene, and the like. Tricyclic fused ring systems are exemplified by a cycloalkyl bicyclic fused ring system fused to an additional cycloalkyl group.

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As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or polycyclic carbon ring of up to 10 atoms in each ring, wherein at least one ring is aromatic, and may be unsubstituted or substituted. Examples of such aryl elements include phenyl, p-toluenyl (4-methylphenyl), naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or

acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "arylalkyl" refers to alkyl groups as described above wherein one or more bonds to hydrogen contained therein are replaced by a bond to an aryl group as described above. It is understood that an "arylalkyl" group is connected to a core molecule through a bond from the alkyl group and that the aryl group acts as a substituent on the alkyl group. Examples of arylalkyl moieties include, but are not limited to, benzyl (phenylmethyl), p-trifluoromethylbenzyl (4-trifluoromethylphenylmethyl), 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and the like.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or polycyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Bicyclic aromatic heteroaryl groups include phenyl, pyridine, pyrimidine or pyridazine rings that are (a) fused to a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (b) fused to a 5- or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (c) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; or (d) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N or S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidyl, aziridinyl, 1,4-dioxanyl, hexahydroazepinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl,

pyrrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinoliny, isoquinoliny, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetra-hydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The term "heterocycle", "heterocyclyl", or "heterocyclic" refers to a mono- or poly-cyclic ring system which can be saturated or contains one or more degrees of unsaturation and contains one or more heteroatoms. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to ten-membered and is either saturated or has one or more degrees of unsaturation. The heterocycle may be unsubstituted or substituted, with multiple degrees of substitution being allowed. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s), heteroaryl ring(s), aryl ring(s), or cycloalkyl ring(s). Examples of heterocycles include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, piperazine, pyrrolidine, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, 1,3-oxathiolane, and the like.

The alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl substituents may be substituted or unsubstituted, unless specifically defined otherwise.

In the compounds of the present invention, alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl groups can be further substituted by replacing one or more hydrogen atoms by alternative non-hydrogen groups. These include, but are not limited to, halo, hydroxy, mercapto, amino, carboxy, cyano and carbamoyl.

The term "substituted" refers to a functional group as described above in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms, provided that normal valencies are maintained and that the substitution results in a stable compound. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Examples of substituent groups include the functional groups

described above, and, in particular, halogens (i.e., F, Cl, Br, and I); alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and trifluoromethyl; hydroxyl; alkoxy groups, such as methoxy, ethoxy, n-propoxy, and isopropoxy; aryloxy groups, such as phenoxy; arylalkyloxy, such as benzyloxy (phenylmethoxy) and p-trifluoromethylbenzyloxy (4-trifluoromethylphenylmethoxy); heteroaryloxy groups; sulfonyl groups, such as trifluoromethanesulfonyl, methanesulfonyl, and p-toluenesulfonyl; nitro, nitrosyl; mercapto; sulfanyl groups, such as methylsulfanyl, ethylsulfanyl and propylsulfanyl; cyano; amino groups, such as amino, methylamino, dimethylamino, ethylamino, and diethylamino; and carboxyl. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

The term "acid" refers to acids under both the Bronsted-Lowry and the Lewis definitions of acids. Under the Bronsted-Lowry definition, acids are defined as proton (H^+) donors. Examples of Bronsted-Lowry acids include, but are not limited to, inorganic acids such as hydrofluoric, hydrochloric, hydrobromic, hydroiodic, perchloric, hypochlorous, sulfuric, sulfurous, sulfamic, phosphoric, phosphorous, nitric, nitrous, and the like; and organic acids such as formic, acetic, trifluoroacetic, p-toluenesulfonic, camphorsulfonic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. Under the Lewis definition, an acid is an electron acceptor capable of accepting electron density by virtue of possessing unoccupied orbitals. Examples of Lewis acids include, but are not limited to, metal salts such as $AlCl_3$, $FeCl_3$, $FeCl_3 \cdot SiO_2$, $CrCl_2$, $HgCl_2$, $CuCl$, $TiCl_4$, $Yb(OTf)_3$, $InOTf$, $TiCl_2(OiPr)_2$, and $Ti(OiPr)_4$; organometallic species such as trimethylaluminum and

dimethylaluminum chloride; and boron species such as BH_3 , $\text{B}(\text{Et})_3$, BF_3 , $\text{BF}_3\text{-OEt}_2$, BBr_3 , $\text{B}(\text{OMe})_3$, and $\text{B}(\text{OiPr})_3$.

5 Examples of bases include, but are not limited to, alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, sodium isopropoxide, sodium tert-butoxide, potassium tert-butoxide, lithium methoxide; alkali metal hydrides, such as lithium hydride, sodium hydride, and potassium hydride; alkali metal bicarbonates and carbonates, such as sodium bicarbonate, sodium carbonate, lithium bicarbonate, lithium carbonate,
10 potassium carbonate, potassium bicarbonate, cesium carbonate, and cesium bicarbonate; organolithium bases, such as methyllithium, n-butyllithium, s-butyllithium, tert-butyllithium, isobutyllithium, phenyllithium, ethyllithium, n-hexyllithium, and isopropyllithium; amide bases, such as lithium amide, sodium amide, potassium amide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium diisopropylamide,
15 lithium diethylamide, lithium dicyclohexylamide, and lithium 2,2,6,6-tetramethylpiperidine; and amine bases, such as pyridine, 4-(dimethylamino)pyridine, trimethylamine, diethylamine, triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), and the like.

20 As used herein, the term “leaving group” refers to a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage, for example, in nucleophilic substitution. Upon heterolytic bond cleavage, leaving groups can be anions or neutral molecules. Examples of leaving groups include, but are not limited to, nitrates ($-\text{ONO}_2$), sulfates ($-\text{OSO}_2\text{OR}$), sulfonates ($-\text{OSO}_2\text{R}$), phosphates ($-\text{OPO}(\text{OH})_2$), phosphate esters ($-\text{OPO}(\text{OR})_2$), boronic
25 esters ($-\text{OB}(\text{OR})_2$), diazonium ($-\text{N}_2^+$), halides, $-\text{OR}_2^+$, $-\text{OH}_2^+$, $-\text{SR}_2^+$, $-\text{NR}_3^+$, and the like. Examples of sulfonate leaving groups include, but are not limited, p-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate, and the like. Examples of phosphate ester leaving groups include, but are not limited to, $-\text{OPO}(\text{OMe})_2$, $-\text{OPO}(\text{OEt})_2$, $-\text{OPO}(\text{OiPr})_2$, and the like.

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As used herein, the term “pharmaceutically active agent” means any substance or compound suitable for administration to a subject and furnishes biological activity or other direct effect in the treatment, cure, mitigation, diagnosis, or prevention of disease, or affects the structure or any function of the subject. Pharmaceutically active agents include, but are not limited to,

substances and compounds described in the Physicians' Desk Reference (PDR Network, LLC; 64th edition; November 15, 2009) and "Approved Drug Products with Therapeutic Equivalence Evaluations" (U.S. Department Of Health And Human Services, 30th edition, 2010), which are hereby incorporated by reference. Pharmaceutically active agents which
5 have pendant carboxylic acid groups may be modified in accordance with the present invention using standard esterification reactions and methods readily available and known to those having ordinary skill in the art of chemical synthesis. Where a pharmaceutically active agent does not possess a carboxylic acid group, the ordinarily skilled artisan will be able to design and incorporate a carboxylic acid group into the pharmaceutically active agent where
10 esterification may subsequently be carried out so long as the modification does not interfere with the pharmaceutically active agent's biological activity or effect. Classes of pharmaceutically active agents include, but are not limited to, anticancer agents, NSAIDs, and statins.

15 The term "anticancer agents" refer to compounds useful for the treatment of various types of cancer. Examples of anticancer agents include, but are not limited to, alitretinoin, all-trans retinoic acid, chlorambucil, methotrexate, doxorubicin hydrochloride, fluorouracil, imiquimod, pemetrexed disodium, aminolevulinic acid, anastrozole, exemestane, nelarabine, azacitidine, bendamustine hydrochloride, bexarotene, bortezomib, bleomycin, irinotecan
20 hydrochloride, capecitabine, carboplatin, daunorubicin hydrochloride, cisplatin, cyclophosphamide, clofarabine, cytarabine, dacarbazine, decitabine, dasatinib, dexrazoxane hydrochloride, docetaxel, doxorubicin hydrochloride, leuprolide acetate, epirubicin hydrochloride, oxaliplatin, erlotinib hydrochloride, etoposide phosphate, raloxifene hydrochloride, fulvestrant, toremifene, letrozole, pralatrexate, fludarabine phosphate,
25 gefitinib, gemcitabine hydrochloride, imatinib mesylate, topotecan hydrochloride, romidepsin, ixabepilone, lapatinib ditosylate, lenalidomide, leucovorin calcium, temozolomide, plerixafor, paclitaxel, sorafenib tosylate, nilotinib, tamoxifen citrate, pazopanib hydrochloride, sunitinib malate, thalidomide, vincristine sulfate, vinblastine, melphalan, zoledronic acid, suberoylanilide hydroxamic acid, valproic acid, and the like.

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The term "NSAIDs" as used herein refers to non-steroidal anti-inflammatory drugs. NSAIDs comprise a structurally and, to a large extent, functionally diverse group of compounds approved for the treatment of patients with a variety of inflammatory diseases. They all have analgesic, antipyretic and anti-inflammatory effects. Broadly, NSAIDs can be categorized

into the following chemical groups: salicylates, arylalkanoic acids (e.g. sulindac), 2-arylpropionic acids (profens), N-arylanthranilic acids (fenamic acids), pyrazolidine derivatives, oxicams, and sulphonanilides. Most of the available NSAIDs are amenable to derivatization as described herein using methods readily available and known to those ordinarily skilled in the art. Examples of NSAIDS include, but are not limited to, acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenprofen calcium, flurobiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, nabumetone, naproxen, lomoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, flosulide, and the like.

The term "statin" as used herein refer to compounds that inhibit HMG-CoA reductase (or 3-hydroxy-3-methyl-glutaryl-CoA reductase). Most of the statins possess a free carboxylic acid group or lactone that is amenable to derivatization as described herein using methods readily available and known to those having ordinary skill in the art. Examples of statins include, but are not limited to, atorvastatin, cerivastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, lovastatin, simvastatin, and the like.

As used herein, abbreviations are defined as follows:

Ac = acetyl

4-DMAP = 4-(dimethylamino)pyridine

DMF = *N,N*-dimethylformamide

EDC = *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide

TBAF = tetra-*n*-butylammonium fluoride

TBS = *tert*-butyldimethylsilyl

TMS = trimethylsilyl

Tf = trifluoromethanesulfonyl

KHMDS = potassium bis(trimethylsilyl)amide or potassium hexamethyldisilazide

AIBN = 1,1'-azobisisobutyronitrile

9-BBN = 9-borabicyclo[3.3.1]nonane

DIBA = diisobutylaluminum

THF = tetrahydrofuran

MeOH = methanol

DCE = 1,2-dichloroethane

Ph = phenyl

Me = methyl

Et = ethyl

5 iPr = isopropyl

n-Bu = n-butyl

i-Bu = isobutyl

s-Bu = *sec*-butyl

t-Bu = *tert*-butyl

10 Ms = methanesulfonyl

Ts = *p*-toluenesulfonyl

SET = single electron transfer

15 In choosing the compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R₁, R₂, etc. are to be chosen in conformity with well-known principles of chemical structure connectivity.

20 The various R groups attached to the aromatic rings of the compounds disclosed herein may be added to the rings by standard procedures, for example those set forth in Advanced Organic Chemistry: Part B: Reaction and Synthesis, Francis Carey and Richard Sundberg, (Springer) 5th ed. Edition. (2007), the content of which is hereby incorporated by reference.

25 The compounds of the instant invention may be in a salt form. As used herein, a "salt" is a salt of the instant compounds which has been modified by making acid or base salts of the compounds. In the case of compounds used for treatment of cancer, the salt is pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as phenols. The salts can be made using an organic or inorganic acid. Such acid salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, 30 formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like. Phenolate salts are the alkaline earth metal salts, sodium, potassium or lithium. The term "pharmaceutically acceptable salt" in this respect, refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the

invention, or by separately reacting a purified compound of the invention in its free base or free acid form with a suitable organic or inorganic acid or base, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, 5 phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, *e.g.*, Berge *et al.* (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

As used herein, "treating" means slowing, stopping or reversing the progression of a disease.
10 An embodiment of "treating cancer" is inhibition of proliferation of tumor cells.

The compositions of this invention may be administered in various forms, including those detailed herein. The treatment with the compound may be a component of a combination therapy or an adjunct therapy, *i.e.* the subject or patient in need of the drug is treated or given 15 another drug for the disease in conjunction with one or more of the instant compounds. This combination therapy can be sequential therapy where the patient is treated first with one drug and then the other or the two drugs are given simultaneously. These can be administered independently by the same route or by two or more different routes of administration depending on the dosage forms employed.

20 As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle, for delivering the instant compounds to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. Liposomes are also a pharmaceutically acceptable carrier.

25 The dosage of the compounds administered in treatment will vary depending upon factors such as the pharmacodynamic characteristics of a specific chemotherapeutic agent and its mode and route of administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent 30 treatment being administered; the frequency of treatment with; and the desired therapeutic effect.

A dosage unit of the compounds may comprise a single compound or mixtures thereof with anti-cancer compounds, or tumor growth inhibiting compounds, or with other compounds

also used to treat neurite damage. The compounds can be administered in oral dosage forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The compounds may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, or introduced directly, e.g. by injection
5 or other methods, into the cancer, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The compounds can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically
10 acceptable carrier) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral, rectal, topical, intravenous or direct injection or parenteral administration. The compounds can be administered alone but are generally mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of carrier is generally
15 chosen based on the type of administration being used. In one embodiment the carrier can be a monoclonal antibody. The active agent can be co-administered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk
20 powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-
25 effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals and other materials to make them compatible
30 with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U. S. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage

forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). All of the aforementioned publications are incorporated by reference herein.

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. The compounds may be administered as components of tissue-targeted emulsions.

The compounds may also be coupled to soluble polymers as targetable drug carriers or as a prodrug. Such polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, polyhydroxyethylasparta-midephenol, or
5 polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or
10 amphipathic block copolymers of hydrogels.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parentally, in sterile liquid dosage forms.

15 Gelatin capsules may contain the active ingredient compounds and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as immediate release products or as sustained release products to provide for
20 continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

For oral administration in liquid dosage form, the oral drug components are combined with
25 any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent
30 granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably
5 contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.
10 Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

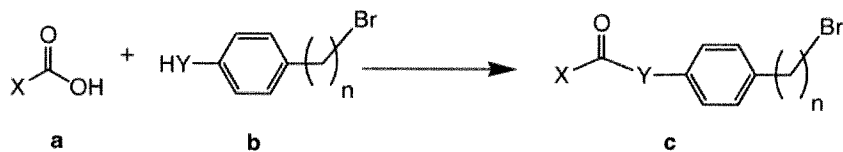
The compounds of the instant invention may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal
15 skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittent throughout the dosage regimen.

Parenteral and intravenous forms may also include minerals and other materials to make them
20 compatible with the type of injection or delivery system chosen.

The compounds and compositions of the invention can be coated onto stents for temporary or permanent implantation into the cardiovascular system of a subject.

25 Below, compounds of the present invention are synthesized according to the general procedures shown in the following synthetic schemes. The "R" groups shown in the following schemes denote any number of generic substituents, such as those described hereinabove. "n" refers to any integer greater than or equal to 1. Preferably, "n" is an integer from 1-20, inclusive. "m" refers to any integer greater than or equal to 1. Preferably, "m" is
30 an integer from 1-200, inclusive.

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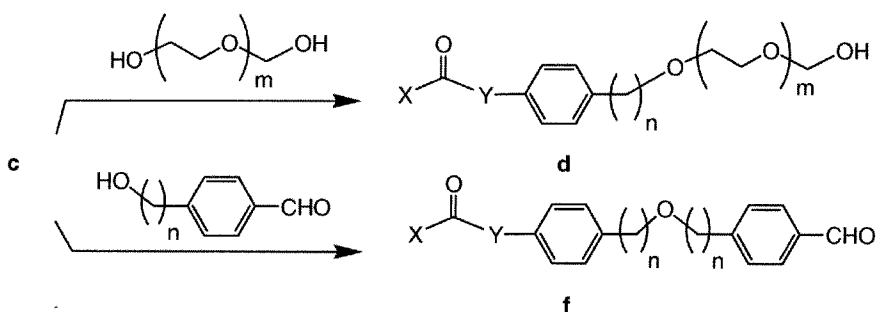


Scheme 1

In general scheme 1, compounds having the structure of compound **c** are synthesized via ester or amide formation between a compound capable of forming an ester bond, such as compound **a**, and compound **b**. “Y” refers to a nucleophilic moiety, including, but not limited to, O, NH, and S.

Ester formation is achieved by any number of esterification reactions known to those having ordinary skill in the art. For example, coupling reagents including, but not limited to, 1,3-diisopropylcarbodiimide (DIC) and N,N'-dicyclohexylcarbodiimide (DCC) can be used in the presence of a suitable base.

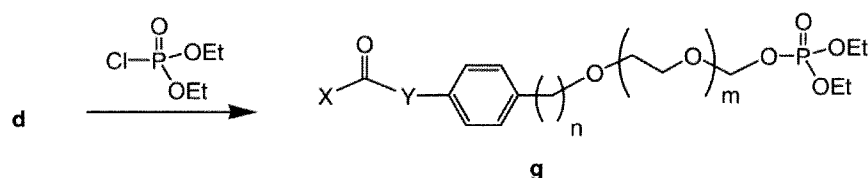
The resulting ester, compound **c**, is conjugated to an ether-containing moiety as shown in scheme 2 through a nucleophilic substitution reaction. Examples of ether-containing moieties include, but are not limited to, polyethylene glycol, polyethylene glycol hydroxymethyl monoether, *para*-hydroxyalkyl benzaldehyde, polyalkylene glycols, and the like. One of ordinary skill in the art of chemical synthesis will appreciate that the free nucleophilic atoms of the ether-containing moieties may be O, N, or S.



Scheme 2

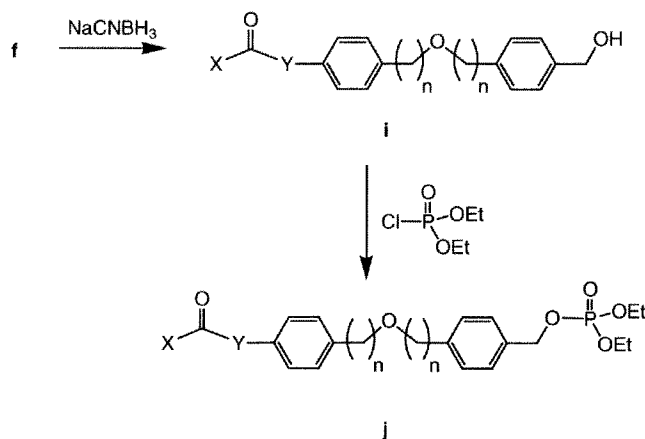
The pendant hydroxyl group of resulting compounds **d** is then converted to a leaving group. Any method known to those of ordinary skill in the art for conversion of hydroxyl groups to functional groups may be used. For example, the conversion of hydroxyl groups to diethyl phosphate functional groups is shown in scheme 3.

5



Scheme 3

10 In general scheme 4, the aldehyde in compound **f** is first reduced to an alcohol by the action of a reducing agent, for example, sodium cyanoborohydride, before conversion to a functional group.



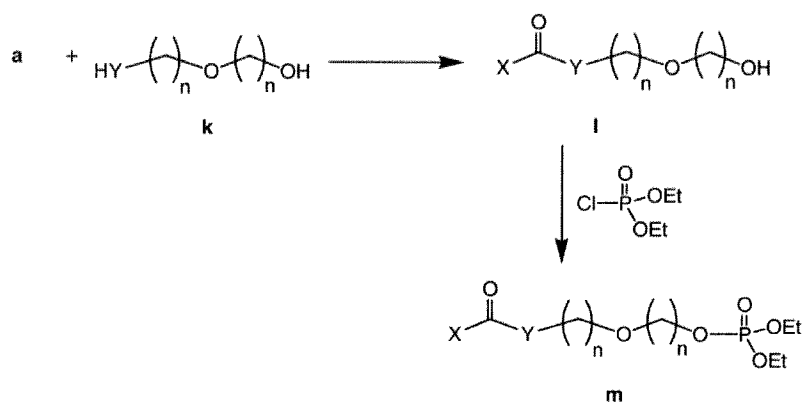
Scheme 4

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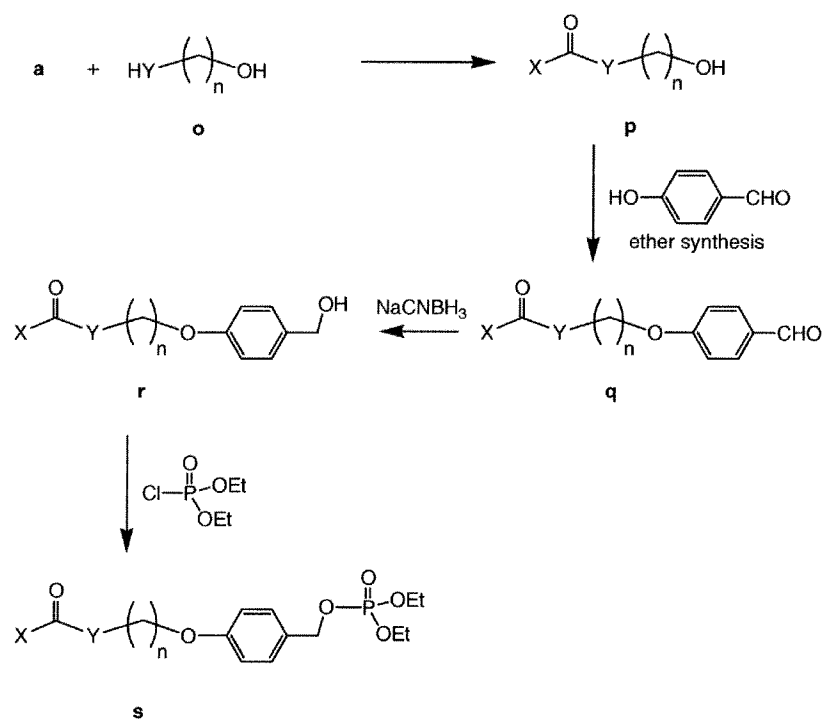
Alternatively, the compounds of the present invention may be synthesized by formation of an ester linkage between compound **a** and an ether-containing moiety wherein the free nucleophilic atoms may be O, N, or S. Various ether-containing moieties are shown in schemes 5, 6, and 7.

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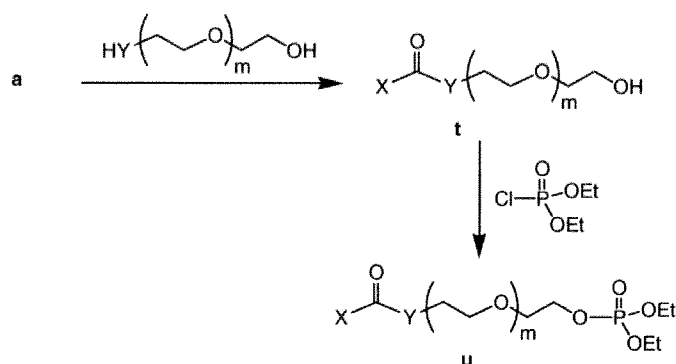


Scheme 5



Scheme 6

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Scheme 7

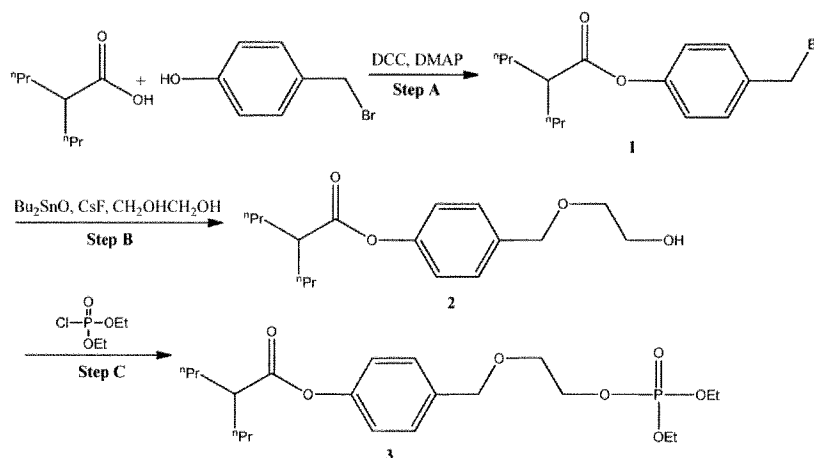
- 5 Those having ordinary skill in the art of organic synthesis will appreciate that modifications to the general procedures shown in the schemes above can be made to yield structurally diverse compounds. For example, where aryl rings are present, all positional isomers are contemplated and may be synthesized using standard aromatic substitution chemistry. The number and types of substituents may also vary around the aryl rings. Furthermore, where
- 10 alkyl groups are present, the chain length may be modified using methods well known to those of ordinary skill in the art. Where ester formation is contemplated, lactones may be used wherein the lactone ring is opened by reaction with a nucleophile, such as an ether-containing moiety described hereinabove. Suitable organic transformations are described in
- 15 March's *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (Wiley-Interscience; 6th edition, 2007), the content of which is hereby incorporated by reference.

The compounds and compositions of the present invention are useful for the prevention and treatment of cancer and other inflammation-related diseases, such as neurodegenerative, rheumatological, and cardiovascular diseases.

20

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

25

Experimental Details**Example 1. Synthesis of Ether-based Compound 3***Scheme S1. Synthesis of ether-based compound 3***Synthetic steps:**

Step A. 1 eq. of valproic acid and 1 eq. p-hydroxybenzylbromide are dissolved in dichloromethane (DCM), with the addition of 1 eq. N, N'-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP) as the catalyst. The mixture is stirred for 3 h at room temperature. Acetone is added to precipitate DCC. After the solvent is removed by vacuum, the product is purified by flash column chromatography to give compound **1**.

Step B. A suspension of 1 eq. of ethylene diol and 1 eq. of dibutyltin oxide in chloroform-methanol is refluxed for 3 h to give a clear solution. After the solvents are removed under reduced pressure to give a white solid, 2 eq. of cesium fluoride are added. After the solid mixture is dried overnight under high vacuum, the mixture is suspended in DMF. To the suspension is added a solution of 1 eq. of compound **1** in DMF, and the mixture is stirred for 24 h at room temperature. After the mixed solvent of ethyl acetate and water are added, the mixture is stirred vigorously for 30 min and then filtered through a pad of silica gel to remove dibutyltin oxide. The filtrate is washed with water and then with brine. Removal of the solvents gives a residue that is purified by column chromatography on silica gel to give compound **2**.

25

Step C. 1 eq. of compound **2** and 1.1 eq. of diethyl chlorophosphate are dissolved in DCM and stirred for 3 h at room temperature. After the solvent is removed by vacuum, the product is purified by flash column chromatography to give compound **3**.

- 5 Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent (CDCl_3 , δ 7.26; CD_3OD , δ 3.30; DMSO, δ 2.49). Data for ^1H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet), and coupling constant in Hertz (Hz).
- 10 ^1H NMR (400 Mhz, CDCl_3): δ 7.30 (d, 2H), 7.05 (d, 2H), 5.04 (d, 2H), 4.09 (m, 6H), 2.60 (m, 1H), 1.71 (m, 2H), 1.20-1.60 (m, 14H), 0.90 (t, 6H).

Derivatives of compound **3** are synthesized using the above method where valproic acid is replaced by aspirin, ibuprofen, or fluvastatin.

References

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9. Shiff S J, Rigas B. Aspirin for cancer. *Nat Med* 1999; 5:1348-9.
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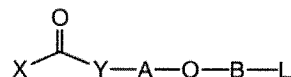
13. Baigent et al. 2005

14. Dale et al. 2006

Claims

What is claimed is:

1. A compound having the structure:

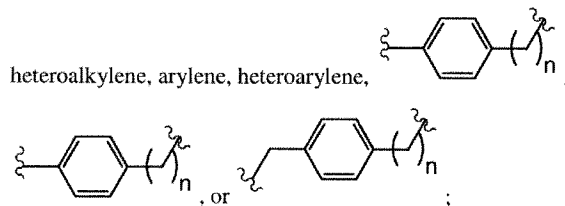


wherein

X is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclic;

Y is -O-, -NH-, or -S-;

A and B are each, independently, alkylene, alkenylene, alkynylene,



L is -ONO₂, -OSO₂R₁, -OSO₂OR₁, -OPO(OR₁)₂, -OB(OR₁)₂, -N₂⁺, -O(R₁)₂⁺, -S(R₁)₂⁺, N(R₁)₃⁺, or halogen,

wherein each instance of R₁ is, independently, H, alkyl, or aryl;

n and m are each, independently, an integer greater than or equal to 1;

wherein when A is alkylene and -(CH₂)_n- and n is 2, L is -OPO(OR₁)₂, -OB(OR₁)₂, -N₂⁺, -O(R₁)₂⁺, -S(R₁)₂⁺, or halogen;

wherein each instance of alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene, heteroalkylene is branched or unbranched, substituted or unsubstituted; and

wherein each instance of cycloalkyl, aryl, heterocyclic, heteroaryl, and heteroarylene is substituted or unsubstituted;

or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof.

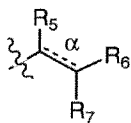
2. The compound of claim 1, wherein

X is $-(CR_2R_3)_a-R_4$,

wherein

a is an integer from 1 to 10;

each instance of R_2 and R_3 are each, independently, H, OH, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, or aryl substituted with C_1 - C_5 alkyl;



R_4 is H or

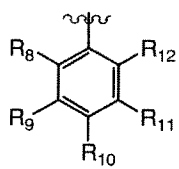
wherein

R_5 is H, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, or C_2 - C_{10} alkynyl;

R_6 and R_7 are each, independently, H, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclic;

α is present or absent;

or



wherein

R_8 , R_9 , R_{10} , R_{11} , and R_{12} are each, independently, H, OH, halogen, -CN, -NO₂,

C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, $-(C=O)-R_{13}$, or $-O-(C=O)-R_{13}$,

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wherein R_{13} is H, -OH, -OR₁₄, -NR₁₄R₁₅, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl,

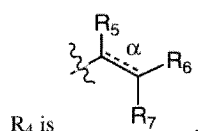
wherein R_{14} and R_{15} are, each, independently, H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein

X is -(CH₂)-(CHOH)-(CH₂)-(CHOH)-R₄,

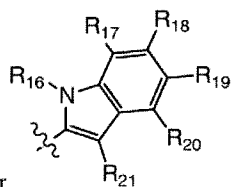
wherein



wherein

R_5 is H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

R_6 and R_7 are each, independently, H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-



wherein R_{16} is H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, or -
(C=O)-R₂₂,

wherein R_{22} is H, -OH, -OR₂₃, -NR₂₃R₂₄, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl,

wherein R_{23} and R_{24} are, each, independently, H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

R_{17} , R_{18} , R_{19} , R_{20} , and R_{21} are each, independently, H, -OH, halogen, -CN, -NO₂, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, -(C=O)-R₂₅, -O-(C=O)-R₂₅, or aryl substituted by halogen,

wherein R_{25} is H, -OH, -OR₂₆, -NR₂₆R₂₇, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl,

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wherein R_{26} and R_{27} are, each, independently, H, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, or C_2 - C_{10} alkynyl;

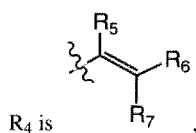
α is present or absent;

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, wherein

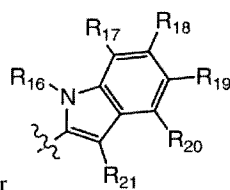
X is $-(CH_2)-(CHOH)-(CH_2)-(CHOH)-R_4$,

wherein



wherein

R_5 is H;



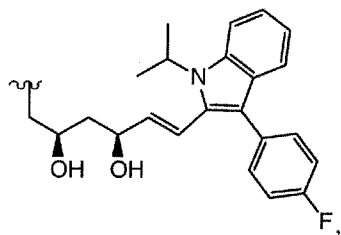
R_6 and R_7 are each, independently, H or

wherein R_{16} is C_1 - C_{10} alkyl;

R_{17} , R_{18} , R_{19} , R_{20} , and R_{21} are each, independently, H or aryl substituted with halogen;

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 4, wherein X is



or a pharmaceutically acceptable salt thereof.

6. The compound of claim 2, wherein

X is $-\text{CR}_2\text{R}_3-\text{R}_4$,

wherein

each instance of R_2 and R_3 are each, independently, C_1 - C_{10} alkyl or aryl substituted with C_1 - C_5 alkyl;

R_4 is H,

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 6, wherein

X is $-\text{CR}_2\text{R}_3-\text{R}_4$,

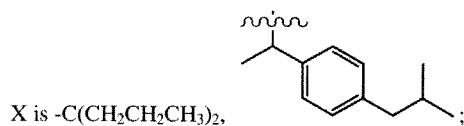
wherein

each instance of R_2 and R_3 are each, independently, methyl, propyl, or aryl substituted with isobutyl;

R_4 is H,

or a pharmaceutically acceptable salt thereof.

8. The compound of claim 7, wherein

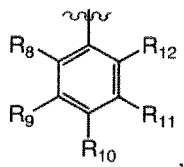


or a pharmaceutically acceptable salt thereof.

9. The compound of claim 2, wherein

X is

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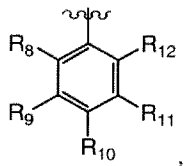
wherein

R₈, R₉, R₁₀, R₁₁, and R₁₂ are each, independently, H, OH, halogen, -CN, -NO₂, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, -(C=O)-R₁₃, or -O-(C=O)-R₁₃, wherein R₁₃ is H, -OH, -OR₁₄, -NR₁₄R₁₅, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl, wherein R₁₄ and R₁₅ are, each, independently, H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 9, wherein

X is



wherein

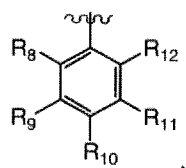
R₈, R₉, R₁₀, R₁₁, and R₁₂ are each, independently, H or -O-(C=O)-R₁₃, wherein R₁₃ is H, -OH, -OR₁₄, -NR₁₄R₁₅, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl, wherein R₁₄ and R₁₅ are, each, independently, H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10, wherein

X is

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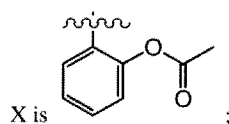


wherein

R₈, R₉, R₁₀, R₁₁, and R₁₂ are each, independently, H or -O-(C=O)-CH₃;

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 11, wherein



X is

;

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1,

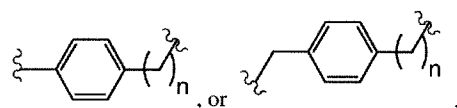
wherein

X is a pharmaceutically active agent;

Y is -O-, -NH-, or -S-;

A is -(CH₂)_n- or ; and

B is -(CH₂CH₂O)_mCH₂-, -(CH₂CH₂O)_mCH₂CH₂-, -(CH₂)_n-,



wherein

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n is an integer from 1 to 20,

m is an integer from 1 to 200;

L is $-\text{ONO}_2$, $-\text{OSO}_2\text{R}_1$, $-\text{OSO}_2\text{OR}_1$, $-\text{OPO}(\text{OR}_1)_2$, $-\text{OB}(\text{OR}_1)_2$, $-\text{N}_2^+$, $-\text{O}(\text{R}_1)_2^+$, $-\text{S}(\text{R}_1)_2^+$, $\text{N}(\text{R}_1)_3^+$, or halogen,

wherein each instance of R_1 is, independently, H, alkyl, or aryl;

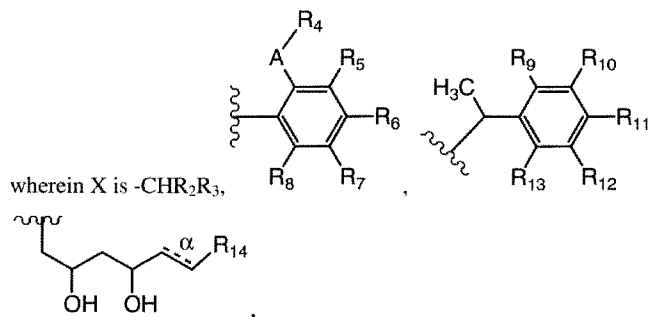
wherein when A is $-(\text{CH}_2)_n-$ and n is 2, L is $-\text{OPO}(\text{OR}_1)_2$, $-\text{OB}(\text{OR}_1)_2$, $-\text{N}_2^+$, $-\text{O}(\text{R}_1)_2^+$, $-\text{S}(\text{R}_1)_2^+$, or halogen;

wherein each instance of alkyl, alkenyl, and alkynyl is branched or unbranched, substituted or unsubstituted; and

wherein each instance of cycloalkyl, aryl, heterocyclic, and heteroaryl is substituted or unsubstituted;

or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13,

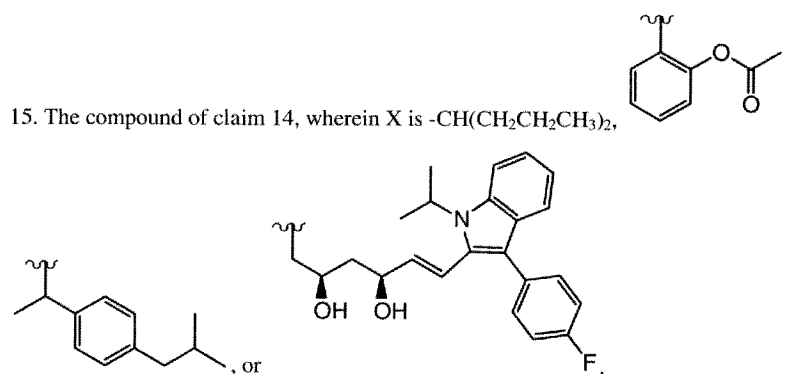


R_9 , R_{10} , R_{11} , R_{12} , and R_{13} are each, independently, halogen, alkyl, aryloxy, or heterocyclic;

R_{14} is heteroaryl or cycloalkyl, and

bond α is present or absent;

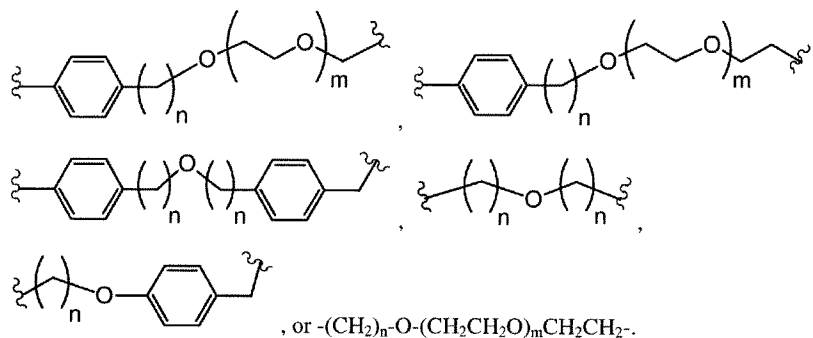
wherein each instance of alkyl is unbranched or branched, substituted or unsubstituted, and each instance of aryl is substituted or unsubstituted.



16. The compound of any one of claims 1-15, wherein Y is O.

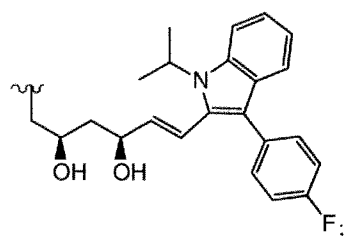
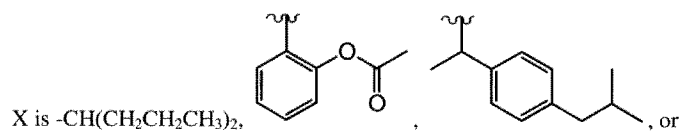
17. The compound of any one of claims 1-15, wherein Y is N or S.

18. The compound of any one of claims 1-15, wherein Z is

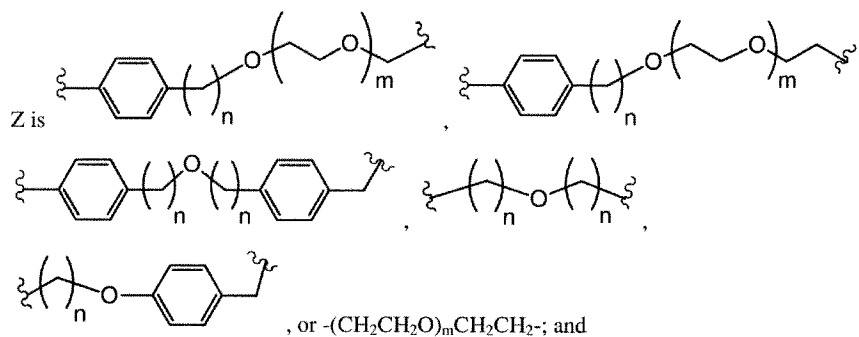


19. The compound of any one of claims 1-15, wherein L is $-\text{OPO}(\text{OCH}_2\text{CH}_3)_2$.

20. The compound of claim 1, 2, or 13, wherein



Y is O;

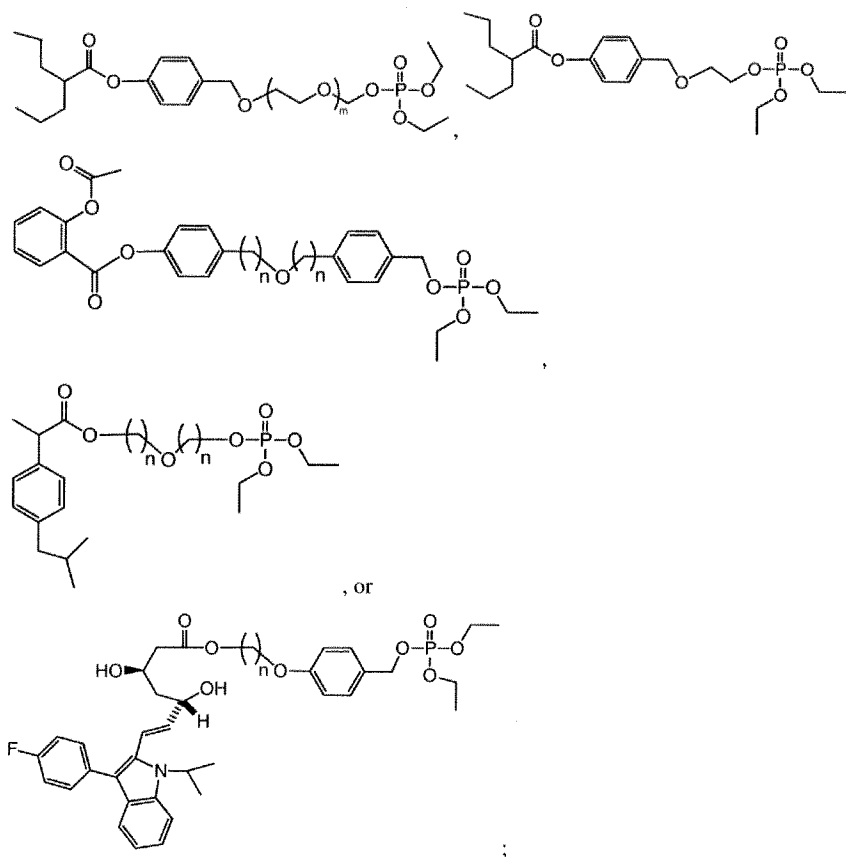


L is $-\text{OPO}(\text{OCH}_2\text{CH}_3)_2$;

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1, 2, or 13 having the structure:

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or a pharmaceutically acceptable salt thereof.