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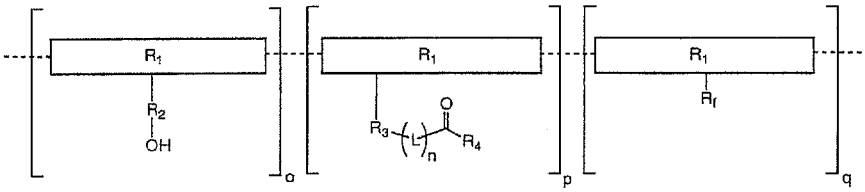
(54) **Title**: POLYMER-BASED THERAPEUTIC AGENTS



(57) **Abstract**: This invention relates to compounds having the structure wherein R_1 is a polyvinyl alcohol or disaccharide repeating unit, and L, R_2, R_3, R_4, and R_f are further described herein.

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POLYMER-BASED THERAPEUTIC AGENTS

This application claims priority of U.S. Provisional Application No. 61/325,206, filed April 16, 2010, the contents of which are hereby incorporated by reference.

This invention was made with government support under grant number CA139454 awarded by the National Institutes of Health. The government has certain rights in the invention.

Throughout this application, certain publications are referenced in parenthesis. Full citations for these publications may be found immediately preceding the claims. The disclosures of these 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

Various polymers have been used extensively for decades in drug development to enhance the pharmacological properties of drugs. An excellent example is the use of polymer-drug conjugates, polymer-directed enzyme prodrug therapy (PDEPT) and polymer-enzyme liposome therapy (PELT). These drugs have been transferred from the laboratory to clinic. (1) Delivery of compounds to the target tissues continues to represent a challenging problem.

Natural polymers, e.g. polysaccharides, have also been used as polymer backbone to load drug onto them. These natural polymers could not only function as drug delivery vehicle, but more importantly, they have specific biological functions. For example, the polysaccharide hyaluronic acid binds to CD44 receptor; receptor CD44 participates in cell adhesion interactions required by tumor cells. Another potentially useful feature of hydrophilic polymers is that when they bear hydrophobic drugs they can form nano-sized micelles, which can protect the drug from degradation and enhance drug uptake by tumors through the "enhanced permeability and retention (EPR) effect" (2).

There is a need to develop compounds with improved circulation time, efficacy and safety profiles for the treatment of cancer. Herein, new polymer-based agents used for the treatment of cancer and inflammation-related disease are described.

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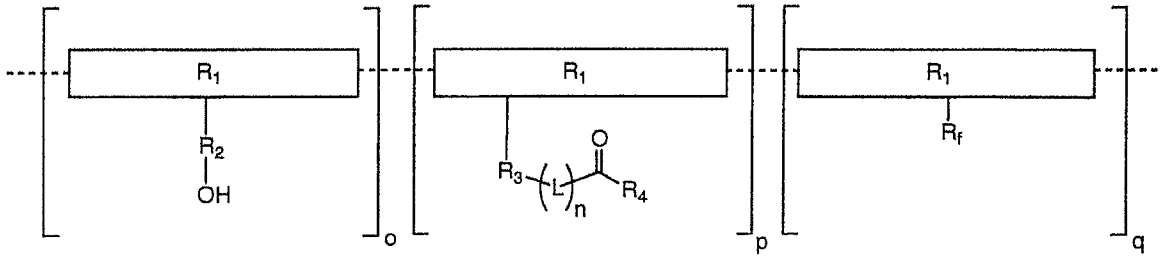
Summary of the Invention

This invention provides a compound having the structure:



wherein

R_1 is a polyvinyl alcohol or disaccharide repeating unit;

R_2 is a direct bond or -(C=O)-;

R_3 is -O- or -(C=O)-;

R_4 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl, arylalkyl, or heteroaryl group;

L is -X-Z-(C=O)-, -X-Z-Y-, alkylene, arylene, or heteroarylene,

wherein X and Y are each, independently, -O- or -NH; and

Z is arylene, $-(CH_2)_m-$, -arylene-$(CH_2)_m-$, or $-(CH_2)_m$-arylene-$(CH_2)_m-$,

wherein each instance of m is an integer greater than or equal to 1;

R_f is $-ONO_2$, $-OSO_2OR_5$, $-OSO_2R_5$, $-OPO(OH)_2$, $-OPO(OR_5)(OR_6)$, $-OB(OR_5)(OR_6)$, $-N_2^+$, halogen, $-O(R_5)_2^+$, $-S(R_5)_2^+$, or $-N(R_5)_3^+$,

wherein each instance of R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

This invention further provides a pharmaceutical composition comprising any of the above compounds and a pharmaceutically acceptable carrier.

This invention provides a method of inhibiting tumor growth in a subject comprising administering to the subject any of the above compounds so as to inhibit tumor growth in the subject.

This invention further provides a method of inhibiting tumor growth in a subject comprising administering to the subject the above pharmaceutical composition so as to inhibit tumor growth in the subject.

Brief Description of the Figures

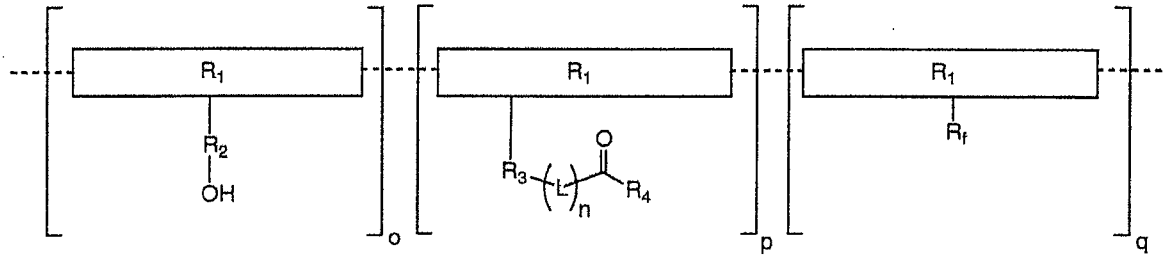
Figure 1. **The general structure of novel polymer-based therapeutic compounds.** The polymer backbone is a synthetic or a natural polymer. Any small organic molecule of drug is linked to the polymer though a linker molecule. Functional groups are further linked onto the polymer backbone.

Figure 2. **Representative polymer-based compounds.** The backbones are polyvinyl alcohol (PVA) and hyaluronic acid (HA). Sulindac and the polymer backbone with phosphate are featured.

Figure 3. **PPS inhibits the growth of human pancreatic xenografts.** Changes in tumor volume during the period of treatment with PPS (phospho-PVA sulindac) are shown. The control group received PBS (phosphate buffered saline). Values are *Mean±SEM* (n=6/group; 12 xenografts/group).

Detailed Description of the Invention

This invention provides a compound having the structure:



wherein

R_1 is a polyvinyl alcohol or disaccharide repeating unit;

R_2 is a direct bond or -(C=O)-;

R_3 is -O- or -(C=O)-;

R_4 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl, arylalkyl, or heteroaryl group;

L is -X-Z-(C=O)-, -X-Z-Y-, alkylene, arylene, or heteroarylene,

wherein X and Y are each, independently, -O- or -NH; and

Z is arylene, $-(CH_2)_m-$, -arylene-$(CH_2)_m-$, or $-(CH_2)_m$-arylene-$(CH_2)_m-$,

wherein each instance of m is an integer greater than or equal to 1;

R_f is $-ONO_2$, $-OSO_2OR_5$, $-OSO_2R_5$, $-OPO(OH)_2$, $-OPO(OR_5)(OR_6)$, $-OB(OR_5)(OR_6)$, $-N_2^+$, halogen, $-O(R_5)_2^+$, $-S(R_5)_2^+$, or $-N(R_5)_3^+$,

wherein each instance of R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

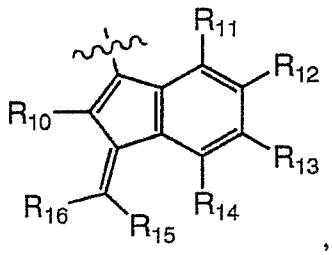
In an embodiment of the compound,

R_4 is $-(CR_7R_8)_a-R_9$,

wherein

a is an integer from 1 to 10;

each instance of R_7 and R_8 are each, independently, H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, or aryl;

R_9 is 

,

wherein

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each, independently, H, OR_{15}, halogen, -CN, $-NO_2$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(C=O)-R_{17}$, $-SO_2-R_{17}$, $-SO-R_{17}$, $-S-R_{17}$, $-NR_{17}R_{18}$,

wherein R_{17} and R_{18} are each, independently, H, -OH, $-OR_{19}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl,

wherein R_{19} is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

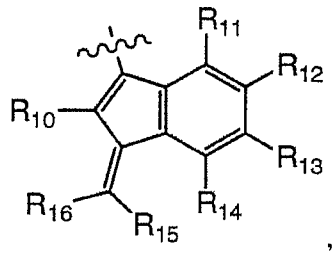
R_{15} and R_{16} are each, independently, H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, or aryl;

or a pharmaceutically acceptable salt thereof.

In another embodiment of the compound,

R_4 is $-CH_2-R_9$,

wherein



R_9 is ,

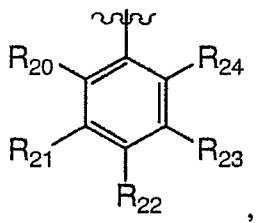
wherein

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each, independently, H, OR_{15}, halogen, -CN, $-NO_2$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(C=O)-R_{17}$, $-SO_2-R_{17}$, $-SO-R_{17}$, $-S-R_{17}$, $-NR_{17}R_{18}$,

wherein R_{17} and R_{18} are each, independently, H, -OH, $-OR_{19}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl,

wherein R_{19} is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

R_{15} and R_{16} are each, independently, H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, or



,

wherein

R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each, independently, H, OH, halogen, -CN, $-NO_2$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(C=O)-R_{25}$, $-SO_2-R_{25}$, $-SO-R_{25}$, $-S-R_{25}$, $-NR_{25}R_{26}$,

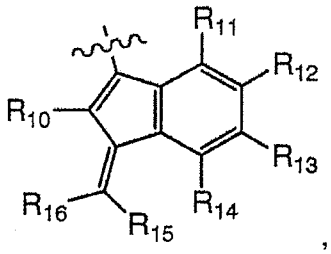
wherein R_{25} and R_{26} are each, independently, H, -OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

or a pharmaceutically acceptable salt thereof.

In an embodiment,

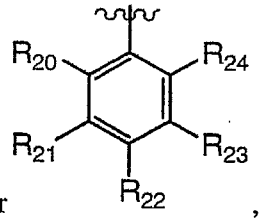
R_4 is $-CH_2-R_9$,

wherein

R_9 is  ,

wherein

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each, independently, H, halogen, or C_1-C_{10} alkyl,

R_{15} and R_{16} are each, independently, H or  ,

wherein

R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each, independently, H or -SO-R_{25},

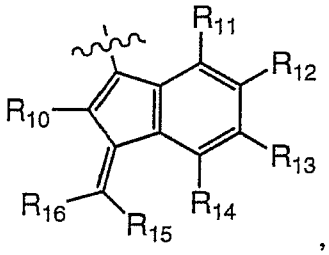
wherein R_{25} is H, -OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment,

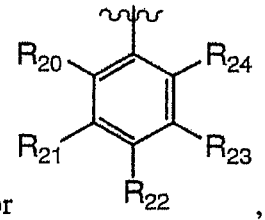
R_4 is -CH_2-R_9,

wherein

R_9 is  ,

wherein

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each, independently, H, F, or -CH_3,

R_{15} and R_{16} are each, independently, H or 

,

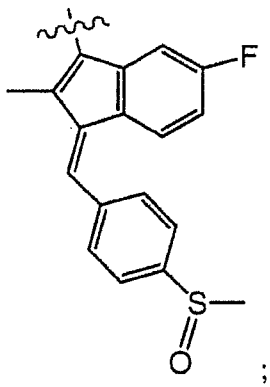
wherein

R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each, independently, H or -SO-R_{25},

wherein R_{25} is $-CH_3$;

or a pharmaceutically acceptable salt thereof.

In a further embodiment,

R_4 is 

;

or a pharmaceutically acceptable salt thereof.

In some embodiments,

R_1 is a polyvinyl alcohol or disaccharide repeating unit;

R_2 is a direct bond or -(C=O)-;

R_3 is -O- or -(C=O)-;

L is $-X-(CH_2)_m-(C=O)-$ or $-X-(CH_2)_m-Y-$,

wherein X and Y are each, independently, -O- or -NH, and

wherein each instance of m is an integer greater than or equal to 1;

R_f is $-OPO(OR_5)(OR_6)$

R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

or a pharmaceutically acceptable salt thereof.

In other embodiments,

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O- or -NH-, and m is an integer greater than or equal to 1;

R_f is $-OPO(OR_5)(OR_6)$

R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

In further embodiments,

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O-, and m is an integer greater than or equal to 1;

R_F is $-OPO(OR_5)(OR_6)$

wherein R_5 and R_6 are each, independently, alkyl;

n is 0 or 1;

o, p, and q are each, independently, an integer grater than or equal to 1;

or a pharmaceutically acceptable salt thereof.

In some embodiments,

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each ethyl;

n is 0 or 1;

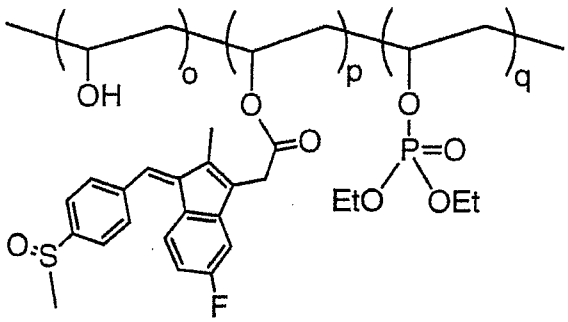
o, p, and q are each, independently, an integer greater than or equal to 1;

or a pharmaceutically acceptable salt thereof.

In some embodiments, o, p, and q are each, independently, an integer from 1 to 400.

In other embodiments, m is an integer from 1 to 20.

In further embodiments, the compound has the structure:



or a pharmaceutically acceptable salt thereof.

In other embodiments,

R_1 is a disaccharide repeating unit;

R_2 is -(C=O)-;

R_3 is -(C=O)-;

L is -X-$(CH_2)_m$-Y-,

wherein X and Y are each, independently, -O- or -NH-, and m is an integer greater than or equal to 1;

R_f is -OPO(OR_5)(OR_6)

R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 1;

o, and p are each, independently, an integer greater than or equal to 1;

q is 0;

or a pharmaceutically acceptable salt thereof.

In further embodiments,

R_1 is a disaccharide repeating unit;

R_2 is -(C=O)-;

R_3 is -(C=O)-;

L is -X-$(CH_2)_m$-Y-,

wherein X and Y are each -NH-, and m is an integer greater than or equal to 1;

n is 1;

o, and p are each, independently, an integer greater than or equal to 1;

q is 0;

or a pharmaceutically acceptable salt thereof.

In embodiments, R_1 is a disaccharide repeating unit comprising heparin.

In embodiments, o and p are each, independently, an integer from 1 to 400.

In other embodiments, the compound has the structure

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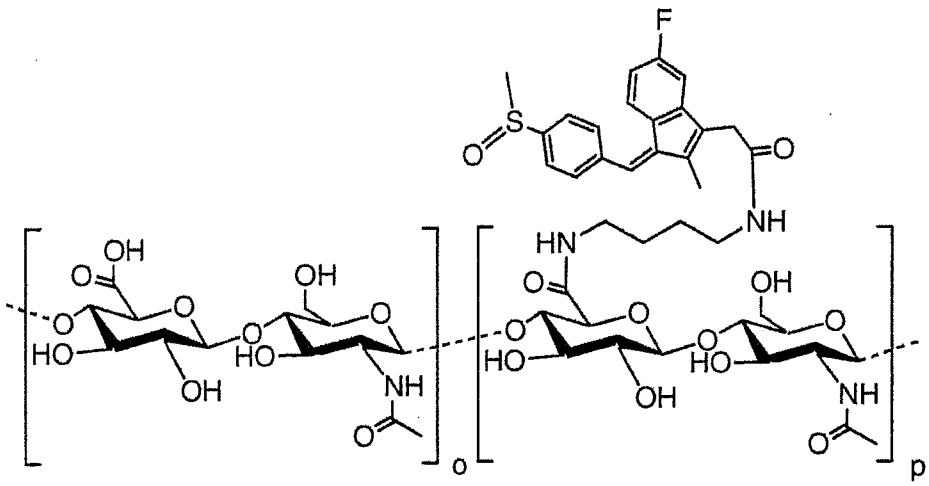
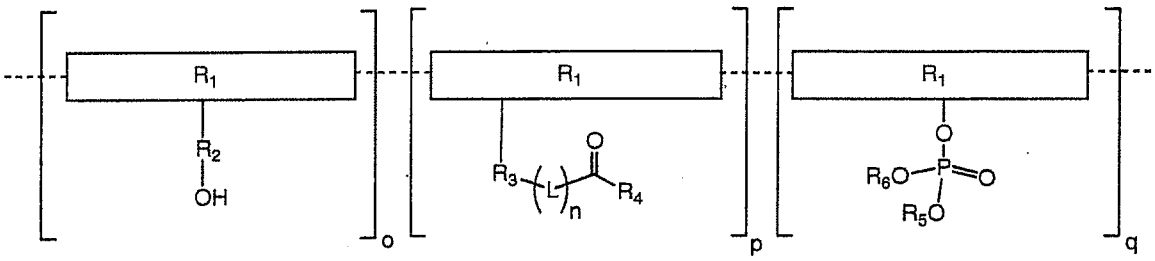


or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound has the structure:



wherein

R_1 is a polyvinyl alcohol or disaccharide repeating unit;

R_2 is a direct bond or -(C=O)-;

R_3 is -O- or -(C=O)-;

R_4 is a pharmaceutically active agent;

L is $-X-(CH_2)_m-(C=O)-$ or $-X-(CH_2)_m-Y-$,

wherein X and Y are each, independently, -O- or -NH, and

wherein each instance of m is an integer greater than or equal to 1;

R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

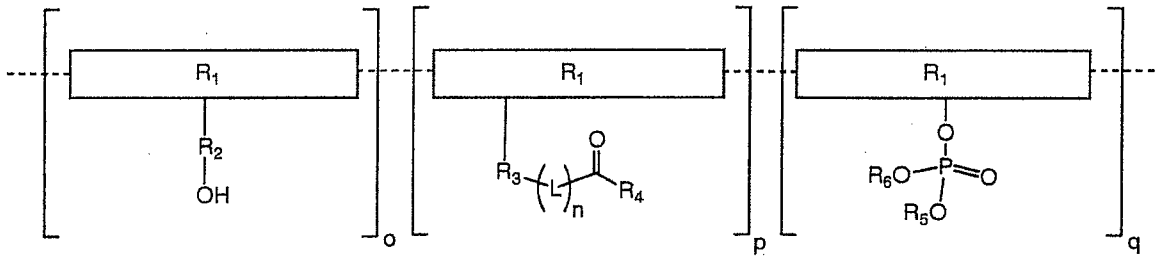
n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound has the structure



wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

R_4 is a pharmaceutically active agent;

L is -X-$(CH_2)_m$-(C=O)-,

wherein X is -O- or -NH-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each, independently, alkyl, alkenyl, or alkynyl;

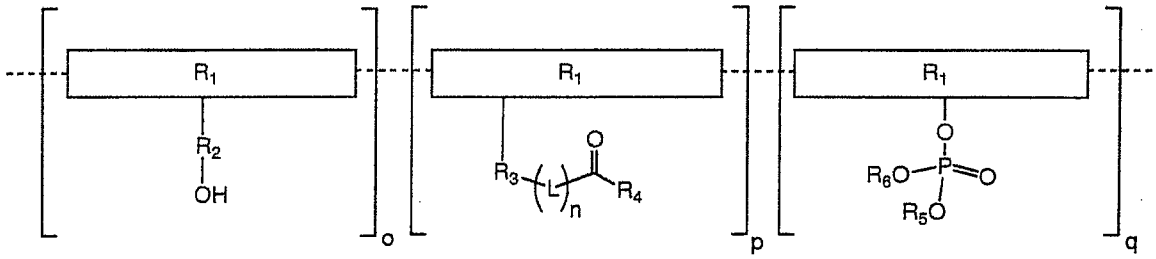
n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

In a further embodiment, the compound has the structure



wherein

R_1 is a disaccharide repeating unit;

R_2 is -(C=O)-;

R_3 is -(C=O)-;

R_4 is a pharmaceutically active agent;

L is $-X-(CH_2)_m-Y-$,

wherein X and Y are each, independently, -O- or -NH-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each, independently, alkyl, alkenyl, or alkynyl;

n is 1;

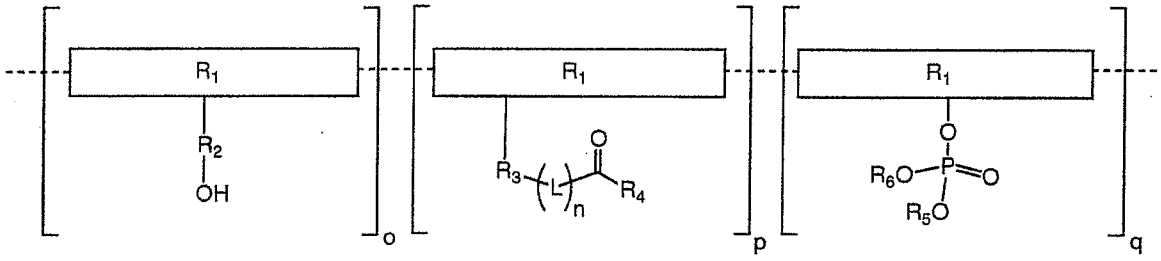
o, and p are each, independently, an integer greater than or equal to 1;

q is 0;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound has the structure



wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

R_4 is a pharmaceutically active agent;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each, independently, alkyl;

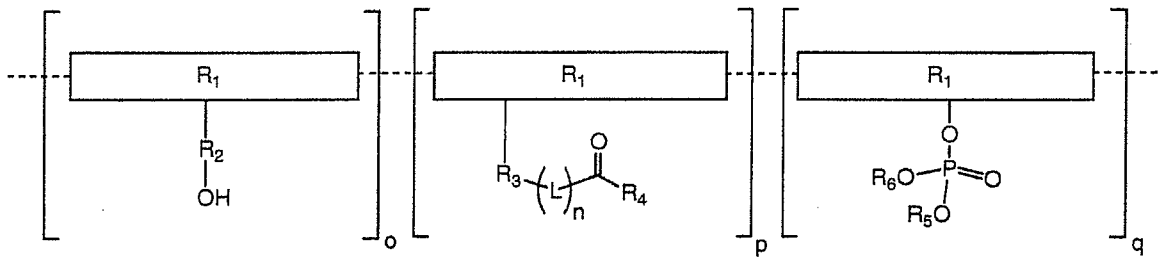
n is 0 or 1;

o, p, and q are each, independently, an integer grater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound has the structure

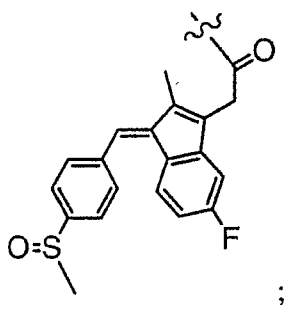


wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

R_4 is  ;

L is -X-$(CH_2)_m$-(C=O)-,

wherein X is -O-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each ethyl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

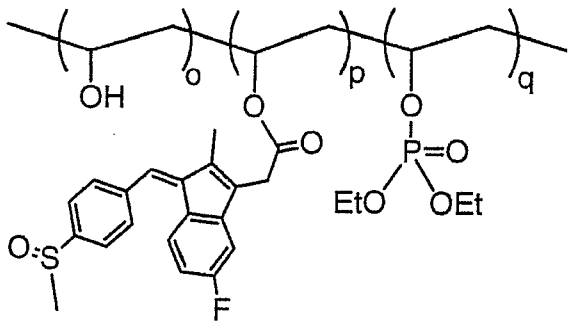
wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

In some embodiments, o, p, and q are each, independently, an integer from 1 to 400.

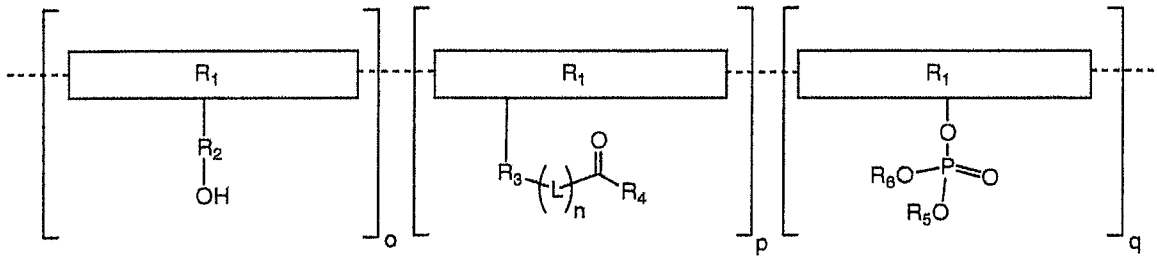
In other embodiments, m is an integer from 1 to 20.

In an embodiment,



or a pharmaceutically acceptable salt thereof.

In an embodiment, the compound has the structure

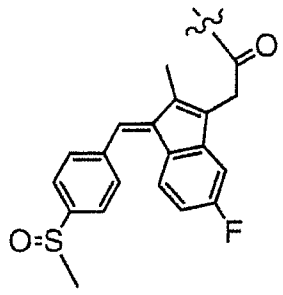


wherein

R_1 is a disaccharide repeating unit;

R_2 is -(C=O)-;

R_3 is -(C=O)-;

R_4 is  ;

L is -X-$(CH_2)_m$-Y-,

wherein X and Y are each -NH-, and m is an integer greater than or equal to 1;

n is 1;

o, and p are each, independently, an integer greater than or equal to 1;

q is 0;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

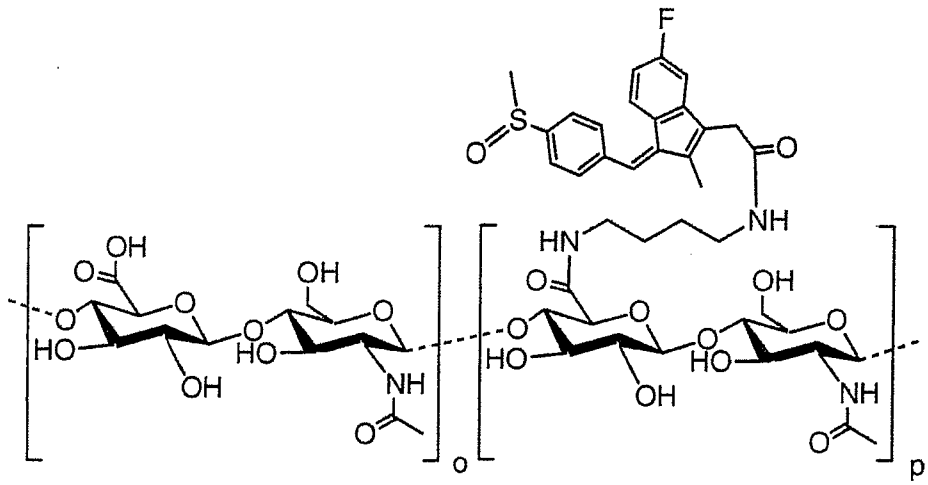
or a pharmaceutically acceptable salt thereof.

In an embodiment, R_1 is a disaccharide repeating unit comprising heparin.

In another embodiment, o and p are each, independently, an integer from 1 to 400.

In a further embodiment, m is an integer from 1 to 20.

In an embodiment, the compound has the structure



or a pharmaceutically acceptable salt thereof.

This invention further provides a pharmaceutical composition comprising any of the above compounds and a pharmaceutically acceptable carrier.

This invention provides a method of inhibiting tumor growth in a subject comprising administering to the subject any of the above compounds so as to inhibit tumor growth in the subject.

This invention further provides a method of inhibiting tumor growth in a subject comprising administering to the subject the above pharmaceutical composition so as to inhibit tumor growth in the subject.

In an embodiment, the tumor is a human pancreatic cancer tumor.

In another embodiment, the tumor is a human breast cancer tumor.

This invention provides methods of preventing or treating cancer in a subject comprising 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 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 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 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 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.

It will be noted that the structure of the compounds of this invention may include an asymmetric carbon atom and thus the compounds occur as racemates, racemic mixtures, and isolated single enantiomers. 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 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 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 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 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 ^{1}H, ^{2}H, or ^{3}H. Furthermore, any compounds containing ^{2}H or ^{3}H may specifically have the 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, butenyl and cyclohexenyl.

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, "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.

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 $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-O-CH_2-CH_3$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$.

Similarly, the term "heteroalkylene" means a divalent radical derived from heteroalkyl. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini. Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied. Examples of heteroalkylene groups include, but are not limited to, $-CH_2-CH_2-O-CH_2-$, $-CH_2-CH_2-NH-CH_2-$, $-CH_2-CH_2-N(CH_3)-CH_2-$, $-CH_2-S-CH_2-CH_2-$, $-O-(CH_2)_4-O-$, $-NH-(CH_2)_4-NH-$, and $-NH-(CH_2)_4-O-$.

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

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.

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 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.

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 pyridizine 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, azetidinyl, 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, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, 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 be 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, isopropryl, 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.

As used herein, "pH" refers to the measure of the acidity or alkalinity of a solution. pH is formally dependent upon the activity of hydronium ions (H_3O+), also referred to as hydrogen ions (H^+), but for very dilute solutions, the molarity of H_3O+ may be used as a substitute with little loss of accuracy. Aqueous solutions at 25 °C with a pH less than 7.0 are considered acidic, while those with a pH greater than 7.0 are considered basic (alkaline). When a pH

level is 7.0, it is defined as 'neutral' at 25 °C because at this pH the concentration of H_3O^+ equals the concentration of OH– in pure water.

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 $AlCl_3$, $FeCl_3$, $FeCl_3$•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, $B(Et)_3$, BF_3, BF_3-OEt_2, BBr_3, $B(OMe)_3$, and $B(OiPr)_3$.

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, 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, lithium diethylamide, lithium dicyclohexylamide, and lithium 2,2,6,6-tetramethylpiperidide; 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.

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

iPr = isopropyl

n-Bu = n-butyl

i-Bu = isobutyl

s-Bu = *sec*-butyl

t-Bu = *tert*-butyl

Ms = methanesulfonyl

Ts = p-toluenesulfonyl

SET = single electron transfer

In choosing the compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R_1, R_2, etc. are to be chosen in conformity with well-known principles of chemical structure connectivity.

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 incoporated by reference.

Those having ordinary skill in the art of organic synthesis will appreciate that modifications to the general procedures shown herein can be made to yield structurally diverse compounds. As described herein, 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 alkyl, alkenyl, and alkynyl groups are present, the chain length may be modified using methods well known to those of ordinary skill in the art. Suitable organic transformations are described in March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (Wiley-Interscience; 6th edition, 2007), the content of which is hereby incoporated by reference.

As used herein, the term "polymer" refers to a molecule containing multiple copies of one or more types of constitutional units, commonly referred to as monomers. As used herein, the term "monomers" may refer to the free monomers and those that are incorporated into polymers, with the distinction being clear from the context in which the term is used.

Polymers may take on a number of configurations, which include, but are not limited to, linear, branched and cyclic configurations. Branched configurations include star-shaped configurations (e.g., configurations in which three or more chains emanate from a single branch point), comb configurations (e.g., configurations having a main chain and a plurality of side chains, also referred to as "graft" configurations), dendritic configurations (e.g., arborescent and hyperbranched polymers), networked configurations (e.g., crosslinked configurations) and the like.

As used herein, "homopolymers" are polymers that contain multiple copies of a single monomer.

As used herein, the term "copolymer" refers to a polymer that contains multiple units of at least two dissimilar monomers. Examples of copolymers include, but are not limited to, random, statistical, gradient, periodic (e.g., alternating) and block copolymers.

Statistical copolymers are copolymers in which the sequence of monomers follows a statistical rule. In a truly random copolymer, the probability of finding a given type of monomer unit at a particular point in the polymer chain is equal to the mole fraction of that monomer in the chain.

The term "block copolymer" refers to copolymers comprising two or more homopolymer subunits, or blocks, linked by covalent bonds. The union of the homopolymer subunits may require an intermediate non-repeating subunit, known as a junction block. Block copolymers may be multi-block copolymers wherein the copolymer comprises multiple, distinct blocks. For example, a copolymer containing two or three distinct blocks are called diblock copolymers and triblock copolymers, respectively.

The term "graft copolymer" refers to a copolymer having a main chain and a plurality of side chains that are structurally distinct from the main chain. The individual side chains of a graft copolymer may be homopolymers or copolymers.

The polymers of this invention include homopolymers and copolymers. When a polymer is a copolymer, it is understood that such a copolymer can be a statistical copolymer, random copolymer, block copolymer, graft copolymer, among others. If chiral centers are present in the polymers of the present invention, all forms of tacticity, including isotactic form, syndiotactic form, and atactic form, among others, are intended to be covered herein. When a copolymer is a block copolymer, it is understood that the tacticity of each block of the copolymer can be the same or different.

The polymers of the present invention may be made by polymerization of monomers using a variety of methods known to one having ordinary skill in the art. Suitable polymerization methods include, but are not limited to, living polymerization techniques, such as atom transfer free radical polymerization (ATRP), reversible addition fragmentation chain transfer (RAFT), ring-opening metathesis polymerization (ROMP), living cationic or living anionic polymerizations, and chain shuttling polymerization. It is understood that substituents and functional groups may be introduced into the polymers prior to or subsequent to polymerization. Prior to polymerization, the constitutional monomers may be functionalized using standard reactions known in the art of chemical synthesis. After polymerization, the resulting polymer may also be modified using standard reactions known in the art of chemical synthesis.

Natural polymers are intended to be encompassed by the present invention. Examples of natural polymers include, but are not limited to, polypeptides, polysaccharides, and nucleic acids.

As used herein, the term "polysaccharide" refers to polymeric carbohydrate structures, formed of repeating units of either monosaccharides or disaccharides, joined together by glycosidic bonds. These structures are often linear, but may contain various degrees of branching. Polysaccharides are often quite heterogeneous. When all the monosaccharides in a polysaccharide are the same type the polysaccharide is called a homopolysaccharide, but when more than one type of monosaccharide is present they are called heteropolysaccharides. One of ordinary skill in the art understands that each repeating unit (monosaccharide or disaacharide) in a polysaccharide may be modified using chemical reactions well known to the ordinary artisan. For example, each repeating unit (monosaccharide or disaacharide) in a polysaccharide may be sulfated or unsulfated.

As used herein, the term "disaccharide" refers to a unit consisting of two carbohydrate structures. The two carbohydrate structures may be the same or different.

A "sample" as used herein means a biological material including, but not limited to, a liquid, coma, a cell, a tissue (including blood), or a derivative thereof including, but not limited to, a fraction, a centrifugate, a cellular component, a tissue slice, or a disaggregated tissue.

Such a sample may be removed from a subject, or if stated, may be *in situ*.

As used herein, the term "tumor" refers to an uncontrolled growth of cells. A tumor may be benign or malignant. Benign tumors are not dangerous to health and are not considered cancerous. Malignant tumors are cancerous; they invade surrounding tissue, are usually capable of producing metastases, may recur after attempted removal, and are likely to cause death of the host unless adequately treated. Left unchecked, malignant cells can eventually spread beyond the original tumor to other parts of the body. Various cancers result in the formation of tumors, including, but not limited to, prostate cancer, breast cancer, endometrial cancer, pancreatic cancer, and colon cancer.

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, 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, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate,

glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, *e.g.*, Berge *et al.* (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

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 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.

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.

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 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 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 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 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 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-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 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.); Modem 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 unilamallar 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 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 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.

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 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 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 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 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. 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 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 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.

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

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 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, chemotherapeutic agents and NSAIDs, among others.

The term "chemotherapeutic agent" refers to a compound useful for the treatment of various types of cancer. Examples of chemotherapeutic 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 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, 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.

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 compounds, compositions, and methods of the present invention are useful in the inhibition of tumor growth and treatment and/or prevention of a variety of cancers, including, but not limited to, breast colon, and pancreatic cancers.

As used herein, "cancer prevention" is the administration of a pharmaceutical agent alone or in combination with other pharmaceutical or natural agents for the prevention of the development of cancer or of its recurrence in subjects at risk for the development of a given cancer or precancerous condition.

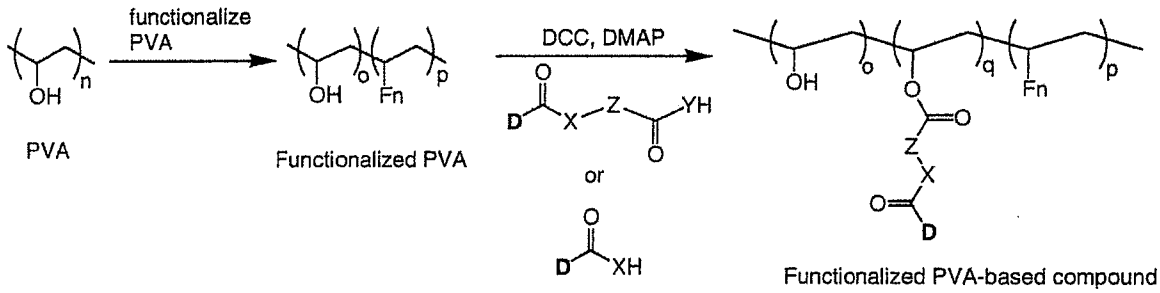
As used herein, "treating" means slowing, stopping or reversing the progression of a disease. An embodiment of "treating cancer" is inhibition of proliferation of tumor cells.

As used herein, "administering" an agent may be performed using any of the various methods or delivery systems well known to those skilled in the art. The administering can be performed, for example, orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery, subcutaneously, intraadiposally, intraarticularly, intrathecally, into a cerebral ventricle, intraventicularly, intratumorally, into cerebral parenchyma or intraparenchchymally.

The compounds, compositions, and methods of the present invention are also useful for treating diseases and/or conditions that involve inflammation. Diseases and/or conditions that involve inflammation include, but are not limited to, rheumatological diseases, autoimmune

diseases, cardiovascular disease, and neurological diseases, such as Alzheimer's disease. The compounds, compositions, and methods of the present invention containing conventional anti-inflammatory agents, such as NSAIDs, are useful as safe analgesic and/or antipyretic agents against pain and fever.

Below, the compounds of the present invention are synthesized according to the general procedures shown in the following synthetic schemes.



Scheme 1.

Scheme 1 depicts a general method for the synthesis of compounds based on PVA polymer. "n", "o", "p", and "q" each, independently, refers to an integer greater than or equal to 1. Preferably, "n", "o", "p", and "q" are each, independently, an integer in the range of 1-400, inclusive.

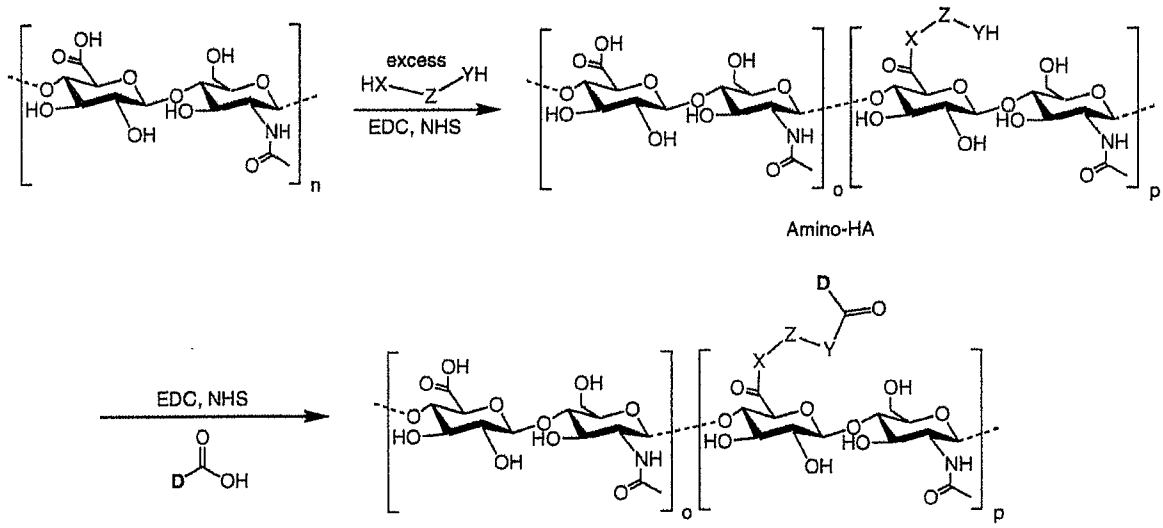
X and Y are each, independently, -O- or -NH-. D is any substituted or unsubstituted alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl, arylalkyl, or heteraryl group. Preferably, D is, or is derived from, a pharmaceutically active agent, which can be synthetic or natural.

"Fn" refers to functional groups that include, but are not limited to, nitrates ($-ONO_2$), sulfates ($-OSO_2OR$), sulfonates ($-OSO_2R$), phosphates ($-OPO(OH)_2$), phosphate esters ($-OPO(OR)_2$), boronic esters ($-OB(OR)_2$), diazonium ($-N_2^+$), halides, $-OR_2^+$, $-OH_2^+$, $-SR_2^+$, and $-NR_3^+$. Examples of sulfonate groups include, but are not limited to, p-toluenesulfonate, methanesulfonate, and trifluoromethanesulfonate. Examples of phosphate ester leaving groups include, but are not limited to, $-OPO(OMe)_2$, $-OPO(OEt)_2$, and $-OPO(O\mathit{i}Pr)_2$.

"Z" refers to any divalent radical. Preferably, Z is arylene, -$(CH_2)_m$-, -arylene-$(CH_2)_m$-, or -$(CH_2)_m$-arylene-$(CH_2)_m$-, where each instance of "m" is an integer greater than or equal to 1, preferably an integer from 1-20, inclusive.

Generally, functionalized PVA is first synthesized by reaction of PVA with a functionalizing agent, such as diethyl chlorophosphate. A compound, **D,** bearing a -COOH group is coupled to a linker molecule forming an ester (where X is O) or amide bond (where X is NH). Finally, the **D**-linker conjugate is linked on to the polymer chain by esterification between the free -OH groups on PVA and the -COOH or -$CONH_2$ group on the linker. Alternatively, compound **D** bearing a -COOH group may be directly reacted with the -OH groups on PVA without the linker.

Ester bond 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. When an amide bond is contemplated, any number of amide bond-forming or peptide-bond forming reactions known to those having ordinary skill in the art may be used. For example, a carboxylic acid may be reacted with a carbodiimide, such as *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC), followed by *N*-hydroxysuccinimide (NHS). The resulting NHS ester intermediate is then reacted with an amine to form the desired amide.



Scheme 2.

Scheme 2 depicts a general method for the synthesis of compounds based on a natural polymer, such as a polysaccharide.

Generally, a polysaccharide having -COOH groups, such as hyaluronic acid, is first functionalized by reaction with a linker HX-Z-YH, where X, Y, and Z are as defined hereinabove. A compound **D** bearing a -COOH group is then coupled to the linker molecule.

One having ordinary skill in the art would understand that the polysaccharide used as the backbone in the compounds of the present invention is not limited so long as it contains at least one -COOH group. Polysaccharides containing glucuronic acid and/or iduronic acid are preferred. Examples of suitable polysaccharides include, but are not limited to, chondroitin, chondroitin sulfate, dermatan, dermatan sulfate, hyaluronic acid, heparin, and heparin sulfate.

All combinations of the various elements described herein are within the scope of the invention.

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.

Experimental Details

As mentioned hereinabove, developing effective new therapeutic agents and/or targeting their delivery to specific tissues continues to be a challenging problem.

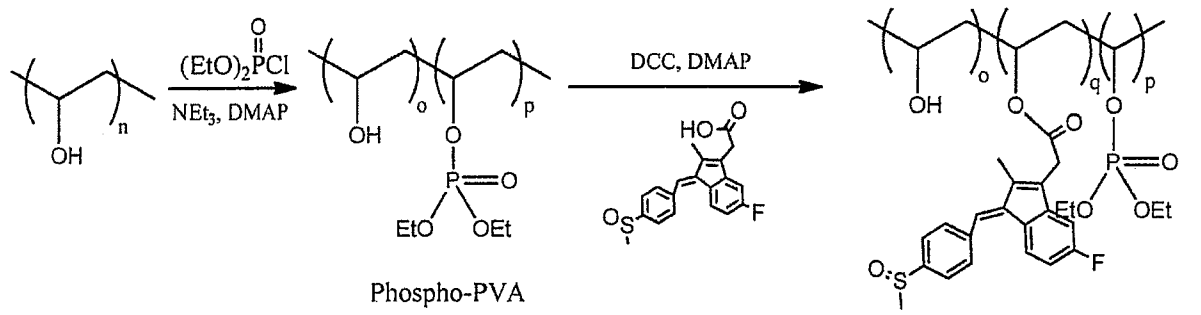
To overcome these difficulties, three classes of drugs based on the principles described herein using a) as a polymer backbone poly(vinyl alcohol) or hyaluronic acid or heparin; b) diethyl phosphate as a functional group c) the NSAID sulindac as the pharmaceutically active agent, and d) 1,4-diaminobutane or no linker at all have been synthesized.

Three exemplary compounds have been evaluated for their anti-cancer effect on human cancer cell lines, both in cell culture systems and as tumor xenograft in nude mice. The compounds of the present invention exhibit considerable efficacy against pancreatic cancer.

Fig. 1 depicts diagrammatically new compounds that incorporate the desirable properties of polymers used in drug development with the need to optimize their pharmacokinetic features. Fig. 2 shows two representative compounds, phospho-PVA sulindac and sulindac-HA.

Example 1. Phospho-PVA sulindac (PPS)

The synthesis of phosphate containing PVA is as follows.



Scheme 3: Synthesis of phospho-PVA sulindac (PPS).

Synthetic procedure:

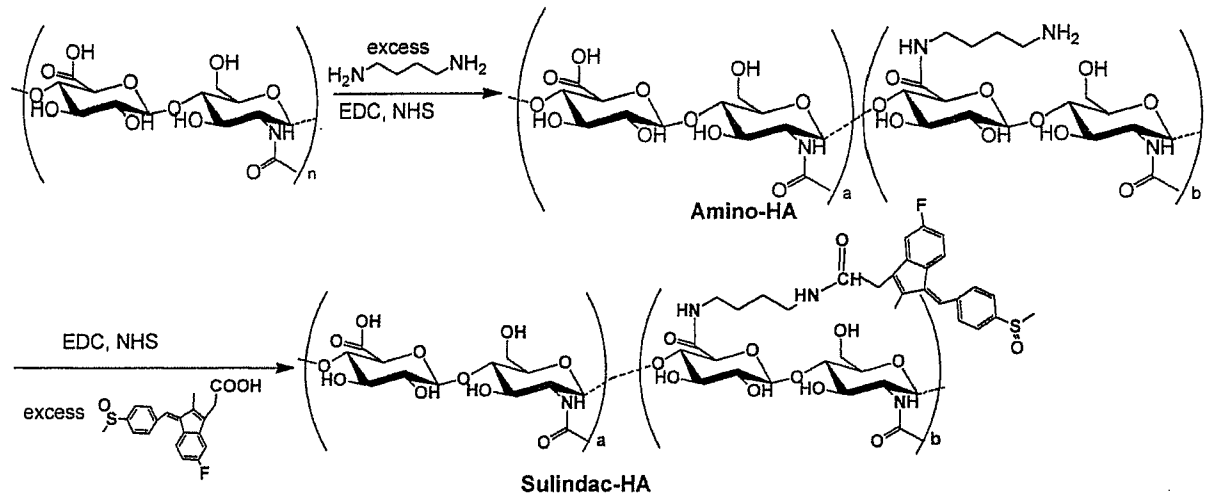
Step A. Synthesis of phospho-PVA (n = 10p)

Chloro diethyl phosphate (1 eq.) was added drop-wise to a solution of PVA (10 eq. OH groups) pre-dissolved in dimethylsulfoxide (DMSO), triethylamine (2.2 eq.) and 4-(dimethylamino)pyridine (DMAP) (catalytic amount, approx. 5 mol %) in anhydrous DMSO at room temperature in a two-neck flask equipped with a condenser under an inert atmosphere. The mixture was stirred at room temperature for 15 h and heated at 50 °C for an additional 3 h. Then the reaction was quenched and precipitated in water (50 mL). The supernatant was dialyzed, first against 1 M NaCl, then against deionized (D. I.) water. The product was obtained by lyophilization typically with a 90% yield.

Step B. Synthesis of Phospho PVA (n = 10q)

Sulindac (1 eq.) in DMSO was added drop-wise into a solution of phosphor PVA (9 eq. OH groups) pre-dissolved in DMSO, with the addition of 1 eq. N, N'-dicyclohexylcarbodiimide (DCC), DMAP as the catalyst. The mixture was stirred at room temperature for 24 h. Then the reaction was quenched and precipitated in water (100 mL). The supernatant were dialyzed first against 1 M NaCl and then against D. I. water. Product was obtained by lyophilization with a typical yield of about 70%.

Example 2. Sulindac-Hyaluronic acid (HA)



Scheme 4: The synthesis of Sulindac-HA.

The linker is bound through an amide bond

Synthetic procedure:

Step A. Synthesis of amino-HA.

Carboxylic acid groups of HA were modified to have amino groups as follows. HA (MW 1.3×10^5 Da) was dissolved in D. I. water with 1 eq. molar of -COOH groups. To this solution, a 10-fold molar excess 1,4-diaminobutane, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC·HCl, 3 eq.) and N-hydroxy-succinimide (NHS, 3 eq.) was added under an inert atmosphere. The mixture was stirred at room temperature for 12 h. Then the reaction mixture was dialyzed first against 1 M NaCl and then against D.I. water. Product was obtained by lyophilization with 80% yield.

Step B. Synthesis of sulindac-HA.

The reaction is similar to the synthesis of amino-HA in step A: amide bond formation was catalyzed by carbondiimide. Briefly, amino-HA was dissolved in D. I. water with 1 eq. molar of $-NH_2$ groups. To this solution, a 10-fold molar excess of sulindac, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC·HCl,3 eq.) and N-hydroxysuccinimide (NHS, 3 eq.) was added under an inert atmosphere. The mixture was stirred at room temperature for 12 h. Then the reaction mixture was dialyzed first against 1 M NaCl and then against D.I. water. Product was obtained by lyophilization with 75% yield.

Example 3. Heparin-sulindac

The synthesis of heparin-sulindac using 1,4-diamino butane as the linker is similar to the synthesis of sulindac-HA. Briefly, high molecular weight heparin (HMWH, MW 1.5×10^5 Da) with an average of 25 -COOH groups on the polysaccharide backbone chain is used. LMWH is first functionalized with amine groups by reacting with 1,4-diamino butane. Then the amino-heparin is further reacted with sulindac to obtain sulindac-heparin.

Example 4. Evaluation of polymer-based compounds against human cancer cell lines in vitro and in vivo

Table 1. The growth inhibitory effect of polymer-based compounds on a human breast cancer cell line.

	PVA	PPS	HA	HA-sulindac	Heparin	Heparin-sulindac
IC_{50} (μg/mL)	>1000	38	>1000	19	>1000	207

As shown in Table 1, the compounds of the present invention inhibit the growth of a human breast cancer cell line. In contrast, PVA, HA, and heparin failed to inhibit breast cancer cell growth even at very high concentrations, with their respective 48-hour IC_{50} values being indeterminable under the experimental conditions tested. IC_{50} is the concentration of a test compound that inhibits cell growth by 50% compared to control after a defined period of time; in this case, after treatment for 24 hours.

PPS inhibits the growth of human pancreatic cancer xenografts

The effect of PPS on xenografts of MIA PaCa-2 human pancreatic cancer cells was evaluated. Xenografts of MIA PaCa-2 human pancreatic cancer cells were grown subcutaneously in nude mice following standard protocols (3). Each animal had two xenografts, one on each side. When the xenografts reached a volume of about 75-100 mm^3, we commenced treatment with PPS (dissolved in PBS) at a dose of 125 mg/kg body weight daily, administered intraperitoneally 5 days per week for a total of 27 days. The tumor volume was determined using an electronic caliber, as described (3).

As shown in Fig. 3, PPS inhibited the growth of the xenografts at all time points. At the time of animal sacrifice, on day 27, PPS inhibited tumor growth by 73% compared to the vehicle (PBS)-treated control group ($p<0.03$).

Without being bound to theory, it is believed that PVA polymers bearing pharmaceutically active agents, including PPS, form nano-sized micelles under physiological conditions, thereby protecting the pharmaceutically active agent and enhancing its efficacy through the enhanced permeability and retention (EPR) effect (4).

Example 5. Evaluation and comparison of the polymer-based compounds against human cancer cell lines

The effect of Polymer-based sulindac on the growth of human cancer cell lines was evaluated by determining the 24-h IC_{50} of PPS, HA-sulindac and Heparin-sulindac (Table 2). Polymer-

based compounds showed enhanced potency in inhibiting cell growth compared to conventional sulindac, with the potency enhancement ranging between 5 and 59-fold.

Table 2. Polymer-based sulindac inhibits the growth of human cancer cells.

IC_{50}, μM

	Breast cancer cell MCF-7(Fold Enhancement)	Colon cancer cell SW480(Fold Enhancement)
Sulindac	1128	900
PPS	28 (40)	21(43)
HA-sulindac	19 (59)	17(53)
Heparin-sulindac	207 (5)	167(5)

Example 6. Micelle formation of PPS.

P*olymer-based sulindac* micelles were formed by the self assembly of hydrophic PVA and hydrophobic sulindac. 10 mg PPS were dissolved in an unselective solvent, 0.1 mL dimethylsulfoxide (DMSO), and 1 ml deionized water was subsequently added dropwise with stirring. The resultant solution was further purified on a Sephadex G-50 column to remove the free PVA or sulindac. The remaining DMSO was removed by dialysis.

Drug concentration was determined by HPLC. A Waters alliance 2695 Separations Module equipped with a Waters 2998 photodiode array detector and a thermo Hypersil BDS C18 column was used (150 x 4.6 mm, particle size 3 μm). *Nuclear magnetic resonance* (NMR, Varian INOVA 500-MHz spectrometer) was also used to confirm the composition and stability of the components.

Size distribution and zeta potential of conjugates were measured at 25°C using a Zetasizer Nano-Zs ((Zetaplus, Brookhaven Instrument, Holtsville, NY). The concentration of self-aggregates was kept constant at 0.3 mg/mL. Zeta Potential Analyzer was used to characterization the size and morphology of each nanoparticle. The hydrodynamic radius (R_h) and polydispersity index (PDI) of particles were measured by the dynamic light scattering.

Table 3. Size distribution and zeta potential of PPS, HA-sulindac and Heparin-sulindac nanoparticles in water.

Nanoparticle	R_h (nm)	PDI	Zeta potential
PPS	209	0.171	-1.49
HA-sulindac	481	0.132	-5.27
Heparin-sulindac	123	0.101	-30.22

References

1. Duncan, R., et al., *Polymer-drug conjugates, PDEPT and PELT: basic principles for design and transfer from the laboratory to clinic.* Journal of Controlled Release, 2001. 74(1-3): p. 135-146.

2. Fang, J., T. Seki, and H. Maeda, *Therapeutic strategies by modulating oxygen stress in cancer and inflammation.* Advanced Drug Delivery Reviews, 2009. 61(4): p. 290-302.

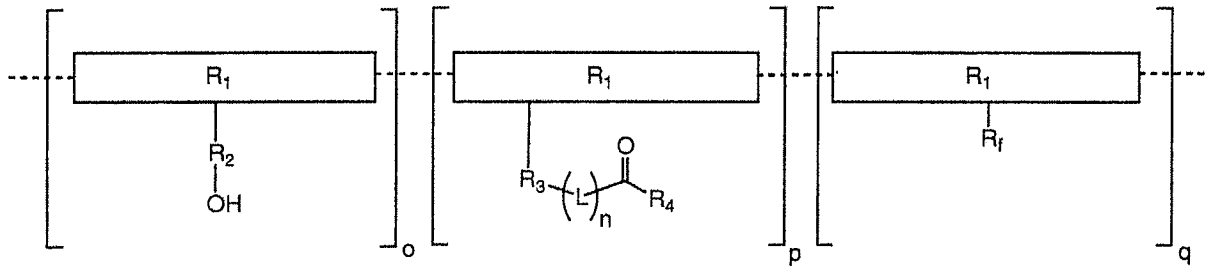
3. Rigas, B. and V. Kozoni, *The novel phenylester anticancer compounds: Study of a derivative of aspirin (phoshoaspirin).* Int J Oncol, 2008. 32(1): p. 97-100.

4. H. Maeda, J. Wu, T. Sawa, Y. Matsumura, K. Hori, *J. Control. Release,* 2000. 65, 271-84.

Claims

What is claimed is:

1. A compound having the structure:



wherein

R_1 is a polyvinyl alcohol or disaccharide repeating unit;

R_2 is a direct bond or -(C=O)-;

R_3 is -O- or -(C=O)-;

R_4 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl, arylalkyl, or heteroaryl group;

L is -X-Z-(C=O)-, -X-Z-Y-, alkylene, arylene, or heteroarylene,

wherein X and Y are each, independently, -O- or -NH; and

Z is arylene, $-(CH_2)_m-$, -arylene-$(CH_2)_m-$, or $-(CH_2)_m$-arylene-$(CH_2)_m-$,

wherein each instance of m is an integer greater than or equal to 1;

R_f is $-ONO_2$, $-OSO_2OR_5$, $-OSO_2R_5$, $-OPO(OH)_2$, $-OPO(OR_5)(OR_6)$, $-OB(OR_5)(OR_6)$, $-N_2^+$, halogen, $-O(R_5)_2^+$, $-S(R_5)_2^+$, or $-N(R_5)_3^+$,

wherein each instance of R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

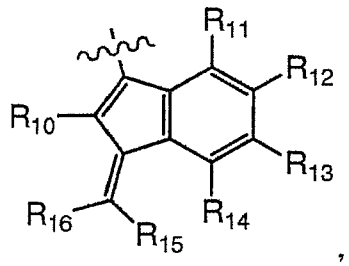
2. The compound of claim 1, wherein

R_4 is $-(CR_7R_8)_a-R_9$,

wherein

a is an integer from 1 to 10;

each instance of R_7 and R_8 are each, independently, H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, or aryl;

R_9 is 

,

wherein

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each, independently, H, OR_{15}, halogen, -CN, $-NO_2$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(C=O)-R_{17}$, $-SO_2-R_{17}$, $-SO-R_{17}$, $-S-R_{17}$, $-NR_{17}R_{18}$,

wherein R_{17} and R_{18} are each, independently, H, -OH, $-OR_{19}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl,

wherein R_{19} is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

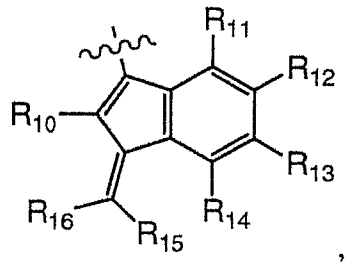
R_{15} and R_{16} are each, independently, H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, or aryl;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein

R_4 is $-CH_2-R_9$,

wherein

R_9 is 

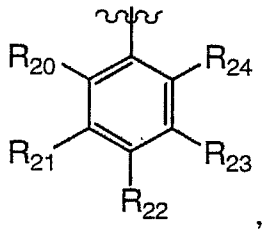
,

wherein

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each, independently, H, OR_{15}, halogen, -CN, $-NO_2$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(C=O)-R_{17}$, $-SO_2-R_{17}$, $-SO-R_{17}$, $-S-R_{17}$, $-NR_{17}R_{18}$,

wherein R_{17} and R_{18} are each, independently, H, -OH, $-OR_{19}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl,

wherein R_{19} is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

R_{15} and R_{16} are each, independently, H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, or 

,

wherein

R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each, independently, H, OH, halogen, -CN, $-NO_2$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(C=O)-R_{25}$, $-SO_2-R_{25}$, $-SO-R_{25}$, $-S-R_{25}$, $-NR_{25}R_{26}$,

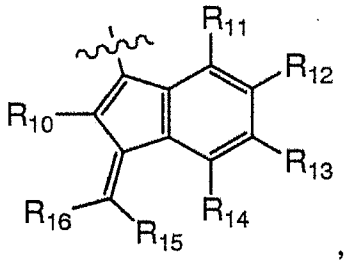
wherein R_{25} and R_{26} are each, independently, H, -OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, wherein

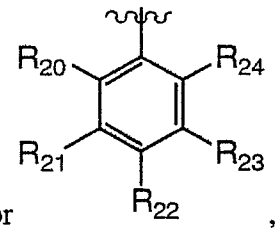
R_4 is $-CH_2-R_9$,

wherein

R_9 is  ,

wherein

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each, independently, H, halogen, or C_1-C_{10} alkyl,

R_{15} and R_{16} are each, independently, H or  ,

wherein

R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each, independently, H or -SO-R_{25},

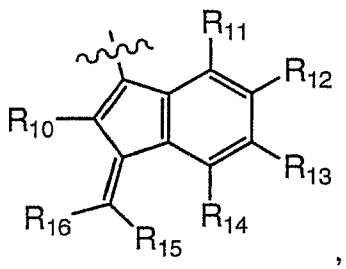
wherein R_{25} is H, -OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl;

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 4, wherein

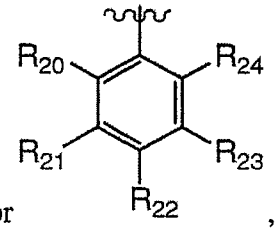
R_4 is -CH_2-R_9,

wherein

R_9 is  ,

wherein

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are each, independently, H, F, or -CH_3,

R_{15} and R_{16} are each, independently, H or 

,

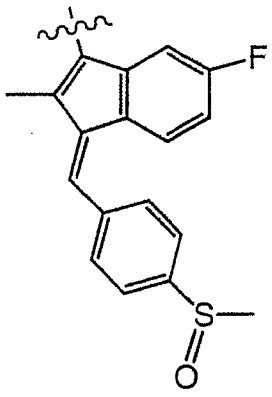
wherein

R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are each, independently, H or -SO-R_{25},

wherein R_{25} is $-CH_3$;

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein

R_4 is 

;

or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, wherein

R_1 is a polyvinyl alcohol or disaccharide repeating unit;

R_2 is a direct bond or -(C=O)-;

R_3 is -O- or -(C=O)-;

L is $-X-(CH_2)_m-(C=O)-$ or $-X-(CH_2)_m-Y-$,

wherein X and Y are each, independently, -O- or -NH, and

wherein each instance of m is an integer greater than or equal to 1;

R_f is $-OPO(OR_5)(OR_6)$

R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

or a pharmaceutically acceptable salt thereof.

8. The compound of any one of claims 1-6, wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O- or -NH-, and m is an integer greater than or equal to 1;

R_f is $-OPO(OR_5)(OR_6)$

R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1-6, wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O-, and m is an integer greater than or equal to 1;

R_f is $-OPO(OR_5)(OR_6)$

wherein R_5 and R_6 are each, independently, alkyl;

n is 0 or 1;

o, p, and q are each, independently, an integer grater than or equal to 1;

or a pharmaceutically acceptable salt thereof.

10. The compound of any one of claims 1-6, wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each ethyl;

n is 0 or 1;

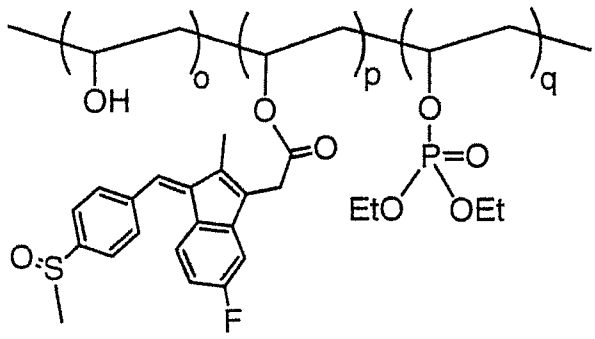
o, p, and q are each, independently, an integer greater than or equal to 1;

or a pharmaceutically acceptable salt thereof.

11. The compound of any one of claims 1-6, wherein o, p, and q are each, independently, an integer from 1 to 400.

12. The compound of any one of claims 1-6, wherein m is an integer from 1 to 20.

13. The compound of any one of claims 1-6 having the structure:



or a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1-6, wherein

R_1 is a disaccharide repeating unit;

R_2 is -(C=O)-;

R_3 is -(C=O)-;

L is $-X-(CH_2)_m-Y-$,

wherein X and Y are each, independently, -O- or -NH-, and m is an integer greater than or equal to 1;

R_f is -OPO(OR_5)(OR_6)

R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

n is 1;

o, and p are each, independently, an integer greater than or equal to 1;

q is 0;

or a pharmaceutically acceptable salt thereof.

15. The compound of any one of claims 1-6, wherein

R_1 is a disaccharide repeating unit;

R_2 is -(C=O)-;

R_3 is -(C=O)-;

L is -X-$(CH_2)_m$-Y-,

wherein X and Y are each -NH-, and m is an integer greater than or equal to 1;

n is 1;

o, and p are each, independently, an integer greater than or equal to 1;

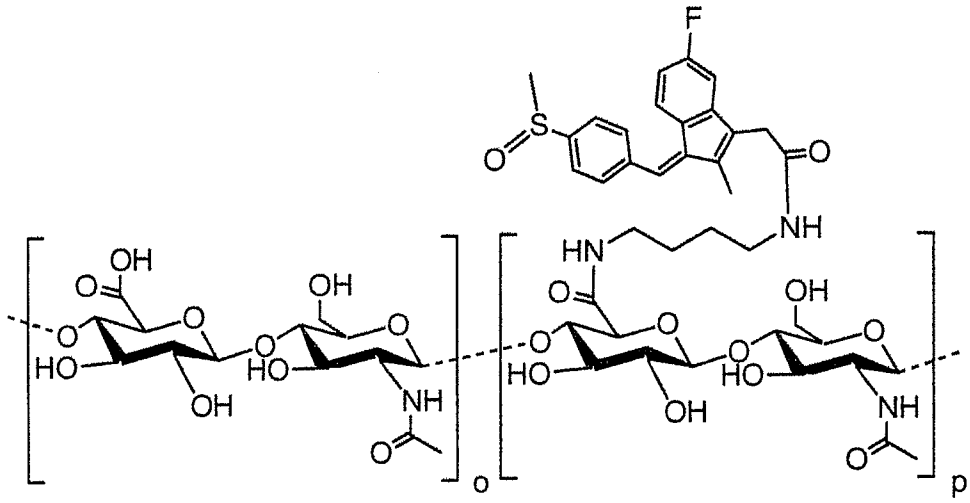
q is 0;

or a pharmaceutically acceptable salt thereof.

16. The compound of any one of claims 1-6 wherein R_1 is a disaccharide repeating unit comprising heparin.

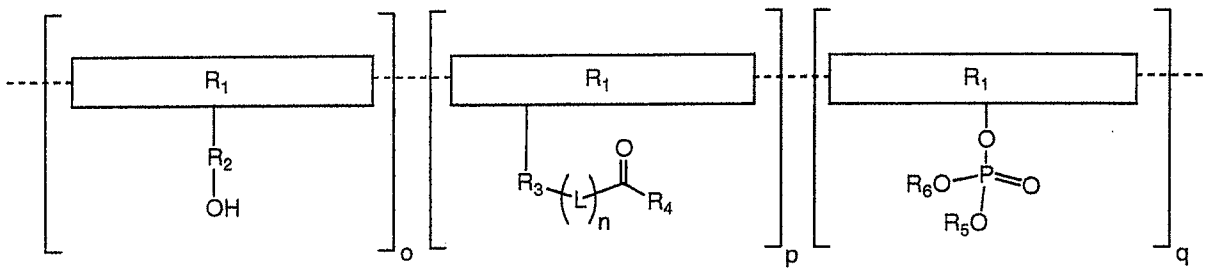
17. The compound of any one of claims 1-6 wherein o and p are each, independently, an integer from 1 to 400.

18. The compound of any one of claims 1-6 having the structure



or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1 having the structure:



wherein

R_1 is a polyvinyl alcohol or disaccharide repeating unit;

R_2 is a direct bond or -(C=O)-;

R_3 is -O- or -(C=O)-;

R_4 is a pharmaceutically active agent;

L is $-X-(CH_2)_m-(C=O)-$ or $-X-(CH_2)_m-Y-$,

wherein X and Y are each, independently, -O- or -NH, and

wherein each instance of m is an integer greater than or equal to 1;

R_5 and R_6 are each, independently, H, alkyl, alkenyl, alkynyl, or aryl;

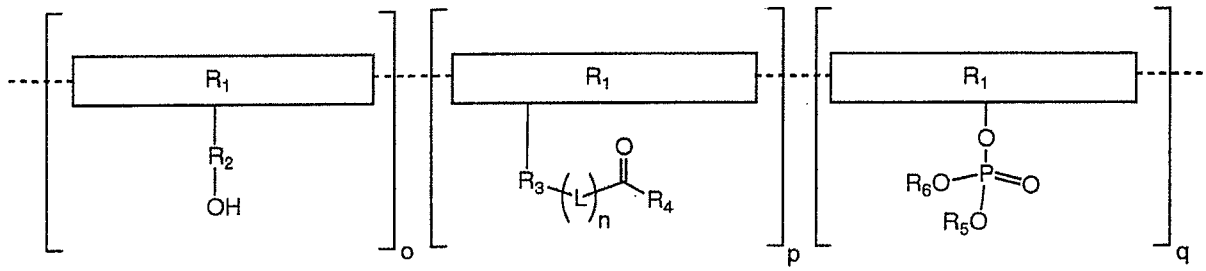
n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

20. The compound of claim 19 having the structure



wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

R_4 is a pharmaceutically active agent;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O- or -NH-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each, independently, alkyl, alkenyl, or alkynyl;

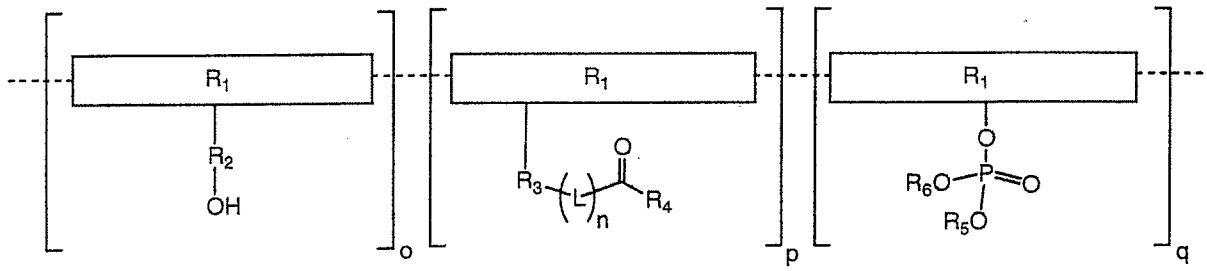
n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 19 having the structure



wherein

R_1 is a disaccharide repeating unit;

R_2 is -(C=O)-;

R_3 is -(C=O)-;

R_4 is a pharmaceutically active agent;

L is -X-$(CH_2)_m$-Y-,

wherein X and Y are each, independently, -O- or -NH-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each, independently, alkyl, alkenyl, or alkynyl;

n is 1;

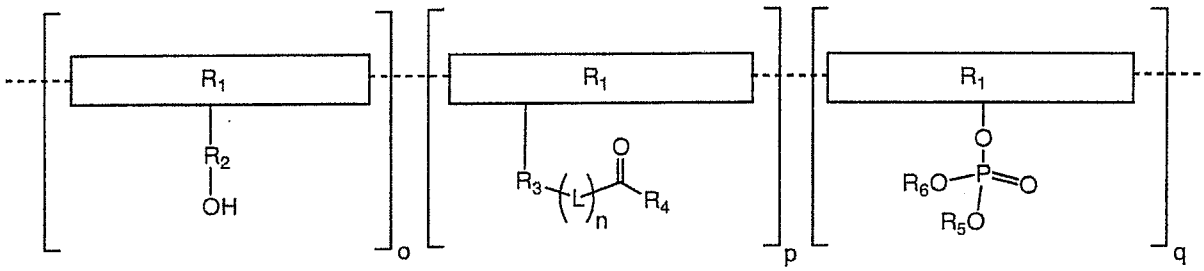
o, and p are each, independently, an integer greater than or equal to 1;

q is 0;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

22. The compound of claim 20 having the structure



wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

R_4 is a pharmaceutically active agent;

L is $-X-(CH_2)_m-(C=O)-$,

wherein X is -O-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each, independently, alkyl;

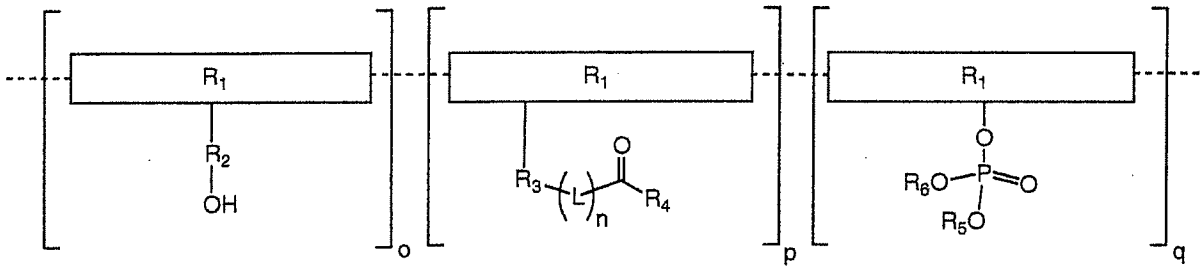
n is 0 or 1;

o, p, and q are each, independently, an integer grater than or equal to 1;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

23. The compound of claim 22 having the structure

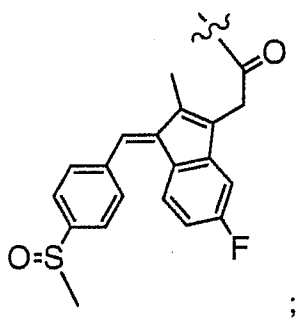


wherein

R_1 is a polyvinyl alcohol repeating unit;

R_2 is a direct bond;

R_3 is -O-;

R_4 is 

;

L is -X-$(CH_2)_m$-(C=O)-,

wherein X is -O-, and m is an integer greater than or equal to 1;

R_5 and R_6 are each ethyl;

n is 0 or 1;

o, p, and q are each, independently, an integer greater than or equal to 1;

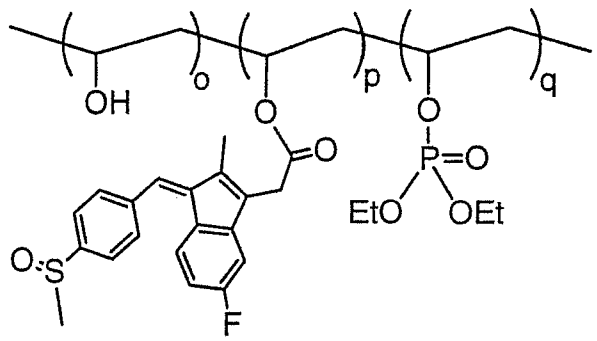
wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

or a pharmaceutically acceptable salt thereof.

24. The compound of any one of claims 19, 20, 22, or 23, wherein o, p, and q are each, independently, an integer from 1 to 400.

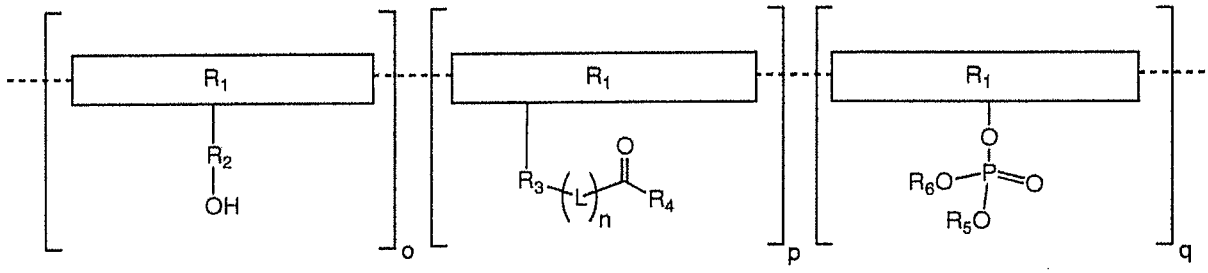
25. The compound of any one of claims 19-23, wherein m is an integer from 1 to 20.

26. The compound of claim 23 having the structure:



or a pharmaceutically acceptable salt thereof.

27. The compound of claim 21 having the structure

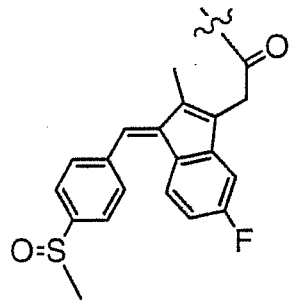


wherein

R_1 is a disaccharide repeating unit;

R_2 is -(C=O)-;

R_3 is -(C=O)-;

R_4 is  ;

L is $-X-(CH_2)_m-Y-$,

wherein X and Y are each -NH-, and m is an integer greater than or equal to 1;

n is 1;

o, and p are each, independently, an integer greater than or equal to 1;

q is 0;

wherein each occurrence of alkyl, heteroalkyl, alkenyl, alkynyl, and alkylene is independently branched or unbranched, substituted or unsubstituted; and each occurrence of cycloalkyl, heterocyclic, aryl, arylalkyl, heteraryl, arylene, and heteroarylene is independently substituted or unsubstituted;

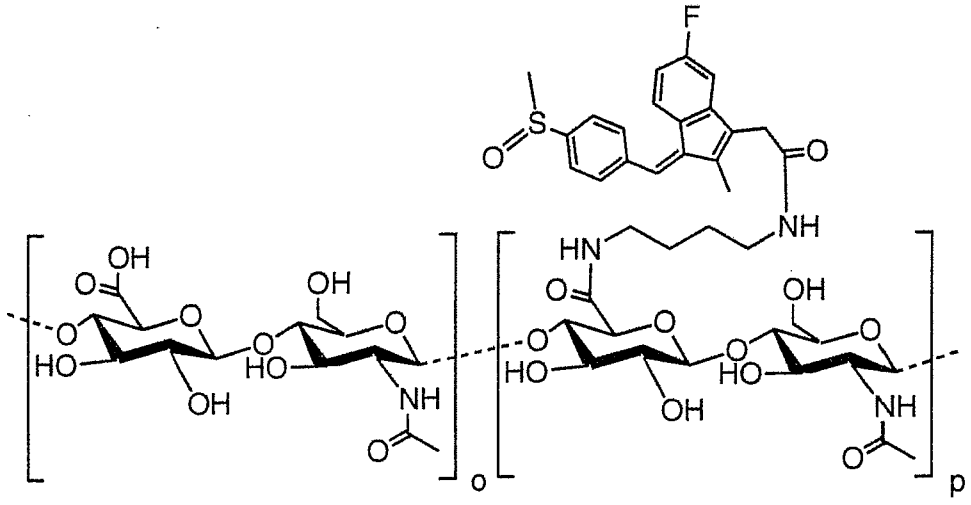
or a pharmaceutically acceptable salt thereof.

28. The compound of claim 21 or 27 wherein R_1 is a disaccharide repeating unit comprising heparin.

29. The compound of claim 21 or 27 wherein o and p are each, independently, an integer from 1 to 400.

30. The compound of claim 21 or 27 wherein m is an integer from 1 to 20.

31. The compound of claim 27 having the structure



or a pharmaceutically acceptable salt thereof.

32. A pharmaceutical composition comprising the compound of any one of claims 1-31 and a pharmaceutically acceptable carrier.

33. A method of inhibiting tumor growth in a subject comprising administering to the subject the compound of any one of claims 1-31 so as to inhibit tumor growth in the subject.

34. A method of inhibiting tumor growth in a subject comprising administering to the subject the pharmaceutical composition of claim 32 so as to inhibit tumor growth in the subject.

35. The method of claim 33 or 34, wherein the tumor is a human pancreatic cancer tumor.

36. The method of claim 33 or 34, wherein the tumor is a human breast cancer tumor.

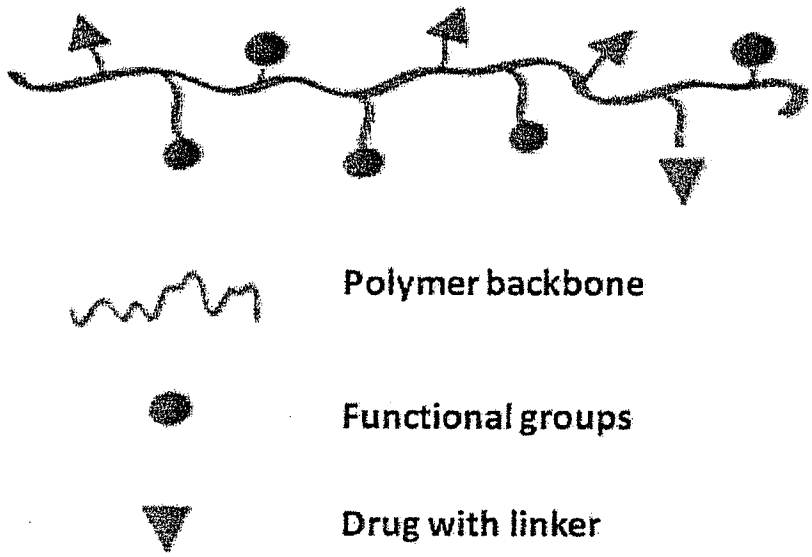
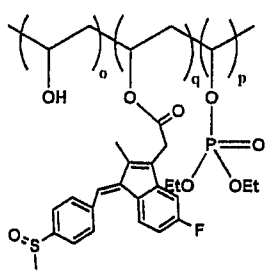
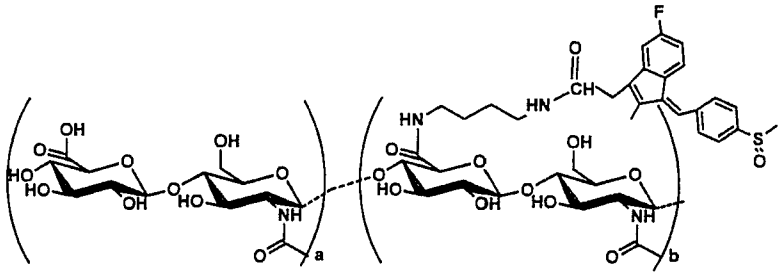


Figure 1.



Phospho-PVA Sulindac (PPS)



Sulindac-HA

Figure 2.

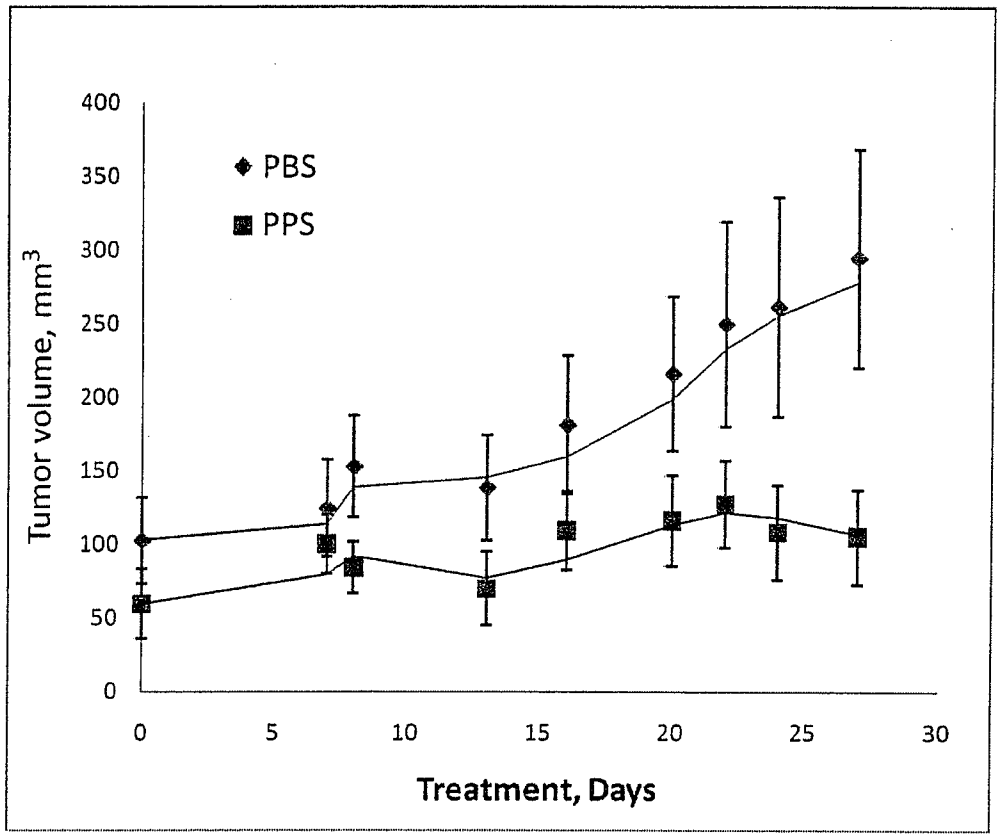

400
350
300
250
200
150
100
50
0
Tumor volume, mm3
PBS
PPS
0
5
10
15
20
25
30
Treatment, Days

Figure 3.