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(54) Title: NSAIDs DERIVATIVES AND USES THEREOF

(57) Abstract: The present invention discloses novel compounds derived from NSAIDs and pharmaceutically acceptable salts thereof. Other aspects of the invention relate to use of the NSAID derivatives in treating inflammatory diseases and pharmaceutical compositions thereof. Non-steroidal anti-inflammatory drugs (NSAIDs) are prototypical agents for treatment of inflammatory conditions. NSAIDs may also have utility as therapeutic agents against many forms of cancers. However, long-term use of NSAIDs may lead to serious side effects affecting the gastrointestinal and renal systems.

NSAIDs DERIVATIVES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of U.S. Provisional Patent Application No. 61/761,848, filed on February 7, 2013, which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are prototypical agents for treatment of inflammatory conditions. NSAIDs may also have utility as therapeutic agents against many forms of cancers. However, long-term use of NSAIDs may lead to serious side effects affecting the gastrointestinal and renal systems.

Recognition that endogenous gaseous mediators, nitric oxide (NO) and hydrogen sulfide (H_2S) can increase mucosal defense mechanisms has led to the development of NO- releasing NSAIDs and H_2S-releasing NSAIDs with increased safety profiles. NO-NSAIDs and HS-NSAIDs, however, have several drawbacks. HS-NSAIDs, for example, have relatively high IC_{50}s for cell growth inhibition. Some NO-NSAIDs can form quinone methide intermediates, raising doubts about the role of NO in their biological activity. Other NO-NSAIDs have high IC_{50}s for cell growth inhibition.

Hybrid dual action compounds that incorporate both NO and H_2S donor components were found to be more potent therapeutic agents than compounds that donate only one of these groups. Such dual action compounds provide improved safety and methods of treatment of inflammatory conditions, such as cancers. Khosrow Kashfi and Ravinder Kodela disclosed some of these compounds in International Publication No. WO 2013/025790 (International Application No. PCT/US2012/050922), the contents of which are incorporated herein in its entirety.

However, there remains a need for additional NSAID derivatives bearing moieties that provide activity against inflammatory conditions, such as cancer, rheumatoid arthritis, intestine inflammation, stomach ulcer, cardiovascular disease, and neurodegenerative disease.

SUMMARY OF THE INVENTION

The present invention relates to compounds of the general formulas with activity towards treating diseases related to inflammation, such as, gastrointestinal diseases, cancer, and cardiovascular diseases.

In one embodiment, the invention relates to a compound of Formula I:

R-X-Y (I)

wherein:

R is a non-steroidal anti-inflammatory drug (NSAID) or R^1-C(O)-X^1-;

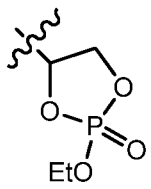
R^1 is an alkyl, cycloalkyl, or aryl;

X^1 is O, S, or NH;

X is an alkyl, a cycloalkyl, an aryl, or $-(CH_2)_{n1}-S_{n2}-(CH_2)_{n1}-$;

n1 is independently an integer from 1 to 20;

n2 is 2, 3, or 4;

Y is independently $-OP(O)(OEt)_2$,  , $-OSO_2R^2$, $-OSO_2OR^2$, $-OB(OR^2)_2$, halo, an H_2S releasing moiety, or an NO releasing moiety;

R^2 is independently $-(CH_2)_{n1}-$;

alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain;

aryl groups are carbocyclic or heterocyclic;

aryl groups may be unsubstituted or substituted with one or more substituent at any position;

cycloalkyl groups are carbocyclic or heterocyclic, fused or unfused, non-aromatic ring systems having a total of 3-16 ring members including substituent rings;

each alkyl or cycloalkyl, independently, may be unsubstituted or substituted with one or more substituent at any position;

alkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, cycloalkyl, or aryl;

cycloalkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, or aryl;

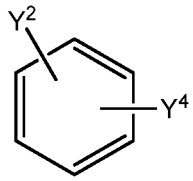
aryl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, aryl, nitro, carboxyl, or –O-C(O)-alkyl;

heterocyclic alkyl and aryl groups have at least one heteroatom selected from oxygen, nitrogen, and sulfur;

R^3 represents alkyl, cycloalkyl, aryl, or halo; and

halo substituents are fluoro, chloro, or bromo.

In another embodiment, the invention relates to a compound of Formula II:



(II)

wherein:

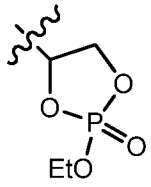
Y^2 is Y^3, –C(O)-X^1-X_{n4}-Y or –X^1-X_{n4}-Y;

Y^4 is –C(O)-X^1-X_{n4}-Y or –X^1-X_{n4}-Y;

R^2 is –$(CH_2)_{n1}$-;

X^1 is O, S, or NH;

X is an alkyl, a cycloalkyl, an aryl, or –$(CH_2)_{n1}$-S_{n2}-$(CH_2)_{n1}$-;

Y is independently –OP(O)(OEt)$_2$,  , -OSO$_2$R^2, -OSO$_2$OR^2, -OB(OR^2)$_2$, halo, an H_2S releasing moiety, or an NO releasing moiety;

Y^3 is an H_2S releasing moiety or an NO releasing moiety;

n1 is independently an integer from 1 to 20;

n2 is 2, 3, or 4;

n4 is 0 or 1;

alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain;

aryl groups are carbocyclic or heterocyclic;

aryl groups may be unsubstituted or substituted with one or more substituent at any position;

cycloalkyl groups are carbocyclic or heterocyclic, fused or unfused, non-aromatic ring systems having a total of 3-16 ring members including substituent rings;

each alkyl or cycloalkyl, independently, may be unsubstituted or substituted with one or more substituent at any position;

alkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, cycloalkyl, or aryl;

cycloalkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, or aryl;

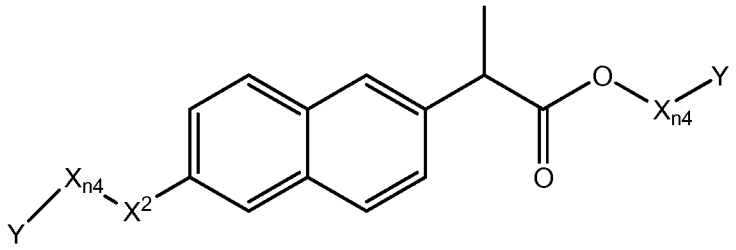
aryl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, aryl, nitro, carboxyl, or –O-C(O)-alkyl;

heterocyclic alkyl and aryl groups have at least one heteroatom selected from oxygen, nitrogen, and sulfur;

R^3 represents alkyl, cycloalkyl, aryl, or halo; and

halo substituents are fluoro, chloro, or bromo.

In another embodiment, the invention relates to a compound of Formula III:

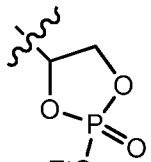


(III)

wherein:

X^2 is O, -C(O)-O-, or –O-C(O)-;

X is independently an alkyl, a cycloalkyl, an aryl, or $–(CH_2)_{n1}-S_{n2}-(CH_2)_{n1}-$;

Y is independently $–OP(O)(OEt)_2$,  , $-OSO_2R^2$, $-OSO_2OR^2$, $-OB(OR^2)_2$, halo, an H_2S releasing moiety, or an NO releasing moiety;

R^2 is $–(CH_2)_{n1}-$;

n1 is independently an integer from 1 to 20;

n2 is 2, 3, or 4;

n4 is 0 or 1;

alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain;

aryl groups are carbocyclic or heterocyclic;

aryl groups may be unsubstituted or substituted with one or more substituent at any position;

cycloalkyl groups are carbocyclic or heterocyclic, fused or unfused, non-aromatic ring systems having a total of 3-16 ring members including substituent rings;

each alkyl or cycloalkyl, independently, may be unsubstituted or substituted with one or more substituent at any position;

alkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, cycloalkyl, or aryl;

cycloalkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, or aryl;

aryl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, aryl, nitro, carboxyl, or –O-C(O)-alkyl;

heterocyclic alkyl and aryl groups have at least one heteroatom selected from oxygen, nitrogen, and sulfur;

R^3 represents alkyl, cycloalkyl, aryl, or halo; and

halo substituents are fluoro, chloro, or bromo.

In another embodiment, the invention relates to a method of treating an inflammatory disease, comprising administering to a subject in need thereof, an effective amount of a compound of Formula I, II, or III.

In yet another embodiment, the invention relates to a pharmaceutical composition comprising a compound of Formula I, II, or III, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

The invention relates to novel NSAID derivatives of Formulas I, II, and III and the novel NSAID derivatives shown in Table I. These NSAID derivatives can be used to treat inflammatory conditions, such as, gastrointestinal diseases, cancer, and cardiovascular diseases.

One embodiment of the invention is Formula I, shown below:

R-X-Y (I).

In Formula I, R represents a non-steroidal anti-inflammatory drug (NSAID) or R^1-C(O)-X^1-. NSAIDs are a well known class of drugs. Some examples of NSAIDs include Aspirin, Naproxen, Sulindac, Ibuprofen, Indomethacin, Valproic acid, Fenamic acid, Flurbiprofen, Diclofenac, Diflunisal, Salsalate, Choline Magnesium Trisalicylate, Dexibuprofen, Fenoprofen, Detoprofen, Dexketoprofen, Oxaprozin, Loxoprofen, Tolmetin, Etodolac, Ketorolac, Aceclofenac, Nabumetone, Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid, Selective COX-2 inhibitors, and Licofelone. Preferred NSAIDs include Aspirin, Naproxen, Sulindac, Ibuprofen, Indomethacin, Valproic acid, Fenamic acid, Flurbiprofen, and Diclofenac.

R^1 represents an alkyl, cycloalkyl, or aryl.

Alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain. Some examples of suitable straight-chained, saturated alkyl groups include methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl groups, dodecyl, hexadecyl, and icosyl. Preferred straight chain, saturated alkyl groups include methyl and ethyl.

Some examples of suitable branched, saturated alkyl groups include iso-propyl, iso-butyl, sec-butyl, t-butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl (isopentyl), 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl (neopentyl), 1-methylpentyl,

2-methylpentyl, 3-methylpentyl, 4-methylpentyl groups, and 2-methyl,5-ethyldecyl. Preferred branched, saturated alkyl groups include isopropyl and t-butyl.

Some examples of unsaturated alkyl groups include ethenyl, ethynyl, propenyl, propargyl, isopropenyl, crotyl, 1-hexenyl, and 1-octenyl.

Cycloalkyl groups are carbocyclic or heterocyclic, fused or unfused, non-aromatic ring systems having a total of 3-16 ring members including substituent rings. Ring systems are monocyclic, bicyclic, tricyclic, or tetracyclic and can be bridged or non-bridged.

Some examples of carbocyclic alkyl groups include cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, and cycloheptanyl. Examples of fused carbocyclic alkyl groups include indenyl, isoindenyl. Bridged groups include bicyclo [2.2.1] heptane, bicyclco [5.2.0] nonane, and bicyclo [5.2.0] nonane.

Some examples of heterocyclic alkyl groups include pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, morpholino, and oxazolidinyl. Examples of fused heterocyclic alkyl groups include benzomorpholino, benzopyrrolidinyl, indolinyl, and benzopiperidinyl.

Aryl groups can be either carbocyclic or heterocyclic.

Carbocyclic aryl groups are fused or unfused ring systems having a total of 6-16 ring members including substituent rings. A preferred unfused carbocyclic aryl group is phenyl.

Some examples of fused carbocyclic aryl groups include naphthyl, phenanthryl, anthracenyl, triphenylenyl, chrysenyl, and pyrenyl.

Heterocyclic aryl groups are fused or unfused ring systems having a total of 5-16 ring members including substituent rings.

Some examples of unfused heterocyclic aryl groups include thiophenyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyridazinyl, pyrimidinyl,

and pyrazinyl. Some examples of fused heterocyclic aryl groups include purinyl, 1,4-diazanaphthalenyl, indolyl, benzimidazolyl, 4,5-diazaphenanthrenyl, benzoxazolyl, isoindolyl, quinolinyl, isoquinolinyl, and benzofuranyl.

Halo substituents are fluoro, chloro, and bromo.

Each alkyl, cycloalkyl, and aryl, independently, may be unsubstituted or substituted with one or more substituent at any position. Alkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, cycloalkyl, or aryl. Cycloalkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, or aryl. Aryl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, aryl, nitro, carboxyl, or –O-C(O)-alkyl.

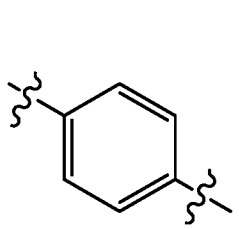
Heterocyclic alkyl and heterocyclic aryl have at least one heteroatom selected from oxygen, nitrogen, and sulfur.

R^3 represents alkyl, cycloalkyl, aryl, or halo.

X^1 represents O, S, or NH. Preferably, X^1 is O.

X is a chain represented by an alkyl, a cycloalkyl, an aryl, or $–(CH_2)_{n1}-S_{n2}-(CH_2)_{n1}-$. X is preferably $–(CH_2)$ $–(CH_2)-S-S-(CH_2)–(CH_2)-$, $–(CH_2)$ $–(CH_2)-S-S-S-(CH_2)–(CH_2)-$, $–(CH_2)$ $–(CH_2)-S-S-S-S-(CH_2)–(CH_2)-$, or $–(CH_2)_4-$.

A chain is defined as a chemical moiety bonded independently at each end to another chemical moiety, *e.g.*, to a group, or to an atom. For example, if X is an alkyl, then the chain could be represented by $–CH_2-CH_2-CH_2-CH_2-CH_2-$ or $–CH_2-CH_2-CH_2-$. If X is an aryl, then X could be represented by, for example,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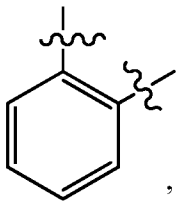
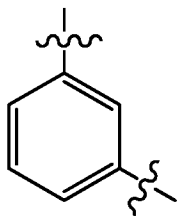

, or

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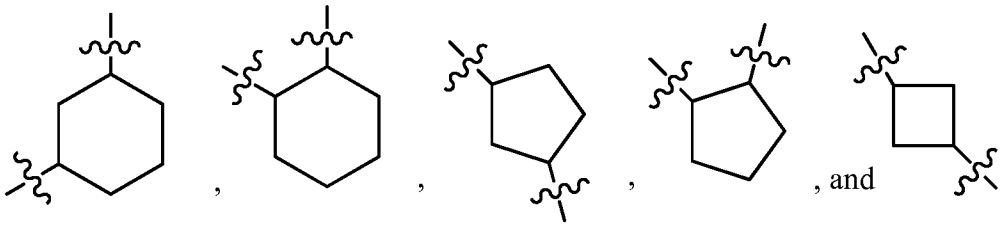
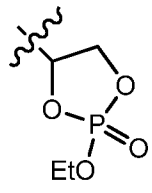
Some examples of cycloalkyl chains are below:

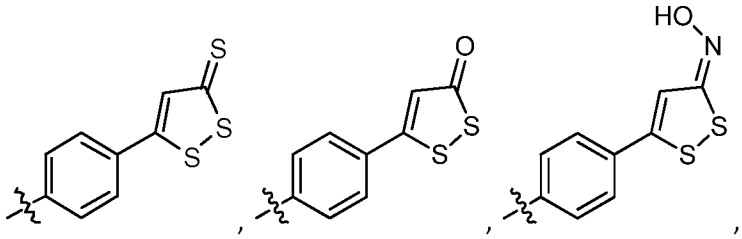


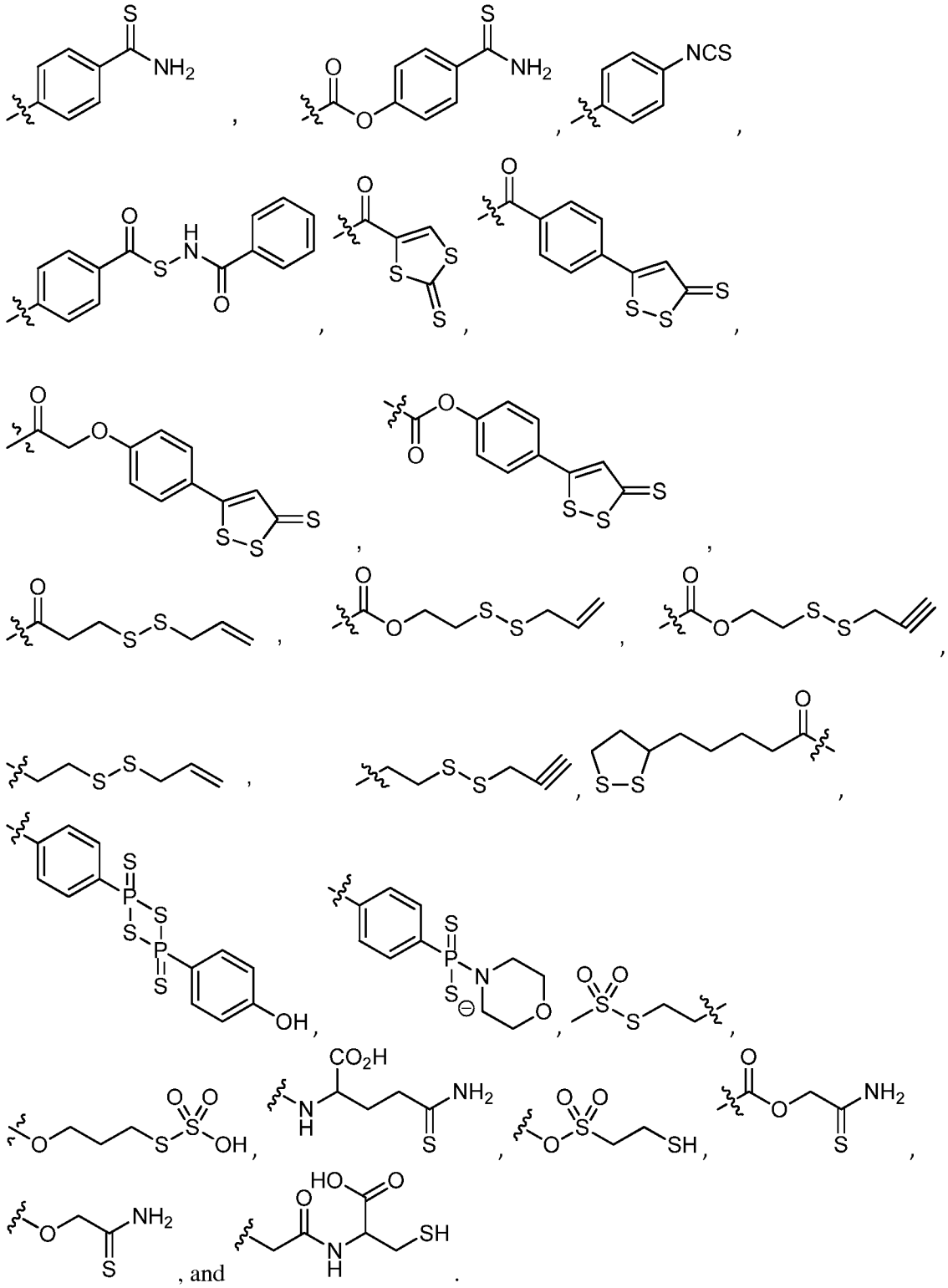
n1 independently represents an integer from 1 to 20, *i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20. Preferably, n1 is 2.

n2 represents 2, 3, or 4. Preferably, n2 is 2.

Y independently represents $-OP(O)(OEt)_2$,  , $-OSO_2R^2$, $-OSO_2OR^2$, $-OB(OR^2)_2$, halo, an H_2S releasing moiety, or an NO releasing moiety. Preferably, Y represents $-OP(O)(OEt)_2$, an H_2S releasing moiety, or an NO releasing moiety.

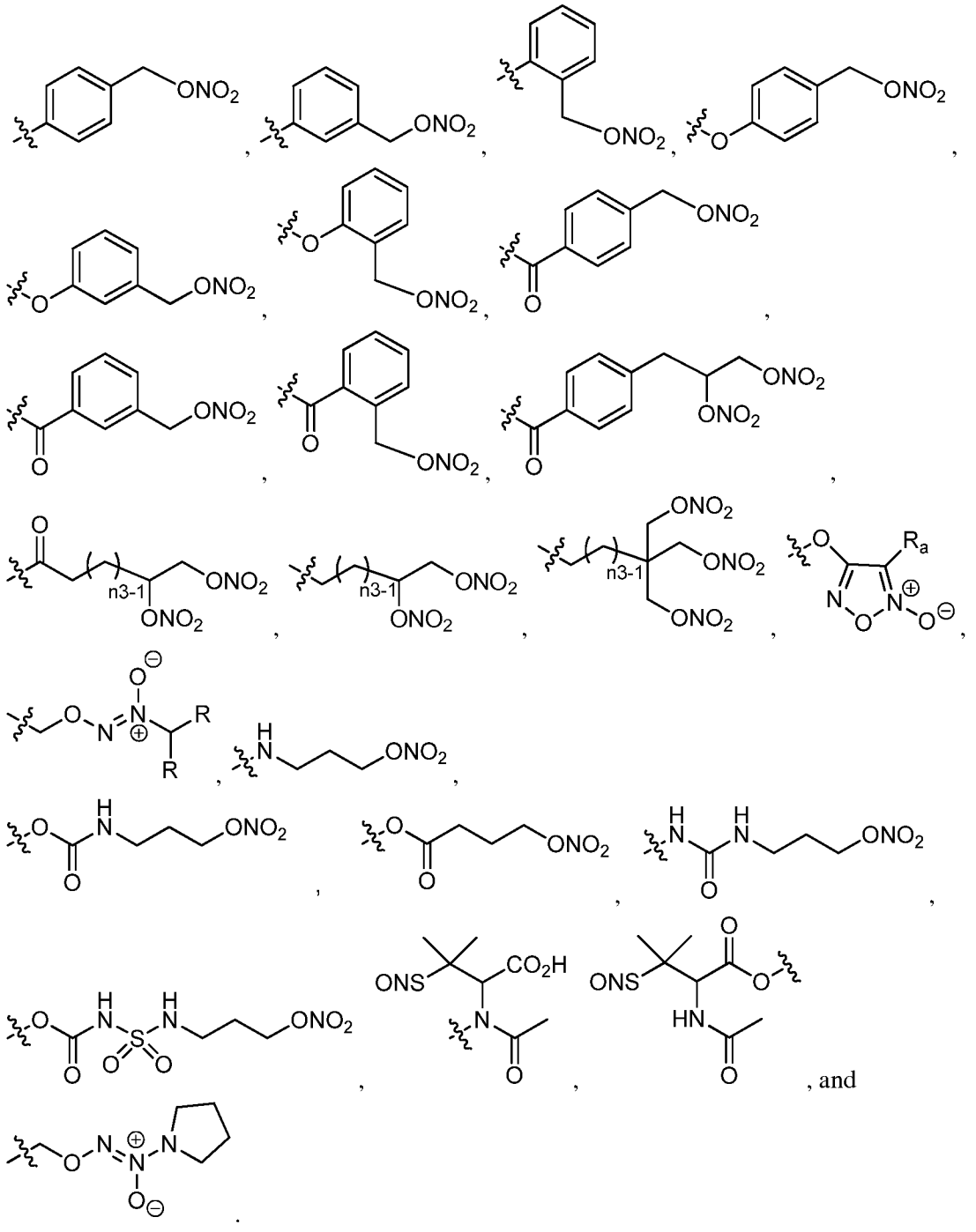
H_2S releasing moieties and NO releasing moieties are well known in the art. As used herein, "a H_2S-releasing moiety" refers to a moiety that can be cleaved from a parent compound to generate H_2S under physiological conditions after the parent compound is administered to a patient. Some examples of H_2S releasing moieties include





As used herein, "a NO-releasing moiety" refers to a moiety that can be cleaved from a parent compound to generate NO under physiological conditions after the parent compound is administered to a patient. Some examples of NO releasing moieties include

-NO, -ONO_2, -C(O)-$(CH_2)_{n3}$-ONO_2, -O-$(CH_2)_{n3}$-ONO_2, -$(CH_2)_{n3}$-ONO_2, -C(O)-CH_2-$C(CH_3)_2$-SNO, -NH-CH_2-$C(CH_3)_2$-SNO, -CH_2-$C(CH_3)_2$-SNO,



, and

.

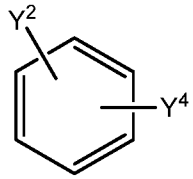
n3 represents 1, 2, 3, 4, 5, 6, or 7.

R_a represents H, C_1-C_{10} alkyl, aryl, $S(O)_2$-aryl, CN, or $CON(R_b)_2$. C_1-C_{10} alkyl groups are alkyl groups with 1-10 carbon atoms in their longest chain.

R_b independently represents H or C_1-C_{10} alkyl.

R^2 is independently $-(CH_2)_{n1}$-.

Another embodiment of the invention is Formula II, shown below:



(II)

Y^2 represents Y^3, $-C(O)-X^1-X_{n4}-Y$, or $-X^1-X_{n4}-Y$.

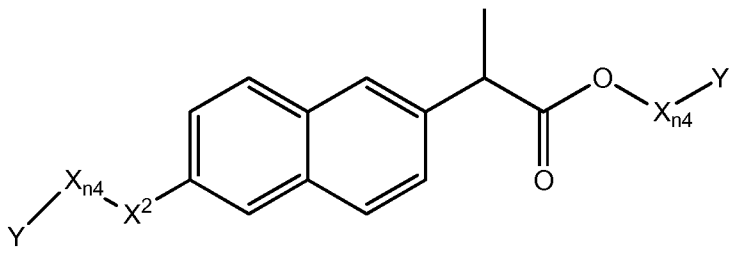
Y^4 represents $-C(O)-X^1-X_{n4}-Y$ or $-X^1-X_{n4}-Y$.

X, X^1, Y, n1, and n2 are as described above.

Y^3 represents an H_2S releasing moiety or an NO releasing moiety. H_2S releasing moieties and NO releasing moieties are described above.

n4 represents 0 or 1.

In another embodiment, the compounds are represented by Formula III, shown below:



(III).

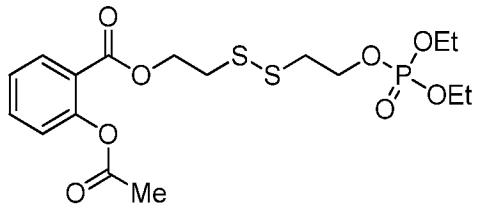
X^2 is O or -C(O)-O-.

X, Y, R^2, n1, n2, and n4 are as described above.

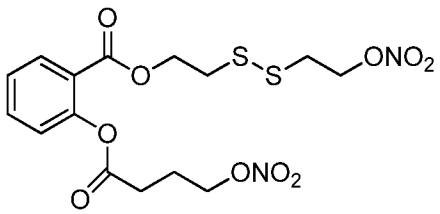
Some of the compounds of the invention may be referred to as hydrogen sulfide-releasing phospho-NSAIDs (POSH-NSAIDs), nitric oxide-releasing phospho-NSAIDs (PONO-NSAIDs), nitric oxide-hydrogen sulfide-releasing phospho-NSAIDs (PO-NOSH-NSAIDs).

Specific examples of compounds of the invention are shown below in Table 1.

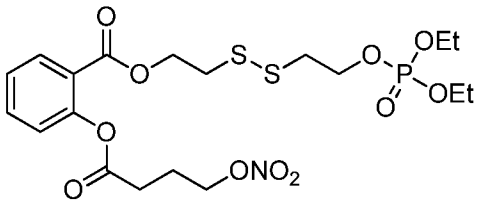
Table 1. Structures of POSH-NSAIDs, PONO- NSAIDs, PO-NOSH-NSAIDs



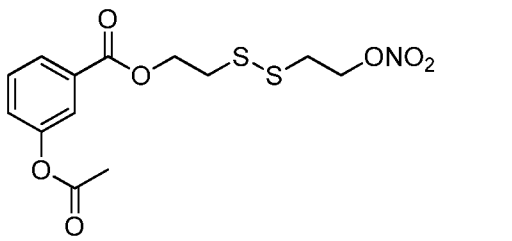
POSH-Aspirin

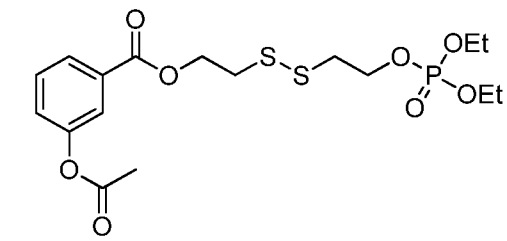


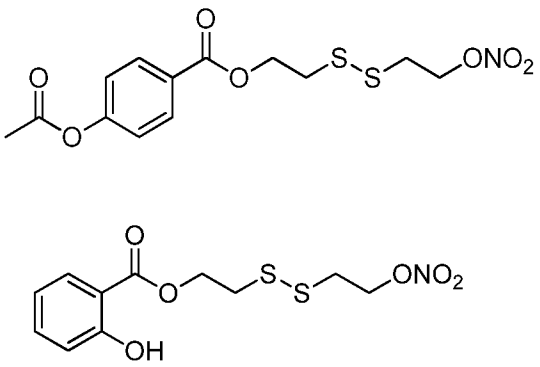
SSNO-Aspirin

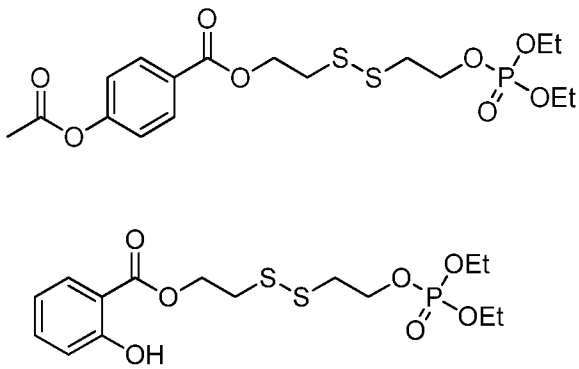


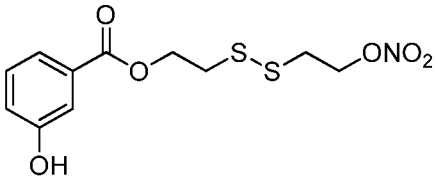
POSH-NO

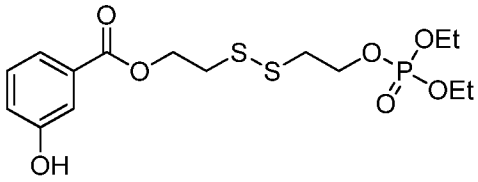


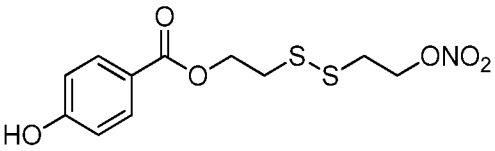


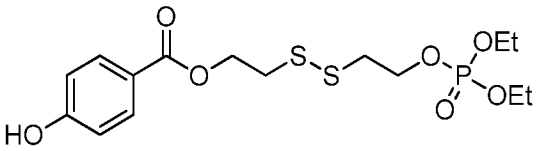


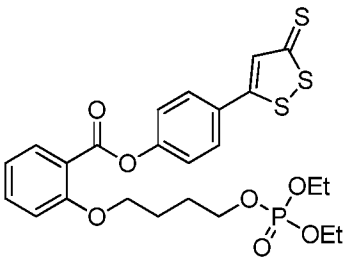


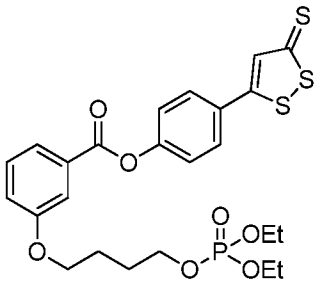


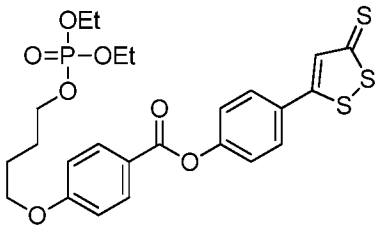


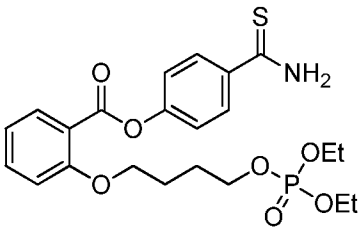


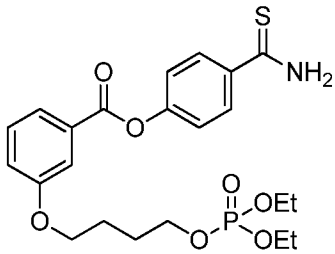


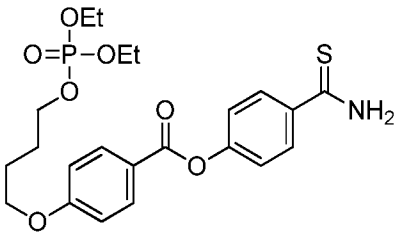


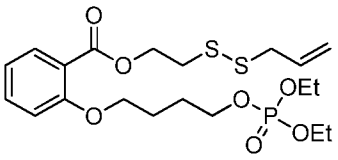


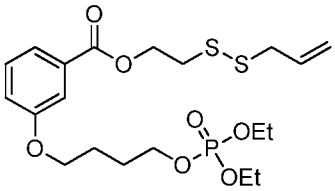


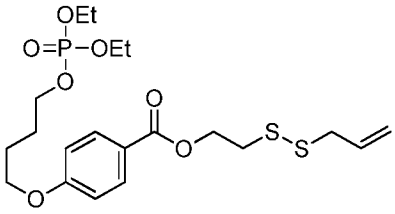


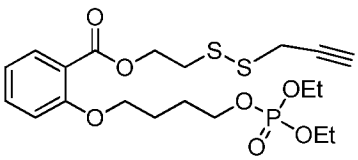


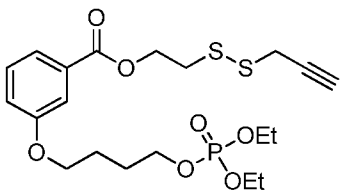


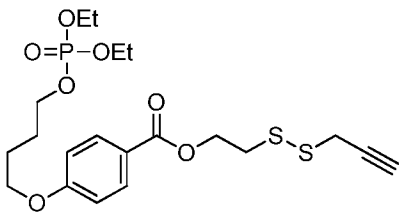












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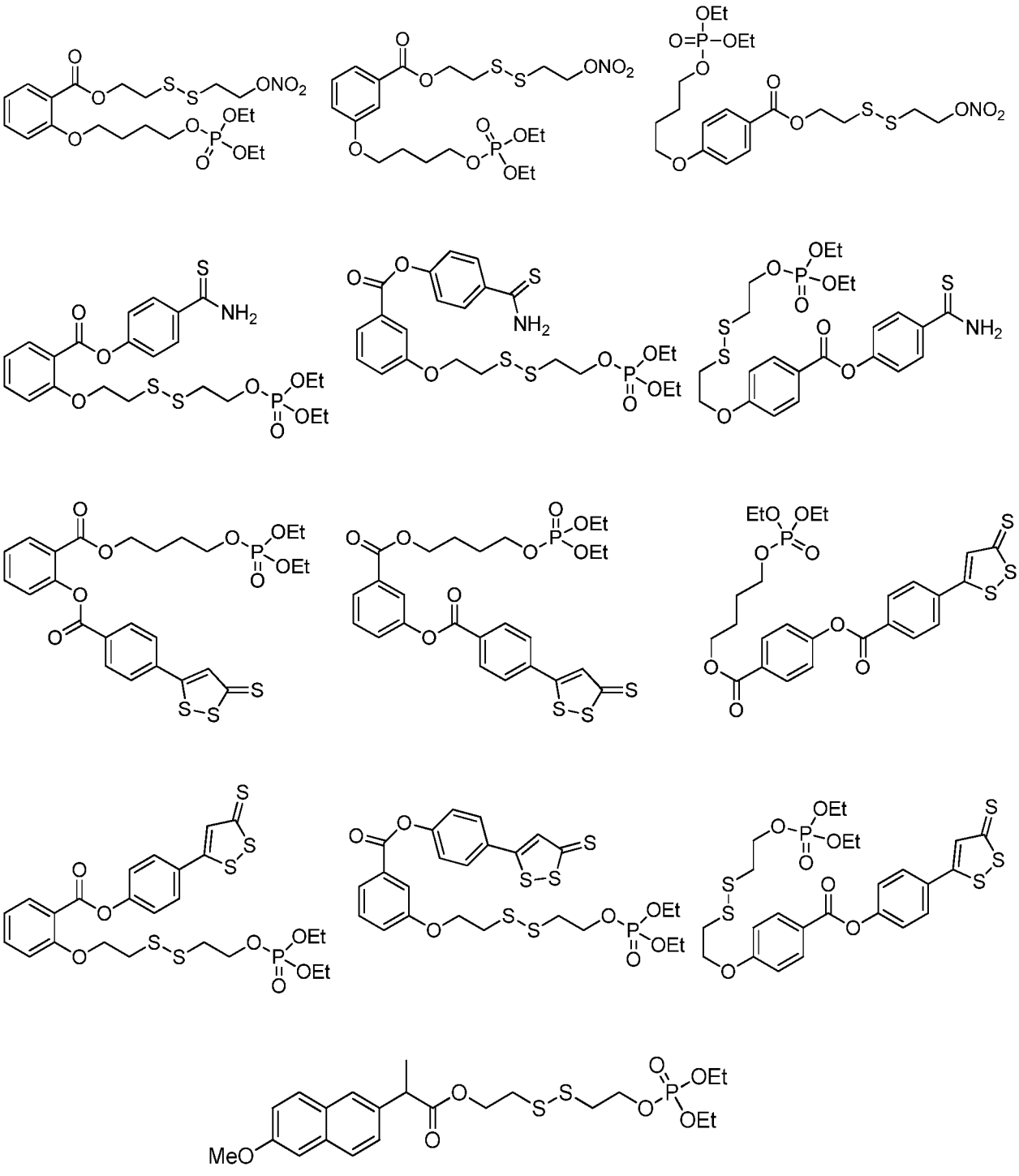

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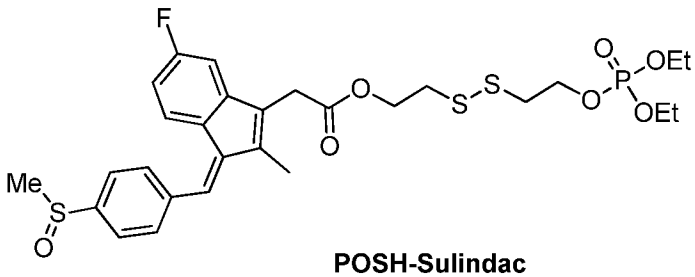

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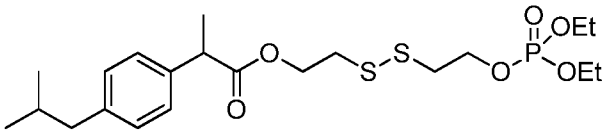
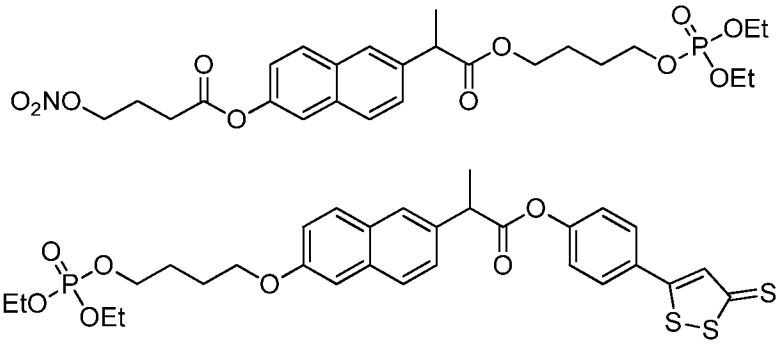
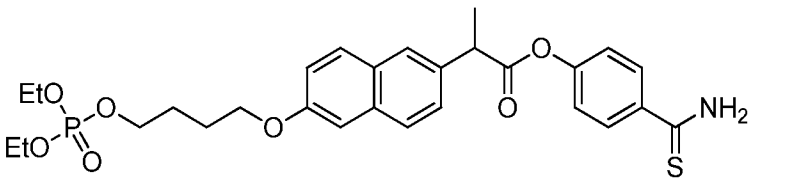
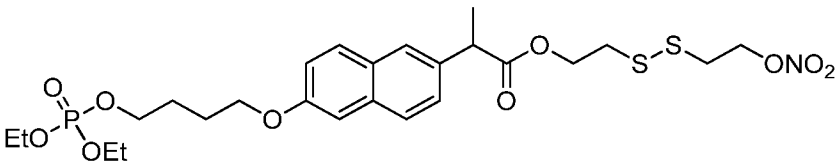
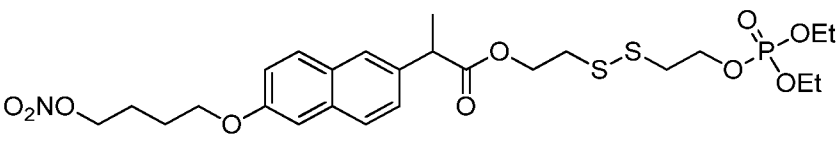


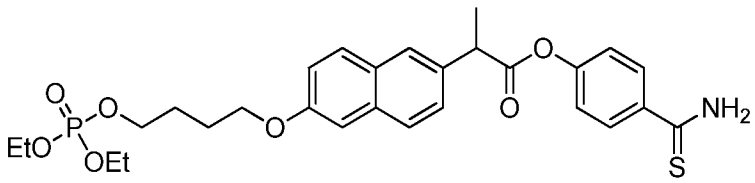
PHOS-Ibuprofen

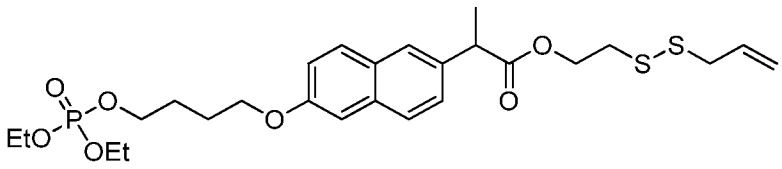


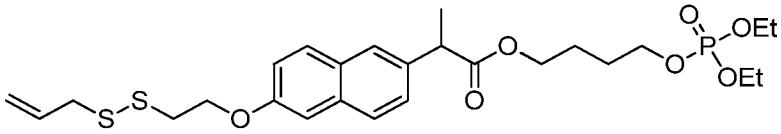


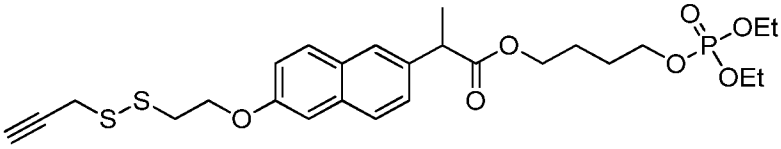


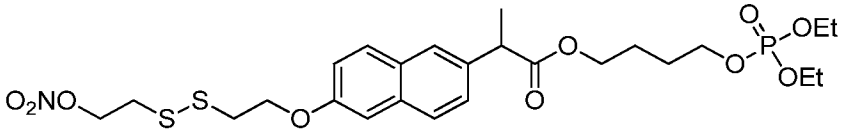


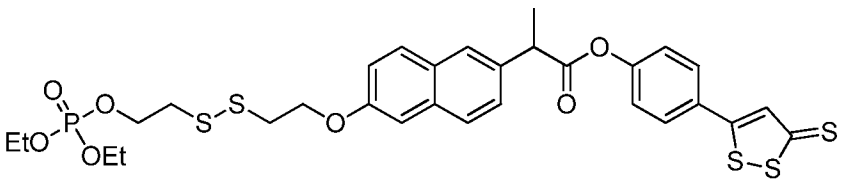


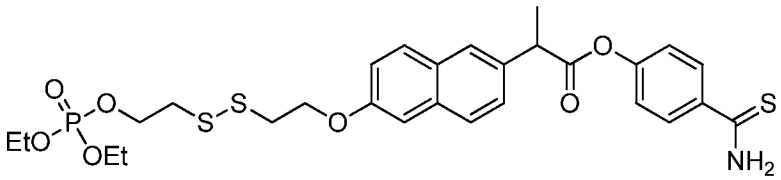


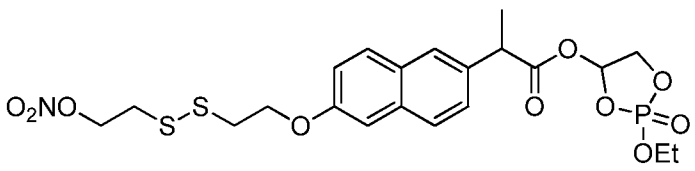


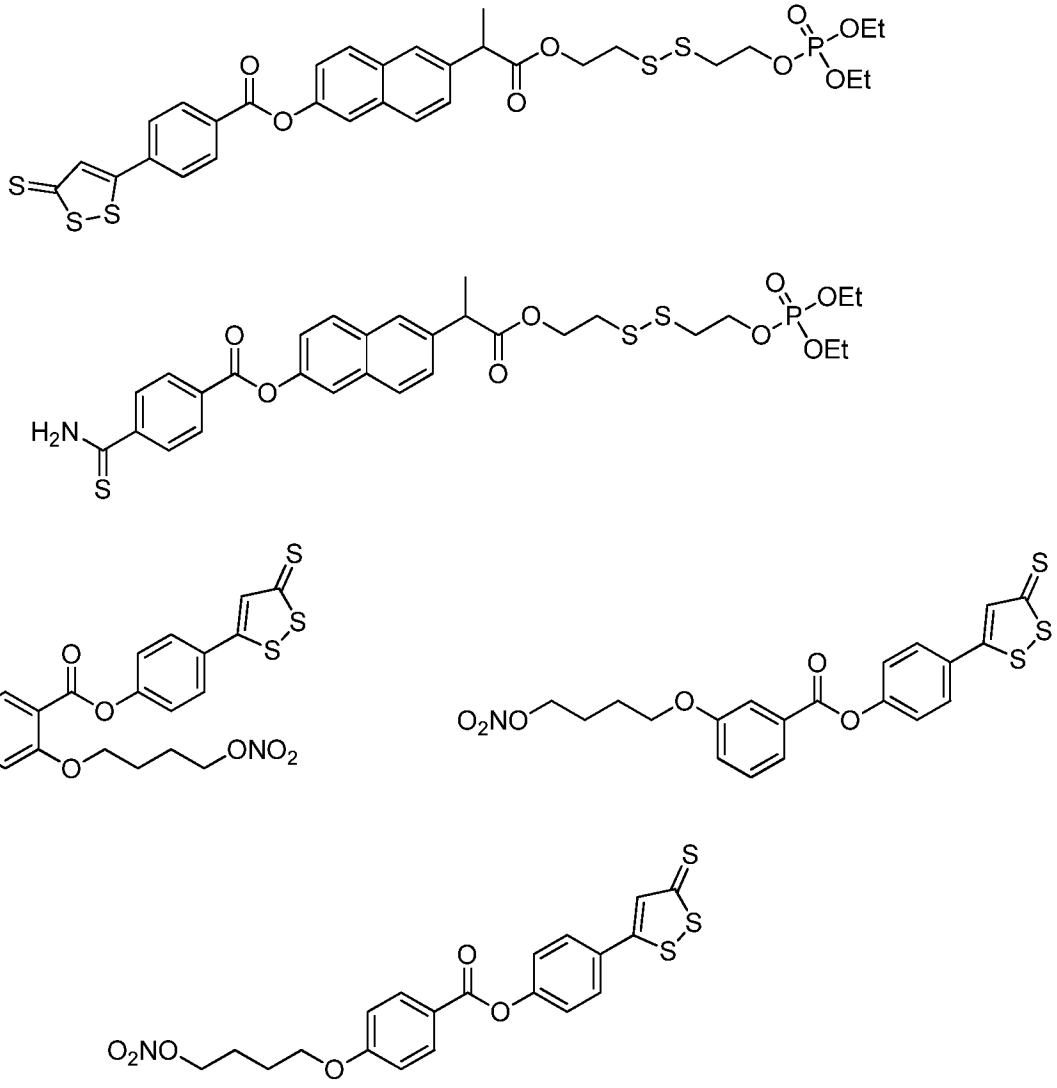








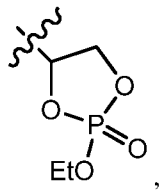
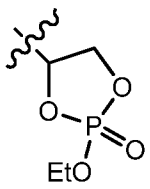


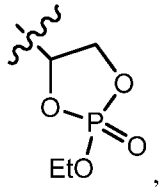


In this specification, groups of various parameters containing multiple members are described. Within a group of parameters, each member may be combined with any one or more of the other members to make additional sub-groups. For example, if the members of a group are a, b, c, d, and e, additional sub-groups specifically contemplated include any two, three, or four of the members, e.g., a and c; a, d, and e; b, c, d, and e; etc.

In some cases, the members of a first group of parameters, e.g., a, b, c, d, and e, may be combined with the members of a second group of parameters, e.g., A, B, C, D, and E. Any member of the first group or of a sub-group thereof may be combined with

any member of the second group or of a sub-group thereof to form additional groups, i.e., b with C; a and c with B, D, and E, etc.

For example, in the present invention, groups of various parameters are defined (e.g. R, X, Y, etc). Each group contains multiple members. For example, Y independently represents $-OP(O)(OEt)_2$,  , $-OSO_2R^2$, $-OSO_2OR^2$, $-OB(OR^2)_2$, halo, an H_2S releasing moiety, or an NO releasing moiety. Each member may be combined with each other member to form additional sub-groups, e.g., $-OP(O)(OEt)_2$, $-OSO_2R^2$, $-OSO_2OR^2$, and an NO releasing moiety; $-OP(O)(OEt)_2$, an H_2S releasing moiety, and an NO releasing moiety; and  , $-OSO_2R^2$, $-OSO_2OR^2$, and $-OB(OR^2)_2$.

The instant invention further contemplates embodiments in which each element listed under one group may be combined with each and every element listed under any other group. For example, R is identified above as representing an NSAID or R^1-C(O)-X^1-. X is identified above as being an alkyl, a cycloalkyl, an aryl, or $-(CH_2)_{n1}$-S_{n2}-$(CH_2)_{n1}$-. Each element of R (an NSAID or R^1-C(O)-X^1-) can be combined with each and every element of X (an alkyl, a cycloalkyl, an aryl, or $-(CH_2)_{n1}$-S_{n2}-$(CH_2)_{n1}$-). For example, in one embodiment, R may be an NSAID such as aspirin and X may be methyl. Alternatively, R may be R^1-C(O)-X^1-, and X may be phenyl, etc. Similarly, a third parameter is Y, in which the elements are defined as $-OP(O)(OEt)_2$,  , $-OSO_2R^2$, $-OSO_2OR^2$, $-OB(OR^2)_2$, halo, an H_2S releasing moiety, or an NO releasing moiety. Each of the above embodiments may be combined with each and every element of R and X. For example, in the embodiment wherein R is an NSAID such as ibuprofen

and X is $-(CH_2)_2$-S-S-$(CH_2)_2$-, Y may be $-OP(O)(OEt)_2$ (or any other chemical moiety within the element of Y).

The compounds of this invention are limited to those that are chemically feasible and stable. Therefore, a combination of substituents or variables in the compounds described above is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Pharmaceutically acceptable salts

The present invention also relates to pharmaceutically acceptable salts of the NSAID derivatives. Pharmaceutically acceptable salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-,

hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

The pharmaceutically acceptable salts of the NSAID derivatives of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

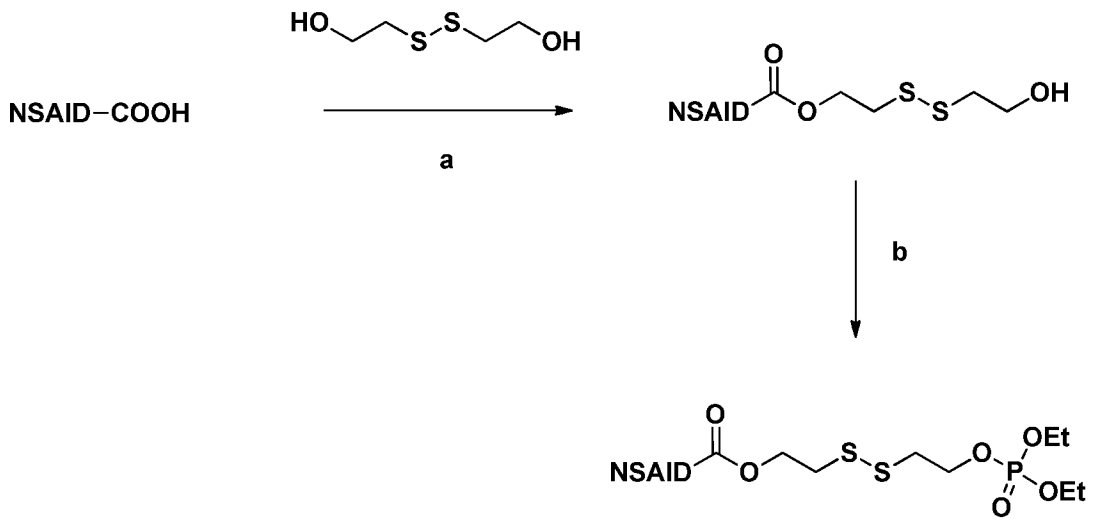
Prodrugs

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the compounds described herein, which are readily convertible in vivo into the required compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Synthesis of the derivatives

The compounds of the invention may be synthesized by methods well known in the art. For example, the POSH-NSAID compounds may be synthesized by treating an NSAID containing a carboxylic acid (**a**) with 2-hydroxyethyl disulfide in the presence of DCC /DMAP in DCM undergo mono esterification. The product is reacted with (b) diethyl chlorophosphate in the presence of triethyl amine and DMAP to yield the desired POSH-NSAID. See Scheme 1, below.

Scheme 1. **Preparation of POSH-NSAID Compounds**



a. DCC/DMAP in DCM at 0°C-rt, 12 h.; **b.** Diethylchlorophosphate, Et_3N, DMAP, EtOAc, rt, 6h

Uses of the derivatives

The invention also relates to a method of treating an inflammatory disease in a subject in need thereof. The method comprises administering to the subject the compound of Formula I, II, or III or a pharmaceutically acceptable salt thereof. The inflammatory disease may be cancer, rheumatoid arthritis, intestine inflammation, stomach ulcer, a cardiovascular disease, or a neurodegenerative disease.

The method and compounds of the invention may be employed alone, or in combination with other anti-inflammatory agents. The combination of these anti-inflammatory agents and the compounds of the invention will provide new agents for the treatment of cancer, rheumatoid arthritis, intestine inflammation, stomach ulcer, a cardiovascular disease, and neurodegenerative disease.

The invention also relates to a pharmaceutical composition including an effective amount of a compound according to Formulas I, II, or III or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

An effective amount of a compound of Formula I, II, or III or a pharmaceutically acceptable salt thereof as used herein is any amount effective to treat a patient afflicted with an inflammatory disease. Modes of administration and doses can be determined by those having skill in the art. An effective amount of the compound will vary with the group of patients (age, sex, weight, etc.), the nature and severity of the condition to be treated, the particular compound administered, and its route of administration. Amounts suitable for administration to humans are routinely determined by physicians and clinicians during clinical trials.

The minimum dose of the compound is the lowest dose at which efficacy is observed. For example, the minimum dose of the compound may be about 0.1mg/kg/day, about 1 mg/kg/day, or about 3 mg/kg/day.

The maximum dose of the compound is the highest dose at which efficacy is observed in a patient, and side effects are tolerable. For example, the maximum dose of the compound may be about 10 mg/kg/day, about 9 mg/kg/day, or about 8 mg/kg/day. In another embodiment, the maximum dose of the compound may be up to about 50 mg/kg/day.

A derivative useful in the methods of the present invention may be administered by any method known in the art. Some examples of suitable modes of administration include oral and systemic administration. Systemic administration can be enteral or parenteral. Liquid or solid (e.g., tablets, gelatin capsules) formulations can be employed.

Parenteral administration of the NSAID derivatives include, for example intravenous, intramuscular, and subcutaneous injections. For instance, a chemical compound may be administered to a patient by sustained release, as is known in the art. Sustained release administration is a method of drug delivery to achieve a certain level of the drug over a particular period of time.

Other routes of administration include oral, topical, intrabronchial, and intranasal administration. For oral administration, liquid or solid formulations may be used. Some examples of formulations suitable for oral administration include tablets, gelatin capsules,

pills, troches, elixirs, suspensions, syrups, and wafers. Intrabronchial administration can include an inhaler spray. For intranasal administration, administration of a chemical compound can be accomplished by a nebulizer or liquid mist.

The chemical compound can be formulated in a suitable pharmaceutical carrier. In this specification, a pharmaceutical carrier is considered to be synonymous with a vehicle or an excipient as is understood by practitioners in the art. Examples of carriers include starch, milk, sugar, certain types of clay, gelatin, stearic acid or salts thereof, magnesium or calcium stearate, talc, vegetable fats or oils, gums and glycols.

The chemical compound can be formulated into a composition containing one or more of the following: a stabilizer, a surfactant, preferably a nonionic surfactant, and optionally a salt and/or a buffering agent.

The stabilizer may, for example, be an amino acid, such as for instance, glycine; or an oligosaccharide, such as for example, sucrose, tetralose, lactose or a dextran. Alternatively, the stabilizer may be a sugar alcohol, such as for instance, mannitol; or a combination thereof. Preferably the stabilizer or combination of stabilizers constitutes from about 0.1% to about 10% weight for weight of the chemical compound.

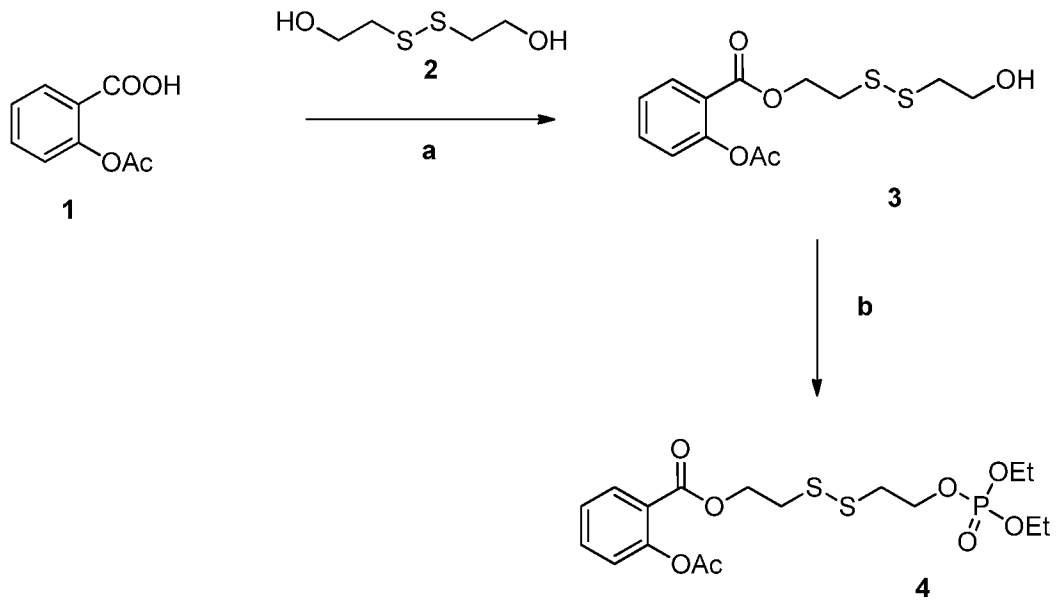
The surfactant is preferably a nonionic surfactant, such as a polysorbate. Some examples of suitable surfactants include Tween 20, Tween 80; a polyethylene glycol or a polyoxyethylene polyoxypropylene glycol, such as Pluronic F-68 at from about 0.001% (w/v) to about 10% (w/v). Other preferred surfactants include Solutol H-15 and Cremophore EL.

The salt or buffering agent may be any salt or buffering agent, such as for example sodium chloride, or sodium/potassium phosphate, respectively. Preferably, the buffering agent maintains the pH of the chemical compound formulation in the range of about 5.5 to about 7.5. The salt and/or buffering agent is also useful to maintain the osmolality at a level suitable for administration to a patient. Preferably the salt or buffering agent is present at a roughly isotonic concentration of about 150 mM to about 300 mM.

The chemical compound can be formulated into a composition which may additionally contain one or more conventional additives. Some examples of such additives include a solubilizer such as, for example, glycerol; an antioxidant such as for example, benzalkonium chloride (a mixture of quaternary ammonium compounds, known as "quart"), benzyl alcohol, chloretone or chlorobutanol; anaesthetic agent such as, for example a morphine derivative; or an isotonic agent etc. As a further precaution against oxidation or other spoilage, the composition may be stored under nitrogen gas in vials sealed with impermeable stoppers.

EXAMPLES

Example 1. Synthesis of POSH-Aspirin



a. DCC/DMAP in DCM at 0°C-rt, 12 h.; b. Diethylchlorophosphate, Et_3N, DMAP, EtOAc, rt, 6h

Aspirin treated (**1**) with 2-hydroxyethyl disulfide (**2**) in the presence of DCC /DMAP in DCM undergoes mono esterification to yield compound **3**. Compound **3** is further treated with diethyl chlorophosphate in the presence of triethyl amine and DMAP to yield the desired POSH-ASA (**4**).

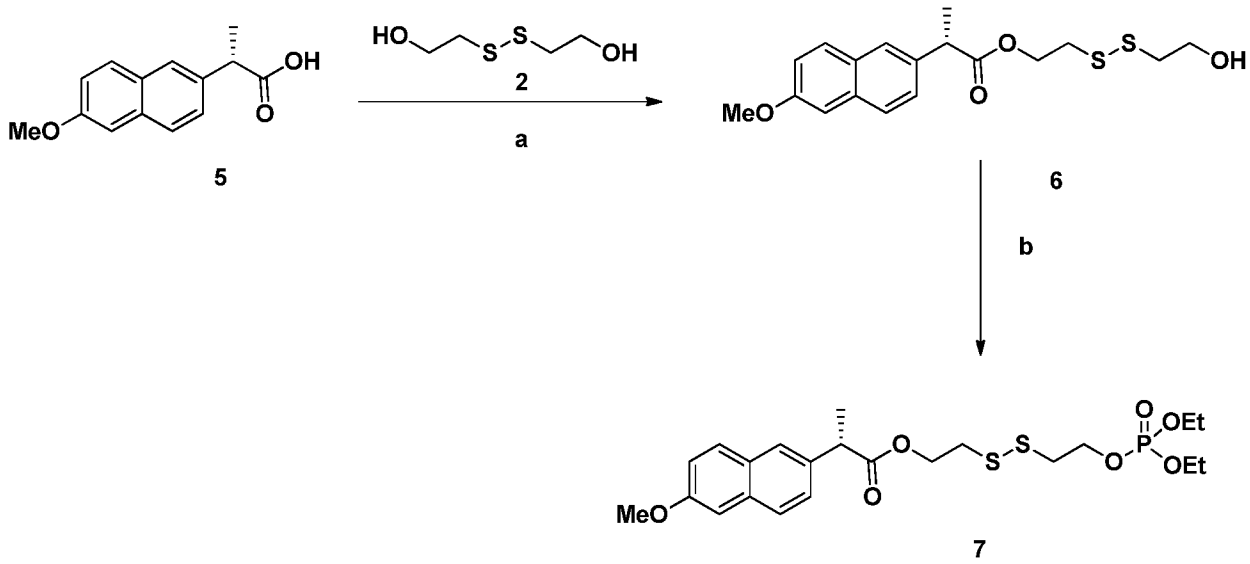
Spectral data for compound **3**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.91 (t, 2H, J = 6.5 Hz), 3.04 (t, 2H, J = 6.5Hz), 3.90 (t, 2H, J = 7.2 Hz), 4.57 (t, 2H, J = 7.2 Hz), 7.13 (d, 2H, J = 8.2 Hz), 7.34 (d, 2H, J = 7.2 Hz), 7.60 (2H, dt, J = 7.2, 1.4 Hz), 8.04 (2H, J = 8.2, 1.4 Hz). EIMS: 317 (M^++1), 339 (M^++Na).

Spectral data for compound **4**

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.36 (m, 6H), 2.36 (s, 3H), 2.98 (t, 2H, J = 6.8 Hz), 3.04 (t, 2H, J = 6.8 Hz), 4.10 (m, 4H), 4.24 (t, 2H, J = 7.2 Hz), 4.56 (t, 2H, J = 7.2 Hz), 7.10 (d, 2H, J = 8.2 Hz), 7.33 (t, 2H, J = 7.2 Hz), 7.58 (2H, t, J = 7.2), 8.02 (2H, J = 8.2). EIMS: 453 (M^++1), 475 (M^++Na).

Example 2. Synthesis of POSH-Naproxen



Naproxen treated (**5**) with 2-hydroxyethyl disulfide (**2**) in the presence of DCC /DMAP in DCM undergoes mono esterification to yield compound **6**. Compound **6** is further treated with diethyl chlorophosphate in the presence of triethyl amine and DMAP to yield POSH-Naproxen (**7**).

Spectral data for compound 6

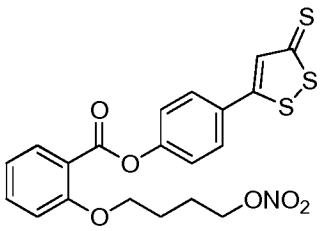
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.33 (t, 6H, J = 7.0 Hz), 1.59 (d, 3H, J = 7.32 Hz), 2.87 (m, 4H), 3.76 (t, 2H, J = 6.6 Hz), 3.90 (s, 3H), 4.12 (m, 1H), 4.2-4.4 (m, 2H), 7.11 (m, 2H), 7.39 (m, 1H), 7.69 (m, 3H). EIMS: 367 (M^++1), 389 (M^++Na).

Spectral data for compound 7

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.57 (d, 3H, J = 7.3 Hz), 2.77 (t, 2H, J = 5.4 Hz), 2.87 (t, 2H, J = 5.4 Hz), 3.87 (m, 1H), 3.91 (s, 3H), 4.11 (m, 4H), 4.20 (m, 2H), 4.34 (m, 2H), 7.13 (m, 2H), 7.40 (dd, 1H, J = 8.31, 1.47 Hz), 7.66 (bs, 1H), 7.40 (d, 2H, J = 8.31, 1.47 Hz), 7.70 (d, 2H, J = 8.8 Hz). EIMS: 503 (M^++1), 525 (M^++Na).

Example 3.

Synthesis of Compound 8 (4-(3-thioxo-3H-1, 2-dithiol-5-yl) phenyl 2-(4-(nitrooxy) butoxy) benzoate):



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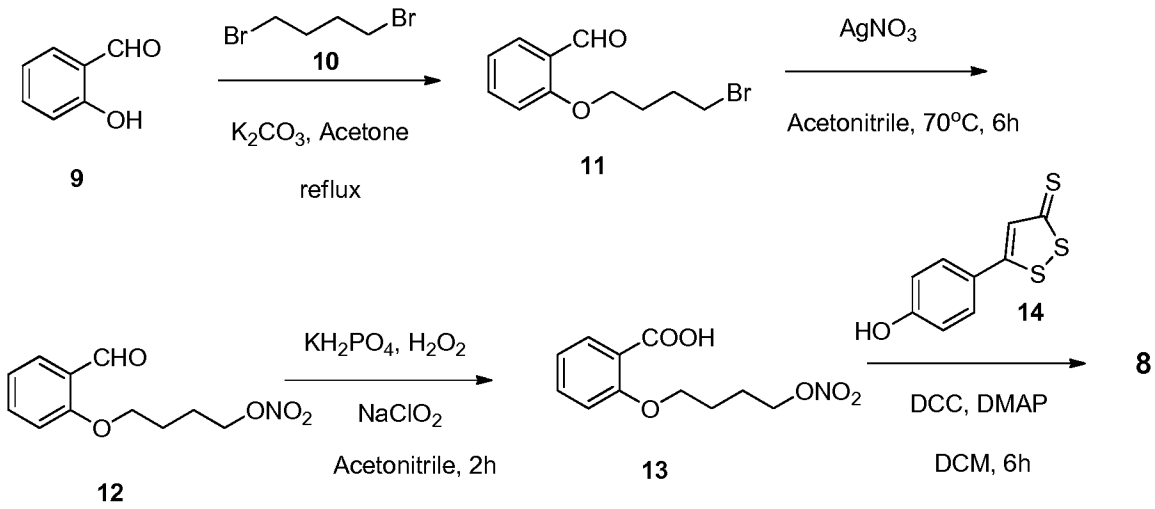


Synthetic scheme for compound 8

Synthesis of compound 11 (*2-(4-bromobutoxy) benzaldehyde*)**:**

To the solution of salicyladehyde (**9,** 1.5 g, 12.29 mmol) in acetone was added K_2CO_3 (2.48 g, 18.04 mmol) and 1, 4-dibromobutane (**10**, 2.65 g, 12.29 mmol). The

whole reaction mixture was refluxed for 12h, after completion of the reaction as checked by TLC, filtered off and concentrated under the reduced pressure to get the crude product. The obtained crude product was purified by silica gel column chromatography by eluting with 20 % hexane/ethyl acetate to afford the pure compound **11** (yield, 2.05 g, 65 %).

Synthesis of compound 12 (*4-(2-formylphenoxy) butyl nitrate*)**:**

To the solution of bromo compound **11** (1.0 g, 3.9 mmol) in CH_3CN (80 mL) was added $AgNO_3$ (1.32 g, 7.8 mmol) and stirred at 70°C for 6 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The obtained crude residue was treated with CH_2Cl_2 (50 mL) and H_2O (50 mL). After separation, the aqueous layer was extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to get the nitro compound **12** with 68 % yield (0.6 g).

^{1}H-NMR (CDCl3, 500 MHz): δ 2.0 (m, 4H), 4.16 (t, *J* = 6.0 Hz, 2H), 4.53 (t, *J* = 6.4 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 7.1 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.45 (s,1H), 7.59 (dt, *J* = 8.8, 1.47 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 8.06 (dd, *J* = 7.3, 1.46 Hz, 1H).

ESIMS: *m/z* 464 (M^++1).

Synthesis of compound 13 (*2-(4-(nitrooxy) butoxy) benzoic acid*)**:**

To the solution of compound **12** (0.5 g, 2.09 mmol) in acetonitrile (30 mL) at 0°C was added a solution of KH_2PO_4 (0.4 g, 2.94 mmol) in water (5 mL) and 30% H_2O_2 (0.25 mL, 2.19 mmol), then added drop wise a solution of 80% $NaClO_2$ (0.3 g, 2.65 mmol) in water (6.0 mL). The whole reaction mixture was stirred at same temperature for 2h. The reaction was completed as monitored by TLC Na_2SO_3 was added to destroy the excess of H_2O_2. After acidification with 6M HCl, the mixture was diluted with H_2O (100 mL) and extracted twice with DCM (50 mL). The organic layer was dried filtered and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography to yield corresponding acid product **13** with 75% yield (0.4 g).

Synthesis of Compound 8 (*4-(3-thioxo-3H-1, 2-dithiol-5-yl) phenyl 2-(4-(nitrooxy) butoxy) benzoate*)**:**

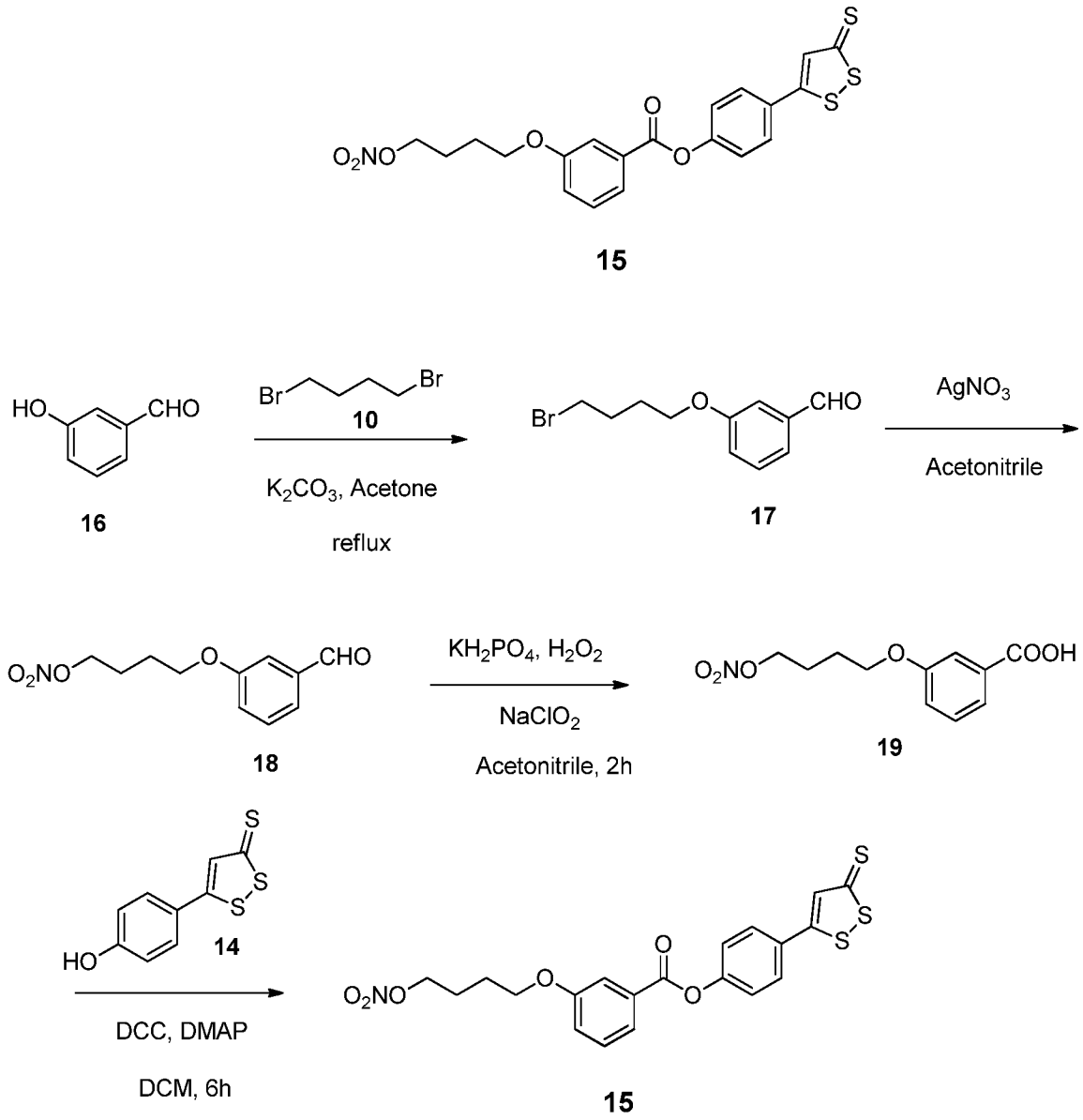
To the solution of 2-(4-(nitrooxy) butoxy) benzoic acid (200.0 mg, 0.78 mmol) in dichloromethane was added DCC (170.0.0 mg, 0.78 mmol), DMAP (9.6 mg, 0.08 mmol) at 0°C under argon atmosphere. Then added ADT-OH ((5-(4-hydroxyphenyl)-3H-1, 2-dithiole-3-Thione, **14**) (178.0 mg, 0.78 mmol) and the whole reaction mixture was stirred at room temperature for overnight. After completion of the reaction as checked by TLC, filtered off and water was added then extracted into dichloromethane (2 x 75 ml). Organic solvent was removed under reduced pressure to get the crude product. Further it was purified by column chromatography to afford pure orange solid (**8,** 4-(3-thioxo-3H-1, 2-dithiol-5-yl) phenyl 2-(4-(nitrooxy) butoxy) benzoate**,** 261.0 mg, 72 % yield).

^{1}H-NMR (CDCl3, 500 MHz): δ 2.0 (m, 4H), 4.16 (t, *J* = 6.0 Hz, 2H), 4.53 (t, *J* = 6.4 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 7.1 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.45 (s,1H), 7.59 (dt, *J* = 8.8, 1.47 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 8.06 (dd, *J* = 7.3, 1.46 Hz, 1H).

ESIMS: *m/z* 464 (M^++1).

Example 4.

Synthesis of compound 15:



Synthetic scheme for compound 15

Synthesis of compound 17 (*3-(4-bromobutoxy) benzaldehyde*)**:**

To the solution of *meta* salicyladehyde (**16,** 2.0 g, 16.38 mmol) in acetone was added K_2CO_3 (2.48 g, 18.04 mmol) and 1, 4-dibromobutane (**10**, 2.65 g, 16.38 mmol).

The whole reaction mixture was refluxed for 18h, after completion of the reaction as checked by TLC, filtered off and concentrated under the reduced pressure to get the crude product. The obtained crude product was purified by silica gel column chromatography by eluting with 20 % hexane/ethyl acetate to afford the pure compound **17** (yield, 1.98 g, 63 %).

Synthesis of compound 18 (4-(3-formylphenoxy) butyl nitrate)**:**

To the solution of bromo compound **17** (1.5 g, 5.85 mmol) in CH_3CN (80 mL) was added $AgNO_3$ (1.98 g, 7.8 mmol) and stirred at 70°C for 10 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The obtained crude residue was treated with CH_2Cl_2 (60 mL) and H_2O (60 mL). After separation, the aqueous layer was extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to get the nitro compound **18** with 68 % yield (0.9 g).

Synthesis of compound 19 (*3-(4-(nitrooxy) butoxy) benzoic acid*)**:**

To the solution of compound **18** (0.75 g, 3.13 mmol) in acetonitrile (50 mL) at 0°C was added a solution of KH_2PO_4 (0.6 g, 4.41 mmol) in water (5 mL) and 30% H_2O_2 (0.375 mL, 3.28 mmol), then added drop wise a solution of 80% $NaClO_2$ (0.45 g, 3.97 mmol) in water (8.0 mL). The whole reaction mixture was stirred at same temperature for 2h. The reaction was completed as monitored by TLC Na_2SO_3 was added to destroy the excess of H_2O_2. After acidification with 6M HCl, the mixture was diluted with H_2O (100 mL) and extracted twice with DCM (50 mL). The organic layer was dried filtered and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography to yield corresponding acid product **19** with 72% yield (0.575 g).

Synthesis of Compound 15 (*4-(3-thioxo-3H-1, 2-dithiol-5-yl) phenyl 3-(4-(nitrooxy) butoxy) benzoate*)**:**

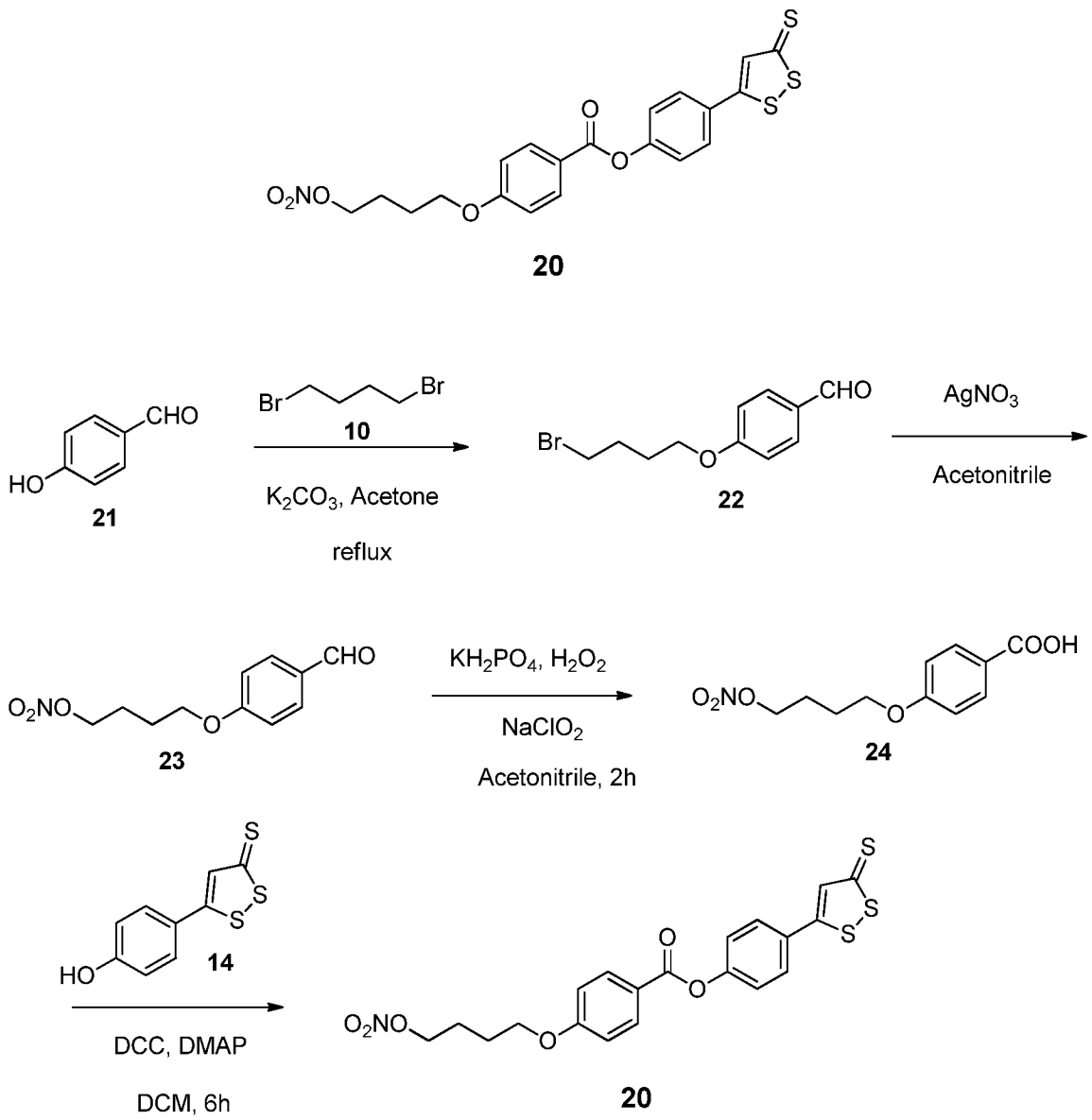
To the solution of *3-(4-(nitrooxy) butoxy) benzoic acid* (**19**, 250.0 mg, 0.97 mmol) in dichloromethane was added DCC (211.4 mg, 0.97 mmol), DMAP (10.2 mg, 0.09 mmol) at 0°C under argon atmosphere. Then added ADT-OH ((5-(4-hydroxyphenyl)-3H-1, 2-dithiole-3-Thione, **14**) (178.0 mg, 0.78 mmol) and the whole reaction mixture was stirred at room temperature for overnight. After completion of the reaction as checked by TLC, filtered off and water was added then extracted into dichloromethane (2 x 75 ml). Organic solvent was removed under reduced pressure to get the crude product. Further it was purified by column chromatography to afford pure orange solid (**15,** *4-(3-thioxo-3H-1, 2-dithiol-5-yl) phenyl 3-(4-(nitrooxy) butoxy) benzoate*, 339.8 mg, 75 % yield).

^{1}H-NMR (CDCl3, 500 MHz): δ 1.97 (m, 4H), 4.09 (t, *J* = 5.37 Hz, 2H), 4.56 (t, *J* = 5.37 Hz, 2H), 7.20 (dd, *J* = 7.8, 1.47 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.44 (t, *J* = 7.82 Hz, 1H), 7.43 (s,1H), 7.60 (bs, 1H), 7.75 (d, *J* = 8.8, 2H), 7.82 (d, *J* = 7.8 Hz, 1H).

ESIMS: *m/z* 464 (M^++1).

Example 5.

Synthesis of compound 20:



Synthetic scheme for compound 20

Synthesis of compound 22 (*4-(4-bromobutoxy) benzaldehyde*)**:**

To the solution of *para* salicyladehyde (**21,** 1.25 g, 10.24 mmol) in acetone was added K_2CO_3 (2.06 g, 15.03 mmol) and 1, 4-dibromobutane (**10**, 2.20 g, 10.24 mmol). The whole reaction mixture was refluxed for 16h, after completion of the reaction as

checked by TLC, filtered off and concentrated under the reduced pressure to get the crude product. The obtained crude product was purified by silica gel column chromatography by eluting with 25 % hexane/ethyl acetate to afford the pure compound **22** (yield, 1.78 g, 68 %).

Synthesis of compound 23 (*4-(4-formylphenoxy) butyl nitrate*)**:**

To the solution of bromo compound **22** (1.5 g, 5.85 mmol) in CH_3CN (80 mL) was added $AgNO_3$ (1.98 g, 7.8 mmol) and stirred at 70°C for 10 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The obtained crude residue was treated with CH_2Cl_2 (60 mL) and H_2O (60 mL). After separation, the aqueous layer was extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to get the nitro compound **23** with 65 % yield (0.86 g).

Synthesis of compound 24 (*4-(4-(nitrooxy) butoxy) benzoic acid*)**:**

To the solution of compound **23** (0.75 g, 3.13 mmol) in acetonitrile (50 mL) at 0°C was added a solution of KH_2PO_4 (0.6 g, 4.42 mmol) in water (8 mL) and 30% H_2O_2 (0.38 mL, 3.28 mmol), then added drop wise a solution of 80% $NaClO_2$ (0.45 g, 3.97 mmol) in water (8.0 mL). The whole reaction mixture was stirred at same temperature for 2h. The reaction was completed as monitored by TLC Na_2SO_3 was added to destroy the excess of H_2O_2. After acidification with 6M HCl, the mixture was diluted with H_2O (100 mL) and extracted twice with DCM (50 mL). The organic layer was dried filtered and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography to yield corresponding acid product **24** with 68% yield (0.54 g).

Synthesis of Compound 20 (*4-(3-thioxo-3H-1, 2-dithiol-5-yl) phenyl 2-(4-(nitrooxy) butoxy) benzoate*)**:**

To the solution of *4-(4-(nitrooxy) butoxy) benzoic acid* (225.0 mg, 0.87 mmol) in dichloromethane was added DCC (190.0 mg, 0.87 mmol), DMAP (11.0 mg, 0.09 mmol)

at 0°C under argon atmosphere. Then added ADT-OH ((5-(4-hydroxyphenyl)-3H-1, 2-dithiole-3-Thione **14** (198.5 mg, 0.87 mmol) and the whole reaction mixture was stirred at room temperature for overnight. After completion of the reaction as checked by TLC, filtered off and water was added then extracted into dichloromethane (2 x 60 ml). Organic solvent was removed under reduced pressure to get the crude product. Further it was purified by column chromatography to afford pure orange solid (**20,** 4-(3-thioxo-3H-1, 2-dithiol-5-yl) phenyl 2-(4-(nitrooxy) butoxy) benzoate**,** 262.0 mg, 68 % yield).

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.97 (m, 4H), 4.10 (t, J = 5.38 Hz, 2H), 4.57 (t, J = 6.4 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.44 (s,1H), 7.74 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H).

ESIMS: *m/z* 464 (M^++1).

Example 6. In Vitro Assays

Materials and Methods:

***Cell culture*:** HT-29, SW-480 and HCT-15 human colon adenocarcinoma, MIA PaCa-2 and BxPC-3 human pancreatic cancer, LNCAP human prostate cancer, A549 human lung cancer, MCF-7 (estrogen receptor positive), MDA-MB 231 and SK-BR-3 (estrogen receptor negative) human breast cancer, and Jurkats human leukemia cell lines were obtained from American Type Tissue Collection (Manassas, VA). All cells lines were grown as monolayers except for the Jurkats which were grown in suspension. The pancreatic and breast cancer cells were grown in Dulbecco's modified Eagle's medium, the prostate, Jurkat, SW-480 and HCT-15 colon cells were grown in RPMI 1640 medium, the lung cells were grown in F-12 and the colon HT-29 cells were grown in McCoy 5A. All media were supplemented with 10% fetal calf serum (Invitrogen, Carlsbad, CA) penicillin (50 U/ml), and streptomycin (50 μg/ml) (Invitrogen, Carlsbad, CA). Cells were seeded on culture dishes at a density of 25×10^3 cells/cm^2 and incubated at 37°C in 5% CO_2 and 90% relative humidity. Single cell suspensions were obtained by trypsinization (0.05% trypsin/EDTA), and cells were counted using a hemocytometer. Viability was determined by the trypan blue dye exclusion method.

MTT Assay: Cell growth inhibitory effect of POSH compounds were measured using a colorimetric MTT assay kit (Roche, Indianapolis, IN). Cancer cells were plated in 96-well plates at a density of 50,000 cells/well. The cells were incubated for 24 h with different concentrations of POSH compounds. After the indicated time, 10µl of MTT dye (3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide, 5 mg/ml in phosphate buffered saline), was added to each well, and the plates were incubated for 2 hours at 37ºC. Then, the media was aspirated, and add 100 µl of the solubilization solution (10% SDS in 0.01 M HCl) was added to each well to solubilize the formant crystals. The absorbance of the plates was measured on an ELISA reader at a wavelength of 570 nm. Each sample was performed in triplicate, and the entire experiment was repeated three times.

Results:

As shown in Table 2, both POSH compounds (i.e., POSH-aspirin (POSH-ASA) and POSH-naproxen (POSH-NAP)) exhibited efficacy in inhibiting cell growth of the tested cancer cell lines and enhanced potency compared to aspirin and naproxen, respectively. POSH-ASA exhibited greater potency than POSH-NAP.

Table 2. IC_{50} (μM) values at 24 h for cell growth inhibition in different cancer cell lines

Agent	Colon			Breast			Pancreas		Lung	Prostate	Leukemia
	HT-29	HCT 15	SW480	MDA MB 231	SKBR3	MCF-7	MIAPa Ca2	BxPC3	A549	LNCAP	Jurkat
ASA	*> 5000 in all cell lines*										
POSH-ASA	0.082 ± 0.006	0.075 ± 0.004	0.092 ± 0.005	0.180 ± 0.007	0.098 ± 0.004	0.242 ± 0.018	0.082 ± 0.008	0.075 ± 0.005	0.083 ± 0.008	0.075 ± 0.005	0.22 ± 0.007
Enhanced Potency	*>60,000*	*>65,000*	*>50,000*	*>25,000*	*>50,000*	*>20,000*	*>60,000*	*>65,000*	*>60,000*	*>65,000*	*>20,000*
NAP	2800 ± 165	2950 ± 215	3110 ± 185	2900 ± 225	2890 ± 147	2100 ± 200	3200 ± 195	2600 ± 85	2650 ± 110	2990 ± 175	2385 ± 177
POSH-NAP	0.15 ± 0.01	0.12 ± 0.008	0.18 ± 0.007	0.15 ± 0.01	0.13 ± 0.007	0.19 ± 0.008	0.088 ± 0.009	0.10 ± 0.02	0.16 ± 0.01	0.13 ± 0.02	0.17 ± 0.01
Enhanced Potency	*~18,000*	*~24,000*	*~17,000*	*~19,000*	*~22,000*	*~11,000*	*~36,000*	*~26,000*	*~16,000*	*~23,000*	*~14,000*

Colon, breast, pancreas, lung, prostate, and leukemia cancer cell lines were treated with various concentrations of POSH-aspirin (POSH-ASA), or POSH-naproxen (POSH-NAP) and their traditional counterparts. Cell numbers were determined at 24h from which IC_{50} values were calculated. The ratios of NSAID/POSH-NSAID represent fold-enhancement in potency of the POSH-NSAID over the parent compound. Results are mean ± SEM of three independent determinations. In all cell lines and for all POSH-NSAIDs $P < 0.001$ compared to the respective parent NSAID.

CLAIMS

1. A compound of Formula I:

R-X-Y (I)

wherein:

R is a non-steroidal anti-inflammatory drug (NSAID) or R^1-C(O)-X^1-;

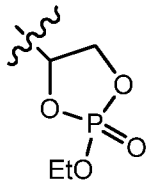
R^1 is an alkyl, cycloalkyl, or aryl;

X^1 is O, S, or NH;

X is an alkyl, a cycloalkyl, an aryl, or $-(CH_2)_{n1}-S_{n2}-(CH_2)_{n1}-$;

n1 is independently an integer from 1 to 20;

n2 is 2, 3, or 4;

Y is independently $-OP(O)(OEt)_2$,  , $-OSO_2R^2$, $-OSO_2OR^2$, $-OB(OR^2)_2$, halo, an H_2S releasing moiety, or an NO releasing moiety;

R^2 is independently $-(CH_2)_{n1}-$;

alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain;

aryl groups are carbocyclic or heterocyclic;

aryl groups may be unsubstituted or substituted with one or more substituent at any position;

cycloalkyl groups are carbocyclic or heterocyclic, fused or unfused, non-aromatic ring systems having a total of 3-16 ring members including substituent rings;

each alkyl or cycloalkyl, independently, may be unsubstituted or substituted with one or more substituent at any position;

alkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, cycloalkyl, or aryl;

cycloalkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, or aryl;

aryl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, aryl, nitro, carboxyl, or –O-C(O)-alkyl;

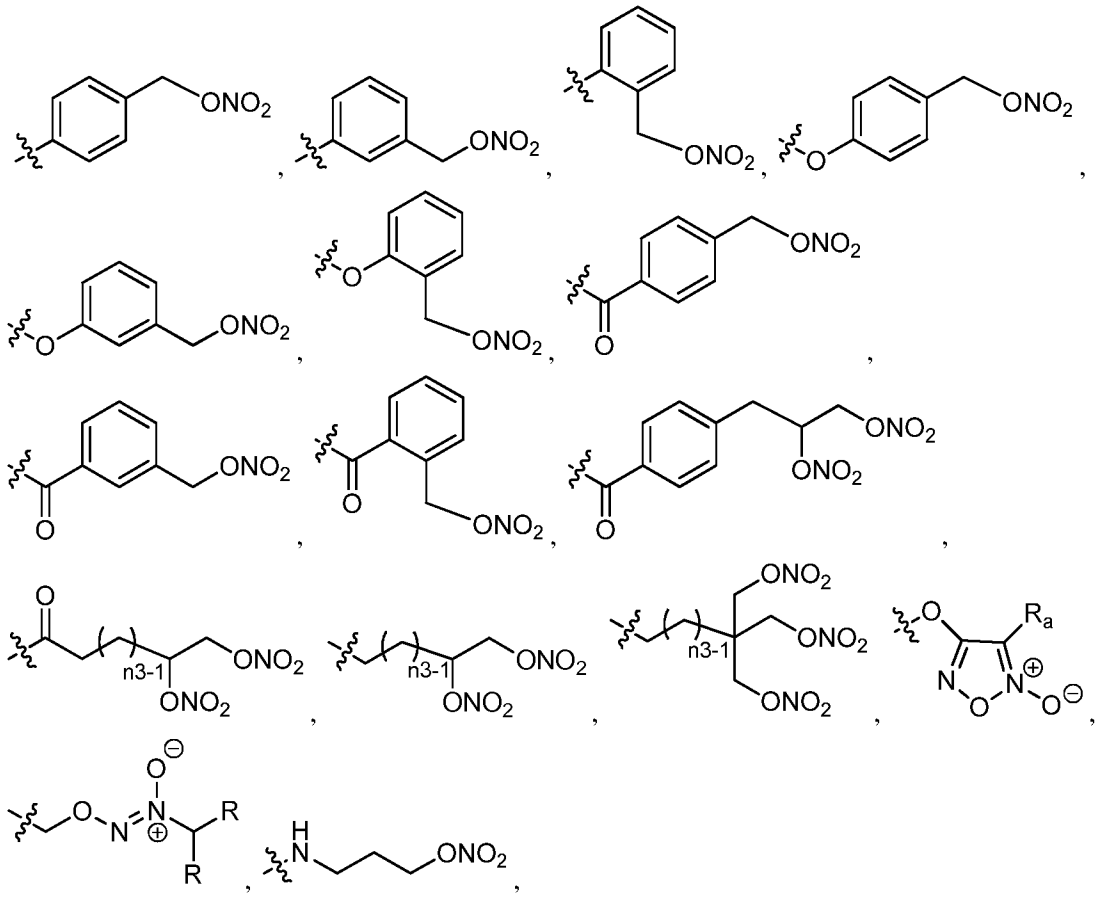
heterocyclic alkyl and aryl groups have at least one heteroatom selected from oxygen, nitrogen, and sulfur;

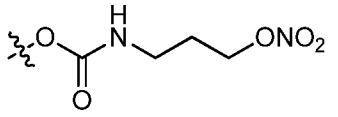
R^3 represents alkyl, cycloalkyl, aryl, or halo; and

halo substituents are fluoro, chloro, or bromo.

2. A compound according to claim 1, wherein R is an NSAID selected from the group consisting of Aspirin, Naproxen, Sulindac, Ibuprofen, Indomethacin, Valproic acid, Fenamic acid, Flurbiprofen, and Diclofenac.

3. A compound according to claim 1, wherein the NO releasing moiety is selected from the group consisting of -NO, $-ONO_2$, $-C(O)-(CH_2)_{n3}-ONO_2$, $-O-(CH_2)_{n3}-ONO_2$, $-(CH_2)_{n3}-ONO_2$, $-C(O)-CH_2-C(CH_3)_2-SNO$, $-NH-CH_2-C(CH_3)_2-SNO$, $-CH_2-C(CH_3)_2-SNO$,

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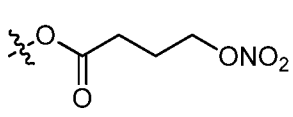
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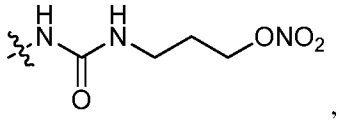
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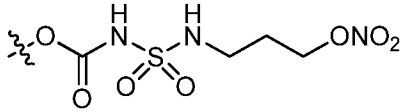
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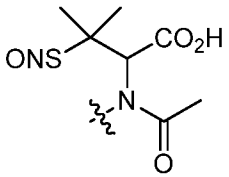
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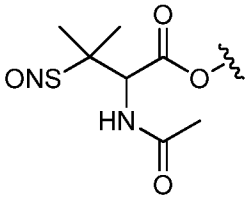
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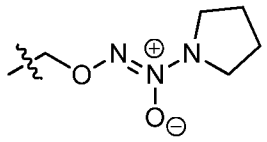
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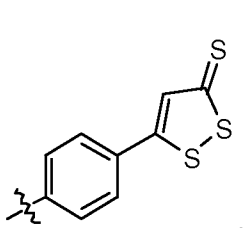
wherein

n3 is 1, 2, 3, 4, 5, 6, or 7;

R_a is H, C_1-C_{10} alkyl, aryl, $S(O)_2$-aryl, CN, or $CON(R_b)_2$; and

R_b is independently H or C_1-C_{10} alkyl.

4. A compound according to claim 1, wherein the H_2S releasing moiety is selected from the group consisting of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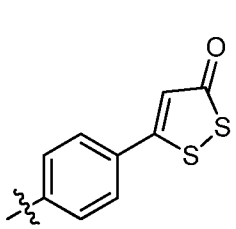
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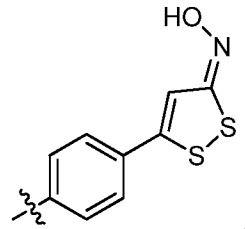
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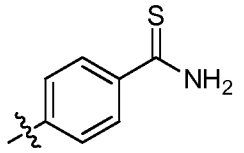
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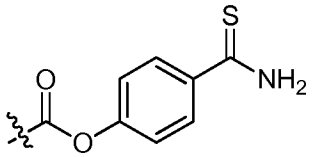
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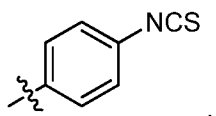
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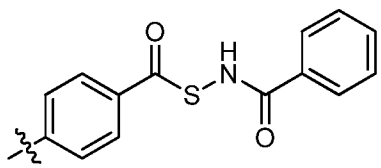
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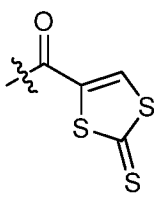
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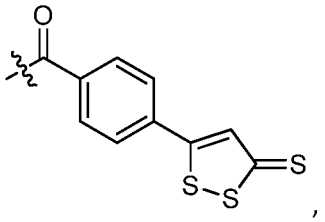
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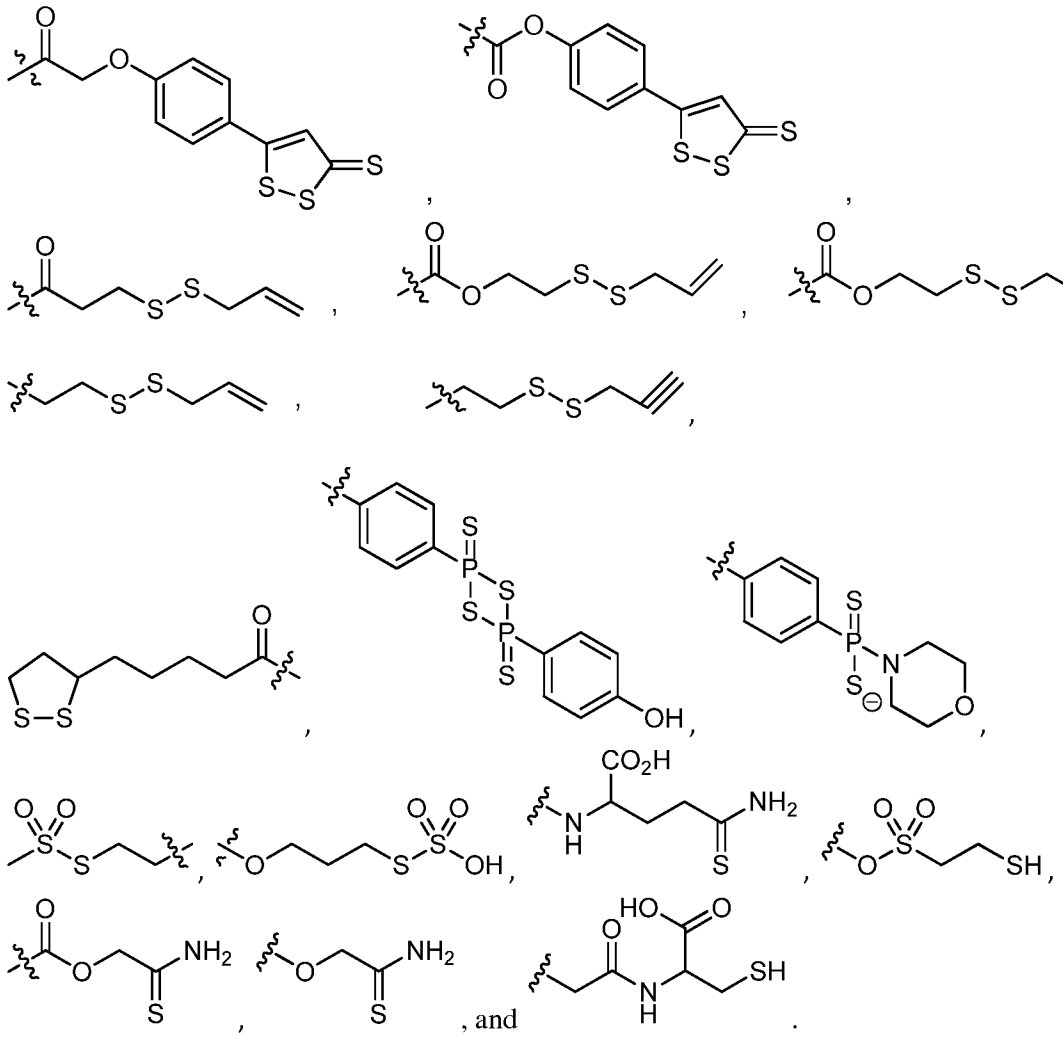
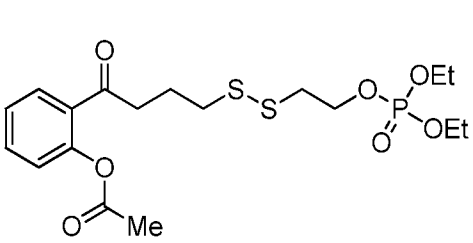


5. A compound according to claim 1, wherein X is $-(CH_2)_2$-S-S-$(CH_2)_2$-, $-(CH_2)_2$-S-S-S-$(CH_2)_2$- , $-(CH_2)_2$-S-S-S-S-$(CH_2)_2$-, or $-(CH_2)_4$-.

6. A compound according to claim 1, wherein Y is $-OP(O)(OEt)_2$.

7. A compound according to claim 1, having the structure: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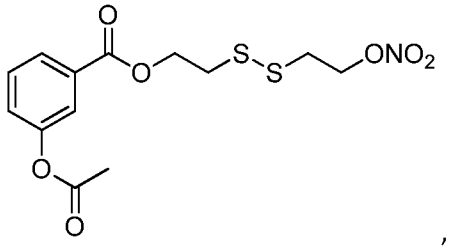
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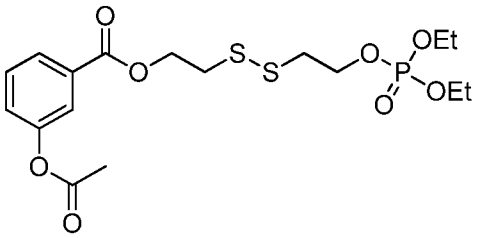
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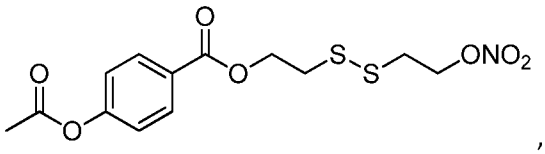
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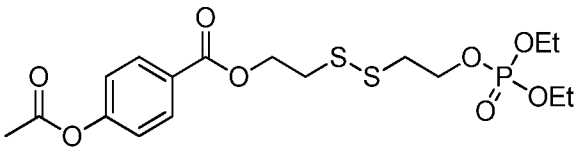
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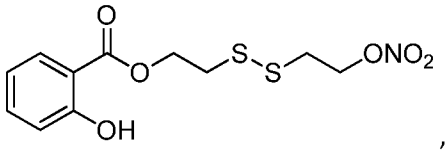
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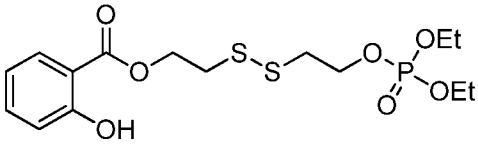
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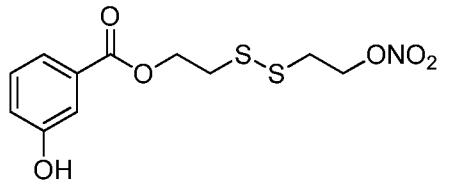
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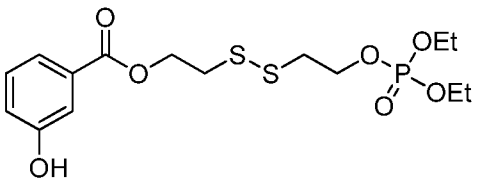
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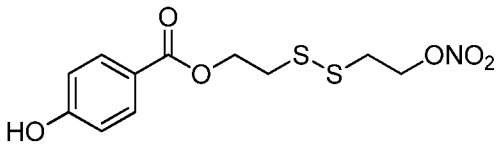
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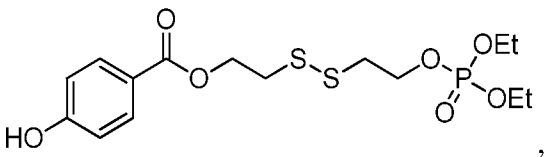
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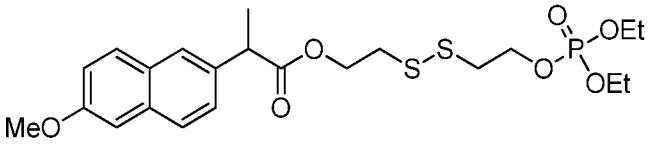
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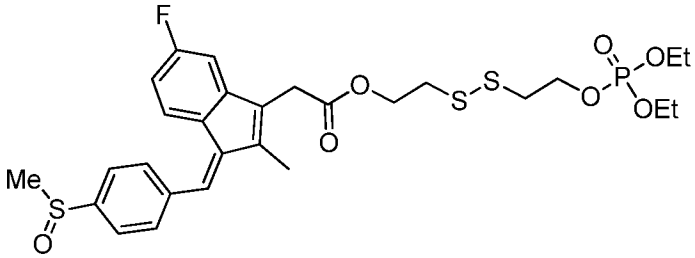

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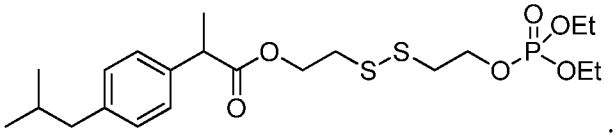

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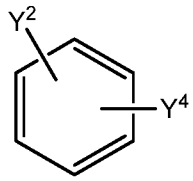
8. A compound of Formula II:



(II)

wherein:

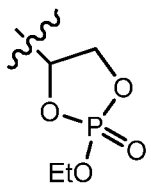
Y^2 is Y^3, –C(O)-X^1-X_{n4}-Y or –X^1-X_{n4}-Y;

Y^4 is –C(O)-X^1-X_{n4}-Y or –X^1-X_{n4}-Y;

R^2 is –$(CH_2)_{n1}$-;

X^1 is O, S, or NH;

X is an alkyl, a cycloalkyl, an aryl, or –$(CH_2)_{n1}$-S_{n2}-$(CH_2)_{n1}$-;

Y is independently –OP(O)$(OEt)_2$,  , -OSO_2R^2, -OSO_2OR^2, -$OB(OR^2)_2$, halo, an H_2S releasing moiety, or an NO releasing moiety;

Y^3 is an H_2S releasing moiety or an NO releasing moiety;

n1 is independently an integer from 1 to 20;

n2 is 2, 3, or 4;

n4 is 0 or 1;

alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain;

aryl groups are carbocyclic or heterocyclic;

aryl groups may be unsubstituted or substituted with one or more substituent at any position;

cycloalkyl groups are carbocyclic or heterocyclic, fused or unfused, non-aromatic ring systems having a total of 3-16 ring members including substituent rings;

each alkyl or cycloalkyl, independently, may be unsubstituted or substituted with one or more substituent at any position;

alkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, cycloalkyl, or aryl;

cycloalkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, or aryl;

aryl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, aryl, nitro, carboxyl, or –O-C(O)-alkyl;

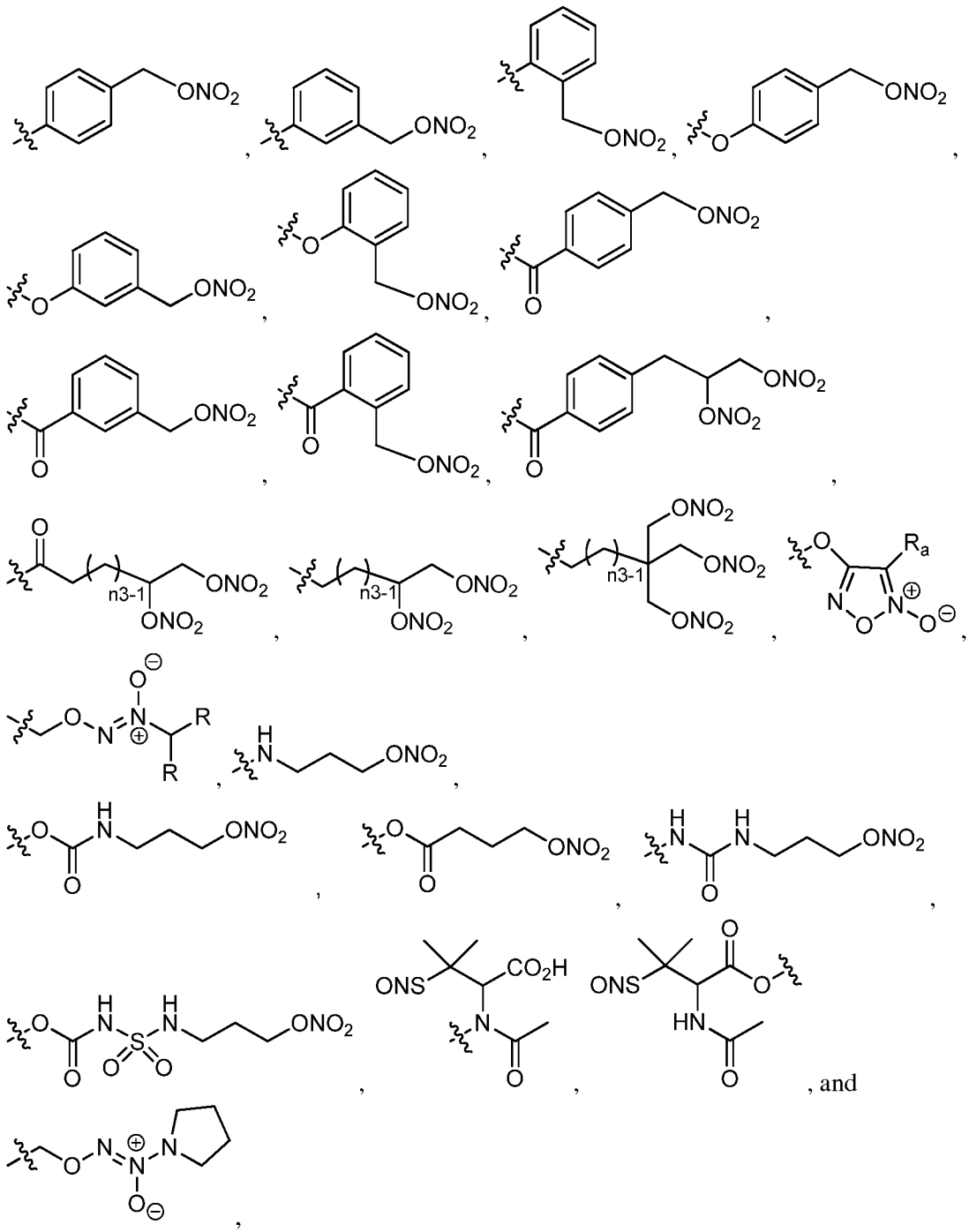
heterocyclic alkyl and aryl groups have at least one heteroatom selected from oxygen, nitrogen, and sulfur;

R^3 represents alkyl, cycloalkyl, aryl, or halo; and

halo substituents are fluoro, chloro, or bromo.

9. A compound according to claim 8, wherein R is an NSAID selected from the group consisting of Aspirin, Naproxen, Sulindac, Ibuprofen, Indomethacin, Valproic acid, Fenamic acid, Flurbiprofen, and Diclofenac.

10. A compound according to claim 8, wherein the NO releasing moiety is selected from the group consisting of -NO, $-ONO_2$, $-C(O)-(CH_2)_{n3}-ONO_2$, $-O-(CH_2)_{n3}-ONO_2$, $-(CH_2)_{n3}-ONO_2$, $-C(O)-CH_2-C(CH_3)_2-SNO$, $-NH-CH_2-C(CH_3)_2-SNO$, $-CH_2-C(CH_3)_2-SNO$,



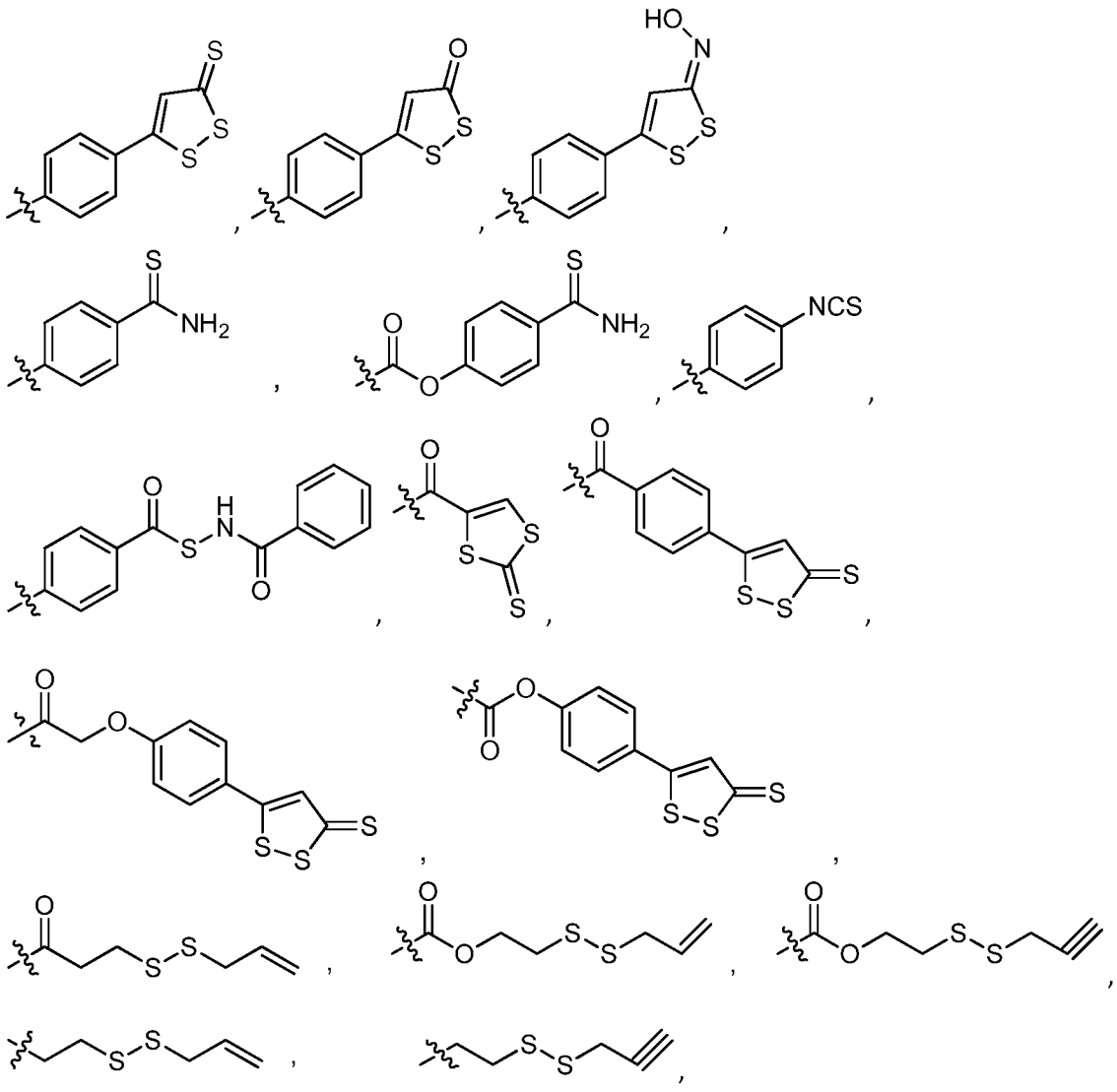
wherein

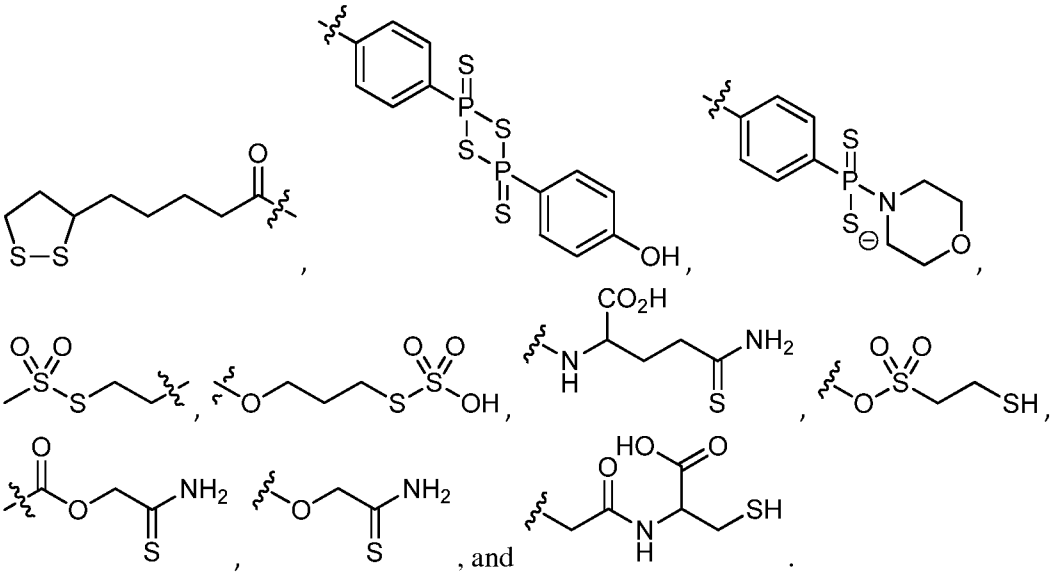
n3 is 1, 2, 3, 4, 5, 6, or 7;

R_a is H, C_1-C_{10} alkyl, aryl, $S(O)_2$-aryl, CN, or $CON(R_b)_2$; and

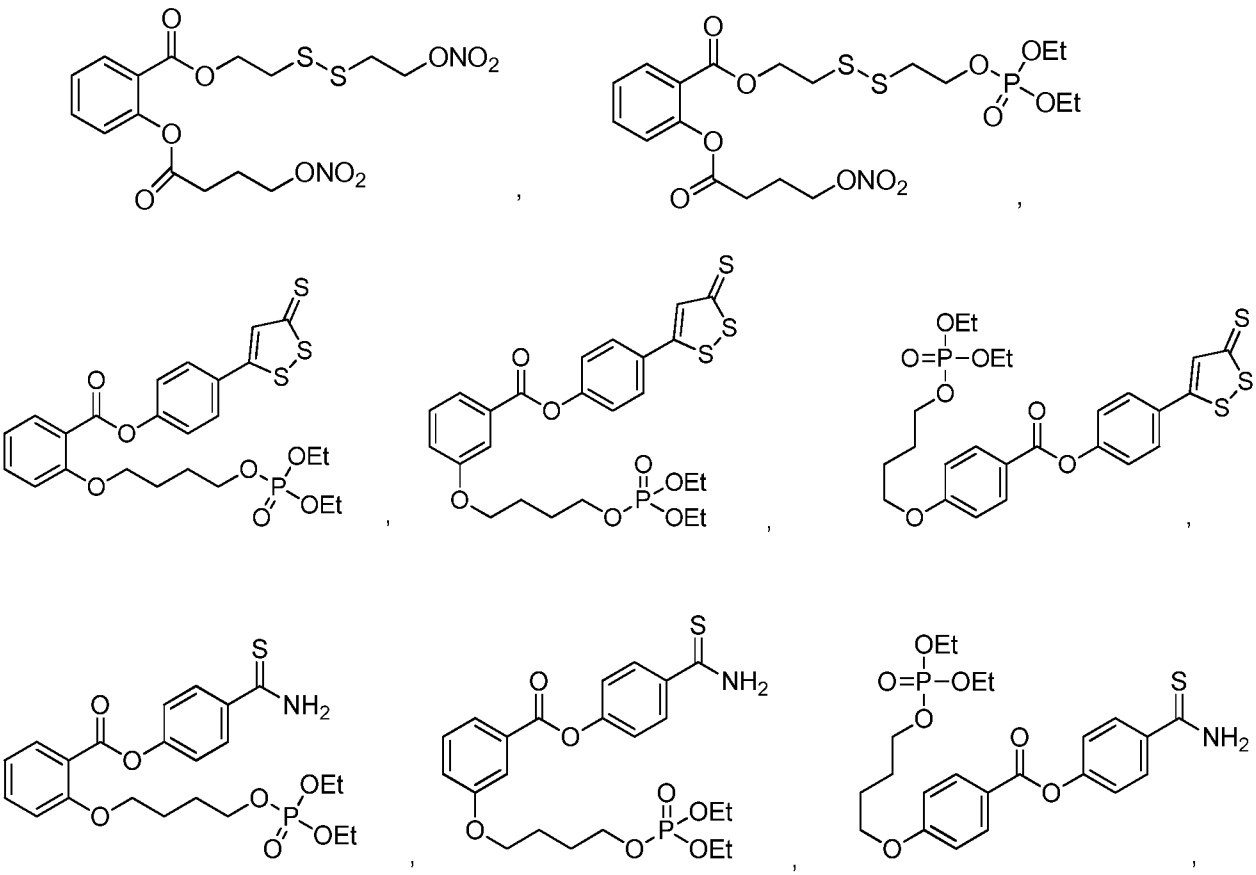
R_b is independently H or C_1-C_{10} alkyl.

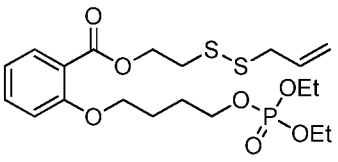
11. A compound according to claim 8, wherein the H_2S releasing moiety is selected from the group consisting of





12. A compound according to claim 8, having the structure:

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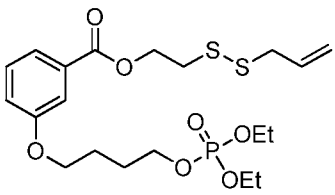
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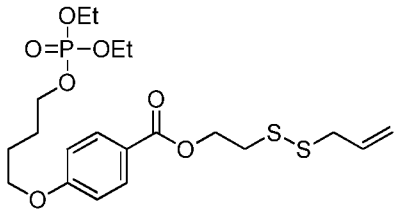
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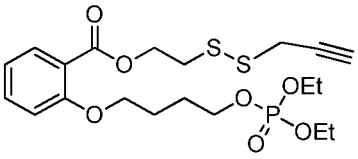
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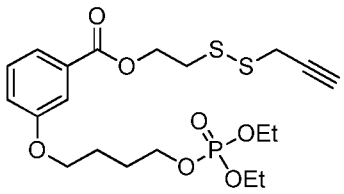
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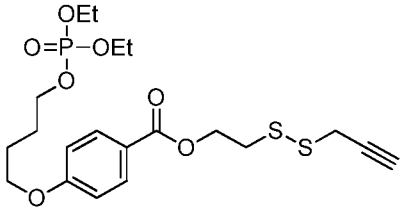
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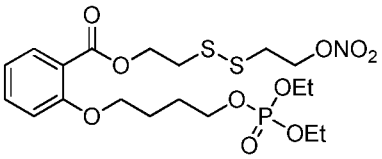
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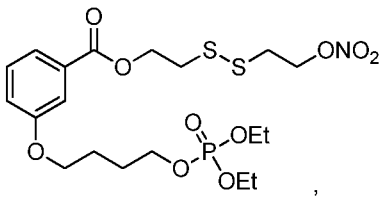
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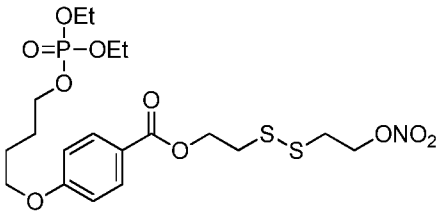
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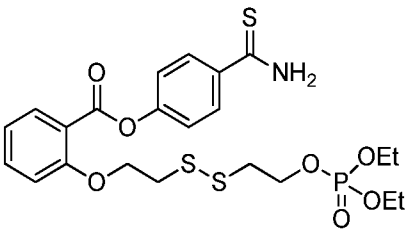
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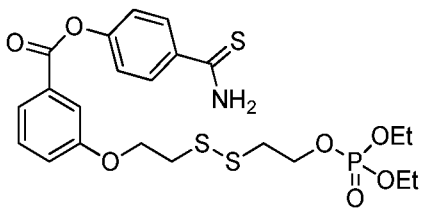
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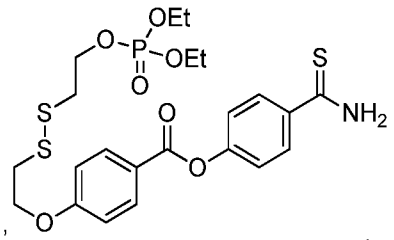
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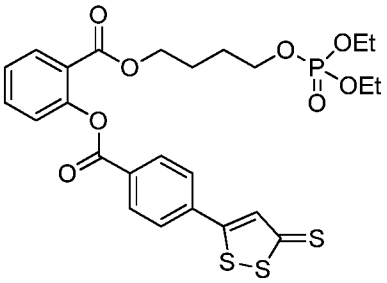
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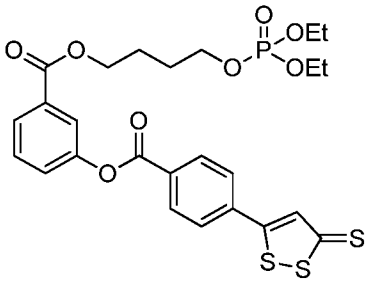
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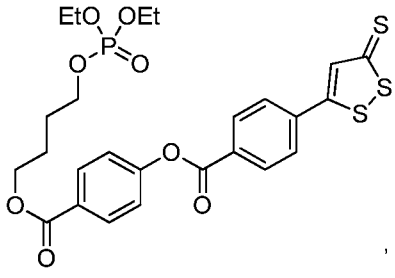
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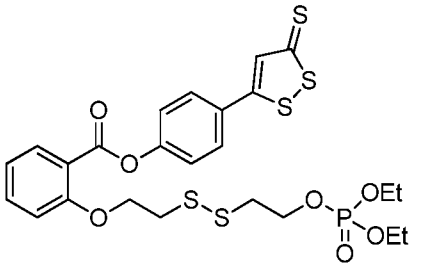
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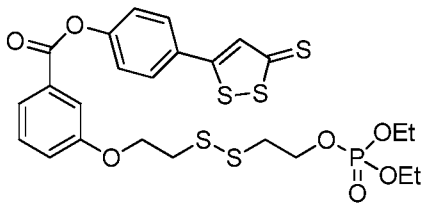
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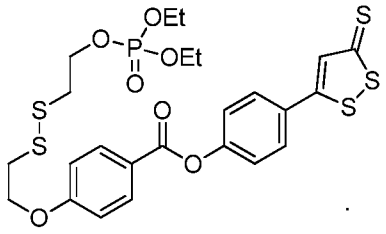
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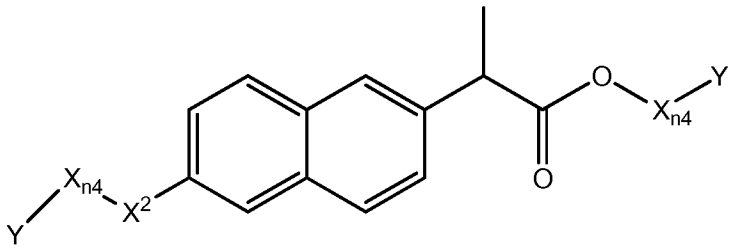
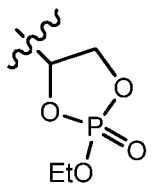
13. A compound of Formula III:


(III)

wherein:

X^2 is O, -C(O)-O-, or –O-C(O)-;

X is independently an alkyl, a cycloalkyl, an aryl, or $–(CH_2)_{n1}-S_{n2}-(CH_2)_{n1}-$;

Y is independently $–OP(O)(OEt)_2$,  , $-OSO_2R^2$, $-OSO_2OR^2$, $-OB(OR^2)_2$, halo, an H_2S releasing moiety, or an NO releasing moiety;

R^2 is $–(CH_2)_{n1}-$;

n1 is independently an integer from 1 to 20;

n2 is 2, 3, or 4;

n4 is 0 or 1;

alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain;

aryl groups are carbocyclic or heterocyclic;

aryl groups may be unsubstituted or substituted with one or more substituent at any position;

cycloalkyl groups are carbocyclic or heterocyclic, fused or unfused, non-aromatic ring systems having a total of 3-16 ring members including substituent rings;

each alkyl or cycloalkyl, independently, may be unsubstituted or substituted with one or more substituent at any position;

alkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, cycloalkyl, or aryl;

cycloalkyl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, or aryl;

aryl substituents are halo, hydroxyl, OR^3, SR^3, NH_2, NHR^3, alkyl, cycloalkyl, aryl, nitro, carboxyl, or –O-C(O)-alkyl;

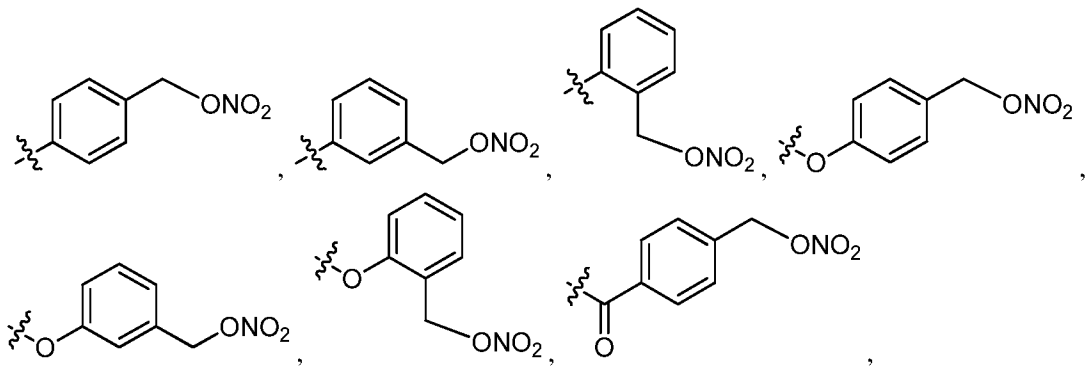
heterocyclic alkyl and aryl groups have at least one heteroatom selected from oxygen, nitrogen, and sulfur;

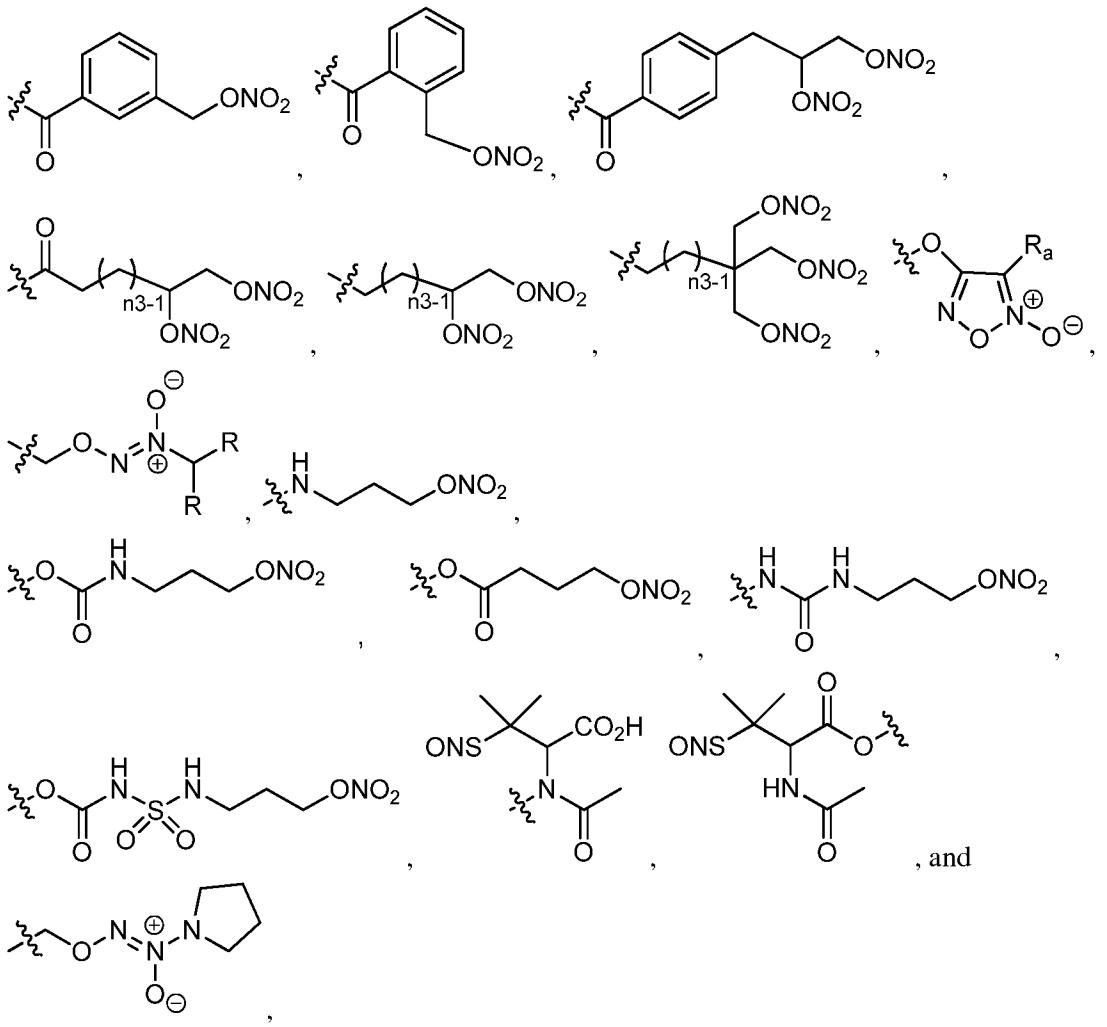
R^3 represents alkyl, cycloalkyl, aryl, or halo; and

halo substituents are fluoro, chloro, or bromo.

14. A compound according to claim 13, wherein R is an NSAID selected from the group consisting of Aspirin, Naproxen, Sulindac, Ibuprofen, Indomethacin, Valproic acid, Fenamic acid, Flurbiprofen, and Diclofenac.

15. A compound according to claim 13, wherein the NO releasing moiety is selected from the group consisting of -NO, $-ONO_2$, $-C(O)-(CH_2)_{n3}-ONO_2$, $-O-(CH_2)_{n3}-ONO_2$, $-(CH_2)_{n3}-ONO_2$, $-C(O)-CH_2-C(CH_3)_2-SNO$, $-NH-CH_2-C(CH_3)_2-SNO$, $-CH_2-C(CH_3)_2-SNO$,





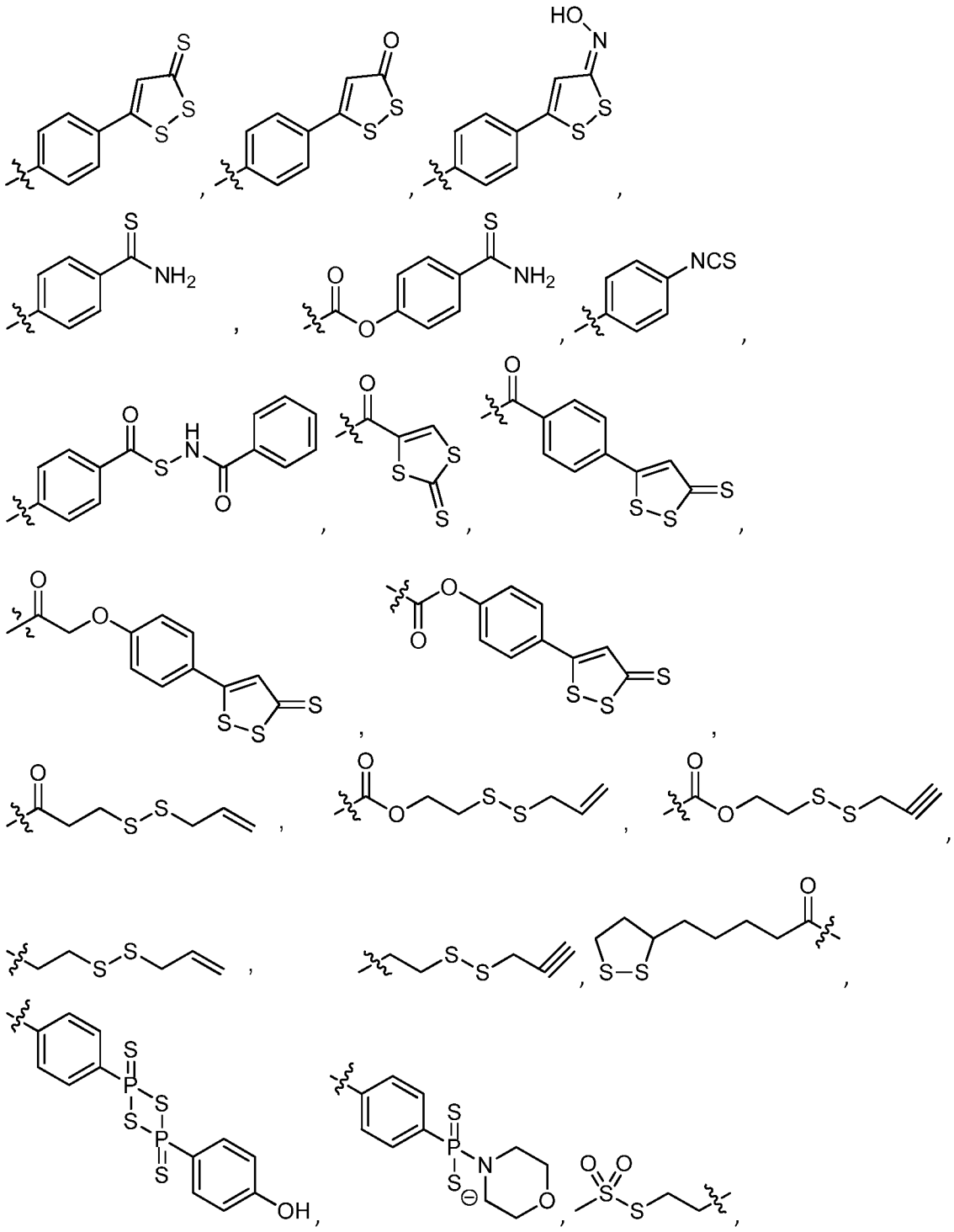
wherein

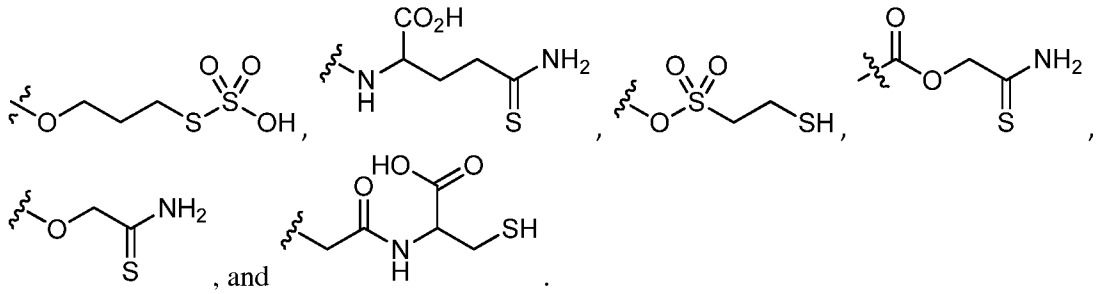
n3 is 1, 2, 3, 4, 5, 6, or 7;

R_a is H, C_1-C_{10} alkyl, aryl, $S(O)_2$-aryl, CN, or $CON(R_b)_2$; and

R_b is independently H or C_1-C_{10} alkyl.

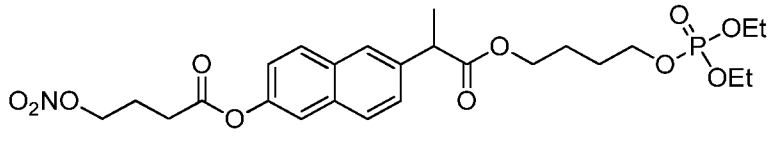
16. A compound according to claim 13, wherein the H_2S releasing moiety is selected from the group consisting of





, and .

17. A compound according to claim 13, having the structure:



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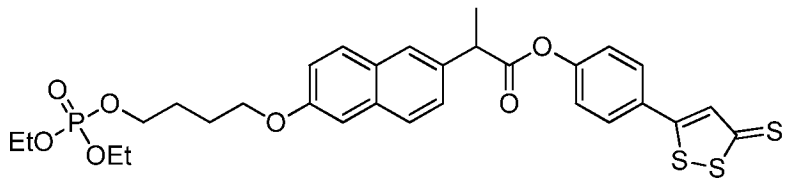

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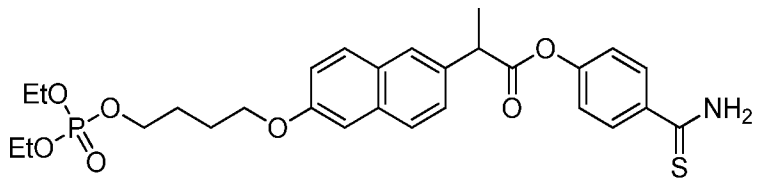

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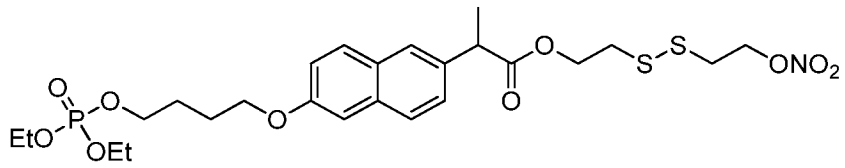

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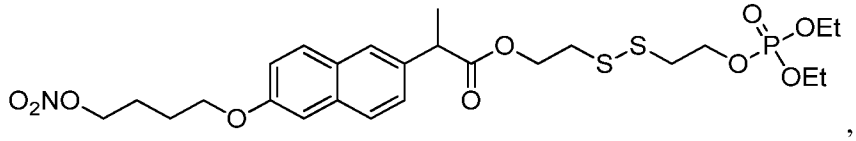

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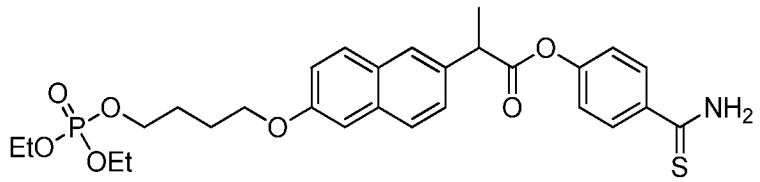

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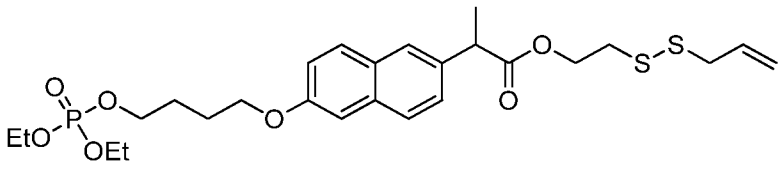

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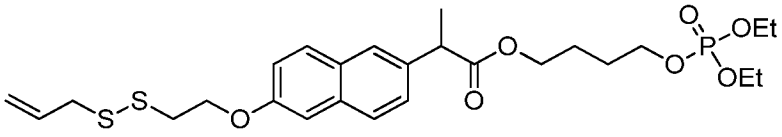

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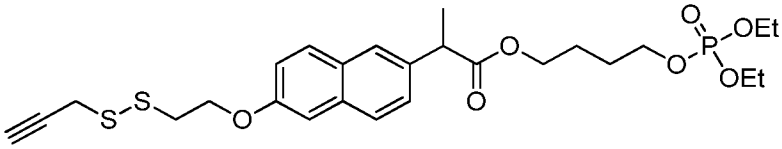

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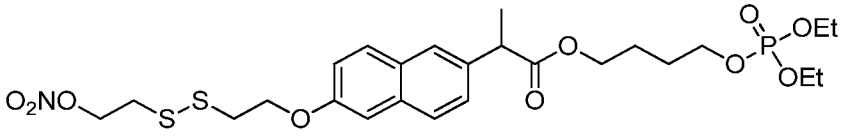

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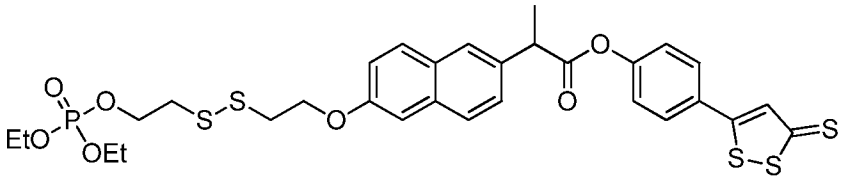

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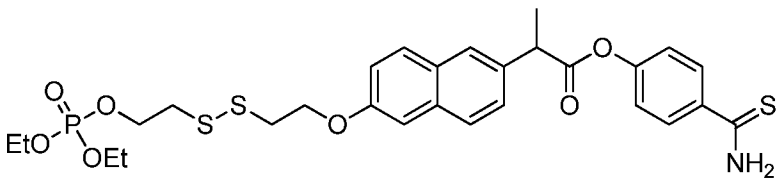

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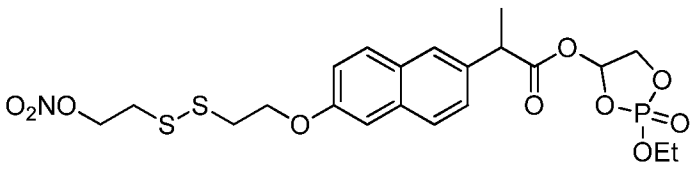

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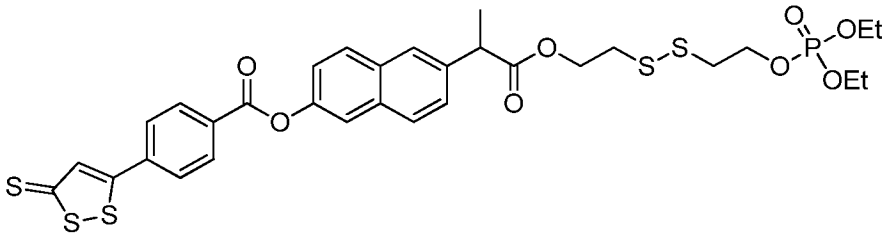

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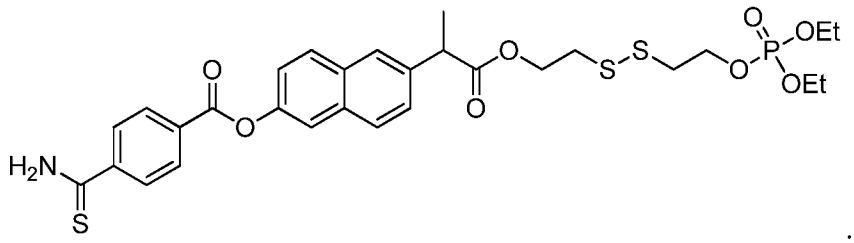

18. A method of treating an inflammatory disease, comprising administering to a subject in need thereof, an effective amount of a compound of claim 1, 8, or 13.

19. The method according to claim 18, wherein the inflammatory disease is cancer, rheumatoid arthritis, intestine inflammation, stomach ulcer, a cardiovascular disease, or a neurodegenerative disease.

20. A pharmaceutical composition comprising a compound according to claim 1, 8, or 13, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/015222

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/661 (2014.01)
USPC - 514/124
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/661 (2014.01)
USPC - 514/121, 124

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/661 (2014.06)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0099137 A1 (RIGAS) 16 April 2009 (16.04.2009) entire document	1, 2, 5, 18-20
A	WO 2011/130486 A2 (RIGAS et al) 20 October 2011 (20.10.2011) entire document	1, 2, 5, 18-20
A	US 2005/0182134 A1 (KASHFI) 18 August 2005 (18.08.2005) entire document	1, 2, 5, 18-20
A	US 6,482,811 B1 (BACANER et al) 19 November 2002 (19.11.2002) entire document	1, 2, 5, 18-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2014	18 JUL 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/015222

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1, 2, 5, and 18-20 (in part) have been analyzed subject to the restriction that the claims read on the Formula I as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a compound of Formula I, wherein: R is a non-steroidal anti-inflammatory drug (NSAID) selected as Aspirin; X is an alkyl; Y is independently -OP(O)(OEt)2; alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain; each alkyl, independently, may be unsubstituted or substituted with one or more substituent at any position; alkyl substituents are halo.

<See Extra Sheet>

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 5, and 18-20 (in part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/015222

<Continued from Box III: Observations where unity of invention is lacking>

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-7 and 18-20 (in part) are drawn to compounds of Formula I.

Group II: claims 8-12 and 18-20 (in part) are drawn to compounds of Formula II.

Group III: claims 13-17 and 18-20 (in part) are drawn to compounds of Formula III.

The first invention of Group I+ is restricted to a compound of Formula I, wherein: R is a non-steroidal anti-inflammatory drug (NSAID) selected as Aspirin; X is an alkyl; Y is independently -OP(O)(OEt)2; alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain; each alkyl, independently, may be unsubstituted or substituted with one or more substituent at any position; alkyl substituents are halo. It is believed that claims 1, 2, 5, and 18-20 (in part) read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound of Formula I, wherein: R is R1-C(O)-X1; R1 is an alkyl; X1 is O; X is an alkyl; Y is independently -OP(O)(OEt)2; alkyl groups are branched or unbranched, saturated or unsaturated, and have 1-20 carbon atoms in their longest chain; each alkyl, independently, may be unsubstituted or substituted with one or more substituent at any position; alkyl substituents are halo. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ through III do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, compounds of Formula I, are not present in Groups II and III; the special technical features of Group II, compounds of Formula II, are not present in Groups I+ and III; and the special technical features of Group III, compounds of Formula III, are not present in Groups I+ and II.

The Groups I+ formulae do not share a significant structural element, requiring the selection of alternatives for the compound variables R, X, and Y.

The Groups I+ through III share the technical features of a compound of Formula I or compounds comprising an -X1-Xn4-Y moiety, a method of treating an inflammatory disease, comprising administering to a subject in need thereof, an effective amount of a compound thereof, and a pharmaceutical composition comprising a compound thereof, and a pharmaceutically acceptable carrier. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2009/0099137 to Rigas teaches a compound of Formula I wherein: R is R1-C(O)X1; R1 is aryl; X1 is O; X is alkyl; Y is the shown ethyl phosphate ring moiety; aryl groups are carbocyclic; aryl groups may be unsubstituted or substituted with one or more substituent at any position; and aryl substituents are - O-C(O)-alkyl (Para. [0128], Two derivatives of aspirin were synthesized. They are referred to as glycero-phospho-aspirin I and glycerophospho-aspirin II, respectively. Their structures are shown below...see structure for Glycero-phospho-aspirin I...); a method of treating an inflammatory disease, comprising administering to a subject in need thereof, an effective amount of a compound thereof (Para. [0121], NSAID based compounds Non-steroidal anti-inflammatory drugs (NSAIDS) comprise a structurally and, to a large extent, functionally diverse group of compounds with nearly 50 individual compounds approved for the treatment of patients with a variety of inflammatory diseases...acetylsalicylic acid (aspirin), have been demonstrated to have an effect against inflammation related diseases such as rheumatologic, cardiovascular, neurodegenerative and cancer, be this effect either therapeutic as, for example, in rheumatoid arthritis, or preventive as, for example, in cancer, coronary artery disease or Alzheimer's disease), and a pharmaceutical composition comprising a compound thereof, and a pharmaceutically acceptable carrier (Para. [0106], methods for the treatment of inflammation-related disorders are provided comprising administering a therapeutically effective amount of a compound of Formula I to a subject in need thereof...or a pharmaceutical composition comprising an inventive compound to a subject in need thereof...; Para. [0110], ...formulation with an appropriate pharmaceutically acceptable carrier in a desired dosage, the pharmaceutical compositions of this invention can be administered to humans...).

The inventions listed in Groups I+ through III therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

<End Box III: Observations where unity of invention is lacking>