ANTIANGIOGENIC COMBINATION THERAPY FOR THE TREATMENT OF CANCER

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Field of the Invention

The present invention relates to methods, combinations and compositions for treating, preventing or reducing the risk of developing a neoplasia disorder in a mammal.

Background of the Invention

Cancer is now the second leading cause of death in the United States. In 1995 over 8,000,000 persons in the United States have been diagnosed with cancer and has accounted for 23.3% of all reported deaths.

Cancer is not fully understood on the molecular level. It is known that exposure of a cell to a carcinogen such as certain viruses, certain chemicals, or radiation, leads to DNA alteration that inactivates a "suppressive" gene or activates an "oncogene." Suppressive genes are growth regulatory genes, which upon mutation, can no longer control cell growth. Oncogenes are initially normal genes (called prooncogenes) that by mutation or altered context of expression become transforming genes. The products of transforming genes cause inappropriate cell growth. More than twenty different normal cellular genes can become oncogenes by genetic alteration. Transformed cells differ from normal cells in many ways, including cell morphology, cell-to-cell interactions, membrane content, cytoskeletal structure, protein secretion, gene expression and mortality (transformed cells can grow indefinitely).

A neoplasm, or tumor, is an abnormal, unregulated, and disorganized proliferation of cell growth, and is generally referred to as cancer. A neoplasm is malignant, or cancerous, if it has properties of destructive growth, invasiveness and metastasis. Invasiveness refers to the local spread of a neoplasm by infiltration or destruction of surrounding tissue, typically breaking through the basal laminas that define the boundaries of the tissues, thereby often entering the body's circulatory system. Metastasis typically refers to the dissemination of tumor cells by lymphotics or blood vessels. Metastasis also refers to the migration of tumor cells by direct extension through serous cavities, or subarachnoid or other spaces. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance.

Cancer today is primarily treated with one or more types of anticancer therapy, including surgery, radiation and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast, colon, or skin, it cannot be used in the treatment of tumors located in other areas, such as the backbone, nor in the treatment of disseminated neoplastic conditions such as leukemia. Radiation therapy involves the exposure of living tissue to ionizing radiation causing death or damage to the exposed cells. Side effects from radiation therapy may be acute and temporary, while others may be irreversible. Chemotherapy involves the disruption of cell replication or cell metabolism. Chemotherapy is used most often in the treatment of breast, lung, and testicular cancer.

The adverse side effects of anticancer therapy is most feared by patients undergoing treatment for cancer. Of these adverse effects pain, nausea and vomiting are the most common and severe side effects. Other adverse side effects include cytopenia, infection, cachexia, mucositis in patients receiving high doses of chemotherapy with bone marrow rescue or radiation therapy; alopecia (hair loss); cutaneous complications, such as pruritis, urticaria, and angioedema; neurological complications; pulmonary and cardiac complications in patients receiving radiation or chemotherapy; and reproductive and endocrine complications. Anticancer

therapy induced side effects significantly impact the quality of life of the patient and may dramatically influence patient compliance with treatment.

Additionally, the adverse side effects associated with anticancer therapy is generally the major dose-limiting toxicity (DLT) in the administration of the therapy. For example, mucositis, is one of the major dose limiting toxicity for several anticancer agents, including the antimetabolite cytotoxic agents 5-FU, and methotrexate, and antitumor antibiotics, such as doxorubicin. Many of these chemotherapy-induced side effects if severe, may lead to hospitalization, or require treatment with analgesics for the treatment of pain.

Adverse side effects induced by anticancer therapy have become of major importance in the clinical management of patients undergoing treatment for cancer or neoplasia disease.

Brief Description of the Invention

In brief, the present invention provides a method for treating, preventing or reducing the risk of developing a neoplasia disorder in a mammal in need thereof, comprising administering to the mammal in a combination therapy an amount of a DNA topoisomerase I inhibiting agent and an amount of a selective cyclooxygenase-2 inhibiting agent wherein the amount of the DNA topoisomerase I inhibiting agent and the selective cyclooxygenase-2 inhibiting agent together make a neoplasia disorder effective amount.

The present invention further provides a pharmaceutical composition comprising a DNA topoisomerase I inhibiting agent and a cyclooxygenase-2 inhibiting agent wherein the DNA topoisomerase I inhibiting agent and the selective cyclooxygenase-2 inhibiting agent together make a neoplasia disorder effective amount.

In another embodiment, the present invention provides a use of a composition in preparation of a medicament useful in treating, preventing or lowering the risk of developing a neoplasia disorder in a mammal in need thereof, the composition comprising an amount of a DNA topoisomerase I inhibiting agent and an amount of a cyclooxygenase-2 inhibiting agent wherein the amount of the

DNA topoisomerase I inhibiting agent and the selective cyclooxygenase-2 inhibiting agent together make a neoplasia disorder effective amount.

The present invention further provides a kit comprising a DNA topoisomerase I inhibiting agent and a selective cyclooxygenase-2 inhibiting agent wherein the DNA topoisomerase I inhibiting agent and the selective cyclooxygenase-2 inhibiting agent together make a neoplasia disorder effective amount.

Another embodiment of the present invention provides a method for the prevention or treatment of DNA topoisomerase I inhibiting agent-related diarrhea in a subject in need of such prevention or treatment wherein the method comprises administering to the subject a diarrhea preventing or treating-effective amount of a source of a COX-2 inhibiting agent, thereby preventing or treating the DNA topoisomerase I inhibiting agent-related diarrhea.

Detailed Description of the Invention

Definitions

In the written descriptions of molecules and groups, molecular descriptors can be combined to produce words or phrases that describe structural groups or are combined to describe structural groups. Such descriptors are used in this document. Common illustrative examples include such terms as aralkyl (or arylalkyl), heteroaralkyl, heterocycloalkyl, cycloalkylalkyl, aralkoxyalkoxycarbonyl, and the like. A specific example of a compound encompassed with the latter descriptor aralkoxyalkoxycarbonyl is C_6H_5-CH_2-CH_2-O-CH_2-O-(C=O)- wherein C_6H_5- is phenyl. It is also to be noted that a structural group can have more than one descriptive word or phrase in the art, for example, heteroaryloxyalkylcarbonyl can also be termed heteroaryloxyalkanoyl. Such combinations are used herein in the description of the processes, compounds and compositions of this invention and further examples are described below. The following list is not intended to be

exhaustive or drawn out but provide illustrative examples of words or phrases (terms) that are used herein.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing one to about twelve carbon atoms, preferably one to about ten carbon atoms, and more preferably one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, and the like.

The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing two to about twenty carbon atoms preferably two to about twelve carbon atoms, and more preferably, two to about six carbon atoms. Examples of suitable alkenyl radicals include ethenyl (vinyl), 2-propenyl, 3-propenyl, allyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 4-methylbutenyl, decenyl, and the like. The term "alkenyl" embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more triple bonds and containing two to about twelve carbon atoms, preferably two to about ten carbon atoms, and more preferably, two to about six carbon atoms. Examples of alkynyl radicals include ethynyl, 2-propynyl, 3-propynyl, decynyl, 1-butynyl, 2-butynyl, 3-butynyl, propargyl, and the like.

The term "acyl", alone or in combination, means a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl, and the like.

The term "carbonyl" or "oxo", alone or in combination, i.e., used with other terms, such as "alkoxycarbonyl", means a -C(=O)- group wherein the remaining two bonds (valences) can be independently substituted. The term carbonyl is also intended to encompass a hydrated carbonyl group $-C(OH)_2-$.

The term "hydrido", alone or in combination, means a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical.

The term "halo", alone or in combination, means halogen such as fluoride, chloride, bromide or iodide.

The term "haloalkyl", alone or in combination, means an alkyl radical having the significance as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals.

More preferred haloalkoxy radicals are haloalkoxy radicals having one to six carbon atoms and one or more halo radicals. Examples of such haloalkyl radicals include chloromethyl, dichloromethyl, trichloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, and the like.

Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy, fluoropropoxy, and the like.

The term "perfluoroalkyl", alone or in combination, means an alkyl group wherein each hydrogen has been replaced by a fluorine atom. Examples of such perfluoroalkyl groups, in addition to trifluoromethyl above, are perfluorobutyl, perfluoroisopropyl, perfluorododecyl and perfluorodecyl.

The term "perfluoroalkoxy", alone or in combination, means a perfluoroalkyl ether radical wherein the term perfluoroalkyl is as defined above. Examples of such perfluoroalkoxy groups, in addition to trifluoromethoxy (F_3C-O-), are perfluorobutoxy, perfluoroisopropoxy, perfluorododecoxy and perfluorodecoxy.

The term "perfluoroalkylthio", alone or in combination, means a perfluoroalkyl thioether radical wherein the term perfluoroalkyl is as defined above. Examples of such perfluoroalkylthio groups, in addition to trifluoromethylthio (F_3C-S-), are perfluorobutylthio, perfluoroisopropylthio, perfluorododecylthio and perfluorodecylthio.

The term "hydroxyalkyl", alone or in combination, means a linear or branched alkyl radical having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. Preferred hydroxyalkyl radicals have one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

The term "thiol" or "sulfhydryl", alone or in combination, means a -SH group. The term "thio" or "thia", alone or in combination, means a thiaether group; i.e., an ether group wherein the ether oxygen is replaced by a sulfur atom.

The term "amino", alone or in combination, means an amine or $-NH_2$ group whereas the term mono-substituted amino, alone or in combination, means a substituted amine -N(H)(substituent) group wherein one hydrogen atom is replaced with a substituent, and disubstituted amine means a $-N(substituent)_2$ wherein two hydrogen atoms of the amino group are replaced with independently selected substituent groups.

Amines, amino groups and amides are compounds that can be designated as primary (I°), secondary (II°) or tertiary (III°) or unsubstituted, mono-substituted or N,N-disubstituted depending on the degree of substitution of the amino nitrogen. Quaternary amine (ammonium)(IV°) means a nitrogen with four substituents [$-N^+(substituent)_4$] that is positively charged and accompanied by a counter ion, whereas N-oxide means one substituent is oxygen and the group is represented as [$-N^+(substituent)_3$-O^-]; i.e., the charges are internally compensated.

The term "cyano", alone or in combination, means a -C-triple bond-N (-C≡N) group.

The term "azido", alone or in combination, means a -N-triple bond-N (-N≡N) group.

The term "hydroxyl", alone or in combination, means a -OH group.

The term "nitro", alone or in combination, means a $-NO_2$ group.

The term "azo", alone or in combination, means a -N=N- group wherein the bonds at the terminal positions can be independently substituted.

The term "hydrazino", alone or in combination, means a -NH-NH- group wherein the depicted remaining two bonds (valences) can be independently substituted. The hydrogen atoms of the hydrazino group can be replaced, independently, with substituents and the nitrogen atoms can form acid addition salts or be quaternized.

The term "sulfonyl", alone or in combination, i.e., linked to other terms such as alkylsulfonyl, means a $-SO_2-$ group wherein the depicted remaining two bonds (valences) can be independently substituted.

The term "sulfoxido", alone or in combination, means a -SO- group wherein the remaining two bonds (valences) can be independently substituted.

The term "sulfone", alone or in combination, means a $-SO_2-$ group wherein the depicted remaining two bonds (valences) can be independently substituted.

The term "sulfenamide", alone or in combination, means a -SON= group wherein the remaining three depicted bonds (valences) can be independently substituted.

The term "sulfide", alone or in combination, means a -S- group wherein the remaining two bonds (valences) can be independently substituted.

The term "alkylthio", alone or in combination, means a radical containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are radicals having alkyl radicals of one to six carbon atoms. Examples of such alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

The term "alkylthioalkyl", alone or in combination, means a radical containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are

radicals having alkyl radicals of one to six carbon atoms. Examples of such alkylthioalkyl radicals include methylthiomethyl, methylthioethyl, ethylthioethyl, and ethylthiomethyl.

The term "alkylsulfinyl", alone or in combination, means a radical containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are radicals having alkyl radicals of one to six carbon atoms. Examples of such alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

The term "alkylsulfonyl", alone or in combination, means an alkyl radical attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are alkylsulfonyl radicals having one to six carbon atoms. Examples of such alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals.

The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl", alone or in combination, mean a NH_2O_2S- radical.

The term "alkoxy" or "alkyloxy", alone or in combination, mean an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "alkoxyalkyl", alone or in combination, means an alkyl radical having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals.

The term "cycloalkyl", alone or in combination, means a cyclic alkyl radical that contains three to about twelve carbon atoms. More preferred cycloalkyl radicals are cycloalkyl radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like

The term "cycloalkylalkyl", alone or in combination, means an alkyl radical as defined above that is substituted by a cycloalkyl radical containing three to about eight, preferably three to about six, carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

The term "cycloalkenyl" means partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkenyl radicals are cycloalkenyl radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclohexenyl, and the like.

The term "heterocyclo" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclo radicals include saturated three- to six-membered heteromonocylic group containing one to four nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated three- to six-membered heteromonocyclic group containing one to two oxygen atoms and one to three nitrogen atoms (e.g. morpholinyl, etc.); saturated three- to six-membered heteromonocyclic group containing one to two sulfur atoms and one to three nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclo radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. A heterocyclic (heterocyclo) portion of a heterocyclocarbonyl, heterocyclooxy-carbonyl, heterocycloalkoxycarbonyl, or heterocycloalkyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle that contains one or more hetero atoms selected from nitrogen, oxygen and sulphur. Heterocyclo compounds include benzofused heterocyclic compounds such as benzo-1,4-dioxane. Such a moiety can be optionally substituted on one or more ring carbon atoms by halogen, hydroxy, hydroxycarbonyl, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) of the ring by alkyl,

aralkoxycarbonyl, alkanoyl, aryl or arylalkyl or on a tertiary nitrogen atom (i.e., =N-) by oxido and that is attached via a carbon atom. The tertiary nitrogen atom with three substituents can also attached to form a N-oxide [=N(O)-] group.

The term "heterocycloalkyl", alone or in combination, means a saturated and partially unsaturated heterocyclo-substituted alkyl radical, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The term "aryl", alone or in combination, means a five- or six-membered carbocyclic aromatic ring-containing moiety or a five- or six-membered carbocyclic aromatic system containing two or three rings wherein such rings are attached together in a pendent manner, or a fused ring system containing two or three rings that have all carbon atoms in the ring; i.e., a carbocyclic aryl radical. The term "aryl" embraces aromatic radicals such as phenyl, indenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted with one or more substituents including alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

The term "heteroaryl", alone or in combination means a five- or six-membered aromatic ring-containing moiety or a fused ring system (radical) containing two or three rings that have carbon atoms and also one or more heteroatoms in the ring(s) such as sulfur, oxygen and nitrogen. Examples of such heterocyclic or heteroaryl groups are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol-4-yl, 1-benzyloxycarbonylimidazol-4-yl, and the like), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, tetrahydrofuryl, thienyl, triazolyl, tetrazolyl, oxazolyl, oxadiazoyl, thiazolyl, thiadiazoyl, indolyl (e.g., 2-indolyl, and the like), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, and the like), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, and the like), tetrahydroquinolinyl (e.g.,

1,2,3,4-tetrahydro-2-quinolyl, and the like), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, and the like), quinoxalinyl, β-carbolinyl, 2-benzofurancarbonyl, benzothiophenyl, 1-, 2-, 4- or 5-benzimidazolyl, and the like radicals.

The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, diphenylethyl 2-phenylethyl, and the like. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

The term "aralkoxy", alone or in combination, means an aralkyl radical attached through an oxygen atom to other radicals.

The term "aralkoxyalkyl", alone or in combination, means an aralkoxy radical attached through an oxygen atom to an alkyl radical.

The term "aralkylthio", alone or in combination, means an aralkyl radical attached to a sulfur atom.

The term "aralkylthioalkyl", alone or in combination, means an aralkylthio radical attached through a sulfur atom to an alkyl radical.

The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O-C(O)- in which the term "aralkyl" has the significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl.

The term "aryloxy", alone or in combination, means a radical of the formula aryl-O- in which the term aryl has the significance given above. The phenoxy radical is an exemplary aryloxy radical.

The term "aminoalkyl", alone or in combination, means an alkyl radical substituted with amino radicals. Preferred are aminoalkyl radicals having alkyl portions having one to six carbon atoms. Examples of such radicals include aminomethyl, aminoethyl, and the like.

The term "alkylamino", alone or in combination, means an amino group which has been substituted with one or two alkyl radicals. Preferred are N-alkylamino radicals having alkyl portions having one to six carbon atoms. Suitable

alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino, and the like.

The term "arylamino", alone or in combination, means an amino group which has been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

The term "aralkylamino", alone or in combination, means an aralkyl radical attached through a nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" mean an amino group which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl, N-phenyl-N-methylaminomethyl, and the like.

The terms "heteroaralkyl" and "heteroaryloxy", alone or in combination, mean a radical structurally similar to aralkyl and aryloxy that are formed from heteroaryl radicals. Exemplary radicals include 4-picolinyl and 2-pyrimidinoxy, respectively.

The terms "alkanoyl" or "alkylcarbonyl", alone or in combination, mean an acyl radical derived from an alkanecarboxylic acid, examples of which include formyl, acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like.

The term "cycloalkylcarbonyl", alone or in combination, means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl, adamantanecarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid that is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl.

The terms "aralkanoyl" or "aralkylcarbonyl", alone or in combination, mean an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like.

The terms "aroyl" or "arylcarbonyl", alone or in combination, mean an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The terms "carboxy" or "carboxyl", whether used alone or in combination, i.e., with other terms, such as "carboxyalkyl", mean a -CO_2H radical.

The term "carboxyalkyl", alone or in combination, means an alkyl radical substituted with a carboxy radical. More preferred carboxyalkyl radicals have alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such carboxyalkyl radicals include carboxymethyl, carboxyethyl, carboxypropyl, and the like.

The term "alkoxycarbonyl", alone or in combination, means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred alkoxycarbonyl radicals have alkyl portions having one to six carbons. Examples of such alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, hexyloxycarbonyl, and the like.

The term "cycloalkylalkoxycarbonyl", alone or in combination, means an acyl group of the formula cycloalkylalkyl-O-CO- wherein cycloalkylalkyl has the significance given above.

The term "aryloxyalkanoyl", alone or in combination, means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above.

The term "heterocyclooxycarbonyl", alone or in combination, means an acyl group having the formula heterocyclo-O-CO- wherein heterocyclo is as defined above.

The term "heterocycloalkanoyl", alone or in combination, means an acyl radical of the formula heterocyclo-substituted alkane carboxylic acid wherein heterocyclo has the significance given above.

The term "heterocycloalkoxycarbonyl", alone or in combination, means an acyl radical of the formula heterocyclo-substituted alkane-O-CO- wherein heterocyclo has the significance given above.

The term "heteroaryloxycarbonyl", alone or in combination, means an acyl radical represented by the formula heteroaryl-O-CO- wherein heteroaryl has the significance given above.

The term "aminocarbonyl" (carboxamide) alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amine reacted with a carboxylic acid wherein the amino (amido nitrogen) group is unsubstituted (-NH_2) or a substituted primary or secondary amino group containing one or more substituents selected from hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, and the like, as recited. A hydroxamate is a N-hydroxycarboxamide.

The term "alkylaminoalkyl", alone or in combination, means a radical having one or more alkyl radicals attached to an aminoalkyl radical.

The term "aryloxyalkyl", alone or in combination, means a radical having an aryl radical attached to an alkyl radical through a divalent oxygen atom.

The term "arylthioalkyl", alone or in combination, means a radical having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

The term "aminoalkanoyl", alone or in combination, means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary or secondary amino group containing substituents independently selected from hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, and the like.

The term "aromatic ring" in combinations such as substituted-aromatic ring sulfone or substituted-aromatic ring sulfoxide means aryl or heteroaryl as defined before.

The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product.

Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal (Group Ia) salts, alkaline earth metal (Group IIa) salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

Combinations and Methods

The present invention provides a method for treating, preventing or reducing the risk of developing a neoplasia disorder in a mammal. The method comprises administering to the mammal in a combination therapy an amount of a DNA topoisomerase I inhibiting agent and a cyclooxygenase-2 inhibiting agent, wherein the DNA topoisomerase I inhibiting agent and the cyclooxygenase-2 inhibiting agent together make a neoplasia disorder effective amount. The present invention further provides a method of halting or slowing the progression of neoplastic disease once it becomes clinically evident. Also provided by the present inventive the methods, combinations and compositions of the present invention are pharmaceutical compositions comprising a DNA topoisomerase I inhibiting agent and a cyclooxygenase-2 inhibiting agent where the individual agents together make a neoplasia disorder effective amount. The present invention also provides a kit comprising a cyclooxygenase-2 inhibiting agent and a DNA topoisomerase I

inhibiting agent. When administered as part of a combination therapy, the cyclooxygenase-2 inhibiting agent together with the DNA topoisomerase I inhibiting agent provide enhanced treatment options for treating, preventing, and reducing the risk of developing neoplastic disease in a mammal as compared to administration of either a DNA topoisomerase I inhibiting agent or a cyclooxygenase-2 inhibiting agent alone.

The present invention further provides a method for the prevention or treatment of DNA topoisomerase I inhibiting agent-related diarrhea in a subject in need of such prevention or treatment wherein the method comprises administering to the subject a diarrhea preventing or treating-effective amount of a source of a COX-2 inhibiting agent, thereby preventing or treating the DNA topoisomerase I inhibiting agent-related diarrhea. Preferably the source of a COX-2 inhibiting agent is a source of a COX-2 selective inhibiting agent, and more preferably a COX-2 selective inhibiting agent. For example the COX-2 selective inhibiting agent can be celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, meloxicam, or ABT-963. Alternatively, the COX-2 selective inhibiting agent can be a chromene COX-2 selective inhibiting agent. In another embodiment, the source of a COX-2 selective inhibiting agent can be a prodrug of a COX-2 selective inhibiting agent. For example, the prodrug can be parecoxib. Preferably the DNA topoisomerase I inhibiting agent is selected from the group consisting of irinotecan; irinotecan hydrochloride; camptothecin; 9-aminocamptothecin; 9-nitrocamptothecin; 9-chloro-10-hydroxy camptothecin; topotecan; lurtotecan; a homosilatecan; 6,8-dibromo-2-methyl-3-[2-(D-xylopyranosylamino)phenyl]-4(3H)-quinazolinone; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-(2E)-2-propenamide; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(3-hydroxyphenylpropyl)-(E)-2-propenamide; 12-beta-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione; N-[2-(dimethylamino)ethyl]-4-acridinecarboxamide, dihydrochloride; and N-[2-(dimethylamino)ethyl]-4-acridinecarboxamide; or a salt of the DNA topoisomerase I inhibiting agent. Preferably the DNA topoisoermerase I inhibiting agent is selected from the group consisting of irinotecan, rubitecan, lurtotecan,

exetecan mesylate, karenitecan, and silatecan; or a salt of one of these agents. More preferably still the DNA topoisomerase I inhibiting agent is irinotecan. When the DNA topoisomerase I inhibiting agent is irinotecan, the source of a COX-2 inhibiting agent is preferably a source of a COX-2 selective inhibiting agent, and more preferably selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, meloxicam, and ABT-963. Alternatively, the source of a COX-2 selective inhibiting agent can be a chromene COX-2 selective inhibiting agent. In another embodiment, when the DNA topoisomerase I inhibiting agent is irinotecan, the source of a COX-2 inhibiting agent can be a prodrug of a COX-2 selective inhibiting agent, preferably parecoxib. For treatment or prevention of the DNA topoisomerase I inhibiting agent-related diarrhea, the source of a COX-2 selective inhibiting agent can be administered to the subject by essentially any convenient route. For example, the source of a COX-2 selective inhibiting agent can be administered orally, parenterally (e.g., intravenously, subcutaneously, or intramuscularly), transdermally, or rectally. The source of a COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent can be administered to the subject in essentially any convenient regimen. For example, the source of the COX-2 selective inhibiting agent can be administered to the subject before treating the subject with the DNA topoisomerase I inhibiting agent. Alternatively, the source of the COX-2 selective inhibiting agent can be administered to the subject concurrently with treating the subject with the DNA topoisomerase I inhibiting agent. In another alternative the source of the COX-2 selective inhibiting agent can be administered to the subject after treating the subject with the DNA topoisomerase I inhibiting agent.

A source of a COX-2 inhibiting agent can be, for example, a source of a COX-2 selective inhibiting agent, or a source of a nonselective cyclooxygenase inhibiting agent. The source of a COX-2 selective inhibiting agent can be, for example, a COX-2 selective inhibiting agent or a prodrug of a COX-2 selective inhibiting agent.

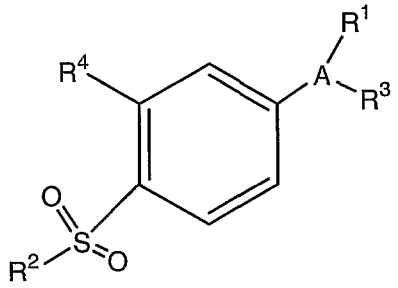
Besides being useful for human treatment, the present invention is also useful for veterinary treatment of companion mammals, exotic animals and farm

animals, including mammals, rodents, and the like. In one embodiment, the mammals include horses, dogs, and cats.

There are many uses for the present inventive combination. For example, DNA topoisomerase I inhibiting agents and COX-2 selective inhibiting agents (or prodrugs thereof) are each believed to be effective antineoplastic or antiangiogenic agents. However, patients treated with a DNA topoisomerase I inhibiting agent frequently experience side effects such as diarrhea. The present inventive combination will allow the subject to be administered a DNA topoisomerase I inhibitor at a therapeutically effective dose yet experience reduced or fewer symptoms of diarrhea. A further use and advantage is that the present inventive combination will allow therapeutically effective individual dose levels of the DNA topoisomerase I inhibitor and the selective cyclooxygenase-2 inhibitor which are lower than the dose levels of each inhibitor when administered to the patient as a monotherapy.

Some therapeutic compounds which are useful in the present inventive combination include compounds which selectively inhibit cyclooxygenase-2 (COX-2) relative to cyclooxygenase-1 (COX-1) (i.e., a "COX-2 selective inhibiting agent"). In one embodiment, the compounds have a selectivity ratio of COX-2 inhibition relative to COX-1 inhibition of at least 50, and in another embodiment have a selectivity ratio of at least 100. Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the treatment, prevention or reduction in the risk of developing neoplasia disease may inhibit enzyme activity through a variety of mechanisms. By way of example, the cyclooxygenase inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme. The use of a COX-2 selective inhibiting agent is highly advantageous in that they minimize the gastric side effects that can occur with non-selective non-steroidal antiinflammatory drugs (NSAIDs), especially where prolonged treatment is expected.

A class of COX-2 selective inhibiting agents useful in the methods, combinations and compositions of the present invention include compounds of Formula 1:



1

wherein

A is a 5- or 6-member ring substituent selected from aryl, heteroaryl, heterocyclo, and cycloalkyl, wherein A is optionally substituted with one or more radicals selected from hydroxy, alkyl, halo, oxo, and alkoxy;

R^1 is cyclohexyl, pyridinyl, or phenyl, wherein R^1 is optionally substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^2 is alkyl or amino;

R^3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocycloalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

R^4 is hydrido or halo;

or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

Within Formula 1 there is a subclass of compounds of particular interest wherein A is thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, or pyridyl;

R^1 is cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, or phenyl, wherein R^1 is optionally substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, alkoxy, halo, alkoxy, and alkylthio;

R^2 is methyl or amino; and

R^3 is halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonyl-alkyl, carboxy-alkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, amino-alkyl, alkylaminoalkyl, N-phenylamino-alkyl, N-phenyl-alkylaminoalkyl, N-alkyl-N-phenyl-alkylamino-alkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, or N-alkyl-N-phenylaminosulfonyl;

or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

A preferred class of compounds within Formula 1 includes compounds wherein A is substituted with one or more radicals selected alkyl, halo, oxo, and alkoxy;

R^1 is pyridyl, cyclohexyl, or phenyl, wherein R^1 is optionally substituted with one or more radicals selected from alkyl, halo, and alkoxy;

R^3 is halo, alkyl, cyano, carboxyl, alkyloxy, phenyl, haloalkyl, or hydroxyalkyl; and

R^4 is hydrido or fluoro;

or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

A family within Formula 1 which are particularly preferred include the following compounds and their pharmaceutically-acceptable salts:

4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone (rofecoxib),

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide (celecoxib),

4-[5-methyl-3-phenyl-3-phenylisoxazol-4-yl]benzensulfonamide (valdecoxib),

4-[5-(3-fluoro-4mthoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]bensenesulfonamide (deracoxib),

4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide (JTE-522),

2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine (MK-663),

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,

2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,

3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,

3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide,

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino] benzenesulfonamide,

1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene,

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

[1,1':2',1"-terphenyl]-4-sulfonamide,

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide,

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, and

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide.

Specific compounds of particular interest within Formula 1 include each of the compounds and pharmaceutically-acceptable salts thereof as follows:

4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone (rofecoxib),

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide (celecoxib),

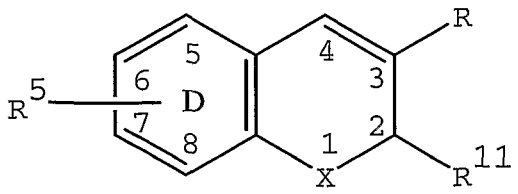
4-[5-methyl-3-phenyl-3-phenylisoxazol-4-yl]benzensulfonamide (valdecoxib),

4-[5-(3-fluoro-4mthoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]bensenesulfonamide (deracoxib),

4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide (JTE-522), and

2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine (MK-663).

As used herein any COX-2 selective inhibiting agent which comprises a 2H-1-benzopyran structure is called a "chromene COX-2 selective inhibiting agent." A class of chromene selective COX-2 inhibiting agents useful in the methods, combinations and compositions of the present invention include compounds of Formula 2.



2

wherein

X is O, S or NR^a;

R^a is alkyl;

R is carboxyl, alkyl, aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl or alkoxycarbonyl;

R^{11} is haloalkyl, alkyl, aralkyl, cycloalkyl or aryl, wherein aryl is optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

R^5 is one or more radicals independently selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or R^5 together with ring Dforms a naphthyl radical;

or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

Within Formula 2 there is a subclass of compounds of particular interest wherein

X is O or S;

R is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

R^{11} is lower haloalkyl, lower cycloalkyl or phenyl; and

R^5 is one or more radicals independently selected from hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5- or 6- membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5- or 6- membered

nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl;

or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

Preferably R is carboxyl; R^{11} is lower haloalkyl; and R^5 is one or more radicals independently selected from hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5- or 6- membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6- membered nitrogen containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

Still other preferred compounds within Formula 2 of interest include compounds wherein R^{11} is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and R^5 is one or more radicals independently selected from hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

Another preferred class of compounds within Formula 2 are compounds wherein R is carboxyl; R^{11} is trifluoromethyl or pentafluorethyl; and R^5 is one or more radicals independently selected from hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-

furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

A family of specific compounds within Formula 2 of particular interest include the following compounds and their isomers and pharmaceutically-acceptable salts:

6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid,

7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid,
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

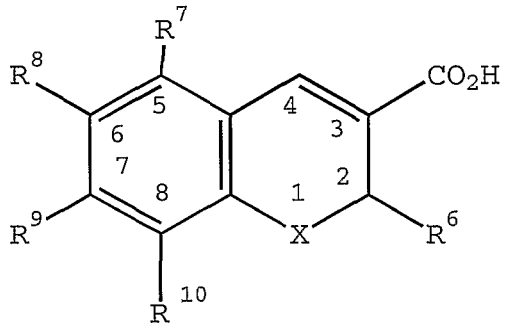
6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid, and

6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

Another class of chromene selective COX-2 inhibiting agents useful in the methods, combinations and compositions of the present invention include compounds of Formula 3:



3

wherein

X is O, S or NR^a;

R^a is alkyl;

R^6 is lower haloalkyl;

R^7 is hydrido or halo;

R^8 is hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, or 5- or 6- membered nitrogen containing heterocyclosulfonyl;

R^9 is hydrido, lower alkyl, halo, lower alkoxy, or aryl; and

R^{10} is hydrido, halo, lower alkyl, lower alkoxy, or aryl;

or an isomer or pharmaceutically-acceptable salt or prodrug thereof.

Within Formula 3 there is a subclass of compounds of particular interest wherein

R^6 is trifluoromethyl or pentafluoroethyl;

R^7 is hydrido, chloro, or fluoro;

R^8 is hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

R^9 is hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

R^{10} is hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl;

or an isomer, tautomer, pharmaceutically-acceptable salt or prodrug thereof.

Specific compounds of interest within Formula 3 include each of the compounds and pharmaceutically-acceptable salts thereof as follows:

6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

7-(1,1-Dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,7-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

5,6-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

2,6-Bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

5,6,7-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,7,8-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6-Bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6-Chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid, and

6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

Specific compounds of particular interest within Formula 3 include each of the compounds and pharmaceutically-acceptable salts thereof as follows:

6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

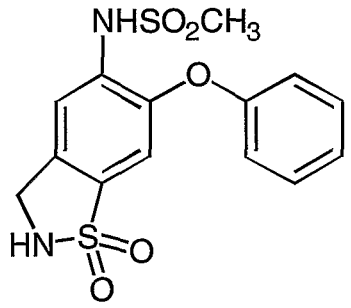
(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

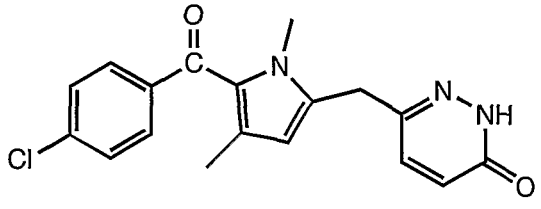
(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, and

6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid.

Other selective cyclooxygenease-2 inhibiting agents useful in the methods, combinations and compositions of the present invention include compounds and pharmaceutically-acceptable salts thereof as follows:

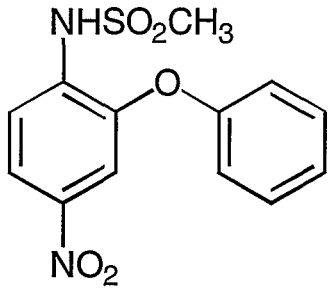


N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide;

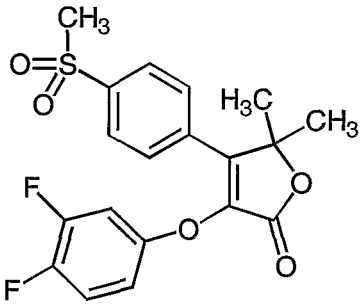


6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone;

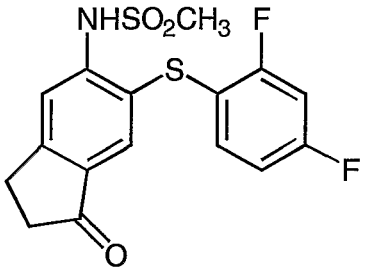
ABT-963, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;



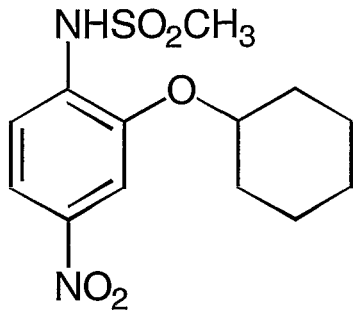
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide;



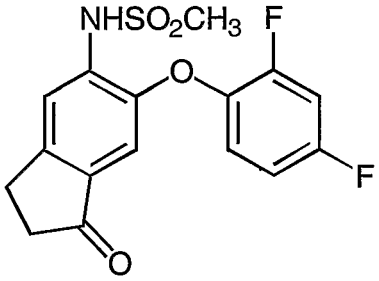
3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone;



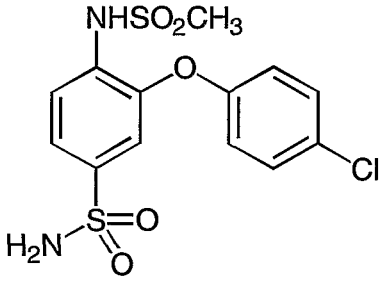
N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;



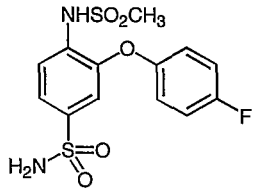
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide;



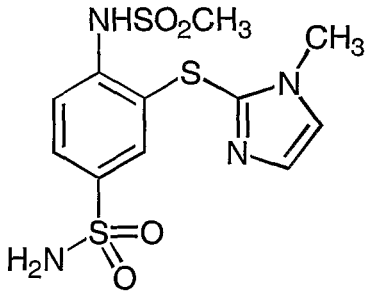
N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;



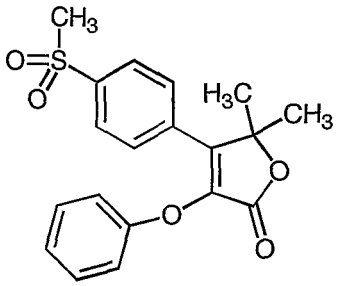
3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide;



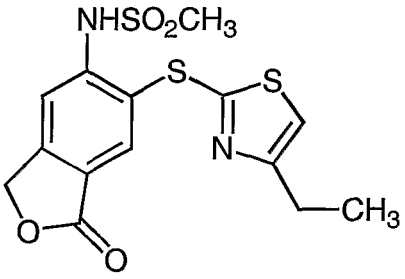
3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide;



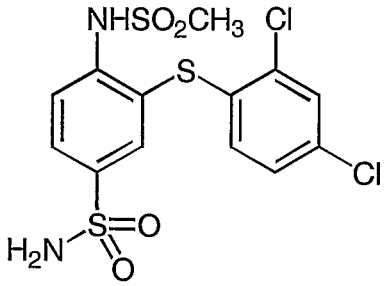
3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide;



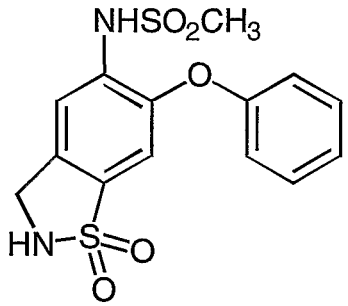
5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone;



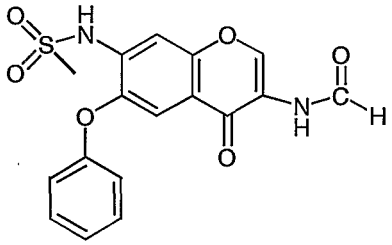
N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide;



3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide;



N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide; and



N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide.

Nonlimiting examples of COX-2 selective inhibiting agents that may be used in the methods, combinations and compositions of the present invention are identified in Table 1 below.

Table 1. COX-2 Inhibitors

Compound	Trade Name	Reference	Dosage
6-chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide, 1,1-dioxide	lornoxicam; Safem®	CAS No. 70374-39-9	
1,5-Diphenyl-3-substituted pyrazoles		WO 97/13755	
	radicicol	WO 96/25928; Kwon et al (Cancer Res(1992) 52 6296)	
	GB-02283745		
	TP-72	Cancer Res. 1998 58 4 717 -723	
1-(4-chlorobenzoyl)-3-[4-(4-fluorophenyl)thiazol-2-ylmethyl]-5-methoxy-2-methy lindole	A-183827.0		
	GR-253035	CAS Registry No. 215522-99-9	
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide; Benzenesulfonamide, 4-(4-cyclohexyl-2-methyl-5-	JTE-522	CAS Registry Number: 180200-68-4; JP 09052882	

Compound	Trade Name	Reference	Dosage
cyclohexyl-2-methyl-5-oxazolyl)-2-fluoro-			
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine			
2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one			
5-[4-(methylsulfonyl)-phenyl]-6-phenyl-thiazolo[3,2-b][1,2,4]triazole	L-768277	CAS Registry No. 180696-49-5	
	L-783003	CAS Registry No. 215435-69-1	
4-(4-(methyl-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;	MK-966; Vioxx®; rofecoxib	US 5968974	12.5-100 mg po
indomethacin-derived indolalkanoic acid		WO 96/37467-9	200 mg/kg/day
1-Methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene		WO 95/30656; WO 95/30652; WO 96/38418; WO 96/38442	
4,4-dimethyl-2-phenyl-3-[4-(methylsulfonyl)phenyl]cyclo butenone			
2-(4-methoxyphenyl)-4-methyl-1-(4-		EP 799823	

Compound	Trade Name	Reference	Dosage
sulfamoylphenyl)pyrrole			
N-[5-(4-fluoro)phenoxy]thiophene-2-methanesulfonamide	RWJ-63556		
5(E)-(3,5-di-tert-butyl-4-hydroxy)benzylidene-2-ethyl-1,2-isothiazolidine-1,1-dioxide	S-2474	EP 595546	
3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one	T-614	DE 3834204	
Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-	celecoxib; Celebrex®	CAS Registry Number: 169590-42-5; US 5466823	
Benzenesulfonamide, 4-(5-methyl-3-phenyl-4-isoxazolyl)-	valdecoxib	CAS Registry Number: 181695-72-7; 5,633,272	
Propanamide, N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]-	parecoxib (prodrug)	CAS Registry Number: 198470-84-7; US 5932598	
4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide	deracoxib	CAS Registry Number: 169590-41-4; US 5521207	

Compound	Trade Name	Reference	Dosage
	meloxicam	US 4233299	15-30 mg/day
	nimesulide	US 3840597	
1,5-Diphenyl-3-substituted pyrazoles		WO 97/13755	
	radicicol	WO 96/25928. Kwon et al (Cancer Res(1992) 52 6296)	
	TP-72	Cancer Res. 1998 58 4 717 -723	
1-(4-chlorobenzoyl)-3-[4-(4-fluoro-phenyl)thiazol-2-ylmethyl]-5-methoxy-2-methy lindole	A-183827.0		
	GR-253035		
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)-pyridine			
2-(3,5-difluoro-phenyl)-3-4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one			
CS 502	Sankyo		
2-(6-methylpyrid-3-yl)-3-(4-methylsulfinylphenyl)-5-chloropyridine	etoricoxib; MK-663; L-791456	WO 98/03484; Bioorg. Med. Chem. Lett. 1998, 8, 2777-	

Compound	Trade Name	Reference	Dosage
		2782	

The following individual references listed in Table No. 2 below, each hereby incorporated by reference, describe various COX-2 selective inhibiting agents suitable for use in the methods, combinations and compositions of the present invention described herein, and processes for their manufacture.

Table No. 2. COX-2 Inhibitor References

WO 99/30721	WO 99/30729	US 5760068	WO 98/15528
WO 99/25695	WO 99/24404	WO 99/23087	FR 27/71005
EP 921119	FR 27/70131	WO 99/18960	WO 99/15505
WO 99/15503	WO 99/14205	WO 99/14195	WO 99/14194
WO 99/13799	GB 23/30833	US 5859036	WO 99/12930
WO 99/11605	WO 99/10332	WO 99/10331	WO 99/09988
US 5869524	WO 99/05104	US 5859257	WO 98/47890
WO 98/47871	US 5830911	US 5824699	WO 98/45294
WO 98/43966	WO 98/41511	WO 98/41864	WO 98/41516
WO 98/37235	EP 86/3134	JP 10/175861	US 5776967
WO 98/29382	WO 98/25896	ZA 97/04806	EP 84/6,689
WO 98/21195	GB 23/19772	WO 98/11080	WO 98/06715
WO 98/06708	WO 98/07425	WO 98/04527	WO 98/03484
FR 27/51966	WO 97/38986	WO 97/46524	WO 97/44027
WO 97/34882	US 5681842	WO 97/37984	US 5686460
WO 97/36863	WO 97/40012	WO 97/36497	WO 97/29776
WO 97/29775	WO 97/29774	WO 97/28121	WO 97/28120
WO 97/27181	WO 95/11883	WO 97/14691	WO 97/13755
WO 97/13755	CA 21/80624	WO 97/11701	WO 96/41645
WO 96/41626	WO 96/41625	WO 96/38418	WO 96/37467

WO 96/37469	WO 96/36623	WO 96/36617	WO 96/31509
WO 96/25405	WO 96/24584	WO 96/23786	WO 96/19469
WO 96/16934	WO 96/13483	WO 96/03385	US 5510368
WO 96/09304	WO 96/06840	WO 96/06840	WO 96/03387
WO 95/21817	GB 22/83745	WO 94/27980	WO 94/26731
WO 94/20480	WO 94/13635	FR 27/70,131	US 5859036
WO 99/01131	WO 99/01455	WO 99/01452	WO 99/01130
WO 98/57966	WO 98/53814	WO 98/53818	WO 98/53817
WO 98/47890	US 5830911	US 5776967	WO 98/22101
DE 19/753463	WO 98/21195	WO 98/16227	US 5733909
WO 98/05639	WO 97/44028	WO 97/44027	WO 97/40012
WO 97/38986	US 5677318	WO 97/34882	WO 97/16435
WO 97/03678	WO 97/03667	WO 96/36623	WO 96/31509
WO 96/25928	WO 96/06840	WO 96/21667	WO 96/19469
US 5510368	WO 96/09304	GB 22/83745	WO 96/03392
WO 94/25431	WO 94/20480	WO 94/13635	JP 09052882
GB 22/94879	WO 95/15316	WO 95/15315	WO 96/03388
WO 96/24585	US 5344991	WO 95/00501	US 5968974
US 5945539	US 5994381	US 5521207	

The rofecoxib used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,968,974.

The celecoxib used in the therapeutic methods, combinations and compositions of the of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

The valdecoxib used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

The parecoxib used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

The deracoxib used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

The Japan Tobacco JTE-522 used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in JP 90/52,882.

The etoricoxib used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in WO document WO 98/03484.

A DNA topoisomerase I inhibitor, or a DNA topoisomerase I inhibiting agent, encompass a wide range of structures that are useful in the methods, combinations and compositions of the present invention. A compound that inhibits DNA topoisomerase I is used in combination with a COX-2 selective inhibiting agent to practice the present invention. Compounds which have inhibitory activity for DNA topoisomerase I can be readily identified by using assays well-known in the art.

Topoisomerase I is a monomeric nuclear enzyme of 100 kDa involved in DNA replication, RNA transcription, mitosis, chromosome condensation, and probably DNA repair. Topoisomerase I forms a covalent complex with DNA which allows the formation of the single-strand breaks necessary for DNA replication. Topoisomerase I also religates those DNA strands after DNA replication. While not wishing to be bound by theory, it is believed that DNA topoisomerase I inhibiting agents bind to this DNA topoisomerase I complex in a reversible manner, resulting in the inhibition of topoisomerase I action. DNA topoisomerase I inhibiting agents have been shown to not only bind to the topoisomerase I enzyme but also to the DNA.

DNA topoisomerase I inhibiting agents of particular interest that can be used with the methods, combinations and compositions of the present invention are provided in Table No. 3, below. The therapeutic compounds of Table No. 3 can be used in the methods, combinations and compositions of the present invention in a variety of forms, including acid form, salt form, racemates, enantiomers, zwitterions, and tautomers. The individual references in Table No. 3 are each herein individually incorporated by reference.

Table No. 3. DNA Topoisomerase I Inhibitors

Table 3: DNA Topoisomerase I Inhibitors					
Compound Name	**Trade Name**	**Reference**	**Dosage**	**Toxicity**	**Oncology Indication**
	Camptothecin	WO 9637496 J. Am. Chem. Soc. 1966;88:3888-90.		myelosuppression, nausea, vomiting, and diarrhea, and hemorrhagic cystitis.	Colon, stomach, and non-small cell lung cancer. Melanoma.
9-amino-20(S)-camptothecin		Cancer Res. 1989; 49:1465-1469. Cancer Res. 1989; 49:4385-4389			Colon, non-small cell lung, and breast cancer. Melanoma.
	GG211	Proc Am Assoc. Cancer Res. 1994; 35:47.		Hematologic toxicity dose limiting.	Colon, ovarian, lung and epidermoid cancer.
	Irinotecan	Cancer Res. 1991; 51:4187-4191. Cancer Res. 1987; 47:5944-5947. Cancer Res. 1990; 50:1715-1720.	20 mg/m^2 for 3 days weekly; 100 mg/m^2 weekly; 150 mg/ m^2 every 2 weeks; 200 mg/m^2 every 3 - 4	Diarrhea and myelosuppression.	Colon, head and neck, non-small cell lung, cervical, esophageal, renal cell, breast, and ovarian cancer.

Table 3: DNA Topoisomerase I Inhibitors					
Compound Name	**Trade Name**	**Reference**	**Dosage**	**Toxicity**	**Oncology Indication**
			weeks; 250 mg/m^2 every 3 - 4 weeks.		Gastric and lung squamous cell carcinomas. Rhabdomysarcoma. Non-Hodgkin's lymphoma. Combination therapy: Recombinant granulocyte colony stimulating factor (G-CSF). 5-fluorouracil. Cisplatin Etoposide
(4S)-4,11-diethyl-4-hydroxy- 9-((4-piperidinopiperidino)carbonyloxy)-1H-pyrano(3',4':6,7)indolizino(1,2-b)quinoline-3,14(4H,12H) dione hydrochloride.	Irinotecan hydrochloride, CPT-11. Camptosar® Injection	US 4604463. EP 56692. JP 60019790.	125 mg/m^2 IV over 90 minutes/wk for 4 weeks followed by 2 week rest. Then repeated at 50 to 150 mg/m^2 doses.	Lethality in mice: 111 mg/kg in mice. Lethality in rats: 73 mg/kg. DLT: diarrhea and neutropenia. Myelosuppression, neutropenia, leukopenia (including lymphocytopenia), and anemia.	Metastatic carcinoma of the colon or rectum. Brain tumor, arcinoma, Lung tumor, Neoplasm, Non-Hodgkin lymphoma, Non-small-cell lung cancer, Ovary tumor, Pancreas tumor, Stomach tumor, Uterine cervix tumor, Uterus

Table 3: DNA Topoisomerase I Inhibitors					
Compound Name	**Trade Name**	**Reference**	**Dosage**	**Toxicity**	**Oncology Indication**
					tumor.
(S)-10-((dimethylamino)methyl)-4-ethyl- 4,9-dihydroxy-1H-pyrano (3', 4':6,7)indolizino(1,2-B)quinoline-3,14-(4H,12H)-dione monohydrochloride	Topotecan hydrochloride; Hycamtin		1.5 mg/ m^2/d IV infusion over 30 minutes for 5 consecutive days, starting on day one of a 21-day course.	DLT: Bone marrow suppression. LD10: mice 75 mg/m^2 single IV infusion. Grade 4 thrombocytopenia, anemia.	Metastatic carcinoma of the ovary. Radio/chemo sensitizer; Breast tumor, Carcinoma, Colon tumor, Glioma, Leukemia, Lung tumor, Lymphoma, Myeloproliferative disorder.
1H-Pyrano[3`,4`:6,7]indolizino[1,2-b]quinoline-3,14(4,H,12H)-dione, 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-, (S)-	Topotecan	EP 321122.	1.5 mg/m^2 X 5 d every 3 wk: Prostate, colorectal, and ovarian cancer. 1.5 mg/m^2 X 5 d every 4 wk: Renal cell cancer.	Maximally tolerated dose: 1.5 mg/m^2 X 5 d every 3 to 4 wk. Myelosuppression dose-limiting toxicity. Subsequent administration of G-CSF lowers severity of neutro-penia, allowing dose escaltion.	Colorectal, small and non-small cell lung cancer; ovarian, esophageal, renal, squamous cell skin, prostate, and epidermoid cancer. Osteogenic sarcoma, rhabdomysarcoma, acute myeloblastic leukemia, chronic myelocytic leukemia in blastic phase. Leiomyosarcoma. Combi-

Table 3: DNA Topoisomerase I Inhibitors					
Compound Name	**Trade Name**	**Reference**	**Dosage**	**Toxicity**	**Oncology Indication**
					nation therapy: Etoposide and cisplatin.
MAG-camptothecin (prodrug)	PNU-166148	*Proc Am Soc. Clin Oncol* 2000 19 May 20-23 Abs 771			Solid tumors,
11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, (S)-	lurtotecan	EP 540099	0.3 to 0.5 mg/m2/day by continuous infusions of 7, 14, and 21 days.	hematological toxicity, myelotoxicity, gastrointestinal toxicity, thrombocytopenia and neutropenia and asthenia	neoplasia
11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, dihydrochloride, (S)-	Lurtotecan dihydrochloride	EP 540099	0.3 to 0.5 mg/m2/day by continuous infusions of 7, 14, and 21 days.	hematological toxicity, myelotoxicity, gastrointestinal toxicity, thrombocytopenia and neutropenia and asthenia	neoplasia

Table 3: DNA Topoisomerase I Inhibitors					
Compound Name	**Trade Name**	**Reference**	**Dosage**	**Toxicity**	**Oncology Indication**
1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 10-amino-4-ethyl-4-hydroxy-, (S)-	9-aminocamptothecin		Dose limiting toxicity consisted of neutropenia.	Maximum tolerated dose = 45 mug/square metre/hr;	Colon tumor, Solid tumor, Neoplasm, Carcinoma, Lung tumor, Colorectal tumor, Pancreas tumor, Stomach tumor, Bladder tumor, Prostate tumor, Head & neck tumor, Renal tumor, Leukemia
	DB-67, camptothecins, homosilatecans	WO 99/09996			Neoplasia
1H-Pyrano[3'.4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, -4-ethyl-4-hydroxy-10-nitro-, (S)-	rubitecan, 9-nitrocamptothecin	*Eur J Haematol* 1994 53 4 246 -248. *Proc Am Assoc. Cancer Res.* 1994 35 Abs 2712. *Int J Cancer* 1993 53 5 863 -871.	Maximum tolerated dose: 1.5 mg/m2/day over five consecutive days repeated every week.	The dose limiting toxicity was hematological, with grade 4 anemia in 29% of patients, neutropenia in 25%, and thrombocytopenia in 18%. Grade 2 or higher toxic effects occurred at each dose	Neoplasm, Pancreas tumor, Ovary tumor, Leukemia, Solid tumor, Myelodysplastic Disease

Table 3: DNA Topoisomerase I Inhibitors					
Compound Name	**Trade Name**	**Reference**	**Dosage**	**Toxicity**	**Oncology Indication**
				level: nausea and vomiting (54%), diarrhea (32%), chemical cystitis (25%), neutropenic sepsis (21%), and weight loss (18%).	
7-[N-(4-methyl-1-piperazino) methylamino]-(20S)-camptothecin	CT-17	*Proc Am Assoc. Cancer Res.* 1999 40 ABS 715			Neoplasia
camptothecin glycoconjugates	BAY-38-3441	*Clin Cancer Res.* 1999 5 11 3862s -3863s. *Proc Am Assoc. Cancer Res.* 2000 41 April 1-5 Abs 3430.			Neoplasia
camptothecin glycoconjugates	BAY-38-3444	*Clin Cancer Res.* 1999 5 11 3862s -3863s.			Neoplasia
4(3H)-Quinazolinone, 6,8-dibromo-2-methyl-3-[2-(D-xylopyranosyl amino)phenyl]-	NSC-665517	*Proc Am Assoc. Cancer Res.* 1995 36 Abs 2659. *Mol Pharmacol* 1995 48 4 658 -665			Carcinoma
2-Propenamide,	AG 490, Tyrphosti				Neoplasia

Table 3: DNA Topoisomerase I Inhibitors					
Compound Name	**Trade Name**	**Reference**	**Dosage**	**Toxicity**	**Oncology Indication**
2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-, (2E)-	n AG 490				
2-Propenamide, 2-cyano-3-(3,4-dihydroxyphenyl)-N-(3-hydroxyphenylpropyl)-, (E)-	AG 555, Tyrphostin AG 555	*Cancer Res.* 1994 54 19 5138 -5142. *Exp Opin Ther Pat* 1998 8 12 1599 -1625			Neoplasia
	NSC-314622	*Proc Am Assoc. Cancer Res.* 1996 431. *Proc Am Assoc. Cancer Res.* 2000 41 April 1-5 Abs 5186.			Neoplasia
	CZ-112; CZ-48	US 5731316			malignant tumors, neoplasia
	HAR-7	*Nci Eortc Symp New Drugs Cancer Ther* 1996 9th Amsterdam Abs 444.			Solid tumors
	NX-211, lurtotecan liposomal	*Proc Am Assoc. Cancer Res.* 1999 40 Abs 751. *Proc Am Soc. Clin Oncol* 1999 18 15-18 May 680.			Neoplasia
5H-	J 107088;	*Proc Am*	maximum		Neoplasia

Table 3: DNA Topoisomerase I Inhibitors

Compound Name	Trade Name	Reference	Dosage	Toxicity	Oncology Indication
Indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione, 12-.beta.-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-	ED-749	*Assoc. Cancer Res.* 1998 39 New Orleans Abs 2864. *Ann Oncol* 1998 9 2 043. *Cancer Res.* 1999 59 17 4271 -4275. *Bioorg Med Chem. Lett* 1999 9 23 3307 -3312.	tolerated dose: 7.5 mg/m2		
4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride	XR-5000,DACA	US 05696131. *Journal Of Medicinal Chemistry* 1987 30 664 - 669		infusion-related arm pain	Brain tumor, Breast tumor, Carcinoma, Colon tumor, Lung tumor, Melanoma, Ovary tumor, Sarcoma, Skin tumor
4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-	NSC 601316	US 05696131. *Journal Of Medicinal Chemistry* 1987 30 664 - 669			Brain tumor, Breast tumor, Carcinoma, Colon tumor, Lung tumor, Melanoma, Ovary tumor, Sarcoma, Skin tumor
9-chloro-10-hydroxy camptothecin	SKF-108025	*Acs* 1994 207th San Diego MEDI 74			Carcinoma
	CZ-105, CZ-107	*Proceedings Of The American Association Of Cancer*			Neoplasia

Table 3: DNA Topoisomerase I Inhibitors					
Compound Name	**Trade Name**	**Reference**	**Dosage**	**Toxicity**	**Oncology Indication**
		Research 1997 38 88 17			
	JSKIV-47	US 05767142. WO 96/36612			Neoplasia
	SKF-107874	*Acs Meeting* 1994 207th San Diego MEDI 74			Carcinoma
	Intoplicine	EP 402232			Solid tumor
	CKD-602	WO 96/21666.			Neoplasia
	Exetacan mesylate; exatecan	EP 737686			Leukemia, Myeloid leukemia, Neoplasm, Non-small-cell lung cancer, Pancreas tumor
	IST-622	EP 159708			Neoplasia
	NB-506	WO 93/11145			Neoplasia
	Pyrazoloa cridine, Parke-Davis	EP 138302			Neoplasia
	XR-5000	US 5696131			Brain tumor, Breast tumor, Carcinoma, Colon tumor, Lung tumor, Melanoma, Ovary tumor, Sarcoma, Skin tumor
	DB-67	WO 99/09996			Neoplasia
	DRF-1042	WO 97/46563			Neoplasia
	F-11782	WO 96/12727			Neoplasia
	XR-5944	WO 98/17650			Neoplasia
	BN-80915	WO 99/11646.			Neoplasia

Other DNA topoisomerase I inhibiting agents of interest that can be used in the methods, combinations and compositions of the present invention include the compounds described in the patents provided in Table No. 4, below. The therapeutic compounds of Table No. 4 can also be used in the methods, combinations and compositions of the present invention in a variety of forms, including acid form, salt form, racemates, enantiomers, zwitterions, and tautomers. The individual references in Table No. 4 are each herein individually incorporated by reference.

Table No. 4. Additional DNA Topoisomerase I Inhibitors

Table 4: Additional DNA Topoisomerase I Inhibitors		
Company	**Reference**	**Oncology Indication**
Abbott Laboratories	WO 97/15676	Neoplasm
Arch Development Corp	WO 96/01127	Neoplasm
Banyu Pharmaceutical Co. Ltd..	EP 388956	Neoplasm
Bayer AG	WO 98/14459	Neoplasm
Bayer AG	WO 98/14468	Neoplasm, Lung tumor
Bayer AG	WO 98/15573	Neoplasm
Bayer AG	WO 98/51703	Neoplasm
BioNumerik Pharmaceuticals Inc.	US 5597829	Neoplasm
BioNumerik Pharmaceuticals Inc.	WO 95/17187	Neoplasm
BioNumerik Pharmaceuticals Inc	WO 95/29677	Neoplasm
BioNumerik Pharmaceuticals Inc.	WO 98/04557	Leukemia, Breast tumor, Colon tumor, Melanoma, Lung tumor, Non-Hodgkin lymphoma, Ovary tumor
BioNumerik Pharmaceuticals Inc.	WO 98/35940	Neoplasm, Leukemia
BioNumerik Pharmaceuticals Inc.	WO 95/28404	Neoplasm
Bristol-Myers Co.	BE-900735	Carcinoma

Table 4: Additional DNA Topoisomerase I Inhibitors		
Company	**Reference**	**Oncology Indication**
Bristol-Myers Squibb Co.	WO 98/07433	Neoplasm
Chong Kun Dang Corp.	WO 96/21666	Neoplasm, Leukemia
Chong Kun Dang Corp.	WO 99/02530	Neoplasm
Daiichi Seiyaku Co Ltd.	JP-9020778	Carcinoma
Dana-Farber Cancer Institute Inc.	WO 97/07797	Prostate disease, Ovary tumor, Breast tumor
Dr Reddys Research Foundation	WO 97/46562	Leukemia, HIV infection
FermaLogic Inc.	US 5554519	Colon tumor
George Washington University	WO 99/65493	Diarrhea, Breast tumor, Ovary tumor, Colon tumor, Melanoma, Lung tumor, Thyroid tumor, Lymphoma, Leukemia
Dr Reddys Research Foundation	WO 97/46564	Leukemia, Neoplasm
Glaxo Inc.	EP 540099	Neoplasm
Glaxo Inc.	GB-2280674	Carcinoma, Neoplasm
Glaxo Inc.	WO 94/25466	Neoplasm
	WO 96/11005	Neoplasm
Istituto Nazionale studio e cura dei tumori	WO 97/31003	Neoplasm
Johns Hopkins University	WO 96/08249	Trypanosomiasis, Leishmania infection
Kaken Pharmaceutical Co. Ltd.	JP-11246469	Neoplasm
Kyorin Pharmaceutical Co. Ltd.	WO 96/41806	Neoplasm
Matrix Pharmaceutical Inc.	WO 98/36776	Neoplasm
Ohio State University	US 5552156	Neoplasm
Pharmacia & Upjohn SpA	WO 95/22549	Neoplasm
Pharmacia & Upjohn SpA	WO 95/32207	Leukemia, Colon tumor
Pharmacia & Upjohn SpA	WO 97/25332	Neoplasm
Pharmacia & Upjohn SpA	WO 98/35969	Carcinoma, Leukemia

Table 4: Additional DNA Topoisomerase I Inhibitors		
Company	**Reference**	**Oncology Indication**
Pharmacia & Upjohn SpA	WO 99/17804	Neoplasm
Pharmacia & Upjohn SpA	WO 95/04736	Neoplasm, Leukemia
Pharmacia & Upjohn SpA	WO 99/05103	Neoplasm
Pharmacia & Upjohn SpA	WO 99/17805	Neoplasm
Pharmacia Inc.	WO 96/11669	Neoplasm, Leukemia
Research Triangle Institute	WO 96/02546	Neoplasm
Research Triangle Institute	WO 91/04260	Neoplasm
Research Triangle Institute	WO 91/05556	Colorectal tumor, Leukemia, Colon tumor
Research Triangle Institute	WO 96/09049	Plasmodium infection
Research Triangle Institute	WO 97/19085	Neoplasm, Leukemia, Colon tumor
Rockefeller University	WO 97/44492	Neoplasm
Rutgers University	US 5767142	Neoplasm, Burkitts lymphoma, Myeloproliferative disorder, Breast tumor
Rutgers University	WO 98/31673	Neoplasm, Fungal infection
Rutgers University	WO 99/31067	Malignant neoplastic disease, Solid tumor, Leukemia
Rutgers University	WO 99/41241	Malignant neoplastic disease, Solid tumor, Leukemia, Lymphoma, Fungal infection
Rutgers University	WO 98/12181	Leukemia, Melanoma, Carcinoma
Rutgers University	WO 99/33824	Solid tumor, Sarcoma, Melanoma, Lymphoma
Sankyo Co Ltd.	JP-7316091	Neoplasm
Shionogi & Co Ltd.	JP-7138165	Carcinoma
SmithKline Beecham Corp.	EP 835938	Staphylococcus infection
SmithKline Beecham Corp.	US 5633016	Solid tumor
SmithKline Beecham Corp.	US 5674872	Ovary tumor
SmithKline Beecham Corp.	WO 92/14469	Neoplasm, Ovary tumor
SmithKline Beecham Corp.	WO 95/03803	Viral infection

Table 4: Additional DNA Topoisomerase I Inhibitors		
Company	**Reference**	**Oncology Indication**
SmithKline Beecham Corp.	WO 96/38146	Neoplasm
SmithKline Beecham Corp.	WO 96/38449	Neoplasm
SmithKline Beecham Corp.	WO 92/05785	Neoplasm
SmithKline Beecham Corp.	WO 92/14471	Neoplasm
SmithKline Beecham Corp.	WO 92/14470	Esophageal disease, Neoplasm
SmithKline Beecham plc	WO 92/07856	Viral infection
Societe de Conseils de Recherches et d`Applications Scientifique	WO 98/28305	Colon tumor, Lung tumor, Breast tumor, viral infection, Parasitic infection
Societe de Conseils de Recherches et d`Applications Scientifique	WO 99/33829	Colon tumor, Lung tumor, Leukemia, Leishmania infection, Plasmodium infection, Trypanosomiasis
Stehlin Foundation For Cancer Research	WO 97/28165	Neoplasm, Carcinoma, Breast tumor
Takeda Chemical Industries Ltd.	EP 556585	Neoplasm
Tanabe Seiyaku Co Ltd.	JP-11071280	Neoplasm, Lung tumor
University of California	US 5698674	Neoplasm, Viral infection
University of Michigan	WO 96/34003	Breast tumor, Lung tumor, Prostate tumor
University of New Jersey	WO 97/29106	Neoplasm, Central nervous system disease
University of New Jersey--	WO 96/36612	Burkitts lymphoma, Leukemia, Myeloproliferative disorder
University of Pittsburgh--	WO 99/01456	Malignant neoplastic disease
Wisconsin Alumni Research Foundation	WO 96/33988	Prostate tumor, Colon tumor, Lung tumor, Melanoma, Breast tumor, HIV infection
Wisconsin Alumni Research Foundation	WO 97/31936	Neoplasm
Xenova Ltd.	WO 98/17649	Neoplasm
Yale University	WO 98/40104	Carcinoma

Additional DNA topoisomerase I inhibiting agents of interest that can be used in the methods, combinations and compositions of the present invention are provided in Table No. 5, below. The therapeutic compounds of Table No. 5 can be used in the methods, combinations and compositions of the present invention in a variety of forms, including acid form, salt form, racemates, enantiomers, zwitterions, and tautomers.

Table No. 5. Additional DNA Topoisomerase I Inhibitors

Table 5: Additional DNA Topoisomerase I Inhibitors	
Compound Name	**Company**
BAY-38-3441	Bayer AG
BNP-1350	BioNumerik
GG-211	Tigen
J-107088	Merck & Co
kareniticin	BioNumerik Pharmaceuticals Inc
L9NC	MD Anderson Cancer Center
lurtotecan, Gilead	Gilead Sciences
MAG-CPT	Pharmacia
PEG-camptothecin, Enzon	Enzon
SN-22995	University of Auckland
TRK-710	Toray Industries Inc
NX-211	Glaxo Wellcome plc
pyrazoloacridine, Wayne State	Non-industrial source
TAS-103	Taiho
XR-5000	Xenova
9-aminocamptothecin	IDEC; Research Triangle Institute
rubitecan	SuperGen; Stehlin Foundation For Cancer Research
10-hydroxycamptothecin derivatives, Chiba	Chiba University
AG-555	Hebrew University of Jerusalem

Table 5: Additional DNA Topoisomerase I Inhibitors	
Compound Name	**Company**
anhydrous delivery system, Matrix	Matrix Pharmaceutical Inc
ascididemin	INSERM
BM-2419-1	Kaken Pharmaceutical Co Ltd.
camptothecin analogs, RTI/BMS	Research Triangle Institute
camptothecin-TCS, Inex	Inex Pharmaceuticals Corp
CT-17	University of Kentucky
DMNQ derivatives, Chungnam University	Chungnam University
DRF-1644	Dr Reddys Research Foundation
dual topoisomerase I/II-directed anticancer drugs, University of Auckland	University of Auckland
HAR-7	Harrier Inc
J-109404	Banyu Pharmaceutical Co Ltd.
julibrosides	Taisho Pharmaceutical Co Ltd.
MPI-5019	Matrix Pharmaceutical Inc
NSC-314622	National Cancer Institute
NU/ICRF-505	Imperial Cancer Research Technology Ltd.
NU-UB-150	Napier University of Edinburgh
topoisomerase I inhibitors, Glaxo	Glaxo Wellcome plc
topoisomerase I inhibitors, MediChem/Mayo	MediChem. Research Inc
topoisomerase I inhibitors, Purdue University/NCI	Purdue University
topoisomerase I inhibitors, SMT	Morphochem Inc
topoisomerase inhibitor, Daiichi	Daiichi Seiyaku Co Ltd.
UCE-1022	Kyowa Hakko Kogyo Co Ltd.
camptothecin, Aphios	Aphios
F-12167	Pierre Fabre
ST-1481	Sigma-Tau

Table 5: Additional DNA Topoisomerase I Inhibitors	
Compound Name	**Company**
topoisomerase inhibitors, BTG	BTG
XR-11576	Xenova
gemifloxacin mesylate	LG Chemical
BN-80245	Institut Henri Beaufour

Specific DNA topoisomerase I inhibiting agents of interest that can be used in the methods, combinations and compositions of the present invention include irinotecan; irinotecan hydrochloride; camptothecin; 9-aminocamptothecin; 9-nitrocamptothecin; 9-chloro-10-hydroxy camptothecin; topotecan; topotecan hydrochloride; lurtotecan; lurtotecan dihydrochloride; lurtotecan (liposomal); homosilatecans; 6,8-dibromo-2-methyl-3-[2-(D-xylopyranosylamino)phenyl]-4(3H)-quinazolinone; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-(2E)-2-propenamide; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(3-hydroxyphenylpropyl)-(E)-2-propenamide; 5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione, 12-.beta.-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-; 4-acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride; and 4-acridinecarboxamide, N-[2-(dimethylamino)ethyl]-.

Included in the methods, combinations and compositions of the present invention are the isomeric forms and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric and galacturonic acids.

Also included in the methods, combinations and compositions of the present invention are the prodrugs of the described compounds and the pharmaceutically-

acceptable salts thereof. The term "prodrug" refers to compounds which are drug precursors which, following administration to a subject and subsequent absorption, are converted to an active species *in vivo* via some process, such as a metabolic process. Other products from the conversion process are easily disposed of by the body. More preferred prodrugs produce products from the conversion process which are generally accepted as safe. Nonlimiting examples of "prodrugs" that can be used in the methods, combinations and compositions of the present invention include parecoxib (propanamide, N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]-), and MAG-camptothecin.

In one embodiment, the methods, combinations and compositions of the present invention can be useful for the treatment or prevention of a neoplasia disorder selected from acral lentiginous melanoma, an actinic keratosis, adenocarcinoma, adenoid cycstic carcinoma, an adenoma, adenosarcoma, adenosquamous carcinoma, an astrocytic tumor, bartholin gland carcinoma, basal cell carcinoma, a bronchial gland carcinoma, capillary carcinoma, a carcinoid, carcinoma, carcinosarcoma, cavernous carcinoma, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma, choriod plexus carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal carcinoma, epitheloid carcinoma, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, a germ cell tumor, glioblastoma, glucagonoma, hemangiblastoma, hemangioendothelioma, a hemangioma, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, a lentigo maligna melanoma, malignant melanoma, a malignant mesothelial tumor, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, a pituitary tumor, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma,

retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, a soft tissue carcinoma, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, a well differentiated carcinoma, and Wilm's tumor.

In another embodiment, the methods, combinations and compositions of the present invention can be useful for the treatment or prevention of a neoplasia disorder where the neoplasia disorder is located in a tissue of the mammal. The tissues where the neoplasia disorder may be located include the lung, breast, skin, stomach, intestine, esophagus, bladder, head, neck, brain, cervical, or ovary of the mammal.

The phrase "neoplasia disorder effective" is intended to qualify the amount of each agent that will achieve the goal of improvement in neoplastic disease severity and the frequency of a neoplastic disease event over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

A "neoplasia disorder effect" or "neoplasia disorder effective amount" is intended to qualify the amount of a selective COX-2 inhibiting agent and a DNA topoisomerase I inhibiting agent required to treat or prevent a neoplasia disorder or relieve to some extent or one or more of the symptoms of a neoplasia disorder, including, but is not limited to: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 4) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 5) inhibition, to some extent, of tumor growth; 6) relieving or reducing to some extent one or more of the symptoms associated with the disorder; and/or 7) relieving or reducing the side effects associated with the administration of anticancer agents.

The phrase "combination therapy" (or "co-therapy") embraces the administration of a selective COX-2 inhibiting agent and a DNA topoisomerase I inhibiting agent as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial

effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients (such as, but not limited to, an antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). Where the combination therapy further comprises radiation treatment, the radiation treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and radiation treatment is

achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

"Therapeutic compound" means a compound useful in the prophylaxis or treatment of a neoplastic disease.

The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

The term "inhibition," in the context of neoplasia, tumor growth or tumor cell growth, may be assessed by delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, among others. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention.

The term "prevention," in relation to neoplasia, tumor growth or tumor cell growth, means no tumor or tumor cell growth if none had occurred, no further tumor or tumor cell growth if there had already been growth.

The term "chemoprevention" refers to the use of agents to arrest or reverse the chronic cancer disease process in its earliest stages before it reaches its terminal invasive and metastatic phase.

The term "clinical tumor" includes neoplasms that are identifiable through clinical screening or diagnostic procedures including, but not limited to, palpation, biopsy, cell proliferation index, endoscopy, mammagraphy, digital mammography, ultrasonography, computed tomagraphy (CT), magnetic resonance imaging (MRI), positron emission tomagraphy (PET), radiography, radionuclide evaluation, CT- or MRI-guided aspiration cytology, and imaging-guided needle biopsy, among others. Such diagnostic techniques are well known to those skilled in the art and are described in Cancer Medicine 4th Edition, Volume One. J.F. Holland, R.C. Bast, D.L. Morton, E. Frei III, D.W. Kufe, and R.R. Weichselbaum (Editors). Williams & Wilkins, Baltimore (1997).

The term "angiogenesis" refers to the process by which tumor cells trigger abnormal blood vessel growth to create their own blood supply. Angiogenesis is believed to be the mechanism via which tumors get needed nutrients to grow and metastasize to other locations in the body. Antiangiogenic agents interfere with these processes and destroy or control tumors. Angiogenesis an attractive therapeutic target for treating neoplastic disease because it is a multi-step process that occurs in a specific sequence, thus providing several possible targets for drug action. Examples of agents that interfere with several of these steps include compounds such as matrix metalloproteinase inhibitors (MMPIs) that block the actions of enzymes that clear and create paths for newly forming blood vessels to follow; compounds, such as $\alpha v\beta 3$ inhibitors, that interfere with molecules that blood vessel cells use to bridge between a parent blood vessel and a tumor; agents, such as selective COX-2 inhibiting agents, that prevent the growth of cells that form new blood vessels; and protein-based compounds that simultaneously interfere with several of these targets.

The present invention also provides a method for lowering the risk of a first or subsequent occurrence of a neoplastic disease event comprising the administration of a prophylactically effective amount of a combination of a DNA

topoisomerase I inhibiting agent and a selective COX-2 inhibiting agent to a patient at risk for such a neoplastic disease event. The patient may already have non-malignant neoplastic disease at the time of administration, or be at risk for developing it.

Patients to be treated with the present combination therapy includes those at risk of developing neoplastic disease or of having a neoplastic disease event. Standard neoplastic disease risk factors are known to the average physician practicing in the relevant field of medicine. Such known risk factors include but are not limited to genetic factors and exposure to carcinogens such as certain viruses, certain chemicals, tobacco smoke or radiation. Patients who are identified as having one or more risk factors known in the art to be at risk of developing neoplastic disease, as well as people who already have neoplastic disease, are intended to be included within the group of people considered to be at risk for having a neoplastic disease event.

Studies indicate that prostaglandins synthesized by cyclooxygenases play a critical role in the initiation and promotion of cancer. Moreover, COX-2 is overexpressed in neoplastic lesions of the colon, breast, lung, prostate, esophagus, pancreas, intestine, cervix, ovaries, urinary bladder, and head and neck. Products of COX-2 activity, i.e., prostaglandins, stimulate proliferation, increase invasiveness of malignant cells, and enhance the production of vascular endothelial growth factor, which promotes angiogenesis. In several in vitro and animal models, COX-2 selective inhibiting agents have inhibited tumor growth and metastasis. The utility of COX-2 selective inhibiting agents as chemopreventive, antiangiogenic and chemotherapeutic agents is described in the literature, see for example Koki et al., Potential utility of COX-2 selective inhibiting agents in chemoprevention and chemotherapy. Exp. Opin. Invest. Drugs (1999) 8(10) pp. 1623-1638.

In addition to cancers *per se*, COX-2 is also expressed in the angiogenic vasculature within and adjacent to hyperplastic and neoplastic lesions indicating that COX-2 plays a role in angiogenesis. In both the mouse and rat, COX-2 selective inhibiting agents markedly inhibited bFGF-induced neovascularization.

Also, COX-2 levels are elevated in tumors with amplification and/or overexpression of other oncogenes including but not limited to c-*myc*, N-*myc*, L-*myc*, K-*ras*, H-*ras*, N-*ras*. Consequently, the administration of a selective COX-2 inhibiting agent and a DNA topoisomerase I inhibitor, in combination with an agent, or agents, that inhibits or suppresses oncogenes is contemplated to prevent or treat cancers in which oncogenes are overexpressed.

Accordingly, there is a need for a method of treating or preventing a cancer in a patient that overexpresses COX-2 and/or an oncogene.

Dosage of a Selective COX-2 Inhibiting Agent and DNA Topoisomerase Inhibiting Agent

Dosage levels of the source of a COX-2 inhibiting agent (e.g., a COX-2 selective inhibiting agent or a prodrug of a COX-2 selective inhibiting agent) on the order of about 0.1 mg to about 10,000 mg of the active antiangiogenic ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 1.0 mg to about 1,000 mg. The amount of active ingredient that may be combined with other anticancer agents to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

A total daily dose of a DNA topoisomerase I inhibiting agent can generally be in the range of from about 0.001 to about 10,000 mg/day in single or divided doses.

It is understood, however, that specific dose levels of the therapeutic agents or therapeutic approaches of the present invention for any particular patient depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the patient, the time of administration, the rate of excretion, the drug combination, and the severity of the particular disease being treated and form of administration.

Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro initially can provide useful guidance on the proper doses for patient administration. Studies in animal models

also generally may be used for guidance regarding effective dosages for treatment of cancers in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective in vitro. Thus, where an compound is found to demonstrate in vitro activity at, e.g., 10 μM, one will desire to administer an amount of the drug that is effective to provide about a 10 μM concentration in vivo. Determination of these parameters are well within the skill of the art.

These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

Dosages, Formulations, and Routes of Administration

The COX-2 selective inhibiting agents and/or DNA topoisomerase I inhibiting agents can be formulated as a single pharmaceutical composition or as independent multiple pharmaceutical compositions. Pharmaceutical compositions according to the present invention include those suitable for oral, inhalation spray, rectal, topical, buccal (e.g., sublingual), or parenteral (e.g., subcutaneous, intramuscular, intravenous, intramedullary and intradermal injections, or infusion techniques) 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 compound which is being used. In most cases, the preferred route of administration is oral or parenteral.

Compounds and composition of the present invention can then be administered orally, by inhalation spray, rectally, topically, buccally or parenterally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The compounds of the present invention can be administered by any conventional means available for use

in conjunction with pharmaceuticals, either as individual therapeutic compounds or as a combination of therapeutic compounds.

The compositions of the present invention can be administered for the prophylaxis or treatment of neoplastic disease or disorders by any means that produce contact of these compounds with their site of action in the body, for example in the ileum, the plasma, or the liver of a mammal.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation. The anions useful in the methods, combinations and compositions of the present invention are, of course, also required to be pharmaceutically acceptable and are also selected from the above list.

The compounds useful in the methods, combinations and compositions of the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, consisting essentially of admixing the components.

The amount of compound in combination that is required to achieve the desired biological effect will, of course, depend on a number of factors such as the specific compound chosen, the use for which it is intended, the mode of administration, and the clinical condition of the recipient.

The compounds of the present invention can be delivered orally either in a solid, in a semi-solid, or in a liquid form. Dosing for oral administration may be with a regimen calling for single daily dose, or for a single dose every other day, or for multiple, spaced doses throughout the day. For oral administration, the

pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. Capsules, tablets, etc., can be prepared by conventional methods well known in the art. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient or ingredients. Examples of dosage units are tablets or capsules, and may contain one or more therapeutic compounds in an amount described herein. For example, in the case of a DNA topoisomerase I inhibitor, the dose range may be from about 0.01 mg to about 5,000 mg or any other dose, dependent upon the specific inhibitor, as is known in the art. When in a liquid or in a semi-solid form, the combinations of the present invention can, for example, be in the form of a liquid, syrup, or contained in a gel capsule (e.g., a gel cap). In one embodiment, when a DNA topoisomerase I inhibiting agent is used in a combination of the present invention, the DNA topoisomerase I inhibiting agent can be provided in the form of a liquid, syrup, or contained in a gel capsule. In another embodiment, when a COX-2 selective inhibiting agent is used in a combination of the present invention, the COX-2 selective inhibiting agent can be provided in the form of a liquid, syrup, or contained in a gel capsule.

Oral delivery of the combinations of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. For some of the therapeutic compounds useful in the methods, combinations and compositions of the present invention the intended effect is to extend the time period over which the active drug molecule is delivered to the site of action by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate,

hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one therapeutic compound useful in the present invention; 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. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions 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 product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more assessory ingredients. Compressed tablets can 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 can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored 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.

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although

administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection or by infusion. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 10% w/w of a compound disclosed herein.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. A suitable daily dose of each active therapeutic compound is one that achieves the same blood serum level as produced by oral administration as described above.

The dose of any of these therapeutic compounds can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 10,000 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by

admixing a compound or compounds of the present invention with one or more conventional solid carriers, for example, cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug; and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include petroleum jelly (e.g., Vaseline), lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound or compounds are generally present at a concentration of from 0.1 to 50% w/w of the composition, for example, from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound or compounds of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound or compounds is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound or compounds can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

In any case, the amount of active ingredients that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

In combination therapy, administration of two or more of the therapeutic agents useful in the methods, combinations and compositions of the present invention may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or in a separate formulation. Independent administration of each therapeutic agent may be accomplished by, for example, oral, inhalation spray, rectal, topical, buccal (e.g., sublingual), or parenteral (e.g., subcutaneous, intramuscular, intravenous,

intramedullary and intradermal injections, or infusion techniques) administration. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. Solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropylmethyl cellulose, together with one or more of a lubricant, preservative, surface active or dispersing agent. The therapeutic compounds may further be administered by any combination of, for example, oral/oral, oral/parenteral, or parenteral/parenteral route.

The therapeutic compounds which make up the combination therapy may be a combined dosage form or in separate dosage forms intended for substantially simultaneous oral administration. The therapeutic compounds which make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two step ingestion. Thus, a regimen may call for sequential administration of the therapeutic compounds with spaced-apart ingestion of the separate, active agents. The time period between the multiple ingestion steps may range from, for example, a few minutes to several hours to days, depending upon the properties of each therapeutic compound such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the therapeutic compound, as well as depending upon the effect of food ingestion and the age and condition of the patient. Circadian variation of the target molecule concentration may also determine the optimal dose interval. The therapeutic compounds of the combined therapy whether administered simultaneously, substantially simultaneously, or sequentially, may involve a regimen calling for administration of one therapeutic compound by oral route and another therapeutic compound by intravenous route. Whether the therapeutic compounds of the combined therapy are administered orally, by inhalation spray, rectally, topically, buccally (e.g., sublingual), or parenterally (e.g., subcutaneous, intramuscular, intravenous and intradermal injections, or infusion techniques), separately or together, each such therapeutic compound will be contained in a suitable pharmaceutical formulation of pharmaceutically-acceptable excipients, diluents or

other formulations components. Examples of suitable pharmaceutically-acceptable formulations containing the therapeutic compounds are given above. Additionally, drug formulations are discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975. Another discussion of drug formulations can be found in Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

Administration Regimen

Any effective treatment regimen can be utilized and readily determined and repeated as necessary to effect treatment. In clinical practice, the compositions containing a COX-2 selective inhibiting agent in combination with a DNA topoisomerase I inhibiting agent , (along with other therapeutic agents) are administered in specific cycles until a response is obtained.

For patients who initially present without advanced or metastatic cancer, a COX-2 selective inhibiting agent based drug in combination with a DNA topoisomerase I inhibiting agent can be used as an immediate initial therapy prior to surgery, chemotherapy, or radiation therapy, and/or as a continuous post-treatment therapy in patients at risk for recurrence or metastasis (for example, in adenocarcinoma of the prostate, risk for metastasis is based upon high PSA, high Gleason's score, locally extensive disease, and/or pathological evidence of tumor invasion in the surgical specimen). The goal in these patients is to inhibit the growth of potentially metastatic cells from the primary tumor during surgery or radiotherapy and inhibit the growth of tumor cells from undetectable residual primary tumor.

For patients who initially present with advanced or metastatic cancer, a COX-2 selective inhibiting agent based drug in combination with a DNA topoisomerase I inhibiting agent is used as a continuous supplement to, or possible replacement for chemotherapeutic regimes. The goal in these patients is to slow or

prevent tumor cell growth from both the untreated primary tumor and from the existing metastatic lesions.

In addition, the invention may be particularly efficacious during post-surgical recovery, where the present compositions and methods may be particularly effective in lessening the chances of recurrence of a tumor engendered by shed cells that cannot be removed by surgical intervention.

Combinations with Other Treatments

The methods, combinations and compositions of the present invention may be used in conjunction with other cancer treatment modalities, including, but not limited to surgery and radiation, hormonal therapy, immunotherapy, cryotherapy, chemotherapy and antiangiogenic therapy. The present invention may be used in conjunction with any current or future therapy.

The following discussion highlights some agents in this respect, which are illustrative, not limitative. A wide variety of other effective agents also may be used.

Surgery and Radiation

In general, surgery and radiation therapy are employed as potentially curative therapies for patients under 70 years of age who present with clinically localized disease and are expected to live at least 10 years. For example, approximately 70% of newly diagnosed prostate cancer patients fall into this category. Approximately 90% of these patients (65% of total patients) undergo surgery, while approximately 10% of these patients (7% of total patients) undergo radiation therapy. Histopathological examination of surgical specimens reveals that approximately 63% of patients undergoing surgery (40% of total patients) have locally extensive tumors or regional (lymph node) metastasis that was undetected at initial diagnosis. These patients are at a significantly greater risk of recurrence. Approximately 40% of these patients will actually develop recurrence within five years after surgery. Results after radiation are even less encouraging. Approximately 80% of patients who have undergone radiation as their primary

therapy have disease persistence or develop recurrence or metastasis within five years after treatment. Currently, most of these surgical and radiotherapy patients generally do not receive any immediate follow-up therapy. Rather, they are monitored frequently for elevated Prostate Specific Antigen ("PSA"), which is the primary indicator of recurrence or metastasis.

Thus, there is considerable opportunity to use the present invention in conjunction with surgical intervention or radiotherapy to inhibit the growth of potentially metastatic cells from the primary tumor, as well as to inhibit the growth of tumor cells from undetectable residual primary tumor. In addition, the invention may be particularly efficacious during post-surgical recovery, where the present compositions and methods may be particularly effective in lessening the chances of recurrence of a tumor engendered by shed cells that cannot be removed by surgical intervention.

Hormonal Therapy

Hormonal ablation is the most effective palliative treatment for the 10% of patients presenting with metastatic prostate cancer at initial diagnosis. Hormonal ablation by medication and/or orchiectomy is used to block hormones that support the further growth and metastasis of prostate cancer. With time, both the primary and metastatic tumors of virtually all of these patients become hormone-independent and resistant to therapy. Approximately 50% of patients presenting with metastatic disease die within three years after initial diagnosis, and 75% of such patients die within five years after diagnosis. Continuous supplementation with NAALADase inhibitor based drugs are used to prevent or reverse this potentially metastasis-permissive state.

Suitable hormonal-type antineoplastic agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to Abarelix; Abbott A-84861; Abiraterone acetate; Aminoglutethimide; anastrozole; Asta Medica AN-207; Antide; Chugai AG-041R; Avorelin; aseranox; Sensus B2036-PEG; Bicalutamide; buserelin; BTG CB-7598; BTG CB-7630; Casodex; cetrolix; clastroban; clodronate disodium; Cosudex; Rotta Research CR-

1505; cytadren; crinone; deslorelin; droloxifene; dutasteride; Elimina; Laval University EM-800; Laval University EM-652; epitiostanol; epristeride; Mediolanum EP 23904; EntreMed 2-ME; exemestane; fadrozole; finasteride; flutamide; formestane; Pharmacia & Upjohn FCE-24304; ganirelix; goserelin; Shire gonadorelin agonist; Glaxo Wellcome GW-5638; Hoechst Marion Roussel Hoe-766; NCI hCG; idoxifene; isocordoin; Zeneca ICI-182780; Zeneca ICI-118630; Tulane University J015X; Schering Ag J96; ketanserin; lanreotide; Milkhaus LDI-200; letrozol; leuprolide; leuprorelin; liarozole; lisuride hydrogen maleate; loxiglumide; mepitiostane; Leuprorelin; Ligand Pharmaceuticals LG-1127; LG-1447; LG-2293; LG-2527; LG-2716; Bone Care International LR-103; Lilly LY-326315; Lilly LY-353381-HCl; Lilly LY-326391; Lilly LY-353381; Lilly LY-357489; miproxifene phosphate; Orion Pharma MPV-2213ad; Tulane University MZ-4-71; nafarelin; nilutamide; Snow Brand NKS01; octreotide; Azko Nobel ORG-31710; Azko Nobel ORG-31806; orimeten; orimetene; orimetine; ormeloxifene; osaterone; Smithkline Beecham SKB-105657; Tokyo University OSW-1; Peptech PTL-03001; Pharmacia & Upjohn PNU-156765; quinagolide; ramorelix; Raloxifene; statin; sandostatin LAR; Shionogi S-10364; Novartis SMT-487; somavert; somatostatin; tamoxifen; tamoxifen methiodide; teverelix; toremifene; triptorelin; TT-232; vapreotide; vorozole; Yamanouchi YM-116; Yamanouchi YM-511; Yamanouchi YM-55208; Yamanouchi YM-53789; Schering AG ZK-1911703; Schering AG ZK-230211; and Zeneca ZD-182780.

In one embodiment, some hormonal agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to, those identified in Table No. 6, below.

Table No. 6. Hormonal agents

Compound	**Common Name/ Trade Name**	**Company**	**Reference**	**Dosage**
2-methoxyestradiol	EntreMed;	EntreMed		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	2-ME			
N-(S)-tetrahydrofuroyl-Gly-D2Nal-D4ClPhe-D3Pal-Ser-NMeTyr-DLys(Nic)-Leu-Lys(Isp)-Pro-DAla-NH2	A-84861	Abbott		
	raloxifene			
[3R-1-(2,2-Dimethoxyethyl)-3-((4-methylphenyl)aminocarbonylmethyl)-3-(N'-(4-me thylphenyl)ureido)-indoline-2-one]	AG-041R	Chugai	WO 94/19322	
	AN-207	Asta Medica	WO 97/19954	
Ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-	toremifene; Fareston®	Orion Pharma	EP 95875	60 mg/d
Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-	tamoxifen Nolvadex®	Zeneca	US 4536516	For patients with breast cancer, the recommended daily dose is 20-40 mg.

Compound	Common Name/ Trade Name	Company	Reference	Dosage
				Dosages greater than 20 mg per day should be divided (morning and evening).
D-Alaninamide N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3 -pyridinyl)-D-alanyl-L-seryl-N6-(3-pyridinylcarbonyl)-L-lysyl-N6-(3-pyridinylcarbonyl)-D-lysyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-	Antide; ORF-23541	Ares-Serono	WO 89/01944	25 or 50microg/ kg sc
	B2036-PEG; Somaver; Trovert	Sensus		
4-Methyl-2-[4-[2-(1-piperidinyl)ethoxy]phen	EM-800; EM-652	Laval University		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
yl]-7-(pivaloyloxy)-3-[4-(pivaloyloxy)phenyl]-2H-1-benzopyran				
	letrozol		US 4749346	
	goserelin		US 4100274	
3-[4-[1,2-Diphenyl-1(Z)-butenyl]phenyl]-2(E)-propenoic acid	GW-5638	Glaxo Wellcome		
Estra-1,3,5(10)-triene-3,17-diol, 7-[9-[(4,4,5,5,5-pentafluoro-pentyl) sulfinyl]-nonyl]-, (7alpha,17beta)-	ICI-182780; Faslodex; ZD-182780	Zeneca	EP 34/6014	250mg/mth
	J015X	Tulane University		
	LG-1127; LG-1447	Ligand Pharmaceuticals		
	LG-2293	Ligand Pharmaceuticals		
	LG-2527; LG-2716	Ligand Pharmaceuticals		
	buserelin,	Peptech		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	Peptech; deslorelin, Peptech; PTL-03001; triptorelin, Peptech			
	LR-103	Bone Care International		
[2-(4-Hydroxyphenyl)-6-hydroxynaphthalen-1-yl] [4-[2-(1-piperdinyl)ethoxy]phenyl]methane hydrochloride	LY-326315	Lilly	WO 9609039	
	LY-353381-HCl	Lilly		
	LY-326391	Lilly		
	LY-353381	Lilly		
	LY-357489	Lilly		
	MPV-2213ad	Orion Pharma	EP 476944	0.3-300 mg
Isobutyryl-Tyr-D-Arg-Asp-Ala-Ile-(4-Cl)-Phe-	MZ-4-71	Tulane University		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-(2-aminobutyryl)-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Nle-Ser 4-guanidinobutylamide				
Androst-4-ene-3,6,17-trione, 14-hydroxy-	NKS01; 14alpha-OHAT; 14OHAT	Snow Brand	EP 300062	
3beta,16beta,17alpha-trihydroxycholest-5-en-22-one-16-O-(2-0-4-methoxybenzoyl-beta-D-xylopyranosyl)-(1-3)(2-0-acetyl-alpha-L-arabinopyranoside)	OSW-1			
Spiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, 11-[4-(dimethylamino)phenyl] -4',5'-dihydro-6-methyl-, (6beta,11beta,17beta)-	Org-31710; Org-31806	Akzo Nobel	EP 289073	
(22RS)-N-(1,1,1-	PNU-	Pharmacia		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5alpha-androst-1-ene-17beta -carboxamide	156765; FCE-28260	& Upjohn		
1-[(benzofuran-2yl)-4-chlorophenylmethyl]imidazole		Menarini		
Tryptamine derivatives		Rhone-Poulenc Rorer	WO 96/35686	
Permanently ionic derivatives of steroid hormones and their antagonists		Pharmos	WO 95/26720	
Novel tetrahydronaphthofuranone derivatives		Meiji Seika	WO 97/30040	
	SMT-487; 90Y-octreotide	Novartis		
D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH2	TT-232			
2-(1H-imidazol-4-ylmethyl)-9H-carbazole	YM-116	Yamanou-chi		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
monohydrochloride monohydrate				
4-[N-(4-bromobenzyl)-N-(4-cyanophenyl)amino]-4H-1,2,4-triazole	YM-511	Yamanou-chi		
2-(1H-imidazol-4-ylmethyl)-9H-carbazole monohydrochloride monohydrate	YM-55208; YM-53789	Yamanou-chi		
	ZK-1911703	Schering AG		
	ZK-230211	Schering AG		
	abarelix	Praecis Pharmace uticals		
Androsta-5,16-dien-3-ol, 17-(3-pyridinyl)-, acetate (ester), (3beta)-	abiraterone acetate; CB-7598; CB-7630	BTG		
2,6-Piperidinedione, 3-(4-aminophenyl)-3-ethyl-	aminoglutet himide; Ciba-16038; Cytadren;	Novartis	US 3944671	

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	Elimina; Orimeten; Orimetene; Orimetine			
1,3-Benzenediacetonitrile,alpha,alpha,alpha',alpha'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-	anastrozole; Arimidex; ICI-D1033; ZD-1033	Zeneca	EP 296749	1mg/day
5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-2-methyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide	avorelin; Meterelin	Medi-olanum	EP 23904	
Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl) sulfonyl]-2-hydroxy-2-methyl-, (+/-)-	bicalutamide; Casodex; Cosudex; ICI-176334	Zeneca	EP 100172	
Luteinizing hormone-releasing factor (pig), 6-[O-(1,1-dimethylethyl)-D-serine] -9-(N-ethyl-	buserelin; Hoe-766; Profact; Receptal;	Hoechst Marion Roussel	GB 15/23623	200-600 microg/day

Compound	Common Name/ Trade Name	Company	Reference	Dosage
L-prolinamide)-10-deglycinamide-	S-746766; Suprecor; Suprecur; Suprefact; Suprefakt			
D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N5-(aminocarbonyl)- D-ol-L-leucyl-L-arginyl-L-prolyl-	cetrorelix; SB-075; SB-75	Asta Medica	EP 29/9402	
Phosphonic acid, (dichloromethylene)bis-, disodium salt-	clodronate disodium, Leiras; Bonefos; Clasto-ban; KCO-692	Schering AG		
Luteinizing hormone-releasing factor (pig), 6-D-tryptophan-9-(N-ethyl-L- prolinamide)-10-deglycinamide-	deslorelin; gonadorelin analogue, Roberts; LHRH analogue,	Roberts	US 4034082	

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	Roberts; Somagard			
Phenol, 3-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butenyl]-, (E)- [CA S]	droloxifene; FK-435; K-060; K-21060E; RP 60850	Klinge	EP 54168	
4-Azaandrost-1-ene-17-carboxamide, N-(2,5-bis(trifluoromethyl)phenyl)-3-oxo-, (5alpha,17beta)-	dutasteride; GG-745; GI-198745	Glaxo Wellcome		
Androstan-17-ol, 2,3-epithio-, (2alpha,3alpha,5alpha,17beta)-	epitiostanol; 10275-S; epithioandrostanol; S-10275; Thiobrestin; Thiodrol	Shionogi	US 3230215	
Androsta-3,5-diene-3-carboxylic acid, 17-(((1,1-dimethylethyl)amino)carbonyl)- (17beta)-	epristeride; ONO-9302; SK&F-105657; SKB-105657	Smith-Kline Beecham	EP 289327	0.4-160mg/day
estrone 3-O-sulfamate	estrone 3-			

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	O-sulfamate			
19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, 3-(2-propanesulfonate) , (17alpha)-	ethinyl estradiol sulfonate; J96; Turisteron	Schering AG	DE 1949095	
Androsta-1,4-diene-3,17-dione, 6-methylene-	exemestane ; FCE-24304	Pharmacia & Upjohn	DE 3622841	5mg/kg
Benzonitrile, 4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)- , monohydrochloride	fadrozole; Afema; Arensin; CGS-16949; CGS-16949A; CGS-20287; fadrozole monohydrochloride	Novartis	EP 165904	1 mg po bid
4-Azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo- , (5alpha,17beta)-	finasteride; Andozac; ChibroProscar;	Merck & Co	EP 155096	5mg/day

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	Finastid; MK-0906; MK-906; Procure; Prodel; Propecia; Proscar; Proskar; Prostide; YM-152			
Propanamide, 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-	flutamide; Drogenil; Euflex; Eulexin; Eulexine; Flucinom; Flutamida; Fugerel; NK-601; Odyne; Prostogenat; Sch-13521	Schering Plough	US 4329364	
Androst-4-ene-3,17-dione, 4-hydroxy-	formestane; 4-HAD; 4-OHA; CGP-	Novartis	EP 346953	250 or 600mg/day po

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	32349; CRC-82/01; Depot; Lentaron			
[N-Ac-D-Nal,D-pCl-Phe,D-Pal,D-hArg(Et)2,hArg(Et)2,D-Ala]GnRH-	ganirelix; Org-37462; RS-26306	Roche	EP 312052	
	gonadorelin agonist, Shire	Shire		
Luteinizing hormone-releasing factor (pig), 6-[O-(1,1-dimethylethyl)-D-serine] -10-deglycinamide-, 2-(aminocarbonyl)hydrazide	goserelin; ICI-118630; Zoladex; Zoladex LA	Zeneca	US 4100274	
	hCG; gonadotrophin; LDI-200	Milkhaus		
	human chorionic gonadotrop	NIH		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	hin; hCG			
Pyrrolidine, 1-[2-[4-[1-(4-iodophenyl)-2-phenyl-1-butenyl]phenoxy]ethyl]-, (E)-	idoxifene; CB-7386; CB-7432; SB-223030	BTG	EP 260066	
	isocordoin	Indena		
2,4(1H,3H)-Quinazolinedione, 3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-	ketanserin; Aseranox; Ketensin; KJK-945; ketanserine; Perketan; R-41468; Serefrex; Serepress; Sufrexal; Taseron	Johnson & Johnson	EP 13612	
L-Threoninamide, 3-(2-naphthalenyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D- tryptophyl-L-lysyl-L-valyl-L-cysteinyl-, cyclic (2-7)-disulfide	lanreotide; Angiopeptin; BIM-23014; Dermopeptin; Ipstyl; Somatuline;	Beaufour-Ipsen	EP 215171	

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	Somatuline LP			
Benzonitrile, 4,4'-(1H-1,2,4-triazol-1-ylmethylene)bis-	letrozole; CGS-20267;Femara	Novartis	EP 236940	2.5mg/day
Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamid e)-10-deglycinamide-	leuprolide, Atrigel; leuprolide, Atrix	Atrix		
Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L- prolinamide)-10-deglycinamide-	leuprorelin; Abbott-43818; Carcinil; Enantone; Leuplin; Lucrin; Lupron; Lupron Depot; leuprolide, Abbott; leuprolide, Takeda; leuprorelin, Takeda;	Abbott	US 4005063	3.75microg sc q 28 days

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	Procren Depot; Procrin; Prostap; Prostap SR; TAP-144-SR			
Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamid e)-10-deglycinamide-	leuprorelin, DUROS; leuprolide, DUROS; leuprorelin	Alza		
1H-Benzimidazole, 5-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]-	liarozole; Liazal; Liazol; liarozole fumarate; R-75251; R-85246; Ro-85264	Johnson & Johnson	EP 260744	300mg bid
Urea, N'-[(8alpha)-9,10-didehydro-6-methylergolin-8-yl]-N,N-diethyl-, (Z)-2-butenedioate (1:1)	lisuride hydrogen maleate; Cuvalit; Dopergin; Dopergine; Eunal;	VUFB		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	Lysenyl; Lysenyl Forte; Revanil			
Pentanoic acid, 4-[(3,4-dichlorobenzoyl)amino] -5-[(3-methoxypropyl) pentylamino]-5-oxo-, (+/-)-	loxiglu-mide; CR-1505	Rotta Research	WO 87/03869	
Androstane, 2,3-epithio-17-[(1-methoxycyclopentyl)oxy]-, (2alpha,3alpha,5alpha,17beta) -	mepitio-stane; S-10364; Thioderon	Shionogi	US 3567713	
Phenol, 4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-[4-(1-methylethyl) phenyl]-1-butenyl]-, dihydrogen phosphate (ester), (E)-	miproxi-fene phosphate; DP-TAT-59; TAT-59	Taiho	WO 87/07609	20mg/day
Luteinizing hormone-releasing factor (pig), 6-[3-(2-naphthalenyl)-D-alanine]-	nafarelin; NAG, Syntex; Nasanyl; RS-94991;	Roche	EP 21/234	

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	RS-94991-298; Synarel; Synarela; Synrelina			
2,4-Imidazolidinedione, 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]-	nilutamide; Anandron; Nilandron; Notostran; RU-23908	Hoechst Marion Roussel	US 4472382	
	obesity gene; diabetes gene; leptin	Lilly	WO 96/24670	
L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L- lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]-	octreotide; Longastatina; octreotide pamoate; Sandostatin; Sandostatin LAR; Sandostatina; Sandostatine; SMS-	Novartis	EP 29/579	

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	201-995			
Pyrrolidine, 1-[2-(p-(7-methoxy-2,2-dimethyl-3-phenyl-4-chromanyl) phenoxy)ethyl]-, trans-	ormeloxifene; 6720-CDRI; Centron; Choice-7; centchroman; Saheli	Central Drug Research Inst.	DE 2329201	
2-Oxapregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-chloro-	osaterone acetate; Hipros; TZP-4238	Teikoku Hormone	EP 193871	
Pregn-4-ene-3,20-dione	progesterone; Crinone	Columbia Laboratories		
Sulfamide, N,N-diethyl-N'-(1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propylbenzo[g]quinolin-3-yl)-, (3alpha,4aalpha,10abeta)- (+/-)-	quinagolide; CV-205-502; Norprolac; SDZ-205-502	Novartis	EP 77754	
L-Proline, 1-(N2-(N-(N-(N-(N-(N-(N-(N-acetyl-3-(2-	ramorelix; Hoe-013; Hoe-013C;	Hoechst Marion Roussel	EP 451791	

Compound	Common Name/ Trade Name	Company	Reference	Dosage
naphthalenyl)-D-alanyl)-4-chl oro-D-phenylalanyl)-D-tryptophyl)-L-seryl)-L-tyrosyl)-O-(6-deoxy-alpha-L-mannopyranosyl)-D-seryl)-L-leucyl)-L-arginyl)-, 2-(aminocarbonyl)hydrazide-	Hoe-2013			
	somatostatin analogues	Tulane University		
Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-	tamoxifen; Ceadan; ICI-46474; Kessar; Nolgen; Nolvadex; Tafoxen; Tamofen; Tamoplex; Tamoxasta; Tamoxen; Tomaxen	Zeneca	US 4536516	
	tamoxifen	Pharmos		

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	methiodide			
Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (z)-	tamoxifen	Douglas		
D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N6-(aminocarbonyl)-D-lysyl-L -leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl-	teverelix; Antarelix	Asta Medica		
Ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-	toremifene; Estrimex; Fareston; FC-1157; FC-1157a; NK-622	Orion Pharma	EP 95875	60mg po
Luteinizing hormone-releasing factor (pig), 6-D-tryptophan-	triptorelin; ARVEKAP ; AY-25650;	Debio-pharm	US 4010125	

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	BIM-21003; BN-52104; Decap-eptyl; WY-42422			
L-Tryptophanamide, D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl- L-valyl-L-cysteinyl-, cyclic (2-7)-disulfide-	vapreotide; BMY-41606; Octastatin; RC-160	Debio-pharm	EP 203031	500 microg sc tid
1H-Benzotriazole, 6-[(4-chlorophenyl)-1H-1,2,4-triazol-1-ylmethyl]-1-methyl-	vorozole; R-76713; R-83842; Rivizor	Johnson & Johnson	EP 293978	2.5 mg/day

Among hormones that may be used in the methods, combinations and compositions of the present inventive include, diethylstilbestrol (DES), leuprolide, flutamide, cyproterone acetate, ketoconazole and amino glutethimide are preferred.

Immunotherapy

The methods, combinations and compositions of the present invention may also be used in combination with monoclonal antibodies in treating cancer. For example monoclonal antibodies may be used in treating prostate cancer. A specific example of such an antibody includes cell membrane-specific anti-prostate antibody.

The present invention may also be used with immunotherapies based on polyclonal or monoclonal antibody-derived reagents, for instance. Monoclonal antibody-based reagents are most preferred in this regard. Such reagents are well known to persons of ordinary skill in the art. Radiolabelled monoclonal antibodies for cancer therapy, such as the recently approved use of monoclonal antibody conjugated with strontium-89, also are well known to persons of ordinary skill in the art.

Cryotherapy

Cryotherapy recently has been applied to the treatment of some cancers. Methods, combinations and compositions of the present invention also could be used in conjunction with an effective therapy of this type.

Chemotherapy

Chemotherapy includes treating a patient with agents that exert antineoplastic effects, i.e., prevent the development, maturation, or spread of neoplastic cells, directly on the tumor cell, e.g., by cytostatic or cytocidal effects, and not indirectly through mechanisms such as biological response modification. There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development that could be used in the methods, combinations and compositions of the present invention for treatment of neoplasia. For convenience of discussion, antineoplastic agents are classified into the following classes, subtypes and species:

ACE inhibitors,
alkylating agents,
angiogenesis inhibitors,
angiostatin,
anthracyclines/DNA intercalators,
anti-cancer antibiotics or antibiotic-type agents,
antimetabolites,
antimetastatic compounds,

asparaginases,

bisphosphonates,

cGMP phosphodiesterase inhibitors,

calcium carbonate,

COX-2 inhibiting agents (e.g., COX-2 selective inhibiting agents or prodrugs of COX-2 selective inhibiting agents)

DHA derivatives,

endostatin,

epipodophylotoxins,

genistein,

hormonal anticancer agents,

hydrophilic bile acids (URSO),

immunomodulators or immunological agents,

integrin antagonists

interferon antagonists or agents,

MMP inhibitors,

miscellaneous antineoplastic agents,

monoclonal antibodies,

nitrosoureas,

NSAIDs,

ornithine decarboxylase inhibitors,

pBATTs,

radio/chemo sensitizers/protectors,

retinoids

selective inhibitors of proliferation and migration of endothelial cells,

selenium,

stromelysin inhibitors,

taxanes,

vaccines, and

vinca alkaloids.

The major categories that some antineoplastic agents fall into include antimetabolite agents, alkylating agents, antibiotic-type agents, immunological agents, interferon-type agents, and a category of miscellaneous antineoplastic agents. Some antineoplastic agents operate through multiple or unknown mechanisms and can thus be classified into more than one category.

A first family of antineoplastic agents which may be used in combination with the present invention consists of antimetabolite-type antineoplastic agents. Antimetabolites are typically reversible or irreversible enzyme inhibitors, or compounds that otherwise interfere with the replication, translation or transcription of nucleic acids. Suitable antimetabolite antineoplastic agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to acanthifolic acid, aminothiadiazole, anastrozole, bicalutamide, brequinar sodium, capecitabine, carmofur, Ciba-Geigy CGP-30694, cladribine, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, cytarabine ocfosfate, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, finasteride, floxuridine, fludarabine phosphate, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, fluorouracil (5-FU), 5-FU-fibrinogen, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, nafarelin, norspermidine, nolvadex, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, stearate; Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT, toremifene, and uricytin.

In one embodiment, some antimetabolite agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to, those identified in Table No. 6, below.

Table No. 6 . Antimetabolite agents

Compound	Common Name/ Trade Name	Company	Reference	Dosage
1,3-Benzenediacetonitrile,alpha,alpha,alpha',alpha'-tetramethyl-5-(1H-1,2,4-triazol-1-ylme thyl)-	anastrozole; Arimidex®	Zeneca	EP 296749	1-mg/day
Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl) sulfonyl]-2-hydroxy-2-methyl-, (+/-)-	bicalutamide; Casodex®	Zeneca	EP 100172	50 mg once daily
	capecitabine	Roche	US 5472949	
Adenosine, 2-chloro-2'-deoxy-; 2-chloro-2'-deoxy-(beta)-D-adenosine)	cladribine; 2-CdA; Leustatin® injection; Leustatin®; Leustat® Leustatine®; RWJ-26251;	Johnson & Johnson	EP 173059	0.09 mg/kg/day for 7 days.
2(1H)-Pyrimidinone, 4-amino-1-[5-O-	cytarabine ocfosfate; ara CMP stearyl	Yamasa Corp	EP 239015	100 - 300 mg/day for 2 weeks

Compound	Common Name/ Trade Name	Company	Reference	Dosage
[hydroxy(octadecyloxy)phosphinyl]-beta-D-arabinofuranosyl]-, monosodium salt	ester; C-18-PCA; cytarabine phosphate stearate; Starasid; YNK-O1; Cytosar-U®			
4-Azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo- , (5alpha,17beta)-	finasteride; Propecia®	Merck & Co	EP 155096	
	fluorouracil (5-FU)		US 4336381	
Fludarabine phosphate. 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-beta-D-arabinofuranosyl)	fludarabine phosphate; 2-F-araAMP; Fludara; Fludara iv; Fludara Oral; NSC-312887; SH-573; SH-584; SH-586;	Southern Research Institute; Berlex	US 4357324	25 mg/m^2/d IV over a period of approx-imately 30 minutes daily for 5 con-secutive days, commenced every 28

Compound	Common Name/ Trade Name	Company	Reference	Dosage
				days.
	gemcitabine	Eli Lily	US 4526988	
N-(4-(((2,4-diamino- 6-pteridinyl)methyl) methylamino)benzoyl)-L- glutamic acid	methotrexate iv, Hyal; HA + methotrexate, Hyal; methotrexate iv, HIT Technolog;	Hyal Pharma-ceutical; American Home Products; Lederle	US 2512572	tropho-blastic diseases: 15 to 30 mg/d orally or intra-muscularly in a five-day course (repeated 3 to 5 times as needed)
Luteinizing hormone-releasing factor (pig), 6-[3-(2-naphthalenyl)-D-alanine]-	nafarelin	Roche	EP 21234	
	pentostatin; CI-825; DCF; deoxycoformycin; Nipent; NSC-218321; Oncopent;	Warner-Lambert	US 3923785	
Ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-	toremifene; Fareston®	Orion Pharma	EP 95875	60 mg/d

Compound	Common Name/ Trade Name	Company	Reference	Dosage
butenyl)phenoxy]-N,N-dimethyl-, (Z)-				

A second family of antineoplastic agents which may be used in combination with the present invention consists of alkylating-type antineoplastic agents. The alkylating agents are believed to act by alkylating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents include nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin, and various nitrosoureas. A disadvantage with these compounds is that they not only attack malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastro-intestinal mucosa, and fetal tissue. Suitable alkylating-type antineoplastic agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to, Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine (BiCNU), Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, dacarbazine, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, etoposide phosphate, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, mycophenolate, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, thiotepa, Yakult Honsha SN-22, spiromUS tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

In one embodiment some alkylating agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to, those identified in Table No. 7, below.

Table No. 7. Alkylating agents

Compound	**Common Name/ Trade Name**	**Company**	**Reference**	**Dosage**
Platinum, diammine[1,1-cyclobu-tanedicarboxylat o(2-)]-, (SP-4-2)-	carboplatin; Pareplatin ®	Johnson Matthey	US 4657927. US 4140707.	360 mg/m(squared) I.V. on day 1 every 4 weeks.
Carmustine, 1,3-bis (2-chloroethyl)-1-nitro-sourea	BiCNU®	Ben Venue Labora-tories, Inc.	JAMA 1985; 253 (11): 1590-1592.	Preferred: 150 to 200 mg/ m^2 every 6 wks.
	etoposide phosphate	Bristol-Myers Squibb	US 4564675	
	thiotepa			
Platinum, diamminedi-chloro-, (SP-4-2)-	cisplatin; Plationol®-AQ	Bristol-Myers Squibb	US 4177263	
dacarbazine	DTIC Dome	Bayer		2 to 4.5mg/kg/da y for 10 days; 250mg/

Compound	Common Name/ Trade Name	Company	Reference	Dosage
				square meter body surface/ day I.V. for 5 days every 3 weeks
ifosfamide	IFEX	Bristol-Meyers Squibb		4-5 g/m (square) single bolus dose, or 1.2-2 g/m (square) I.V. over 5 days.
	cyclophosph-amide		US 4537883	
cis-diaminedichloro platinum	Platinol® Cisplatin®	Bristol-Myers Squibb		20 mg/M^2 IV daily for a 5 day cycle.

A third family of antineoplastic agents which may be used in methods, combinations and compositions of the present invention is the antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-

Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

In one embodiment, some antibiotic anticancer agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to, those agents identified in Table No. 8, below.

Table No. 8. Antibiotic anticancer agents

Compound	**Common Name/ Trade Name**	**Company**	**Reference**	**Dosage**
4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-	mycophenolate mofetil	Roche	WO 91/19498	1 to 3 gm/d

Compound	Common Name/ Trade Name	Company	Reference	Dosage
3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (E)-				
	mitoxantrone		US 4310666	
	doxorubicin		US 3590028	
Mitomycin and/or mitomycin-C	Mutamycin	Bristol-Myers Squibb Oncology/Immun-ology		After full hemato-logical recovery from any previous chemo-therapy: 20 mg/m^2 intra-venously as a single dose via a function-ing intra-venous catheter.

A fourth family of antineoplastic agents which may be used in methods, combinations and compositions of the present invention consists of synthetic nucleosides. Several synthetic nucleosides have been identified that exhibit anticancer activity. A well known nucleoside derivative with strong anticancer activity is 5-fluorouracil (5-FU). 5-Fluorouracil has been used clinically in the treatment of malignant tumors, including, for example, carcinomas, sarcomas, skin cancer, cancer of the digestive organs, and breast cancer. 5-Fluorouracil, however, causes serious adverse reactions such as nausea, alopecia, diarrhea, stomatitis,

leukocytic thrombocytopenia, anorexia, pigmentation, and edema. Derivatives of 5-fluorouracil with anti-cancer activity have been described in U.S. Pat. No. 4,336,381. Further 5-FU derivatives have been described in the following patents listed in Table No. 9, hereby individually incorporated by reference herein.

Table No. 9. 5-Fu derivatives

JP 50-50383	JP 50-50384	JP 50-64281
JP 51-146482	JP 53-84981	

U.S. Pat. No. 4,000,137 discloses that the peroxidate oxidation product of inosine, adenosine, or cytidine with methanol or ethanol has activity against lymphocytic leukemia. Cytosine arabinoside (also referred to as Cytarabin, araC, and Cytosar) is a nucleoside analog of deoxycytidine that was first synthesized in 1950 and introduced into clinical medicine in 1963. It is currently an important drug in the treatment of acute myeloid leukemia. It is also active against acute lymphocytic leukemia, and to a lesser extent, is useful in chronic myelocytic leukemia and non-Hodgkin's lymphoma. The primary action of araC is inhibition of nuclear DNA synthesis. Handschumacher, R. and Cheng, Y., "Purine and Pyrimidine Antimetabolites", Cancer Medicine, Chapter XV-1, 3rd Edition, Edited by J. Holland, et al., Lea and Febigol, publishers.

5-Azacytidine is a cytidine analog that is primarily used in the treatment of acute myelocytic leukemia and myelodysplastic syndrome.

2-Fluoroadenosine-5'-phosphate (Fludara, also referred to as FaraA) is one of the most active agents in the treatment of chronic lymphocytic leukemia. The compound acts by inhibiting DNA synthesis. Treatment of cells with F-araA is associated with the accumulation of cells at the G1/S phase boundary and in S phase; thus, it is a cell cycle S phase-specific drug. InCorp of the active metabolite, F-araATP, retards DNA chain elongation. F-araA is also a potent inhibitor of ribonucleotide reductase, the key enzyme responsible for the formation of dATP. 2-Chlorodeoxyadenosine is useful in the treatment of low grade B-cell neoplasms such as chronic lymphocytic leukemia, non-Hodgkins' lymphoma, and hairy-cell

leukemia. The spectrum of activity is similar to that of Fludara. The compound inhibits DNA synthesis in growing cells and inhibits DNA repair in resting cells.

A fifth family of antineoplastic agents which may be used in methods, combinations and compositions of the present invention consists of a miscellaneous family of antineoplastic agents including, but not limited to alpha-carotene, alpha-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristo-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, calcium carbonate, Calcet, Calci-Chew, Calci-Mix, Roxane calcium carbonate tablets, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Cell Pathways CP-461, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, DFMO, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel, Encore Pharmaceuticals E7869, elliprabin, elliptinium acetate, Tsumura EPMTC, ergotamine, etoposide, etretinate, Eulexin®, Cell Pathways Exisulind® (sulindac sulphone or CP-246), fenretinide, Merck Research Labs Finasteride, Florical, Fujisawa FR-57704, gallium nitrate, gemcitabine, genkwadaphnin, Gerimed, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, irinotecan, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, ketoconazole, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leucovorin, levamisole, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, Materna, NCI (US) MAP, marycin, Merrel Dow MDL-27048,

Medco MEDR-340, megestrol, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone, Monocal, mopidamol, motretinide, Zenyaku Kogyo MST-16, Mylanta, N-(retinoyl)amino acids, Nilandron; Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, Nephro-Calci tablets, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, retinoids, Encore Pharmaceuticals R-flurbiprofen, Sandostatin; Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, Scherring-Plough SC-57050, Scherring-Plough SC-57068, selenium(selenite and selenomethionine), SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, Sugen SU-101, Sugen SU-5416, Sugen SU-6668, sulindac, sulindac sulfone; superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides, Yamanouchi YM-534, Zileuton, ursodeoxycholic acid, and Zanosar.

In one embodiment, some miscellaneous agents that may be used in the methods, combinations and compositions of the present invention include, but are not limited to, those identified in Table No. 10, below.

Table No. 10. Miscellaneous agents

Compound	Common Name/ Trade Name	Company	Reference	Dosage
Flutamide; 2-methyl- N-(4-nitro-3-(trifluoro-methyl)phenyl) propanamide	Eulexin®	Schering Corp		750 mg/d in 3 8-hr doses.
	Ketoconazle		US 4144346	
	leucovorin		US 4148999	
	levamisole		GB 11/20406	
	megestrol		US 4696949	
	paclitaxel		US 5641803	
Nilutamide 5,5-dimethyl 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidinedion e	Nilandron	Hoechst Marion Roussel		A total daily dose of 300 mg for 30 days followed thereafter by three tablets (50 mg each) once a day for a total daily dosage of 150 mg.
	Vinorelbine		EP 0010458	
	vinblastine			
	vincristine			
Octreotide acetate L-cysteinamide, D-phenylalanyl-L-	Sandostatin	Sandoz Pharma-ceuticals		s.c. or i.v. administration Acromegaly:

Compound	Common Name/ Trade Name	Company	Reference	Dosage
cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-NSAIDs-(2-hydroxy-1-(hydroxymethyl)propyl)-, cyclic-disulfide; (R-(R*,R*) acetate salt				50 - 300 mcgm tid. Carcinoid tumors: 100 - 600 mcgm/d (mean = 300 mcgm/d) Vipomas: 200-300 mcgm in first two weeks of therapy
Streptozocin Streptozocin 2-deoxy-2-(((methylnitrosamino)carbonyl)amino)-alpha(and beta)-D-glucopyranose)	Zanosar	Pharmacia & Upjohn		i.v. 1000 mg/M2 of body surface per week for two weeks.
Selenium			EP 804927	
L-selenomethionine	Aces®	J.R. Carlson Laborat-ories		
calcium carbonate				
sulindac sulfone	Exisuland®		US 5858694	

Compound	Common Name/ Trade Name	Company	Reference	Dosage
ursodeoxycholic acid			US 5843929	
	Cell Pathways CP-461			

Additional antineoplastic agents that may be used in the methods, combinations and compositions of the of the present invention include those described in the individual patents listed in Table No. 11 below, each of which is hereby individually incorporated by reference.

Table No. 11. Antineoplastic agents

EP 0296749	EP 0882734	EP 00253738	GB 02/135425
WO 09/832762	EP 0236940	US 5338732	US 4418068
US 4692434	US 5464826	US 5061793	EP 0702961
EP 0702961	EP 0702962	EP 0095875	EP 0010458
EP 0321122	US 5041424	JP 60019790	WO 09/512606
US 4,808614	US 4526988	CA 2128644	US 5455270
WO 99/25344	WO 96/27014	US 5695966	DE 19547958
WO 95/16693	WO 82/03395	US 5789000	US 5902610
EP 189990	US 4500711	FR 24/74032	US 5925699
WO 99/25344	US 4537883	US 4808614	US 5464826
US 5366734	US 4767628	US 4100274	US 4584305
US 4336381	JP 5050383	JP 5050384	JP 5064281
JP 51146482	JP 5384981	US 5472949	US 5455270
US 4140704	US 4537883	US 4814470	US 3590028
US 4564675	US 4526988	US 4100274	US 4604463

US 4144346	US 4749713	US 4148999	GB 11/20406
US 4696949	US 4310666	US 5641803	US 4418068
US 5,004758	EP 0095875	EP 0010458	US 4935437
US 4,278689	US 4820738	US 4413141	US 5843917
US 5,858694	US 4330559	US 5851537	US 4499072
US 5,217886	WO 98/25603	WO 98/14188	

Table No. 13 provides illustrative examples of median dosages for selected cancer agents that may be used in present invention. It should be noted that specific dose regimen for the chemotherapeutic agents below depends upon dosing considerations based upon a variety of factors including the type of neoplasia; the stage of the neoplasm; the age, weight, sex, and medical condition of the patient; the route of administration; the renal and hepatic function of the patient; and the particular combination employed.

Table No. 13. Median dosages for selected cancer agents.

NAME OF CHEMOTHERAPEUTIC AGENT	MEDIAN DOSAGE
Asparaginase	10,000 units
Bleomycin Sulfate	15 units
Carboplatin	50-450 mg.
Carmustine	100 mg.
Cisplatin	10-50 mg.
Cladribine	10 mg.
Cyclophosphamide (lyophilized)	100 mg.-2 gm.
Cyclophosphamide (non-lyophilized)	100 mg.-2 gm.
Cytarabine (lyophilized	100 mg.-2 gm.

powder)	
Dacarbazine	100 mg.-200 mg.
Dactinomycin	0.5 mg.
Daunorubicin	20 mg.
Diethylstilbestrol	250 mg.
Doxorubicin	10-150 mg.
Etidronate	300 mg.
Etoposide	100 mg.
Floxuridine	500 mg.
Fludarabine Phosphate	50 mg.
Fluorouracil	500 mg.-5 gm.
Goserelin	3.6 mg.
Granisetron Hydrochloride	1 mg.
Idarubicin	5-10 mg.
Ifosfamide	1-3 gm.
Leucovorin Calcium	20-350 mg.
Leuprolide	3.75-7.5 rng.
Mechlorethamine	10 mg.
Medroxyprogesterone	1 gm.
Melphalan	50 mg.
Methotrexate	20 mg.-1 gm.
Mitomycin	5-40 mg.
Mitoxantrone	20-30 mg.
Ondansetron Hydrochloride	40 mg.
Paclitaxel	30 mg.
Pamidronate Disodium	30-90 mg.
Pegaspargase	750 units
Plicamycin	2,500 mcgm.
Streptozocin	1 gm.
Thiotepa	15 mg.
Teniposide	50 mg.

Vinblastine	10 mg.
Vincristine	1-5 mg.
Aldesleukin	22 million units
Epoetin Alfa	2,000-10,000 units
Filgrastim	300-480 mcgm.
Immune Globulin	500 mg.-10 gm.
Interferon Alpha-2a	3-36 million units
Interferon Alpha-2b	3-50 million units
Levamisole	50 mg.
Octreotide	1,000-5,000 mcgm.
Sargramostim	250-500 mcgm.

The anastrozole used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,935,437. The capecitabine used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,472,949. The carboplatin used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,455,270. The Cisplatin used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,140,704. The cyclophoshpamide used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,537,883. The eflornithine (DFMO) used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,413,141. The docetaxel used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,814,470. The doxorubicin used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 3,590,028. The etoposide used in the therapeutic methods, combinations and compositions of

the present invention can be prepared in the manner set forth in U.S. Patent No. 4,564,675. The fluorouracil used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,336,381. The gemcitabine used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,526,988. The goserelin used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,100,274. The irinotecan used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,604,463. The ketoconazole used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,144,346. The letrozole used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,749,713. The leucovorin used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,148,999. The levamisole used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in GB 11/20,406. The megestrol used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,696,949. The mitoxantrone used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,310,666. The paclitaxel used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,641,803. The Retinoic acid used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,843,096. The tamoxifen used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,418,068. The topotecan used in the therapeutic methods, combinations and compositions of the present

invention can be prepared in the manner set forth in U.S. Patent No. 5,004,758. The toremifene used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in EP 095,875. The vinorelbine used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in EP 010,458. The sulindac sulfone used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,858,694. The selenium (selenomethionine) used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in EP 08/04,927. The ursodeoxycholic acid used in the therapeutic methods, combinations and compositions of the present invention can be prepared in the manner set forth in WO 97/34,608. Ursodeoxycholic acid can also be prepared according to the manner set forth in EP 05/99,282. Finally, ursodeoxycholic acid can be prepared according to the manner set forth in U.S. Patent No. 5,843,929.

In another embodiment, antineoplastic agents that may be used in the methods, combinations and compositions of the present invention include: anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, cyclophosphamide, docetaxel, doxorubicin, etoposide, Exisulind®, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO).

The phrase "taxane" includes a family of diterpene alkaloids all of which contain a particular eight (8) member "taxane" ring structure. Taxanes such as paclitaxel prevent the normal post division breakdown of microtubules which form to pull and separate the newly duplicated chromosome pairs to opposite poles of the cell prior to cell division. In cancer cells which are rapidly dividing, taxane therapy causes the microtubules to accumulate which ultimately prevents further division of the cancer cell. Taxane therapy also affects other cell processes dependant on

microtubules such as cell motility, cell shape and intracellular transport. The major adverse side-effects associated with taxane therapy can be classified into cardiac effects, neurotoxicity, haematological toxicity, and hypersensitivity reactions. (See Exp. Opin. Thera. Patents (1998) 8(5), hereby incorporated by reference). Specific adverse side-effects include neutropenia, alopecia, bradycardia, cardiac conduction defects, acute hypersensitivity reactions, neuropathy, mucositis, dermatitis, extravascular fluid accumulation, arthralgias, and myalgias. Various treatment regimens have been developed in an effort to minimize the side effects of taxane therapy, but adverse side-effects remain the limiting factor in taxane therapy.

It has been recently discovered in vitro that COX-2 expression is elevated in cells treated with taxanes. Elevated levels of COX-2 expression are associated with inflammation and generation of other COX-2 derived prostaglandin side effects. Consequently, when taxane therapy is provided to a patient, the administration of a COX-2 selective inhibiting agent is contemplated to reduce the inflammatory and other COX-2 derived prostaglandin side effects associated with taxane therapy. It is contemplated that the of addition of a DNA topoisomerase I inhibiting agent will further improve therapy options for treating, preventing or reducing the risk of developing neoplastic disease.

Taxane derivatives have been found to be useful in treating refractory ovarian carcinoma, urothelial cancer, breast carcinoma, melanoma, non-small-cell lung carcinoma, gastric, and colon carcinomas, squamous carcinoma of the head and neck, lymphoblastic, myeloblastic leukemia, and carcinoma of the esophagus.

Paclitaxel is typically administered in a 15-420 mg/m^2 dose over a 6 to 24 hour infusion. For renal cell carcinoma, squamous carcinoma of head and neck, carcinoma of esophagus, small and non-small cell lung cancer, and breast cancer, paclitaxel is typically administered as a 250 mg/m^2 24 hour infusion every 3 weeks. For refractory ovarian cancer paclitaxel is typically dose escalated starting at 110 mg/m^2. Docetaxel is typically administered in a 60 - 100 mg/M^2 i.v. over 1 hour, every three weeks. It should be noted, however, that specific dose regimen depends upon dosing considerations based upon a variety of factors including the type of

neoplasia; the stage of the neoplasm; the age, weight, sex, and medical condition of the patient; the route of administration; the renal and hepatic function of the patient; and the particular agents and combination employed.

In one embodiment, paclitaxel is used in the methods, combinations and compositions of the present invention in combination with a COX-2 selective inhibiting agent, a DNA topoisomerase I inhibiting agent and with cisplatin, cyclophosphamide, or doxorubicin for the treatment of breast cancer. In another embodiment paciltaxel is used in combination with a COX-2 selective inhibiting agent, a DNA topoisomerase I inhibiting agent and cisplatin or carboplatin, and ifosfamide for the treatment of ovarian cancer.

In another embodiment docetaxal is used in the methods, combinations and compositions of the present invention in combination with a COX-2 selective inhibiting agent, a DNA topoisomerase I inhibiting agent and with cisplatin, cyclophosphamide, or doxorubicin for the treatment of ovary and breast cancer and for patients with locally advanced or metastatic breast cancer who have progressed during anthracycline based therapy.

The following references listed in Table No. 14 below, hereby individually incorporated by reference herein, describe various taxanes and taxane derivatives suitable for use in the methods, combinations and compositions of the present invention, and processes for their manufacture.

Table No. 14. Taxanes and taxane derivatives

EP 694539	EP 683232	EP 639577	EP 627418
EP 604910	EP 797988	EP 727492	EP 767786
EP 767376	US 5886026	US 5880131	US 5879929
US 5871979	US 5869680	US 5871979	US 5854278
US 5840930	US 5840748	US 5827831	US 5824701
US 5821363	US 5821263	US 5811292	US 5808113
US 5808102	US 5807888	US 5780653	US 5773461
US 5770745	US 5767282	US 5763628	US 5760252

US 5760251	US 5756776	US 5750737	US 5744592
US 5739362	US 5728850	US 5728725	US 5723634
US 5721268	US 5717115	US 5716981	US 5714513
US 5710287	US 5705508	US 5703247	US 5703117
US 5700669	US 5693666	US 5688977	US 5684175
US 5683715	US 5679807	US 5677462	US 5675025
US 5670673	US 5654448	US 5654447	US 5646176
US 5637732	US 5637484	US 5635531	US 5631278
US 5629433	US 5622986	US 5618952	US 5616740
US 5616739	US 5614645	US 5614549	US 5608102
US 5599820	US 5594157	US 5587489	US 5580899
US 5574156	US 5567614	US 5565478	US 5560872
US 5556878	US 5547981	US 5539103	US 5532363
US 5530020	US 5508447	US 5489601	US 5484809
US 5475011	US 5473055	US 5470866	US 5466834
US 5449790	US 5442065	US 5440056	US 5430160
US 5412116	US 5412092	US 5411984	US 5407816
US 5407674	US 5405972	US 5399726	US 5395850
US 5384399	US 5380916	US 5380751	US 5367086
US 5356928	US 5356927	US 5352806	US 5350866
US 5344775	US 5338872	US 5336785	US 5319112
US 5296506	US 5294737	US 5294637	US 5284865
US 5284864	US 5283253	US 5279949	US 5274137
US 5274124	US 5272171	US 5254703	US 5254580
US 5250683	US 5243045	US 5229526	US 5227400
US 5200534	US 5194635	US 5175,315	US 5136060
US 5015744	WO 98/38862	WO 95/24402	WO 93/21173
EP 681574	EP 681575	EP 568203	EP 642503
EP 667772	EP 668762	EP 679082	EP 681573
EP 688212	EP 690712	EP 690853	EP 710223

EP 534708	EP 534709	EP 605638	EP 669918
EP 855909	EP 605638	EP 428376	EP 428376
EP 534707	EP 605637	EP 679156	EP 689436
EP 690867	EP 605637	EP 690867	EP 687260
EP 690711	EP 400971	EP 690711	EP 400971
EP 690711	EP 884314	EP 568203	EP 534706
EP 428376	EP 534707	EP 400971	EP 669918
EP 605637	US 5015744	US 5175315	US 5243045
US 5283253	US 5250683	US 5254703	US 5274124
US 5284864	US 5284865	US 5350866	US 5227400
US 5229526	US 4876399	US 5136060	US 5336785
US 5710287	US 5714513	US 5717115	US 5721268
US 5723634	US 5728725	US 5728850	US 5739362
US 5760219	US 5760252	US 5384399	US 5399726
US 5405972	US 5430160	US 5466834	US 5489601
US 5532363	US 5539103	US 5574156	US 5587489
US 5618952	US 5637732	US 5654447	US 4942184
US 5059699	US 5157149	US 5202488	US 5750736
US 5202488	US 5549830	US 5281727	US 5019504
US 4857653	US 4924011	US 5733388	US 5696153
WO 93/06093	WO 93/06094	WO 94/10996	WO 9/10997
WO 94/11362	WO 94/15599	WO 94/15929	WO 94/17050
WO 94/17051	WO 94/17052	WO 94/20088	WO 94/20485
WO 94/21250	WO 94/21251	WO 94/21252	WO 94/21623
WO 94/21651	WO 95/03265	WO 97/09979	WO 97/42181
WO 99/08986	WO 99/09021	WO 93/06079	US 5202448
US 5019504	US 4857653	US 4924011	WO 97/15571
WO 96/38138	US 5489589	EP 781778	WO 96/11683
EP 639577	EP 747385	US 5422364	WO 95/11020

EP 747372	WO 96/36622	US 5599820	WO 97/10234
WO 96/21658	WO 97/23472	US 5550261	WO 95/20582
WO 97/28156	WO 96/14309	WO 97/32587	WO 96/28435
WO 96/03394	WO 95/25728	WO 94/29288	WO 96/00724
WO 95/02400	EP 694539	WO 95/24402	WO 93/10121
WO 97/19086	WO 97/20835	WO 96/14745	WO 96/36335

U.S. Patent No. 5,019,504 describes the isolation of paclitaxel and related alkaloids from culture grown *Taxus brevifolia* cells. U.S. Patent No. 5,675,025 describes methods for synthesis of Taxol®, Taxol® analogues and intermediates from baccatin III. U.S. Patent No. 5,688,977 describes the synthesis of Docetaxel from 10-deacetyl baccatin III. U.S. Patent No. 5,202,488 describes the conversion of partially purified taxane mixture to baccatin III. U.S. Patent No. 5,869,680 describes the process of preparing taxane derivatives. U.S. Patent No. 5,856,532 describes the process of the production of Taxol®. U.S. Patent No. 5,750,737 describes the method for paclitaxel synthesis. U.S. Patent No. 6,688,977 describes methods for docetaxel synthesis. U.S. Patent No. 5,677,462 describes the process of preparing taxane derivatives. U.S. Patent No. 5,594,157 describes the process of making Taxol® derivatives.

Some taxanes and taxane derivatives that may be used in the methods, combinations and compositions of the present invention are described in the patents listed in Table No. 15 below, and are hereby individually incorporated by reference herein.

Table No. 15. Some preferred taxanes and taxane derivatives

US 5015744	US 5136060	US 5175315	US 5200534
US 5194635	US 5227400	US 4924012	US 5641803
US 5059699	US 5157049	US 4942184	US 4960790
US 5202488	US 5675025	US 5688977	US 5750736
US 5684175	US 5019504	US 4814470	WO 95/01969

The phrase "retinoid" includes compounds which are natural and synthetic analogues of retinol (Vitamin A). The retinoids bind to one or more retinoic acid receptors to initiate diverse processes such as reproduction, development, bone formation, cellular proliferation and differentiation, apoptosis, hematopoiesis, immune function and vision. Retinoids are required to maintain normal differentiation and proliferation of almost all cells and have been shown to reverse/suppress carcinogenesis in a variety of in vitro and in vivo experimental models of cancer, see (Moon et al., Ch. 14 Retinoids and cancer. *In* The Retinoids, Vol. 2. Academic Press, Inc. 1984). Also see Roberts et al. Cellular biology and biochemistry of the retinoids. *In* The Retinoids, Vol. 2. Academic Press, Inc. 1984, hereby incorporated by reference), which also shows that vesanoid (tretinoid trans retinoic acid) is indicated for induction of remission in patients with acute promyelocytic leukemia (APL).

A synthetic description of retinoid compounds, hereby incorporated by reference, is described in: Dawson MI and Hobbs PD. The synthetic chemistry of retinoids: in The retinoids, 2nd edition. MB Sporn, AB Roberts, and DS Goodman(eds). New York: Raven Press, 1994, pp 5-178.

Lingen et al. describe the use of retinoic acid and interferon alpha against head and neck squamous cell carcinoma (Lingen, MW et al., Retinoic acid and interferon alpha act synergistically as antiangiogenic and antitumor agents against human head and neck squamous cell carcinoma. Cancer Research 58 (23) 5551-5558 (1998), hereby incorporated by reference).

Iurlaro et al. describe the use of beta interferon and 13-cis retinoic acid to inhibit angiogenesis. (Iurlaro, M et al., Beta interferon inhibits HIV-1 Tat-induced angiogenesis: synergism with 13-cis retinoic acid. European Journal of Cancer 34 (4) 570-576 (1998), hereby incorporated by reference).

Majewski et al. describe Vitamin D3 and retinoids in the inhibition of tumor cell-induced angiogenesis. (Majewski, S et al., Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis. J. Invest. Dermatology. Symposium Proceedings, 1 (1), 97-101 (1996), hereby incorporated by reference).

Majewski et al. describe the role of retinoids and other factors in tumor angiogenesis. (Majewski, S et al., Role of cytokines, retinoids and other factors in tumor angiogenesis. Central-European journal of Immunology 21 (4) 281-289 (1996), hereby incorporated by reference).

Bollag describes retinoids and alpha-interferon in the prevention and treatment of neoplastic disease. (Bollag W. Retinoids and alpha-interferon in the prevention and treatment of preneoplastic and neoplastic diseases. Chemotherapie Journal, (Suppl) 5 (10) 55-64 (1996), hereby incorporated by reference).

Bigg, HF et al. describe all-trans retinoic acid with basic fibroblast growth factor and epidermal growth factor to stimulate tissue inhibitor of metalloproteinases from fibroblasts. (Bigg, HF et al., All-trans-retoic acid interacts synergystically with basic fibroblast growth factor and epidermal growth factor to stimulate the production of tissue inhibitor of metalloproteinases from fibroblasts. Arch. Biochem. Biophys. 319 (1) 74-83 (1995), hereby incorporated by reference).

Nonlimiting examples of retinoids that may be used in the methods, combinations and compositions of the present invention are identified in Table No. 16 below.

Table No. 16. Retinoids

Compound	**Common Name/ Trade Name**	**Company**	**Reference**	**Dosage**
CD-271	Adapaline		EP 199636	
Tretinoin trans	Vesanoid	Roche		45

retinoic acid		Holdings		mg/M^2/day as two evenly divided doses until complete remission
2,4,6,8-Nonatetraenoic acid, 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-, ethyl ester, (all-E)-	etretinate isoetretin; Ro-10-9359; Ro-13-7652; Tegison; Tigason	Roche Holdings	US 4215215	.25 - 1.5 mg/kg/day
Retinoic acid, 13-cis-	isotretinoin Accutane; Isotrex; Ro-4-3780; Roaccutan; Roaccutane	Roche Holdings	US 4843096	.5 to 2 mg/kg/day
	Roche Ro-40-0655	Roche Holdings		
	Roche Ro-25-6760	Roche Holdings		
	Roche Ro-25-9022	Roche Holdings		
	Roche Ro-25-9716	Roche Holdings		
Benzoic acid, 4-[[3,5-	TAC-101	Taiho Pharmaceuti		

bis(trimethylsilyl)benzoyl]amino]-		cal		
Retinamide, N-(4-hydroxyphenyl)-	fenretinide 4-HPR; HPR; McN-R-1967			50 - 400 mg/kg/day
(2E,4E,6E)-7-(3,5-Di-tert-butylphenyl)-3-methylocta-2,4,6-trienoic acid	LGD-1550 ALRT-1550; ALRT-550; LG-1550	Ligand Pharma-ceuticas; Allergan USA		20 microg/m2/day to 400 microg/m2/day administered as a single daily oral dose
	Molecular Design MDI-101		US 4885311	
	Molecular Design MDI-403		US 4677120	
Benzoic acid, 4-(1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)eth enyl)-	bexarotene LG-1064; LG-1069; LGD-1069; Targretin; Targretin Oral; Targretin Topical Gel		WO 94/15901	

Benzoic acid, 4-(1-(5,6,7,8-tetrahydro-3,5,8,8-pentamethyl-2-naphthalenyl)ethen yl)-	bexarotene, soft gel bexarotene, Ligand; bexaroten	R P Scherer		
(2E,4E)-3-methyl-5-[3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)- thiopen-2-yl]-penta-2,4-dienoic acid			WO 96/05165	
	SR-11262 F	Hoffmann-La Roche Ltd.		
	BMS-181162	Bristol Myers Squibb	EP 476682	
N-(4-hydroxyphenyl) retinamide	IIT Research Institute		Cancer Research 39, 1339-1346 (1979)	
	AGN-193174	Allergan USA	WO 96/33716	

The following individual patent references listed in Table No. 17 below, hereby individually incorporated by reference, describe various retinoid and retinoid derivatives suitable for use in the methods, combinations and compositions of the present invention described herein, and processes for their manufacture.

Table No. 17. Retinoids

US 4215215	US 4885311	US 4677120	US 4105681
US 5260059	US 4503035	US 5827836	US 3878202
US 4843096	WO 96/05165	WO 97/34869	WO 97/49704
EP 19/9636	WO 96/33716	WO 97/24116	WO 97/09297
WO 98/36742	WO 97/25969	WO 96/11686	WO 94/15901
WO 97/24116	CH 61/6134	DE 2854354	EP 579915
US 5547947	EP 552624	EP 728742	EP 331983
EP 476682			

In one embodiment, retinoids that may be used in the methods, combinations and compositions of the present invention include Accutane; Adapalene; Allergan AGN-193174; Allergan AGN-193676; Allergan AGN-193836; Allergan AGN-193109; Aronex AR-623; BMS-181162; Galderma CD-437; Eisai ER-34617; Etrinate; Fenretinide; Ligand LGD-1550; lexacalcitol; Maxia Pharmaceuticals MX-781; mofarotene; Molecular Design MDI-101; Molecular Design MDI-301; Molecular Design MDI-403; Motretinide; Eisai 4-(2-[5-(4-methyl-7-ethylbenzofuran-2-yl)pyrrolyl]) benzoic acid; Johnson & Johnson N-[4-[2-thyl-1-(1H-imidazol-1-yl)butyl]phenyl]-2-benzothiazolamine; Soriatane; Roche

SR- 11262; Tocoretinate; Advanced Polymer Systems trans-retinoic acid; UAB Research Foundation UAB-8; Tazorac; TopiCare; Taiho TAC-101; and Vesanoid.

CGMP phosphodiesterase inhibitors, including sulindac sulfone (Exisuland®) and CP-461 for example, are apoptosis inducers and do not inhibit the cyclooxygenase pathways. CGMP phosphodiesterase inhibitors increase apoptosis in tumor cells without arresting the normal cycle of cell division or altering the cell's expression of the p53 gene.

Ornithine decarboxylase is a key enzyme in the polyamine synthesis pathway that is elevated in most tumors and premalignant lesions. Induction of cell growth and proliferation is associated with dramatic increases in ornithine decarboxylase activity and subsequent polyamine synthesis. Further, blocking the formation of polyamines slows or arrests growth in transformed cells. Consequently, polyamines are thought to play a role in tumor growth. Difluoromethylornithine (DFMO) is a potent inhibitor of ornithine decarboxylase that has been shown to inhibit carcinogen-induced cancer development in a variety of rodent models (Meyskens et al. Development of Difluoromethylornithine (DFMO) as a chemoprevention agent. Clin. Cancer Res. 1999 May, 5(%):945-951, hereby incorporated by reference, herein). DFMO is also known as 2-difluoromethyl-2,5-diaminopentanoic acid, or 2-difluoromethyl-2,5-diaminovaleric acid, or a-(difluoromethyl) ornithine; DFMO is marketed under the tradename Elfornithine®. Therefore, the use of DFMO in combination with a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agent is contemplated to treat or prevent cancer, including but not limited to colon cancer or colonic polyps.

Populations with high levels of dietary calcium have been reported to be protected from colon cancer. In vivo, calcium carbonate has been shown to inhibit colon cancer via a mechanism of action independent from COX-2 inhibition. Further, calcium carbonate is well tolerated. A combination therapy consisting of calcium carbonate, a COX-2 selective inhibiting agent, and a DNA topoisomerase I inhibiting agent is contemplated to treat or prevent cancer, including but not limited to colon cancer or colonic polyps.

Several studies have focused attention on bile acids as a potential mediator of the dietary influence on colorectal cancer risk. Bile acids are important detergents for fat solubilization and digestion in the proximal intestine. Specific transprot processes in the apical domain of the terminal ileal enterocyte and basolateral domain of the hepatocyte account for the efficient conservation in the enterohepatic circulation. Only a small fraction of bile acids enter the colon; however, perturbations of the cycling rate of bile acids by diet (e.g. fat) or surgery may increase the fecal bile load and perhaps account for the associated increased risk of colon cancer. (Hill MJ, Bile flow and colon cancer. 238 Mutation Review, 313 (1990). Ursodeoxycholate (URSO), the hydrophilic 7-beta epimer of chenodeoxycholate, is non cytotoxic in a variety of cell model systems including colonic epithelia. URSO is also virtually free of side effects. URSO, at doses of 15mg/kg/day used primarily in biliary cirrhosis trials were extremely well tolerated and without toxicity. (Pourpon et al., A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. 324 New Engl. J. Med. 1548 (1991)). While the precise mechanism of URSO action is unknown, beneficial effects of URSO therapy are related to the enrichment of the hepatic bile acid pool with this hydrophilic bile acid. It has thus been hypothesized that bile acids more hydrophilic than URSO will have even greater beneficial effects than URSO. For example, tauroursodeoxycholate (TURSO) the taurine conjugate of URSO. Non-steroidal anti-inflammatory drugs (NSAIDs) can inhibit the neoplastic transformation of colorectal epithelium. The likely mechanism to explain this chemopreventive effect is inhibition of prostaglandin synthesis. NSAIDs inhibit cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandins and thromboxanes. However, the potential chemopreventive benefits of NSAIDs such as sulindac or mesalamine are tempered by their well known toxicities and moderately high risk of intolerance. Abdominal pain, dispepsia, nausea, diarrhea, constipation, rash, dizziness, or headaches have been reported in up to 9% of patients. The elderly appear to be particularly vulnerable as the incidence of NSAID-induced gastroduodenal ulcer disease, including gastrointestinal bleeding, is higher in those over the age of 60; this is also the age group most likely to develop colon cancer,

and therefore most likely to benefit from chemoprevention. The gastrointestinal side effects associated with NSAID use result from the inhibition of COX-1, an enzyme responsible for maintenance of the gastric mucosa. Therefore, the use of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agent in combination with URSO is contemplated to treat or prevent cancer, including but not limited to colon cancer or colonic polyps; it is contemplated that this treatment will result in lower gastrointestinal side effects than the combination of standard NSAIDs and URSO.

An additional class of antineoplastic agents that may be used in the methods, combinations and compositions of the present invention include nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). However, for the purposes of the present invention the definition of an NSAID does not include the "selective COX-2 inhibiting agents" described herein. Thus the phrase "nonsteroidal antiinflammatory drug" or "NSAID" includes agents that specifically inhibit COX-1, without significant inhibition of COX-2; or inhibit COX-1 and COX-2 at substantially the same potency. The potency and selectivity for the enzyme COX-1 and COX-2 can be determined by assays well known in the art, see for example, Cromlish and Kennedy, Biochemical Pharmacology, Vol. 52, pp 1777-1785, 1996.

Examples of NSAIDs that can be used in the combinations of the present invention include sulindac, indomethacin, naproxen, diclofenac, tolectin, fenoprofen, phenylbutazone, piroxicam, ibuprofen, ketophen, mefenamic acid, tolmetin, flufenamic acid, nimesulide, niflumic acid, piroxicam, tenoxicam, phenylbutazone, fenclofenac, flurbiprofen, ketoprofen, fenoprofen, acetaminophen, salicylate and aspirin.

Additionally, it has been recently discovered in vitro that COX-2 expression is upregulated in cells overexpressing the HER-2/neu oncogene. (Subbaramaiah et al., Increased expression of COX-2 in HER-2/neu-overexpressing breast cancer. Cancer Research (submitted for publication Fall 1999)). In this study, markedly

increased levels of PGE_2 production, COX-2 protein and mRNA were detected in HER-2/neu transformed mammary epithelial cells compared to a non-transformed partner cell line. Amplification and/or overexpression of HER-2/nue (ErbB2) occurs in 20-30% of human breast and ovarian cancers as well as in 5-15% of gastric and esophageal cancers and is associated with poor prognosis. Products of COX-2 activity, i.e., prostaglandins, stimulate proliferation, increase invasiveness of malignant cells, and enhance the production of vascular endothelial growth factor, which promotes angiogenesis. Further, HER-2/neu induces the production of angiogenic factors such as vascular endothelial growth factor.

Consequently, the administration of an anti HER-2/neu antibodies such as trastuzumab (Herceptin®) and other therapies directed at inhibiting HER-2/neu, in combination with a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agent is contemplated to prevent or treat cancers in which HER-2/neu is overexpressed.

Methods for the production of anti-ErbB2 antibodies are described in WO 99/31,140.

Molecular Tumor Markers

The term "tumor marker" or "tumor biomarker" encompasses a wide variety of molecules with divergent characteristics that appear in body fluids or tissue in association with a clinical tumor and also includes tumor-associated chromosomal changes. Tumor markers fall primarily into three categories: molecular or cellular markers, chromosomal markers, and serological or serum markers. Molecular and chromosomal markers complement standard parameters used to describe a tumor (i.e. histopathology, grade, tumor size) and are used primarily in refining disease diagnosis and prognosis after clinical manifestation. Serum markers can often be measured many months before clinical tumor detection and are thus useful as an early diagnostic test, in patient monitoring, and in therapy evaluation.

Molecular markers of cancer are products of cancer cells or molecular changes that take place in cells because of activation of cell division or inhibition of apoptosis. Expression of these markers can predict a cell's malignant potential. Because cellular markers are not secreted, tumor tissue samples are generally

required for their detection. Non-limiting examples of molecular tumor markers that can be used in the methods, combinations and compositions of the present invention are listed in Table No. 18, below.

Table No. 18. Non-limiting Examples of Molecular Tumor Markers

Tumor	**Marker**
Breast	p53
Breast, Ovarian	ErbB-2/Her-2
Breast	S phase and ploidy
Breast	pS2
Breast	MDR2
Breast	urokinase plasminogen activator
Breast, Colon, Lung	*myc* family

Chromosomal Tumor Markers

Somatic mutations and chromosomal aberrations have been associated with a variety of tumors. Since the identification of the Philadelphia Chromosome by Nowel and Hungerford, a wide effort to identify tumor-specific chromosomal alterations has ensued. Chromosomal cancer markers, like cellular markers, are can be used in the diagnosis and prognosis of cancer. In addition to the diagnostic and prognostic implications of chromosomal alterations, it is hypothesized that germ-line mutations can be used to predict the likelihood that a particular person will develop a given type of tumor. Non-limitin examples of chromosomal tumor markers that can be used in the methods, combinations and compositions of the present invention are listed in Table No. 19, below.

Table No. 19. Non-limiting Examples of Chromosomal Tumor Markers

Tumor	**Marker**
Breast	1p36 loss

Breast	6q24-27 loss
Breast	11q22-23 loss
Breast	11q13 amplification
Breast	*TP53* mutation
Colon	Gain of chromosome 13
Colon	Deletion of short arm of chromosome 1
Lung	Loss of 3p
Lung	Loss of 13q
Lung	Loss of 17p
Lung	Loss of 9p

Serological Tumor Markers

Serum markers including soluble antigens, enzymes and hormones comprise a third category of tumor markers. Monitoring serum tumor marker concentrations during therapy provides an early indication of tumor recurrence and of therapy efficacy. Serum markers are advantageous for patient surveillance compared to chromosomal and cellular markers because serum samples are more easily obtainable than tissue samples, and because serum assays can be performed serially and more rapidly. Serum tumor markers can be used to determine appropriate therapeutic doses within individual patients. For example, the efficacy of a combination regimen consisting of chemotherapeutic and antiangiogenic agents can be measured by monitoring the relevant serum cancer marker levels. Moreover, an efficacious therapy dose can be achieved by modulating the therapeutic dose so as to keep the particular serum tumor marker concentration stable or within the reference range, which may vary depending upon the indication. The amount of therapy can then be modulated specifically for each patient so as to minimize side effects while still maintaining stable, reference range tumor marker levels. Table No. 20 provides non-limiting examples of serological tumor markers that can be used in the present invention.

Table No. 20. Non-limiting Examples of Serum Tumor Markers

Cancer Type	Marker
Germ Cell Tumors	a-fetoprotein (AFP)
Germ Cell Tumors	human chorionic gonadotrophin (hCG)
Germ Cell Tumors	placental alkaline phosphatase (PLAP)
Germ Cell Tumors	lactate dehydrogenase (LDH)
Prostate	prostate specific antigen (PSA)
Breast	carcinoembryonic antigen (CEA)
Breast	MUC-1 antigen (CA15-3)
Breast	tissue polypeptide antigen (TPA)
Breast	tissue polypeptide specific antigen (TPS)
Breast	CYFRA 21.1
Breast	soluble *erb*-B-2
Ovarian	CA125
Ovarian	OVX1
Ovarian	cancer antigen CA72-4
Ovarian	TPA
Ovarian	TPS
Gastrointestinal	CD44v6
Gastrointestinal	CEA
Gastrointestinal	cancer antigen CA19-9
Gastrointestinal	NCC-ST-439 antigen (Dukes C)
Gastrointestinal	cancer antigen CA242
Gastrointestinal	soluble *erb*-B-2
Gastrointestinal	cancer antigen CA195
Gastrointestinal	TPA
Gastrointestinal	YKL-40
Gastrointestinal	TPS
Esophageal	CYFRA 21-1
Esophageal	TPA
Esophageal	TPS

Esophageal	cancer antigen CA19-9
Gastric Cancer	CEA
Gastric Cancer	cancer antigen CA19-9
Gastric Cancer	cancer antigen CA72-4
Lung	neruon specific enolase (NSE)
Lung	CEA
Lung	CYFRA 21-1
Lung	cancer antigen CA 125
Lung	TPA
Lung	squamous cell carcinoma antigen (SCC)
Pancreatic cancer	ca19-9
Pancreatic cancer	ca50
Pancreatic cancer	ca119
Pancreatic cancer	ca125
Pancreatic cancer	CEA
Renal Cancer	CD44v6
Renal Cancer	E-cadherin
Renal Cancer	PCNA (proliferating cell nuclear antigen)

Examples

Germ Cell Cancers

Non-limiting examples of tumor markers useful in the methods, combinations and compositions of the present invention for the detection of germ cell cancers include, but are not limited to, a-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and its beta subunit (hCGb), lactate dehydrogenase (LDH), and placental alkaline phosphatase (PLAP).

AFP has an upper reference limit of approximately -10 kU/L after the first year of life and may be elevated in germ cell tumors, hepatocellular carcinoma and also in gastric, colon, biliary, pancreatic and lung cancers. AFP serum half life is

approximately five days after orchidectomy. According to EGTM recommendations, AFP serum levels less than 1,000 kU/L correlate with a good prognosis, AFP levels between 1,000 and 10,000 kU/L, inclusive, correlate with intermediate prognosis, and AFP levels greater than 10,000 U/L correlate with a poor prognosis.

HCG is synthesized in the placenta and is also produced by malignant cells. Serum hCG concentrations may be increased in pancreatic adenocarcinomas, islet cell tumors, tumors of the small and large bowel, hepatoma, stomach, lung, ovaries, breast and kidney. Because some tumors only hCGb, measurement of both hCG and hCGb is recommended. Normally, serum hCG in men and pre-menopausal women is as high as -5 U/L while post-menopausal women have levels up to -10 U/L. Serum half life of hCG ranges from 16-24 hours. According to the EGTM, hCG serum levels under 5000 U/L correlate with a good prognosis, levels between 5000 and 50000 U/L, inclusively correlate with an intermediate prognosis, and hCG serum levels greater than 50000 U/L correlate with a poor prognosis. Further, normal hCG half lives correlate with good prognosis while prolonged half lives correlate with poor prognosis.

LDH is an enzyme expressed in cardiac and skeletal muscle as well as in other organs. The LDH-1 isoenzyme is most commonly found in testicular germ cell tumors but can also occur in a variety of benign conditions such as skeletal muscle disease and myocardial infarction. Total LDH is used to measure independent prognostic value in patients with advanced germ cell tumors. LDH levels less than 1.5 x the reference range are associated with a good prognosis, levels between 1.5 and 10 x the reference range, inclusive, are associated with an intermediate prognosis, and levels more than 10 x the reference range are associated with a poor prognosis.

PLAP is a enzyme of alkaline phosphatase normally expressed by placental syncytiotrophoblasts. Elevated serum concentrations of PLAP are found in seminomas, non-seminomatous tumors, and ovarian tumors, and may also provide a marker for testicular tumors. PLAP has a normal half life after surgical resection of between 0.6 and 2.8 days.

Prostate Cancer

A non-limiting example of a tumor marker useful in the methods, combinations and compositions of the present invention for the detection of prostate cancer is prostate specific antigen (PSA). PSA is a glycoprotein that is almost exclusively produced in the prostate. In human serum, uncomplexed f-PSA and a complex of f-PSA with a1-anthichymotrypsin make up total PSA (t-PSA). T-PSA is useful in determining prognosis in patients that are not currently undergoing anti-androgen treatment. Rising t-PSA levels via serial measurement indicate the presence of residual disease.

In 1993, the molecular cloning of a prostate-specific membrane antigen (PSMA) was reported as a potential prostate carcinoma marker and hypothesized to serve as a target for imaging and cytotoxic treatment modalities for prostate cancer. Antibodies against PSMA have been described and examined clinically for diagnosis and treatment of prostate cancer. In particular, Indium-111 labelled PSMA antibodies have been described and examined for diagnosis of prostate cancer and itrium-labelled PSMA antibodies have been described and examined for the treatment of prostate cancer.

Breast Cancer

Non-limiting examples of serum tumor markers useful in the methods, combinations and compositions of the present invention for the detection of breast cancer include, but is not limited to carcinoembryonic antigen (CEA) and MUC-1 (CA 15.3). Serum CEA and CA15.3 levels are elevated in patients with node involvement compared to patients without node involvement, and in patients with larger tumors compared to smaller tumors. Normal range cutoff points (upper limit) are 5-10 mg/L for CEA and 35-60 u/ml for CA15.3. Additional specificity (99.3%) is gained by confirming serum levels with two serial increases of more than 15%.

Ovarian Cancer

A non-limiting example of a tumor marker useful in the methods, combinations and compositions of the present invention for the detection of ovarian cancer is CA125. Normally, women have serum CA125 levels between 0-35 kU/L;

99% of post-menopausal women have levels below 20 kU/L. Serum concentration of CA125 after chemotherapy is a strong predictor of outcome as elevated CA125 levels are found in roughly 80% of all patients with epithelial ovarian cancer. Further, prolonged CA125 half-life or a less than 7-fold decrease during early treatment is also a predictor of poor disease prognosis.

Gastrointestinal Cancers

A non-limiting example of a tumor marker useful in the methods, combinations and compositions of the present invention for the detection of colon cancer is carcinoembryonic antigen (CEA). CEA is a glycoprotein produced during embryonal and fetal development and has a high sensitivity for advanced carcinomas including those of the colon, breast, stomach and lung. High pre- or postoperative concentrations (>2.5 ng/ml) of CEA are associated with worse prognosis than are low concentrations. Further, some studies in the literature report that slow rising CEA levels indicates local recurrence while rapidly increasing levels suggests hepatic metastasis.

Lung Cancer

Examples of serum markers useful in the methods, combinations and compositions of the present invention to monitor lung cancer therapy include, but are not limited to, CEA, cytokeratin 19 fragments (CYFRA 21-1), and Neuron Specific Enolase (NSE).

NSE is a glycolytic isoenzyme of enolase produced in central and peripheral neurons and malignant tumors of neuroectodermal origin. At diagnosis, NSE concentrations greater than 25 ng/mL are suggestive of malignancy and lung cancer while concentrations greater than 100 ng/mL are suggestive of small cell lung cancer.

CYFRA 21-1 is a tumor marker test which uses two specific monoclonal antibodies against a cytokeratin 19 fragment. At diagnosis, CYFRA 21-1 concentrations greater than 10 ng/mL are suggestive of malignancy while concentrations greater than 30 ng/mL are suggestive of lung cancer.

Accordingly, dosing of the COX-2 selective inhibiting agent (or prodrug thereof) and the DNA topoisomerase I inhibiting agents (or other combination therapies of the present invention) may be determined and adjusted based on measurement of tumor markers in body fluids or tissues, particularly based on tumor markers in serum. For example, a decrease in serum marker level relative to baseline serum marker prior to administration of the cylcooxygenase-2 inhibitor and the DNA topoisomerase I inhibiting agents indicates a decrease in cancer-associated changes and provides a correlation with inhibition of the cancer. In one embodiment, therefore, the method of the present invention comprises administering the COX-2 selective inhibiting agent and the DNA topoisomerase I inhibiting agents at doses that in combination result in a decrease in one or more tumor markers, particularly a decrease in one or more serum tumor markers, in the mammal relative to baseline tumor marker levels.

Similarly, decreasing tumor marker concentrations or serum half lives after administration of the combination indicates a good prognosis, while tumor marker concentrations which decline slowly and do not reach the normal reference range predict residual tumor and poor prognosis. Further, during follow-up therapy, increases in tumor marker concentration predicts recurrent disease many months before clinical manifestation.

In addition to the above examples, Table No. 21, below, lists several references that describe tumor markers and their use in detecting and monitoring tumor growth and progression.

Table No. 21. Tumor marker references.

European Group on Tumor Markers Publications Committee. Consensus Recommendations. Anticancer Research *19*: 2785-2820 (1999)
Human Cytogenetic Cancer Markers. Sandra R. Wolman and Stewart Sell (eds.). Totowa, New Jersey: Humana Press. 1997
Cellular Markers of Cancer. Carleton Garrett and Stewart Sell (eds.). Totowa,

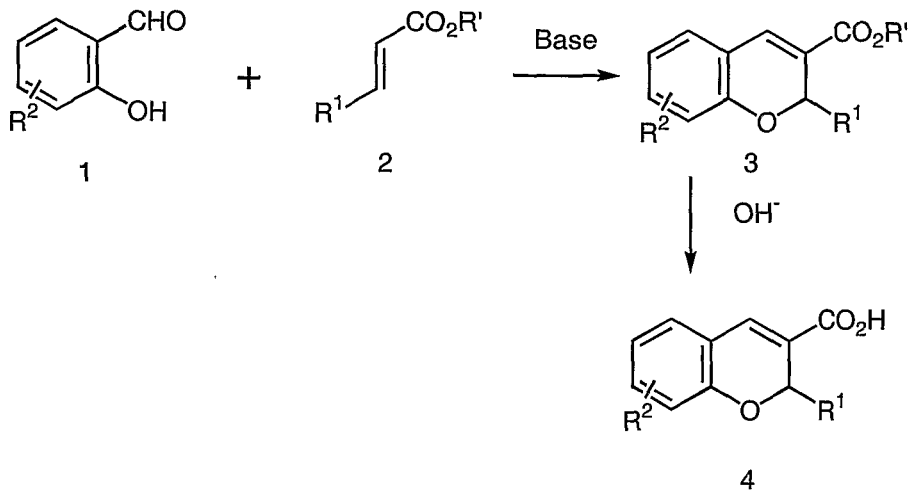
New Jersey: Human Press. 1995

All of the various cell types of the body can be transformed into benign or malignant neoplasia or tumor cells and are contemplated as objects of the invention. A "benign" tumor cell denotes the non-invasive and non-metastasized state of a neoplasm. In man the most frequent tissue in which neoplasia disease occurs is lung, followed by colorectal, breast, prostate, bladder, pancreas, and then ovary. Other prevalent types of cancer include leukemia, central nervous system cancers, including brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer.

General Synthetic Procedures for Compounds of Formulas 2 and 3

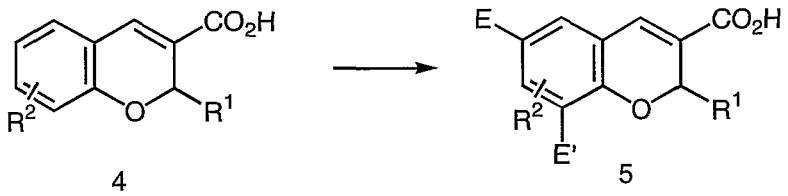
The compounds of Formulas 2 and 3 can be synthesized according to the following procedures of Schemes 1-16, wherein the R^1-R^6 substituents are as defined for Formulas I-II, above, except where further noted.

SCHEME 1



Synthetic Scheme 1 illustrates the general method for the preparation of a wide variety of substituted 2H-1-benzopyran derivatives **3** and **4**. In step 1, a representative ortho-hydroxybenzaldehyde (salicylaldehyde) derivative **1** is condensed with an acrylate derivative **2** in the presence of base, such as potassium carbonate in a solvent such as dimethylformamide, to afford the desired 2H-1-benzopyran ester **3**. An alternative base-solvent combination for this condensation includes an organic base such as triethylamine and a solvent such as dimethyl sulfoxide. In step 2 the ester is hydrolyzed to the corresponding acid, such as by treatment with aqueous base (sodium hydroxide) in a suitable solvent such as ethanol to afford after acidification the substituted 2H-1-benzopyran-3-carboxylic acid **4**.

SCHEME 2

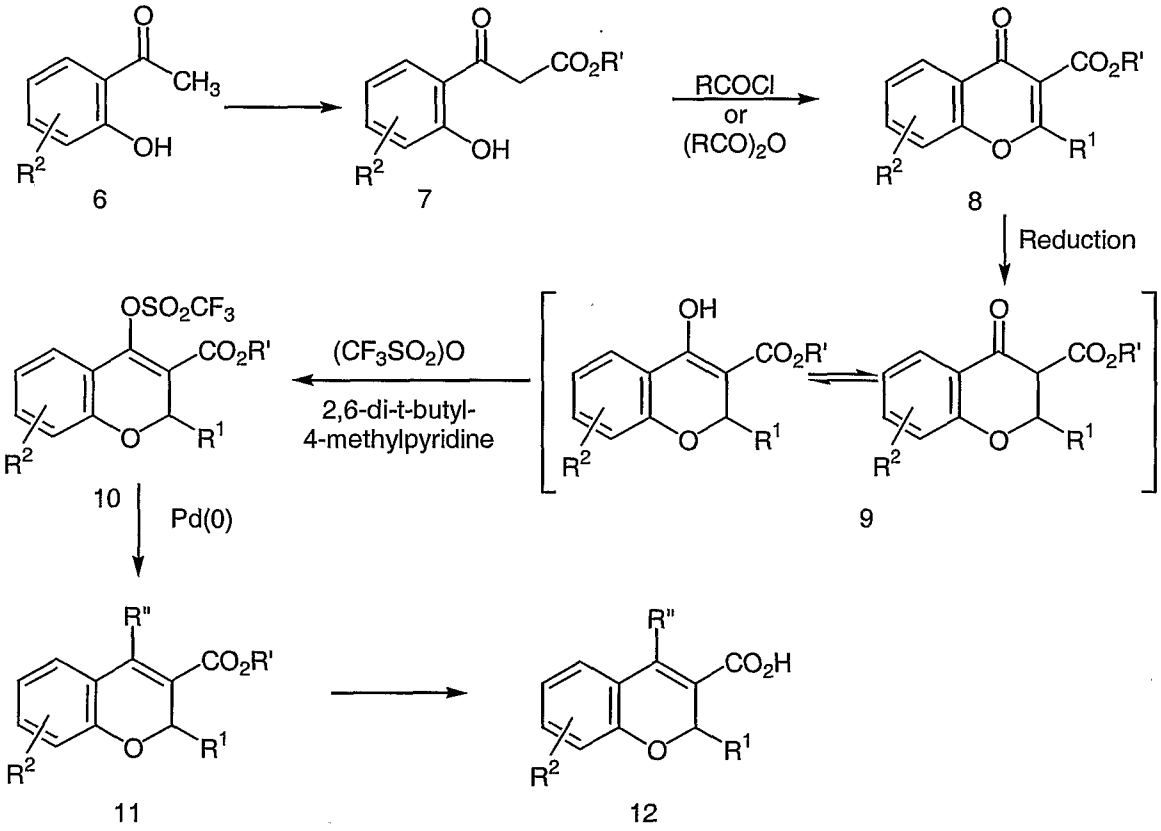


E, E' = halogen, acyl, sulfonyl

Synthetic Scheme 2 shows the general method for functionalizing selected 2H-1-benzopyrans. Treatment of the 2H-1-benzopyran carboxylic acid **4** or ester **3** with an electrophillic agent makes a 6-substituted 2H-1-benzopyran **5**. A wide variety of electrophillic agents react selectively with 2H-1-benzopyrans **4** in the 6-position to provide new analogs in high yield. Electrophillic reagents such as halogen (chlorine or bromine) give the 6-halo derivatives. Chlorosulfonic acid reacts to afford the 6-position sulfonyl chloride that can further be converted to a sulfonamide or sulfone. Friedel-Crafts acylation of **4** provides 6-acylated 2H-1-benzopyrans in good to excellent yield. A number of other electrophiles can be used to selectively react with these 2H-1-benzopyrans in a similar manner. A 6-position substituted 2H-1-benzopyran can react with an electrophilic reagent at the 8-position using similar chemistries to that described for electrophilic substitution

of the 6-position. This yields an 2H-1-benzopyran which is substituted at both the 6 and 8 positions.

SCHEME 3

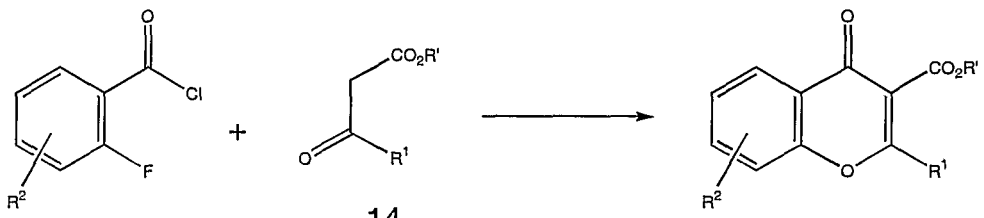


Synthetic Scheme 3 illustrates a second general synthesis of substituted 2H-1-benzopyran-3-carboxylic acids which allows substitution at position 4 of the 2H-1-benzopyran. In this case a commercially or synthetically available subtituted ortho-hydroxy acetophenone **6** is treated with two or more equivalents of a strong base such as lithium bis(trimethylsilyl)amide in a solvent such as tetrahydrofuran (THF), followed by reaction with diethyl carbonate to afford the beta-keto ester **7**. Ester **7** is condensed with an acid chloride or anhydride in the presence of a base such as potassium carbonate in a solvent such as toluene with heat to afford 4-oxo-4H-1-benzopyran **8**. Reduction of the olefin can be accomplished by a variety of agents including sodium borohydride ($NaBH_4$) in solvent mixtures such as ethanol

and tetrahydrofuran (THF), or by use of triethylsilane in a solvent such as trifluoroacetic acid, or by catalytic reduction using palladium on charcoal and hydrogen gas in a solvent such as ethanol to yield the new beta-keto ester **9** (two tautomeric structures shown). Acylation of the oxygen of the ketone enolate in the presence of a base such as 2,6-di-tert-butyl-4-methylpyridine, an acylating agent such as trifluoromethanesulfonic anhydride, and using a solvent such as methylene chloride yields the enol-triflate **10**. Triflate **10** can be reduced with reagents such as tri-n-butyltin hydride, lithium chloride and a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium (0) in a solvent such as tetrahydrofuran to yield 2H-1-benzopyran ester **11** where R" is hydrogen. The ester **11** can be saponified with a base such as 2.5 N sodium hydroxide in a mixed solvent such as tetrahydrofuran-ethanol-water (7:2:1) to yield the desired substituted 2H-1-benzopyran-3-carboxylic acid.

To incorporate a carbon fragment R^3 one can treat triflate **10** with reagents known to undergo "cross-coupling" chemistries such a tributylethyenyltin , lithium chloride and a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium (0) in a solvent such as tetrahydrofuran to yield 2H-1-benzopyran ester **11** where R^3 is a vinyl moiety. The ester **6** can be saponified with a base such as 2.5 N sodium hydroxide in a mixed solvent such as tetrahydrofuran-ethanol-water (7:2:1) to yield the desired 4-vinyl-2H-1-benzopyran-3-carboxylic acid (**12**, R" = CH_2CH-). Similarly triflate **10** can be converted under similar conditions using tri-n-butylphenyltin to 2H-1-benzopyran where R^3 = phenyl and by hydrolysis of the ester converted to the carboxylic acid **12** where R^3 = phenyl. Using a similar strategy, substituents which be incorporated as substitutent R^3 can be substituted olefins, substituted aromatics, substuted heteroaryl, acetylenes and substituted acetylenes.

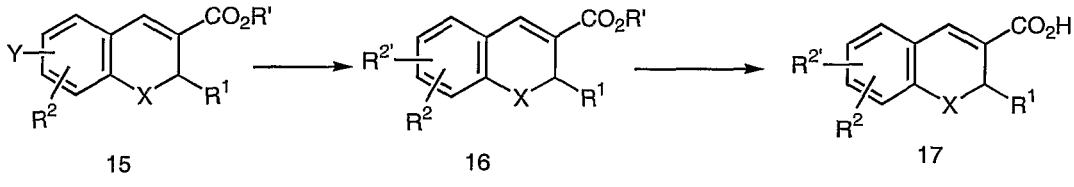
SCHEME 4



13 14 8

Synthetic Scheme 4 shows an alternative general procedure for the preparation of 4-oxo-4H-1-benzopyran **8**. Treatment of an ortho-fluorobenzoyl chloride with an appropriately substituted beta-keto ester **14** with a base such as potassium carbonate in a solvent such as toluene provides 4-oxo-4H-1-benzopyran **8**. 4-Oxo-4H-1-benzopyran **8** can be converted to 2H-1-benzopyran **12** as described in Scheme 3.

SCHEME 5



15 16 17

Y = Br, I, CF_3SO_3

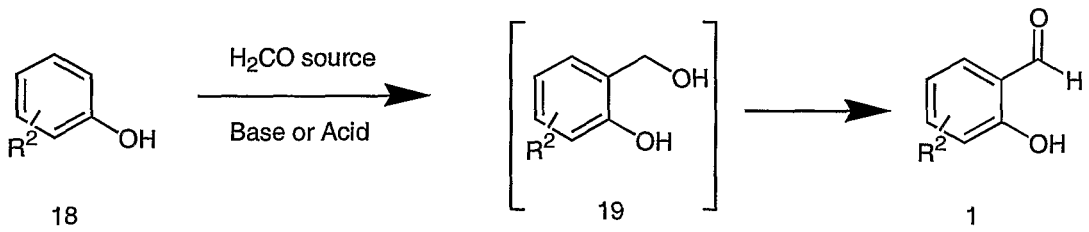
Synthetic Scheme 5 shows a general method for substitution of the aromatic ring of the 2H-1-benzopyran. This can be accomplished through organo-palladium mediated "cross-coupling" chemistries using a palladium (0) catalyst to couple benzopyran **15** at position Y, where Y is iodide, bromide or triflate, with an acetylene, olefin, nitrile, or aryl coupling agent. Substituted acetylenes as the coupling agent will provide the corresponding substituted acetylene. Substituted aryl moieties can be incorporated using arylboronic acids or esters; nitriles can be incorporated by use of zinc (II) cyanide. The resulting ester **16** can be converted to carboxylic acid **17** as described in Scheme 1.

Another approach to substitution of the aryl moiety of the benzopyran **15** is to convert Y, where Y is iodide or bromide, to a perfluoroalkyl moiety. Exemplary

of this transformation is the conversion of **15** (Y = iodide) to **16** ($R^{2'}$ =pentafluoroethyl) using a potassium pentafluoropropionate and copper (I) iodide in hexamethylphosphoramide (HMPA). The resulting ester **16** can be converted to carboxylic acid **15** as described in Scheme 1.

A similar method adds substitution of the aromatic ring in dihydroquinoline-3-carboxylates. This can be accomplished through organopalladium couplings with aryl iodides, bromides, or triflates and various coupling agents (R. F. Heck, *Palladium Reagents in Organic Synthesis*. Academic Press 1985). When using a suitable palladium catalyst such as tetrakis(triphenyl-phospine)palladium(0) in this reaction, coupling agents such as alkynes provide disubstituted alkynes, phenyl boronic acids afford biphenyl compounds, and cyanides produce arylcyano compounds. A number of other palladium catalysts and coupling reagents could be used to selectively react with appropriately substituted dihydroquinoline-3-carboxylates in a similar manner.

SCHEME 6



Synthetic Scheme 6 shows a general synthetic route for conversion of a commercially or synthetically available substituted phenol into a substituted salicylaldehyde. Several different methods which utilize formaldehyde or a chemically equivalent reagent are described in detail below.

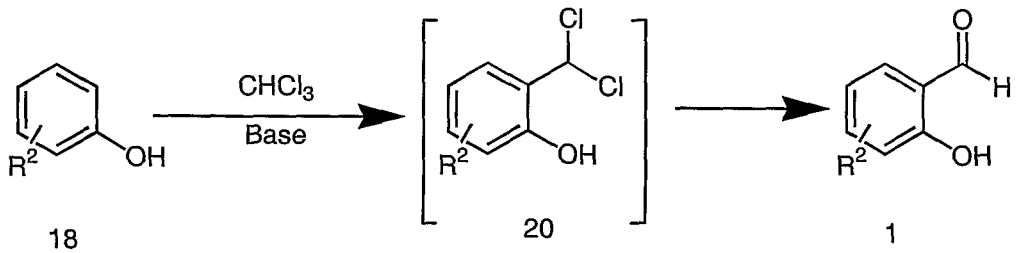
Reaction of an appropriately substituted phenol **18** in basic media with formaldehyde (or chemical equivalent) will yield the corresponding salicylaldehyde **1**. The intermediate, ortho-hydroxymethylphenol **19**, will under appropriate reaction conditions be oxidized to the salicylaldehyde **1** in situ. The reaction commonly employs ethyl magnesium bromide or magnesium methoxide(one

equivalent) as the base, toluene as the solvent, paraformaldehyde (two or more equivalents) as the source of formaldehyde, and employs hexamethylphoramide (HMPA) or *N,N,N',N'*-tetramethylethylenediamine (TMEDA). (See: Casiraghi, G. et al., J.C.S.Perkin I, **1978**, 318-321.)

Alternatively an appropriately substituted phenol **18** may react with formaldehyde under aqueous basic conditions to form the substituted ortho-hydroxybenzyl alcohol **19** (See: a) J. Leroy and C. Wakselman, J. Fluorine Chem., 40, 23-32 (**1988**). b) A. A. Moshfegh, et al., Helv. Chim. Acta., 65, 1229-1232 (**1982**)). Commonly used bases include aqueous potassium hydroxide or sodium hydroxide. Formalin (38% formaldehyde in water) is commonly employed as the source of formaldehyde. The resulting ortho-hydroxybenzyl alcohol **19** can be converted to the salicylaldehyde **1** by an oxidizing agent such as manganese (IV) dioxide in a solvent such as methylene chloride or chloroform (See: R-G. Xie, et al., Synthetic Commun. 24, 53-58 (**1994**)).

An appropriately substituted phenol **18** can be treated under acidic conditions with hexamethylenetetramine (HMTA) to prepare the salicylaldehyde **1** (Duff Reaction; See: Y. Suzuki, and H. Takahashi, Chem. Pharm. Bull., 31, 1751-1753 (**1983**)). This reaction commonly employs acids such as acetic acid, boric acid, methanesulfonic acid, or trifluoromethanesulfonic acid. The source of formaldehyde commonly used is hexamethylenetetramine.

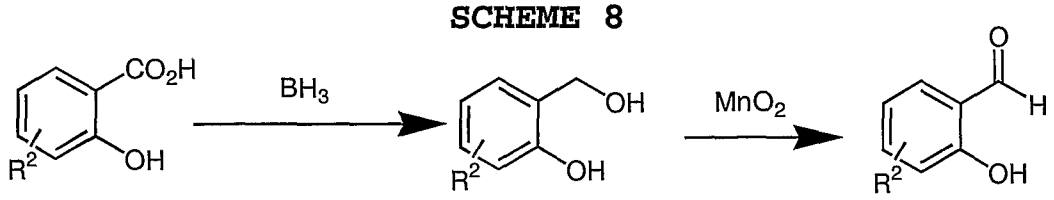
SCHEME 7



Synthetic Scheme 7 shows the Reimer-Tiemann reaction in which an commercially or synthetically available appropriately substituted phenol **18** will

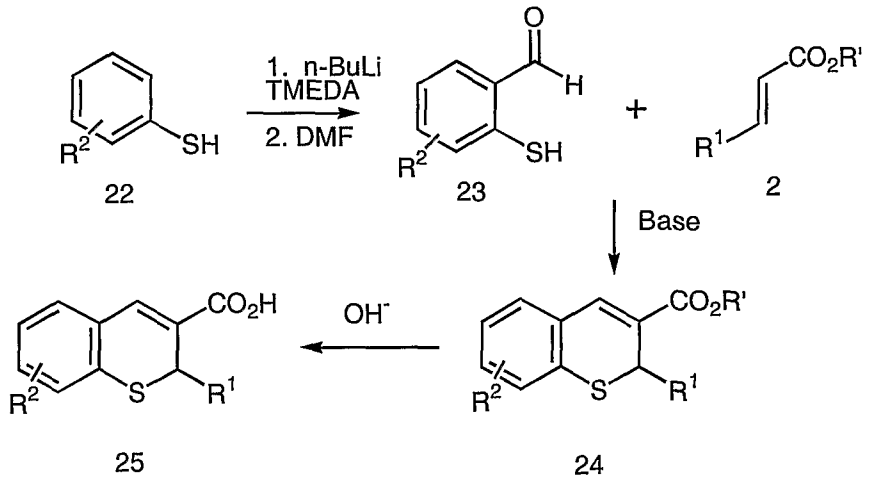
under basic conditions react with chloroform to yield a substituted salicylaldehyde **1** (See: Cragoe, E.J.; Schultz, E.M., U.S. Patent 3 794 734, 1974).

SCHEME 8



Synthetic Scheme 8 shows the conversion of a commercially or synthetically available appropriately substituted salicylic acid **21** to its respective salicylaldehyde **1** via an intermediate 2-hydroxybenzyl alcohol **19**. Reduction of the salicylic acid **21** can be accomplished with a hydride reducing agent such as borane in a solvent such as tetrahydrofuran. Treatment of the intermediate 2-hydroxybenzyl alcohol **19** with an oxidizing agent such as manganese (IV) oxide in a solvent such as methylene chloride or chloroform provides salicylaldehyde **1**.

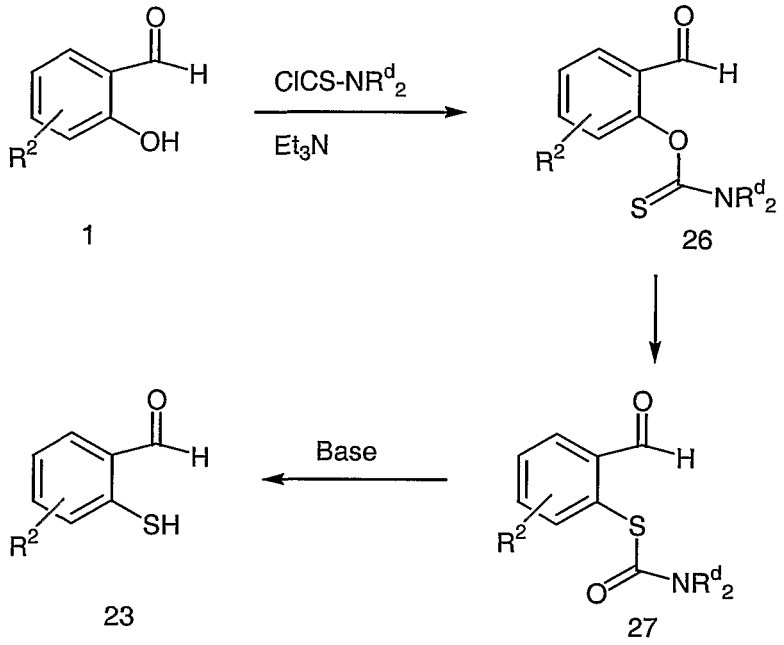
SCHEME 9



Synthetic Scheme 9 illustrates a general synthetic method for preparation of a wide variety of substituted 2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acids (**25**). In step 1, an appropriately commercially or synthetically available substituted thiophenol **22** is ortho-metallated with a base such as n-butyllithium employing TMEDA (*N,N,N',N'*-tetramethylethylenediamine) followed by treatment

with dimethylformamide to provide the 2-mercaptobenzaldehyde **23**. Condensation of the 2-mercaptobenzaldehyde **23** with an acrylate **2** in the presence of base provides ester **24** which can be saponified in the presence of aqueous base to afford the substituted 2H-1-benzothiopyran-3-carboxylic acids **25**.

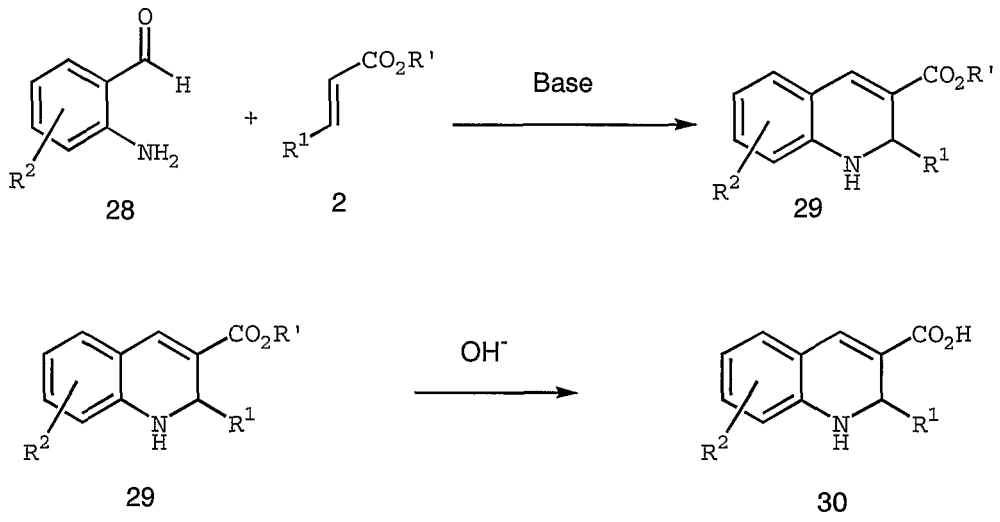
SCHEME 10



Synthetic Scheme 10 shows a method for preparing a substituted 2-mercaptobenzaldehyde from an appropriate commercially or synthetically available substituted salicylaldehyde. In step 1, the phenolic hydroxyl of salicylaldehyde **1** is converted to the corresponding O-aryl thiocarbamate **26** by acylation with an appropriately substituted thiocarbamoyl chloride such as *N,N*-dimethylthiocarbamoyl chloride in a solvent such as dimethylformamide using a base such as triethylamine. In Step 2, O-aryl thiocarbamate **26** rearranges to S-aryl thiocarbamate **27** when heated sufficiently such as to 200 °C using either no solvent or a solvent such as *N,N*-dimethylaniline (See: A. Levai, and P. Sebok, Synth. Commun., 22 1735-1750 (**1992**)). Hydrolysis of S-aryl thiocarbamate **27** with a base such as 2.5 N sodium hydroxide in a solvent mixture such as tetrahydrofuran and ethanol yields the substituted 2-mercaptobenzaldehyde **23** which can be

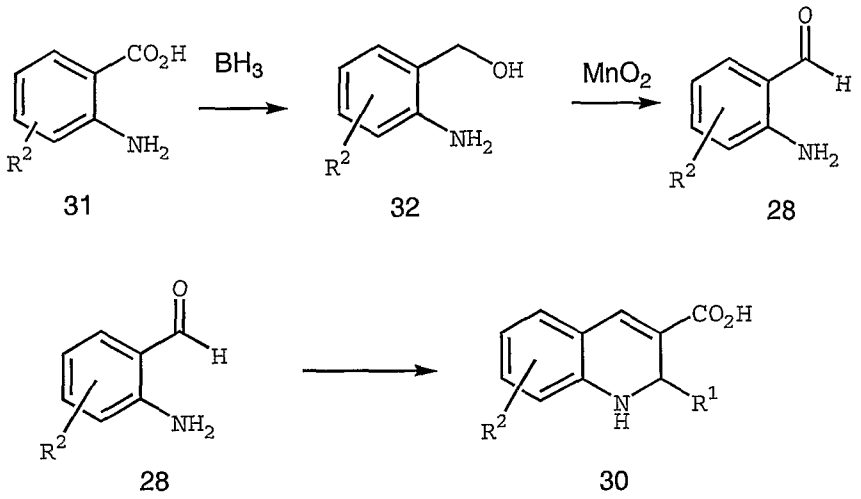
converted to the substituted 2H-1-benzothiopyran-3-carboxylic acids **25** as described in Scheme 9.

SCHEME 11



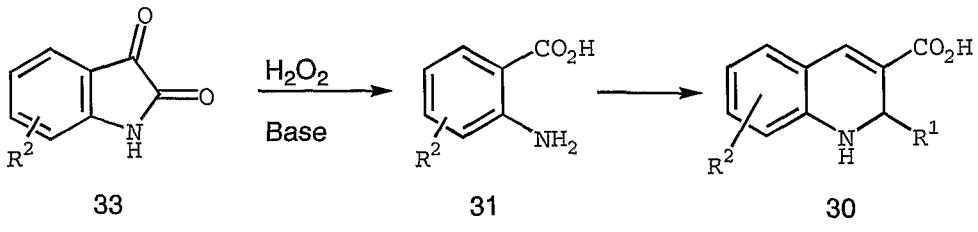
Synthetic Scheme 11 illustrates the general method for the preparation of a wide variety of dihydroquinoline-3-carboxylic acid derivatives **30**. R^2 represents the aromatic substitution of commercially and synthetically available 2-aminobenzaldeydes **28**. The 2-amino-benzaldehyde derivative **28**, where R^2 represents various substitutions, is condensed with a acrylate derivative **2** in the presence of base such as potassium carbonate, triethylamine, or diazbicyclo[2.2.2]undec-7-ene in solvents such as dimethylformamide to afford the dihydroquinoline-3-carboxylate esters **29**. The ester **29** can be saponified to the corresponding acid, such as by treatment with aqueous inorganic base such as 2.5 N sodium hydroxide in a suitable solvent such as ethanol to afford after acidification the desired dihydroquinoline-3-carboxylic acid **30**.

SCHEME 12



Synthetic Scheme 12 illustrates the preparation of dihydroquinoline-3-carboxylic acid **30** from 2-aminobenzoic acids **31**. R^2 represents the aromatic substitution of commercially and synthetically available 2-aminobenzoic acids **31**. Reduction of the representative 2-aminobenzoic acid **31** to the desired 2-aminobenzyl alcohol **32** was accomplished with a hydride reducing agent such as borane in a solvent such as tetrahydrofuran. Treatment of the desired 2-aminobenzyl alcohol **32** with an oxidizing agent such as manganese(IV)oxide in a solvent such as methylene chloride provides the representative 2-aminobenzaldehydes **28**. (C. T. Alabaster, et al. *J. Med. Chem. 31*, 2048-2056 (**1988**)) The 2-aminobenzaldehydes were converted to the desired dihydroquinoline-3-carboxylic acid **30** as described in Scheme 11.

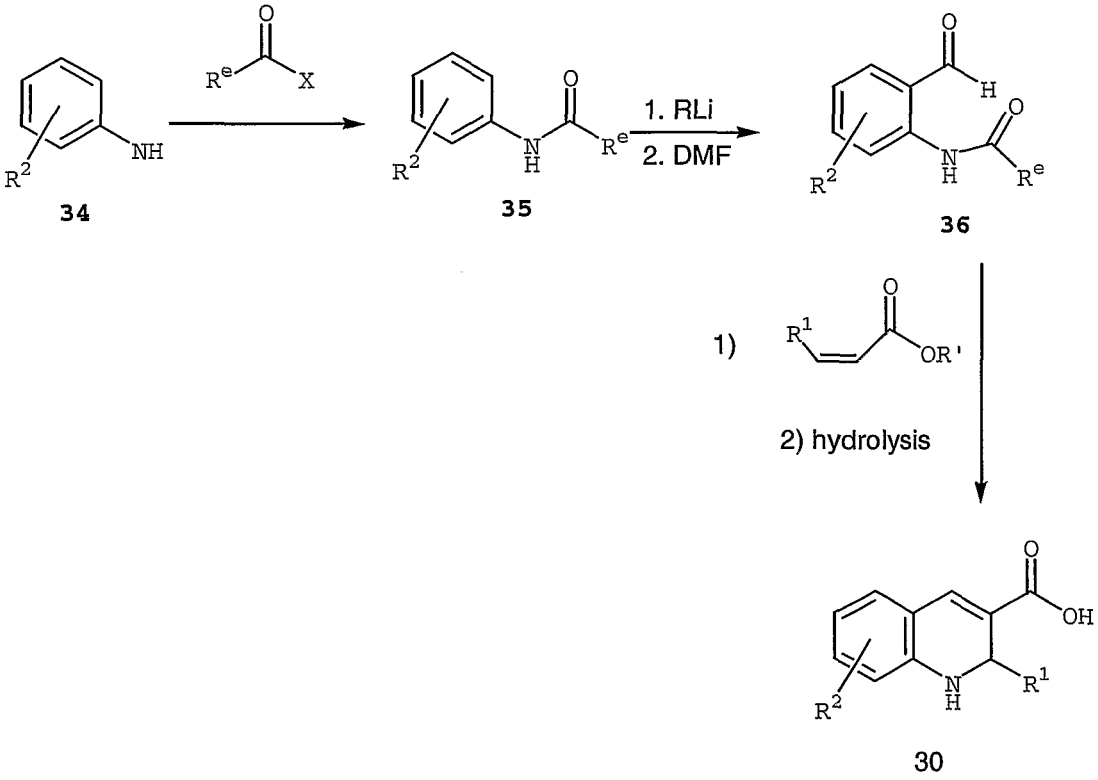
SCHEME 13



Synthetic Scheme 13 illustrates the general method for the preparation of a wide variety of dihydroquinoline-3-carboxylic acid derivatives **30** from isatins **33**.

R^2 represents the aromatic substitution of commercially and synthetically available isatins **33**. A representative isatin **33** was treated with basic peroxide generated from hydrogen peroxide and a base such as sodium hydroxide to afford the desired representative 2-aminobenzoic acids **31**. (M. S. Newman and M. W. Lougue, J. Org. Chem., *36*, 1398-1401 (**1971**)) The 2-aminobenzoic acids **31** are subsequently converted to the desired dihydroquinoline-3-carboxylic acid derivatives **30** as described in synthetic Scheme 12.

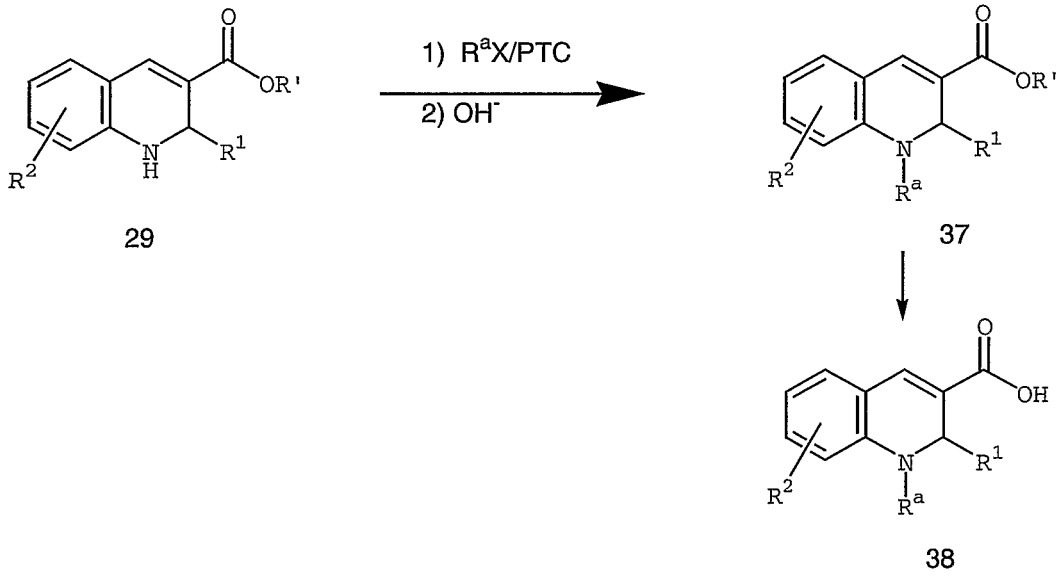
SCHEME 14



Synthetic Scheme 14 is another general method for the preparation of dihydroquinoline-3-carboxylic acid derivatives **30**. In step 1, an appropriate commercially or synthetically available substituted aniline **34** can be treated with an acylating reagent such as pivaloyl chloride yielding an amide **35**. The *ortho*-dianion of amide **35** is prepared by treating amide **35** with organo-lithium bases such as *n*-butyllithium or *tert*-butyllithium in tetrahydrofuran at low temperature.

The dianion is quenched with dimethylformamide to afford the acylated-2-amino-benzaldehydes **36**. (J. Turner, *J. Org. Chem.*, 48, 3401-3408 (**1983**)) Reaction of these aldehydes in the presence of bases such as lithium hydride with a acrylate followed by work up with aqueous inorganic bases and hydrolysis, such as by treatment with aqueous base (sodium hydroxide) in a suitable solvent such as ethanol affords, after acidification, a dihydroquinoline-3-carboxylic acid **30**.

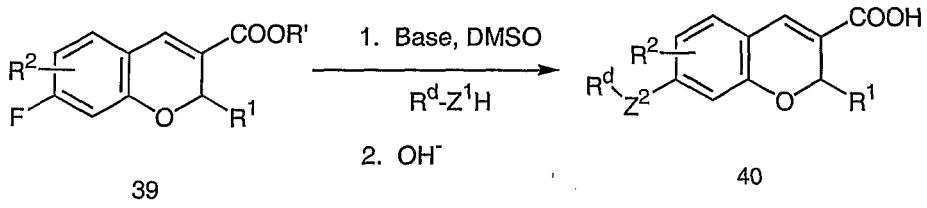
SCHEME 15



29 37 38

Synthetic Scheme 15 shows a general method for alkylation of the nitrogen of dihydroquinoline-3-carboxylate ester derivatives **29**. The step involves treatment of dihydroquinoline-3-carboxylate ester derivatives **29** with alkyl halides such as iodoethane in the presence of phase transfer catalysts such a tetrabutylammonium iodide, and a base such as caustic (50% aqueous sodium hydroxide) in a solvent such as dichloromethane. These conditions afford the N-alkylated dihyrdoquinoline-3-carboxylate esters **37**. Saponification of **37** with aqueous base provides N-alkylated-dihyroquinoline-3-carboxylic acid derivatives **38**.

SCHEME 16



39 40

Synthetic Scheme 16 shows a general method for the preparation of a 7-ether (Z^1=O) or thioether (Z^1=S) substituted benzopyran-3-carboxylic ester. An appropriately substituted phenol, thiophenol, hydroxy-heterocycle, mercaptoheterocycle, alcohol, or alkylthiol can be condensed under basic conditions using a base such as potassium carbonate in a solvent such as dimethysulfoxide, at temperature above room temperature, such as 100 °C, with an appropriately substituted 7-fluorobenzopyran derivative **30** to yield the corresponding ether or thioether. Hydrolysis of the ester with an aqueous base such as lithium hydroxide or sodium hydroxide in a solvent mixture such as tetrahydrofuran-ethanol-water yields acid **40**. When appropriate, a thioether (Z^2=S) can be oxidized to the sulfoxide (Z^2=SO) or sulfone (Z^2=SO_2) with an oxidant such as OXONE® or m-CPBA either before or after ester hydrolysis. In this chemistry R^d can include aryl, heteroaryl, heterocyclic, alicyclic, branched or linear aliphatic, branched or linear perfluoro-aliphatic moiety.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formulas 2 and 3. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

The following abbreviations are used:

HCl - hydrochloric acid

MgSO4 - magnesium sulfate

Na2SO4 - sodium sulfate

DMF - dimethylformamide

THF - tetrahydrofuran

NaOH - sodium hydroxide

EtOH - ethanol

K_2CO_3 - potassium carbonate

$CDCl_3$ - deuterated chloroform

CD_3OD - deuterated methanol

Et_2O - diethyl ether

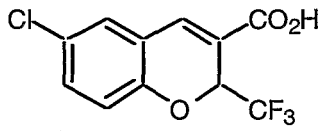
EtOAc - ethyl acetate

$NaHCO_3$ - sodium bicarbonate

$KHSO_4$ - potassium sulfate

$NaBH_4$ - sodium borohydride

Example 1



6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

Step 1. Preparation of ethyl 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylate.

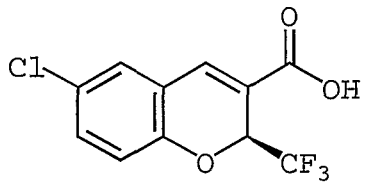
A mixture of 5-chlorosalicylaldehyde (20.02 g, 0.128 mole) and ethyl 4,4,4-trifluorocrotonate (23.68 g, 0.14 mole) was dissolved in anhydrous DMF, warmed to 60 °C and treated with anhydrous K_2CO_3 (17.75 g, 0.128 mole). The solution was maintained at 60 °C for 20 hours, cooled to room temperature, and diluted with water. The solution was extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford 54.32 g of an oil. The oil was dissolved in 250 mL of methanol and 100 mL of water, whereupon a white solid formed that was isolated by filtration, washed with water and dried *in vacuo*, to afford the ester as a yellow solid (24.31 g,

62%): mp 62-64 °C. 1H NMR (CDCl3/90 MHz) 7.64 (s, 1H), 7.30-7.21 (m, 2H), 6.96 (d, 1H, *J* = Hz), 5.70 (q, 1H, *J* = Hz), 4.30 (q, 2H, *J* = 7.2 Hz), 1.35 (t, 3H, *J* =7.2 Hz).

Step 2. Preparation of 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid.

A solution of the ester from Step 1 (13.02 g, 42 mmole) was dissolved in 200 mL of methanol and 20 mL of water, treated with lithium hydroxide (5.36 g, 0.128 mole) and stirred at room temperature for 16 hours. The reaction mixture was acidified with 1.2 N HCl, whereupon a solid formed that was isolated by filtration. The solid was washed with 200 mL of water and 200 mL of hexanes and dried *in vacuo* to afford the title compound as a yellow solid (10.00 g, 85%): mp 181-184 °C.

Example 2



(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

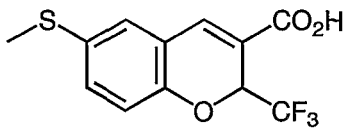
To a solution of 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (Example 1, Step 2)(12.00 g, 43.07 mmol) and (S)(-)-α-methylbenzylamine (2.61 g, 21.54 mmol) in methyl-*tert*-butyl ether (30 mL) was slowly added n-heptane (200 mL) until the mixture became cloudy. The mixture was heated (steam bath) to boiling and set aside for 24 h during which time crystals formed. Filtration of the suspension yielded a crystalline product (5.5 g) which was recrystallized from methyl-*tert*-butyl ether (30 mL) and n-heptane (200 mL) yielding upon filtration a white solid (3.1 g). This solid was dissolved in EtOAc (100 mL) and

washed with 1 N hydrochloric acid (50 mL) and brine (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo* yielding a white solid. Recrystallization of this solid from methyl-t-butyl ether/n-heptane yielded the title compound as the highly enriched isomer, a white solid (2.7 g, 45%): mp 126.7-128.9 °C. ^{1}H NMR ($CDCl_3$/300 MHz) 7.78 (s, 1H), 7.3-7.1 (m, 3H), 6.94 (d, 1H, J = *8.7* Hz), 5.66 (q, 1H, J = *6.9* Hz). Anal. Calc'd for $C_{11}H_6O_3F_3Cl$: C, 47.42; H, 2.17; N, 0.0. Found: C, 47.53; H, 2.14; N, 0.0. This compound was determined to have an optical purity of greater than 90% ee.

Procedure for determining optical purity.

To a solution of the free acid (title compound) (0.005 g, 0.017 mmol) in ethyl acetate (1.5 mL) in a test tube was added (trimethylsilyl)diazomethane (30 μL of 2.0 N solution in hexanes, 60 mmol). The resulting yellow solution was warmed until the solution began to gently boil and then was allowed to cool to room temperature and stand for 0.08 hours. With vigorous mixing, the solution was quenched with aqueous 1 N HCl (1.5 mL). The layers were separated and a sample of the ethyl acetate fraction (0.3 mL) was transferred to a vial, concentrated under a stream of nitrogen, was diluted with hexane (total of 1 mL) and a sample (10 μL) analyzed by chiral chromatography. The HPLC utilized a Daicel ChiralPak AD column eluting with 10% isopropanol-hexane at 0.5 mL/min using a UV detector set at 254 nM.

Example 2



6-(Methylthio)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Step 1. Preparation of 5-(methylthio)salicylaldehyde.

Ethyl magnesium bromide (38 mL of a 3.0 M solution in diethyl ether, 113.8 mmole) was chilled with an ice-water bath. To the chilled solution was added a solution of 4-(methylthio)phenol (15.95 g, 113.8 mmole) in diethyl ether (30 mL) over 0.15 hour during which time gas was evolved. The reaction was held at 0 °C for 0.5 hour, at room temperature for 0.5 hour, and the addition funnel replaced with a distillation head. Toluene (100 mL) was added and the diethyl ether was distilled out of the reactor. The reaction was cooled, toluene (250 mL) and hexamethylphosphoramide (HMPA) (19.8 mL, 20 .4 g, 113.8 mmole) were added, and the resulting mixture was stirred for 0.25 hours. The distillation head was replaced with a condenser and paraformaldehyde (8.5 g, 284.4 mmole) was added. The reaction was heated to 90 °C for 3 hours. The reaction mixture was cooled to room temperature, was acidified with 1N HCl and the layers separated. The organic phase was washed with water, and with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a solid. This solid was purified by silica chromatography (hexanes-ethyl acetate, 5:1) yielding the salicylaldehyde as a yellow crystalline solid (6.01 g) of suitable purity to be used in the next reaction without further purification.

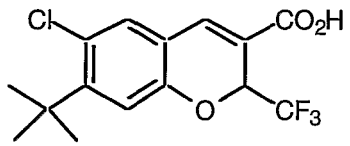
Step 2. Preparation of ethyl 6-(methylthio)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylate.

5-Methylthiosalicylaldehyde (Step 1)(2.516 g, 14.96 mmole) was added to dimethylformamide (3.5 mL), potassium carbonate (2.27 g, 16.45 mmole) and ethyl 4,4,4-trifluorocrotonate (3.3 mL, 3.8 g, 22.4 mmole). The mixture was heated to 65 °C for 3 h. The reaction was cooled to room temperature, poured into H_2O (50 mL), and extracted with diethyl ether (2 X 75 mL). The combined ethereal phases were washed with aqueous $NaHCO_3$ solution (3 X 50 mL), aqueous 2 N HCl solution (3 X 50 mL), and brine (3 X 50 mL), dried over $MgSO_4$, filtered, diluted with isooctane and partially concentrated *in vacuo* causing the precipitation of the ethyl ester (2.863 g, 60 %) as a yellow powder: mp 87.8-89.6 °C This ester was of suitable purity to use without further purification.

Step 3. Preparation of 6-(methylthio)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

The ester (Step 2) was hydrolyzed to form the carboxylic acid via a method similar to that described in Example 1, Step 2: mp 166.3-167.9 °C. ^{1}H NMR (acetone-d_6/300 MHz) 7.87 (s, 1H), 7.43 (d, 1H, J = 2.2 Hz), 7.33 (dd, 1H, J = 8.5, 2.4 Hz), 6.98 (d, 1H, J = 8.5 Hz), 5.79 (q, 1H, J = 7.0 Hz), 2.48 (s, 3H). FABLRMS *m/z* 291 (M+H). ESHRMS *m/z* 289.0152 (M-H, Calc'd 289.0146). Anal. Calc'd for $C_{12}H_9F_3O_3S_1$: C, 49.66; H, 3.13; S, 11.05. Found: C, 49.57; H,3.02; S, 11.37.

Example 3



6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

Step 1. Preparation of 4-*tert*-butylsalicylaldehyde.

A five liter three-neck round bottom flask equipped with overhead mechanical stirrer and condenser was charged with trifluoroacetic acid (2.4 L). A mixture of 3-*tert*-butylphenol (412 g, 2.8 mole) and HMTA (424 g, 3.0 mole) was added portion-wise causing an exotherm. With cooling, the temperature was maintained under 80 °C. The reaction was heated at 80 °C for one hour, then cooled, and water (2 L) added. After 0.5 hour additional water (4 L) was added and the mixture was extracted with ethyl acetate (6 L). The organic extract was washed with water and brine. The resulting organic phase was divided into 2 L volumes and each diluted with water (1 L), and solid $NaHCO_3$ added until the mixture was neutralized. The organic phases were isolated and combined, dried over $MgSO_4$,

filtered and concentrated *in vacuo* yielding an oil. This oil was distilled at 95 °C (0.8 mm) yielding the desired salicylaldehyde as an oil (272.9 g, 56 %) which was of sufficient purity to be used without further purification.

Step 2. Preparation of ethyl 7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylate.

A one liter three-neck flask was charged with 4-*tert*-butylsalicylaldehyde (Step 1)(100.0 g, 0.56 mole), dimethylformamide (110 mL), and potassium carbonate (79.9 g, 0.58 mole) causing the temperature of the mixture to rise to 40 °C. Ethyl 4,4,4-trifluorocrotonate (118.0 g, 0.70 mole) in dimethylformamide (110 mL) was added and the mixture heated to 60 °C at which time the reaction temperature rose to 70 °C. The reaction was cooled to 60 °C, maintained at 60 °C (with added heating) for 8.5 hours and cooled to room temperature. Ethyl acetate (600 mL) and 3 N HCl (600 mL) were added, mixed, and the layers separated. The aqueous phase was extracted with ethyl acetate and the organic phases were combined. The combined organic phases were washed with brine-water (1:1), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*, yielding a semi-solid. Hexane (600 mL) was added with mixing and the mixture was filtered. The filtrate was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding a solid. This solid was dissolved in hot ethanol (600 mL). Water (190 mL) was added which induced crystallization. Filtration of the mixture and drying of the product provided the desired ester as a crystalline solid (131.3 g, 71%): mp 91.0-94.9 °C. This material was of suitable purity to be used in subsequent steps without further purification.

Step 3. Preparation of ethyl 6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylate.

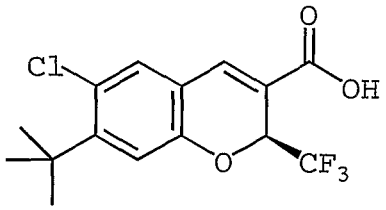
A one liter three-neck flask equipped with mechanical stirrer and gas inlet tube was charged with the ester (Step 2) (100 g, 0.3 mole) and acetic acid (300 mL). While cooling (water bath) the reaction mixture, chlorine gas (37.6 g, 0.53 mole) was added which caused the temperature to rise to 48 °C. After stirring for two

hours, the reaction was cooled in an ice-water bath to 15 °C. Zinc powder (19.5 g, 0.3 mole) was added in one portion which caused the temperature to rise to 72 °C. After cooling to room temperature additional zinc powder (5.0 g, 0.08 mole) was added and the mixture was stirred for 0.5 hour longer. The crude mixture was filtered through diatomaceous earth and was concentrated *in vacuo* yielding an oil. The oil was dissolved in ethyl acetate (700 mL) washed with brine-water (1:1, 1 L) and brine (0.5 L). The resulting aqueous phase was extracted with ethyl acetate (700 mL). This ethyl acetate phase was washed with brine-water (1:1, 1 L) and brine (0.5 L). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding the title compound as a yellow oil (116 g, 106 %). This material, which contained some entrained ethyl acetate, was of suitable purity to be used in subsequent steps without further purification.

Step 4. Preparation of 6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

To a solution of the ester (Step 3) (116 g, 0.3 mole) in methanol (500 mL) and tetrahydrofuran (500 mL) in a one liter flask was added aqueous sodium hydroxide (2.5 N, 240 mL, 0.6 mole). After stirring overnight, the pH of the solution was adjusted to 1 with concentrated hydrochloric acid and the solution was extracted with ethyl acetate. The ethyl acetate phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding a solid. This solid was dissolved in hot ethanol (500 mL). Water (500 mL) was added and upon cooling to room temperature crystals formed which were collected by vacuum filtration. The crystals were washed with ethanol-water (3:7, 3 X 200 mL) and dried providing the title acid as a crystalline solid (91.6 g, 91 %): mp 194.9-196.5 °C. 1H NMR (acetone-*d6*/300 MHz) 7.86 (s, 1H), 7.52 (s, 1H), 7.12 (s, 1H), 5.83 (q, 1H, $J = 7.1$ Hz), 1.48 (s, 9H). Anal. Calc'd for C15H14ClF3O3: C, 53.83; H, 4.22; Cl, 10.59. Found: C, 53.92; H, 4.24; Cl, 10.50.

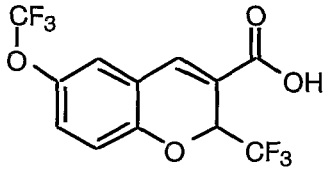
Example 4



(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

To a solution of 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (Example 3)(11.4 g, 34.1 mmol) and (S)(-)-2-amino-3-phenyl-1-propanol (2.57 g, 17.00 mmol) was added n-heptane (200 mL) and the mixture set aside for 16 hours. The resulting suspension was filtered yielding a solid (3.8 g). This solid was recrystallized from 2-butanone (20 mL) and n-heptane (200 mL) yielding upon filtration a white solid (3.0 g). This solid was dissolved in ethyl acetate (100 mL) and washed with 1 N HCl (50 mL) and brine (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo* yielding a white solid. This solid was recrystallized from n-heptane yielding the title compound of high optical purity as a crystalline solid (1.7 g, 30%): mp 175.4-176.9 °C. 1H NMR (acetone-*d6*/300 MHz) 7.86 (s, 1H), 7.52 (s, 1H), 7.12 (s, 1H), 5.83 (q, 1H, $J = 7.1$ Hz), 1.48 (s, 9H). Anal. Calc'd for $C_{15}H_{14}O_3F_3Cl$: C, 53.83; H, 4.22; N, 0.0; Cl, 10.59. Found: C, 53.78; H, 4.20; N, 0.0; Cl, 10.65. This compound was determined to have an optical purity of greater than 90% ee. Chiral purity was determined as describe in Example 2.

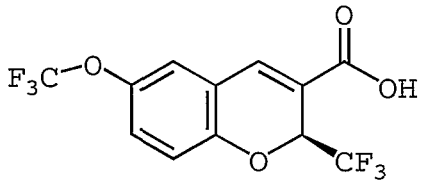
Example 5



6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

5-(Trifluoromethoxy)salicylaldehyde was converted to the title compound by a similar procedure to that described in Example 1: mp 118.4-119.5 °C. 1H NMR (acetone-*d6*/300 MHz) 7.95 (s, 1H), 7.54 (d, 1H, J = 2.1 Hz), 7.39 (dd, 1H, J = 2.4 Hz, and J = 9.0 Hz), 7.02 (d, 1H, J = 9.0 Hz), 5.88 (q H-F, 1H, J = 7.2 Hz). FABHRMS *m/z* 329.0228 (M+H, Calc'd 329.0249). Anal. Calc'd for C12H6F6O4: C, 43.92; H, 1.84. Found: C, 43.84; H, 1.87.

Example 6

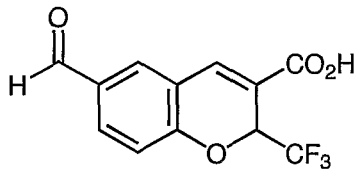


(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

To a solution of 6-trifluoromethoxy-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid (Example 5)(17.72 g, 54.00 mmol) and (-)cinchonidine (7.95 g, 27.04 mmol) in methyl-*tert*-butyl ether (100 mL) heated on a steam-bath was added n-heptane (200 mL). The mixture was heated on the steam bath to boiling and allowed to cool for 4 h during which time crystals formed. Filtration of the suspension yielded a crystalline solid (18.7 g). This solid was dissolved in 2-butanone (30 mL) followed by the addition of n-heptane (500 mL). After standing for 16 hours, the resulting suspension was filtered yielded a white solid (10.3 g). This solid was dissolved in ethyl acetate (150 mL), washed with 1 N hydrochloric acid (100 mL) and brine (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* yielding a viscous yellow oil (5.2 g, 59%): ^{1}H NMR (acetone-*d6*/300 MHz) 7.16 (s, 1H), 6.77 (d, 1H, J = *2.7* Hz), 6.94 (d, 1H, J = *8.7* Hz), 6.64 (m, 1H), 6.39 (d, 1H, J = *8.7* Hz) 5.13 (q, 1H, J = *7.2* Hz). Anal. Calc'd for $C_{12}H_6O_4F_6$: C, 43.92; H, 1.84; N, 0.0. Found: C, 43.79; H, 1.83; N, 0.0. This

compound was determined to have an optical purity of greater than 90% ee. Chiral purity was determined as describe in Example 2.

Example 7



6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

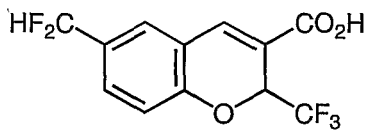
Step 1. Preparation of ethyl 6-formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylate.

A 50 mL round bottom flask was charged with 5-formylsalicylaldehyde (3.21 g, 21.39 mmol), ethyl 4,4,4-trifluorocrotonate (3.50 mL, 3.96 g, 23.53 mmol), dimethylformamide (15 mL) and potassium carbonate (2.95 g, 21.39 mmol) and heated to 60 °C for 12 hours. Additional ethyl 4,4,4-trifluorocrotonate (3.50 mL, 3.96 g, 23.53 mmol) was added and the reaction heated for 16 hours at 75 °C. After cooling to room temperature, the reaction was partitioned between H_2O and diethyl ether. The organic phase was washed with saturated $NaHCO_3$ solution, $KHSO_4$ solution (0.25 M), brine, treated with decolorizing carbon (warmed gently). The resulting black suspension was dried over $MgSO_4$, vacuum filtered through diatomaceous earth, and concentrated *in vacuo* yielding an orange crystalline mass. This material was recrystallized from hot hexanes yielding the ester (1.51 g, 24 %) as orange crystals: mp 84.3-86.2 °C. 1H NMR (acetone-*d6*/300 MHz) 9.96 (s, 1H), 8.06 (d, 1H, J = 2Hz), 8.02 (s, 1H), 7.99 (dd, 1H, J = 8.5, 2.0Hz), 7.24 (d, 1H, J = 8.5 Hz), 5.99 (q, 1H, J = 7.1 Hz), 4.43-4.25 (m, 2H), 1.34 (t, 3H, J = 7.3 Hz). FABLRMS *m/z* 301 (M+H). EIHRMS *m/z* 300.0605 (M+, Calc'd 300.0609). Anal. Calc'd for C14H11F3O4: C, 56.01; H, 3.69. Found: C, 56.11; H, 3.73.

Step 2. Preparation of 6-formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

The ester (Step 1) was converted to the acid via a method similar to that described in Example 1, Step 2: mp 211.3-215.7 °C. 1H NMR (acetone-*d6*/300 MHz) 9.97 (s, 1H), 8.07 (d, 1H, *J* = 2.0Hz), 8.03 (s, 1H), 8.00 (dd, 1H, *J* = 8.3, 2.0 Hz), 7.25 (d, 1H, *J* = 8.5 Hz), 5.98 (q, 1H, *J* = 6.9 Hz). FABLRMS *m/z* 273 (M+H). EIHRMS *m/z* 272.0266 (M+, Calc'd 272.0296). Anal. Calc'd for C12H7F3O4: C, 52.95; H, 2.59. Found: C, 52.62; H, 2.58.

Example 8



6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Step 1. Preparation of ethyl 6-(difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylate.

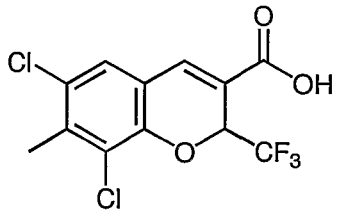
Ethyl 6-formyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylate (Example 7, Step 1)(1.672 g, 5.569 mmol) in methylene chloride (1.5 mL) was added to methylene chloride (1.5 mL) and diethylaminosulfur trifluoride (DAST) (0.74 mL, 0.898 g, 5.569 mmol) over 0.07 hours via syringe. After stirring for 20 hours the reaction was poured into aqueous HCl (2.0 N) and the mixture was extracted with diethyl ether. The ethereal phase was washed with dilute aqueous HCl (2.0 N), saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding a clear colorless oil. This oil was purified by flash chromatography (Silica gel 60, Eluant (5:1; Hexanes : Ethyl Acetate) yielding ethyl 6-difluoromethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylate (0.96 g, 54 %) as an oil which solidified upon standing. This product was of sufficient purity to be used in the next step without further purification: 1H NMR (acetone-*d6*/300 MHz) 7.97 (s, 1H), 7.74 (s, 1H), 7.65 (d, 1H, *J* = 8.5 Hz), 7.18 (d, 1H, *J* = 8.5 Hz), 6.90 (t,

1H, J = 56.0 Hz), 5.94 (q, 1H, J = 7.0 Hz), 4.40-4.25 (m, 2H), 1.34 (t, 3H, J = 7.0 Hz).

Step 2. Preparation of 6-(difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

Aqueous NaOH (1.31 mL, 3.277 mmol, 2.5 M solution) was added in one portion to the ester (Step 1)(0.880 g, 2.731 mmol) in THF:EtOH:H_2O (7:2:1, 10 mL). The resulting solution was stirred for 60 hours. The reaction mixture was partially concentrated *in vacuo* to remove the organic solvents and was diluted with H_2O. The resulting aqueous solution was washed with diethyl ether, sparged with nitrogen to remove trace ether, and acidified with concentrated HCl. The resulting oily suspension was extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding the title compound (0.483 g, 60%) as an oil which solidified as a white crystalline mass: mp 134.7-136.2 °C. 1H NMR (acetone-*d6*/300 MHz) 7.97 (s, 1H), 7.73 (s, 1H), 7.67 (dd, 1H, J = 8.5, 1.0 Hz), 7.17 (d, 1H, J = 8.5 Hz), 6.89(t, 1H, J = 56.2 Hz), 5.90 (q, 1H, J = 7.1 Hz). FAB-ESLRMS *m/z* 293 (M-H). EIHRMS *m/z* 293.0235 (M-H, Calc'd 293.0237). Anal. Calc'd for C12H7F5O3: C, 49.00; H, 2.40. Found: C, 48.78; H,2.21.

Example 9



6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Step 1. Preparation of 3,5-dichloro-4-methylsalicylaldehyde.

2,4-Dichloro-3-methylphenol (25.0 g, 141.2 mmol) was added to methanesulfonic acid (100 mL). With stirring, hexamethylenetetramine (HMTA)

(39.8g, 282.4 mmol) and additional methanesulfonic acid (100 mL) was added portion-wise during which time the reaction began to froth and exotherm. The resulting mixture was heated to 100 °C for 3 hours. The crude ocher colored suspension was cooled to 50 °C and poured over a mechanically stirred mixture of ice-water (2 L). A yellow precipitate was formed which was collected by vacuum filtration. This solid was purified by flash chromatography (silica, hexanes-methylene chloride, 9:10) yielding the salicylaldehyde as a pale yellow powder (6.17 g, 21%; mp 94.0-95.1 °C) of suitable purity to use without further purification.

Step 2. Preparation of ethyl 6,8-dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylate.

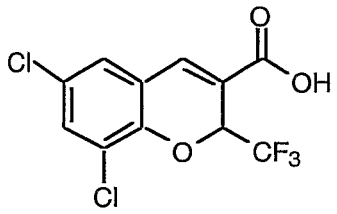
A mixture of 3,5-dichloro-4-methylsalicylaldehyde (Step 1)(5.94 g, 29.0 mmol) and ethyl 4,4,4-trifluorocrotonate (7.67 g, 45.6 mmol) dissolved in anhydrous DMSO (10 mL) was treated with triethylamine (5.88 g, 58.1 mmol). The reaction was stirred at 85 °C for 49 hours then cooled in ice and filtered to give an orange solid. The solid was dissolved in ethyl acetate (100 mL), washed with 3 N HCl (2 x 50 mL), saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow solid (8.63 g, 84%): mp 117.1-119.5 °C. ^1H NMR ($CDCl_3$/300 MHz) 7.63 (s, 1H), 7.17 (s, 1H), 5.80 (q, 1H, J = 6.6 Hz), 4.33 (m, 2H), 2.48 (s, 3H), 1.35 (t, 3H, J = 7.1 Hz).

Step 3. Preparation of 6,8-dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

The ester from Step 2 (8.39 g 23.6 mmol) was dissolved in THF (30 mL) and ethanol (20 mL), treated with 2.5 N sodium hydroxide (20 mL, 50 mmol), and stirred at room temperature for 3.5 hours. The reaction mixture was concentrated *in vacuo*, acidified with 3 N HCl, filtered, and recrystallized from ethanol/ water to yield a yellow solid (6.0 g, 78%): mp 229.9-230.9 °C. ^1H NMR (acetone-*d6*/300 MHz) 7.90 (s, 1H), 7.58 (s, 1H), 6.00 (q, 1H, J = 6.8 Hz), 2.50 (s, 3H). FABLRMS *m/z* 325 (M-H). FABHRMS *m/z* 324.9636 (M-H, Calc'd 324.9646). Anal. Calc'd

for $C_{12}H_7Cl_2F_3O_3$: C, 44.07; H, 2.16; Cl, 21.68. Found: C, 44.06; H, 2.21; Cl, 21.74.

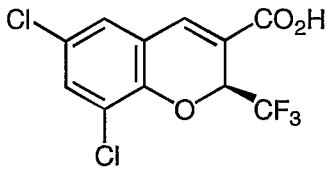
Example 10



6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

3,5-Dichlorosalicylaldehyde was converted to the title compound by a procedure similar to that described in Example 9, Steps 2 & 3: mp 212.8-216.8 °C. 1H NMR (CDCl3/300 MHz) 7.77 (s, 1H), 7.41 (d, 1H, *J* = 2.4 Hz), 7.18 (d, 1H, *J* = 2.2 Hz), 5.82 (q, 1H, *J* = 6.7 Hz). FABLRMS *m/z* 311 (M-H). FABHRMS *m/z* 312.9644 (M+H, Calc'd 312.9646). Anal. Calc'd for C11H5F3Cl2O3: C, 42.20; H, 1.61. Found: C, 42.50; H, 1.71.

Example 11



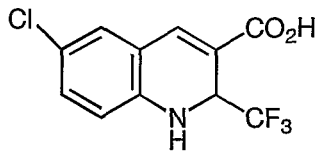
(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid (Example 10)(300 g, 1.04 mol) was added to ethyl acetate (750 mL). The mixture was stirred for 5 minutes, warmed to 70 °C and held at this temperature for 5 minutes. The resulting solution was cooled to 50 °C and (s)-(-)-α-methylbenzylamine (58 g, 0.48 mol)was added. Heptane (1880 mL) was added and

the mixture stirred for 0.5 hour, then stirring was discontinued. The reaction was allowed to cool to 22 °C and stand for 8 hours. The salt crystallized during this time and was collected by vacuum filtration. The solid was washed with ethyl acetate-heptane (1:3, 2 X 50 mL). The solid obtained was dried at 40 °C under vacuum (20 mm) for 24 hours to give the salt(35 g, 16 %).

A three-neck 2 L round bottom flask was purged with nitrogen and was charged with deionized water (750 mL) and the salt (103 g, 0.24 mole; This material was obtained using a similar procedure to that described above). To the resulting stirred suspension was added concentrated HCl (37 mL) drop-wise over 0.5 hours with good stirring below 20 °C causing the free carboxylic acid to precipitate. After stirring for 2 hours, the suspension was vacuum filtered and the solid washed with deionized water (5 X 50 mL; until the washings were neutral). The solid was dried at 40 °C under vacuum (20 mm) for 12 hours yielding the title compound as a solid (74 g, 100%): mp 166.0-168.4 °C. 1H NMR (acetone-*d6*/300 MHz) 7.94 (s, 1H), 7.60 (s, 2H), 6.04 (q, 1H, J = 6.8 Hz). ESHRMS m/z 310.9489 (M-H, Calc'd 310.9450). This compound was determined to have an optical purity of greater than 90% ee. The optical purity was determined by the method described in Example 2.

Example 12



6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

Step 1. Preparation of 2-amino-5-chlorobenzaldehyde.

2-Amino-5-chlorobenzyl alcohol (4.8 g, 30 mmol) and activated manganese (IV) oxide (21 g, 240 mmol) were refluxed in chloroform (100 mL) for 1 hour. The contents were allowed to cool, filtered through diatomaceous earth and

concentrated *in vacuo* to afford the 2-amino-5-chlorobenzaldehyde as a dark solid (4.14 g, 81%): mp 74-76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 9.80 (s, 1H), 7.42 (s, 1H), 7.23 (d, 1H, J = 7.0 Hz), 6.60 (d, 1H, J = 7.0 Hz).

Step 2. Preparation of ethyl 6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylate.

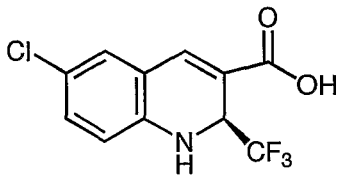
The 2-amino-5-chlorobenzaldehyde from Step 1 (15.0 g, 96 mmol), anhydrous potassium carbonate (27.6 g, 200 mmol), and ethyl 4,4,4-trifluorocrotonate (34 mL, 200 mmol) were mixed in anhydrous dimethyformamide (60 mL) and heated at 100 °C for 7 hours. The contents were allowed to cool and partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous layer was extracted with ethyl acetate (1 x 100 mL). The ethyl acetate extracts were combined and washed with brine (1 x 200 mL), dried over $MgSO_4$, and concentrated *in vacuo* leaving a dark oil which solidified upon standing. The solid was purified by flash chromatography (silica gel; ethyl acetate-hexanes, 1:9). Fractions containing the desired product were combined, concentrated *in vacuo* and the residue recrystallized from ethyl acetate-hexanes to afford the ethyl 6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylate as a yellow solid (16.36 g, 56%): mp 132.6-134.2 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.61 (s, 1H), 7.10 (m, 2H), 6.55 (d, 1H, J = 8.0 Hz), 5.10 (q, 1H, J = 6.0 Hz), 4.55 (brs, 1H), 4.23 (m, 2H), 1.32 (t, 3H, J = 7.0 Hz). FABHRMS m/z 306.0468 ($M+H^+$, Calc'd 306.0509). Anal. Calc'd for $C_{13}H_{11}NO_2F_3Cl$: C, 51.08; H, 3.63; N, 4.58. Found: C, 50.81; H, 3.49; N, 4.72.

Step 3. Preparation of 6-chloro-1,2-dihydro-2-(trifluoro-methyl)-3-quinolinecarboxylic acid.

The ester from Step 2 (1.7 g, 5.6 mmol) and 2.5 N sodium hydroxide (4.4 mL, 11 mmol) were mixed in tetrahydrofuran (25 mL), methanol (10 mL), and water (25 mL). After stirring overnight, contents were concentrated *in vacuo* to remove the THF and methanol. The aqueous solution remaining was extracted with diethyl ether (2 x 100 mL). The resulting aqueous layer was acidified with 2 N HCl

causing the precipitation of an oil. The oil was purified by flash chromatography on silica gel, eluting with ethyl acetate-hexanes (1:1). Fractions containing the desired product were combined, and concentrated *in vacuo*. The residue was triturated with dichloromethane, and filtered to afford the 6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid as a yellow solid (0.645 g, 41 %): mp 187.8-188.8 °C. ^{1}H NMR (acetone-d_6, 300 MHz) 7.69 (s, 1H), 7.36 (s, 1H), 7.15 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 8.0 Hz), 6.60 (brs, 1H), 5.20 (m, 1H). ESHRMS *m/z* 276.0040 (M-H,Calc'd 276.0039). Anal. Calc'd for $C_{11}H_7NO_2F_3Cl$ + 2.6% H_2O: C, 46.39; H, 2.98; N, 4.92. Found: C, 45.99; H, 2.54; N, 4.85.

Example 13

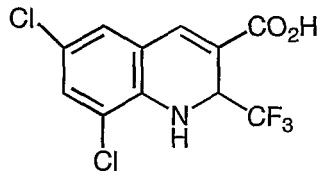


(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

To a solution of 6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid (Example 12)(6.75 g, 24.3 mmol) in ethyl acetate (25 mL) was added (S)-(-)-a-methylbenzylamine (1.50 g, 12.2 mmol). To the resulting solution was added hexanes (50 mL) with mixing. Stirring was discontinued and the reaction held static at room temperature for 16 hours during which time yellow crystals formed. The crystals were collected and washed with ethyl acetate-hexanes (100 mL, 1:2). The resulting yellow solid (932 mg) was dissolved in ethyl acetate (20 mL) and extracted with 1 N HCl (3 x 10 mL). The organic layer was dried over sodium sulfate and solvent removed at reduced pressure. The (s)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid was obtained as a yellow solid (648 mg, 10% yield). mp 173-176 °C. ^{1}H NMR (acetone-d_6, 300 MHz) 7.80 (s, 1H), 7.35(d, 1H, J = 2.2 Hz), 7.18 (d, 1H, J = 8.0, J = 2.2 Hz), 6.86 (d, 1H, J = 8.0 Hz), 6.60 (brs, 1H), 5.20 (m, 1H). Anal. Calc'd. for $C_{11}H_7NO_2F_3Cl$ C, 47.40 H,

2.54; N, 5.40. Found C, 47.49; H, 2.60; N, 4.98. The compound was determined to have an optical purity greater than 90% ee. Optical purity was determined by HPLC as described in Example 2.

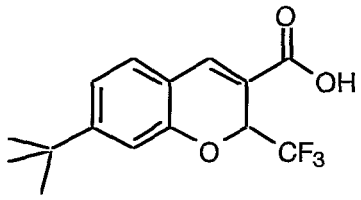
Example 14



6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

The 1,2-dihydro-3-quinolinecarboxylic acid was prepared by a procedure similar to that described in Example 12: mp 223.4-225.7 °C. ^{1}H NMR (acetone-d_6, 300 MHz) 7.82 (s, 1H), 7.40 (m, 2H), 6.53 (brs, 1H), 5.40 (m, 1H). ESHRMS *m/z* 309.9657 (M-H, Calc'd 309.9649). Anal. Calc'd for $C_{11}H_6NO_2F_3Cl_2$: C, 42.34; H, 1.94; N, 4.49. Found: C, 42.20; H, 1.74; N, 4.52.

Example 15

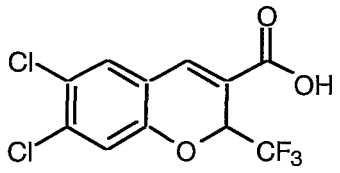


7-(1,1-Dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

Ethyl 7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylate (Example 3, Step 2) was hydrolyzed to the carboxylic acid via a procedure similar to that described in Example 1, Step 2: mp 165.6-166.8 °C. 1H NMR (acetone-*d6*/300 MHz) 7.86 (s, 1H), 7.38 (d, 1H, J = 8.1 Hz), 7.15 (dd, 1H, J

= 1.8 Hz, and J = 7.8 Hz), 7.05 (bs, 1H), 5.79 (q H-F, 1H, J = 7.2 Hz), 1.32 (s, 9H). FABHRMS *m/z* 301.1033 (M+H, Calc'd 301.1051). Anal. Calc'd for C15H15F3O3: C, 60.00; H, 5.04. Found: C, 59.80; H, 5.10.

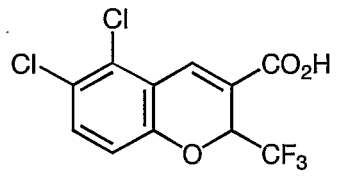
Example 16



6,7-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

3,4-Dichlorophenol was converted to the title compound by a procedure similar to that described in Example 2: mp 196.1-198.3 °C. 1H NMR (acetone-*d6*/300 MHz) 7.90 (s, 1H), 7.74 (s, 1H), 7.30 (s, 1H), 5.88 (q, 1H, J = 6.9 Hz). FABLRMS *m/z* 314 (M+H). Anal. Calc'd for C11H5Cl2F3O3: C, 42.20; H, 1.61. Found: C, 42.31; H, 1.65.

Example 17

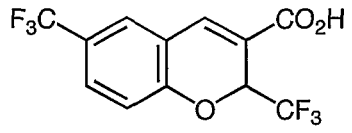


5,6-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

5,6-Dichlorosalicylaldehyde was prepared by the procedure described in Cragoe, E.J.; Schultz, E.M., U.S. Patent 3 794 734, 1974. This salicylaldehyde was converted to the title compound by a similar procedure to that described in Example 1: mp 211.5-213.5 °C. 1H NMR (acetone-*d6*/300 MHz) 8.09 (s, 1H), 7.63 (d, 1H, J = 8.9 Hz), 7.12 (d, 1H, J = 8.9 Hz), 5.94 (q, 1H, J = 7.0 Hz). ESLRMS *m/z* 311

(M-H). EIHRMS *m/z* 311.9583 (M+, Calc'd 311.9568). Anal. Calc'd for C11H5Cl2F3O3: C, 42.20; H, 1.61. Found: C, 42.33; H, 1.67.

Example 18



2,6-Bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Step 1. Preparation of Ethyl 2,6-bis(trifluoromethyl)-4-oxo-4H-1-benzopyran-3-carboxylate.

To a stirred solution of ethyl 4,4,4-trifluoroacetoacetate (3.22 mL, 4.06 g, 22.07 mmol) in toluene (100 mL) was added portion-wise sodium hydride (0.971 g, of 60 % oil dispersion reagent, 22.07 mmol) causing gas evolution. After gas evolution has subsided, 2-fluoro-5-(trifluoromethyl)benzoyl chloride (5.00 g, 22.07 mmol) was added. The reaction was stirred at room temperature for 24 hours, then heated to 105 °C for 24 hours. After cooling to room temperature, the reaction was diluted with diethyl ether and the resulting solution was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding a slightly sticky white solid. This solid was triturated with hexanes yielding the desired ester(3.05 g, 39 %) as a white powder: mp 116-120.1 °C. 1H NMR ($CDCl_3$/300 MHz) 8.52 (d, 2H, J =1.6 Hz), 8.03 (dd, 1H, J = 8.9, 2.2Hz), 7.71 (d, 1H, J = 8.9 Hz), 4.48 (q, 2H, J = 7.3 Hz), 1.39 (t, 3H, J = 7.3 Hz). FABLRMS *m/z* 355 (M+H). Anal. Calc'd for C14H8F6O4: C, 47.45; H, 2.28. Found: C, 47.59; H, 2.43.

Step 2. Preparation of ethyl 2,6-bis(trifluoromethyl)-4-oxo-dihydrobenzopyran-3-carboxylate.

A 250 mL round bottom flask was charged with ethyl 2,6-bis(trifluoromethyl)-benzopyran-4-one-3-carboxylate (Step 1)(2.307 g, 6.513

mmol) and THF (20 mL) yielding a pale yellow solution. Ethanol (20 mL) was added and the reaction chilled in an ice-salt bath. While maintaining the reaction temperature at below 9 °C, $NaBH_4$ (0.246 g, 6.513 mmol) was added in two portions and the mixture stirred 1 h. The crude reaction mixture was poured into a vigorously stirred mixture of ice (200 mL) and concentrated HCl (12 N, 5 mL) yielding a precipitate. Vacuum filtration of the resulting suspension yielded the desired keto ester (2.204 g, 87%) as faint pink powder of suitable purity to use in the next step without further purification: mp 71.8-76.9 °C. 1H NMR (acetone-*d6*/300 MHz) 12.71 (br s, 1H exch), 8.01 (d, 1H, J = 2.0 Hz), 8.01 (d, 1H, J = 2.0 Hz), 7.88 (dd, 1H, J = 8.7, 1.8 Hz), 7.31 (d, 1H, J = 8.7Hz), 5.98 (q, 1H, J = 6.6 Hz), 4.51-4.28 (m, 2H), 1.35 (t, 3H, J = 7.0 Hz). FABLRMS *m/z* 355 (M-H). ESHRMS *m/z* 355.0394 (M-H, Calc'd 355.0405).
Anal. Calc'd for C14H10F6O4: C, 47.21; H, 2.83. Found: C, 47.31; H,2.97.

Step 3. Preparation of ethyl 2,6-bis(trifluoromethyl)-4-trifluoromethanesulfonato-2H-1-benzopyran-3-carboxylate.

A 50 mL 3-neck Morton flask fitted with addition funnel, 2 stoppers was charged with 2.6-di-*tert*-butylpyridine (1.576 g, 1.50 mmol), methylene chloride (12 mL), and then via syringe was added trifluoromethanesulfonic anhydride (1.08 mL, 1.80 g, 1.25 mmol). To this solution was added dropwise a solution the keto ester (Step 2) (1.822 g, 5.115 mmol) in methylene chloride (10 mL) over 0.33 h and the reaction stirred for 48 h. The resulting off-white suspension was transferred to a 100 mL round bottom flask and was concentrated *in vacuo*. The residue was suspended in diethyl ether (50 mL) and vacuum filtered to remove salts. The filtrate was further diluted with diethyl ether (50 mL) and was washed with ice cold HCl solution (2 N), brine, and dried over Na_2CO_3, filtered and concentrated *in vacuo* yielding the desired triflate (1.64 g, 66%) as a tan clumpy powder of suitable purity to use in the next step without further purification.

Step 4. Preparation of ethyl 2,6-bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylate.

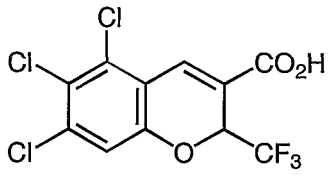
A 25 mL pear flask was charged with LiCl (0.136 g, 3.219 mmol), affixed to a high vacuum line and heated with a heat gun removing superficial water. The flask was allowed to cool to room temperature, and tetrakis(triphenylphosphine)palladium(0)(0.124 g, 0.107 mmol) and THF (2 mL) were added. A reflux condenser was affixed to the flask and the apparatus was purged with nitrogen. A solution of the triflate(Step 3)(0.524 g, 1.073 mmol)in THF (2 mL) and tri-n-butyltin hydride (0.32 mL, 0.34 g, 1.18 mmol) were added sequentially via syringe. The resulting light orange solution was heated to 50 °C with stirring for 1 h, 60 °C for one hour, and 65 °C for one hour. The reaction was allowed to cool to room temperature and was poured into 2 N HCl, stirred, and extracted with hexanes. The hexane phase was dried over $MgSO_4$, filtered and concentrated yielding a light brown oil. The oil was dissolved in hexane and was washed with aqueous ammonium fluoride solution. The resulting hexane phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* yielding a dull yellow oily solid which solidified as a flaky powder (0.443 g). This solid was purified by flash silica chromatography (eluant: hexanes-methylene chloride, 4:1) yielding ethyl 2,6-di-trifluoromethyl-2H-1-benzopyran-3-carboxylate(0.069 g, 19 %) as a white crystalline solid of suitable purity to proceed with the next step.

Step 5. Preparation of 2,6-bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

To a stirred solution of the ester (Step 4) (0.065 g, 0.191 mmol) in THF-EtOH-H_2O (7:2:1, 1 mL) was added NaOH solution (0.084 mL, 0.210 mmol)in one portion at room temperature and allowed to stir overnight. The reaction was partially concentrated *in vacuo* yielding a pale yellow clear syrup. The syrup was diluted with water (5 mL) and brine (1mL) and was washed with diethyl ether (3 X 5 mL). The resulting aqueous phase was sparged with nitrogen to remove trace ether. With stirring, concentrated HCl was added to the aqueous phase causing the formation of a very fine white precipitate. This suspension was extracted with diethyl ether and the ether dried over Na_2SO_4, filtered, and concentrated by slow

evaporation at atmospheric pressure. The resulting product was recrystallized from hexanes and ethyl acetate yielding the title compound (0.038 g, 64 %) as a fine tan powder: mp 143.5-145.2 °C. 1H NMR (acetone-*d6*/300 MHz) 11.97-11.67 (br s, 1H), 8.03 (s, 1H), 7.92 (s, 1H), 7.77 (d, 1H, J = 8.5 Hz), 7.26 (d, 1H, J = 8.7 Hz), 5.96 (q, 1H, J = 7.0 Hz). FABLRMS *m/z* 311 (M-H). ESHRMS *m/z* 311.0107 (M-H, Calc'd 311.0143).

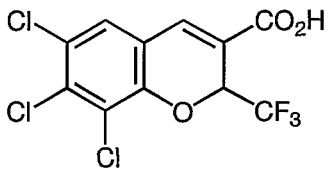
Example 19



5,6,7-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

3,4,5-Trichlorophenol was converted to 4,5,6-trichlorosalicylaldehyde via a procedure similar to that described in Example 9, Step 1. The 4,5,6-trichlrorsalicylaldehyde was converted to the title compound by a procedure similar to that described in Example 1: mp 236.2-239.3 °C. 1H NMR (acetone-*d6*/300 MHz) 8.05 (s, 1H), 7.40 (s, 1H), 5.99 (q, 1H, J = 7.0 Hz). ESLRMS *m/z* 345 (M-H). ESHRMS *m/z* 344.9113 (M-H, Calc'd 344.9100). Anal. Calc'd for C11H4Cl3F3O3 + 0.89 wt % H_2O: C, 37.68; H, 1.25; Cl, 30.33. Found: C, 37.48; H,1.25; Cl, 30.33.

Example 20

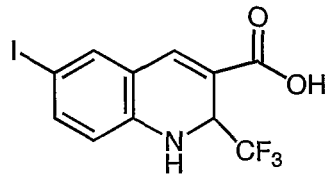


6,7,8-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

2,3,4-Trichlorophenol was converted to 3,4,5-trichlorosalicylaldehyde via a procedure similar to that described in Example 9, Step 1. The 3,4,5-

trichlrorsalicylaldehyde was converted to the title compound by a procedure similar to that described in Example 1: mp 222.0-225.3 °C. 1H NMR (acetone-*d6*/300 MHz) 7.94 (s, 1H), 7.78 (s, 1H), 6.07 (q, 1H, *J* = 7.0 Hz). ESLRMS *m/z* 345 (M-H). EIHRMS *m/z* 344.9117 (M-H, Calc'd 344.9100). Anal. Calc'd for C11H4Cl3F3O3 + 1.56 wt % H_2O: C, 37.43; H, 1.32; Cl, 30.13. Found: C, 37.79; H,0.93; Cl, 29.55.

Example 21



6-Iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

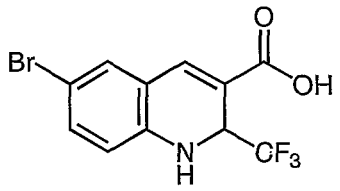
Step 1. Preparation of ethyl 6-iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylate.

A mixture of 5-iodo-2-aminobenzaldehyde (24.0 g, 96.7 mmol), diazbicyclo[2.2.2]-undec-7-ene (32.2 g, 212.0 mmol), and ethyl 4,4,4-trifluorocrotonate (35.7 g, 212.0 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (48 mL) was heated at 60 °C for 8 hours. The solution was cooled to room temperature and the solution poured into ethyl acetate-hexanes (1:1, 500 mL). The solution was extracted with 2.5 N aqueous hydrochloric acid (2 x 200 mL), saturated aqueous ammonium chloride (2 x 200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting dark yellow oil was dissolved in hexanes (100 mL) and fine yellow crystals formed upon standing. Vacuum filtration of this suspension yielded ethyl 6-iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylate as fine yellow crystals (19.3 g, 50 % yield): mp 137-138 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.62 (s, 1H), 7.36-7.48 (m, 2H), 6.43 (d, *J* = 8.2 Hz), 5.36 (brs, 1H), 5.11 (q, 1H, J = 7.1 Hz), 4.25 -4.35 (m, 2H), 1.34 (t, 3H, J = 7.0 Hz). ESHRMS *m/z* 395.9716 (M-H, Calc'd 395.9708).

Step 2. Preparation of 6-iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

Hydrolysis of the ester (Step 1) was performed by a procedure similar to that described in Example 12, Step 3, yielding the carboxylic acid. mp 188-192 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.668 (s, 1H), 7.46 (d, 1H, J = 2.2 Hz), 7.39 (dd, 1H, J = 8.4, 2.2 Hz), 6.52 (d, 1H, J = 8.4 Hz), 5.01 (q, 1H, J = 7.5 Hz). ESHRMS *m/z* 367.9401 (M, Calc'd 367.9395).

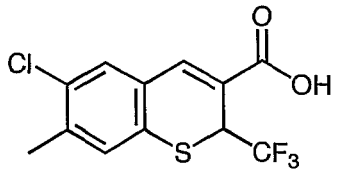
Example 22



6-Bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid

The 1,2-dihydro-3-quinolinecarboxylic acid was prepared by a procedure similar to that described in Example 21: mp 185-186 °C. ^{1}H NMR (CD_3OD/300 MHz) 7.68 (s, 1H), 7.31 (d, 1H, J = 2.2 Hz), 7.23 (dd, 1H, J = 8.7, 2.2 Hz), 6.64 (d, 1H, J = 8.7 Hz), 5.01 (q, 1H, J = 7.5 Hz). EIHRMS *m/z* 319.9519 (M, Calc'd 319.9534). Anal. Calc'd for $C_{11}H_7BrF_3NO_2$: C, 41.02; H, 2.19; N, 4.35; Found: C, 41.27, H, 2.23, N, 4.26.

Example 23



6-Chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid

Step 1. Preparation of N,N-dimethyl-O-(4-chloro-2-formyl-5-methylphenyl)thiocarbamate.

A mixture of 5-chloro-4-methylsalicylaldehyde (12.96 g, 76.0 mmol) and triethylamine (11.58 g, 114.4 mmol) was dissolved in anhydrous DMF (15 mL) treated with *N,N*-dimethylthiocarbamoyl chloride (11.25 g, 91.0 mmol) and stirred at room temperature for 16 hours. The reaction was treated with 3 N HCl (50 mL) and filtered to give an orange solid. The solid was dissolved in ethyl acetate washed with 3 N HCl, water, brine, dried over anhydrous MgSO4, filtered and concentrated *in vacuo* to afford a brown solid (16.79 g) which was recrystallized from diethyl ether/hexane to give the O-aryl thiocarbamate as a tan solid (4.92 g, 25%): ^{1}H NMR (acetone-*d6*/300 MHz) 9.96 (s, 1H), 7.80 (s, 1H), 7.19 (s, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 2.43 (s, 3H).

Step 2. Preparation of N,N-dimethyl-S-(4-chloro-2-formyl-5-methylphenyl)thiocarbamate.

The O-aryl thiocarbamate (Step 1) (4.92 g, 19.1 mmol) was dissolved in *N,N*-dimethylaniline (25 mL) and immersed in and stirred at 200 °C for 1.5 hours. The reaction mixture was cooled to room temperature and poured into a mixture of 3 N HCl (200 mL) and ice. Filtration gave a brown semisolid which was dissolved in ethyl acetate, washed with 3 N HCl, brine, dried over anhydrous MgSO4, filtered and concentrated *in vacuo* to afford the S-arylthiocarbamate as a brown oil (3.80 g, 77%) which was used in the next step without further purification.

Step 3. Preparation of ethyl 6-chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylate.

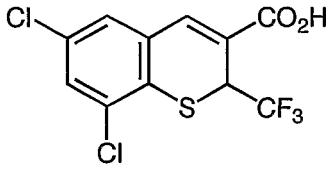
The S-arylthiocarbamate (Step 2) (3.80 g, 14.7 mmol) was dissolved in THF (10 mL) and ethanol (10 mL), treated with 2.5 N sodium hydroxide (16.5 mL, 34.2 mmol), and stirred at room temperature for 0.9 hours. The reaction was diluted with diethyl ether and washed with 3 N HCl, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude substituted 2-mercaptobenzaldehyde as a brown oil (2.82 g). This oil was added to DMF (10 mL) and ethyl 4,4,4-

trifluorocrotonate (3.89 g, 23.1 mmol). With stirring, K_2CO_3 (3.23 g, 23.4 mmol) was added causing the reaction to become a deep red. The reaction was stirred at room temperature for 14.5 hours, acidified with 3 N HCl, extracted with ethyl acetate. The resulting organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid (6.36 g) which was used in the next step without further purification.

Step 4. Preparation of 6-chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid

The ester from Step 3 (2.02 g, 6.0 mmol) was dissolved in THF (10 mL) and ethanol (10 mL), treated with 2.5 N sodium hydroxide (5.5 mL, 13.8 mmol), and stirred at room temperature for 4.8 hours. The reaction mixture was concentrated *in vacuo*, acidified with 3 N HCl yielding a suspension. The solid was collected by filtration and was recrystallized from ethanol-water to yield the title compound as a yellow solid (0.20 g, 11%): mp 240.5-241.7 °C. ^{1}H NMR (acetone-*d6*/300MHz) 7.99 (s, 1H), 7.67 (s, 1H), 7.43 (s, 1H), 4.99 (q, 1H, J = 8.5 Hz), 2.39 (s, 3H). FABLRMS *m/z* 307 (M-H). FABHRMS *m/z* 306.9831 (M-H, Calc'd 306.9807). Anal. Calc'd for $C_{12}H_8ClF_3O_2S$: C, 46.69; H, 2.61; Cl, 11.48. Found: C, 46.78; H, 2.61; Cl, 11.41.

Example 24



6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

The 2H-1-benzothiopyran-3-carboxylic acid was prepared by a procedure similar to the method described in Example 23: mp 217.9-220.3 °C. 1H NMR (acetone-*d6*/300 MHz) 12.50-11.20 (br s, 1H exch.), 8.06 (s, 1H), 7.75 (d, 1H, J = 2.0 Hz), 7.64 (d, 1H, J = 2.2 Hz), 5.23 (q, 1H, J = 8.5).

Therapeutic Illustrations

The following non-limiting illustrative examples describe various neoplasia disorders or cancer diseases and therapeutic approaches that may be used in the present invention, and are for illustrative purposes only. Some COX-2 selective inhibiting agents (or prodrugs thereof) that can be used in the below non-limiting illustrations include, but are not limited to celecoxib, rofecoxib, valdecoxib, parecoxib, deracoxib, MK-663 and JTE-522, and some DNA topoisomerase I inhibiting agents that can be used with the below non-limiting illustrations include, for example, irinotecan, rubitecan, lurtotecan, exetecan mesylate, karenitecan, or silatecan.

Illustration 1

Lung Cancer

In many countries including Japan, Europe and America, the number of patients with lung cancer is fairly large and continues to increase year after year and is the most frequent cause of cancer death in both men and women. Although there are many potential causes for lung cancer, tobacco use, and particularly cigarette smoking, is the most important. Additionally, etiologic factors such as exposure to asbestos, especially in smokers, or radon are contributory factors. Also occupational hazards such as exposure to uranium have been identified as an important factor. Finally, genetic factors have also been identified as another factor that increase the risk of cancer.

Lung cancers can be histologically classified into non-small cell lung cancers (e.g. squamous cell carcinoma (epidermoid), adenocarcinoma, large cell carcinoma (large cell anaplastic), etc.) and small cell lung cancer (oat cell). Non-small cell lung cancer (NSCLC) has different biological properties and responses to chemotherapeutics from those of small cell lung cancer (SCLC). Thus,

chemotherapeutic formulas and radiation therapy are different between these two types of lung cancer.

Non-Small Cell Lung Cancer

Where the location of the non-small cell lung cancer tumor can be easily excised (stage I and II disease) surgery is the first line of therapy and offers a relatively good chance for a cure. However, in more advanced disease (stage IIIa and greater), where the tumor has extended to tissue beyond the bronchopulmonary lymph nodes, surgery may not lead to complete excision of the tumor. In such cases, the patient's chance for a cure by surgery alone is greatly diminished. Where surgery will not provide complete removal of the NSCLC tumor, other types of therapies must be utilized.

Today radiation therapy is the standard treatment to control unresectable or inoperable NSCLC. Improved results have been seen when radiation therapy has been combined with chemotherapy, but gains have been modest and the search continues for improved methods of combining modalities.

Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproductive cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various consideration but the two most important considerations are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. In one embodiment a course of treatment for a patient undergoing radiation therapy for NSCLC will be a treatment with daily administration of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents and a treatment schedule over a 5 to 6 week period with a total dose of 50 to 60 Gy administered to the patient in a single daily fraction of 1.8 to 2.0 Gy, 5 days a week. A Gy is an abbreviation for Gray and refers to 100 rad of dose.

However, as NSCLC is a systemic disease, and radiation therapy is a local modality, radiation therapy as a single line of therapy is unlikely to provide a cure for NSCLC, at least for those tumors that have metastasized distantly outside the zone of treatment. Thus, the use of radiation therapy with other modality regimens of the present invention have important potential beneficial effects for the treatment of NSCLC.

Generally, radiation therapy has been combined temporally with chemotherapy to improve the outcome of treatment. There are various terms to describe the temporal relationship of administering radiation therapy in combination with a COX-2 selective inhibiting agent, a DNA topoisomerase I inhibiting agents and chemotherapy, and the following examples are some treatment regimens and are provided for illustration only and are not intended to limit the use of other combinations. "Sequential" therapy refers to the administration of chemotherapy and/or a COX-2 selective inhibiting agent and/or a DNA topoisomerase I inhibiting agents and/or radiation therapy separately in time in order to allow the separate administration of chemotherapy and/or a COX-2 selective inhibiting agent and/or a DNA topoisomerase I inhibiting agents and/or radiation therapy. "Concomitant" therapy refers to the administration of chemotherapy and/or a COX-2 selective inhibiting agent and/or a DNA topoisomerase I inhibiting agents and/or radiation therapy on the same day. Finally, "alternating therapy refers to the administration of radiation therapy on the days in which chemotherapy and/or a COX-2 selective inhibiting agent and/or a DNA topoisomerase I inhibiting agents would not have been administered if it was given alone.

Several chemotherapeutic agents have been shown to be efficacious against NSCLC. In one embodiment, chemotherapeutic agents that can be used in the methods, combinations and compositions of the present invention against NSCLC include etoposide, carboplatin, methotrexate, 5-Fluorouracil, epirubicin, doxorubicin, taxol, inhibitor of normal mitotic activity; and cyclophosphamide. In another embodiment, chemotherapeutic agents that may be used in the methods,

combinations and compositions of the present invention active against NSCLC include cisplatin, ifosfamide, mitomycin C, epirubicin, vinblastine, and vindesine.

Other agents that are under investigation for use against NSCLC include: camptothecins, a topoisomerase 1 inhibitor; navelbine (vinorelbine), a microtubule assembly inhibitor; gemcitabine, a deoxycytidine analogue; fotemustine, a nitrosourea compound; and edatrexate, an antifol.

The overall and complete response rates for NSCLC has been shown to increase with use of combination chemotherapy as compared to single-agent treatment. Haskel CM: Chest. 99: 1325, 1991; Bakowski MT: Cancer Treat Rev 10:159, 1983; Joss RA: Cancer Treat Rev 11:205, 1984.

In one embodiment, therapy for the treatment of NSCLC is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with one or more of the following combinations of antineoplastic agents: 1) itosfamide, cisplatin, etoposide; 2) cyclophosphamide, doxorubicin, cisplatin; 3) isofamide, carboplatin, etoposide; 4) bleomycin, etoposide, cisplatin; 5) isofamide, mitomycin, cisplatin; 6) cisplatin, vinblastine; 7) cisplatin, vindesine; 8) mitomycin C, vinblastine, cisplatin; 9) mitomycin C, vindesine, cisplatin; 10) isofamide, etoposide; 11) etoposide, cisplatin; 12) isofamide, mitomycin C; 13) fluorouracil, cisplatin, vinblastine; 14) carboplatin, etoposide; or radiation therapy.

Small Cell Lung Cancer

Approximately 15 to 20 percent of all cases of lung cancer reported worldwide is small cell lung cancer (SCLC). Ihde DC: Cancer 54:2722, 1984. Currently, treatment of SCLC incorporates multi-modal therapy, including chemotherapy, radiation therapy and surgery. Response rates of localized or disseminated SCLC remain high to systemic chemotherapy, however, persistence of the primary tumor and persistence of the tumor in the associated lymph nodes has led to the integration of several therapeutic modalities in the treatment of SCLC.

In one embodiment, a therapy for the treatment of lung cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective

inhibiting agent and a DNA topoisomerase I inhibiting agents, in combination with one or more of the following antineoplastic agents: vincristine, cisplatin, carboplatin, cyclophosphamide, epirubicin (high dose), etoposide (VP-16) I.V., etoposide (VP-16) oral, isofamide, teniposide (VM-26), and doxorubicin. Other single-agents chemotherapeutic agents that may be used in the methods, combinations and compositions of the present invention include BCNU (carmustine), vindesine, hexamethylmelamine (altretamine), methotrexate, nitrogen mustard, and CCNU (lomustine). Other chemotherapeutic agents under investigation that have shown activity against SCLC include iroplatin, gemcitabine, lonidamine, and taxol. Single-agent chemotherapeutic agents that have not yet shown activity against SCLC include mitoguazone, mitomycin C, aclarubicin, diaziquone, bisantrene, cytarabine, idarubicin, mitomxantrone, vinblastine, PCNU and esorubicin.

Another contemplated therapy for the treatment of SCLC is a combination of neoplasia disorder effective amounts a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with one or more of the following combinations of antineoplastic agents: 1) etoposide (VP-16), cisplatin; 2) cyclophosphamide, adriamycin [(doxorubicin), vincristine, etoposide (VP-16)]; 3) Cyclophosphamide, adriamycin(doxorubicin), vincristine; 4) Etoposide (VP-16), ifosfamide, cisplatin; 5) etoposide (VP-16), carboplatin; 6) cisplatin, vincristine (Oncovin), doxorubicin, etoposide.

Additionally, radiation therapy in conjunction with combinations of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents and/or systemic chemotherapy is contemplated to be effective at increasing the response rate for SCLC patients. The typical dosage regimen for radiation therapy ranges from 40 to 55 Gy, in 15 to 30 fractions, 3 to 7 times week. The tissue volume to be irradiated is determined by several factors and generally the hilum and subcarnial nodes, and bilateral distal nodes up to the thoracic inlet are treated, as well as the primary tumor up to 1.5 to 2.0 cm of the margins.

Illustration 2

Colorectal Cancer

Survival from colorectal cancer depends on the stage and grade of the tumor, for example precursor adenomas to metastatic adenocarcinoma. Generally, colorectal cancer can be treated by surgically removing the tumor, but overall survival rates remain between 45 and 60 percent. Colonic excision morbidity rates are fairly low and is generally associated with the anastomosis and not the extent of the removal of the tumor and local tissue. In patients with a high risk of reoccurrence, however, chemotherapy has been incorporated into the treatment regimen in order to improve survival rates.

Tumor metastasis prior to surgery is generally believed to be the cause of surgical intervention failure and up to one year of chemotherapy is required to kill the non-excised tumor cells. As severe toxicity is associated with the chemotherapeutic agents, only patients at high risk of recurrence are placed on chemotherapy following surgery. Thus, the incorporation of a COX-2 and a DNA topoisomerase I inhibiting agents into the management of colorectal cancer will play an important role in the treatment of colorectal cancer and lead to overall improved survival rates for patients diagnosed with colorectal cancer.

In one embodiment, a combination therapy for the treatment of colorectal cancer is surgery, followed by a regimen of one or more chemotherapeutic agents and a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents, cycled over a one year time period. In another embodiment, a combination therapy for the treatment of colorectal cancer is a regimen of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents, followed by surgical removal of the tumor from the colon or rectum and then followed be a regimen of one or more chemotherapeutic agents and a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agent, cycled over a one year time period. In still another embodiment, a therapy for the treatment of colon cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

In another embodiment, a therapy for the treatment of colon cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with fluorouracil and Levamisole. Typically, fluorouracil and Levamisole are used in combination.

In yet another embodiment, a therapy for the treatment of colon cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with fluorouracil and leucovorin. Typically, fluorouracil and leucovorin are used in combination.

Illustration 3

Breast Cancer

Today, among women in the United States, breast cancer remains the most frequent diagnosed cancer. One in 8 women in the United States are at risk of developing breast cancer in their lifetime. Age, family history, diet, and genetic factors have been identified as risk factors for breast cancer. Breast cancer is the second leading cause of death among women.

Different chemotherapeutic agents are known in art for treating breast cancer. Cytoxic agents used for treating breast cancer include doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, mitomycin C, mitoxantrone, taxol, and epirubicin.

In the treatment of locally advanced noninflammatory breast cancer, a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents can be used to treat the disease in combination with surgery, radiation therapy and/or chemotherapy. Combinations of chemotherapeutic agents, radiation therapy and surgery that can be used in combination with the present invention include, but are not limited to the following combinations: 1) doxorubicin, vincristine, radical mastectomy; 2) doxorubicin, vincristine, radiation therapy; 3) cyclophosphamide, doxorubicin, 5-flourouracil, vincristine, prednisone, mastectomy; 4)

cyclophosphamide, doxorubicin, 5-flourouracil, vincristine, prednisone, radiation therapy; 5) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen, radiation therapy for pathologic complete response; 6) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen, mastectomy, radiation therapy for pathologic partial response; 7) mastectomy, radiation therapy, levamisole; 8) mastectomy, radiation therapy; 9) mastectomy, vincristine, doxorubicin, cyclophosphamide, levamisole; 10) mastectomy, vincristine, doxorubicin, cyclophosphamide; 11) mastectomy, cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, halotestin, radiation therapy; 12) mastectomy, cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, halotestin.

In the treatment of locally advanced inflammatory breast cancer, a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents can be used to treat the disease in combination with surgery, radiation therapy or with chemotherapeutic agents. In one embodiment combinations of chemotherapeutic agents, radiation therapy and surgery that can be used in combination with the present invention include, but or not limited to the following combinations: 1) cyclophosphamide, doxorubicin, 5-fluorouracil, radiation therapy; 2) cyclophosphamide, doxorubicin, 5-fluorouracil, mastectomy, radiation therapy; 3) 5-fluorouracil, doxorubicin, clyclophosphamide, vincristine, prednisone, mastectomy, radiation therapy; 4) 5-fluorouracil, doxorubicin, clyclophosphamide, vincristine, mastectomy, radiation therapy; 5) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, radiation therapy; 6) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, mastectomy, radiation therapy; 7) doxorubicin, vincristine, methotrexate, radiation therapy, followed by vincristine, cyclophosphamide, 5-florouracil; 8) doxorubicin, vincristine, cyclophosphamide, methotrexate, 5-florouracil, radiation therapy, followed by vincristine, cyclophosphamide, 5-florouracil; 9) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine, tamoxifen; 10) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, followed by

cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine, tamoxifen; 11) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine, tamoxifen;; 12) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine; 13) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine, tamoxifen; 14) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine; 15) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine; 16) 5-florouracil, doxorubicin, cyclophosphamide followed by mastectomy, followed by 5-florouracil, doxorubicin, cyclophosphamide, followed by radiation therapy.

In the treatment of metastatic breast cancer, a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents can be used to treat the disease in combination with surgery, radiation therapy and/or with chemotherapeutic agents. In one embodiment, combinations of chemotherapeutic agents that can be used in combination with a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents of the present invention, include, but are not limited to the following combinations: 1) cyclophosphamide, methotrexate, 5-fluorouracil; 2) cyclophosphamide, adriamycin, 5-fluorouracil; 3) cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone; 4) adriamycin, vincristine; 5) thiotepa, adriamycin, vinblastine; 6) mitomycin, vinblastine; 7) cisplatin, etoposide.

Illustration 4

Prostate Cancer

Prostate cancer is now the leading form of cancer among men and the second most frequent cause of death from cancer in men. It is estimated that more than 165,000 new cases of prostate cancer were diagnosed in 1993, and more than 35,000 men died from prostate cancer in that year. Additionally, the incidence of prostate cancer has increased by 50% since 1981, and mortality from this disease has continued to increase. Previously, most men died of other illnesses or diseases before dying from their prostate cancer. We now face increasing morbidity from prostate cancer as men live longer and the disease has the opportunity to progress.

Current therapies for prostate cancer focus exclusively upon reducing levels of dihydrotestosterone to decrease or prevent growth of prostate cancer. In addition to the use of digital rectal examination and transrectal ultrasonography, prostate-specific antigen (PSA) concentration is frequently used in the diagnosis of prostate cancer.

In one embodiment, a therapy for the treatment of prostate cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

U.S. Pat. No. 4,472,382 discloses treatment of benign prostatic hyperplasia (BPH) with an antiandrogen and certain peptides which act as LH-RH agonists.

U.S. Pat. No. 4,596,797 discloses aromatase inhibitors as a method of prophylaxis and/or treatment of prostatic hyperplasia.

U.S. Pat. No. 4,760,053 describes a treatment of certain cancers a LHRH agonist with an antiandrogen and/or an antiestrogen and/or at least one inhibitor of sex steroid biosynthesis.

U.S. Pat. No. 4,775,660 discloses a method of treating breast cancer with a combination therapy which may include surgical or chemical prevention of ovarian secretions and administering an antiandrogen and an antiestrogen.

U.S. Pat. No. 4,659,695 discloses a method of treatment of prostate cancer in susceptible male animals including humans whose testicular hormonal secretions

are blocked by surgical or chemical means, e.g. by use of an LHRH agonist, which comprises administering an antiandrogen, e.g. flutamide, in association with at least one inhibitor of sex steroid biosynthesis, e.g. aminoglutethimide and/or ketoconazole.

Illustration 5

Bladder Cancer

The classification of bladder cancer is divided into three main classes: 1) superficial disease, 2) muscle-invasive disease, and 3) metastatic disease.

Currently, transurethral resection (TUR), or segmental resection, account for first line therapy of superficial bladder cancer, i.e., disease confined to the mucosa or the lamina propria. However, intravesical therapies are necessary, for example, for the treatment of high-grade tumors, carcinoma in situ, incomplete resections, recurrences, and multifocal papillary. Recurrence rates range from up to 30 to 80 percent, depending on stage of cancer.

Therapies that are currently used as intravesical therapies include chemotherapy, immuontherapy, bacille Calmette-Guerin (BCG) and photodynamic therapy. The main objective of intravesical therapy is twofold: to prevent recurrence in high-risk patients and to treat disease that cannot by resected. The use of intravesical therapies must be balanced with its potentially toxic side effects. Additionally, BCG requires an unimpaired immune system to induce an antitumor effect. Chemotherapeutic agents that are known to be of limited use against superficial bladder cancer include Cisplatin, actinomycin D, 5-fluorouracil, bleomycin, and cyclophosphamide methotrexate.

In the treatment of superficial bladder cancer, a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents can be used to treat the disease in combination with surgery (TUR), chemotherapy and/or intravesical therapies.

A therapy for the treatment of superficial bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a

DNA topoisomerase I inhibiting agents in combination with: thiotepa (30 to 60 mg/day), mitomycin C (20 to 60 mg/day), and doxorubicin (20 to 80 mg/day).

In one embodiment, intravesicle immunotherapeutic agent that may be used in the methods, combinations and compositions of the present invention is BCG. A daily dose ranges from 60 to 120 mg, depending on the strain of the live attenuated tuberculosis organism used.

In another embodiment, a photodynamic therapeutic agent that may be used with the present invention is Photofrin I, a photosensitizing agent, administered intravenously. It is taken up by the low-density lipoprotein receptors of the tumor cells and is activated by exposure to visible light. Additionally, neomydium YAG laser activation generates large amounts of cytotoxic free radicals and singlet oxygen.

In the treatment of muscle-invasive bladder cancer, a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents can be used to treat the disease in combination with surgery (TUR), intravesical chemotherapy, radiation therapy, and/or radical cystectomy with pelvic lymph node dissection.

In one embodiment, radiation dose for the treatment of bladder cancer is between 5,000 to 7,000 cGY in fractions of 180 to 200 cGY to the tumor. Additionally, 3,500 to 4,700 cGY total dose is administered to the normal bladder and pelvic contents in a four-field technique. Radiation therapy should be considered only if the patient is not a surgical candidate, but may be considered as preoperative therapy.

In another embodiment, combination of surgery and chemotherapeutic agents that can be used in combination with a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents of the present invention is cystectomy in conjunction with five cycles of cisplatin (70 to 100 mg/m(square)); doxorubicin (50 to 60 mg/m(square); and cyclophosphamide (500 to 600 mg/m(square).

In one embodiment, a therapy for the treatment of superficial bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

In another embodiment, a combination for the treatment of superficial bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with one or more of the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; and 2) cisplatin, 5-fluorouracil. A combination of chemotherapeutic agents that can be used in combination with radiation therapy and a COX-2 selective inhibiting agent and a DNA topoisomerase inhibitor is a combination of cisplatin, methotrexate, vinblastine.

Currently no curative therapy exists for metastatic bladder cancer. The present invention contemplates an effective treatment of bladder cancer leading to improved tumor inhibition or regression, as compared to current therapies. In the treatment of metastatic bladder cancer, a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents can be used to treat the disease in combination with surgery, radiation therapy and/or with chemotherapeutic agents.

In one embodiment a therapy for the treatment of metastatic bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents. In another embodiment, therapy for the treatment of metastatic bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with one or more of the following combinations of antineoplastic agents: 1) cisplatin and methotrexate; 2) doxorubicin, vinblastine, cyclophosphamide, and 5-fluorouracil; 3) vinblastine, doxorubicin, cisplatin, methotrexate; 4) vinblastine, cisplatin, methotrexate; 5) cyclophosphamide, doxorubicin, cisplatin; 6) 5-fluorouracil, cisplatin.

Illustration 6

Pancreas Cancer

Approximately 2% of new cancer cases diagnoses in the United States is pancreatic cancer. Pancreatic cancer is generally classified into two clinical types: 1) adenocarcinoma (metastatic and non-metastatic), and 2) cystic neoplasms (serous cystadenomas, mucinous cystic neoplasms, papillary cystic neoplasms, acinar cell systadenocarcinoma, cystic choriocarcinoma, cystic teratomas, angiomatous neoplasms).

In one embodiment, a therapy for the treatment of non-metastatic adenocarcinoma that may be used in the methods, combinations and compositions of the present invention include the use of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents along with preoperative biliary tract decompression (patients presenting with obstructive jaundice); surgical resection, including standard resection, extended or radial resection and distal pancreatectomy (tumors of body and tail); adjuvant radiation; and/or chemotherapy.

In one embodiment for the treatment of metastatic adenocarcinoma, a therapy consists of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents of the present invention in combination with continuous treatment of 5- fluorouracil, followed by weekly cisplatin therapy.

In another embodiment a combination therapy for the treatment of cystic neoplasms is the use of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents along with resection.

Illustration 7

Ovary Cancer

Celomic epithelial carcinoma accounts for approximately 90% of ovarian cancer cases. In one embodiment, a therapy for the treatment of ovary cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

Single agents that can be used in combination with a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents include, but are not limited to: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin,

5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha, and interferon gamma.

In another embodiment, combinations for the treatment of celomic epithelial carcinoma is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with one or more of the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamthylmelamine, cyclophosphamide, doxorubicin, cisplatin; 3) cyclophosphamide, hexamehtylmelamine, 5-fluorouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin, cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10) hexamethylmelamine, doxorubicin, carboplatin; 11) cyclophosphamide, hexamethlmelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

Germ cell ovarian cancer accounts for approximately 5% of ovarian cancer cases. Germ cell ovarian carcinomas are classified into two main groups: 1) dysgerminoma, and nondysgerminoma. Nondysgerminoma is further classified into teratoma, endodermal sinus tumor, embryonal carcinoma, chloricarcinoma, polyembryoma, and mixed cell tumors.

In one embodiment, a therapy for the treatment of germ cell carcinoma is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

In another embodiment, a therapy for the treatment of germ cell carcinoma is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with one or more of the following combinations of antineoplastic agents: 1) vincristine, actinomycin D, cyclophosphamide; 2) bleomycin, etoposide, cisplatin; 3) vinblastine, bleomycin, cisplatin.

Cancer of the fallopian tube is the least common type of ovarian cancer, accounting for approximately 400 new cancer cases per year in the United States. Papillary serous adenocarcinoma accounts for approximately 90% of all malignancies of the ovarian tube.

In one embodiment, a therapy for the treatment of fallopian tube cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

In another embodiment, a therapy for the treatment of fallopian tube cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with on or more of the following of antineoplastic agents: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin, 5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha, and interferon gamma.

In still another embodiment, therapy for the treatment of fallopian tube cancer is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with one or more of the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamthylmelamine, cyclophosphamide, doxorubicin, cisplatin; 3) cyclophosphamide, hexamehtylmelamine, 5-fluorouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin, cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10) hexamethylmelamine, doxorubicin, carboplatin; 11) cyclophosphamide, hexamethlmelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

Illustration 8

Central Nervous System Cancers

Central nervous system cancer accounts for approximately 2% of new cancer cases in the United States. Common intracranial neoplasms include glioma, meninigioma, neurinoma, and adenoma.

In one embodiment, a therapy for the treatment of central nervous system cancers is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents.

In another embodiment, a therapy for the treatment of malignant glioma is a combination of neoplasia disorder effective amounts of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents in combination with one or more of the following combinations of therapies and antineoplastic agents:: 1) radiation therapy, BCNU (carmustine); 2) radiation therapy, methyl CCNU (lomustine); 3) radiation therapy, medol; 4) radiation therapy, procarbazine; 5) radiation therapy, BCNU, medrol; 6) hyperfraction radiation therapy, BCNU; 7) radiation therapy, misonidazole, BCNU; 8) radiation therapy, streptozotocin; 9) radiation therapy, BCNU, procarbazine; 10) radiation therapy, BCNU, hydroxyurea, procarbazine, VM-26; 11) radiation therapy, BNCU, 5-flourouacil; 12) radiation therapy, Methyl CCNU, dacarbazine; 13) radiation therapy, misonidazole, BCNU; 14) diaziquone; 15) radiation therapy, PCNU; 16) procarbazine (matulane), CCNU, vincristine. A dose of radiation therapy is about 5,500 to about 6,000 cGY. Radiosensitizers include misonidazole, intra-arterial Budr and intravenous iododeoxyuridine (IUdR). It is also contemplated that radiosurgery may be used in combinations with a COX-2 selective inhibiting agent and an DNA topoisomerase I inhibiting agents.

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Illustration 9

Table Nos. 22 and 23 provide additional non-limiting illustrative examples of combination therapies that can be used in the methods, combinations and compositions of the present invention. In each combination identified in Table Nos. 22 and 23, the individual combination is used in combination with an

aromatase inhibiting agent. Exemplary aromatase inhibiting agents that can be used in the below non-limiting illustrative examples include anastrozole, atamestane, exemestane, fadrozole, finrozol, formestane, letrozole, minamestane, MR-20492, Testolactone, YM-511, and vorozole. Other examples of aromatase inhibiting agents that can be used in the combinations of the below examples are provided in Table No. 3, above. Additionally, non-limiting illustrative examples of combinations of COX-2 selective inhibiting agents and aromatase inhibiting agents are provided in Table No. 24 below. Table No. 22 provides non-limiting illustrative examples of a COX-2 selective inhibiting agent in combination with a single antineoplastic agent in the treatment of an illustrative neoplasia disorder. Table No. 23 provides non-limiting illustrative examples of a COX-2 selective inhibiting agent in combination with multiple antineoplastic agents in the treatment of an illustrative neoplasia disorder.

Table No. 22. A COX-2 Inhibiting Agent in Combination with a Single Antineoplastic Agent.

COX-2 Inhibitor	**Antineoplastic Agents**	**Indication**
Celecoxib	Anastrozole	Breast
Celecoxib	Capecitabine	Breast
Celecoxib	Docetaxel	Breast
Celecoxib	Gemcitabine	Breast, Pancreas
Celecoxib	Letrozole	Breast
Celecoxib	Megestrol	Breast
Celecoxib	Paclitaxel	Breast
Celecoxib	Tamoxifen	Breast
Celecoxib	Toremifene	Breast
Celecoxib	Vinorelbine	Breast, Lung
Celecoxib	Topotecan	Lung
Celecoxib	Etoposide	Lung

Celecoxib	Fluorouracil	Colon
Celecoxib	Irinotecan (CPT-11)	Colon, Bladder
Celecoxib	Retinoids	Colon
Celecoxib	DFMO	Colon
Celecoxib	Ursodeoxycholic acid	Colon
Celecoxib	Calcium carbonate	Colon
Celecoxib	Selenium	Colon
Celecoxib	Sulindac sulfone	Colon
Celecoxib	Carboplatin	Brain
Celecoxib	Goserelin Acetate	Prostate
Celecoxib	Cisplatin	Lung
Celecoxib	Ketoconazole	Prostate
Rofecoxib	Anastrozole	Breast
Rofecoxib	Capecitabine	Breast
Rofecoxib	Docetaxel	Breast
Rofecoxib	Gemcitabine	Breast, Pancreas
Rofecoxib	Letrozole	Breast
Rofecoxib	Megestrol	Breast
Rofecoxib	Paclitaxel	Breast
Rofecoxib	Tamoxifen	Breast
Rofecoxib	Toremifene	Breast
Rofecoxib	Vinorelbine	Breast, Lung
Rofecoxib	Topotecan	Lung
Rofecoxib	Etoposide	Lung
Rofecoxib	Fluorouracil	Colon
Rofecoxib	Irinotecan (CPT-11)	Colon, Bladder
Rofecoxib	Retinoids	Colon
Rofecoxib	DFMO	Colon
Rofecoxib	Ursodeoxycholic acid	Colon
Rofecoxib	Calcium carbonate	Colon

Rofecoxib	Selenium	Colon
Rofecoxib	Sulindac sulfone	Colon
Rofecoxib	Carboplatin	Brain
Rofecoxib	Goserelin Acetate	Prostate
Rofecoxib	Cisplatin	Lung
Rofecoxib	Ketoconazole	Prostate
Valdecoxib	Anastrozole	Breast
Valdecoxib	Capecitabine	Breast
Valdecoxib	Docetaxel	Breast
Valdecoxib	Gemcitabine	Breast, Pancreas
Valdecoxib	Letrozole	Breast
Valdecoxib	Megestrol	Breast
Valdecoxib	Paclitaxel	Breast
Valdecoxib	Tamoxifen	Breast
Valdecoxib	Toremifene	Breast
Valdecoxib	Vinorelbine	Breast, Lung
Valdecoxib	Topotecan	Lung
Valdecoxib	Etoposide	Lung
Valdecoxib	Fluorouracil	Colon
Valdecoxib	Irinotecan (CPT-11)	Colon, Bladder
Valdecoxib	Retinoids	Colon
Valdecoxib	DFMO	Colon
Valdecoxib	Ursodeoxycholic acid	Colon
Valdecoxib	Calcium carbonate	Colon
Valdecoxib	Selenium	Colon
Valdecoxib	Sulindac sulfone	Colon
Valdecoxib	Carboplatin	Brain
Valdecoxib	Goserelin Acetate	Prostate
Valdecoxib	Cisplatin	Lung
Valdecoxib	Ketoconazole	Prostate

Deracoxib	Anastrozole	Breast
Deracoxib	Capecitabine	Breast
Deracoxib	Docetaxel	Breast
Deracoxib	Gemcitabine	Breast, Pancreas
Deracoxib	Letrozole	Breast
Deracoxib	Megestrol	Breast
Deracoxib	Paclitaxel	Breast
Deracoxib	Tamoxifen	Breast
Deracoxib	Toremifene	Breast
Deracoxib	Vinorelbine	Breast, Lung
Deracoxib	Topotecan	Lung
Deracoxib	Etoposide	Lung
Deracoxib	Fluorouracil	Colon
Deracoxib	Irinotecan (CPT-11)	Colon, Bladder
Deracoxib	Retinoids	Colon
Deracoxib	DFMO	Colon
Deracoxib	Ursodeoxycholic acid	Colon
Deracoxib	Calcium carbonate	Colon
Deracoxib	Selenium	Colon
Deracoxib	Sulindac sulfone	Colon
Deracoxib	Carboplatin	Brain
Deracoxib	Goserelin Acetate	Prostate
Deracoxib	Cisplatin	Lung
Deracoxib	Ketoconazole	Prostate
JTE-522	Anastrozole	Breast
JTE-522	Capecitabine	Breast
JTE-522	Docetaxel	Breast
JTE-522	Gemcitabine	Breast, Pancreas
JTE-522	Letrozole	Breast
JTE-522	Megestrol	Breast

JTE-522	Paclitaxel	Breast
JTE-522	Tamoxifen	Breast
JTE-522	Toremifene	Breast
JTE-522	Vinorelbine	Breast, Lung
JTE-522	Topotecan	Lung
JTE-522	Etoposide	Lung
JTE-522	Fluorouracil	Colon
JTE-522	Irinotecan (CPT-11)	Colon, Bladder
JTE-522	Retinoids	Colon
JTE-522	DFMO	Colon
JTE-522	Ursodeoxycholic acid	Colon
JTE-522	Calcium carbonate	Colon
JTE-522	Selenium	Colon
JTE-522	Sulindac sulfone	Colon
JTE-522	Carboplatin	Brain
JTE-522	Goserelin Acetate	Prostate
JTE-522	Cisplatin	Lung
JTE-522	Ketoconazole	Prostate
MK-663	Anastrozole	Breast
MK-663	Capecitabine	Breast
MK-663	Docetaxel	Breast
MK-663	Gemcitabine	Breast, Pancreas
MK-663	Letrozole	Breast
MK-663	Megestrol	Breast
MK-663	Paclitaxel	Breast
MK-663	Tamoxifen	Breast
MK-663	Toremifene	Breast
MK-663	Vinorelbine	Breast, Lung
MK-663	Topotecan	Lung
MK-663	Etoposide	Lung

MK-663	Fluorouracil	Colon
MK-663	Irinotecan (CPT-11)	Colon, Bladder
MK-663	Retinoids	Colon
MK-663	DFMO	Colon
MK-663	Ursodeoxycholic acid	Colon
MK-663	Calcium carbonate	Colon
MK-663	Selenium	Colon
MK-663	Sulindac sulfone	Colon
MK-663	Carboplatin	Brain
MK-663	Goserelin Acetate	Prostate
MK-663	Cisplatin	Lung
MK-663	Ketoconazole	Prostate

Table No. 23. A COX-2 Inhibiting Agent in Combination with Multiple Antineoplastic Agents.

COX-2 Inhibitor	**Antineoplastic Agents**	**Indication**
Celecoxib	Doxorubicin and Cyclophosphamide	Breast
Celecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Celecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Celecoxib	Mitoxantrone, Fluorouracil and Leucovorin	Breast
Celecoxib	Vinblastine, Doxorubicin, Thiotepa, and	Breast

	Fluoxymestrone	
Celecoxib	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Celecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Celecoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Celecoxib	Fluorouracil, Levamisole	Colon
Celecoxib	Leucovorin, Fluorouracil	Colon
Celecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Celecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Celecoxib	Etoposide, Carboplatin	Lung
Celecoxib	Etoposide, Cisplatin	Lung
Celecoxib	Paclitaxel, Carboplatin	Lung
Celecoxib	Gemcitabine, Cisplatin	Lung
Celecoxib	Paclitaxel, Cisplatin	Lung
Rofecoxib	Doxorubicin and Cyclophosphamide	Breast
Rofecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Rofecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Rofecoxib	Mitoxantrone, Flourouracil and Leucovorin	Breast
Rofecoxib	Vinblastine, Doxorubicin,	Breast

	Thiotepa, and Fluoxymestrone	
Rofecoxib	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Rofecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Rofecoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Rofecoxib	Fluorouracil, Levamisole	Colon
Rofecoxib	Leucovorin, Fluorouracil	Colon
Rofecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Rofecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Rofecoxib	Etoposide, Carboplatin	Lung
Rofecoxib	Etoposide, Cisplatin	Lung
Rofecoxib	Paclitaxel, Carboplatin	Lung
Rofecoxib	Gemcitabine, Cisplatin	Lung
Rofecoxib	Paclitaxel, Cisplatin	Lung
Valdecoxib	Doxorubicin and Cyclophosphamide	Breast
Valdecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Valdecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Valdecoxib	Mitoxantrone, Fluorouracil and Leucovorin	Breast

Valdecoxib	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Valdecoxib	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Valdecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Valdecoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Valdecoxib	Fluorouracil, Levamisole	Colon
Valdecoxib	Leucovorin, Fluorouracil	Colon
Valdecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Valdecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Valdecoxib	Etoposide, Carboplatin	Lung
Valdecoxib	Etoposide, Cisplatin	Lung
Valdecoxib	Paclitaxel, Carboplatin	Lung
Valdecoxib	Gemcitabine, Cisplatin	Lung
Valdecoxib	Paclitaxel, Cisplatin	Lung
Deracoxib	Doxorubicin and Cyclophosphamide	Breast
Deracoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Deracoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Deracoxib	Mitoxantrone, Fluorouracil	Breast

	and Leucovorin	
Deracoxib	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Deracoxib	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Deracoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
Deracoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Deracoxib	Fluorouracil, Levamisole	Colon
Deracoxib	Leucovorin, Fluorouracil	Colon
Deracoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Deracoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Deracoxib	Etoposide, Carboplatin	Lung
Deracoxib	Etoposide, Cisplatin	Lung
Deracoxib	Paclitaxel, Carboplatin	Lung
Deracoxib	Gemcitabine, Cisplatin	Lung
Deracoxib	Paclitaxel, Cisplatin	Lung
JTE-522	Doxorubicin and Cyclophosphamide	Breast
JTE-522	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
JTE-522	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast

JTE-522	Mitoxantrone, Flourouracil and Leucovorin	Breast
JTE-522	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
JTE-522	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
JTE-522	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
JTE-522	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
JTE-522	Fluorouracil, Levamisole	Colon
JTE-522	Leucovorin, Fluorouracil	Colon
JTE-522	Cyclophosphamide, Doxorubicin, Etoposide	Lung
JTE-522	Cyclophosphamide, Doxorubicin, Vincristine	Lung
JTE-522	Etoposide, Carboplatin	Lung
JTE-522	Etoposide, Cisplatin	Lung
JTE-522	Paclitaxel, Carboplatin	Lung
JTE-522	Gemcitabine, Cisplatin	Lung
JTE-522	Paclitaxel, Cisplatin	Lung
MK-663	Doxorubicin and Cyclophosphamide	Breast
MK-663	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
MK-663	Cyclophosphamide, Fluorouracil and	Breast

	Mitoxantrone	
MK-663	Mitoxantrone, Fluorouracil and Leucovorin	Breast
MK-663	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
MK-663	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
MK-663	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
MK-663	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
MK-663	Fluorouracil, Levamisole	Colon
MK-663	Leucovorin, Fluorouracil	Colon
MK-663	Cyclophosphamide, Doxorubicin, Etoposide	Lung
MK-663	Cyclophosphamide, Doxorubicin, Vincristine	Lung
MK-663	Etoposide, Carboplatin	Lung
MK-663	Etoposide, Cisplatin	Lung
MK-663	Paclitaxel, Carboplatin	Lung
MK-663	Gemcitabine, Cisplatin	Lung
MK-663	Paclitaxel, Cisplatin	Lung
MK-663	Doxorubicin and Cyclophosphamide	Breast
MK-663	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
MK-663	Cyclophosphamide,	Breast

	Fluorouracil and Mitoxantrone	
MK-663	Mitoxantrone, Fluorouracil and Leucovorin	Breast
MK-663	Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
MK-663	Cyclophosphamide, Methotrexate, Fluorouracil	Breast
MK-663	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast
MK-663	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
MK-663	Fluorouracil, Levamisole	Colon
MK-663	Leucovorin, Fluorouracil	Colon
MK-663	Cyclophosphamide, Doxorubicin, Etoposide	Lung
MK-663	Cyclophosphamide, Doxorubicin, Vincristine	Lung
MK-663	Etoposide, Carboplatin	Lung
MK-663	Etoposide, Cisplatin	Lung
MK-663	Paclitaxel, Carboplatin	Lung
MK-663	Gemcitabine, Cisplatin	Lung
MK-663	Paclitaxel, Cisplatin	Lung

Illustration 10

Table No. 24 illustrates examples of some combinations of the present invention where the combination comprises a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agent.

Table No. 24. Combinations of COX-2 selective inhibiting agents and DNA topoisomerase I inhibiting agents

COX-2 selective inhibiting agent	DNA topoisomerase I inhibiting agent
Celecoxib	irinotecan
Rofecoxib	irinotecan
Valdecoxib	irinotecan
Deracoxib	irinotecan
JTE-522	irinotecan
MK-663	irinotecan
Celecoxib	camptothecin
Rofecoxib	camptothecin
Valdecoxib	camptothecin
Deracoxib	camptothecin
JTE-522	camptothecin
MK-663	camptothecin
Celecoxib	lurtotecan
Rofecoxib	lurtotecan
Valdecoxib	lurtotecan
Deracoxib	lurtotecan
JTE-522	lurtotecan
MK-663	lurtotecan
Celecoxib	homosilatecans
Rofecoxib	homosilatecans
Valdecoxib	homosilatecans
Deracoxib	homosilatecans
JTE-522	homosilatecans
MK-663	homosilatecans
Celecoxib	9-amino camptothecin

Rofecoxib	9-amino camptothecin
Valdecoxib	9-amino camptothecin
Deracoxib	9-amino camptothecin
JTE-522	9-amino camptothecin
MK-663	9-amino camptothecin
Celecoxib	9-nitrocamptothecin
Rofecoxib	9-nitrocamptothecin
Valdecoxib	9-nitrocamptothecin
Deracoxib	9-nitrocamptothecin
JTE-522	9-nitrocamptothecin
MK-663	9-nitrocamptothecin
Celecoxib	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
Rofecoxib	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
Valdecoxib	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
Deracoxib	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
JTE-522	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
MK-663	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-
Celecoxib	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
Rofecoxib	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
Valdecoxib	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
Deracoxib	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
JTE-522	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
MK-663	4-Acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride
Celecoxib	topotecan

Rofecoxib	topotecan
Valdecoxib	topotecan
Deracoxib	topotecan
JTE-522	topotecan
MK-663	topotecan
Celecoxib	topotecan hydrochloride
Rofecoxib	topotecan hydrochloride
Valdecoxib	topotecan hydrochloride
Deracoxib	topotecan hydrochloride
JTE-522	topotecan hydrochloride
MK-663	topotecan hydrochloride

Evaluation of COX-1 and COX-2 activity *in vitro*

The COX-2 selective inhibiting agents of this invention exhibit inhibition *in vitro* of COX-2. The COX-2 inhibition activity of the compounds illustrated in the Examples above were determined by the following methods. The COX-2 inhibition activity of the other cyclooxygease-2 inhibitors of the present invention may also be determined by the following methods.

a. Preparation of recombinant COX baculoviruses

Recombinant COX-1 and COX-2 were prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 μg of baculovirus transfer vector DNA into SF9 insect cells (2x108) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See

M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (107-108 pfu/mL) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX-1 and COX-2 activity

COX activity is assayed as PGE2 formed/μg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 μM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C/room temperature by transferring 40 μl of reaction mix into 160 μl ELISA buffer and 25 μM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

c. Fast assay for COX-1 and COX-2 activity

COX activity was assayed as PGE2 formed/μg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 μM

phenol,1 μM heme, 300 μM epinephrine) with the addition of 20 μl of 100 μM arachidonic acid (10 μM). Compounds were pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after two minutes at 37°C/room temperature by transferring 40 μl of reaction mix into 160 μl ELISA buffer and 25 μM indomethacin. The PGE2 formed was measured by standard ELISA technology (Cayman Chemical). Results are shown below in Table 25.

TABLE 25.

Example	**COX-2*** IC_{50} μM	**COX-1*** IC_{50} μM
1	0.7	43
2	*>0.1*	*16.7*
3	<0.1	64.4
4	<0.1	20.5
5	<0.1	18.8
6	<0.1	6.7
7	0.7	>500
8	*<0.1*	*1.6*
9	0.9	1.0
10	*<0.1*	*1.5*
11	<0.1	0.7
12	0.6	>500
13	0.2	>100
14	0.2	9.7
15	3.6	57
16	<0.1	94.6
17	<0.1	1.6
18	<0.1	5.6

19	*<0.1*	*1.4*
20	<0.1	2.8
21	0.8	>100
22	0.4	>100
23	<0.1	365
24	<0.1	0.2

* fast assay

Biological Evaluation

A combination therapy of a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents for the treatment or prevention of a neoplasia disorder in a mammal can be evaluated as described in the following tests.

1. Lewis Lung Model:

Mice are injected subcutaneously in the left paw (1 x 10^6 tumor cells suspended in 30 % Matrigel) and tumor volume is evaluated using a phlethysmometer twice a week for 30-60 days. Blood is drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data is expressed as the mean +/- SEM. Student's and Mann-Whitney tests is used to assess differences between means using the InStat software package. Celecoxib given in the diet at doses between 160-3200 ppm retards the growth of these tumors. The inhibitory effect of celecoxib is dose-dependent and ranges from 48 % to 85 % as compared with the control tumors. Analysis of lung metastasis is done in all the animals by counting metastasis in a stereomicroscope and by histochemical analysis of consecutive lung sections. Celecoxib does not affect lung metastasis at the lower dose of 160 ppm, however surface metastasis is reduced by more than 50 % when given at doses between 480-3200 ppm. In addition, histopathological analysis revealed that celecoxib dose-dependently reduces the size of the metastasic lesions in the lung.

2. HT-29 Model:

Mice are injected subcutaneously in the left paw (1 x 10^6 tumor cells suspended in 30 % Matrigel) and tumor volume is evaluated using a phlethysmometer twice a week for 30-60 days. Implantation of human colon cancer cells (HT-29) into nude mice produces tumors that reach 0.6-2 ml between 30-50 days. Blood is drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data is expressed as the mean +/- SEM. Student's and Mann-Whitney tests is used to assess differences between means using the InStat software package.

A. Mice injected with HT-29 cancer cells are treated with a DNA topoisomerase I inhibiting agents i.p at doses of 50 mg/kg on days 5,7 and 9 in the presence or absence of celecoxib in the diet. The efficacy of both agents is determined by measuring tumor volume.

B. In a second assay, mice injected with HT-29 cancer cells are treated with a DNA topoisomerase I inhibiting agents on days 12 through 15. Mice injected with HT-29 cancer cells are treated with a DNA topoisomerase I inhibiting agents i.p at doses of 50 mg/kg on days 12, 13, 14, and 15 in the presence or absence of celecoxib in the diet. The efficacy of both agents is determined by measuring tumor volume.

C. In a third assay, mice injected with HT-29 colon cancer cells are treated with a DNA topoisomerase I inhibiting agents i.p 50 mg/kg on days 14 through 17 in the presence or absence of celecoxib (1600ppm) and valdecoxib (160 ppm) in the diet. The efficacy of both agents is determined by measuring tumor volume.

3. NFSA Tumor Model:

The NFSA sarcoma is a nonimmunogenic and prostaglandin producing tumor that spontaneously developed in C3Hf/Kam mice. It exhibits an increased radioresponse if indomethacin is given prior to tumor irradiation. The NFSA tumor is relatively radioresistant and is strongly infiltrated by inflammatory mononuclear

cells, primarily macrophages which secrete factors that stimulate tumor cell proliferation. Furthermore, this tumor produces a number of prostaglandins, including prostaglandin E_2 and prostaglandin I_2.

Solitary tumors are generated in the right hind legs of mice by the injection of 3 x 10^5 viable NFSA tumor cells. Treatment with a COX-2 selective inhibiting agent (6 mg/kg body weight) and a DNA topoisomerase I inhibiting agents or vehicle (0.05% Tween 20 and 0.95% polyethylene glycol) given in the drinking water is started when tumors are approximately 6 mm in diameter and the treatment ia continued for 10 consecutive days. Water bottles are changed every 3 days. In some experiments, tumor irradiation is performed 3-8 days after initiation of the treatment. The end points of the treatment are tumor growth delay (days) and TCD_{50} (tumor control dose 50, defined as the radiation dose yielding local tumor cure in 50% of irradiated mice 120 days after irradiation). To obtain tumor growth curves, three mutually orthogonal diameters of tumors are measured daily with a vernier caliper, and the mean values are calculated.

Local tumor irradiation with single γ-ray doses of 30, 40, or 50 Gy is given when these tumors reach 8 mm in diameter. Irradiation to the tumor is delivered from a dual-source ^{137}Cs irradiator at a dose rate of 6.31 Gy/minute. During irradiation, unanesthetized mice are immobilized on a jig and the tumor is centered in a circular radiation field 3 cm in diameter. Regression and regrowth of tumors is followed at 1-3 day intervals until the tumor diameter reaches approximately 14 mm.

The magnitude of tumor growth delay as a function of radiation dose with or without treatment with a COX-2 selective inhibiting agent and a DNA topoisomerase I inhibiting agents is plotted to determine the enhancement of tumor response to radiation. This requires that tumor growth delay after radiation be expressed only as the absolute tumor growth delay, i.e., the time in days for tumors treated with radiation to grow from 8 to 12 mm in diameter minus the time in days for untreated tumors to reach the same size. It also requires that the effect of the combined a COX-2 selective inhibiting agent and DNA topoisomerase I inhibiting agents plus-radiation treatment be expressed as the normalized tumor growth delay.

Normalized tumor growth delay is defined as the time for tumors treated with both a COX-2 selective inhibiting agent and radiation to grow from 8 to 12 mm in diameter minus the time in days for tumors treated with a COX-2 selective inhibiting agent and DNA topoisomerase I inhibiting agents alone to reach the same size.

The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the methods, combinations and compositions of the present invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

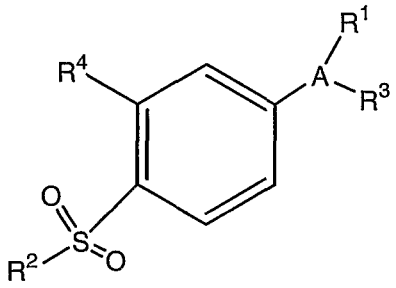
What is claimed is:

1. A method for treating, preventing or reducing the risk of developing a neoplasia disorder in a mammal in need thereof, comprising administering to the mammal in a combination therapy an amount of a DNA topoisomerase I inhibiting agent and an amount of a selective COX-2 inhibiting agent wherein the amount of the DNA topoisomerase I inhibiting agent and the selective COX-2 inhibiting agent together make a neoplasia disorder effective amount.

2. The method of claim 1 wherein the DNA topoisomerase I inhibiting agent is selected from the group consisting of irinotecan; irinotecan hydrochloride; camptothecin; 9-aminocamptothecin; 9-nitrocamptothecin; 9-chloro-10-hydroxy camptothecin; topotecan; topotecan hydrochloride; lurtotecan; lurtotecan dihydrochloride; lurtotecan (liposomal); homosilatecans; 6,8-dibromo-2-methyl-3-[2-(D-xylopyranosylamino)phenyl]-4(3H)-quinazolinone; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-(2E)-2-propenamide; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(3-hydroxyphenylpropyl)-(E)-2-propenamide; 5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione, 12-.beta.-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-; 4-acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride; and 4-acridinecarboxamide, N-[2-(dimethylamino)ethyl]-.

3. The method of claim 2 wherein the DNA topoisomerase I inhibiting agent is selected from the group consisting of irinotecan, irinotecan hydrochloride, camptothecin, 9-aminocamptothecin, 9-nitrocamptothecin, 9-chloro-10-hydroxy camptothecin, topotecan, topotecan hydrochloride, lurtotecan, lurtotecan dihydrochloride, lurtotecan (liposomal), and homosilatecans.

4. The method of claim 1 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 1:



1

or a pharmaceutically-acceptable salt or prodrug thereof,

wherein

A is a 5- or 6-member ring substituent selected from the group consisting of heterocyclyl and carbocyclyl, wherein A is optionally substituted with one or more radicals selected from the group consisting of hydroxy, alkyl, halo, oxo, and alkoxy;

R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein R^1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^2 is selected from the group consisting of alkyl and amino;

R^3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocycloalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-

phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

R^4 is selected from the group consisting of hydrido and halo.

5. The method of claim 4 wherein A is selected from the group consisting of thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, and pyridyl.

6. The method of claim 5 wherein A is substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, hydroxy and alkoxy.

7. The method of claim 4 wherein R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, and phenyl are optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, alkoxy, halo, alkoxy, and alkylthio.

8. The method of claim 7 wherein R^1 is selected from the group consisting of pyridyl, cyclohexyl, and phenyl, wherein R^1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

9. The method of claim 4 wherein R^2 is selected from the group consisting of methyl and amino.

10. The method of claim 4 wherein R^3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, hydroxyl, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonyl-alkyl, carboxy-alkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, amino-alkyl, alkylaminoalkyl, N-phenylamino-alkyl, N-phenyl-alkylaminoalkyl, N-alkyl-N-phenyl-alkylamino-alkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl.

11. The method of claim 10 wherein R^3 is a selected from the group consisting of halo, alkyl, cyano, carboxyl, alkyloxy, phenyl, haloalkyl, and hydroxyalkyl.

12. The method of claim 4 wherein the selective COX-2 inhibiting agent is selected from the group consisting of
rofecoxib,
celecoxib,
valdecoxib,
deracoxib,
etoricoxib,
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,
2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,
4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,
3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,
N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,
3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,
4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,
3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,
4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,
3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,
5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,
4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,
4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,
N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,
3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide,
5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,
N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,
3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino] benzenesulfonamide,
1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene,

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

[1,1':2',1"-terphenyl]-4-sulfonamide,

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide,

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, and

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide.

13. The method of claim 12 wherein the selective COX-2 inhibiting agent is rofecoxib.

14. The method of claim 12 wherein the selective COX-2 inhibiting agent is celecoxib.

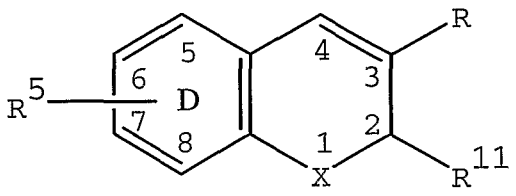
15. The method of claim 12 wherein the selective COX-2 inhibiting agent is valdecoxib.

16. The method of claim 12 wherein the selective COX-2 inhibiting agent is deracoxib.

17. The method of claim 12 wherein the selective COX-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

18. The method of claim 12 wherein the selective COX-2 inhibiting agent is etoricoxib.

19. The method of claim 1 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 2:



2

or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein

X is selected from the group consisting of O, S and NR^a;

R^a is alkyl;

R is selected from the group consisting of carboxyl, alkyl, aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein aryl is optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^5 is one or more radicals independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino,

aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl, wherein R^5 together with ring D optionally forms a naphthyl radical.

20. The method of claim 19 wherein X is selected from the group consisting of O and S.

21. The method of claim 19 wherein R is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl.

22. The method of claim 21 wherein R is carboxyl.

23. The method of claim 19 wherein R^{11} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl.

24. The method of claim 23 wherein R^{11} is lower haloalkyl.

25. The method of claim 24 wherein R^{11} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl.

26. The method of claim 25 wherein R^{11} is selected from the group consisting of trifluoromethyl and pentafluorethyl.

27. The method of claim 19 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5- or 6- membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5- or 6-membered nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl.

28. The method of claim 27 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl.

29. The method of claim 28 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl.

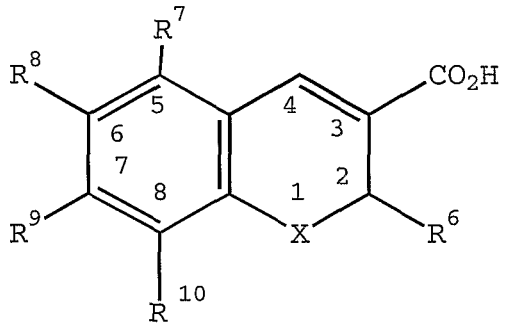
30. The method of claim 19 wherein the selective COX-2 inhibiting agent is selected from the group consisting of
6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid,
7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid,
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid, and

6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

31. The method of claim 1 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 3:



3

or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein

X is selected from the group consisting of O and S;

R^6 is lower haloalkyl;

R^7 is selected from the group consisting of hydrido and halo;

R^8 is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, and 5- or 6-membered nitrogen containing heterocyclosulfonyl;

R^9 is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{10} is selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl.

32. The method of claim 31 wherein R^6 is selected from the group consisting of trifluoromethyl and pentafluoroethyl.

33. The method of claim 31 wherein R^7 is selected from the group consisting of hydrido, chloro, and fluoro.

34. The method of claim 31 wherein R^8 is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl.

35. The method of claim 31 wherein R^9 is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl.

36. The method of claim 31 wherein R^{10} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl.

37. The method of claim 31 wherein the selective COX-2 inhibiting agent is selected from the group consisting of
6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

7-(1,1-Dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,7-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

5,6-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

2,6-Bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

5,6,7-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,7,8-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6-Bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6-Chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid, and

6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

38. The method of claim 37 wherein the selective COX-2 inhibiting agent is selected from the group consisting of

6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, and

6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid.

39. The method of claim 1 wherein the selective COX-2 inhibiting agent is selected from compounds that correspond in structure, and pharmaceutically acceptable salts thereof, of the group consisting of:

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide,

6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide,
5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,
N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,
3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide,
N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide.

40. The method of claim 1 wherein the neoplasia disorder is selected from the group consisting of a lung, a breast, a skin, a stomach, an intestine, an esophagus, a bladder, a head, a neck, a brain, a cervical, and an ovary neoplasia disorder.

41. The method of claim 1 wherein the neoplasia disorder is selected from the group consisting of acral lentiginous melanoma, an actinic keratosis, adenocarcinoma, adenoid cycstic carcinoma, an adenoma, adenosarcoma, adenosquamous carcinoma, an astrocytic tumor, bartholin gland carcinoma, basal cell carcinoma, a bronchial gland carcinoma, capillary carcinoma, a carcinoid, carcinoma, carcinosarcoma, cavernous carcinoma, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma, choriod plexus carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal carcinoma, epitheloid carcinoma, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, a germ cell tumor, glioblastoma, glucagonoma, hemangiblastoma,

hemangioendothelioma, a hemangioma, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, a lentigo maligna melanoma, malignant melanoma, a malignant mesothelial tumor, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, a pituitary tumor, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, a soft tissue carcinoma, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, a well differentiated carcinoma, and Wilm's tumor.

42. The method of claim 1 wherein the selective COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent are formulated in a single composition.

43. The method of claim 1 wherein the selective COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent are provided as a separate component of a kit.

44. The method of claim 1 wherein the mammal is a human.

45. The method of claim 1 wherein the selective COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent are administered in a sequential manner.

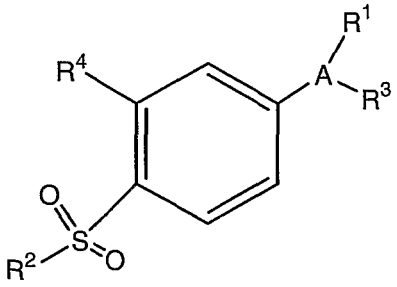
46. The method of claim 1 wherein the selective COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent are administered in a substantially simultaneous manner.

47. A pharmaceutical composition comprising a DNA topoisomerase I inhibiting agent and a COX-2 inhibiting agent wherein the DNA topoisomerase I inhibiting agent and the selective COX-2 inhibiting agent together make a neoplasia disorder effective amount.

48. The pharmaceutical composition of claim 47 wherein the DNA topoisomerase I inhibiting agent is selected from the group consisting of irinotecan; irinotecan hydrochloride; camptothecin; 9-aminocamptothecin; 9-nitrocamptothecin; 9-chloro-10-hydroxy camptothecin; topotecan; topotecan hydrochloride; lurtotecan; lurtotecan dihydrochloride; lurtotecan (liposomal); homosilatecans; 6,8-dibromo-2-methyl-3-[2-(D-xylopyranosylamino)phenyl]-4(3H)-quinazolinone; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-(2E)-2-propenamide; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(3-hydroxyphenylpropyl)-(E)-2-propenamide; 5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione, 12-.beta.-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-; 4-acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride; and 4-acridinecarboxamide, N-[2-(dimethylamino)ethyl]-.

49. The pharmaceutical composition of claim 48 wherein the DNA topoisomerase I inhibiting agent is selected from the group consisting of irinotecan, irinotecan hydrochloride, camptothecin, 9-aminocamptothecin, 9-nitrocamptothecin, 9-chloro-10-hydroxy camptothecin, topotecan, topotecan hydrochloride, lurtotecan, lurtotecan dihydrochloride, lurtotecan (liposomal), and homosilatecans.

50. The pharmaceutical composition of claim 47 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 1:



1

or a pharmaceutically-acceptable salt or prodrug thereof,

wherein

A is a 5- or 6-member ring substituent selected from the group consisting of heterocyclyl and carbocyclyl, wherein A is optionally substituted with one or more radicals selected from the group consisting of hydroxy, alkyl, halo, oxo, and alkoxy;

R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein R^1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^2 is selected from the group consisting of alkyl and amino;

R^3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocycloalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-

phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

R^4 is selected from the group consisting of hydrido and halo.

51. The pharmaceutical composition of claim wherein A is selected from the group consisting of thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, and pyridyl.

52. The pharmaceutical composition of claim 51 wherein A is substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, hydroxy and alkoxy.

53. The pharmaceutical composition of claim 50 wherein R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, and phenyl are optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, alkoxy, halo, alkoxy, and alkylthio.

54. The pharmaceutical composition of claim 53 wherein R^1 is selected from the group consisting of pyridyl, cyclohexyl, and phenyl, wherein R^1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

55. The pharmaceutical composition of claim 50 wherein R^2 is selected from the group consisting of methyl and amino.

56. The pharmaceutical composition of claim 50 wherein R^3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, hydroxyl, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonyl-alkyl, carboxy-alkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, amino-alkyl, alkylaminoalkyl, N-phenylamino-alkyl, N-phenyl-alkylaminoalkyl, N-alkyl-N-phenyl-alkylamino-alkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl.

57. The pharmaceutical composition of claim 56 wherein R^3 is a selected from the group consisting of halo, alkyl, cyano, carboxyl, alkyloxy, phenyl, haloalkyl, and hydroxyalkyl.

58. The pharmaceutical composition of claim 50 wherein the selective COX-2 inhibiting agent is selected from the group consisting of
rofecoxib,
celecoxib,
valdecoxib,
deracoxib,
etoricoxib,

4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,
2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one,
N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,
4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,
3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,
N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,
3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,
4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,
3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,
4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,
3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,
5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,
4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,
4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,
N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,
3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide,
5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,
N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino] benzenesulfonamide,

1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene,

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

[1,1':2',1"-terphenyl]-4-sulfonamide,

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide,

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, and

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide.

59. The pharmaceutical composition of claim 58 wherein the selective COX-2 inhibiting agent is rofecoxib.

60. The pharmaceutical composition of claim 58 wherein the selective COX-2 inhibiting agent is celecoxib.

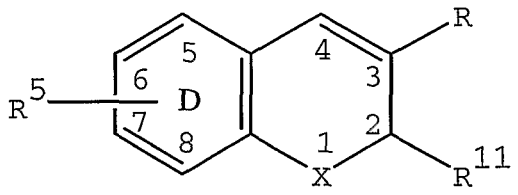
61. The pharmaceutical composition of claim 58 wherein the selective COX-2 inhibiting agent is valdecoxib.

62. The pharmaceutical composition of claim 58 wherein the selective COX-2 inhibiting agent is deracoxib.

63. The pharmaceutical composition of claim 58 wherein the selective COX-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

64. The pharmaceutical composition of claim 58 wherein the selective COX-2 inhibiting agent is etoricoxib.

65. The pharmaceutical composition of claim 50 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 2:



2

or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein

X is selected from the group consisting of O, S and NR^a;

R^a is alkyl;

R is selected from the group consisting of carboxyl, alkyl, aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein aryl is optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^5 is one or more radicals independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl, wherein R^5 together with ring D optionally forms a naphthyl radical.

66. The pharmaceutical composition of claim 65 wherein X is selected from the group consisting of O and S.

67. The pharmaceutical composition of claim 65 wherein R is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl.

68. The pharmaceutical composition of claim 67 wherein R is carboxyl.

69. The pharmaceutical composition of claim 65 wherein R^{11} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl.

70. The pharmaceutical composition of claim 69 wherein R^{11} is lower haloalkyl.

71. The method of claim 70 wherein R^{11} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl,

pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl.

72. The pharmaceutical composition of claim 71 wherein R^{11} is selected from the group consisting of trifluoromethyl and pentafluorethyl.

73. The pharmaceutical composition of claim 65 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5- or 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5- or 6- membered nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl.

74. The pharmaceutical composition of claim 73 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl.

75. The pharmaceutical composition of claim 74 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy,

trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl.

76. The pharmaceutical composition of claim 65 wherein the selective COX-2 inhibiting agent is selected from the group consisting of
6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid,
7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid,
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

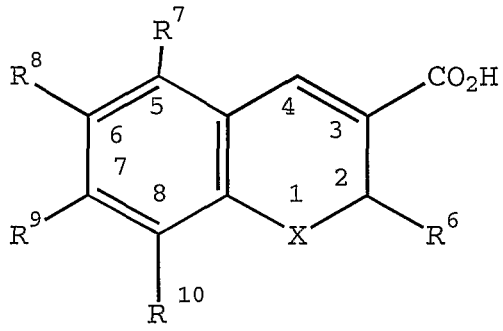
6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid, and

6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

77. The pharmaceutical composition of claim 47 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 3:



3

or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein

X is selected from the group consisting of O and S;

R^6 is lower haloalkyl;

R^7 is selected from the group consisting of hydrido and halo;

R^8 is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, and 5- or 6-membered nitrogen containing heterocyclosulfonyl;

R^9 is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{10} is selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl.

78. The pharmaceutical composition of claim 77 wherein R^6 is selected from the group consisting of trifluoromethyl and pentafluoroethyl.

79. The pharmaceutical composition of claim 77 wherein R^7 is selected from the group consisting of hydrido, chloro, and fluoro.

80. The pharmaceutical composition of claim 77 wherein R^8 is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl.

81. The pharmaceutical composition of claim 77 wherein R^9 is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl.

82. The pharmaceutical composition of claim 77 wherein R^{10} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl.

83. The pharmaceutical composition of claim 77 wherein the selective COX-2 inhibiting agent is selected from the group consisting of 6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

7-(1,1-Dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,7-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

5,6-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

2,6-Bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

5,6,7-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,7,8-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6-Bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6-Chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid, and

6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

84. The pharmaceutical composition of claim 83 wherein the selective COX-2 inhibiting agent is selected from the group consisting of
6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, and
6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid.

85. The pharmaceutical composition of claim 47 wherein the selective COX-2 inhibiting agent is selected from compounds that correspond in structure, and pharmaceutically acceptable salts thereof, of the group consisting of:
N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide,
6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,

3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,

3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide,

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide,

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide.

86. The pharmaceutical composition of claim 47 wherein the neoplasia disorder is selected from the group consisting of a lung, a breast, a skin, a stomach, an intestine, an esophagus, a bladder, a head, a neck, a brain, a cervical, and an ovary neoplasia disorder.

87. The pharmaceutical composition of claim 47 wherein the neoplasia disorder is selected from the group consisting of acral lentiginous melanoma, an actinic keratosis, adenocarcinoma, adenoid cycstic carcinoma, an adenoma, adenosarcoma, adenosquamous carcinoma, an astrocytic tumor, bartholin gland carcinoma, basal cell carcinoma, a bronchial gland carcinoma,

capillary carcinoma, a carcinoid, carcinoma, carcinosarcoma, cavernous carcinoma, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma, choriod plexus carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal carcinoma, epitheloid carcinoma, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, a germ cell tumor, glioblastoma, glucagonoma, hemangiblastoma, hemangioendothelioma, a hemangioma, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, a lentigo maligna melanoma, malignant melanoma, a malignant mesothelial tumor, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, a pituitary tumor, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, a soft tissue carcinoma, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, a well differentiated carcinoma, and Wilm's tumor.

88. The pharmaceutical composition of claim 47 wherein the composition is provided as a separate component of a kit.

89. The pharmaceutical composition of claim 47 wherein the composition is administered orally, rectally, topically, bucally, or parenterally.

90. The pharmaceutical composition of claim 47 wherein the composition is a tablet, capsule, cachet, lozenge, dispensable powder, granule, solution, suspension, emulsion or liquid.

91. The pharmaceutical composition of claim 47 wherein the selective COX-2 inhibiting agent is present in an amount from about 0.1 mg to about 10,000 mg.

92. The pharmaceutical composition of claim 47 wherein the DNA topoisomerase I inhibiting agent is present in an amount from about 0.001 mg to about 10,000 mg.

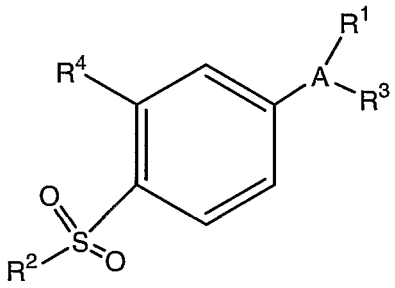
93. Use of a composition in preparation of a medicament useful in treating, preventing or lowering the risk of developing a neoplasia disorder in a mammal in need thereof, the composition comprising an amount of a DNA topoisomerase I inhibiting agent and an amount of a COX-2 inhibiting agent wherein the amount of the DNA topoisomerase I inhibiting agent and the selective COX-2 inhibiting agent together make a neoplasia disorder effective amount.

94. The use of claim 93 wherein the DNA topoisomerase I inhibiting agent is selected from the group consisting of irinotecan; irinotecan hydrochloride; camptothecin; 9-aminocamptothecin; 9-nitrocamptothecin; 9-chloro-10-hydroxy camptothecin; topotecan; topotecan hydrochloride; lurtotecan; lurtotecan dihydrochloride; lurtotecan (liposomal); homosilatecans; 6,8-dibromo-2-methyl-3-[2-(D-xylopyranosylamino)phenyl]-4(3H)-quinazolinone; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-(2E)-2-propenamide; 2-cyano-3-(3,4-dihydroxyphenyl)-N-(3-hydroxyphenylpropyl)-(E)-2-propenamide; 5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione, 12-.beta.-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-; 4-

acridinecarboxamide, N-[2-(dimethylamino)ethyl]-, dihydrochloride; and 4-acridinecarboxamide, N-[2-(dimethylamino)ethyl]-.

95. The use of claim 93 wherein the DNA topoisomerase I inhibiting agent is selected from the group consisting of irinotecan, irinotecan hydrochloride, camptothecin, 9-aminocamptothecin, 9-nitrocamptothecin, 9-chloro-10-hydroxy camptothecin, topotecan, topotecan hydrochloride, lurtotecan, lurtotecan dihydrochloride, lurtotecan (liposomal), and homosilatecans.

96. The use of claim 93 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 1:



1

or a pharmaceutically-acceptable salt or prodrug thereof,

wherein

A is a 5- or 6-member ring substituent selected from the group consisting of heterocyclyl and carbocyclyl, wherein A is optionally substituted with one or more radicals selected from the group consisting of hydroxy, alkyl, halo, oxo, and alkoxy;

R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein R^1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^2 is selected from the group consisting of alkyl and amino;

R^3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy,

alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocycloalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-phenylaminoalkyl, N-phenylalkylaminoalkyl, N-alkyl-N-phenylalkylaminoalkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl; and

R^4 is selected from the group consisting of hydrido and halo.

97. The use of claim 96 wherein A is selected from the group consisting of thienyl, oxazolyl, furyl, furanone, pyrrolyl, thiazolyl, imidazolyl, benzofuryl, indenyl, benzithienyl, isoxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, cyclopentenone, benzopyranopyrazolyl, phenyl, and pyridyl.

98. The use of claim 97 wherein A is substituted with one or more radicals selected from the group consisting of alkyl, halo, oxo, hydroxy and alkoxy.

99. The use of claim 96 wherein R^1 is selected from the group consisting of cyclohexyl, pyridinyl, and phenyl, wherein cyclohexyl, pyridinyl, and phenyl are optionally substituted with one or more radicals selected from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, phenylamino, nitro, alkoxyalkyl, alkylsulfinyl, alkoxy, halo, alkoxy, and alkylthio.

100. The use of claim 99 wherein R^1 is selected from the group consisting of pyridyl, cyclohexyl, and phenyl, wherein R^1 is optionally substituted with one or more radicals selected from the group consisting of alkyl, halo, and alkoxy.

101. The use of claim 96 wherein R^2 is selected from the group consisting of methyl and amino.

102. The use of claim 96 wherein R^3 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, aryl, heteroaryl, oxo, hydroxyl, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, phenyl, haloalkyl, heterocyclo, cycloalkenyl, phenylalkyl, heterocyclylalkyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, phenylcarbonyl, phenylalkylcarbonyl, phenylalkenyl, alkoxyalkyl, phenylthioalkyl, phenyloxyalkyl, alkoxyphenylalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-phenylaminocarbonyl, N-alkyl-N-phenylaminocarbonyl, alkylaminocarbonyl-alkyl, carboxy-alkyl, alkylamino, N-arylamino, N-arylkylamino, N-alkyl-N-arylkylamino, N-alkyl-N-arylamino, amino-alkyl, alkylaminoalkyl, N-phenylamino-alkyl, N-phenyl-alkylaminoalkyl, N-alkyl-N-phenyl-alkylamino-alkyl, N-alkyl-N-phenylaminoalkyl, phenyloxy, phenylalkoxy, phenylthio, phenylalkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-phenylaminosulfonyl, phenylsulfonyl, and N-alkyl-N-phenylaminosulfonyl.

103. The use of claim 102 wherein R^3 is a selected from the group consisting of halo, alkyl, cyano, carboxyl, alkyloxy, phenyl, haloalkyl, and hydroxyalkyl.

104. The use of claim 96 wherein the selective COX-2 inhibiting agent is selected from the group consisting of

rofecoxib,
celecoxib,
valdecoxib,
deracoxib,
etoricoxib,
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,
2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one,
N-[[4-(5-methyl-3-phenylisoxazol-4yl]phenyl]sulfonyl]propanamide,
4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,
3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,
N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,
3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,
4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,
3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,
4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,
3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,
5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,
4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide,
4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,
N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,
3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,

3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide,

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino] benzenesulfonamide,

1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene,

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

[1,1':2',1"-terphenyl]-4-sulfonamide,

4-(methylsulfonyl)-1,1',2],1"-terphenyl,

4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide,

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, and

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide.

105. The use of claim 104 wherein the selective COX-2 inhibiting agent is rofecoxib.

106. The use of claim 104 wherein the selective COX-2 inhibiting agent is celecoxib.

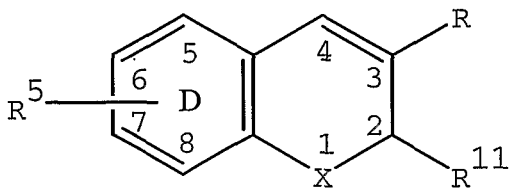
107. The use of claim 104 wherein the selective COX-2 inhibiting agent is valdecoxib.

108. The use of claim 104 wherein the selective COX-2 inhibiting agent is deracoxib.

109. The use of claim 104 wherein the selective COX-2 inhibiting agent is 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide.

110. The use of claim 104 wherein the selective COX-2 inhibiting agent is etoricoxib.

111. The use of claim 93 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 2:



2

or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein

X is selected from the group consisting of O, S and NR^a;

R^a is alkyl;

R is selected from the group consisting of carboxyl, alkyl, aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein aryl is optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^5 is one or more radicals independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl, wherein R^5 together with ring D optionally forms a naphthyl radical.

112. The use of claim 111 wherein X is selected from the group consisting of O and S.

113. The use of claim 111 wherein R is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl.

114. The use of claim 113 wherein R is carboxyl.

115. The use of claim 111 wherein R^{11} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl.

116. The use of claim 115 wherein R^{11} is lower haloalkyl.

117. The method of claim 115 wherein R^{11} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl.

118. The use of claim 117 wherein R^{11} is selected from the group consisting of trifluoromethyl and pentafluorethyl.

119. The use of claim 111 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5- or 6- membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5- or 6-membered nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl.

120. The use of claim 119 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl.

121. The use of claim 120 wherein R^5 is one or more radicals independently selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl.

122. The use of claim 111 wherein the selective COX-2 inhibiting agent is selected from the group consisting of
6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid,
7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid,
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

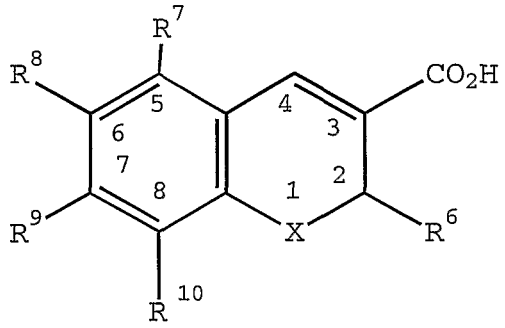
6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid, and

6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

123. The use of claim 93 wherein the selective COX-2 inhibiting agent is selected from compounds of Formula 3:



3

or an isomer or pharmaceutically-acceptable salt or prodrug thereof, wherein

X is selected from the group consisting of O and S;

R^6 is lower haloalkyl;

R^7 is selected from the group consisting of hydrido and halo;

R^8 is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower

dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, and 5- or 6-membered nitrogen containing heterocyclosulfonyl;

R^9 is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{10} is selected from the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl.

124. The use of claim 123 wherein R^6 is selected from the group consisting of trifluoromethyl and pentafluoroethyl.

125. The use of claim 123 wherein R^7 is selected from the group consisting of hydrido, chloro, and fluoro.

126. The use of claim 123 wherein R^8 is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl.

127. The use of claim 123 wherein R^9 is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl.

128. The use of claim 123 wherein R^{10} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl.

129. The use of claim 123 wherein the selective COX-2 inhibiting agent is selected from the group consisting of

6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

7-(1,1-Dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,7-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

5,6-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

2,6-Bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

5,6,7-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,7,8-Trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6-Bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

6-Chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid, and

6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.

130. The use of claim 129 wherein the selective COX-2 inhibiting agent is selected from the group consisting of

6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6-Trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6-Formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-(Difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6,8-Dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,

(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid, and

6,8-Dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid.

131. The use of claim 93 wherein the selective COX-2 inhibiting agent is selected from compounds that correspond in structure, and pharmaceutically acceptable salts thereof, of the group consisting of:

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide,

6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,
3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,
N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,
N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,
3-(4-chlorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-(4-fluorophenoxy)-4-[(methylsulfonyl)amino]benzenesulfonamide,
3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide,
5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,
N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,
3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide,
N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide.

132. The use of claim 93 wherein the neoplasia disorder is selected from the group consisting of a lung, a breast, a skin, a stomach, an intestine, an esophagus, a bladder, a head, a neck, a brain, a cervical, and an ovary neoplasia disorder.

133. The use of claim 93 wherein the neoplasia disorder is selected from the group consisting of acral lentiginous melanoma, an actinic keratosis, adenocarcinoma, adenoid cycstic carcinoma, an adenoma, adenosarcoma, adenosquamous carcinoma, an astrocytic tumor, bartholin gland carcinoma,

basal cell carcinoma, a bronchial gland carcinoma, capillary carcinoma, a carcinoid, carcinoma, carcinosarcoma, cavernous carcinoma, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma, choriod plexus carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal carcinoma, epitheloid carcinoma, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, a germ cell tumor, glioblastoma, glucagonoma, hemangiblastoma, hemangioendothelioma, a hemangioma, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, a lentigo maligna melanoma, malignant melanoma, a malignant mesothelial tumor, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, a pituitary tumor, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, a soft tissue carcinoma, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, a well differentiated carcinoma, and Wilm's tumor.

134. The method of claim 93 wherein the selective COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent are formulated in a single composition.

135. The use of claim 93 wherein the selective COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent are provided as a separate component of a kit.

136. The use of claim 93 wherein the mammal is a human.

137. The use of claim 93 wherein the selective COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent are administered in a sequential manner.

138. The use of claim 93 wherein the selective COX-2 inhibiting agent and the DNA topoisomerase I inhibiting agent are administered in a substantially simultaneous manner.

139. A kit comprising a DNA topoisomerase I inhibiting agent and a selective COX-2 inhibiting agent wherein the DNA topoisomerase I inhibiting agent and the selective COX-2 inhibiting agent together make a neoplasia disorder effective amount.

140. A method for the prevention or treatment of DNA topoisomerase I inhibiting agent-related diarrhea in a subject in need of such prevention or treatment wherein the method comprises administering to the subject a diarrhea preventing or treating-effective amount of a source of a COX-2 inhibitor, thereby preventing or treating the DNA topoisomerase I inhibiting agent-related diarrhea.

141. The method of Claim 140 wherein the source of a COX-2 inhibiting agent is a source of a COX-2 selective inhibiting agent.

142. The method of Claim 141 wherein the source of a COX-2 selective inhibiting agent is a COX-2 selective inhibiting agent.

143. The method of Claim 142 wherein the COX-2 selective inhibiting agent is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, meloxicam, and ABT-963.

144. The method of Claim 142wherein the COX-2 selective inhibiting agent is celecoxib.

145. The method of Claim 142 wherein the COX-2 selective inhibiting agent is valdecoxib.

146. The method of Claim 142 wherein the COX-2 selective inhibiting agent is deracoxib.

147. The method of Claim 142 wherein the COX-2 selective inhibiting agent is rofecoxib.

148. The method of Claim 142 wherein the COX-2 selective inhibiting agent is etoricoxib.

149. The method of Claim 142 wherein the COX-2 selective inhibiting agent is meloxicam.

150. The method of Claim 142 wherein the COX-2 selective inhibiting agent is ABT-963.

151. The method of Claim 142 wherein the COX-2 selective inhibiting agent is a chromene COX-2 selective inhibiting agent.

152. The method of Claim 141 wherein the source of a COX-2 selective inhibiting agent is a prodrug of a COX-2 selective inhibiting agent.

153. The method of Claim 152 wherein the prodrug of a COX-2 inhibiting agent is parecoxib.

154. The method of Claim 140 wherein the DNA topoisomerase I inhibiting agent is selected from the group consisting of:

irinotecan;
irinotecan hydrochloride;
camptothecin;
9-aminocamptothecin;
9-nitrocamptothecin;
9-chloro-10-hydroxy camptothecin;
topotecan;
lurtotecan;
a homosilatecan;
6,8-dibromo-2-methyl-3-[2-(D-xylopyranosylamino)phenyl]-4(3H)-quinazolinone;
2-cyano-3-(3,4-dihydroxyphenyl)-N-(phenylmethyl)-(2E)-2-propenamide;
2-cyano-3-(3,4-dihydroxyphenyl)-N-(3-hydroxyphenylpropyl)-(E)-2-propenamide;
12-beta-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;
N-[2-(dimethylamino)ethyl]-4-acridinecarboxamide, dihydrochloride; and
N-[2-(dimethylamino)ethyl]-4-acridinecarboxamide;

or a salt of the DNA topoisomerase I inhibiting agent.

155. The method of Claim 154 wherein the DNA topoisoermerase I inhibiting agent is selected from the group consisting of irinotecan, rubitecan, lurtotecan, exetecan mesylate, karenitecan, and silatecan;

or a salt thereof.

156. The method of Claim 155 wherein the DNA topoisomerase I inhibiting agent is irinotecan or a salt thereof.

157. The method of Claim 156 wherein the source of a COX-2 inhibiting agent is a source of a COX-2 selective inhibiting agent.

158. The method of Claim 157 wherein the source of the COX-2 inhibiting agent is selected from the group consisting of celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, meloxicam, and ABT-963.

159. The method of Claim 158 wherein the source of the COX-2 inhibiting agent is celecoxib.

160. The method of Claim 158 wherein the source of the COX-2 inhibiting agent is valdecoxib.

161. The method of Claim 158 wherein the source of the COX-2 inhibiting agent is deracoxib.

162. The method of Claim 158 wherein the source of the COX-2 inhibiting agent is rofecoxib.

163. The method of Claim 158 wherein the source of the COX-2 inhibiting agent is etoricoxib.

164. The method of Claim 158 wherein the source of the COX-2 inhibiting agent is meloxicam.

165. The method of Claim 158 wherein the source of the COX-2 inhibiting agent is ABT-963.

166. The method of Claim 157 wherein the source of a COX-2 selective inhibiting agent is a chromene COX-2 selective inhibiting agent.

167. The method of Claim 157 wherein the source of a COX-2 selective inhibiting agent is a prodrug of a COX-2 selective inhibiting agent.

168. The method of Claim 167 wherein the produrg of a COX-2 selective inhibiting agent is parecoxib.

169. The method of Claim 155 wherein the DNA topoisomerase I inhibiting agent is ribitecan or a salt thereof.

170. The method of Claim 155 wherein the DNA topoisomerase I inhibiting agent is lurtotecan or a salt thereof.

171. The method of Claim 155 wherein the DNA topoisomerase I inhibiting agent is exetecan mesylate.

172. The method of Claim 155 wherein the DNA topoisomerase I inhibiting agent is karenitecan or a salt thereof.

173. The method of Claim 155 wherein the DNA topoisomerase I inhibiting agent is silatecan or a salt thereof.

174. The method of Claim 141 wherein the source of a COX-2 selective inhibiting agent is administered to the subject orally.

175. The method of Claim 141 wherein the source of a COX-2 selective inhibiting agent is administered to the subject parenterally.

176. The method of Claim 175 wherein the source of the COX-2 selective inhibiting agent is administered to the subject intravenously.

177. The method of Claim 141 wherein the source of the COX-2 selective inhibiting agent is administered to the subject transdermally.

178. The method of Claim 141 wherein the source of the COX-2 selective inhibiting agent is administered to the subject rectally.

179. The method of Claim 141 wherein the source of the COX-2 selective inhibiting agent is administered to the subject before treating the subject with the DNA topoisomerase I inhibiting agent.

180. The method of Claim 141 wherein the source of the COX-2 selective inhibiting agent is administered to the subject concurrently with treating the subject with the DNA topoisomerase I inhibiting agent.

181. The method of Claim 141 wherein the source of the COX-2 selective inhibiting agent is administered to the subject after treating the subject with the DNA topoisomerase I inhibiting agent.