Title: SUBSTITUTED FNO (2-[FURAN-2-YL] NAPHTHALENI-1-OL) DERIVATIVES AS ANTI-CANCER AGENTS

Abstract: Compounds of Formulas I are described, along with methods of using such compounds for the treatment of cancer and pharmaceutical formulations thereof.
Substituted FNO (2-[furan-2-yl] naphthalen-1-ol) 
Derivatives as Anti-Cancer Agents

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under NIH grant CA 17625. The Government has certain rights to this invention.

FIELD OF THE INVENTION

The present invention concerns active compounds, formulations thereof, and methods of use thereof, particularly in methods of treating cancer.

BACKGROUND OF THE INVENTION

Breast cancer is the most common malignancy and the second leading cause of cancer deaths in women today.\(^1\),\(^2\) According to the American Cancer Society, breast cancer accounts for more than one quarter of cancers diagnosed in US women. Estrogens play crucial role in breast cancer development and growth, and estrogen-stimulated growth in tumor cells (as well as in normal cells) requires estrogen receptors (ERs).\(^3\) It has been shown that about two-third of human breast tumors express higher levels of ERs than normal breast tissues.\(^4\) Much effort has been devoted to block estrogen formation and action.\(^2\) The most widely used therapy for antagonizing ER function is the antiestrogen tamoxifen (TAM), which binds to ER and blocks downstream signaling. However, current breast cancer therapies like TAM achieve meaningful clinical results in only 30-40% of patients, because drug resistance usually develops after one or two years of treatment (Scheme 1).\(^2\) This resistance occurs via several mechanisms, including the induction of estrogen-independent pathways for breast cancer cell growth, like over-expression human epidermal growth factor receptor 2 (HER2), and functional crosstalk between ER and HER2\(^5\)-\(^7\).
**Scheme 1.** Structure of tamoxifen, neo-tanshinlactone (1) and a first generation optimized analog (2)

A common clinical strategy to overcome drug resistance is to utilize combination of anti-estrogen and other cytotoxic drugs, such as anastrozole, an aromatase inhibitor.\(^8\)\(^9\) However, cancer often relapses so there is a need to develop new drug chemotypes with new mechanisms of action. Neo-tanshinlactone (1) (Scheme 1), a component of a Chinese traditional medicine Tanshen, showed significant selective activity as compared to TAM.\(^10\) Compound 2 (Scheme 1), a congener of compound 1 is about twice as active against MCF-7 and SK-BR-3 cell lines as compound 1.\(^11\) As a tetracyclic natural product, compound 1 may be more structurally complex than is necessary for optimal pharmacologic effect. Buried within the structure of such a lead compound is a pharmacophoric moiety that, if it can be clearly defined, may be ‘dissected out’. This would represent a biologically active, simpler molecule that may have improved synthetic tractability and be more useful as a scaffold for further analog design.
SUMMARY OF THE INVENTION

A first aspect of the present invention is a compound of Formula I:

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R1A, R1B, R2A, R2B, R3A, R3B, R4A, R4B, R5, R6, R7, R8, R9, R', and R'' are each independently selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R10, OC(=O)OR10, OC(=O)N(R10)2, O(CH2)mN(R10)2, C(=O)N(R10)2, and O(CH2)mCOOR10 where m is 1-5 and R10 is H or lower alkyl;

or R' and R1A together form a covalent bond;

or R1B and R2A together form a covalent bond;

or R2B and R3A together form a covalent bond;

or R3B and R4A together form a covalent bond;

or R4B and R'' together form a covalent bond;

or R8 and R9 together form a covalent bond;

or R7 and R8 together form =Z, where Z is selected from the group consisting of O, S, and NH;

X1 is OR11, SR11, N(R11)2, S(O), or S(O)2. R11 is selected from the group consisting of H, lower alkyl, heteroaryl, aryl, C(=O)R12, C(=O)OR12, C(=O)N(R12)2, (CH2)mN(R12)2, and (CH2)mCOOR12 where m is 1-5 and R12 is H or lower alkyl;
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X₂ is C(=O)R₁₃, C(=S)R₁₃, C(=NR₁₄)R₁₃, CH₂R₁₃, S(O), or S(O₂). R₁₃ is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl. R₁₄ is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl;

or X₁ and X₂ together form a covalent linking group selected from the group consisting of -O-C(=O)-, -S-C(=O)-, -N(R₁₁)-C(=O)-, -S(O)-C(=O)-, -S(O₂)-C(=O)-, -O-C(=S)-, -S-C(=S)-, -N(R₁₁)-C(=S)-, -S(O)-C(=S)-, -S(O₂)-C(=S)-, -O-C(=NR₁₄)-, -S-C(=NR₁₄)-, -N(R₁₁)-C(=NR₁₄)-, -S(O)-C(=NR₁₄)-, -S(O₂)-C(=NR₁₄)-, -O-CHR₁₃-, -S-CHR₁₃-, or -N(R₁₁)-CHR₁₃-, -S(O)-CHR₁₃-, -S(O₂)-CHR₁₃-, -O-S(O)-, -S-S(O)-, -N(R₁₁)-S(O)-, -S(O)-S(O)-, -S(O₂)-S(O)-, -O-S(O₂)-, -S-S(O₂)-, -N(R₁₁)-S(O₂)-, -S(O)-S(O₂)-, or -S(O₂)-S(O₂)-;

X₃ is selected from the group consisting of O, S, NH to form a heterocycle, and (CH₂)ₙ where n is 1-2;

or a pharmaceutically acceptable salt or prodrug thereof.

A second aspect of the present invention is a compound of Formula Ia:

![La](image)

wherein:

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are each independently selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R₁₀, OC(=O)OR₁₀,
OC(\(\equiv\)O)N(R_{10})_2, \(O(CH_2)mN(R_{10})_2, \(C(\equiv\)O)N(R_{10})_2, \) and \(O(CH_2)mCOOR_{10}\)
where \(m\) is 1-5 and \(R_{10}\) is H or lower alkyl;

or \(R_6\) and \(R_8\) together form a covalent bond;

or \(R_7\) and \(R_8\) together form \(=Z\), where \(Z\) is selected from the group consisting of O, S, and NH;

\(X_1\) is OR_{11}, SR_{11}, or N(R_{11})_2. \(R_{11}\) is selected from the group consisting of H, lower alkyl, heteroaryl, aryl, \(C(\equiv\)O)R_{12}, \(C(\equiv\)O)OR_{12}, \(C(\equiv\)O)N(R_{12})_2, \(CH_2)mN(R_{12})_2, \) and \(CH_2)mCOOH\) where \(m\) is 1-5 and \(R_{12}\) is H or lower alkyl;

\(X_2\) is \(C(\equiv\)O)R_{13}, \(C(\equiv\)S)R_{13}, \(C(\equiv\)NR_{14})R_{13}, or \(CH_2)_pR_{13}. \(R_{13}\) is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl. \(R_{14}\) is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl;

\(X_3\) is selected from the group consisting of O, S, NH to form a heterocycle, and \((CH_2)_p\) where \(p\) is 1-2;

or a pharmaceutically acceptable salt or prodrug thereof.

A further aspect of the present invention is a pharmaceutical formulation comprising an active compound as described herein, in a pharmaceutically acceptable carrier (e.g., an aqueous carrier).

A still further aspect of the present invention is a method of treating a cancer, comprising administering to a human or animal subject in need thereof a treatment effective amount (e.g., an amount effective to treat, slow the progression of, etc.) of a compound as described above, and further described below. Examples of cancers that may be treated include, but are not limited to, skin cancer, lung cancer including small cell lung cancer and non-small cell lung cancer, testicular cancer, lymphoma, leukemia, Kaposi’s sarcoma, esophageal cancer, stomach cancer, colon cancer, breast cancer, endometrial cancer, ovarian cancer, central nervous system cancer, liver cancer and prostate cancer.
A still further aspect of the invention is the use of an active compound or active agent as described herein for the preparation of a medicament for carrying out a method of treatment as described herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be described more fully hereinafter. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

The term "alkyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decy1, and the like.

"Lower alkyl" as used herein, is a subset of alkyl and refers to a straight or branched chain hydrocarbon group containing from 1 to 4 carbon atoms. Representative examples of lower alkyl include, but are not limited to, methyl,
ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, and the like.

"Alkenyl," as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of "alkenyl" include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl and the like. "Loweralkenyl" as used herein, is a subset of alkenyl and refers to a straight or branched chain hydrocarbon group containing from 1 to 4 carbon atoms.

"Alkoxy," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxy group, as defined herein. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

"Alkythio" as used herein refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkythio include, but are not limited, methylthio, ethylthio, tert-butylthio, hexylthio, and the like.

"Lower alkoxy" as used herein, is a subset of alkoxy and refers to a lower alkyl group, as defined herein, appended to the parent molecular moiety through an oxy group, as defined herein. Representative examples of lower alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, and the like.

"Alkylene" as used herein means alkyl or loweralkyl in which one, two, three or more (e.g., all) hydrogens thereon have been replaced with halo. Examples of alkylene include but are not limited to trifluoromethyl, chloromethyl, 2-chloroethyl, 2-bromoethyl, and 2-iodoethyl. Alkylene may also be referred to as haloalkyl or perhaloalkyl (e.g. fluoroalkyl; perfluoroalkyl).

"Cycloalkyl," as used herein, refers to a saturated cyclic hydrocarbon group
containing from 3 or 4 to 6 or 8 carbons. Representative examples of cycloalkyl include, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

"Heterocycle," as used herein, refers to a monocyclic- or a bicyclic-ring system. Monocyclic ring systems are exemplified by any 5 or 6 membered ring containing 1, 2, 3, or 4 heteroatoms independently selected from oxygen, nitrogen and sulfur. The 5 membered ring has from 0-2 double bonds and the 6 membered ring has from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidine, azepine, aziridine, diazepine, 1,3-dioxolane, dioxane, dithiane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazoline, isothiazolidine, isoxazole, isoxazoline, isoxazolidine, morpholine, oxadiazole, oxadiazoline, oxadiazolidine, oxazole, oxazoline, oxazolidine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrimidine, pyridazine, pyrrole, pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrazine, tetrazole, thiadiazole, thiadiazoline, thiadiazolidine, thiazole, thiazoline, thiazolidine, thiophene, thiomorpholine, thiomorpholine sulfone, thiopyran, triazine, triazole, trithiane, and the like. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system as defined herein. Representative examples of bicyclic ring systems include but are not limited to, for example, benzimidazole, benzothiazole, benzothiadiazole, benzothiophene, benzoazadiazole, benzoxazole, benzofuran, benzopyran, benzothiopyran, benzodioxide, 1,3-benzodioxole, cinnoline, indazole, indole, indoline, indolizine, naphthyridine, isobenzofuran, isobenzothiophene, isoindole, isoindoline, isoquinoline, phthalazine, pyranopyridine, quinoline, quinolizine, quinoxaline, quinazoline, tetrahydroisoquinoline, tetrahydroquinoline, thiopyranopyridine, and the like. Heterocycle groups of this invention can be substituted with 1, 2, or 3 substituents, such as substituents independently selected from alkenyl, alkenyloxy, alkoxy, alkoxyalkoxy, alkoxy carbonyl, alkyl, alkyl carbonyl, alkyl carboxyloxy, alkyl sulfanyl, alkyl sulfonfyl, alkylthio, alkynyl, ary, azido, arylalkoxy, arylalkoxycarbonyl, arylalkyl, aryloxy, carboxy, cyano, formyl, oxo,
halo, haloalkyl, haloalkoxy, hydroxy, hydroxyalkyl, mercapto, nitro, sulfamyl, sulfo, sulfonate, \(-NR' R''\) (wherein, \(R\) and \(R''\) are independently selected from hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl and formyl), and \(-C(O)NRR'\) (wherein, \(R\) and \(R'\) are independently selected from hydrogen, alkyl, aryl, and arylalkyl).

"Aryl" as used herein refers to an aromatic species containing 1 to 5 aromatic rings, either fused or linked, and either unsubstituted or substituted with 1 or more typically selected from the group consisting of lower alkyl, modified lower alkyl, aryl, aralkyl, lower alkoxy, thioalkyl, hydroxyl, thio, mercapto, amino, imino, halo, cyano, nitro, nitroso, azido, carboxy, sulfide, sulfone, sulfoxyl, phosphoryl, silyl, silyloxy, and boronyl; and lower alkyl substituted with one or more groups selected from lower alkyl, alkoxy, thioalkyl, hydroxyl thio, mercapto, amino, imino, halo, cyano, nitro, nitroso, azido, carboxy, sulfide, sulfone, sulfoxyl, phosphoryl, silyl, silyloxy, and boronyl. Typical aryl groups contain 1 to 3 fused aromatic rings, and more typical aryl groups contain 1 aromatic ring or 2 fused aromatic rings. Aromatic groups herein may or may not be heterocyclic.

"Heteroaryl" as used herein refers to an aryl, as defined herein, that is heterocyclic.

"Halo" as used herein refers to any halogen group, such as chloro, fluoro, bromo, or iodo.

"Oxo" as used herein, refers to a \(=O\) moiety.

"Oxy," as used herein, refers to a \(-O-\) moiety.

"Thio" as used herein refers to a \(-S-\) moiety.

"Amine" or "amino group" is intended to mean the radical \(-NH2\).

"Substituted amino" or "substituted amine" refers to an amino group, wherein one or two of the hydrogens is replaced by a suitable substituent. Disubstituted amines may have substituents that are bridging, i.e., form a heterocyclic ring structure that includes the amine nitrogen as the linking atom to the parent compound. Examples of substituted amino include but are not
limited to alkylamino, dialkylamino, and heterocyclo (where the heterocyclo is linked to the parent compound by a nitrogen atom in the heterocyclic ring or heterocyclic ring system).

"Alkylamino" is intended to mean the radical –NHR', where R' is alkyl.

"Dialkylamino" is intended to mean the radical NR'R", where R' R" are each independently an alkyl group.

"Aminoalkyl" refers to an alkyl substituent which is further substituted with one or more amino groups.

Dashed lines (e.g., ---) as used herein represent that the respective atoms are connected by either a single or double bond.

"Treat" or "treating" as used herein refers to any type of treatment that imparts a benefit to a patient afflicted with a disease, including improvement in the condition of the patient (e.g., in one or more symptoms), delay in the progression of the disease, prevention or delay of the onset of the disease, etc.

"Treatment effective amount" as used herein refers to an amount of the active compound effective to treat the disease, slow or delay the progression of the disease, prevent or delay of the onset of the disease, etc.

"Pharmaceutically acceptable" as used herein means that the compound or composition is suitable for administration to a subject to achieve the treatments described herein, without unduly deleterious side effects in light of the severity of the disease and necessity of the treatment.

"Inhibit" as used herein means that a potential effect is partially or completely eliminated.
The present invention is concerned primarily with the treatment of human subjects, but may also be employed for the treatment of other animal subjects (i.e., mammals such as dogs, cats, horses, etc. or avians) for veterinary purposes. Mammals are preferred, with humans being particularly preferred.

A. Active Compounds.

Active compounds of the present invention are described below, and may be formulated and used in the compositions and methods described below.

Active compounds of the invention include compounds of Formula I:

\[
\text{Formula I}
\]

wherein:

- \( R_{1A}, R_{1B}, R_{2A}, R_{2B}, R_{3A}, R_{3B}, R_{4A}, R_{4B}, R_5, R_6, R_7, R_8, R_9, R', \) and \( R'' \) are each independently selected from the group consisting of \( H, \) lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, aryl, \( \text{OC}(=\text{O})R_{10}, \) \( \text{OC}(=\text{O})\text{OR}_{10}, \) \( \text{OC}(=\text{O})\text{N}(R_{10})_2, \) \( \text{O}(\text{CH}_2)\text{mN}(R_{10})_2, \) \( \text{C}(=\text{O})\text{N}(R_{10})_2, \) and \( \text{O}(\text{CH}_2)\text{mCOOR}_{10} \) where \( m \) is 1-5 and \( R_{10} \) is \( H \) or lower alkyl;

- or \( R' \) and \( R_{1A} \) together form a covalent bond;

- or \( R_{1B} \) and \( R_{2A} \) together form a covalent bond;

- or \( R_{2B} \) and \( R_{3A} \) together form a covalent bond;

- or \( R_{3B} \) and \( R_{4A} \) together form a covalent bond;

- or \( R_{4B} \) and \( R'' \) together form a covalent bond;

- or \( R_8 \) and \( R_9 \) together form a covalent bond;
or R7 and R8 together form =Z, where Z is selected from the group consisting of O, S, and NH;

X1 is OR11, SR11, N(R11)2, S(O), or S(O2). R11 is selected from the group consisting of H, lower alkyl, heteroaryl, aryl, C(=O)R12, C(=O)OR12, C(=O)N(R12)2, (CH2)mN(R12)2, and (CH2)mCOOR12 where m is 1-5 and R12 is H or lower alkyl;

X2 is C(=O)R13, C(=S)R13, C(=NR14)R13, CH2R13, S(O), or S(O2). R13 is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl. R14 is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl;

or X1 and X2 together form a covalent linking group selected from the group consisting of -O-C(=O)-, -S-C(=O)-, -N(R11)-C(=O)-, -S(O)-C(=O)-, -S(O2)-C(=O)-, -O-C(=S)-, -S-C(=S)-, -N(R11)-C(=S)-, -S(O)-C(=S)-, -S(O2)-C(=S)-, -O-C(=NR14)-, -S-C(=NR14)-, -N(R11)-C(=NR14)-, -S(O)-C(=NR14)-, -S(O2)-C(=NR14)-, -O-CHR13-, -S-CHR13-, or -N(R11)-CHR13-, -S(O)-CHR13-, -S(O2)-CHR13-, -O-S(O)-, -S-S(O)-, -N(R11)-S(O)-, -S(O)-S(O)-, -S(O2)-S(O)-, -O-S(O2)-, -S-S(O2)-, -N(R11)-S(O2)-, -S(O)-S(O2)-, -S(O2)-S(O2)-;

X3 is selected from the group consisting of O, S, NH to form a heterocycle, and (CH2)p where p is 1-2;

n is 0 or 1;

or a pharmaceutically acceptable salt or prodrug thereof.

Active compounds of the invention also include compounds of Formula Ia:
wherein:

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are each independently selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, aryl, O\(\text{C}(\equiv \text{O})\)R₁₀, OC\(\text{C}(\equiv \text{O})\)OR₁₀, OC\(\text{C}(\equiv \text{O})\)N(R₁₀)₂, O(CH₂)mN(R₁₀)₂, C\(\equiv \text{O})\)N(R₁₀)₂, and O(CH₂)mCOOR₁₀ where m is 1-5 and R₁₀ is H or lower alkyl;

or R₈ and R₉ together form a covalent bond;

or R₇ and R₈ together form =Z, where Z is selected from the group consisting of O, S, and NH;

X₁ is OR₁₁, SR₁₁, or N(R₁₁)₂. R₁₁ is selected from the group consisting of H, lower alkyl, heteroaryl, aryl, C\(\equiv \text{O})\)R₁₂, C\(\equiv \text{O})\)OR₁₂, C\(\equiv \text{O})\)N(R₁₂)₂, (CH₂)mN(R₁₂)₂, and (CH₂)mCOOR₁₂ where m is 1-5 and R₁₂ is H or lower alkyl;

X₂ is C\(\equiv \text{O})\)R₁₃, C\(\equiv \text{S})\)R₁₃, C\(\equiv \text{NR}_{1₄})\)R₁₃, or CH₂R₁₃. R₁₃ is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl. R₁₄ is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl;

X₃ is selected from the group consisting of O, S, NH to form a heterocycle, and (CH₂)_p where p is 1-2;

or a pharmaceutically acceptable salt or prodrug thereof.

In some embodiments of Formula I, n is 0.

In some embodiments of Formula I, n is 1.
In some embodiments of Formula I, X₁ and X₂ together form a covalent linking group selected from the group consisting of –O-C(=O)–, –S-C(=O)–, –N(R₁₁)-C(=O)–, –S(O)-C(=O)–, –S(O₂)-C(=O)–, –O-C(=S)–, –S-C(=S)–, –N(R₁₁)-C(=S)–, –S(O)-C(=S)–, –S(O₂)-C(=S)–, –O-C(=NR₁₄)–, –S-C(=NR₁₄)–, –N(R₁₁)-C(=NR₁₄)–, –S(O)-C(=NR₁₄)–, –S(O₂)-C(=NR₁₄)–, –O-CHR₁₃–, –S-CHR₁₃–, or –N(R₁₁)-CHR₁₃–, –S(O)-CHR₁₃–, –S(O₂)-CHR₁₃–, –O-S(O)–, –S-S(O)–, –N(R₁₁)-S(O)–, –S(O)-S(O)–, –S(O₂)-S(O)–, –O-S(O₂)–, –S-S(O₂)–, –N(R₁₁)-S(O₂)–, –S(O)-S(O₂)–, –S(O₂)-S(O₂)–.

In some embodiments of Formula I, R₁₁, R₁₉, R₂₆, R₃₅, R₄₅, R₅, R₂₆, R₇, R₈, R₉, R', and R'' are each independently selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R₁₀, OC(=O)OR₁₀, OC(=O)N(R₁₀)₂, O(CH₂)mN(R₁₀)₂, C(=O)N(R₁₀)₂, and O(CH₂)mCOOR₁₀ where m is 1-5 and R₁₀ is H or lower alkyl.

In some embodiments of Formula I, R₄₅ and R₄₆ are each independently selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R₁₀, OC(=O)OR₁₀, OC(=O)N(R₁₀)₂, O(CH₂)mN(R₁₀)₂, C(=O)N(R₁₀)₂, and O(CH₂)mCOOR₁₀ where m is 1-5 and R₁₀ is H or lower alkyl.

In some embodiments of Formula I, X₁ is OR₁₁, SR₁₁, or N(R₁₁)₂. R₁₁ is selected from the group consisting of H, lower alkyl, heteroaryl, aryl, C(=O)R₁₂, C(=O)OR₁₂, C(=O)N(R₁₂)₂, (CH₂)mN(R₁₂)₂, and (CH₂)mCOOR₁₂ where m is 1-5 and R₁₂ is H or lower alkyl and X₂ is C(=O)R₁₃, C(=S)R₁₃, C(=NR₁₄)R₁₃, or CH₂R₁₃. R₁₃ is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl. R₁₄ is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl.

In some embodiments of Formula I, R' and R₁₁, R₂₆ and R₃₅, and R₄₅ and R'' together form a covalent bond.

In some embodiments of Formula I or Formula Ia the compound is aromatic.

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In some embodiments of Formula Ia, X₃ is CH₂, S, or NH.

In some embodiments of Formula Ia, X₁ is not O when X₂ is C=O.

In some embodiments of Formula Ia, R₈ and R₉ together form a covalent bond.

In some embodiments of Formula Ia, R₇ and R₈ together form =Z, where Z is selected from the group consisting of O, S, and NH.

In some embodiments of Formula Ia, at least one of R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ is selected from the group consisting of lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R₁₀, OC(=O)OR₁₀, OC(=O)N(R₁₀)₂, O(CH₂)mN(R₁₀)₂, C(=O)N(R₁₀)₂, and O(CH₂)mCOOR₁₀, where m is 1-5 and R₁₀ is H or lower alkyl.

B. Formulations and pharmaceutically acceptable salts.

The term "active agent" as used herein, includes the pharmaceutically acceptable salts of the compound of Formula I or Formula Ia. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (b) salts formed from elemental anions such as chlorine, bromine, and iodine.

Active agents used to prepare compositions for the present invention may alternatively be in the form of a pharmaceutically acceptable free base of active agent. Because the free base of the compound is less soluble than the
salt, free base compositions are employed to provide more sustained release of active agent to the target area. Active agent present in the target area which has not gone into solution is not available to induce a physiological response, but serves as a depot of bioavailable drug which gradually goes into solution.

Active compounds of the invention include prodrugs thereof. A "prodrug" is a compound that, upon in vivo administration, is metabolized by one or more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound of Formula I or Formula Ia. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes (e.g., by conversion of a carboxylic acid to the corresponding C1-C4 ester or amide thereof). The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can produce prodrugs of the compound in accordance with known techniques (see, e.g., Nogrady (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392).

The compounds of the present invention are useful as pharmaceutically active agents and may be utilized in bulk form. More preferably, however, these compounds are formulated into pharmaceutical formulations for administration. Any of a number of suitable pharmaceutical formulations may be utilized as a vehicle for the administration of the compounds of the present invention.

The compounds of the present invention may be formulated for administration for the treatment of a variety of conditions hi the manufacture of a pharmaceutical formulation according to the invention, the compounds of the present invention and the physiologically acceptable salts thereof, or the acid derivatives of either (hereinafter referred to as the "active compound") are typically admixed with, inter alia, an acceptable carrier. The carrier must, of
course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.5% to 95% by weight of the active compound. One or more of each of the active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above).

In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding,
in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations may be administered by means of subcutaneous, intravenous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, Pharmaceutical Research 3:318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound.

Suitable formulations comprise citrate or bis\(\text{tris}\) buffer (pH 6) or ethanol/water and contain from 0.01 to 0.2M active ingredient.
C. Methods of Use.

In addition to the compounds of the formulas described herein, the present invention also provides useful therapeutic methods. For example, the present invention provides a method of inducing cytotoxicity against tumor cells, or treating a cancer or tumor in a subject in need thereof.

Cancer cells which may be inhibited include cells from skin cancer, small cell lung cancer, non-small cell lung cancer, testicular cancer, lymphoma, leukemia, Kaposi's sarcoma, esophageal cancer, stomach cancer, colon cancer, breast cancer, endometrial cancer, ovarian cancer, central nervous system cancer, liver cancer and prostate cancer.

Subjects which may be treated using the methods of the present invention are typically human subjects although the methods of the present invention may be useful for veterinary purposes with other subjects, particularly mammalian subjects including, but not limited to, horses, cows, dogs, rabbits, fowl, sheep, and the like. As noted above, the present invention provides pharmaceutical formulations comprising the compounds of formulae described herein, or pharmaceutically acceptable salts thereof, in pharmaceutically acceptable carriers for any suitable route of administration, including but not limited to oral, rectal, topical, buccal, parenteral, intramuscular, intradermal, intravenous, and transdermal administration.

The therapeutically effective dosage of any specific compound will vary somewhat from compound to compound, patient to patient, and will depend upon the condition of the patient and the route of delivery. As a general proposition, a dosage from about 0.1 to about 50 mg/kg will have therapeutic efficacy, with still higher dosages potentially being employed for oral and/or aerosol administration. Toxicity concerns at the higher level may restrict intravenous dosages to a lower level such as up to about 10 mg/kg, all weights being calculated based upon the weight of the active base, including the cases where a salt is employed. Typically a dosage from about 0.5 mg/kg to about 5 mg/kg will be employed for intravenous or intramuscular
administration. A dosage from about 10 mg/kg to about 50 mg/kg may be employed for oral administration.

The present invention is explained in greater detail in the following non-limiting examples.

Example 1

Synthesis and Biological Evaluation of Novel Substituted FNO (2-[furan-2-yl] naphthalen-1-ol) Derivatives as Anti-Cancer Agents

To study the individual contribution of the A-, C-, and D-rings of compound 1 to the selective activity against breast cancer cells, we first prepared four novel ring opened model compounds (4-7) (Scheme 2). Preliminary structural-activity study results showed that only compound 5 with an opened C-ring (cleavage of bond 2) showed significant anti-breast cancer cytotoxic activity (less than two-fold lower potency than the parent compound 3 against MCF-7 cell replication). Further structural modification of compound 5 generated a series of 2-(furan-2-yl) naphthalen-1-ol derivatives, especially compound 19, which retained potent anti-breast cancer cytotoxic activity as well as high selectivity against different breast cancer cell lines. Interestingly, a close structurally related derivative compound 21 showed broad in vitro cytotoxicity against all human cancer cell lines tested. Preliminary pharmacophore study and dihedral energy analysis demonstrated that compound 19 could form a conformation close to the tetracyclic structure of 1 and 2 via intramolecular hydrogen bonding. In comparison, the conformation of compound 21 was more flexible, which could account for the broader spectrum of activity we observed.
Scheme 2. Design of ring-opened model compounds (4-7)

As a first step in the current work, we investigated the individual contribution of A-, C-, and D-rings of the neo-tanshinlactone molecule to the biological activity. Systematic structural simplification of compound 3 by removal of A-, C-, and D-rings afforded the model compounds 4-7, respectively (Scheme 2). The chemistry for the synthesis of target compounds is illustrated in Scheme 3. Intermediate compound 9 was obtained via a tandem alkylation/intramolecular aldolisation reaction with commercially available compound 8. Compound 4 was obtained by treatment of 9 with boron tribromide at 50 °C and 2-iodopropane to remove the methyl group and install an isopropyl group. Compound 5 was synthesized through hydrolysis of the lactone ring of compound 10. Compound 11 underwent an esterification reaction with furan-3-carbonyl chloride to provide compound 6. Compound 7 was synthesized through a substitution reaction from compound 12.

Scheme 3

Reagents and conditions: (a) HOAc, NH$_2$OAc, chloroacetone, toluene, EtOH, 95 °C, 65%; (b) (i) BBr$_3$, DCM, 50°C; (ii) 2-iodopropane, CsCO$_3$, DMF, 50°C, 30%; (c) 5% NaOH(aq), reflux, 93%; (d) furan-3-carbonyl chloride, DIEA, DMAP, DMF, 46%; (e) 3-bromoprop-1-yn, K$_2$CO$_3$, acetone.
Compounds 4-7 were tested for in vitro anticancer activity against two human breast cancer cell lines MCF-7 (ER+) and SK-BR-3 (HER2+) (Table 1). Compound 4, without an A-ring moiety, showed much lower activity than its tetracyclic analog 3. The activity of compound 5, a C-ring opened compound, was comparable to that of the ring-closed compound 3 against MCF-7 replication (less than twofold difference). However, compound 6, a bond-3 cleaved C-ring opened compound, was inactive against the tested breast cancer cells. Compound 7, a D-ring opened compound, showed marginal activity against the two breast cancer cell lines. The results demonstrated that the A-ring and D-ring are important in maintaining the molecule's biological activity. The explanation for the SAR results may be that intramolecular hydrogen bonding between –COOH and OH groups in compound 5 maintains the structural conformation in a more ring-like structure. Interestingly, a tetracycle-formed structure seems essential for the interaction of drug ligands with the binding site(s) on ER or ER-related breast cancer cell growth factor, such as HER2.

**Table 1.** In vitro Anticancer Activity of Compounds 3-7 against Breast Cancer Cell Lines

<table>
<thead>
<tr>
<th>compounds</th>
<th>MCF-7(ER+)</th>
<th>SK-BR-3 (HER2+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>12.0</td>
<td>10.8</td>
</tr>
<tr>
<td>5</td>
<td>6.0</td>
<td>7.0</td>
</tr>
<tr>
<td>6</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>7</td>
<td>20.0</td>
<td>16.0</td>
</tr>
</tbody>
</table>

mean ED<sub>50</sub> (µg/mL), Standard error of independent determinations was less than 5%.

Compound 5 was selected for further structure optimization in order to develop SAR and to identify more active derivatives with the desired biological properties. We expected that substitutions around the 5-scaffold could affect the three-dimensional structure of the molecule and also target interaction, which will translate into changes in anti-breast cancer activity. This
speculation prompted us to design, synthesize, and test 12 new analogues (Scheme 4, Table 2). Hydrolysis of compound 13 afforded compound 14. Methylation of compound 14 was achieved by using the phase transfer agent 18-crown-6 as reported by Stephen A. Glover. Compound 16 was synthesized with thionyl chloride and methanol at room temperature. Compound 18 was obtained by reduction of compound 13 with lithium aluminum hydride.

Scheme 4

Reagents and conditions: (a) 5% NaOH (aq), reflux; (b) 18-crown-6, Mel, CH₃CN, 90 °C; (c) SOCl₂, MeOH, rt; (d) LiAlH₄, THF.

In order to test for a potential relationship between the intramolecular hydrogen bond (COOH- and OH-groups) and the selective in vitro anti-breast cancer activity, a specific target (19-21) sub-set was designed. Compound 19, with OH-group at R₄ position and COOH-group at R₅ position, could form an intramolecular hydrogen bond. Compound 20 was obtained through methylation of the hydroxy group in compound 19, which effectively removed one hydrogen donor. In addition, both hydrogen bond donors of compound 19 were blocked with methyl groups affording compound 21. Compounds 22-30 were designed to further study the SAR. The newly synthesized analogues (19-30) were initially tested for in vitro anticancer activity against two human breast cancer cell lines: MCF-7 (ER+) and SK-BR-3 cells (HER2+) (Table 2). Both compound 19 and 21 showed similar activity to TAM with ED₅₀ values of 3.3 μg/mL and 2.5 μg/mL against MCF-7, while compound 19 showed five
times better activity than TAM, with ED₅₀ values of 0.95 μg/mL against SK-BR-3 cells, and compound 21 showed about four times better activity than TAM, with ED₅₀ values of 1.2 μg/mL against SK-BR-3 cells. Compound 20 displayed similar activity to TAM. The SAR study suggested that R₁ position influenced the in vitro anticancer activity and hydrophobic groups were favored from the ED₅₀ values of compounds 19, 22, and 23. R₂ position preferred a methyl group to an ethyl group (19 vs 26). R₃ position favored a hydrogen rather than a methyl group (19 vs 27).

**Table 2. Structure and cytotoxicity of analogs (19-30)**

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>(ER⁺)</th>
<th>(HER2⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>19</td>
<td>Et</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>COOH</td>
<td>3.3</td>
</tr>
<tr>
<td>20</td>
<td>Et</td>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>COOH</td>
<td>4.3</td>
</tr>
<tr>
<td>21</td>
<td>Et</td>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>COOMe</td>
<td>2.5</td>
</tr>
<tr>
<td>22</td>
<td>OMe</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>COOH</td>
<td>23</td>
</tr>
<tr>
<td>23</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>COOH</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>COOH</td>
<td>18</td>
</tr>
<tr>
<td>25</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>OMe</td>
<td>COOMe</td>
<td>8.5</td>
</tr>
<tr>
<td>26</td>
<td>Et</td>
<td>Et</td>
<td>H</td>
<td>OH</td>
<td>COOH</td>
<td>5.1</td>
</tr>
<tr>
<td>27</td>
<td>Et</td>
<td>Me</td>
<td>Me</td>
<td>OH</td>
<td>COOH</td>
<td>8.5</td>
</tr>
<tr>
<td>28</td>
<td>OEt</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>COOH</td>
<td>7.5</td>
</tr>
<tr>
<td>29</td>
<td>Et</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>CH₂OH</td>
<td>12</td>
</tr>
<tr>
<td>30</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>CH₂OH</td>
<td>7</td>
</tr>
</tbody>
</table>
mean ED$_{50}$ (µg/mL). Standard error of independent determinations was less than 5%.

To examine the question of human tumor-tissue-type selectivity, active compounds 19, 21, and 22 (ED$_{50}$ values >4.0 µg/mL were considered not active) were selected to test against a limited but diverse human cancer cell lines using compound 2 as a positive control and "gold-standard". Compound 19 and 22 were only active against certain breast cancer cell lines and not active against other tumor tissue cells tested, such as lung cancer cell line A549 or prostate cancer cell line DU145, which demonstrated that these two compounds had high tissue selectivity. More interestingly, compounds 19 and 22 also showed very high selectivity against different breast cancer cell lines. Compound 19 was ten times more potent against ZR-7-51 (ER+,HER2+) (ED$_{50}$ values of 0.3 µg/mL) than MCF-7 (ER+) (ED$_{50}$ values of 3.3 µg/mL) and three times more potent against ZR-7-51 (ER+,HER2+) than SK-BR-3 (HER2+) (ED$_{50}$ values of 0.9 µg/mL). Compound 22 was 38 times more potent against ZR-7-51 (ER+,HER2+) (ED$_{50}$ values of 0.6 µg/mL) than MCF-7 (ER+) (ED$_{50}$ values of 23 µg/mL) and 6 times more potent against ZR-7-51 (ER+,HER2+) than SK-BR-3 (HER2+) (ED$_{50}$ values of 3.5 µg/mL). Compound 2 was three times more potent against ZR-7-51 than MCF-7 and had similar potency against ZR-7-51 and SK-BR-3. Thus, compounds 19 and 22 were more potent against ZR-75-1 cell line than cell lines over-expressing either ER or HER2 (MCF-7 or SK-BR-3), and much more potent than cell lines not over-expressing ER or HER2 (remaining cells of the panel). Unexpectedly, compound 21 showed potent activity against all cancer cell lines tested.
Table 3. Cytotoxicity of Compounds against Tumor Cell Lines

<table>
<thead>
<tr>
<th></th>
<th>MCF-7 (ER+)</th>
<th>SK-BR-3 (HER2+)</th>
<th>ZR-75-1 (ER+,HER2+)</th>
<th>MDA MB-231 (ER-)</th>
<th>A549</th>
<th>DU145</th>
<th>KB</th>
<th>KBvin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>&gt;10</td>
<td>10.6</td>
<td>15.9</td>
<td>13.1</td>
<td>13.2</td>
</tr>
<tr>
<td>19</td>
<td>3.3</td>
<td>1.0</td>
<td>0.3</td>
<td>&gt;10</td>
<td>10.6</td>
<td>8.7</td>
<td>9.1</td>
<td>7.0</td>
</tr>
<tr>
<td>21</td>
<td>2.5</td>
<td>1.2</td>
<td>1.3</td>
<td>2.3</td>
<td>1.5</td>
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<tr>
<td>22</td>
<td>23</td>
<td>3.5</td>
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<td>&gt;10</td>
<td>10.1</td>
<td>8.2</td>
<td>9.7</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Mean ED$_{50}$ (µg/mL). Standard error of independent determinations was less than 5%.

In summary, current data has led to new developments and insights about the neo-tanshinlactone-based selective breast cancer actives. We demonstrated that aromatic rings A and D were important for the activity. Importantly, we discovered that ring C could be opened through hydrolysis of the ester bond while keeping the desired biological activity. A new class of C-ring opened compounds, 2-(furan-2-yl) naphthalen-1-ol derivatives, was subsequently developed. Compounds 19 and 22 exhibited much higher selectivity against certain breast cancer cell lines than neo-tanshinlactone analog compound 2. In addition, compound 21 had potent activity against all cell lines tested, suggesting a different mechanism of action from its structural derivatives. Conformational analysis and dihedral energy analysis of compounds 19 and 21 proved that intramolecular hydrogen bonding was important to form a rigid conformation and improved the in vitro anticancer selectivity of compound 19. Overall, these results establish a new scaffold as a promising structure for the development of investigational anti-breast cancer agents, and novel target compounds incorporating the important structural features identified herein are being synthesized for testing and will be reported in due course.

Example 2

Tanshinone I (1) and tanshinone IIA (2) differ structurally in the ring-A system: the former has an aromatic ring, while the latter has a non-aromatic ring
(Figure 1). Compounds 1 and 2 have been studied extensively for their antitumor effects, and display different activities and selectivities. Recent studies indicated that 1 reduced metastasis and tumorigenesis by inhibition of IL-8, while 2 induced cell differentiation and apoptosis. Neo-tanshinlactone (3) (Figure 1), reported by our group previously, showed significant and selective in vitro anti-breast cancer activity. We further studied how the individual rings in 3 influence the in vitro activity, and the results led to the discovery of a novel class of potential anti-breast cancer agents, 2-(furan-2-yl)naphthalen-1-ol derivatives, such as analog 4. However, it remained unclear how ring A affects the activity and selectivity of 3- and 4-analogs. To answer this question, we designed derivatives with two new scaffolds, tetrahydroteanoshinlactone (5, TNT) and tetrahydronaphthalene-1-ol (6, TNO). Like 2, both TNT and TNO derivatives have a non-aromatic ring-A. Different ring sizes, including five- and six-membered rings, were studied, and 14 new analogs were designed. Described below are the synthesis and biological evaluation of 5- and 6-analogs.
Figure 1. Structures of tanshinone I (1), tanshinone IIA (2), neotanshininlactone (3), analog 4, and two newly designed scaffolds 5-6

As shown in Scheme 5, compound 8 was synthesized by Negishi cross-coupling reaction of compound 7 with 4-methylpent-3-enyl zinc(II) bromide in 96% yield. Treatment of 8 with AlCl₃ followed by demethylation gave 9 in 84% yield. Compounds 10 and 11, with five- and six-membered rings, respectively, are commercially available. Compounds 9-11 underwent the previously reported two-step ring closure reactions to afford furochromenones 15-17, which were hydrolyzed by using sodium hydroxide to give ring-opened compounds 18-20. Compound 20, with gem-dimethyl substitution on ring-A, showed significant cytotoxic activity (Table 4), and was chosen for further modification to study the functions of the hydroxyl and carboxylic acid groups (21-28). The selective methylation of the hydroxy group on 20 was achieved by the addition of Mel and 18-crown-6 ether to the crude hydrolysis mixture of 17 without work-up. The resulting carboxylic acid 21 was converted to methyl ester 22 with thionyl chloride and MeOH at room temperature. Meanwhile, the reduction of 20 with lithium aluminum hydride afforded diol 23, which was treated with iodomethane and iodoethane in the presence of Cs₂CO₃ to generate ethers 24 and 25, respectively. The remaining primary alcohol of 24 was alkylated with iodomethane and iodoethane in the presence of NaH to obtain 26 and 27, respectively. Acetate 28 was obtained by acetylation of 24 with Ac₂O.
Reactions and conditions: (a) 4-methylpent-3-enylzinc(II) bromide, Pd(Cl\(_2\))(dpdf), THF, reflux, 1h; (b) (i) AlCl\(_3\), DCM, 0 °C, 15 min; (ii) BBr\(_3\), CH\(_2\)Cl\(_2\); (c) malonic acid, PPA, 75 °C, 3 h; (d) chloroacetone, HOAc/NH\(_2\)OAc, toluene/EtOH, reflux, 24 h; (e) 5% NaOH (aq), reflux; (f) NaOH, 18-crown-6, Mel, CH\(_3\)CN, 90 °C; (g) SOCl\(_2\), MeOH, rt; (h) LiAlH\(_4\), THF; (i) Mel or EtI, Cs\(_2\)CO\(_3\), acetone, 50 °C; (g) Mel or EtI, NaH, THF, rt; (k) Ac\(_2\)O, Et\(_3\)N, DMAP, CH\(_2\)Cl\(_2\).
Table 4. *In Vitro* Cytotoxic Activity of 15-28

<table>
<thead>
<tr>
<th>Compd</th>
<th>SK-BR-3</th>
<th>ZR-75-1</th>
<th>MDA-MB-231</th>
<th>A549</th>
<th>DU145</th>
<th>KB</th>
<th>KB-vin</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.8</td>
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<td>54.2</td>
<td>58.3</td>
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<td>&gt;37</td>
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<td>1.0</td>
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Mean ED$_{50}$ (µM), Standard error of independent determinations was less than 5%.

The newly synthesized analogs 15-28 were tested for *in vitro* cytotoxic activity against a panel of human tumor cell lines according to previously published
methods (Table 4).^{11} Cell lines include: SK-BR-3 (estrogen receptor negative, HER2 over-expressing breast cancer), ZR-75-1 (estrogen receptor positive breast cancer), MDA-MB-231 (estrogen receptor negative breast cancer), A549 (non small cell lung cancer), DU145 (prostate cancer cell line), KB (nasopharyngeal carcinoma), and KB-vin (vincristine-resistant MDR KB subline).

Among the three tetrahydronoctanolinactone (TNT) derivatives, 15 showed no activity against any tumor cell line tested, which suggested that the five-membered ring A was not favored. Compound 16 was three- to seven-fold more potent than 17 against SK-BR-3, ZR-75-1, A549, and KB-vin cell lines. However, while 16 was less potent compared with 3 against SK-BR-3 and ZR-75-1 breast cancer cell lines, it also showed a broader antitumor spectrum, with greatly enhanced potency against A549 and KB-vin. The results suggested that ring-A could affect the potency and tumor-tissue type selectivity dramatically.

Among tetrahydronaphthalene-1-ol (TNO) derivatives, compounds 18 and 19 displayed only marginal antitumor activity, while 20 showed potent and broad antitumor activity against all tumor cell lines tested (ED$_{50}$ 0.7 μM against SK-BR-3; 1.7 μM against ZR-75-1). Thus, a non-aromatic six-membered ring-A with gem-dimethyl substitution was favored for cytotoxic activity, in comparison with unsubstituted five- and six-membered rings. As to the tumor-tissue type selectivity, 20 was significantly active against all tumor cell lines tested except MDA-MB-231, while 3 and 4 were active against two of the breast cancer cell lines, though in contrast to 20, they lack the gem dimethyls and are essentially planar. These results demonstrated that, by changing the molecular conformation and orientation, introduction of a non-aromatic ring-A could greatly influence the antitumor activity against all cell types. In our prior SAR studies of neo-tanshinlanctone (3) and the ring-opened analog 4, the presence of two functional groups from the opened lactone ring-C was critical for antitumor activity, which encouraged us to study comparable derivatives of 20 with ether and ester groups of various sizes. As seen in Table 4, 21-28 showed only moderate to marginal activity against all tumor cell lines tested, but interestingly, still displayed low sensitivity against MDA-MB-231 compared
with other tumor cell lines. For example, 25 and 28 showed four-fold higher potency against SK-BR-3 than MDA-MB-231. In summary, the current SAR study indicated that the optimal substituents on the phenyl and furanyl rings are hydroxy and carboxylic acid groups. The preliminary results indicated that the identities of the ring A, hydroxy, and carboxylic acid groups are important to antitumor activity and selectivity. More analogs will be synthesized and evaluated to establish detailed structure-activity relationships (SAR) of this new series of compounds.

In conclusion, tetrahydronotanshinlactone (TNT) and tetrahydronaphthalene (TNO) derivatives were prepared in order to investigate the effect of the non-aromatic ring-A on in vitro antitumor activity. The results indicated that a non-aromatic ring-A could dramatically affect both activity and tumor cell line selectivity, particularly the non-breast cell lines that were studied. Based on this study, a novel class of antitumor agents, TNO derivatives, was discovered and developed. Compound 20 was the most potent analog with an ED$_{50}$ value of 0.7 µM against the SK-BR-3 cell line, and showed broader antitumor activity compared with 3 and 4. Further SAR and mechanism of action studies are ongoing and progress will be reported in due course. In summary, 20 is a promising new lead compound with a novel skeleton for further development toward a new potential clinical trials candidate.

Spectroscopic data:

1-Methyl-7,8-dihydrocyclopenta[h]furo[3,2-c] chromen-10(6H) - one (15): $^1$H NMR (300 MHz, CDCl$_3$, ppm): δ 2.19 (s, J = 7.5 Hz, 2H, CH$_2$CH$_2$CH$_2$), 2.36 (d, J = 1.5 Hz, 3H, CH$_3$), 3.04 (t, J = 7.5 Hz, 2H, CH$_2$CH$_2$CH$_2$), 3.14 (t, J = 7.5 Hz, 2H, CH$_2$CH$_2$CH$_2$), 7.19 (d, J = 7.8 Hz, 1H, aromatic), 7.36 (q, J = 1.2 Hz, 1H, OCH$_3$), 7.63 (d, J = 8.1 Hz, 1H, aromatic); HRMS Calcd for C$_{15}$H$_{13}$O$_3$ (M+H$^+$): 241.0859, found: 241.0858.

1-Methyl-8,9-dihydro-6H-benzo[h]furo[3,2-c]chromen-11(7H)-one (16): $^1$H NMR (300 MHz, CDCl$_3$, ppm): δ 1.80-1.86 (m, 4H, CH$_2$CH$_2$CH$_2$CH$_2$), 2.35 (d, J = 1.2 Hz, 3H, CH$_3$), 2.84 (t, J = 5.7 Hz, 2H, CH$_2$CH$_2$CH$_2$CH$_2$), 2.94 (t, J = 6.0 Hz, 2H, CH$_2$CH$_2$CH$_2$CH$_2$), 7.01 (d, J = 8.4 Hz, 1H, aromatic), 7.34 (d, J = 0.9 Hz, 1H, OCH$_3$), 7.51 (d, J = 8.1 Hz, 1H, aromatic); HRMS Calcd for C$_{16}$H$_{15}$O$_3$ (M+H$^+$): 255.1016, found: 255.1012.
38% yield; mp 101-103 °C; 1H NMR (300 MHz, CDCl3, ppm): δ 1.33 (s, 6H, C(CH3)2), 1.67-1.71 (m, 2H, CCH2CH2CH2), 1.84-1.88 (m, 2H, CCH2CH2CH2), 2.35 (d, J = 1.2 Hz, 3H, CH3), 2.97 (t, J = 6.3 Hz, 2H, CCH2CH2CH2), 7.32 (d, J = 8.4 Hz, 1H, aromatic), 7.35 (q, J = 1.2 Hz, 1H, OCH3), 7.61 (d, J = 8.7 Hz, 1H, aromatic); HRMS Calcd for C18H19O3 (M+H+) : 283.1329, found: 283.1315.

2-(4-Hydroxy-2,3-dihydro-1H-inden- 5-yl)-4-methylfuran-3-carboxylic acid (18):
1H NMR (300 MHz, CD3OD, ppm): δ 2.06 (p, J = 7.5 Hz, 2H, CH2CH2CH2), 2.20 (d, J = 0.9 Hz, 3H, CH3), 2.89 (q, J = 7.5 Hz, 4H, CH2CH2CH2), 4.94 (s, 1H, OCH3), 6.83 (d, J = 7.8 Hz, 1H, aromatic), 7.14 (d, J = 7.8 Hz, 1H, aromatic), 7.30 (d, J = 0.9 Hz, 1H, OCH3); MS: m/z 257 (M-H+).

2-(1-Hydroxy-5,6,7,8-tetrahydroanaphthalen-2-yl)-4-methylfuran-3-carboxylic acid (19): 1H NMR (300 MHz, CD3COCD3, ppm): δ 1.75-1.77 (m, 4H, CH2), 2.20 (d, J = 1.2 Hz, 3H, CH3), 2.69-2.75 (m, 4H, CH2), 6.67 (d, J = 8.4 Hz, 1H, aromatic), 7.10 (d, J = 8.4 Hz, 1H, aromatic), 7.43 (s, 1H, OCH3); HRMS Calcd for C16H15O4 (M-H+): 271.0970, found: 271.0971.

2-(1-Hydroxy-5,5-dimethyl-5,6,7,8-tetrahydroanaphthalen-2-yl)-4- methylfuran-3-carboxylic acid (20): 1H NMR (300 MHz, CD3OD, ppm): δ 1.28 (s, 6H, C(CH3)2), 1.62-1.66 (m, 2H, CH2), 1.78-1.82 (m, 2H, CH2), 2.21(d, J = 1.5 Hz, 3H, CH3), 2.70 (t, J = 6.3 Hz, 2H, CH2), 6.96 (d, J = 8.4 Hz, 1H, aromatic), 7.13 (d, J = 8.4 Hz, 1H, aromatic), 7.33 (d, J = 1.2 Hz, 1H, OCH3); HRMS Calcd for C18H19O4 (M-H+): 301.1434, found: 301.1425.

2-(1-Methoxy-5,5-dimethyl-5,6,7,8-tetrahydroanaphthalen-2-yl)-4- methylfuran-3-carboxylic acid (21): 1H NMR (300 MHz, CDCl3, ppm): δ 1.30 (s, 6H, C(CH3)2), 1.63-1.67 (m, 2H, CCH2CH2CH2), 1.77-1.83 (m, 2H, CCH2CH2CH2), 2.36 (d, J = 0.9 Hz, 3H, CH3), 2.76 (t, J = 6.3 Hz, 1H, CCH2CH2CH2), 3.52 (s, 3H, OCH3), 7.16 (d, J = 8.4 Hz, 1H, aromatic), 7.23 (d, J = 8.4 Hz, 1H, aromatic), 7.29 (d, J = 1.5 Hz, 1H, OCH3); MS: m/z 315 (M-H+).

Methyl 2-(1-methoxy-5,5-dimethyl-5,6,7,8- tetrahydroanaphthalen-2-yl)-4- methylfuran-3-carboxylate (22): 1H NMR (300 MHz, CDCl3, ppm): δ 1.30 (s, 6H, C(CH3)2), 1.63-1.67 (m, 2H, CCH2CH2CH2), 1.77-1.83 (m, 2H, CCH2CH2CH2), 2.20 (d, J = 1.2 Hz, 3H, CH3), 2.75 (t, J = 6.3 Hz, 1H, CCH2CH2CH2), 3.46 (s, 3H, OCH3), 3.72 (s, 3H, COOCH3), 7.14 (d, J = 8.1 Hz, 1H, aromatic), 7.23 (d, J = 8.1 Hz, 1H, aromatic), 7.27 (d, J = 0.9 Hz, 1H, OCH3); MS: m/z 329 (M-H+). 2-(3-

(Hydroxymethyl)-4-methylfuran-2-yl)-5,5-dimethyl-5,6,7,8- tetrahydroanaphthalene-1-ol (23): 1H NMR (300 MHz, CDCl3, ppm): δ 1.30 (s, 6H, C(CH3)2), 1.63-1.67 (m, 2H, CCH2CH2CH2), 1.80-1.84 (m, 2H, CCH2CH2CH2), 2.11 (d, J = 0.9 Hz, 3H, CH3), 2.71 (t, J = 6.3 Hz, 2H, CCH2CH2CH2), 4.58 (s, 1H, CH2OH), 6.97 (d, J = 8.4 Hz, 1H, aromatic), 7.20
(d, J = 8.4 Hz, 1H, aromatic), 7.28 (d, J = 0.9 Hz, 1H, OCH); MS: m/z 385 (M-H^+).

(2-(1-methoxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4-methylfuran-3-yl)methanol (24): ^1^H NMR (300 MHz, CDCl₃, ppm): δ 1.30 (s, 6H, (CH₃)₂), 1.64-1.68 (m, 2H, CCH₂CH₂CH₂), 1.77-1.83 (m, 2H, CCH₂CH₂CH₂), 2.12 (d, J = 0.9 Hz, 3H, CH₃), 2.69 (t, J = 6.3 Hz, 1H, CH₂OH), 2.77 (t, J = 6.3 Hz, 2H, CCH₂CH₂CH₂), 3.46 (s, 3H, OCH₃), 4.41 (d, J = 5.7 Hz, 2H, CH₂OH), 7.16-7.22 (m, 2H, aromatic), 7.27 (d, J = 0.9 Hz, 1H, OCH); MS: m/z 323 (M+Na^+).

(2-(1-Ethoxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4-methylfuran-3-yl)methanol (25): ^1^H NMR (300 MHz, CDCl₃, ppm): δ 1.18 (t, J = 7.2 Hz, 3H, CH₃CH₂), 1.30 (s, 6H, (CH₃)₂), 1.64-1.68 (m, 2H, CCH₂CH₂CH₂), 1.77-1.83 (m, 2H, CCH₂CH₂CH₂), 2.12 (d, J = 0.9 Hz, 3H, CH₃), 2.76 (t, J = 6.3 Hz, 1H, CCH₂CH₂CH₂), 2.87 (br, 1H, CH₂OH), 3.58 (q, J = 7.2 Hz, 2H, CCH₂CH₃), 4.39 (s, 2H, CH₂OH), 7.18 (s, 2H, aromatic), 7.26 (d, J = 0.3 Hz, 1H, OCH); MS: m/z 313 (M-H^+).

2-(1-Methoxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-3-(methoxymethyl)-4-methylfuran (26). 44 % yield; ^1^H NMR (300 MHz, CDCl₃, ppm): δ 1.30 (s, 6H, (CH₃)₂), 1.64-1.67 (m, 2H, CCH₂CH₂CH₂), 1.77-1.83 (m, 2H, CCH₂CH₂CH₂), 2.10 (d, J = 1.2 Hz, 3H, CH₃), 2.77 (t, J = 6.3 Hz, 1H, CCH₂CH₂CH₂), 3.33 (s, 3H, CH₂OCH₃), 3.49 (s, 3H, OCH₃), 4.32 (s, 2H, CH₂OCH₃), 7.17 (dd, J = 8.4 Hz, 2H, aromatic), 7.28 (d, J = 1.2 Hz, 1H, OCH); MS: m/z 315 (M+H^+).

2-(1-Ethoxy-5,5-dimethyl-5,6,7,8- tetrahydronaphthalen-2-yl)-3-(methoxymethyl)-4-methylfuran (27): ^1^H NMR (300 MHz, CDCl₃, ppm): δ 1.19 (t, J = 7.2 Hz, 3H, CH₂CH₃), 1.30 (s, 6H, (CH₃)₂), 1.64-1.67 (m, 2H, CCH₂CH₂CH₂), 1.77-1.83 (m, 2H, CCH₂CH₂CH₂), 2.09 (d, J = 0.9 Hz, 3H, CH₃), 2.77 (t, J = 6.3 Hz, 1H, CCH₂CH₂CH₂), 3.32 (s, 3H, CH₂OCH₃), 3.59 (q, J = 6.9 Hz, 2H, CH₂CH₃), 4.32 (s, 2H, CH₂OCH₃), 7.16 (dd, J = 8.1 Hz, 2H, aromatic), 7.26 (d, J = 0.9 Hz, 1H, OCH); MS: m/z 329 (M+H^+).

(2-(1-Methoxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4-methylfuran-3-yl)methyl acetate (28): ^1^H NMR (300 MHz, CDCl₃, ppm): δ 1.30 (s, 6H, (CH₃)₂), 1.63-1.67 (m, 2H, CCH₂CH₂CH₂), 1.77-1.83 (m, 2H, CCH₂CH₂CH₂), 2.06 (s, 3H, CH₂OCOCH₃), 2.06 (d, J = 0.9 Hz, 3H, CH₃), 2.76 (t, J = 6.3 Hz, 1H, CCH₂CH₂CH₂), 3.48 (s, 3H, OCH₃), 5.01 (s, 2H, CH₂OCOCH₃), 7.13-7.19 (m, 2H, aromatic), 7.30 (d, J = 1.2 Hz, 1H, OCH); MS: m/z 365 (M+Na^+).
References


What is claimed is:

1. A compound of Formula I:

```
R1A, R1B, R2A, R2B, R3A, R3B, R4A, R4B, R5, R6, R7, R8, R9, R', and R'' are each independently selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R10, OC(=O)OR10, OC(=O)N(R10)2, O(CH2)mN(R10)2, C(=O)N(R10)2, and O(CH2)mCOOR10 where m is 1-5 and R10 is H or lower alkyl;

or R' and R1A together form a covalent bond;

or R1B and R2A together form a covalent bond;

or R2B and R3A together form a covalent bond;

or R3B and R4A together form a covalent bond;

or R4B and R'' together form a covalent bond;

or R6 and R9 together form a covalent bond;

or R7 and R8 together form =Z, where Z is selected from the group consisting of O, S, and NH;

X1 is OR11, SR11, N(R11)2, S(O), or S(O2). R11 is selected from the group consisting of H, lower alkyl, heteroaryl, aryl, C(=O)R12, C(=O)OR12, C(=O)N(R12)2, (CH2)mN(R12)2, and (CH2)mCOOR12 where m is 1-5 and R12 is H or lower alkyl;
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X₂ is C(=O)R₁₃, C(=S)R₁₃, C(=NR₁₄)R₁₃, CH₂R₁₃, S(O), or S(O₂). R₁₃ is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl. R₁₄ is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl;

or X₁ and X₂ together form a covalent linking group selected from the group consisting of –O-C(=O)–, –S-C(=O)–, –N(R₁₁)–C(=O)–, –S(O)–C(=S)–, –S(O₂)–C(=S)–, –O-C(=S)–, –S-C(=SR₁₄)–, –N(R₁₄)–C(=NR₁₄)–, –S(O)–C(=NR₁₄)–, –S(O₂)–C(=NR₁₄)–, –O-CHR₁₃–, –S-CHR₁₃–, or –N(R₁₁)-CHR₁₃–, –S(O)-CHR₁₃–, –S(O₂)-CHR₁₃–, –O-S(O)–, –S-S(O)–, –N(R₁₁)-S(O)–, –S(O)-S(O)–, –S(O₂)-S(O)–, –O-S(O₂)–, –S-S(O₂)–, –N(R₁₁)-S(O₂)–, –S(O)-S(O₂)–, –S(O₂)-S(O₂)–;

X₃ is selected from the group consisting of O, S, NH to form a heterocycle, and (CH₂)ₚ where p is 1-2;

n is 0 or 1;

or a pharmaceutically acceptable salt or prodrug thereof.

2. The compound of claim 1, wherein n is 0.

3. The compound of claim 1, wherein n is 1.

4. The compound of any of claims 1-3, wherein X₁ and X₂ together form a covalent linking group selected from the group consisting of –O-C(=O)–, –S-C(=O)–, –N(R₁₁)-C(=O)–, –S(O)-C(=O)–, –S(O₂)-C(=O)–, –O-C(=S)–, –S-C(=S)–, –N(R₁₁)-C(=S)–, –S(O)-C(=S)–, –S(O₂)-C(=S)–, –O-C(=NR₁₄)–, –S-C(=NR₁₄)–, –N(R₁₁)-C(=NR₁₄)–, –S(O)-C(=NR₁₄)–, –S(O₂)-C(=NR₁₄)–, –O-CHR₁₃–, –S-CHR₁₃–, or –N(R₁₁)-CHR₁₃–, –S(O)-CHR₁₃–, –S(O₂)-CHR₁₃–, –O-S(O)–, –S-S(O)–, –N(R₁₁)-S(O)–, –S(O)-S(O)–, –S(O₂)-S(O)–, –O-S(O₂)–, –S-S(O₂)–, –N(R₁₁)-S(O₂)–, –S(O)-S(O₂)–, –S(O₂)-S(O₂)–.

5. The compound of any of claims 1-4, wherein R₁₆, R₁₈, R₂₆, R₂₈, R₃₆, R₄₆, R₅, R₆, R₇, R₈, R₉, R', and R" are each independently selected
from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoaalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R_{10}, OC(=O)OR_{10}, OC(=O)N(R_{10})_2, O(CH_2)mN(R_{10})_2, C(=O)N(R_{10})_2, and O(CH_2)mCOOR_{10} where m is 1-5 and R_{10} is H or lower alkyl.

6. The compound of any of claims 1-5, wherein R_{4A} and R_{4B} are each independently selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoaalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R_{10}, OC(=O)OR_{10}, OC(=O)N(R_{10})_2, O(CH_2)mN(R_{10})_2, C(=O)N(R_{10})_2, and O(CH_2)mCOOR_{10} where m is 1-5 and R_{10} is H or lower alkyl.

7. The compound of any of claims 1-3 or 5-6, wherein X_1 is OR_{11}, SR_{11}, or N(R_{11})_2, R_{11} is selected from the group consisting of H, lower alkyl, heteroaryl, aryl, C(=O)R_{12}, C(=O)OR_{12}, C(=O)N(R_{12})_2, (CH_2)mN(R_{12})_2, and (CH_2)mCOOR_{12} where m is 1-5 and R_{12} is H or lower alkyl and X_2 is C(=O)R_{13}, C(=S)R_{13}, C(=NR_{14})R_{13}, or CH_2R_{13}. R_{13} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoaalkyl, alkylamino, nitro, heteroaryl, and aryl. R_{14} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl.

8. The compound of any of claims 1-4 or 7, wherein R' and R_{1A}, R_{2B} and R_{3A}, and R_{4B} and R'' together form a covalent bond.

9. A compound of Formula Ia:

![Formula Ia](image)

wherein:

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are each independently selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino,
aminoalkyl, alkylamino, nitro, heteroaryl, aryl, OC(=O)R_{10}, OC(=O)OR_{10}, OC(=O)N(R_{10})_2, O(CH_2)mN(R_{10})_2, C(=O)N(R_{10})_2, and O(CH_2)mCOOR_{10} where m is 1-5 and R_{10} is H or lower alkyl;

or R_3 and R_9 together form a covalent bond;

or R_7 and R_8 together form =Z, where Z is selected from the group consisting of O, S, and NH;

X_1 is OR_{11}, SR_{11}, or N(R_{11})_2. R_{11} is selected from the group consisting of H, lower alkyl, heteroaryl, aryl, C(=O)R_{12}, C(=O)OR_{12}, C(=O)N(R_{12})_2, (CH_2)mN(R_{12})_2, and (CH_2)mCOOR_{12} where m is 1-5 and R_{12} is H or lower alkyl;

X_2 is C(=O)R_{13}, C(=S)R_{13}, C(=NR_{14})R_{13}, or CH_2R_{13}. R_{13} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl. R_{14} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl;

X_3 is selected from the group consisting of O, S, NH to form a heterocycle, and (CH_2)_p where p is 1-2;

or a pharmaceutically acceptable salt or prodrug thereof.

10. The compound of claim 9, wherein X_1 is OR_{11} or SR_{11} and R_{11} is selected from the group consisting of H and lower alkyl.

11. The compound of claim 9, wherein X_1 is OR_{11}, SR_{11}, and R_{11} is selected from the group consisting of heteroaryl, aryl, C(=O)R_{12}, C(=O)OR_{12}, C(=O)N(R_{12})_2, (CH_2)mN(R_{12})_2, and (CH_2)mCOOR_{12} where m is 1-5 and R_{12} is H or lower alkyl.

12. The compound of claim 9, wherein X_1 is N(R_{11})_2, and R_{11} is selected from the group consisting of H and lower alkyl.

13. The compound of claim 9, wherein X_1 is N(R_{11})_2, and R_{11} is selected from the group consisting of heteroaryl, aryl, C(=O)R_{12}, C(=O)OR_{12},
C(=O)N(R_{12})_2, (CH_2)mN(R_{12})_2, and (CH_2)mCOOR_{12} where m is 1-5 and R_{12} is H or lower alkyl.

14. The compound of claim 9-13, wherein X_2 is C(=O)R_{13}, C(=S)R_{13}, C(=NR_{14})R_{13}, or CH_2R_{13}, R_{13} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl, and R_{14} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl.

15. The compound of claim 9-13, wherein X_2 is C(=O)R_{13} or C(=S)R_{13}, and R_{13} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, and halo.

16. The compound of claim 9-13, wherein X_2 is C(=O)R_{13} or C(=S)R_{13}, and R_{13} is selected from the group consisting of amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl.

17. The compound of claim 9-13, wherein X_2 is C(=NR_{14})R_{13} or CH_2R_{13}, R_{13} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, or halo, and R_{14} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl.

18. The compound of claim 9-13, wherein X_2 is C(=NR_{14})R_{13}, or CH_2R_{13}, R_{13} is selected from the group consisting of amino, aminoalkyl, alkylamino, nitro, heteroaryl, and aryl, and R_{14} is selected from the group consisting of H, lower alkyl, hydroxy, lower alkoxy, heteroaryl, and aryl.

19. The compound of claim 9-13, wherein X_2 is COOH.

20. The compound of claim 9-19, wherein X_3 is CH_2, S, or NH.

21. The compound of claim 9-20, wherein R_9 and R_9 together form a covalent bond.

22. The compound of claim 9-20, wherein R_7 and R_8 together form =Z, where Z is selected from the group consisting of O, S, and NH.
23. The compound of claim 9-20, wherein at least one of \( R_1, R_2, R_3, R_4, \)
\( R_5, R_6, R_7, R_8, \) and \( R_9 \) are each independently selected from the group
consisting of \( H, \) lower alkyl, hydroxy, lower alkoxy, halo, amino, aminoalkyl,
alkeylamino, nitro, heteroaryl, aryl, \( OC(=O)R_{10}, OC(=O)OR_{10}, OC(=O)N(R_{10})_2, \)
\( O(CH_2)mN(R_{10})_2, C(=O)N(R_{10})_2, \) and \( O(CH_2)mCOOR_{10} \) where \( m \) is 1-5 and
\( R_{10} \) is \( H \) or lower alkyl.

24. A pharmaceutical formulation comprising a compound of claim 9-23
in a pharmaceutically acceptable carrier.

25. The pharmaceutical formulation of claim 24, wherein said carrier is
an aqueous carrier.

26. A method of treating a cancer, comprising administering to a
human or animal subject in need thereof a treatment effective amount of a
compound of claim 9-22.

27. The method of claim 26, wherein said cancer is selected from the
group consisting of skin cancer, lung cancer, testicular cancer, lymphoma,
leukemia, Kaposi's sarcoma, esophageal cancer, stomach cancer, colon
cancer, breast cancer, endometrial cancer, ovarian cancer, central nervous
system cancer, liver cancer and prostate cancer.

28. The method of claim 26, wherein said cancer is breast cancer.

29. The use of a compound of claim 9-23 for treating cancer, or for the
preparation of a medicament for treating cancer.

30. The use of claim 29, wherein said cancer is selected from the
group consisting of skin cancer, lung cancer, testicular cancer, lymphoma,
leukemia, Kaposi's sarcoma, esophageal cancer, stomach cancer, colon
cancer, breast cancer, endometrial cancer, ovarian cancer, central nervous
system cancer, liver cancer and prostate cancer.

31. The use of claim 29, wherein said cancer is breast cancer.