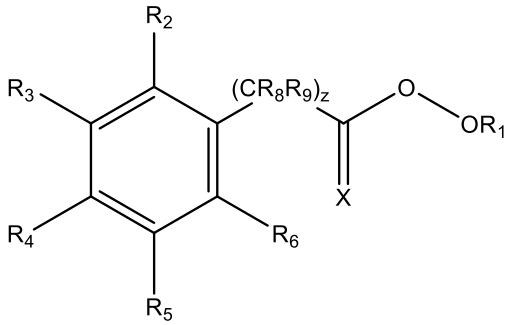
SUMMARY ~~OF THE INVENTION~~

[0006a] In an aspect of the present disclosure, there is provided a use of a compound of formula:



a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomers thereof,

in the manufacture of a medicament for modulating a Src kinase,

wherein X is O or S;

R_1 is a hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, or lower alkynyl; $-(CH_2)_mR_7$; $(CH_2)_m$-OH; $-(CH_2)_m$-O-lower alkyl; $-(CH_2)_m$-O-lower alkenyl; $-(CH_2)_n$-O-$(CH_2)_m$-R_7; $-(CH_2)_m$-SH; $-(CH_2)_m$-S-lower alkyl; $-(CH_2)_m$-S-lower alkenyl; $-(CH_2)_n$-S-$(CH_2)_m$-R_7;

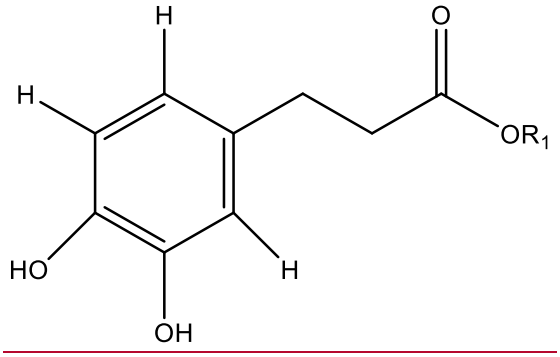
each of R_2, R_3, R_4, R_5, and R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_mR_7$, $-(CH_2)_m$-OH, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n$-O-$(CH_2)_m$-R_7, $-(CH_2)_m$-SH, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, $-(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_7, R_8, and R_9 each independently represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl, or heterocycle; and

wherein each occurrence of m is independently an integer ranging from 1 to 9, each occurrence of n is independently an integer ranging from 1 to 9; and

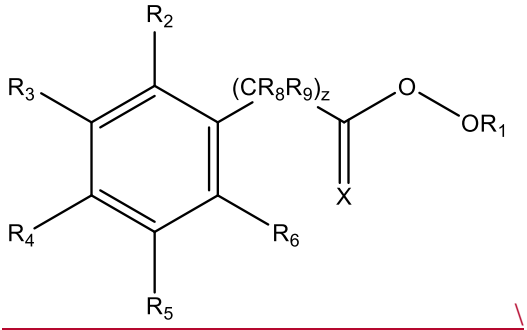
z is an integer ranging from 1 to 9.

[0006b] In another aspect of the present disclosure, there is provided a prodrug of formula:



wherein R_1 comprises esters including ethyl esters, morpholinoethanol esters, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives; carbamates including N,N-dimethylaminocarbonyl of hydroxy functional groups, and N-acyl derivatives.

[0006c] In a further aspect of the present disclosure, there is provided a use of a compound of the following structure in the manufacture of a medicament for treating chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), breast cancer, and colon cancer:



a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomers thereof,

wherein X is O or S;

R_1 is a hydrogen, a substituted or unsubstituted lower alkyl, lower alkenyl, or lower alkynyl; $-(CH_2)_mR_7$; $(CH_2)_m$-OH; $-(CH_2)_m$-O-lower alkyl; $-(CH_2)_m$-O-lower alkenyl; $-(CH_2)_n$-O-$(CH_2)_m$-R_7; $-(CH_2)_m$-SH; $-(CH_2)_m$-S-lower alkyl; $-(CH_2)_m$-S-lower alkenyl; $-(CH_2)_n$-S-$(CH_2)_m$-R_7;

each of R_2, R_3, R_4, R_5, and R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_mR_7$, $-(CH_2)_m$-OH, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n$-O-$(CH_2)_m$-R_7, $-(CH_2)_m$-SH, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, $-(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_7, R_8, and R_9 each independently represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl, or heterocycle; and

wherein each occurrence of m is independently an integer ranging from 1 to 9, each occurrence of n is independently an integer ranging from 1 to 9; and

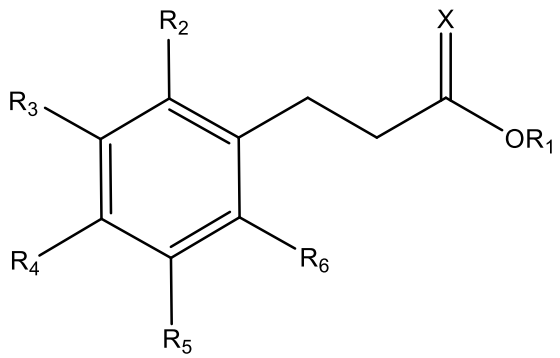
z is an integer ranging from 1 to 9.

[0007] The ~~invention~~ present disclosure generally encompasses compounds that inhibit a specific tyrosine kinase (*i.e.,* Src kinase) and compositions including such compounds as well as combinations of such compositions with known cancer drugs to treat and prevent cancer.

[0008] In another ~~embodiment~~example, the present disclosure~~invention~~ encompasses methods of use of the compositions including active compounds or derivatives and metabolites thereof in any disease conditions where Src tyrosine kinase or Src family kinases (SFKs) activity has been implicated, for example, but not limited to, the development, maintenance, progression, and metastatic spread of cancers.

[0009] In certain ~~embodiment~~examples, the compound and compositions are effective against human cancer and tumor cells including, but not limited to, those associated with chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), breast cancer (e.g., Triple negative, HER2+ etc), and colon cancer.

[0010] In one ~~embodiment~~example, the Compounds Of The Present Disclosure ~~Invention~~ includes compounds of the following structure:



Formula I

[0011] wherein X is O or S;

[0012] R_1 is a hydrogen, or a substituted or unsubstituted substituent including but not limited to lower alkyl, a lower alkenyl, a lower alkynyl, $-(CH_2)_mR_7$, $(CH_2)_m$-OH, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n$-O-$(CH_2)_m$-R_7, $-(CH_2)_m$-SH, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, $-(CH_2)_n$-S-$(CH_2)_m$-R_7

[0013] each of R_2-R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower

alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_mR_7$, $(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, --$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7

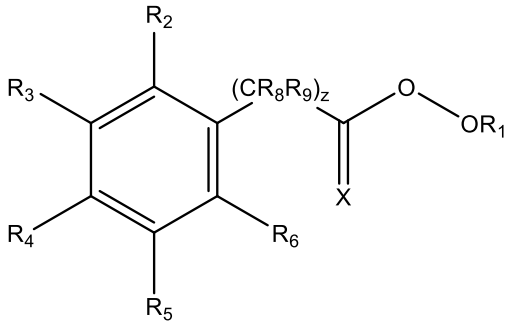
[0014] R_7 represents, for each occurrence, hydrogen, hydroxyl, or a substituted or unsubstituted

alkyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl, or heterocycle; and

[0015] wherein each occurrence of m is independently an integer ranging from 1 to 9, and each occurrence of n is independently an integer ranging from 1 to 9;

[0016] or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of steroisomers thereof.

[0017] In another ~~embodiment~~example, the Compounds Of The Present Disclosure ~~Invention~~ includes compounds of the following structure:



Formula II

[0018] wherein X is O or S;

[0019] R_1 is a hydrogen, or a substituted or unsubstituted substituent including but not limited to lower alkyl, a lower alkenyl, a lower alkynyl, -$(CH_2)_mR_7$, $(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7

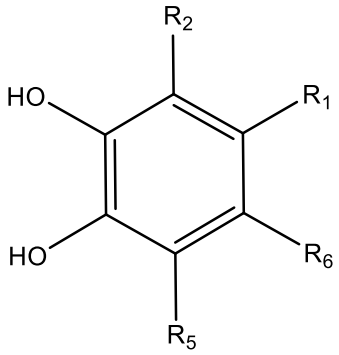
[0020] each of R_2-R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_mR_7$, $(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, --$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7

[0021] R_7, R_8, and R_9 each independently represents, for each occurrence, hydrogen, hydroxyl, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl, or heterocycle; and

[0022] wherein each occurrence of m and n is separately and independently an integer ranging from 1 to 9, and each occurrence of z is independently an integer ranging from 1 to 9;

[0023] or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of steroisomers thereof.

[0024] In another ~~embodiment~~example, , the Compounds Of The Present Disclosure ~~Invention~~ includes compounds of the following structure:



Formula III

[0025] R_1 is a hydrogen, or a substituted or unsubstituted substituent including but not limited to lower alkyl, a lower alkenyl, a lower alkynyl, $-(CH_2)_mR_7$, $-(CH_2)_m$-OH, $-(CH_2)_m(=X)XR_7$, $-(CH_2)_m(=X)R_7$, $-(CH_2)_m$-X-lower alkyl, $-(CH_2)_m$-X-lower alkenyl, $-(CH_2)_n$-X-$(CH_2)_m$-R_7, $-(CH_2)_m$-XR_7

[0026] wherein X is O or S;

[0027] each of R_2, R_5, and R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_mR_7$, $(CH_2)_m$-OH, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n$-O-$(CH_2)_m$-R_7, --$(CH_2)_m$-SH, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, $-(CH_2)_n$-S-$(CH_2)_m$-R_7

[0028] R'$_7$ represents, for each occurrence, hydrogen, hydroxyl, or a substituted or unsubstituted alkyl, acyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl, or heterocycle; and

[0029] wherein each occurrence of m is independently an integer ranging from 1 to 9, and each occurrence of n is independently an integer ranging from 1 to 9;

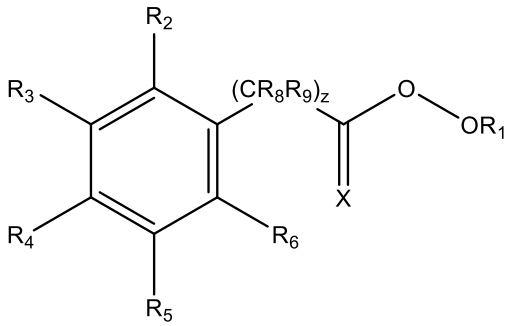
[0030] or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of steroisomers thereof.

[0031] In certain ~~embodiment~~example<u>s</u>, R_1 is a straight chain or branched alkyl having six or fewer carbon atoms (e.g., C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another ~~embodiment~~example, a straight chain or branched alkyl has four or fewer carbon atoms.

[0032] The present ~~invention~~ disclosure relates to a method of treating or preventing cancer by administering a composition including a compound of Formula (I) or (II) or a (III) pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to a subject in need thereof, where administration of the composition of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, results in

one or more of the following: prevention of cancer cell proliferation by accumulation of cells in one or more phases of the cell cycle (e.g. G1, G1/S, G2/M), or induction of cell senescence, or promotion of tumor cell differentiation; promotion of cell death in cancer cells via cytotoxicity, necrosis or apoptosis, without a significant amount of cell death in normal cells, antitumor activity in animals with a therapeutic index of at least 2. As used herein, "therapeutic index" is the maximum tolerated dose divided by the efficacious dose.

[0033] In certain ~~embodiment~~examples, the ~~invention~~ present disclosure encompasses methods of modulating a Src kinase comprising administering a following structure:



Formula II

[0034] wherein X is O or S;

[0035] R_1 is a hydrogen, or a substituted or unsubstituted substituent including but not limited to lower alkyl, a lower alkenyl, a lower alkynyl, -$(CH_2)_mR_7$, $(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7

[0036] each of R_2-R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_mR_7$, $(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, --$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7

[0037] R_7, R_8, and R_9 each independently represents, for each occurrence, hydrogen, hydroxyl, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl, or heterocycle; and

[0038] wherein each occurrence of m and n is separately and independently an integer ranging from 1 to 9, and each occurrence of z is independently an integer ranging from 1 to 9;

[0039] or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of steroisomers thereof.

[0040] In certain ~~embodiment~~examples, R_3 and R_4 are each -OH.

[0041] In certain ~~embodiment~~examples, R_2 and R_3 are each -OH.

[0042] In certain ~~embodiment~~examples, z is 2 and R_8 and R_9 are each -H.

[0043] In certain ~~embodiment~~examples, z is 2; R_1, R_2, R_5, R_6, R_8 and R_9 are each -H; and R_3 and R_4 are each -OH.

[0044] In certain ~~embodiment~~examples, X is O.

[0045] In certain ~~embodiment~~examples,

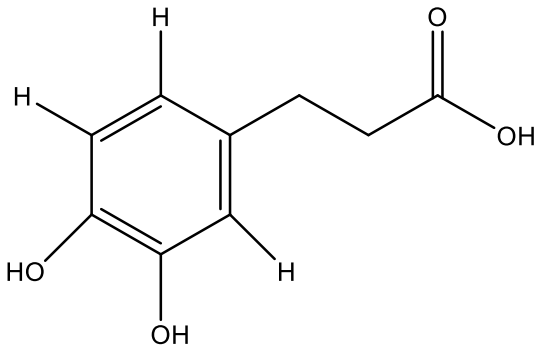
[0046] R_1, R_2, R_3, R_6, R_8, and R_9 are each -H;

[0047] R_4 and R_5 are each -OH;

[0048] X is O; and

[0049] Z is 2.

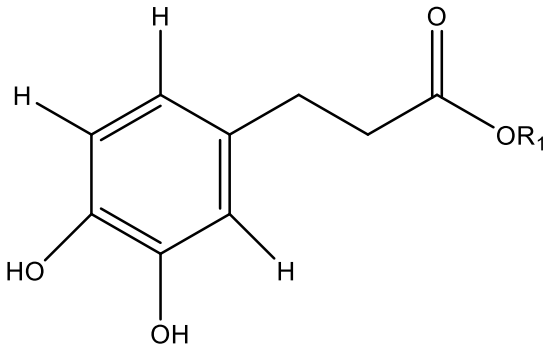
[0050] In certain ~~embodiment~~examples, the compound of formula II has the following structure:



Exemplary Compound E05

[0051] or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of steroisomers thereof.

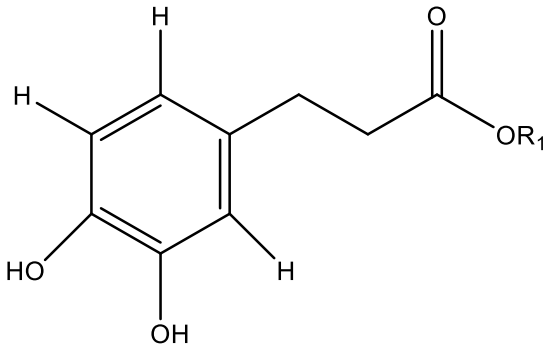
[0052] In certain ~~embodiment~~examples, the compound of formula II is a prodrug of the following structure:



Formula IV

[0053] wherein R_1 comprises esters including ethyl esters, morpholinoethanol esters, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives; carbamates including N,N-dimethylaminocarbonyl of hydroxy functional groups, and N-acyl derivatives.

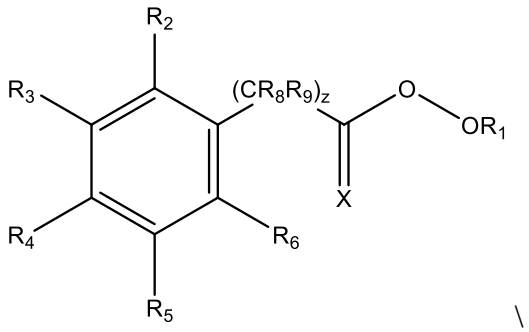
[0054] The ~~invention~~ present disclosure also encompasses prodrugs of formula:



Formula IV

[0055] wherein R_1 comprises esters including alkyl esters, morpholinoethanol esters, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives; carbamates including N,N-dimethylaminocarbonyl of hydroxy functional groups, and N-acyl derivatives.

[0056] In other ~~embodiment~~examples, the ~~invention~~ present disclosure encompasses methods of treating cancer including chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), breast cancer, and colon cancer comprising administering a following structure:



\

Formula II

[0057] wherein X is O or S;

[0058] R_1 is a hydrogen, or a substituted or unsubstituted substituent including but not limited to lower alkyl, a lower alkenyl, a lower alkynyl, -$(CH_2)_mR_7$, $(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7

[0059] each of R_2-R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_mR_7$, $(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, --$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7

[0060] R_7, R_8, and R_9 each independently represents, for each occurrence, hydrogen, hydroxyl, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl,

or heterocycle; and

[0061] wherein each occurrence of m and n is separately and independently an integer ranging from 1 to 9, and each occurrence of z is independently an integer ranging from 1 to 9;

[0062] or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of steroisomers thereof.

[0063] In certain ~~embodiment~~examples, R_3 and R_4 are each -OH.

[0064] In certain ~~embodiment~~examples, R_2 and R_3 are each -OH.

[0065] In certain ~~embodiment~~examples, z is 2 and R_8 and R_9 are each -H.

[0066] In certain ~~embodiment~~examples, z is 2; R_1, R_2, R_5, R_6, R_8 and R_9 are each -H; and R_3 and R_4 are each -OH.

[0067] In certain ~~embodiment~~examples, X is O.

[0068] In certain ~~embodiment~~examples,

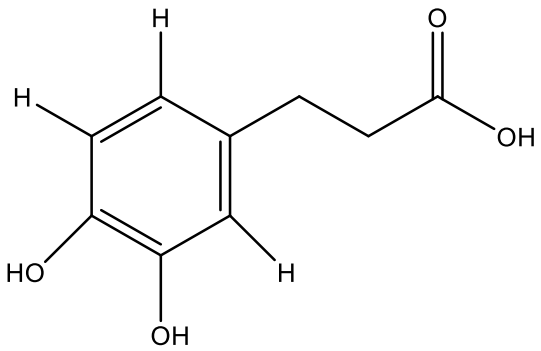
[0069] R_1, R_2, R_3, R_6, R_8, and R_9 are each -H;

[0070] R_4 and R_5 are each -OH;

[0071] X is O; and

[0072] Z is 2.

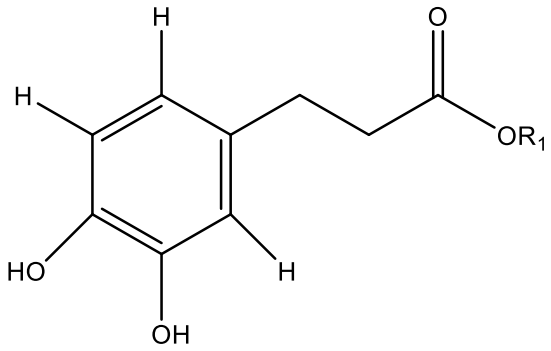
[0073] In certain ~~embodiment~~examples, the compound of formula II has the following structure:



Exemplary Compound E05

[0074] or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of steroisomers thereof.

[0075] In certain ~~embodiment~~examples, the compound of formula II is a prodrug of the following structure:



Formula IV

[0076] wherein R1 comprises esters including ethyl esters, morpholinoethanol esters, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives; carbamates including N,N-dimethylaminocarbonyl of hydroxy functional groups, and N-acyl derivatives.

[0077] In certain ~~embodiment~~examples, the ~~invention~~ present disclosure further encompasses administration of one or more additional therapeutic agents comprising anticancer agents or chemotherapeutic agents.

[0078] One skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel et al., Current Protocols in Molecular Biology, John Wiley and Sons, Inc. (2005); Sambrook et al., Molecular Cloning, A Laboratory Manual (3.sup.th edition), Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (2000); Coligan et al., Current Protocols in Immunology, John Wiley & Sons, N.Y.; Enna et al., Current Protocols in Pharmacology, John Wiley & Sons, N.Y.; Fingl et al., The Pharmacological Basis of Therapeutics (1975), Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 18.sup.th edition (1990). These texts can, of course, also be referred to in making or using an ~~aspect~~ example of the invention.

[0079] The present ~~invention~~ disclosure provides effective therapeutic methods for modulating tumor growth or metastasis wherein a combination of agents is employed. The methods of the present ~~invention~~ disclosure provide advantages such as greater overall efficacy, for example, in achieving synergy or avoiding antagonism, and allow, where desired, a reduction in the amount of one or more of the individual agents employed with a concomitant reduction in side effects. Further, where the tumor to be treated is not optimally responsive to a given anticancer agent, use of the present combination therapy methods can nonetheless provide effective treatment.

[0080] As used herein, the phrase "effective amount" of a compound or pharmaceutical composition refers to an amount sufficient to modulate tumor growth or metastasis in an animal, especially a human, including without limitation decreasing tumor growth or size or preventing formation of tumor growth in an animal lacking any tumor formation prior to

administration, i.e., prophylactic administration.

[0081] As used herein, the terms "tumor", "tumor growth" or "tumor tissue" can be used interchangeably, and refer to an abnormal growth of tissue resulting from uncontrolled progressive multiplication of cells and serving no physiological function. A solid tumor can be malignant, e.g. tending to metastasize and being life threatening, or benign. Examples of solid tumors that can be treated or prevented according to a method of the present ~~invention~~ disclosure include sarcomas and carcinomas such as, but not limited to: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, colorectal cancer, gastric cancer, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, liver metastases, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, thyroid carcinoma such as anaplastic thyroid cancer, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma such as small cell lung carcinoma and non-small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

[0082] Moreover, tumors comprising dysproliferative changes (such as metaplasias and dysplasias) can be treated or prevented with a pharmaceutical composition or method of the present disclosure ~~invention~~ in epithelial tissues such as those in the cervix, colon, esophagus, and lung. Thus, the present disclosure ~~invention~~ provides for treatment of conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W.B. Saunders Co., Philadelphia, pp. 68 to 79). Hyperplasia is a form of controlled cell proliferation involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. For example, endometrial hyperplasia often precedes endometrial cancer. Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplasia can occur in epithelial or connective tissue cells. Atypical metaplasia involves a somewhat disorderly

metaplastic epithelium. Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation, and is often found in the cervix, respiratory passages, oral cavity, and gall bladder. For a review of such disorders, see Fishman et al., 1985, Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia.

[0083] The present disclosure ~~invention~~ encompasses treating and/or preventing various types of leukemia. Leukemia is a cancer of the early blood-forming cells. Most often, leukemia is a cancer of the white blood cells, but some leukemias start in other blood cell types. There are several types of leukemia, which are divided based mainly on whether the leukemia is acute (fast growing) or chronic (slower growing), and whether it starts in myeloid cells or lymphoid cells. Different types of leukemia have different treatment options and outlooks. Acute lymphocytic (or lymphoblastic) leukemia is sometimes called ALL. It starts in the bone marrow where blood cells are made. It is more common in children than in adults. Acute myeloid leukemia is also called acute myelocytic leukemia, acute myelogenous leukemia, acute granulocytic leukemia, acute non-lymphocytic leukemia, or sometimes just AML. It is most common in older people. Chronic lymphocytic leukemia (CLL) is a type of cancer that starts in white blood cells (called lymphocytes) in the bone marrow. CLL mainly affects older adults and accounts for about one-third of all leukemias. Chronic myeloid leukemia (CML) is also known as chronic myelogenous leukemia. It's a type of cancer that starts in the blood-forming cells of the bone marrow and invades the blood. About 15% of leukemias in adults are CML. Chronic myelomonocytic leukemia (CMML) is a type of cancer that starts in blood-forming cells of the bone marrow and invades the blood. It affects mainly older adults.

[0084] The present methods can, for example, be carried out using a single pharmaceutical composition comprising both an Aur-A inhibitor and Src inhibitor (dasatinib) (when administration is to be simultaneous) or using two or more pharmaceutical compositions separately comprising the Src inhibitor and dasatinib (when administration is to be simultaneous or sequential). The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and preferably do not produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human.

[0085] A pharmaceutical composition of the present disclosure ~~invention~~ can be administered by any

suitable route, for example, by injection, by oral, pulmonary, nasal or other forms of administration. In general, pharmaceutical compositions contemplated to be within the scope of the invention, comprise, inter alia, pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions can include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc., or into liposomes. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of components of a pharmaceutical composition of the present invention. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712 which are herein incorporated by reference. A pharmaceutical composition of the present disclosure ~~invention~~ can be prepared, for example, in liquid form, or can be in dried powder, such as lyophilized form. Particular methods of administering such compositions are described infra.

[0086] The present disclosure ~~invention~~ is directed towards methods for modulating tumor growth and metastasis comprising, the administration of an Aur-A inhibitor such as those listed above and at least one Src inhibitor, preferably dasatinib. The agents of the present disclosure ~~invention~~ can be administered separately (e.g, formulated and administered separately), or in combination as a pharmaceutical composition of the present invention. Administration can be achieved by any suitable route, such as parenterally, transmucosally, e.g., orally, nasally, or rectally, or transdermally. Preferably, administration is parenteral, e.g., via intravenous injection. Alternative means of administration also include, but are not limited to, intra-arteriole, intramuscular, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial administration, or by injection into the tumor(s) being treated or into tissues surrounding the tumor(s).

[0087] In yet another ~~embodiment~~example, a pharmaceutical composition of the present disclosure ~~invention~~ can be delivered in a controlled release system, such as using an intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In a particular ~~embodiment~~example, a pump may be used [see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)]. In another ~~embodiment~~example, polymeric materials can be used [see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Press: Boca Raton, Fla.

(1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley: New York (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)]. In yet another ~~embodiment~~example, a controlled release system can be placed in proximity of the target tissues of the animal, thus requiring only a fraction of the systemic dose [see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)]. In particular, a controlled release device can be introduced into an animal in proximity of the site of inappropriate immune activation or a tumor. Other controlled release systems are discussed in the review by Langer [Science 249:1527-1533 (1990)].

BRIEF DESCRIPTION OF THE FIGURES

[0088] FIGURE 1 illustrates and exemplary embodiment of a chromatography profile of the fractions indentified in the initial Capture Step.

[0089] FIGURE 2 illustrates and exemplary embodiment of a chromatography profile of the fractions indentified in the Intermediate Step.

[0090] FIGURE 3 illustrates and exemplary embodiment of a chromatography profile of the fractions indentified in the Polishing Step.

[0091] FIGURE 4 illustrates and exemplary embodiment of a chromatography profile of the fractions indentified in the Desalting Step.

[0092] FIGURE 5 illustrates and exemplary embodiment of a Proton (^{1}H) NMR profile of the purified compound E05.

[0093] FIGURE 6 illustrates and exemplary embodiment of a Carbon (^{13}C) NMR profile of the purified compound E05.

[0094] FIGURE 7 illustrates and exemplary embodiment of a distortionless enhancement by polarization transfer (DEPT) profile of the purified compound E05.

[0095] FIGURE 8 illustrates and exemplary embodiment of a infrared (IR) profile of the purified compound E05.

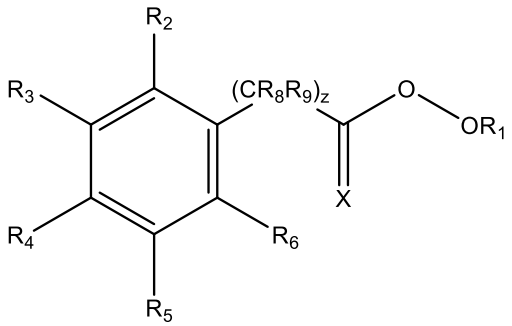
[0096] FIGURE 9a illustrates and exemplary embodiment of a LC-MS spectra of purified compound E05.

[0097] FIGURE 9b illustrates and exemplary embodiment of a MS spectra of purified compound E05.

[0098] FIGURE 10 illustrates and exemplary embodiment of a ORTEP view of compound

CLAIMS

1. Use of a compound of formula~~A method of modulating a Src kinase comprising administering a following structure~~:



~~**Formula II**~~

a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomers thereof,

in the manufacture of a medicament for modulating a Src kinase,

wherein X is O or S;

R_1 is a hydrogen, ~~or~~ a substituted or unsubstituted ~~substituent including but not limited to~~ lower alkyl, ~~a~~ lower alkenyl, ora lower alkynyl;~~,~~ -$(CH_2)_mR_7$;~~,~~ $(CH_2)_m$-OH;~~,~~ -$(CH_2)_m$-O-lower alkyl;~~,~~ -$(CH_2)_m$-O-lower alkenyl;~~,~~ -$(CH_2)_n$-O-$(CH_2)_m$-R_7;~~,~~ -$(CH_2)_m$-SH;~~,~~ -$(CH_2)_m$-S-lower alkyl;~~,~~ -$(CH_2)_m$-S-lower alkenyl;~~,~~ -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

each of R_2, R_3, R_4, R_5, and ~~-~~R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_mR_7$, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, ~~-~~$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_7, R_8, and R_9 each independently represents, for each occurrence, hydrogen~~,~~ ~~hydroxyl~~, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl, or heterocycle; and

wherein each occurrence of m is~~and n is separately and~~ independently an integer ranging from 1 to 9, each occurrence of n is independently an integer ranging from 1 to 9; and

~~each occurrence of~~ z is ~~independently~~ an integer ranging from 1 to 9~~;~~

~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomers thereof~~.

2. The use ~~method~~ of claim 1, wherein R_3 and R_4 are each -OH.

3. The use ~~method~~ of claim 1, wherein R_2 and R_3 are each -OH.

4. The use ~~method~~ of claim 1, wherein z is 2 and R_8 and R_9 are each -H.

5. The use ~~method~~ of claim 1,

wherein z is 2;

R_1, R_4~~R_2~~, R_5, R_6, R_8 and R_9 are each -H; and

R_2 and R_3 ~~and R_4~~ are each -OH.

6. The use ~~method~~ of claim 1, wherein X is O.

7. The use ~~method~~ of claim 1, wherein

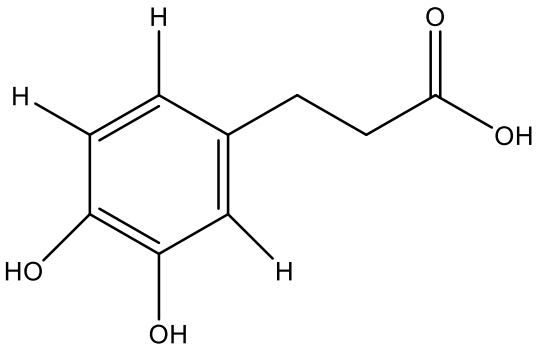
R_1, R_2, R_5~~R_3~~, R_6, R_8, and R_9 are each -H;

R_3 and R_4 are each -OH;

X is O; and

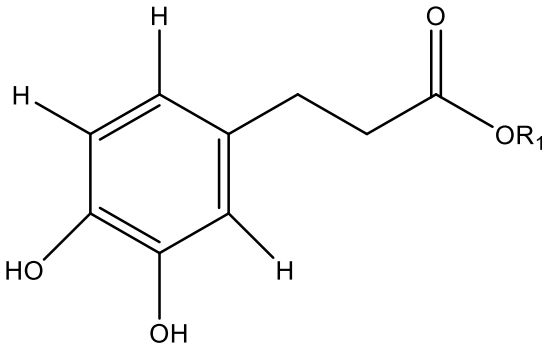
z~~Z~~ is 2.

8. The use ~~method~~ of claim 1, wherein the compound ~~of formula II~~ has the following structure:



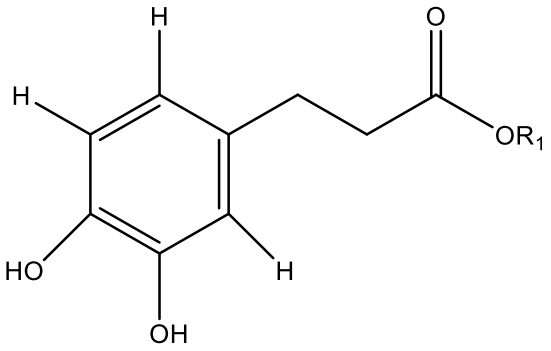
or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomers thereof.

9. The use ~~method~~ of claim 1, wherein the compound ~~of formula II~~ is a prodrug of the following structure:



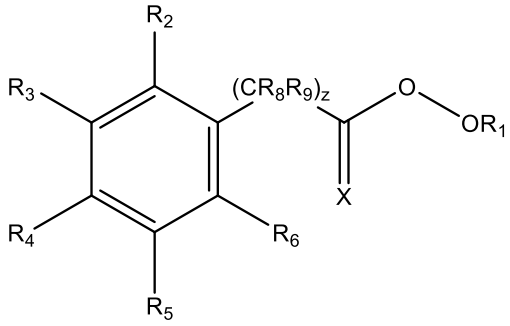
wherein R_1 comprises esters including ethyl esters, morpholinoethanol esters, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives; carbamates including N,N-dimethylaminocarbonyl of hydroxy functional groups, and N-acyl derivatives.

10. A prodrug of formula:



wherein R_1 comprises esters including ethyl esters, morpholinoethanol esters, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives; carbamates including N,N-dimethylaminocarbonyl of hydroxy functional groups, and N-acyl derivatives.

11. Use of a compound of the following structure in the manufacture of a medicament for ~~A method of~~ treating chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), breast cancer, and colon cancer ~~comprising administering a following structure~~:



\

~~Formula II~~

a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of stereoisomers thereof,

wherein X is O or S;

R_1 is a hydrogen, ~~or~~ a substituted or unsubstituted ~~substituent including but not limited to~~ lower alkyl, ~~a~~ lower alkenyl, ora~~n~~ lower alkynyl;~~,~~ -$(CH_2)_mR_7$;~~,~~ $(CH_2)_m$-OH;~~,~~ -$(CH_2)_m$-O-lower alkyl;~~,~~ -$(CH_2)_m$-O-lower alkenyl;~~,~~ -$(CH_2)_n$-O-$(CH_2)_m$-R_7;~~,~~ -$(CH_2)_m$-SH;~~,~~ -$(CH_2)_m$-S-lower alkyl;~~,~~ -$(CH_2)_m$-S-lower alkenyl;~~,~~ -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

each of R_2, R_3, R_4, R_5, and ~~-~~R_6 is independently a hydrogen, a hydroxyl, a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, an amino, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_mR_7$, ~~-~~$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, ~~-~~-$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_7, R_8, and R_9 each independently represents, for each occurrence, hydrogen~~,~~ ~~hydroxyl~~, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, benzyl, cycloalkyl, cycloalkenyl, or heterocycle; and

wherein each occurrence of m is~~and n is separately and~~ independently an integer ranging from 1 to 9, each occurrence of n is independently an integer ranging from 1 to 9; and

~~each occurrence of~~ z is ~~independently~~ an integer ranging from 1 to 9~~;~~

~~or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of steroisomers thereof~~.

12. The use~~method~~ of claim 11, wherein R_3 and R_4 are each -OH.

13. The use~~method~~ of claim 11, wherein R_2 and R_3 are each -OH.

14. The use~~method~~ of claim 11, wherein z is 2 and R_8 and R_9 are each -H.

15. The use~~method~~ of claim 11,

wherein z is 2;

R_1, R_4~~R_2~~, R_5, R_6, R_8 and R_9 are each -H; and

R_2 and R_3 ~~and R_4~~ are each -OH.

16. The use~~method~~ of claim 11, wherein X is O.

17. The use~~method~~ of claim 11, wherein

R_1 is -H or an optionally substituted lower alkyl,

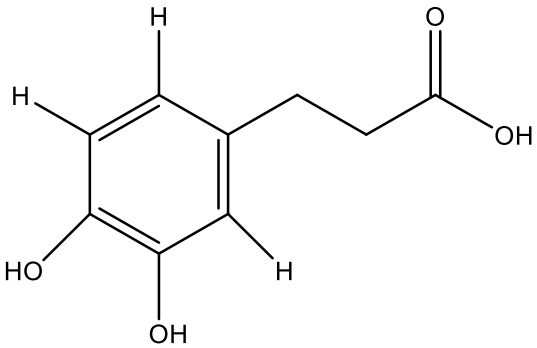
R_2, R_5~~R_3~~, R_6, R_8, and R_9 are each -H;

R_3 and R_4 ~~and R_5~~ are each -OH;

X is O; and

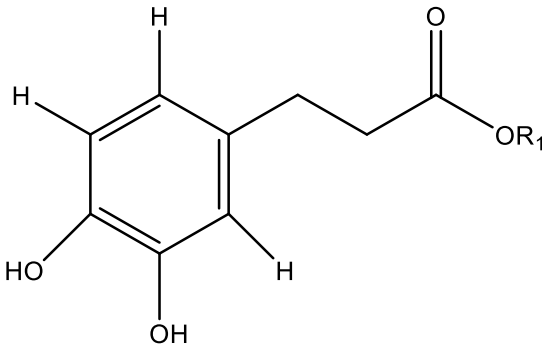
z~~Z~~ is 2.

18. The use~~method~~ of claim 11, wherein the compound ~~of formula II~~ has the following structure:



or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate or mixture of ~~steroisomers~~stereoisomers thereof.

19. The use~~method~~ of claim 11, wherein the compound ~~of formula II~~ is a prodrug of the following structure:



wherein R1 comprises esters including ethyl esters, morpholinoethanol esters, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives; carbamates including N,N-dimethylaminocarbonyl of hydroxy functional groups, and N-acyl derivatives.

20. The use~~method~~ of claim 11, ~~further comprising administration of~~ wherein the compound is to be administered, and one or more additional therapeutic agents comprising anticancer agents or chemotherapeutic agents are to be further administered.