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(71) Applicant *(for all designated States except US)*: **THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, MSC 7660, Bethesda, Maryland 20892-7660 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MALONEY, David J.** [US/US]; 1721 Canal Clipper Court, Point of Rocks, Maryland 21777 (US). **BANTUKALLU, Ganesha Rai** [IN/US]; 1021 Arlington Blvd., #1009, Arlington, Virginia 22209 (US). **JADHAV, Ajit** [US/US]; 27358 Bridle Place, Chantilly, Virginia 20152 (US). **WILSON III, David M.** [US/US]; 3207 Dillon Street, Baltimore, Maryland MD (US). **SIMEONOV, Anton** [US/US]; 7805 Green Twig Road, Bethesda, Maryland 20817 (US).

(74) Agents: **PILLAI, Xavier** et al.; LEYDIG, VOIT & MAYER, LTD., Two Prudential Plaza, Suite 4900, 180 N. Stetson Avenue, Chicago, Illinois 60601 (US).

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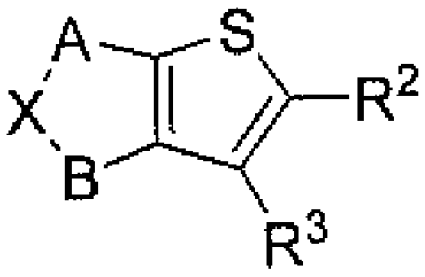
(54) Title: INHIBITORS OF HUMAN APURINIC/APYRIMIDINIC ENDONUCLEASE 1



(I).

(57) Abstract: Disclosed are inhibitors of human APE1, for example, of formula (I), wherein A, B, X, R^2, and R^3 are as defined herein, that are useful in treating an APE1 mediated disease or disorder, e.g., cancer. Also disclosed is a composition comprising a pharmaceutically suitable carrier and at least one compound of the invention, a method of treating cancer in a mammal and a method of potentiating treatment of cancer.

INHIBITORS OF HUMAN APURINIC/APYRIMIDINIC ENDONUCLEASE 1

CROSS-REFERENCE TO A RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 61/480,145, filed April 28, 2011, which is incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Apurinic/apyrimidinic endonuclease (APE1) is the primary mammalian enzyme responsible for the removal of abasic (or AP) sites in DNA. Such lesions can arise as products of the repair activity of DNA glycosylases, which carry out the first step of base excision repair (BER), or as products of spontaneous or damage-induced hydrolysis of the N-glycosidic bond that connects the base to the sugar moiety of the phosphodiester DNA backbone. APE1 initiates AP site repair by catalyzing a Mg^{2+}-facilitated strand incision event immediately 5' to the lesion, leaving behind a single-strand break with a normal 3'-hydroxyl residue and a 5'-abasic fragment. Other proteins of BER, such as DNA polymerase β and DNA ligase 3, complete the repair response by removing the remaining abasic residue, replacing the missing nucleotide, and sealing the final nick. Besides being the predominant repair enzyme for AP sites in DNA, APE1 also possesses repair nuclease activities against various non-conventional 3'-blocking terminal groups, such as phosphoglycolates, phosphates, and chain-terminating nucleoside analogs. In addition, APE1 has other roles in regulating gene expression, most notably through its capacity to modulate the DNA binding activity of several transcription factors, e.g. AP-1, p53 and NF-κB, via a poorly understood redox mechanism.

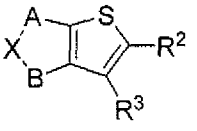
[0003] APE1 protein levels and intracellular distribution have been correlated with cancer type and stage, as well as responsiveness to clinical DNA-damaging agents such as the alkylator temozolomide (TMZ) and the antimetabolite 5-fluorouracil. Thus, it has been postulated that APE1 would be an attractive target in anti-cancer treatment paradigms involving DNA-interactive drugs, where strategic regulation of its repair activity would improve the therapeutic efficacy and clinical outcome. Compounds **1** and **2** (Figure 1) have been reported as inhibitors of APE1. As a result, attempts have been made to identify small molecules that inhibit APE1 repair endonuclease activity.

[0004] In view of the foregoing, there is an unmet need for new inhibitors of APE1 of an animal, in particular, inhibitors of human APE1.

BRIEF SUMMARY OF THE INVENTION

[0005] The invention provides compounds that are potent inhibitors of human APE1. In addition, the present invention provides compositions comprising these compounds and methods of using these compounds as therapeutic agents in the treatment of human APE1 mediated diseases or disorders, in particular, in the treatment of cancer.

[0006] The invention provides a compound of the formula:



wherein X is NR^1, O, S, or SO_2,

A is $-(CR^5R^6)-(CR^7R^8)_m-$,

B is $-(CR^9R^{10})-(CR^{11}R^{12})_n-$

R^1, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are the same or different and are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when m is 0 and n is 1, R^1 and R^5 and/or R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond, or when m is 1 and n is 0, R^5 and R^7 and/or R^1 and R^9, together with the carbon atoms to which they are attached, form a bond,

R^2 is selected from the group consisting of $-NHCOR^4$, $-NH_2$, heterocyclyl, -NH-heterocyclyl, and -COOH, wherein the heterocyclyl is optionally substituted with an alkyl group,

R^3 is heterocyclyl, wherein the heterocyclyl is optionally substituted with an alkyl group or an aryl group, wherein the aryl group is optionally further substituted with one or more substituents selected from the group consisting of halo, dihaloalkyl, trihaloalkyl, nitro, hydroxy, alkoxy, aryloxy, amino, substituted amino, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, thio, alkylthio, and arylthio,

R^4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkoxy, alkenyl, alkynyl, alkynylalkyl, aryl, arylalkyl, heterocyclyl, and arylheterocyclyl, and

m and n are independently 0, 1, or 2,

or a pharmaceutically acceptable salt thereof.

[0007] The invention also provides a pharmaceutical composition comprising a compound or salt of the invention and a pharmaceutically acceptable carrier.

[0008] The invention further provides a method for treating a human APE1 disorder, for example, cancer, comprising administering an effective amount of the compound on the invention to a mammal afflicted therewith.

[0009] The invention additionally provides a method for potentiating or enhancing anticancer activity of an anticancer agent, the method comprising administering to a patient in need thereof an effective amount of an anticancer agent and a compound or salt of the invention.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

[0010] Figure 1 depicts the structures of compounds **1** and **2**, two previously reported APE1 inhibitors.

[0011] Figure 2 depicts the Lineweaver-Burk plots for compounds **3** and **52**, in accordance with an embodiment of the invention.

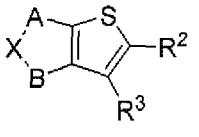
[0012] Figure 3 depicts the (A) representative electrophoretic mobility shift assays for compounds **3** and **52** and (B) relative APE1-DNA complex formation with and without compounds **3** and **52**, in accordance with an embodiment of the invention.

[0013] Figure 4 illustrates the results of a HeLa whole cell extract AP site incision assay for compounds **3** and **52**, in accordance with an embodiment of the invention.

[0014] Figures 5A and 5B depict the HeLa cell viability exhibited by compounds **3** and **52**, respectively, alone, or in combination with either methyl methanesulfonate or temolozomide.

DETAILED DESCRIPTION OF THE INVENTION

[0015] In an embodiment, the invention provides a compound of the formula:



wherein X is NR^1, O, S, or SO_2,

A is $-(CR^5R^6)-(CR^7R^8)_m-$,

B is $-(CR^9R^{10})-(CR^{11}R^{12})_n-$

R^1, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are the same or different and are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when m is 0 and n is 1, R^1 and R^5 and/or R^9 and R^{11}, together with the carbon atoms to which they

are attached, form a bond, or when m is 1 and n is 0, R^5 and R^7 and/or R^1 and R^9, together with the carbon atoms to which they are attached, form a bond,

R^2 is selected from the group consisting of -$NHCOR^4$, -NH_2, heterocyclyl, -NH-heterocyclyl, and -COOH, wherein the heterocyclyl is optionally substituted with an alkyl group,

R^3 is heterocyclyl, wherein the heterocyclyl is optionally substituted with an alkyl group or an aryl group, wherein the aryl group is optionally further substituted with one or more substituents selected from the group consisting of halo, dihaloalkyl, trihaloalkyl, nitro, hydroxy, alkoxy, aryloxy, amino, substituted amino, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, thio, alkylthio, and arylthio,

R^4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkoxy, alkenyl, alkynyl, alkynylalkyl, aryl, arylalkyl, heterocyclyl, and arylheterocyclyl, and

m and n are independently 0, 1, or 2,

with the proviso that when A is CH_2, B is CH_2CH_2, R^1 is alkyl, alkylcarbonyl, or alkoxycarbonyl, and R^3 is 2-benzothiazolyl, R^2 is not $NHCOR^4$ wherein R^4 is alkyl, arylalkyl, heterocyclyl, or arylheterocyclyl,

or a pharmaceutically acceptable salt thereof.

[0016] In accordance with an embodiment, R^2 is $NHCOR^4$.

[0017] In accordance with any of the above embodiments, m is 0 and n is 1.

[0018] In accordance with any of the above embodiments, R^4 is alkyl.

[0019] In accordance with any of the above embodiments, X is NR^1.

[0020] In accordance with any of the above embodiments, R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when m is 0 and n is 1, R^1 and R^5 and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

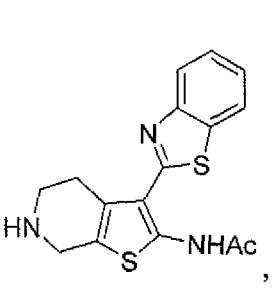
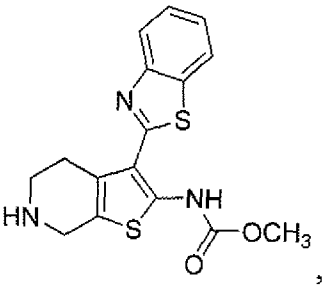
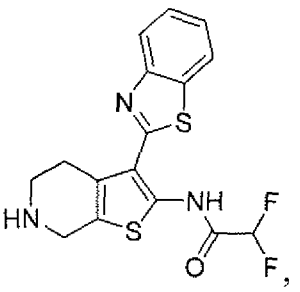
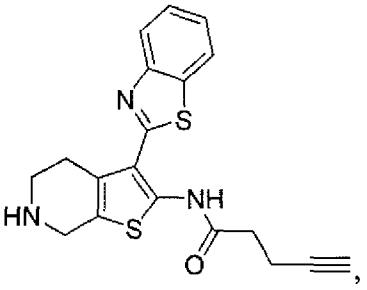
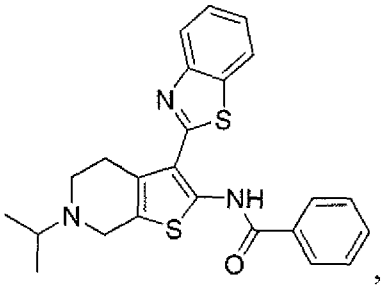
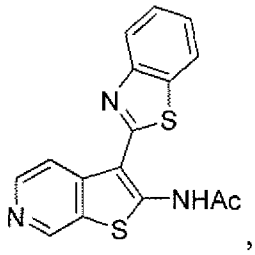
[0021] In accordance with any of the above embodiments, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are hydrogen, or, when m is 0 and n is 1, R^1 and R^5 and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

[0022] In accordance with any of the above embodiments, R^3 is selected from the group consisting of benzothiazol-2-yl, benzothiophene-2-yl, benzothiophene-3-yl, benzoxazol-2-yl, and indol-2-yl.

[0023] In accordance with a preferred embodiment, R^3 is benzothiazol-2-yl.

[0024] In accordance with certain preferred embodiments, wherein R^3 is selected from the group consisting of furan-2-yl, tetrazolyl, thiazol-2-yl, arylthiazol-2-yl, and optionally substituted arylthiazol-2-yl.

[0025] In certain preferred embodiments, the invention provides a compound selected from the group consisting of: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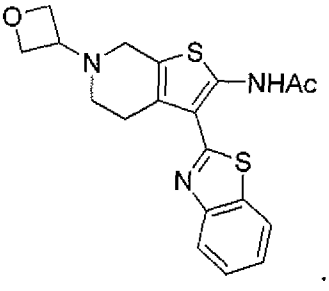
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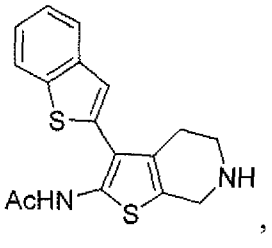
[0026] In certain preferred embodiments, the invention provides a compound selected from the group consisting of: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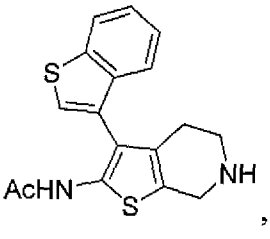
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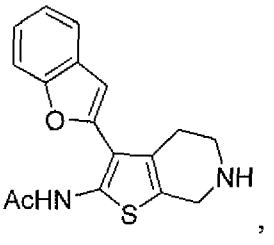
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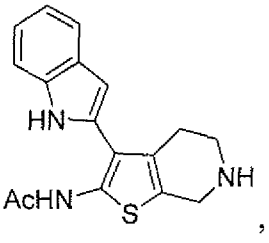
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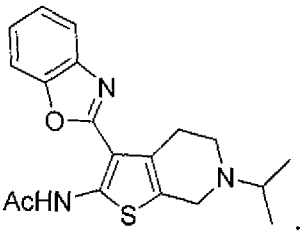
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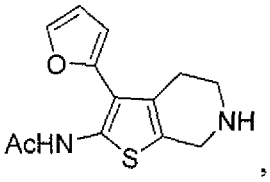
[0027] In certain preferred embodiments, the invention provides a compound selected from the group consisting of:



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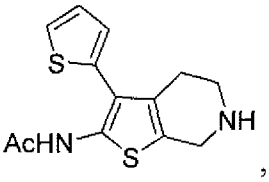

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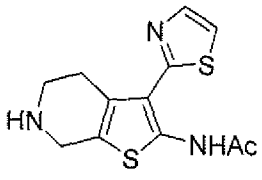

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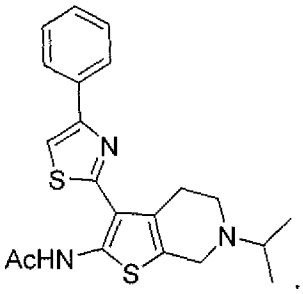

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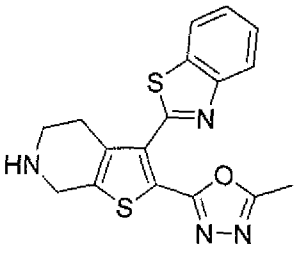
[0028] In accordance with certain embodiments, R^2 is heterocyclyl optionally substituted with alkyl.

[0029] In accordance with certain embodiments, m is 0 and n is 1.

[0030] In certain preferred embodiments, the invention provides a compound selected from the group consisting of:



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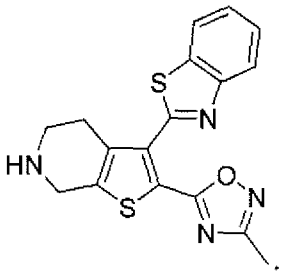

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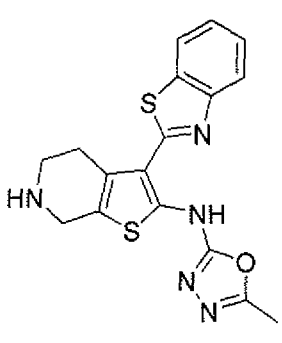
[0031] In certain embodiments, R^2 is -NH-heterocyclyl optionally substituted with alkyl.

[0032] In certain embodiments, m is 0 and n is 1.

[0033] In certain preferred embodiments, the invention provides a compound selected from the group consisting of:



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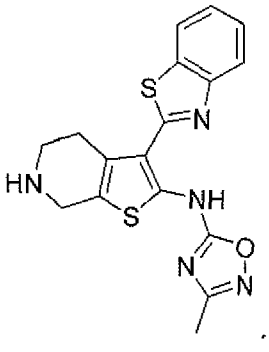

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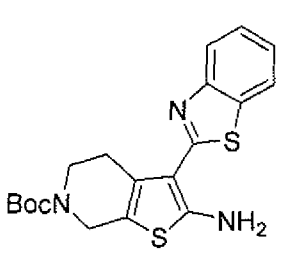
[0034] In certain embodiments, R^2 is $-NH_2$.

[0035] In certain preferred embodiments, the invention provides a compound selected from the group consisting of:



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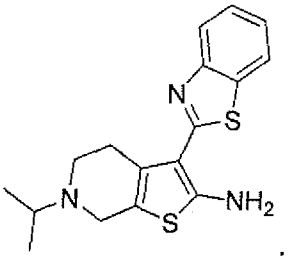
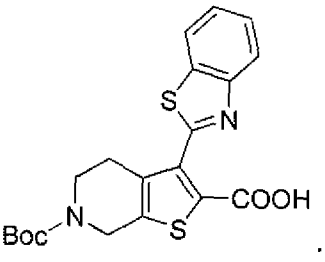


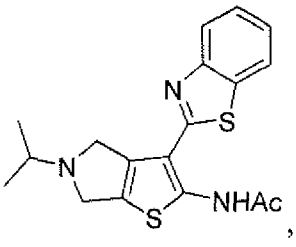
[0036] In certain embodiments, R^2 is –COOH.

[0037] In a certain preferred embodiment, the compound is:



[0038] In certain embodiments, m and n are both 0.

[0039] In a certain preferred embodiment, the compound is selected from the group consisting of:



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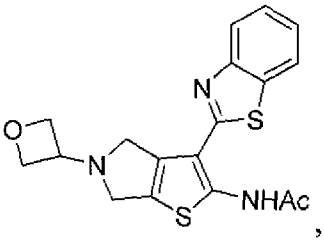

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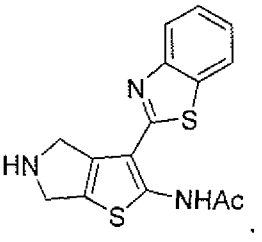
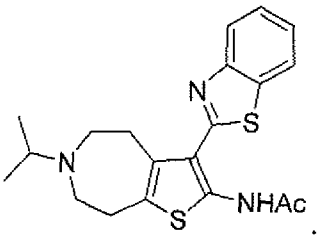


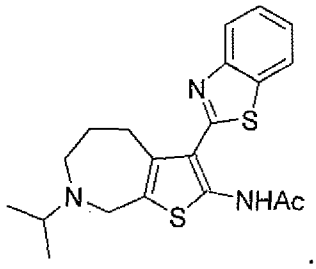
[0040] In certain embodiments, m and n are both 1.

[0041] In a certain preferred embodiment, the compound is:



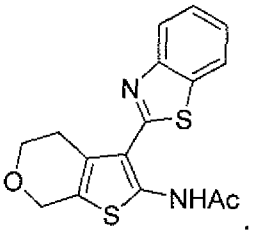
[0042] In certain embodiments, m is 2 and n is 0.

[0043] In a certain preferred embodiment, the compound is:



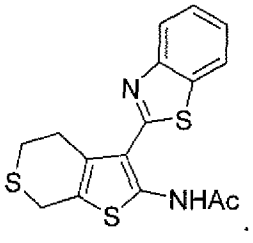
[0044] In certain embodiments, X is O.

[0045] In a certain preferred embodiment, the compound is:



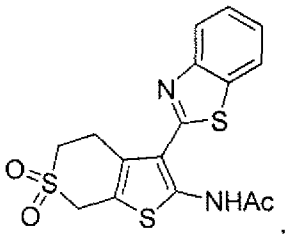
[0046] In certain embodiments, X is S.

[0047] In a certain preferred embodiment, the compound is:



[0048] In certain embodiments, X is SO_2.

[0049] In a certain preferred embodiment, the compound is:



[0050] Referring now to terminology used generically herein, the term "alkyl" means a straight-chain or branched alkyl substituent containing from, for example, 1 to about 6 carbon atoms, preferably from 1 to about 4 carbon atoms, more preferably from 1 to 2 carbon atoms. Examples of such substituents include methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isoamyl, hexyl, and the like.

[0051] The term "alkenyl," as used herein, means a linear alkenyl substituent containing at least one carbon-carbon double bond and from, for example, about 2 to about 6 carbon atoms (branched alkenyls are about 3 to about 6 carbons atoms), preferably from about 2 to about 5 carbon atoms (branched alkenyls are preferably from about 3 to about 5 carbon atoms), more preferably from about 3 to about 4 carbon atoms. Examples of such substituents include vinyl, propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, isobutenyl, *tert*-butenyl, pentenyl, isopentenyl, hexenyl, and the like.

[0052] The term "alkynyl," as used herein, means a linear alkynyl substituent containing at least one carbon-carbon triple bond and from, for example, 2 to about 6 carbon atoms (branched alkynyls are about 3 to about 6 carbons atoms), preferably from 2 to about 5 carbon atoms (branched alkynyls are preferably from about 3 to about 5 carbon atoms), more preferably from about 3 to about 4 carbon atoms. Examples of such substituents include ethynyl, propynyl, isopropynyl, *n*-butynyl, *sec*-butynyl, isobutynyl, *tert*-butynyl, pentynyl, isopentynyl, hexynyl, and the like.

[0053] The term "cycloalkyl," as used herein, means a cyclic alkyl substituent containing from, for example, about 3 to about 8 carbon atoms, preferably from about 4 to about 7 carbon atoms, and more preferably from about 4 to about 6 carbon atoms. Examples of such substituents include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. The cyclic alkyl groups may be unsubstituted or further substituted with alkyl groups such as methyl groups, ethyl groups, and the like.

[0054] The term "oxacycloalkyl," as used herein, means a cyclic alkyl substituent containing from, for example, about 3 to about 8 carbon atoms, preferably from about 4 to about 7 carbon atoms, and more preferably from about 4 to about 6 carbon atoms, and further containing an oxygen atom as part of the oxacycloalkyl ring. Examples of such substituents include oxetanyl, tetrahydrofuryl, tetrahydropyranyl, oxepanyl, and the like. The oxacycloalkyl groups may be unsubstituted or further substituted with alkyl groups such as methyl groups, ethyl groups, and the like.

[0055] The term "heterocyclyl," as used herein, refers to a monocyclic or bicyclic 5- or 6-membered ring system containing one or more heteroatoms selected from the group consisting of O, N, S, and combinations thereof. The heterocyclyl group can be any suitable heterocyclyl group and can be an aliphatic heterocyclyl group, an aromatic heterocyclyl group, or a combination thereof. The heterocyclyl group can be a monocyclic heterocyclyl group or a bicyclic heterocyclyl group. Suitable bicyclic heterocyclyl groups include

monocylic heterocyclyl rings fused to a C_6-C_{10} aryl ring. When the heterocyclyl group is a bicyclic heterocyclyl group, both ring systems can be aliphatic or aromatic, or one ring system can be aromatic and the other ring system can be aliphatic as in, for example, dihydrobenzofuran. Preferably, the heterocyclyl group is an aromatic heterocyclyl group. Non-limiting examples of suitable heterocyclyl groups include furanyl, thiopheneyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazole, 3-methyl-1,2,4-oxadiazole, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, benzothiopheneyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolinyl, benzothiazolinyl, and quinazolinyl. The heterocyclyl group is optionally substituted with 1, 2, 3, 4, or 5 substituents as recited herein such as with alkyl groups such as methyl groups, ethyl groups, and the like, or with aryl groups such as phenyl groups, naphthyl groups and the like, wherein the aryl groups can be further substituted with, for example halo, dihaloalkyl, trihaloalkyl, nitro, hydroxy, alkoxy, aryloxy, amino, substituted amino, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, thio, alkylthio, arylthio, and the like, wherein the optional substituent can be present at any open position on the heterocyclyl group.

[0056] The term "-NH-heterocyclyl," as used herein, refers to a heterocyclyl group as defined herein which is connected to the parent molecule by way of an –NH- linking group. The –NH- linking group can be connected to the NH-heterocyclyl at any open position of the NH-heterocyclyl group. Examples of suitable –NH-heterocyclyl groups include 5-methyl-1,3,4-oxadiazol-2-amino, 3-methyl-1,2,4-oxadiazol-5-amino, and the like.

[0057] The term "arylalkyl," as used herein, refers to an alkyl group linked to a C_6-C_{10} aryl ring and further linked to a molecule via the alkyl group. The term "alkylaryl," as used herein, refers to a C_6-C_{10} aryl ring linked to an alkyl group and further linked to a molecule via the aryl group.

[0058] The term "alkylcarbonyl," as used herein, refers to an alkyl group linked to a carbonyl group and further linked to a molecule via the carbonyl group, e.g., alkyl-C(=O)-. The term "alkoxycarbonyl," as used herein, refers to an alkoxy group linked to a carbonyl group and further linked to a molecule via the carbonyl group, e.g., alkyl-O-C(=O)-.

[0059] Whenever a range of the number of atoms in a structure is indicated (e.g., a C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_2-C_{12}, C_2-C_8, C_2-C_6, C_2-C_4 alkyl, alkenyl, alkynyl, etc.), it is specifically contemplated that any sub-range or individual number of carbon atoms falling within the indicated range also can be used. Thus, for instance, the recitation of a range of 1-

8 carbon atoms (e.g., C_1-C_8), 1-6 carbon atoms (e.g., C_1-C_6), 1-4 carbon atoms (e.g., C_1-C_4), 1-3 carbon atoms (e.g., C_1-C_3), or 2-8 carbon atoms (e.g., C_2-C_8) as used with respect to any chemical group (e.g., alkyl, alkylamino, etc.) referenced herein encompasses and specifically describes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and/or 12 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 1-7 carbon atoms, 1-8 carbon atoms, 1-9 carbon atoms, 1-10 carbon atoms, 1-11 carbon atoms, 1-12 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon atoms, 2-7 carbon atoms, 2-8 carbon atoms, 2-9 carbon atoms, 2-10 carbon atoms, 2-11 carbon atoms, 2-12 carbon atoms, 3-4 carbon atoms, 3-5 carbon atoms, 3-6 carbon atoms, 3-7 carbon atoms, 3-8 carbon atoms, 3-9 carbon atoms, 3-10 carbon atoms, 3-11 carbon atoms, 3-12 carbon atoms, 4-5 carbon atoms, 4-6 carbon atoms, 4-7 carbon atoms, 4-8 carbon atoms, 4-9 carbon atoms, 4-10 carbon atoms, 4-11 carbon atoms, and/or 4-12 carbon atoms, etc., as appropriate). Similarly, the recitation of a range of 6-10 carbon atoms (e.g., C_6-C_{10}) as used with respect to any chemical group (e.g., aryl) referenced herein encompasses and specifically describes 6, 7, 8, 9, and/or 10 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 6-10 carbon atoms, 6-9 carbon atoms, 6-8 carbon atoms, 6-7 carbon atoms, 7-10 carbon atoms, 7-9 carbon atoms, 7-8 carbon atoms, 8-10 carbon atoms, and/or 8-9 carbon atoms, etc., as appropriate).

[0060] The term "halo" or "halogen," as used herein, means a substituent selected from Group VIIA, such as, for example, fluorine, bromine, chlorine, and iodine.

[0061] The term "aryl" refers to an unsubstituted or substituted aromatic carbocyclic substituent, as commonly understood in the art, and the term "C_6-C_{10} aryl" includes phenyl and naphthyl. It is understood that the term aryl applies to cyclic substituents that are planar and comprise 4n+2 π electrons, according to Hückel's Rule.

[0062] The phrase "pharmaceutically acceptable salt" is intended to include nontoxic salts synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, and *Journal of Pharmaceutical Science*, *66*, 2-19 (1977).

[0063] Suitable bases include inorganic bases such as alkali and alkaline earth metal bases, e.g., those containing metallic cations such as sodium, potassium, magnesium, calcium and the like. Non-limiting examples of suitable bases include sodium hydroxide, potassium hydroxide, sodium carbonate, and potassium carbonate. Suitable acids include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, benzenesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, maleic acid, tartaric acid, fatty acids, long chain fatty acids, and the like. Preferred pharmaceutically acceptable salts of inventive compounds having an acidic moiety include sodium and potassium salts. Preferred pharmaceutically acceptable salts of inventive compounds having a basic moiety (e.g., a dimethylaminoalkyl group) include hydrochloride and hydrobromide salts. The compounds of the present invention containing an acidic or basic moiety are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof.

[0064] It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

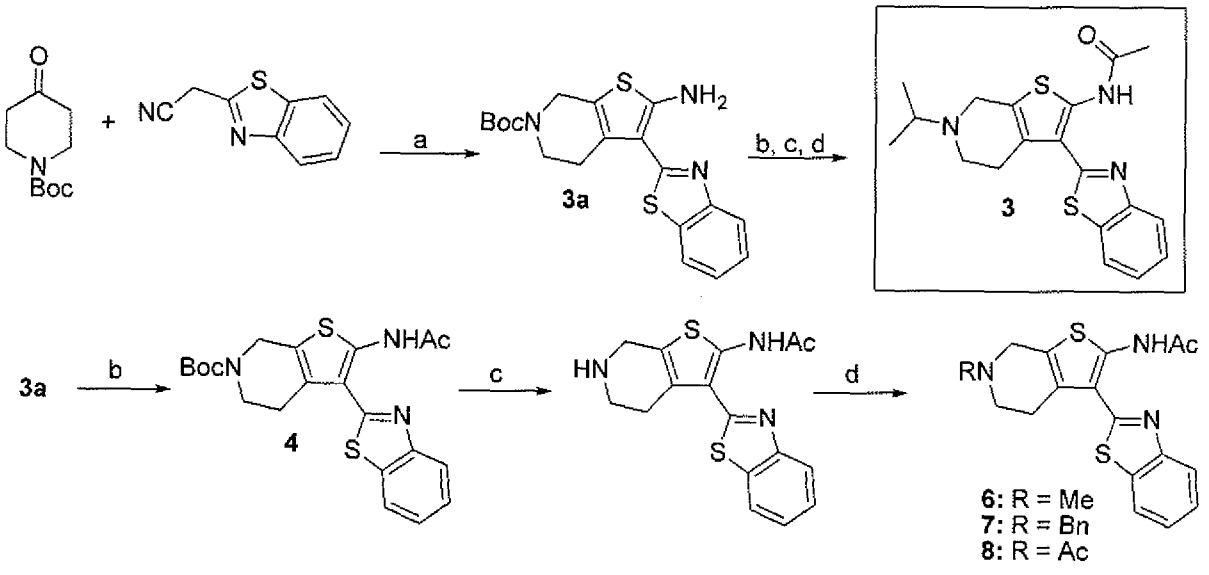
[0065] It is further understood that the above compounds and salts may form solvates, or exist in a substantially uncomplexed form, such as the anhydrous form. As used herein, the term "solvate" refers to a molecular complex wherein the solvent molecule, such as the crystallizing solvent, is incorporated into the crystal lattice. When the solvent incorporated in the solvate is water, the molecular complex is called a hydrate. Pharmaceutically acceptable solvates include hydrates, alcoholates such as methanolates and ethanolates, acetonitrilates and the like. These compounds can also exist in polymorphic forms.

[0066] Chemistry

[0067] The synthesis of the compound **3** commenced with treatment of commercially available N-(Boc)-4-piperidone with 2-benzothiazoleacetonitrile in the presence of elemental sulfur and morpholine to afford key intermediate **3a** as shown in Scheme 1. Acetylation of the 2-amino group, Boc-deprotection with trifluoroacetic acid (TFA) and reductive amination with acetone and $NaCNBH_3$ gave the desired compound **3** in good yield. Starting with intermediate **3a**, several different N-substituted analogs were synthesized including R = Me

(**6**) (via reductive amination with formaldehyde), R = Bn (**7**) (via reductive amination with benzaldehyde) and R = Ac (**8**) (via acylation with AcCl).

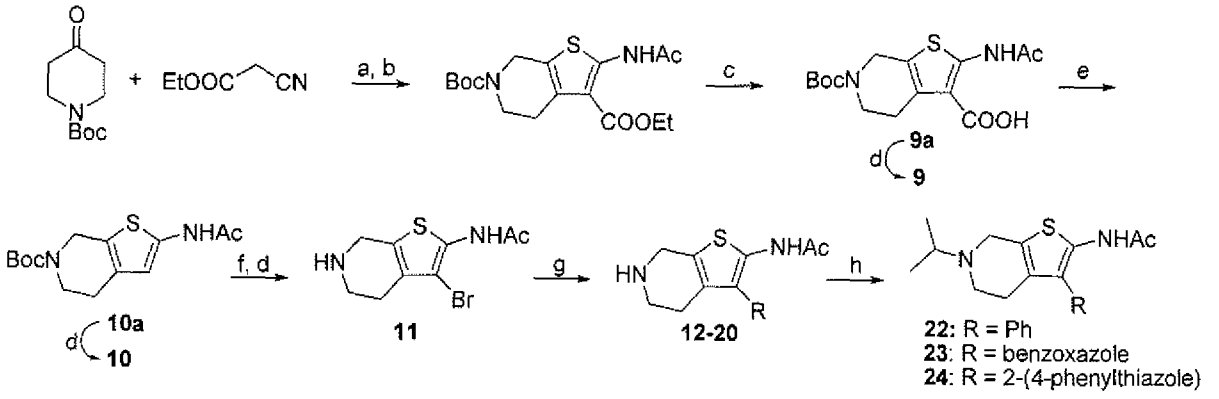
[0068] Scheme 1



Reagents and conditions: (a) S, morpholine, EtOH, reflux, 1 h (87%); (b) AcCl, Hunig's base, CH_2Cl_2, rt, 1 h (91%); (c) TFA, CH_2Cl_2, rt, 1 h (99%); (d) **3**: acetone, $NaCNBH_3$, MeOH, rt, 6 h (75%); **6**: 30% formaldehyde (aq.), $NaCNBH_3$, MeOH, rt, 6 h; **7**: PhCHO, $NaCNBH_3$, MeOH, 6 h; **8**: AcCl, Hunig's base, CH_2Cl_2, rt.

[0069] The synthesis of analogs **9-24** is shown in Scheme 2. Reaction of N-(Boc)-4-piperidone with ethyl 2-cyanoacetate using the conditions described above (S, morpholine) followed by acetylation and subsequent saponification of the formed ethyl ester gave the desired 3-COOH intermediate **9a**. Decarboxylation using dimethylacetamide at 170 °C for two hours in a microwave gave the des-carboxy product **10a** in 77% yield after optimization of the reaction conditions. Typically, this transformation is carried out with copper using quinoline as the solvent or oxalic acid in isopropanol, both at elevated temperatures. The conditions are quite mild and a wide range of functional groups are tolerated. Subsequent bromination of 10a using Br_2 in chloroform at -10 °C followed by Boc-deprotection gave **11** in good yield. Importantly, it was found that the late-stage Suzuki coupling could be accomplished using the unprotected piperidine via treatment of **11** with various commercially available boronic acids in the presence of $Pd(PPh_3)_4$, Na_2CO_3, DME at 150 °C in the microwave to give **12-20** in good yields. Reductive amination with acetone, $NaCNBH_3$ and methanol as the solvent provided the N-isoproyl analogues **22-24**.

[0070] Scheme 2

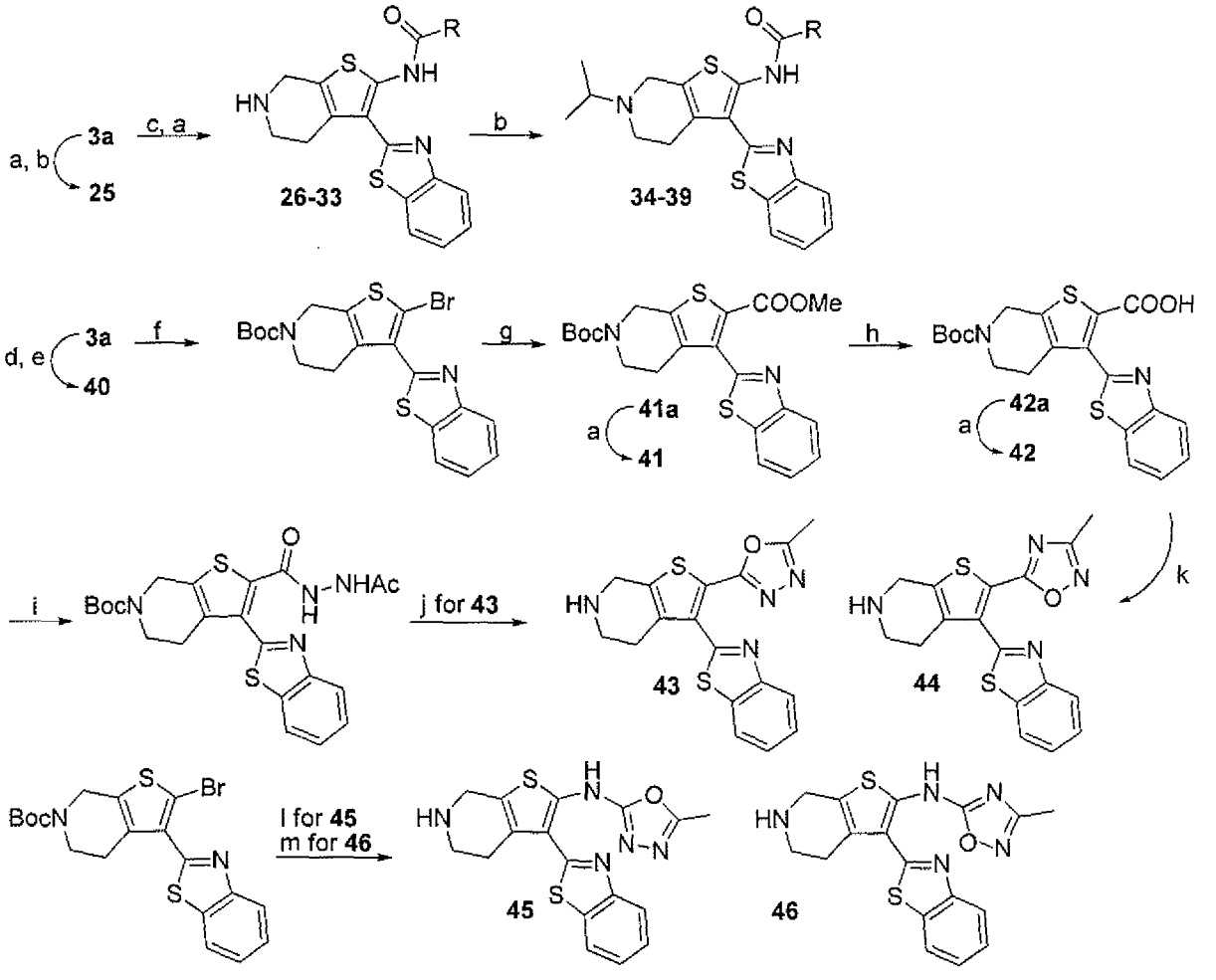


Reagents and conditions: (a) S, morpholine, EtOH, reflux, 2 h (84%); (b) AcCl, Hunig's base, CH_2Cl_2, rt, 1 h (91%); (c) LiOH, THF/H_2O, reflux, 24 h, (65%); (d) TFA, CH_2Cl_2, rt, 0.5 h; (e) dimethylacetamide, 170 °C, μW, 2 h, (77%); (f) Br_2, $CHCl_3$, -10 °C, 1 h (70%); (g) R-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, 150 °C, μW, 0.5-1.5 h; (h) acetone, $NaCNBH_3$, MeOH, rt, 6-10 h.

[0071] Analogs **25-46** were synthesized as shown in Scheme 3. Analog **25**, in which the 2-amino group was left unacetylated, was prepared in 2-steps from common intermediate **3a** via Boc-deprotection and regioselective reductive amination of the piperidine moiety with acetone and $NaCNBH_3$. Analogs **26-33**, involved either reaction with the requisite acid chloride or in the case of compounds **31**, **33**, and **36**, EDC-mediated peptide coupling conditions were utilized to afford the desired products in good yields. The synthesis of des-amino oxadiazole analogs **43** and **44** commenced with conversion of the 2-amino group to the corresponding bromide using tert-butyl nitrite and copper bromide in acetonitrile. Palladium-catalyzed carboxylation was achieved using cat. $Pd(OAc)_2$, catalytic dppp, in DMSO-MeOH under an atmosphere of CO(g) to afford the desired methyl ester derivative **41a** in XX% yield. Saponification of **41a** with LiOH in a THF/MeOH/H2O mixture gave carboxylic acid **42a** in high yield. Formation of the acylhydrazide was accomplished using acetohydrazide and EDC in DMF. Dehydrative cyclization was achieved using Burgess Reagent in THF at 100 °C in the microwave to give after Boc-deprotection (TFA, CH_2Cl_2) the 1,3,4-substituted oxadiazole **43** in good yield. 1,2,4-oxadiazole derivative **44** was prepared in 3-steps from intermediate **42a** via treatment with N'-hydroxyacetimidamide, HATU, Hunig's base to afford the cyclized product which after Boc-deprotection gave the desired product **44**. Access to analogs **45** and **46** was achieved via Buchwald-Hartwig-type cross couplings of the requisite commercially available amino-oxadiazole (5-methyl-1,3,4-oxadiazol-2-amine: **45**

and 3-methyl-1,2,4-oxadiazol-5-amine: **46** using $Pd_2(dba)_3$, Xanthphos, cesium carbonate at 125 °C in the microwave for two hours following by Boc-deprotection.

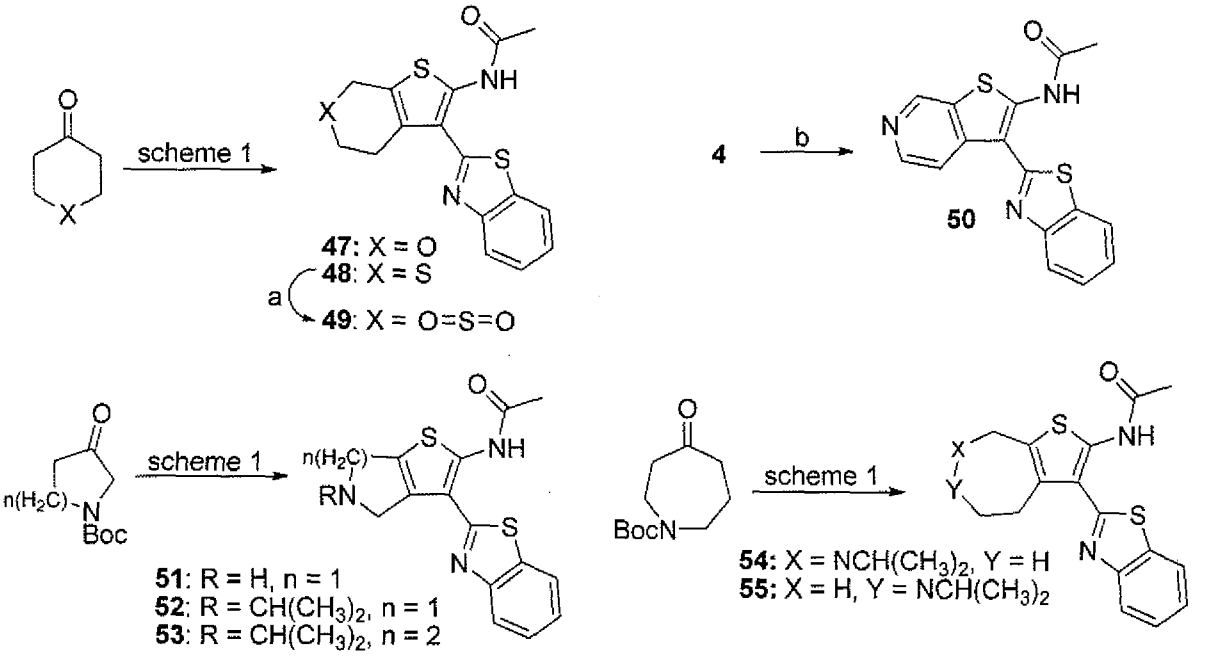
[0072] Scheme 3



Reagents and conditions: (a) TFA, CH_2Cl_2, rt, 0.5 h; (b) acetone, $NaCNBH_3$, MeOH, rt, 6 h; (c) RC(O)Cl, $(iPr)_2NEt$, CH_2Cl_2, rt; **31**,**33**,**36**: RC(O)OH, EDC, DMAP, DMF, rt, 1 h, (85-90%); (d) $NaNO_2$, HCl-H_2SO_4, 0 °C, 2 h; (e) H_3PO_2, rt, 1 h; (f) *t*-$BuNO_2$, $CuBr_2$, MeCN, 0 °C→rt, 4 h; (g) $Pd(OAc)_2$, dppp, $CO_{(g)}$ (1 atm), NEt_3, DMSO-MeOH (1:1), 60 °C, 24 h, (69); (h) LiOH, THF/MeOH/H_2O (6:2:1), rt, 3 h, (91%); (i) acetohydrazide, EDC, DMF, rt, 2 h (97%); (j) Burgess reagent, THF, 100 °C, μW, 0.5 h, (73%), then TFA, CH_2Cl_2, rt, 0.5 h; (k) *N'*-hydroxyacetimidamide, HATU, $(iPr)_2NEt$, 50 °C-15 min. then 150 °C-15 min. μW, 1 h, then TFA, CH_2Cl_2, rt, 0.5 h; (l) 5-methyl-1,3,4-oxadiazol-2-amine, $Pd_2(dba)_3$, Xanthphos, Cs_2CO_3, dioxane, 125 °C, μW, 2 h, then TFA, CH_2Cl_2, rt, 0.5 h; (m) 3-methyl-1,2,4-oxadiazol-5-amine, $Pd_2(dba)_3$, Xanthphos, Cs_2CO_3, dioxane, 125 °C, μW, 2 h, then TFA, CH_2Cl_2, rt, 0.5 h.

[0073] As shown in Scheme 4, various heteroatoms were installed in place of the piperidine nitrogen of lead compound **3** (e.g. O: **47**, S: **48** and SO_2: **49**). Accordingly, the synthesis of **47** and **48** were carried out in a manner similar to that shown in Scheme 1, however instead of N-(Boc)-4-piperidone which was used for the synthesis of compound **3**, tetrahydropyran-4-one and tetrahydro-thiopyran-4-one was used for the preparation of **47** and **48**, respectively. Synthesis of sulfone derivative **49** was accomplished via treatment of **48** with m-CPBA in methylene chloride at 0 °C. Pyridine analog **50** was obtained via MnO_2 oxidation of intermediate **4** (Scheme 1). As with compounds **47** and **48**, 5-membered analogs **51** and **52** were prepared using the route described in scheme 1 except N-Boc-3-pyrrolidinone was used as the starting material whereas for **53**, N-(Boc)-3-piperidone was utilized. Analogs **54** and **55** were synthesized from 1-Boc-4-azepanone which upon cyclization (S, morpholine) gave two separable regioisomers that were easily distinguishable by ^{1}H NMR, which were both carried through the described sequence to provide the desired products.

[0074] Scheme 4



Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h, (81%); (b) MnO_2, toluene, 120 °C, μW, 10 min., (49%).

[0075] The present invention is further directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one compound or salt described herein.

[0076] It is preferred that the pharmaceutically acceptable carrier be one that is chemically inert to the active compounds and one that has no detrimental side effects or toxicity under the conditions of use.

[0077] The choice of carrier will be determined in part by the particular compound of the present invention chosen, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. The following formulations for oral, aerosol, nasal, pulmonary, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, intrathecal, intratumoral, topical, rectal, and vaginal administration are merely exemplary and are in no way limiting.

[0078] The pharmaceutical composition can be administered parenterally, e.g., intravenously, subcutaneously, intradermally, or intramuscularly. Thus, the invention provides compositions for parenteral administration that comprise a solution or suspension of the inventive compound or salt dissolved or suspended in an acceptable carrier suitable for parenteral administration, including aqueous and non-aqueous isotonic sterile injection solutions.

[0079] Overall, the requirements for effective pharmaceutical carriers for parenteral compositions are well known to those of ordinary skill in the art. See, e.g., Banker and Chalmers, eds., *Pharmaceutics and Pharmacy Practice*, J. B. Lippincott Company, Philadelphia, pp. 238-250 (1982), and Toissel, *ASHP Handbook on Injectable Drugs*, 4th ed., pp. 622-630 (1986). Such solutions can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compound or salt of the present invention may be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol, dimethylsulfoxide, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose,

hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[0080] Oils useful in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils useful in such formulations include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

[0081] Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

[0082] The parenteral formulations can contain preservatives and buffers. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0083] Topical formulations, including those that are useful for transdermal drug release, are well-known to those of skill in the art and are suitable in the context of the invention for application to skin. Topically applied compositions are generally in the form of liquids, creams, pastes, lotions and gels. Topical administration includes application to the oral mucosa, which includes the oral cavity, oral epithelium, palate, gingival, and the nasal mucosa. In some embodiments, the composition contains at least one active component and a

suitable vehicle or carrier. It may also contain other components, such as an anti-irritant. The carrier can be a liquid, solid or semi-solid. In embodiments, the composition is an aqueous solution. Alternatively, the composition can be a dispersion, emulsion, gel, lotion or cream vehicle for the various components. In one embodiment, the primary vehicle is water or a biocompatible solvent that is substantially neutral or that has been rendered substantially neutral. The liquid vehicle can include other materials, such as buffers, alcohols, glycerin, and mineral oils with various emulsifiers or dispersing agents as known in the art to obtain the desired pH, consistency and viscosity. It is possible that the compositions can be produced as solids, such as powders or granules. The solids can be applied directly or dissolved in water or a biocompatible solvent prior to use to form a solution that is substantially neutral or that has been rendered substantially neutral and that can then be applied to the target site. In embodiments of the invention, the vehicle for topical application to the skin can include water, buffered solutions, various alcohols, glycols such as glycerin, lipid materials such as fatty acids, mineral oils, phosphoglycerides, collagen, gelatin and silicone based materials.

[0084] Formulations suitable for oral administration can consist of (a) liquid solutions, such as a therapeutically effective amount of the inventive compound dissolved in diluents, such as water, saline, or orange juice, (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules, (c) powders, (d) suspensions in an appropriate liquid, and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base,

such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are known in the art.

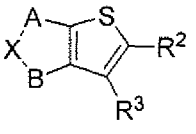
[0085] The compound or salt of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. The compounds are preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of active compound are 0.01%-20% by weight, preferably 1%-10%. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such surfactants are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1%-20% by weight of the composition, preferably 0.25%-5%. The balance of the composition is ordinarily propellant. A carrier can also be included as desired, e.g., lecithin for intranasal delivery. These aerosol formulations can be placed into acceptable pressurized propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer. Such spray formulations may be used to spray mucosa.

[0086] Additionally, the compound or salt of the present invention may be made into suppositories by mixing with a variety of bases, such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

[0087] It will be appreciated by one of ordinary skill in the art that, in addition to the aforedescribed pharmaceutical compositions, the compound or salt of the present invention may be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes. Liposomes serve to target the compounds to a particular tissue, such as lymphoid tissue or cancerous hepatic cells. Liposomes can also be used to increase the half-life of the inventive compound. Liposomes useful in the present invention include emulsions, foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions, lamellar layers and the like. In these preparations, the active agent to be delivered is incorporated as part of a liposome, alone or in conjunction with a suitable chemotherapeutic agent. Thus, liposomes filled with a desired inventive compound or salt thereof, can be directed to the site of a specific tissue type, hepatic cells, for example, where the liposomes then deliver the selected

compositions. Liposomes for use in the invention are formed from standard vesicle-forming lipids, which generally include neutral and negatively charged phospholipids and a sterol, such as cholesterol. The selection of lipids is generally guided by consideration of, for example, liposome size and stability of the liposomes in the blood stream. A variety of methods are available for preparing liposomes, as described in, for example, Szoka et al., *Ann. Rev. Biophys. Bioeng.*, *9*, 467 (1980), and U.S. Patents 4,235,871, 4,501,728, 4,837,028, and 5,019,369. For targeting to the cells of a particular tissue type, a ligand to be incorporated into the liposome can include, for example, antibodies or fragments thereof specific for cell surface determinants of the targeted tissue type. A liposome suspension containing a compound or salt of the present invention may be administered intravenously, locally, topically, etc. in a dose that varies according to the mode of administration, the agent being delivered, and the stage of disease being treated.

[0088] The invention further provides a method for treating an APE1 mediated disease or disorder. The method comprises administering to an animal afflicted therewith.an effective amount of a compound of the formula:



wherein X is NR^1, O, S, or SO_2,

A is $-(CR^5R^6)-(CR^7R^8)_m-$,

B is $-(CR^9R^{10})-(CR^{11}R^{12})_n-$

R^1, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are the same or different and are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when m is 0 and n is 1, R^1 and R^5 and/or R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond, or when m is 1 and n is 0, R^5 and R^7 and/or R^1 and R^9, together with the carbon atoms to which they are attached, form a bond,

R^2 is selected from the group consisting of $-NHCOR^4$, $-NH_2$, heterocyclyl, -NH-heterocyclyl, and -COOH, wherein the heterocyclyl is optionally substituted with an alkyl group,

R^3 is heterocyclyl, wherein the heterocyclyl is optionally substituted with an alkyl group or an aryl group, wherein the aryl group is optionally further substituted with one or more substituents selected from the group consisting of halo, dihaloalkyl, trihaloalkyl, nitro,

hydroxy, alkoxy, aryloxy, amino, substituted amino, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, thio, alkylthio, and arylthio,

R^4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkoxy, alkenyl, alkynyl, alkynylalkyl, aryl, arylalkyl, heterocyclyl, and arylheterocyclyl, and

m and n are independently 0, 1, or 2,

or a pharmaceutically acceptable salt thereof.

[0089] In accordance with an embodiment, R^2 is $NHCOR^4$.

[0090] In accordance with any of the above embodiments, m is 0 and n is 1.

[0091] In accordance with any of the above embodiments, R^4 is alkyl.

[0092] In accordance with any of the above embodiments, X is NR^1.

[0093] In accordance with any of the above embodiments, R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when m is 0 and n is 1, R^1 and R^5 and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

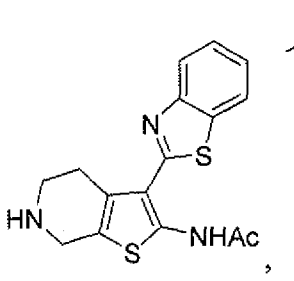
[0094] In accordance with any of the above embodiments, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are hydrogen, or, when m is 0 and n is 1, R^1 and R^5 and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

[0095] In accordance with any of the above embodiments, R^3 is selected from the group consisting of benzothiazol-2-yl, benzothiophene-2-yl, benzothiophene-3-yl, benzoxazol-2-yl, and indol-2-yl.

[0096] In accordance with a preferred embodiment, R^3 is benzothiazol-2-yl.

[0097] In accordance with certain preferred embodiments, wherein R^3 is selected from the group consisting of furan-2-yl, tetrazolyl, thiazol-2-yl, arylthiazol-2-yl, and optionally substituted arylthiazol-2-yl.

[0100] In certain preferred embodiments, the compound is selected from the group consisting of:



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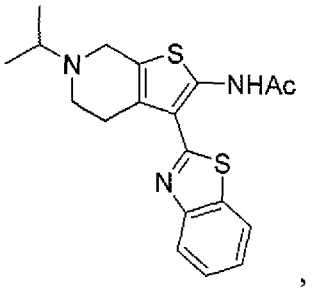

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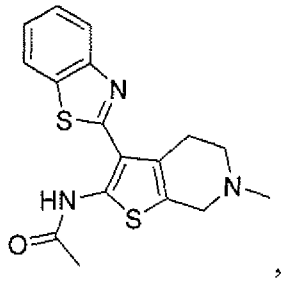

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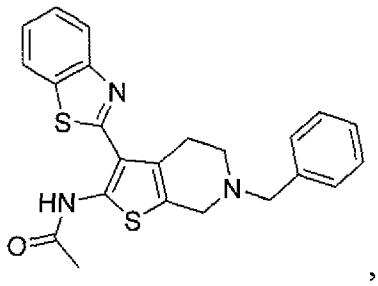
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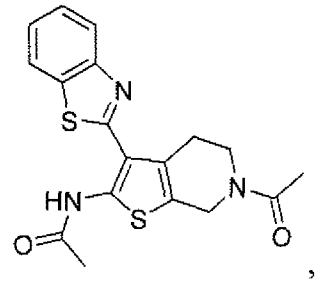
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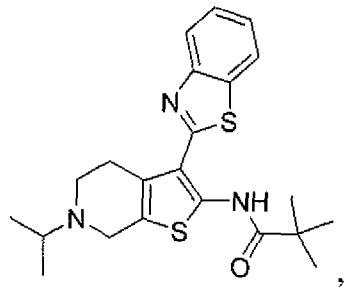
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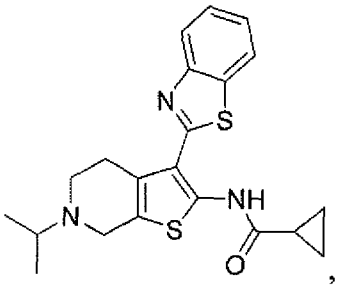
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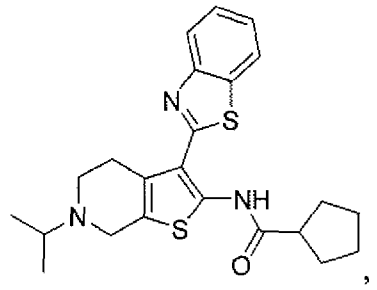
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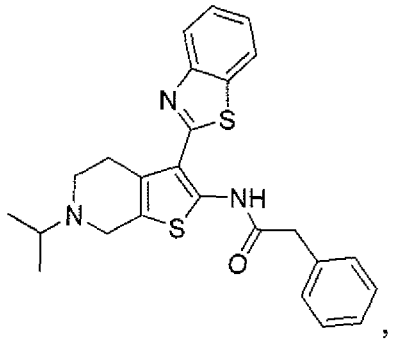
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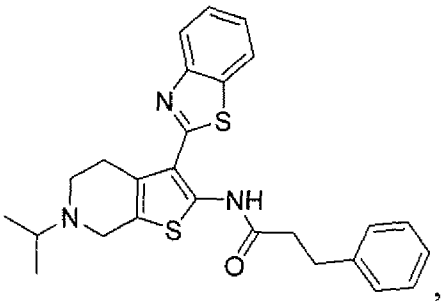
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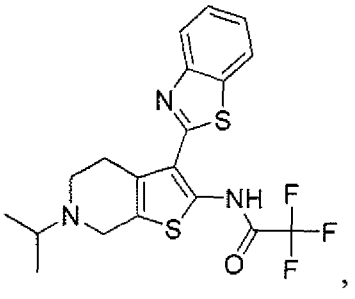
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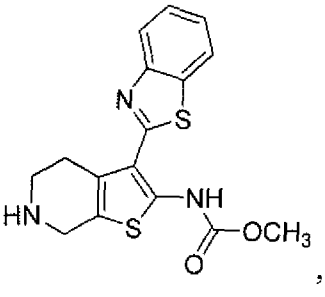
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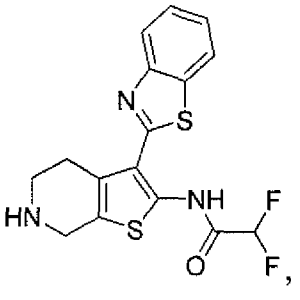
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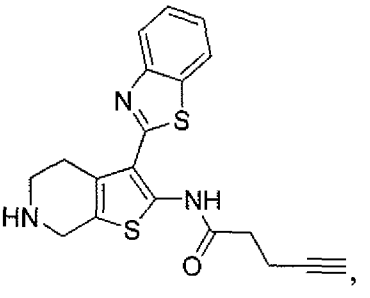
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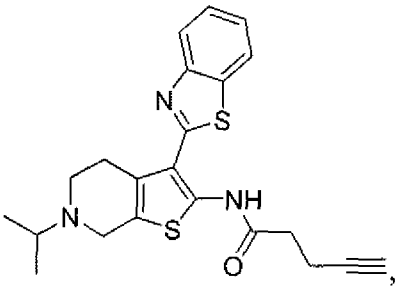
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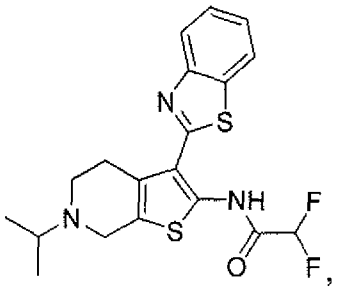
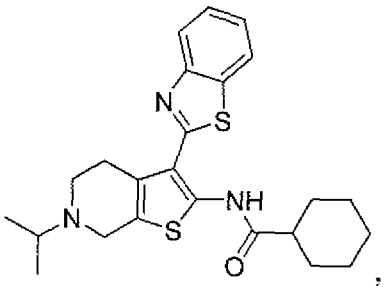
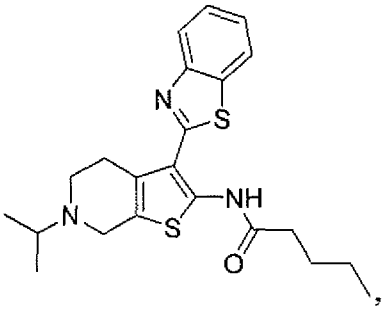
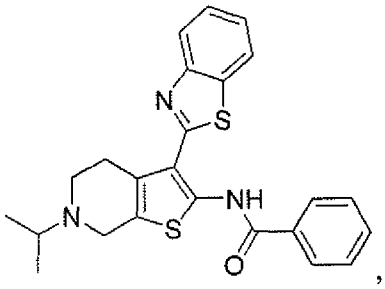
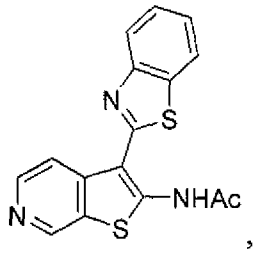
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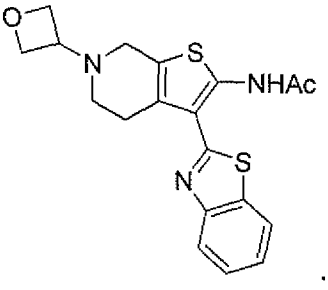
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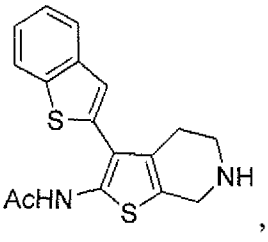
[0101] In certain preferred embodiments, the compound is selected from the group consisting of: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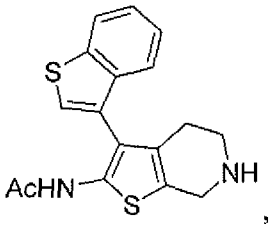
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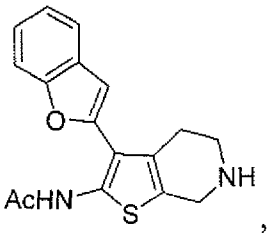
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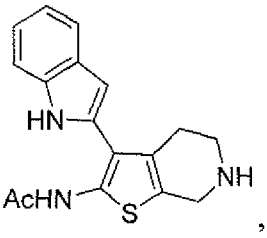
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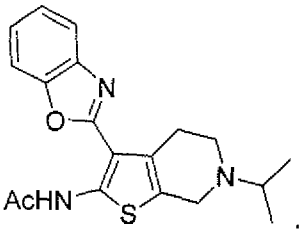
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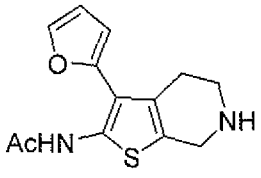
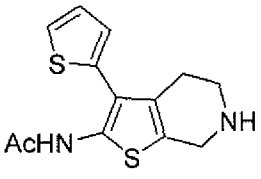
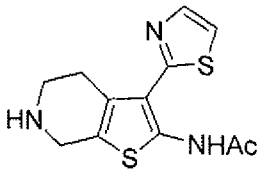
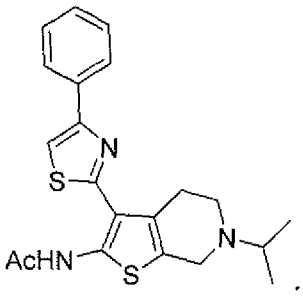
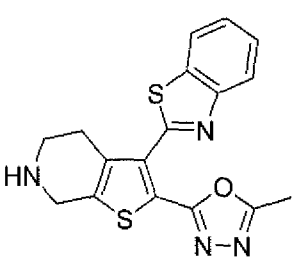
[0102] In certain preferred embodiments, the compound is selected from the group consisting of:

[0103] In accordance with certain embodiments, R^2 is heterocyclyl optionally substituted with alkyl.

[0104] In accordance with certain embodiments, m is 0 and n is 1.

[0105] In certain preferred embodiments, the compound is selected from the group consisting of: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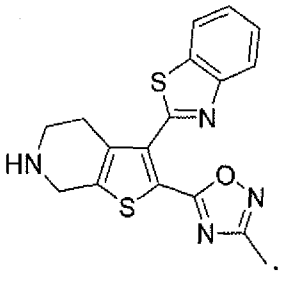
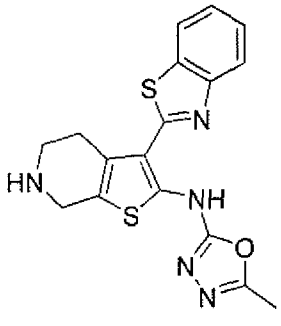


[0106] In certain embodiments, R^2 is -NH-heterocyclyl optionally substituted with alkyl.

[0107] In certain embodiments, m is 0 and n is 1.

[0108] In certain preferred embodiments, the compound is selected from the group consisting of: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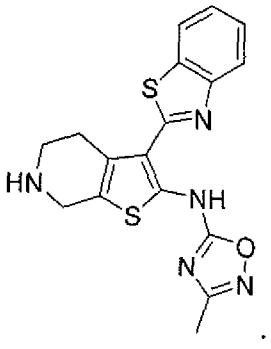
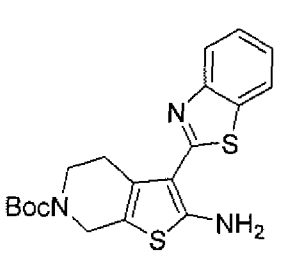


[0109] In certain embodiments, R^2 is $-NH_2$.

[0110] In certain preferred embodiments, the compound is selected from the group consisting of:



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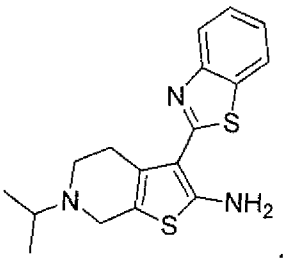
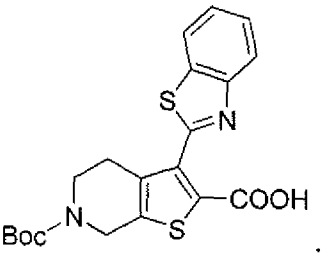


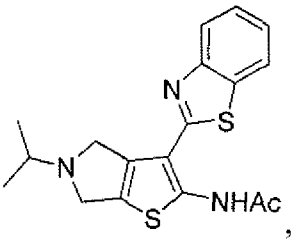
[0111] In certain embodiments, R^2 is –COOH.

[0112] In a certain preferred embodiment, the compound is:



[0113] In certain embodiments, m and n are both 0.

[0114] In a certain preferred embodiment, the compound is selected from the group consisting of:



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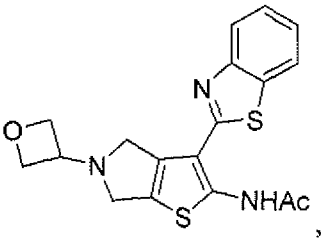

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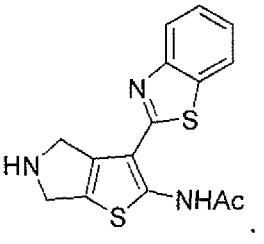
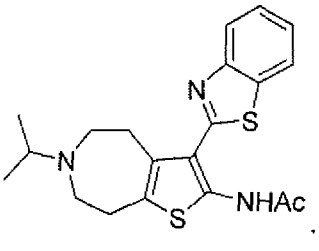


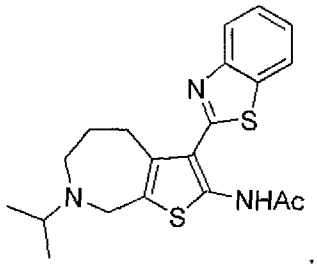
[0115] In certain embodiments, m and n are both 1.

[0116] In a certain preferred embodiment, the compound is:



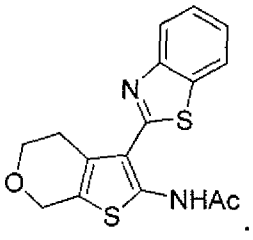
[0117] In certain embodiments, m is 2 and n is 0.

[0118] In a certain preferred embodiment, the compound is:



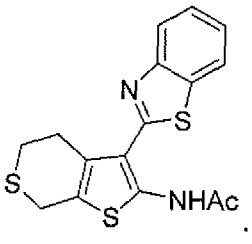
[0119] In certain embodiments, X is O.

[0120] In a certain preferred embodiment, the compound is:



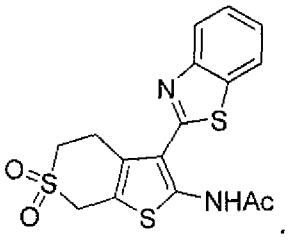
[0121] In certain embodiments, X is S.

[0122] In a certain preferred embodiment, the compound is:



[0123] In certain embodiments, X is SO_2.

[0124] In a certain preferred embodiment, the compound is:



[0125] Preferably, the animal is a mammal. More preferably, the mammal is a human.

[0126] The term "mammal" includes, but is not limited to, the order Rodentia, such as mice, and the order Logomorpha, such as rabbits. It is preferred that the mammals are from the order Carnivora, including Felines (cats) and Canines (dogs). It is more preferred that the mammals are from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). It is most preferred that the mammals

are of the order Primates, Ceboids, or Simioids (monkeys) or of the order Anthropoids (humans and apes). An especially preferred mammal is the human. Furthermore, the subject can be the unborn offspring of any of the forgoing hosts, especially mammals (e.g., humans), in which case any screening of the subject or cells of the subject, or administration of compounds to the subject or cells of the subject, can be performed in utero.

[0127] In accordance with an embodiment, the invention provides a method of treating or preventing cancer comprising administering to a patient in need thereof a therapeutically effective amount of a compound or salt as recited for the method for treating an APE1 mediated disease or disorder. The cancer can be any suitable cancer responsive to inhibition of human APE1, for example, cancers in which APE1 is overexpressed.

[0128] In accordance with another embodiment, the invention provides a method of treating cancer. The cancer can be any suitable cancer. For example, the cancer may be adrenocortical carcinoma, AIDS-related lymphoma, AIDS-related malignancies, anal cancer, cerebellar astrocytoma, extrahepatic bile duct cancer, bladder cancer, osteosarcoma/malignant fibrous histiocytoma, brain stem glioma, ependymoma, visual pathway and hypothalamic gliomas, breast cancer, bronchial adenomas/carcinoids, carcinoid tumors, gastrointestinal carcinoid tumors, carcinoma, adrenocortical, islet cell carcinoma, primary central nervous system lymphoma, cerebellar astrocytoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, clear cell sarcoma of tendon sheaths, colon cancer, colorectal cancer, cutaneous t-cell lymphoma, endometrial cancer, ependymoma, esophageal cancer, Ewing's sarcoma/family of tumors, extracranial germ cell tumors, extragonadal germ cell tumors, extrahepatic bile duct cancer, eye cancers, including intraocular melanoma, and retinoblastoma, gallbladder cancer, gastrointestinal carcinoid tumor, ovarian germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, Hodgkin's disease, hypopharyngeal cancer, hypothalamic and visual pathway glioma, intraocular melanoma, Kaposi's sarcoma, laryngeal cancer, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia, malignant mesothelioma, malignant thymoma, medulloblastoma, melanoma, intraocular melanoma, merkel cell carcinoma, metastatic squamous neck cancer with occult primary, multiple endocrine neoplasia syndrome, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndrome, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer,

neuroblastoma, oral cancer, oral cavity and lip cancer, oropharyngeal cancer, osteosarcoma/malignant fibrous histiocytoma of bone, ovarian cancer, ovarian low malignant potential tumor, pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pheochromocytoma, pituitary tumor, pleuropulmonary blastoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, transitional cell cancer (e.g. renal pelvis and ureter), retinoblastoma, rhabdomyosarcoma, salivary gland cancer, malignant fibrous histiocytoma of bone, soft tissue sarcoma, sezary syndrome, skin cancer, small intestine cancer, stomach (gastric) cancer, supratentorial primitive neuroectodermal and pineal tumors, cutaneous t-cell lymphoma, testicular cancer, malignant thymoma, thyroid cancer, gestational trophoblastic tumor, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms' tumor.

[0129] In any of the embodiments of the invention, the cancer can be any cancer in any organ, for example, a cancer is selected from the group consisting of glioma, thyroid carcinoma, breast carcinoma, small-cell lung carcinoma, non-small-cell carcinoma, gastric carcinoma, colon carcinoma, gastrointestinal stromal carcinoma, pancreatic carcinoma, bile duct carcinoma, CNS carcinoma, ovarian carcinoma, endometrial carcinoma, prostate carcinoma, renal carcinoma, anaplastic large-cell lymphoma, leukemia, multiple myeloma, mesothelioma, and melanoma, and combinations thereof.

[0130] In accordance with other embodiments, the invention provides a method of potentiating or enhancing anticancer activity of an anticancer agent, the method comprising coadministering to a patient in need thereof an effective amount of an anticancer agent and a compound or salt as recited for the method for treating an APE1 mediated disease or disorder. The anticancer agent can be chosen from reversible DNA binders, DNA alkylators, DNA strand breakers, and disruptors of DNA replication.

[0131] Examples of suitable reversible DNA binders include topetecan hydrochloride, irinotecan (CPT11 - Camptosar), rubitecan, exatecan, nalidixic acid, TAS-103, etoposide, acridines (e.g., amsacrine, aminocrine), actinomycins (e.g., actinomycin D), anthracyclines (e.g., doxorubicin, daunorubicin), benzophenainse, XR 11576/MLN 576, benzopyridoindoles, Mitoxantrone, AQ4, Etopside, Teniposide, epipodophyllotoxins, and bisintercalating agents such as triostin A and echinomycin.

[0132] Examples of suitable DNA alkylators include sulfur mustard, the nitrogen mustards (e.g., mechlorethamine), chlorambucil, melphalan, ethyleneimines (e.g., triethylenemelamine, carboquone, diaziquone), methyl methanesulfonate, busulfan, CC-1065,

duocarmycins (e.g., duocarmycin A, duocarmycin SA), metabolically activated alkylating agents such as nitrosoureas (e.g., carmustine, lomustine, (2-chloroethyl)nitrosoureas), triazne antitumor drugs such as triazenoimidazole (e.g., dacarbazine), mitomycin C, leinamycin, and the like.

[0133] Examples of suitable DNA strand breakers include doxorubicin and daunorubicin (which are also reversible DNA binders), other anthracyclines, bleomycins, tirapazamine, enediyne antitumor antibiotics such as neocarzinostatin, esperamicins, calicheamicins, dynemicin A, hedarcidin, C-1027, N1999A2, esperamicins, zinostatin, and the like.

[0134] An example of a disruptor of DNA replication is 5-fluorodeoxyuridine, also known as floxuridine. 5-Fluorodeoxyuridine is an FDA-approved drug for the treatment of hepatic colon metastases and is known to have activity in multiple cancers, including ovarian cancer. See, e.g., Power DG et al., *Mol Cancer Ther* 2009;8:1015–25; Ardalan B,et al., *J Cancer Res Clin Oncol* 2004;130:561–6; Vokes EE, et al., *Cancer Chemother Pharmacol* 1991;28:69–73; Damascelli B et al., *Cancer* 1991;68:995–8; Leichman L et al., *J Clin Oncol* 1992;10:1933–42; Newman E et al., *Semin Oncol* 2005;32:S97–100; Muggia FM et al., *Gynecol Oncol* 1996;61:395–402; Brenner B et al., *Ann Oncol* 2006;17:1404–11; Israel VK et al., *Cancer Chemother Pharmacol* 1995;37:32–8; Muggia FM et al., *Chemother Pharmacol* 1991;28:241–50.

[0135] "Treatment" refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or pathological condition after it has begun to develop. As used herein, the term "ameliorating," with reference to a disease or pathological condition, refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease, a slower progression of the disease, an improvement in the overall health or well-being of the subject, or by other parameters well known in the art that are specific to the particular disease. Treatment of cancer can be evidenced, for example, by a reduction in tumor size, a reduction in tumor burden, a reduction in clinical symptoms resulting from the cancer, or other parameters well known in the art that are specific to the cancer. The phrase "treating a disease" refers to inhibiting the full development of a disease or condition, for example, in a subject who is at risk for a disease such as cancer, particularly a metastatic cancer.

[0136] By the term "coadminister" is meant that each of the at least two compounds be administered during a time frame wherein the respective periods of biological activity

overlap. Thus, the term includes sequential as well as coextensive administration of two or more drug compounds. The compounds can be administered simultaneously, separately (chronologically staggered), cyclically, or sequentially and in any order, e.g., before or after.

[0137] One skilled in the art will appreciate that suitable methods of utilizing a compound and administering it to a human for the treatment or prevention of disease states, in particular, cancer, which would be useful in the method of the present invention, are available. Although more than one route can be used to administer a particular compound, a particular route can provide a more immediate and more effective reaction than another route. Accordingly, the described methods are merely exemplary and are in no way limiting.

[0138] The dose administered to a mammal, particularly, a human, in accordance with the present invention should be sufficient to effect the desired response. Such responses include reversal or prevention of the bad effects of the disease for which treatment is desired or to elicit the desired benefit. One skilled in the art will recognize that dosage will depend upon a variety of factors, including the age, condition, and body weight of the human, as well as the source, particular type of the disease, and extent of the disease in the human. The size of the dose will also be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular compound and the desired physiological effect. It will be appreciated by one of skill in the art that various conditions or disease states may require prolonged treatment involving multiple administrations.

[0139] Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. The present inventive method typically will involve the administration of about 0.1 to about 300 mg of one or more of the compounds described above per kg body weight of the mammal.

[0140] The therapeutically effective amount of the compound or compounds administered can vary depending upon the desired effects and the factors noted above. Typically, dosages will be between 0.01 mg/kg and 250 mg/kg of the subject's body weight, and more typically between about 0.05 mg/kg and 100 mg/kg, such as from about 0.2 to about 80 mg/kg, from about 5 to about 40 mg/kg or from about 10 to about 30 mg/kg of the subject's body weight. Thus, unit dosage forms can be formulated based upon the suitable

ranges recited above and the subject's body weight. The term "unit dosage form" as used herein refers to a physically discrete unit of therapeutic agent appropriate for the subject to be treated.

[0141] Alternatively, dosages are calculated based on body surface area and from about 1 mg/m^2 to about 200 mg/m^2, such as from about 5 mg/m^2 to about 100 mg/m^2 will be administered to the subject per day. In particular embodiments, administration of the therapeutically effective amount of the compound or compounds involves administering to the subject from about 5 mg/m^2 to about 50 mg/m^2, such as from about 10 mg/m^2 to about 40 mg/m^2 per day. It is currently believed that a single dosage of the compound or compounds is suitable, however a therapeutically effective dosage can be supplied over an extended period of time or in multiple doses per day. Thus, unit dosage forms also can be calculated using a subject's body surface area based on the suitable ranges recited above and the desired dosing schedule.

[0142] The invention further provides a use of a compound or salt of the invention in the manufacture of a medicament for treating or preventing a disease. The medicament typically is a pharmaceutical composition as described herein.

[0143] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLES

[0144] General Chemistry. Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon or nitrogen in dried glassware. Indicated reaction temperatures refer to those of the reaction bath, while room temperature (rt) is noted as 25 °C. All solvents were of anhydrous quality purchased from Aldrich Chemical Co. and used as received. Commercially available starting materials and reagents were purchased from Aldrich and were used as received.

[0145] Analytical thin layer chromatography (TLC) was performed with Sigma Aldrich TLC plates (5 x 20 cm, 60 Å, 250 μm). Visualization was accomplished by irradiation under a 254 nm UV lamp. Chromatography on silica gel was performed using forced flow (liquid) of the indicated solvent system on Biotage KP-Sil pre-packed cartridges and using the Biotage SP-1 automated chromatography system. ^1H- and ^{13}C NMR spectra were recorded on a Varian Inova 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$ 7.26 ppm, 77.00 ppm, DMSO-d_6 2.49 ppm, 39.51 ppm for ^1H, ^{13}C respectively). Data are reported as follows: chemical shift, multiplicity

(s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Low resolution mass spectra (electrospray ionization) were acquired on an Agilent Technologies 6130 quadrupole spectrometer coupled to the HPLC system. High resolution mass spectral data was collected in-house using and Agilent 6210 time-of-flight mass spectrometer, also coupled to an Agilent Technologies 1200 series HPLC system. If needed, products were purified via a Waters semi-preparative HPLC equipped with a Phenomenex Luna™ C18 reverse phase (5 micron, 30 x 75 mm) column having a flow rate of 45 mL/min. The mobile phase was a mixture of acetonitrile (0.025% TFA) and H_2O (0.05% TFA), and the temperature was maintained at 50 °C.

[0146] Samples were analyzed for purity on an Agilent 1200 series LC/MS equipped with a Luna™ C18 reverse phase (3 micron, 3 x 75 mm) column having a flow rate of 0.8-1.0 mL/min over a 7-minute gradient and a 8.5 minute run time. Purity of final compounds was determined to be >95%, using a 3 μL injection with quantitation by AUC at 220 and 254 nm (Agilent Diode Array Detector).

[0147] APE1 qHTS Assay

[0148] Inhibition of APE1 activity was screened by utilizing double-stranded short substrate containing tetrahydrofuran (THF) abasic site labeled with rhodamine-type fluorophore (TAMRA) at the 5'-end and with non-fluoresscent Black Hole Quencher-2 (BHQ-2) at the opposing 3'-end. An increase in the fluorescence intensity due to incision of the basic site by APE1 was used to measure the enzyme activity. Three μL of enzyme were dispensed to 1536-well Greiner black solid bottom plates. Compounds (23 nL) were transferred via Kalypsys pintool. The plates were incubated for 15 min at room temperature, and then 1 μL of substrate solution was added to start the reaction. The plates were immediately transferred into ViewLux High-throughput CCD imager (Perkin-Elmer) in order to measure the reaction progress in kinetic mode (three reads every 60 sec) using 525 nm excitation and 498 nm emission fluorescence protocol. The fluorescence intensity difference between the third and the first time points was used to compute reaction progress. Reagents and Controls: Substrate: 50 nM final concentraton of TAMRA/BHQ-2 substrate dispensed throughout the plate. Enzyme: 0.75 nM APE1 final concentration in columns 1, 2, 5-48. Column 1 is neutral (100% activity). Control: Pintool transfer of control inhibitor NSC-13755 to column 2 of all assasy plates. Two-fold, 16 pt dilution in duplicate to produce final concentrations in the 5.75 μM – 0.175 nM range. Buffer columns in columns 3 and 4 were usd as negative control (no enzyme).

[0149] Radiotracer Incision Assay (RIA)

[0150] Recombinant wild type APE1 protein was purified as previously described (Erzberger et al., NAR, 1998). Fifty pg of APE1 (~140 pM) was incubated without (positive control containing 1% DMSO) or with 100 μM of the indicated inhibitor at room temperature in RIA buffer (50 mM Tris pH 7.5, 25 mM NaCl, 1 mM $MgCl_2$, 1 mM DTT, 0.01% Tween - 20) for 15 min. One-half pmol of 32P 5'-radiolabeled AP-DNA substrate (18 mer) was added to a 10 μL final volume (see Wilson et al., JBC, 1995), and the reactions were incubated at 37 °C for 5 min and stopped by adding stop buffer (0.05% Bromophenol blue/ Xylene cyanol dissolved in 95% formamide, 20 mM EDTA) and heating at 95 °C for 10 min. Intact substrate was separated from incised product on a 15% polyacrylamide denaturing gel in tris boric acid EDTA buffer. Following electrophoresis, the gel was subjected to standard phosphoimager analysis using the ImageQuant 5.2 software, and the percent incision activity (amount of substrate converted to product) was calculated. For IC50 determinations (i.e. the concentration of inhibitor at which 50% inactivation was observed), 50 pg of APE1 (~140 pM) was incubated without or with increasing concentrations (1 nM to 100 μM) of the indicated inhibitor as above and the percent incision activity was determined. IC50s were extrapolated from duplicate experimental sets after plotting the results using PRISM software.

[0151] Electrophoretic Mobility Shift Assay (EMSA)

[0152] Three hundred ng of APE1 (~0.8 μM) was incubated without inhibitor (positive control, 1% DMSO) or with increasing concentrations of inhibitor (1, 3, 10, 30 and 100 μM) in binding buffer (50 mM Tris pH 7.5, 25 mM NaCl, 1 mM EDTA, 1 mM DTT, 10% glycerol, 0.01% Tween 20) for 10 min on ice, and then radiolabeled ^{32}P AP-DNA substrate (100 fmol) was added to a 10 mL final volume. Following incubation on ice for 5 min, samples were subjected to non-denaturing polyacrylamide gel electrophoresis (20 mM Tris pH 7.5, 10 mM sodium acetate, 0.5 mM EDTA, 8% polyacrylamide, 2.5% glycerol) for 2 hr at 120 V in electrophoresis buffer (20 mM Tris pH 7.5, 10 mM sodium acetate, 0.5 mM EDTA) to separate the APE1-DNA complex from unbound radiolabeled DNA (see Wilson et al., NAR, 1997). After electrophoresis, the gel was subjected to standard phosphoimager analysis as above, and the percentage of substrate DNA in complex with APE1 was determined.

[0153] Enzyme Kinetic Studies

[0154] Ten pg of APE1 (~28 pM) was incubated without (positive control, 1% DMSO) or with 5 μM of the indicated inhibitor at room temperature in RIA buffer (see above) for 15 min. Varying concentrations of 32P radiolabeled AP-DNA substrate (i.e. 5, 10, 25, 50, or 100 nM) were then added to a 10 mL final volume, and the reactions were incubated at 37 °C for 5 min, stopped, and analyzed as above. Lineweaver – Burk plots of 1/V versus 1/[S] were used to determine KM and kcat, and the mode of inhibition.

[0155] HeLa Whole Cell Extract Incision Assays

[0156] HeLa cells maintained in DMEM with 10% fetal bovine serum and 1% Penicillin-Streptomycin were harvested, washed with 1X PBS, and re-suspended in hypotonic ice cold lysis buffer (50 mM Tris pH 7.4, 1 mM EDTA, 1 mM DTT, 10% glycerol, 0.5 mM PMSF). The suspension was frozen at -80 °C for at least 30 min and then slowly thawed at 4 °C for ~1 hr. KCl was then added to the cell suspension to a final concentration of 222 mM, followed by incubation on ice for 30 min and clarification by centrifugation at 12,000 xg for 15 min at 40C. The supernatant (whole cell extract) was retained, the protein concentration determined using the Bio-Rad Bradford reagent, and aliquots stored until needed at -80 °C.

[0157] Three hundred ng of HeLa whole cell extract was incubated with 0, 50 or 100 mM of the indicated inhibitor at room temperature for 15 min. prior to the addition of 0.5 pmol of 32P radiolabeled AP-DNA substrate (final volume of 10 μL). The reaction mix was then transferred to 37 °C for 5 min. to allow for incision. Following addition of stop buffer and heat denaturation, the reaction products were analyzed as above.

EXAMPLE 1

[0158] This Example illustrates a general procedure for the synthesis of 3,6-disubstituted-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-amine (Procedure A): A mixture of appropriate ketone (1 mmol, 1 eq), substituted acetonitrile (1 mmol, 1 eq), sulfur (1 mmol, 1 eq) in ethanol (0.2 molar reaction concentration) was added morpholine (1 mmol, 1 eq) and stirred under reflux for 0.5 to 1 h. Excess solvent was removed under diminished pressure. The product was purified on a Biotage™ silica gel column or by recrystallization.

EXAMPLE 2

[0159] This Example illustrates a general procedure for acylation (Procedure B): A mixture of appropriate amine (1 mmol, 1 eq) and Hunig's base (2 mmol, 2 eq) in dichloromethane (0.2 molar reaction concentration) was added acetyl chloride/substituted acid chlorides (1.5 mmol, 1.5 eq) at 0 °C and then stirred at room temperature for 1 h. Excess

solvent was removed under diminished pressure and the residue was purified on a Biotage™ silica gel column. Elution with 10-20 % ethyl acetate in hexanes gave the pure products.

EXAMPLE 3

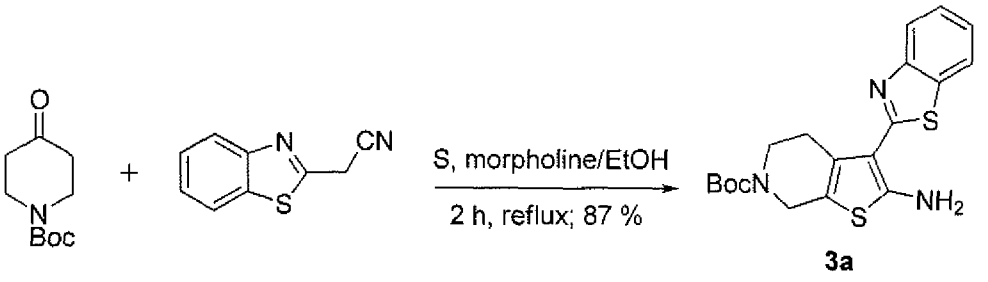
[0160] This Example illustrates a general Procedure for the deprotection of Boc (Procedure C): To the boc-protected amine (2.328 mmol) in dichloromethane (15 mL) was added TFA (5 mL) and the resulting mixture was stirred at room temperature for 1 h. Excess solvent was evaporated, neutralized with 10 % sodium bicarbonate and the product was collected by filtration or purified on a preparative HPLC (for compound being tested).

EXAMPLE 4

[0161] This Example illustrates a general Procedure for reductive amination (Procedure D): A mixture of the appropriate amine (1 mmol, 1 eq) and acetone/appropriate carbonyl compound (10 mmol, 10 eq) in a mixture of MeOH/THF (4/2 mL, 0.2 molar reaction concentration) was added sodium cyanoborohydride (3 mmol, 3 eq) and few drops of acetic acid. The reaction mixture was stirred at room temperature for 6-10 h. Volatiles were removed and the crude solid was purified on a preparative HPLC.

EXAMPLE 5

[0162] This Example illustrates a synthesis of t-butyl 2-amino-3-(benzo[d]thiazol-2-yl)-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate: This compound was prepared following Procedure A. A mixture of 1-boc-4-piperidone (1.5 g, 7.53 mmol, 1 eq), 2-(benzo[d]thiazol-2-yl)acetonitrile (1.312 g, 7.53 mmol, 1 eq), sulfur (0.241 g, 7.53 mmol, 1 eq) in EtOH (30 mL) was added morpholine (0.66 mL, 7.53 mmol, 1 eq) and stirred under reflux for 1 h. Excess solvent was removed under diminished pressure. The product was purified on a Biotage™ silica gel column. Elution with 5-40% ethyl acetate in hexanes gave the product. Yield: 87 % (2.55 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.44 (s, 9 H), 2.84 (m, 2 H), 3.66 (t, J = 5.4 Hz, 2 H), 4.36 (s, 2 H), 7.31 (t, J = 7.6 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 1 H), 7.89 (d, J = 8.0 Hz, 1 H), 8.00 (d, J = 7.8 Hz, 1 H) and 8.14 (s, 2 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{19}H_{22}N_3O_2S_2$, 388.1159; found 388.1153.



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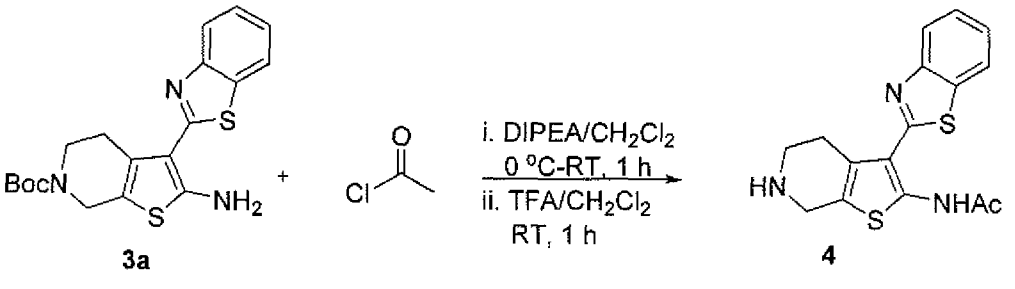
EXAMPLE 6

[0163] Ths Example illustrates a general procedure for acetylation: This compound was prepared following Procedure B. A mixture of tert-butyl 2-amino-3-(benzo[d]thiazol-2-yl)-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (1.6 g, 4.13 mmol, 1 eq) and Hunig's base (1.4 mL, 8.26 mmol, 2 eq) in dichloromethane (25 mL) was added acetyl chloride (0.35 mL, 4.95 mmol, 1.5 eq) at 0 °C and then stirred at room temperature for 1 h. Excess solvent was removed under diminished pressure and the residue was purified on a Biotage® silica gel column. Elution with 10% ethyl acetate in hexanes gave the product. Yield: 91 % (1.62 g).

[0164] To the above product (1 g, 2.328 mmol) in dichloromethane (15 mL) was added TFA (5 mL) and the resulting mixture was stirred at room temperature for 1 h (Procedure C). Excess solvent was evaporated, neutralized with 10 % sodium bicarbonate and the precipitate was collected by filtration. The product was dried to provide a yellow solid. Yield: 99 % (0.76 g).

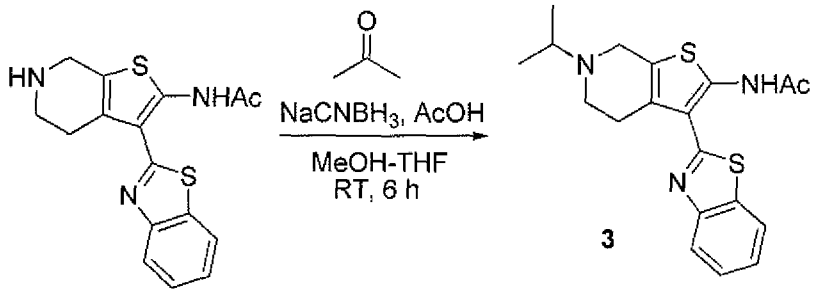
[0165] LC-MS: rt (min) = 2.95 (4.5 min run); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 3 H), 2.78 (m, 2 H), 3.02 (t, J = 5.6 Hz, 2 H), 3.80 (s, 2 H), 7.41 - 7.48 (m, 1 H), 7.53 - 7.60 (m, 1 H) and 8.11 (t, J = 7.8 Hz, 2 H); HRMS (ESI) m/z (M+Na)+ calcd. for C16H16N3OS2, 330.0741; found 330.0736.



EXAMPLE 7

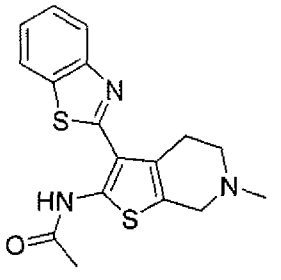
[0166] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**3**): This compound was prepared following Procedure D. N-(3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (0.1 g, 0.304 mmol, 1 eq) and acetone (0.22 mL, 3.04 mmol, 10 eq) in a mixture of MeOH/THF (4/2 mL) was treated with sodium cyanoborohydride (0.057 g, 0.911 mmol, 3 eq) and a few drops of acetic acid. The reaction mixture was stirred at room temperature for 6 h. Volatiles were removed and the crude solid was purified on a preparative HPLC. Yield: 75 % (0.11 g).

[0167] LC-MS: rt (min) = 4.42; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (d, J = 6.3 Hz, 6 H), 2.36 (s, 3 H), 3.29 - 3.55 (m, 2 H), 3.65 – 3.74 (m, 1 H), 4.55 – 4.61 (m, 2 H), 4.72 (s, 2 H), 7.49 (t, J = 7.6 Hz, 1 H), 7.60 (t, J = 7.7 Hz, 1 H), 8.16 (dd, J = 8.0 and 3.7 Hz, 2 H) and 12.06 (s, 1H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{19}H_{22}N_3OS_2$, 372.1203; found 372.1199.



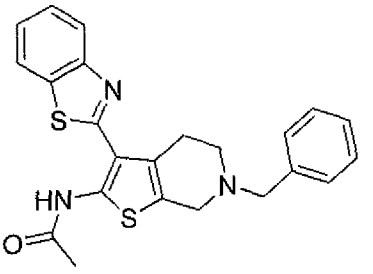
EXAMPLE 8

[0168] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**6**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 4.24; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3 H), 2.98 (s, 3 H), 3.21 - 3.29 (m, 2 H), 3.49 – 3.65 (m, 2 H), 4.45 (s, 2 H), 7.50 (t, J = 7.6 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 8.19 (m, 2 H), and 12.51 (s, 1 H); HRMS (ESI) m/z (M+Na)+ calcd. for $C_{17}H_{17}N_3OS_2Na$, 366.0705; found 366.0702.



EXAMPLE 9

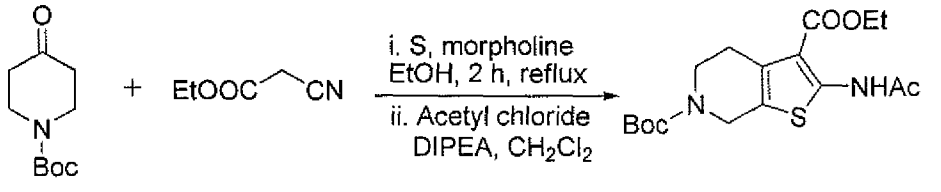
[0169] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**7**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 4.88; ^{1}H NMR (400 MHz, DMSO-d6) δ 2.32 (s, 3 H), 2.84 (t, J = 5.5 Hz, 2 H), 2.89 – 2.95 (m, 2 H), 3.57 (s, 2 H), 3.71 (s, 2 H), 7.25 - 7.32 (m, 1 H), 7.33 - 7.41 (m, 4 H), 7.46 (t, J = 7.8 Hz, 1 H), 7.58 (t, J = 7.8 Hz, 1 H), 8.14 (d, J = 8.4 Hz, 2 H) and 12.59 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{23}H_{22}N_3OS_2$, 420.1210; found 420.1207.



7

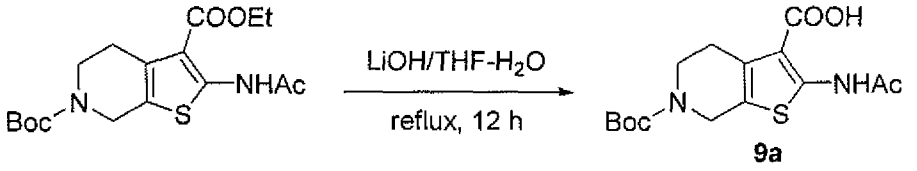
EXAMPLE 10

[0170] This Example illustrates a synthesis of 6-tert-butyl 3-ethyl 2-acetamido-4,5-dihydrothieno[2,3-c]pyridine-3,6(7H)-dicarboxylate: This compound was prepared following the general procedure A (Yield after recrystallization from ethanol, 84%) (Reference 1) and Procedure B (Yield after purification on a Biotage™ silica gel column with 10 % ethyl acetate in hexanes, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, J = 7.1 Hz, 3 H), 1.41 (s, 9 H), 2.24 (s, 3 H), 2.73 - 2.81 (m, 2 H), 3.55 (t, J = 5.3 Hz, 2 H), 4.28 (q, J = 7.1 Hz, 2 H), 4.43 (s, 2 H) and 10.94 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{25}N_2O_5S$, 369.1490; found 369.1477.



EXAMPLE 11

[0171] This Example illustrates a synthesis of 2-acetamido-6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (**9a**): To a solution of 6-tert-butyl 3-ethyl 2-amino-4,5-dihydrothieno[2,3-c]pyridine-3,6(7H)-dicarboxylate (1 mmol, 1 eq) in THF (4 mL) was added a solution of lithium hydroxide in water (1 mL) and refluxed for 12 h. Reaction mixture was neutralized (pH = 7) with 10 % HCl. The precipitate was collected by filtration and dried under vacuum. The crude product was acetylated following Procedure B. The crude acetylated product was purified on a Biotage™ silica gel column. Elution with 40 % ethyl acetate (contains 0.05 % acetic acid) in hexanes. Yield 65 %. ^{1}H NMR (400 MHz, DMSO-d_6); δ 1.41 (s, 9 H), 2.22 (s, 3 H), 2.74 – 2.79 (m, 2 H), 3.54 (t, J = 5.5 Hz, 2 H), 4.42 (s, 2 H), 11.14 (s, 1 H) and 13.17 (br, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{15}H_{21}N_2O_5S$, 341.1177; found 341.1167.



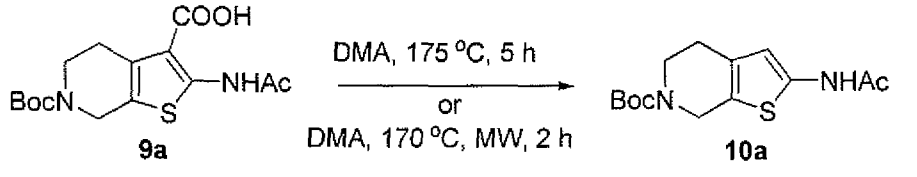
9a

EXAMPLE 12

[0172] This Example illustrates a synthesis of tert-butyl 2-acetamido-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (**10a**). Method I: A solution of 2-acetamido-6-(t-butoxycarbonyl)-4,5,6,7-tetrahydro- thieno[2,3-c]pyridine-3-carboxylic acid (1.5 g, 4.41 mmol) in dimethylacetamide (9 mL) was heated in MW for 2 h at 170 °C. The product was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. The crude residue obtained after evaporation of the solvent was purified on a Biotage™ silica gel column. Elution with 50 % ethyl acetate in hexanes gave the pure product. Yield: 77 % (1.306 g).

[0173] Method II: A solution 2-acetamido-6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (6 g, 17.63 mmol) in DMA (35 mL) was stirred at 175 °C for 5 h in an open round bottomed flask. The reaction was then worked up and purified as described for Method I. Yield: 65 % (3.4 g).

[0174] LC-MS: rt (min) = 5.18; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 (s, 9 H), 2.03 (s, 3 H), 2.50 - 2.54 (m, 2 H), 3.55 (t, J = 5.7 Hz, 2 H), 4.41 (s, 2 H), 6.33 (s, 1 H) and 10.99 (s, 1 H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 22.5, 24.8, 28.0, 79.1, 109.9, 121.9, 129.9, 137.7, 153.9 and 166.1.



9a 10a

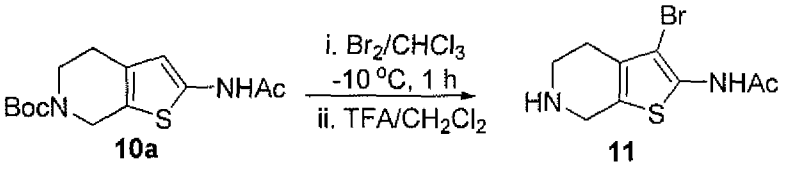
EXAMPLE 13

[0175] This Example illustrates a synthesis of tert-butyl 2-acetamido-3-bromo-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (**11**): A solution of tert-butyl 2-acetamido-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (1.98 g, 6.68 mmol, 1eq) in chloroform (67 mL) was added bromine (0.344 mL, 6.68 mmol, 1 eq) in chloroform (10 mL) at -10 oC over a period of 1 h (faster addition removes the Boc group). After completion of the addition, the reaction mixture was diluted with chloroform and the organic layer was washed with sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate

and concentrated. The crude product was purified on a Biotage™ silica gel column. Elution with 25 % ethyl acetate in hexanes gave the pure product. Yield: 70 % (1.76 g).

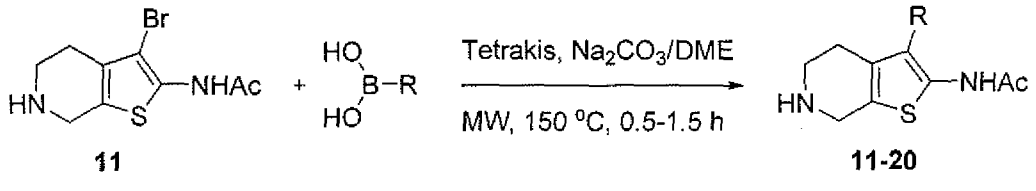
[0176] LC-MS: rt (min) = 3.60 (4.5 min run); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 1.60 (br. s., 1 H), 2.26 (s, 3 H), 2.53 – 2.59 (m, 2 H), 3.67 – 3.72 (m, 2 H), 4.53 (s, 2 H) and 7.8 (s, 1H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{14}H_{20}BrN_2O_3S$, 375.0384; found 375.0375.

[0177] The above product was deprotected with TFA using general procedure C to get the compound (11). LC-MS: rt (min) = 2.64; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 3 H), 2.40 - 2.49 (m, 2 H), 3.12 (t, J = 5.7 Hz, 2 H), 3.94 (s, 2 H) and 10.32 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_9H_{12}BrN_2OS$, 274.9860; found 274.9855.



EXAMPLE 14

[0178] This Example illustrates a general procedure for Suzuki coupling: A mixture of N-(3-bromo-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (0.05g, 0.182 mmol, 1 eq), appropriate boronic acid or pinacol ester (0.273 mmol, 1.5 eq) and a 2M solution of sodium carbonate (2-4 eq) in dimethoxy ethane (2 mL) was bubbled with argon for 5 minutes. Tetrakis (5-10 mol %) was then added and heated in microwave at 150 °C for 0.5-1.5 h. The solvent was evaporated in a blow down unit. The residue was re-dissolved in 2 mL DMF, filtered through thiol cartridge and purified in a preparative HPLC.

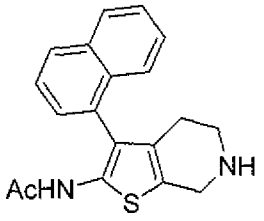


EXAMPLE 15

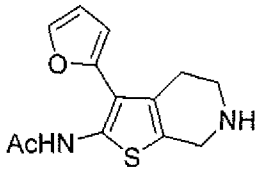
[0179] The following compounds were prepared in accordance with the method of Example 14.

[0180] N-(3-(naphthalen-1-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**12**): LC-MS: rt (min) = 3.79; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (s, 3 H), 2.13 - 2.34 (m, 2 H), 3.30 – 3.38 (m, 2 H), 4.31 - 4.39 (m, 2 H), 7.33 (d, J = 6.1 Hz, 1 H), 7.40 - 7.51 (m,

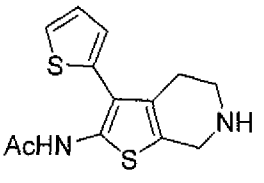
2 H), 7.53 - 7.64 (m, 2 H), 8.02 – 8.04 (m, 2 H) and 10.06 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{19}H_{20}N_2OS$, 323.1213; found 323.1215.



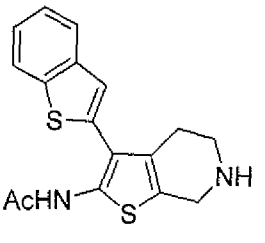
[0181] N-(3-(furan-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**13**): LC-MS: rt (min) = 3.07; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.16 (s, 3 H), 2.78 - 2.86 (m, 2 H), 3.39 – 3.45 (m, 2 H), 4.28 (s, 2 H), 6.58 - 6.66 (m, 2 H), 7.76 – 7.85 (m, 1 H), and 10.26 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{13}H_{15}N2O_2S$, 263.0849; found 263.0849.



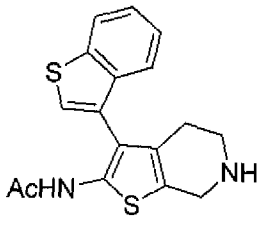
[0182] N-(3-(thiophen-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**14**): LC-MS: rt (min) = 3.14; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.06 (s, 3 H), 2.63 - 2.72 (m, 2 H), 3.01 – 3.30 (m, 3 H), 4.23 - 4.33 (m, 2 H), 7.04 - 7.12 (m, 1 H), 7.17 - 7.25 (m, 1 H), 7.64 - 7.71 (m, 1 H) and 10.24 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{13}H_{15}N_2OS_2$, 279.062; found 279.0618.



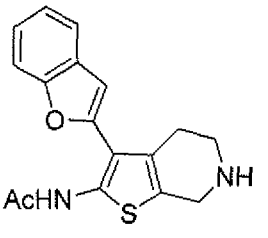
[0183] N-(3-(benzo[b]thiophen-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**15**): LC-MS: rt (min) = 3.94; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.07 (s, 3 H), 2.72 – 2.76 (m, 2 H), 3.32 - 3.43 (m, 2 H), 4.30 (s, 2 H), 7-37 - 7.41 (m, 3 H), 7.86 - 7.93 (m, 1 H), 7.98 - 8.05 (m, 1 H) and 10.48 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{17}N_2OS_2$, 329.0777; found 329.0767.



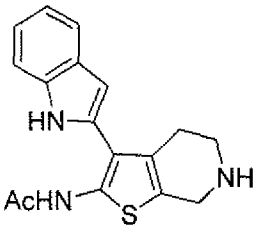
[0184] N-(3-(benzo[b]thiophen-3-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**16**): LC-MS: rt (min) = 3.79; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95 (s, 3 H), 2.32 – 2.46 (m, 2 H), 3.35 - 3.41 (m, 2 H), 4.32 (s, 2 H), 7.25 - 7.35 (m, 1 H), 7.36 - 7.47 (m, 2 H), 7.73 (s, 1H), 8.01 - 8.13 (m, 1 H) and 10.23 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{17}N_2OS_2$, 329.0777; found 329.0773.



[0185] N-(3-(benzofuran-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**17**): LC-MS: rt (min) = 3.89; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (s, 3 H), 2.85 - 2.94 (m, 2 H), 3.38 - 3.47 (m, 2 H), 4.31 (s, 2 H), 7.04 (s, 1 H), 7.31 (ddd, J = 12.7, 7.6 and 1.2 Hz, 2 H), 7.62 (d, J = 7.8 Hz, 1 H), 7.68 (d, J = 7.2 Hz, 1 H) and 10.57 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{17}N_2O_2S$, 313.1005; found 313.1006.



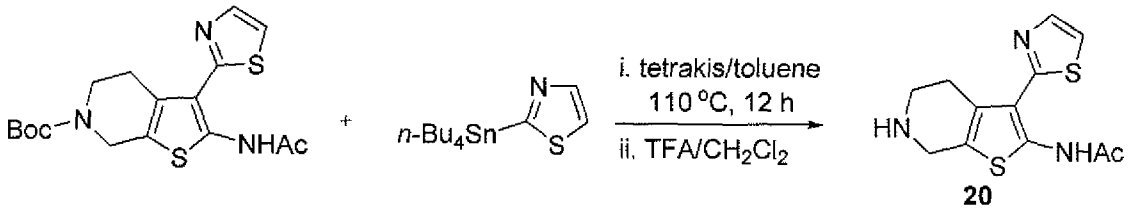
[0186] N-(3-(1H-indol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**18**): LC-MS: rt (min) = 3.77; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.08 (s, 3 H), 2.72 - 2.80 (m, 2 H), 3.34 - 3.43 (m, 2 H), 4.31 (s, 2 H), 6.43 - 6.48 (m, 1 H), 6.99 - 7.05 (m, 1 H), 7.08 - 7.15 (m, 1 H), 7.38 - 7.43 (m, 1 H), 7.54 - 7.59 (m, 1 H), 10.39 (m, 1 H) and 11.19 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{17}N_3OS$, 312.1165; found 312.1165.



EXAMPLE 16

[0187] This Example illustrates a synthesis of N-(3-(thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**20**): A mixture of t-butyl 2-acetamido-3-bromo-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (0.1 g, 0.266 mmol, 1 eq) and 2-

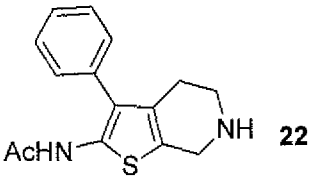
(tributylstannyl)thiazole (0.084 ml, 0.266 mmol, 1 eq) in toluene (2 ml) was bubbled with argon for 5 minutes. Tetrakis (0.031 g, 0.027 mmol, 0.1 eq) was then added and stirred for 12 h at 110 oC. Excess solvent solvent was removed and the residue was dissolved in DCM and treated with TFA. The crude product was finally purified on a preparative HPLC. LC-MS: rt (min) = 3.35; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.26 (s, 3 H), 3.03 - 3.11 (m, 2 H), 3.07 (t, J = 5.7 Hz, 2 H), 4.49 (t, J = 5.7 Hz, 2 H), 7.85 (d, J = 3.3 Hz, 1 H), 8.06 (d, J = 3.3 Hz, 1 H) and 12.34 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{12}H_{14}N_3OS_2$, 280.0573; found 280.0573.



EXAMPLE 17

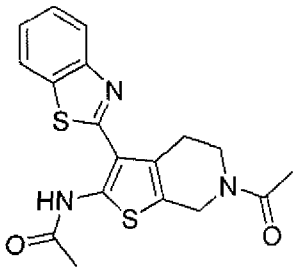
[0188] This Example illustrates several embodiments of the invention.

[0189] N-(3-phenyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**22**): LC-MS: rt (min) = 3.25; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01 (s, 3 H), 2.53 - 2.59 (m, 2 H), 3.31 – 3.36 (m, 2 H), 4.29 (s, 2 H), 7.26 (d, J = 7.0 Hz, 2 H), 7.38 - 7.42 (m, 1 H), 7.45 – 7.51 (m, 2 H) and 10.10 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{16}H_{17}N_2OS$, 273.1056; found 273.1056.

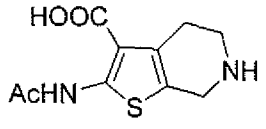


22

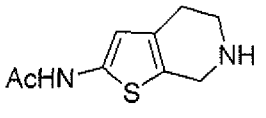
[0190] N-(6-acetyl-3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**8**): This compound was prepared by acetylation of N-(3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide with acetyl chloride. LC-MS: rt (min) = 5.87; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (s, 3 H), 2.33 (s, 3 H), 2.89 – 2.95 (m, 2 H), 3.01 - 3.06 (m, 2 H), 4.63 (s, 2 H), 7.47 (t, J = 7.5 Hz, 1 H), 7.59 (t, J = 7.6 Hz, 1 H), 8.16 (dd, J = 7.9 and 3.81 Hz, 2 H) and 12.53 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{18}H_{18}N_3O2S_2$, 372.0835; found 372.0826.



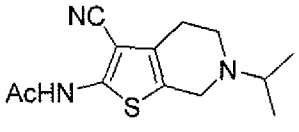
[0191] 2-Acetamido-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (**9**): This compound was prepared by de-protecting **9a** using procedure C. LC-MS: rt (min) = 3.25; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 2.99 (t, J = 5.5 Hz, 2 H), 3.33 - 3.40 (m, 2 H), 4.24 (s, 2 H), 11.19 (s, 1 H) and 13.44 (br, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{10}H_{13}N_2O_3S$, 241.0641; found 241.0640.



[0192] N-(4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**10**): This compound was prepared by de-protecting 10a using procedure C. LC-MS: rt (min) = 1.33; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.05 (s, 3 H), 2.76 (t, J = 5.8 Hz, 2 H), 3.35 (t, J = 6.2 Hz, 2 H), 4.22 (s, 2 H), 6.40 (s, 1 H) and 11.19 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_9H_{13}N_2OS$, 197.0743; found 197.0744.

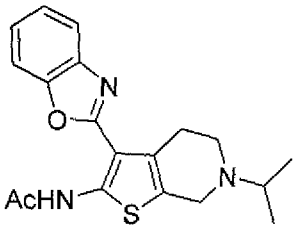


[0193] N-(3-cyano-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**21**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 2.78; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (d, J = 5.5 Hz, 6 H), 2.22 (s, 3 H), 2.88 - 2.95 (m, 2 H), 3.39 – 3.45 (m, 1H), 3.63 - 3.80 (m, 2 H), 4.31 – 4.47 (m, 2 H), and 11.93 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{13}H_{18}N_3OS$, 264.1165; found 264.1165.

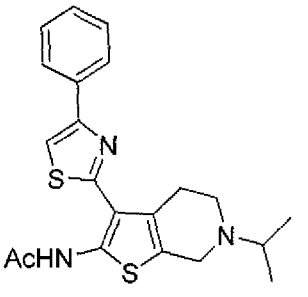


[0194] N-(3-(benzo[d]oxazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**23**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 4.24; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 (d, J = 6.5 Hz, 6 H), 2.32 (s, 3 H), 2.76 - 2.82 (m, 2 H), 2.84 - 2.95 (m, 1 H), 2.96 - 3.05 (m, 2 H), 3.61 (s, 2 H), 7.38 - 7.46 (m, 2 H), 7.73 -

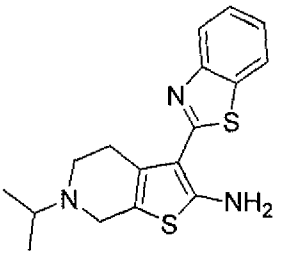
7.78 (m, 1 H), 7.79 - 7.84 (m, 1 H) and 11.65 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{19}H_{22}N_3O_2S$, 356.1439; found 356.1430.



[0195] N-(6-isopropyl-3-(4-phenylthiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (**24**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 4.72; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, J = 5.3 Hz, 6 H), 2.33 (s, 3 H), 3.13 - 3.22 (m, 1 H), 3.24 - 3.32 (m, 2 H), 3.64 – 3.89 (m, 2 H), 4.40 – 4.55 (m, 2 H), 7.39 - 7.47 (m, 1 H), 7.53 (t, J = 7.6 Hz, 2 H), 8.03 (d, J = 7.4 Hz, 2 H), 8.24 (s, 1 H) and 12.42 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{21}H_{24}N_3OS_2$, 398.1367; found 398.1361.

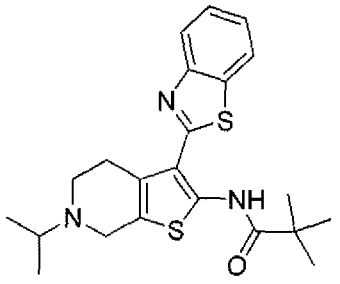


[0196] 3-(Benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-amine (**25**): This compound was prepared following Procedures A, C and D. LC-MS: rt (min) = 4.88; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (d, J = 6.3 Hz, 6 H), 3.11 (t, J = 5.4 Hz, 2 H), 3.43 - 3.52 (m, 2 H), 3.57 (m, 1 H), 4.23 (s, 2 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 8.04 (d, J = 7.8 Hz, 1 H) and 9.26 (br, 2 H), HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{20}N_3S_2$, 330.1105; found 330.110.



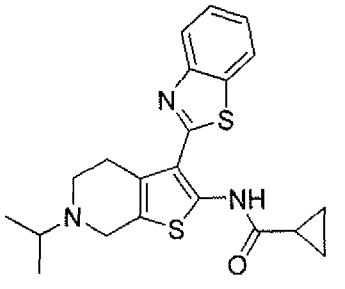
[0197] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)pivalamide (**126**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 4.82; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 - 1.41 (m, 15 H), 3.21 - 3.31 (m, 1 H), 3.38 - 3.48 (m, 2 H), 3.67 - 3.94 (m, 2 H), 4.40 - 4.61 (m, 2 H), 7.52 (t, J = 7.6 Hz, 1 H), 7.64

(t, J = 7.7 Hz, 1 H), 8.01 (d, J = 8.0 Hz, 1 H), 8.22 (d, J = 7.8 Hz, 1 H) and 13.24 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{22}H_{28}N_3OS_2$, 414.168; found 414.1677.



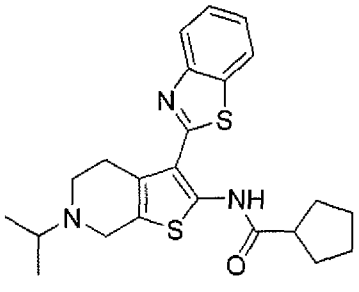
126

[0198] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)cyclopropanecarboxamide (**127**): This compound was prepared following Procedures A-D. LC-MS: rt (min) =4.82 ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 - 1.06 (m, 4 H), 1.35 (br. s., 6 H), 2.11 - 2.19 (m, 1 H), 3.16 - 3.29 (m, 1 H), 3.36 - 3.46 (m, 2 H), 3.64 - 3.92 (m, 2 H), 4.36 - 4.60 (m, 2 H), 7.51 (t, J = 7.5 Hz, 1 H), 7.62 (t, J = 7.6 Hz, 1 H), 8.21 (t, J = 8.2 Hz, 2 H) and 12.84 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{21}H_{24}N_3OS_2$, 398.1355; found 398.1358.



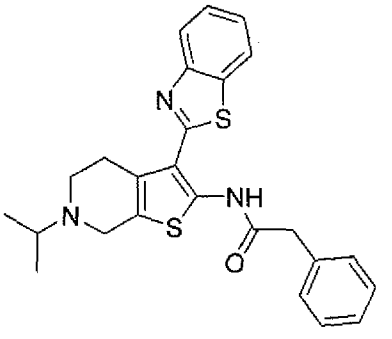
127

[0199] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)cyclopentanecarboxamide (**128**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 5.31; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, J = 5.7 Hz, 6 H), 1.64 - 1.79 (m, 4 H), 1.79 - 1.90 (m, 2 H), 2.03 - 2.13 (m, 2 H), 3.13 (quin, J = 8.1 Hz, 1 H), 3.21 - 3.30 (m, 1 H), 3.36 - 3.44 (m, 2 H), 3.66 - 3.93 (m, 2 H), 4.39 - 4.61 (m, 2 H), 7.51 (t, J = 7.5 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 8.09 - 8.24 (m, 2 H) and 12.81 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{23}H_{28}N_3OS_2$, 426.168; found 426.1678.



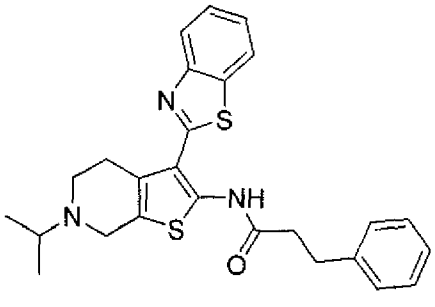
128

[0200] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-2-phenylacetamide (**129**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 5.15; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, J = 5.3 Hz, 6 H), 3.17 - 3.25 (m, 1 H), 3.26 – 3.39 (m, 2 H), 3.66 - 3.91 (m, 2 H), 4.04 (s, 2 H), 4.37 - 4.60 (m, 2 H), 7.32 - 7.40 (m, 1 H), 7.40 - 7.52 (m, 5 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 8.16 (d, J = 8.0 Hz, 1 H) and 12.52 (s, 1 H) HRMS (ESI) m/z (M+H)+ calcd. for $C_{25}H_{26}N_3OS_2$, 448.1523; found 448.1521.



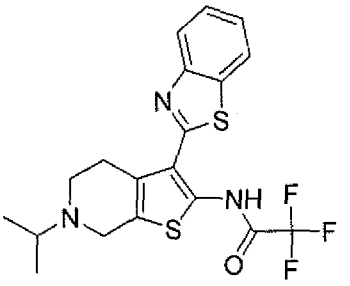
129

[0201] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-3-phenylpropanamide (**130**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 5.35; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, J = 5.7 Hz, 6 H), 2.95 - 3.01 (m, 2 H), 3.02 - 3.09 (m, 2 H), 3.16 - 3.27 (m, 1 H), 3.37 – 3.46 (m, 2 H), 3.67 - 3.92 (m, 2 H), 4.35 - 4.60 (m, 2 H), 7.11 - 7.20 (m, 1 H), 7.22 - 7.36 (m, 4 H), 7.50 (t, J = 7.6 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 8.17 (dd, J = 16.0 and 8.0 Hz, 2 H) and 12.59 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{26}H_{28}N_3OS_2$, 462.1658; found 462.1661.



130

[0202] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-2,2,2-trifluoroacetamide (**131**): This compound was prepared following Procedure A followed by EDC coupling with TFA and then Procedures C-D. LC-MS: rt (min) = 5.18; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (dd, J = 6.3 and 3.3 Hz, 6 H), 3.23 - 3.446 (m, 3 H, merged in water peak), 3.55 - 3.88 (m, 2 H), 4.41 – 4.58 (m, 2 H), 7.38 - 7.55 (m, 2 H) and 7.76 - 8.25 (m, 2 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{19}H_{19}F_3N_3OS_2$, 426.0925; found 426.0926.



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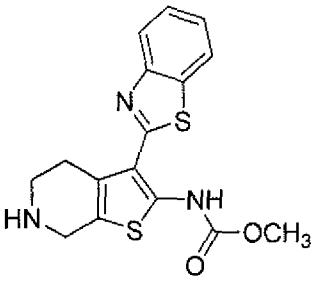
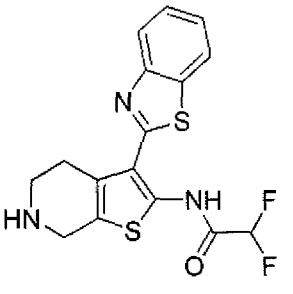
[0203] Methyl 3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-ylcarbamate (**32**): This compound was prepared following Procedures A-C. LC-MS: rt (min) = 4.24; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.14 - 3.22 (m, 2 H), 3.46 - 3.54 (m, 2 H), 3.83 (s, 3 H), 4.36 (s, 2 H), 7.49 (t, J = 7.5 Hz, 1 H), 7.59 (t, J = 7.6 Hz, 1 H), 8.05 (d, J = 8.0 Hz, 1 H), 8.18 (d, J = 8.0 Hz, 1 H), 9.29 (br. 1 H) and 11.88 (br, 1H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{16}H_{16}N_3O_2S_2$, 346.0678; found 346.0683.

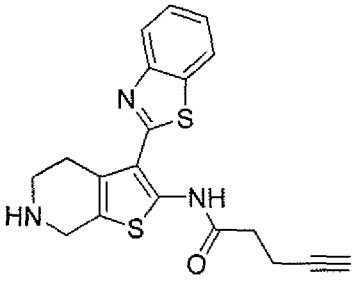


[0204] N-(3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-2,2-difluoro -acetamide (**33**): This compound was prepared following Procedure A followed by EDC coupling with difluoroacetic acid and then Procedures C. LC-MS: rt (min) = 4.69; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.18 - 3.28 (m, 2 H), 3.55 (t, J = 5.8 Hz, 2 H), 4.41 (s, 2 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.63 (t, J = 7.5 Hz, 1 H), 8.02 (d, J = 8.0 Hz, 1 H), 8.22 (d, J = 7.8 Hz, 1 H) and 13.64 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{16}H_{14}F_2N_3OS_2$, 366.055; found 366.0546.

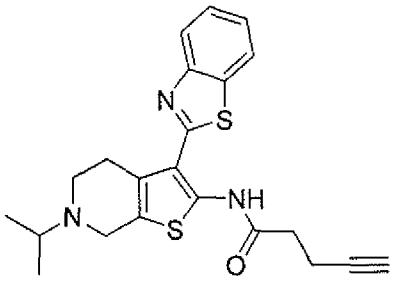


[0205] N-(3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)pent-4-ynamide (**34**): This compound was prepared following Procedure A-C. LC-MS: rt (min) = 4.58; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.56 - 2.71 (m, 2 H), 2.82 - 2.90 (m, 3 H), 3.14 - 3.23 (m, 2 H), 3.49 – 3.55 (m, 2 H), 4.36 (s, 2 H), 7.50 (t, J = 7.7 Hz, 1 H), 7.62 (t, J = 7.7

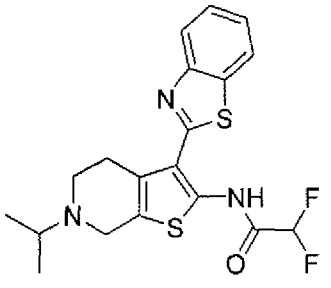
Hz, 1 H), 8.19 (dd, J = 8.1 and 2.5 Hz, 2 H) and 12.64 (s, 1 H); HRMS (ESI) m/z (M+Na)+ calcd. for $C_{19}H_{17}N_3OS_2Na$, 390.0705; found 390.0707.



[0206] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)pent-4-ynamide (**35**): This compound was prepared following Procedure A-D. LC-MS: rt (min) = 4.76; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, J = 5.4 Hz, 6 H), 2.60 (td, J = 7.0 and 2.4 Hz, 2 H), 2.83 - 2.95 (m, 3 H), 3.17 - 3.28 (m, 1 H), 3.67 - 3.91 (m, 2 H), 4.40 - 4.63 (m, 2 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.62 (t, J = 7.6 Hz, 1 H), 8.20 (dd, J = 8.0 and 3.7 Hz, 2 H) and 12.63 (s, 1 H); HRMS (ESI) m/z (M+Na)+ calcd. for $C_{22}H_{24}N_3OS_2$, 410.1355; found 410.1355.

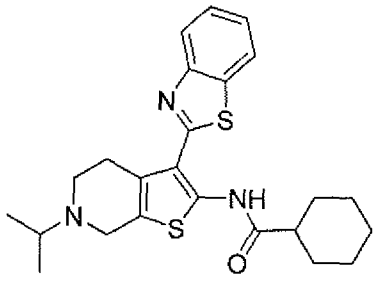


[0207] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-2,2-difluoroacetamide(**36**): This compound was prepared following Procedure A followed by EDC coupling with difluoroacetic acid and then Procedures C-D. LC-MS: rt (min) = 4.87; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (d, J = 5.3 Hz, 6 H), 3.20 - 3.29 (m, 1 H), 3.65 - 3.95 (m, 2 H), 4.47 – 4.61 (m, 2 H), 7.50 - 7.69 (m, 2 H), 8.00 - 8.29 (m, 2 H) and 13.63(m, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{19}H_{20}N_3OS_2$, 408.101; found 408.101.

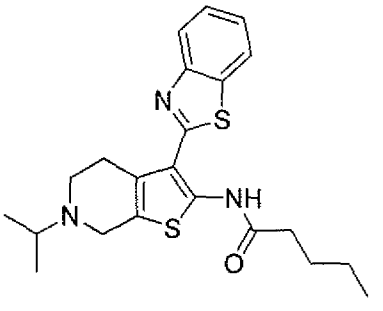


[0208] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)cyclohexanecarboxamide (**37**): This compound was prepared following Procedure A-D.

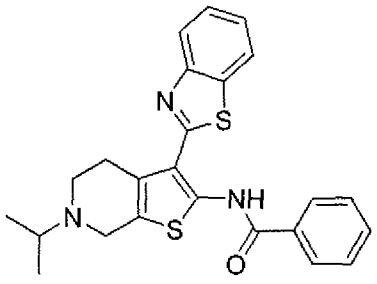
LC-MS: rt (min) = 5.51; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 - 1.62 (m, 12 H), 1.74 - 1.87 (m, 2 H), 2.04 – 2.10 (m, 2 H), 2.58 - 2.67 (m, 1 H), 3.26 - 3.34 (m, 3 H), 3.52 - 3.85 (m, 2 H), 4.02 – 4.45 (m, 2 H), 7.50 (t, J = 7.5 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 8.01 - 8.23 (m, 2 H) and 12.89 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{24}H_{30}N_3OS_2$, 440.1825; found 440.1823.



[0209] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)pentanamide (**38**): This compound was prepared following Procedure A-D. LC-MS: rt (min) = 5.19; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.95 (t, J = 7.3 Hz, 3 H), 1.29 - 1.49 (m, 8 H), 1.66 - 1.80 (m, 2 H), 2.65 (t, J = 7.5 Hz, 2 H), 3.17 - 3.28 (m, 1 H), 3.35 - 3.49 (m, 2 H), 3.68 - 3.93 (m, 2 H), 4.37 - 4.59 (m, 2 H), 7.51 (t, J = 7.5 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 8.03 - 8.32 (m, 2 H) and 12.67 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{22}H_{28}N_3OS_2$, 414.168; found 414.1675.

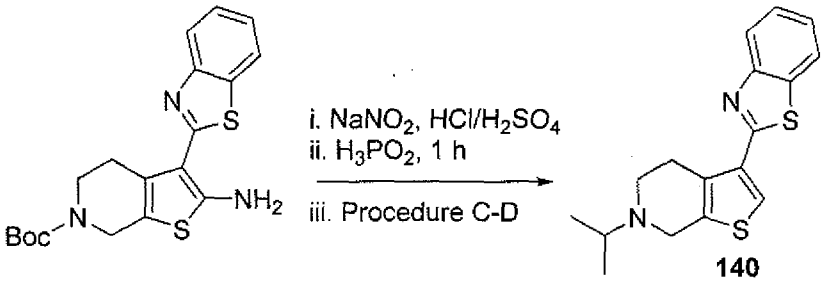


[0210] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)benzamide (**39**): This compound was prepared following Procedure A-D. LC-MS: rt (min) = 5.27; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (d, J = 5.3 Hz, 6 H), 3.35 - 3.51 (m, 3 H), 3.69 - 3.97 (m, 2 H), 4.40 - 4.69 (m, 2 H), 7.55 (t, J = 7.6 Hz, 1 H), 7.68 (t, J = 7.6 Hz, 1 H), 7.74 - 7.82 (m, 3 H), 8.12 - 8.27 (m, 4 H) and 13.92 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{24}H_{24}N_3OS_2$, 434.1355; found 434.1355.



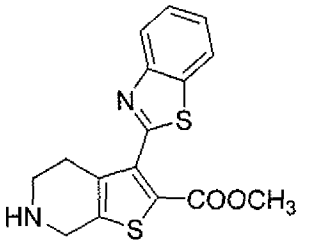
EXAMPLE 18

[0211] This Example illustrates a synthesis of 2-(4,5,6,7-Tetrahydrothieno[2,3-c]pyridin-3-yl)benzo[d]thiazole (**140**): t-Butyl 2-amino-3-(benzo[d]thiazol-2-yl)-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (1 g, 2.58 mmol, 1 eq) and hydrochloric acid (0.16 mL, 5.16 mmol, 2 eq) in sulfuric acid (2 mL) was slowly added sodium nitrite (0.267 g, 3.87 mmol, 1.5 eq) at 0 oC. After stirring for 1 h at 0 oC, phosphinic acid (1.703 g, 25.8 mmol, 10 eq) was added and stirred further an hour. The reaction mixture was slowly neutralized with saturated bicarbonate and the product was collected by filtration. This crude product was converted into compound 40 following Procedures C-D and further purified in a preparative HPLC. LC-MS: rt (min) = 1.33; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (d, J = 5.5 Hz, 6 H), 3. 49 - 3.58 (m, 1 H), 3.67 - 3.88 (m, 2 H), 4.47 - 4.72 (m, 2 H), 7.48 (t, J = 7.6 Hz, 1 H), 7.55 (t, J = 7.6 Hz, 1 H), 8.03 (d, J = 8.0 Hz, 1 H), 8.15 (d, J = 7.8 Hz, 1 H) and 8.38 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{19}N_2S_2$, 315.0984; found 315.0986.



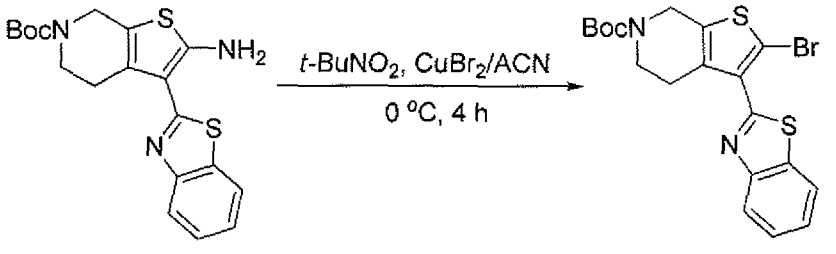
EXAMPLE 19

[0212] This Example illustrates a synthesis of Methyl 3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-2-carboxylate (**41**): This compound was prepared from 41a following Procedure C. LC-MS: rt (min) = 3.72; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.73 – 2.81 (m, 2 H), 3.38 - 3.41 (m, 2 H), 3.74 (s, 3 H), 4.51 (s, 2 H), 7.51 - 7.64 (m, 2 H), 8.10 (d, J = 7.8 Hz, 1 H), 8.21 (d, J = 7.8 Hz, 1 H) and 9.17 (br, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{16}H_{15}N_2O_2S_2$, 331.0575; found 331.0575.



EXAMPLE 20

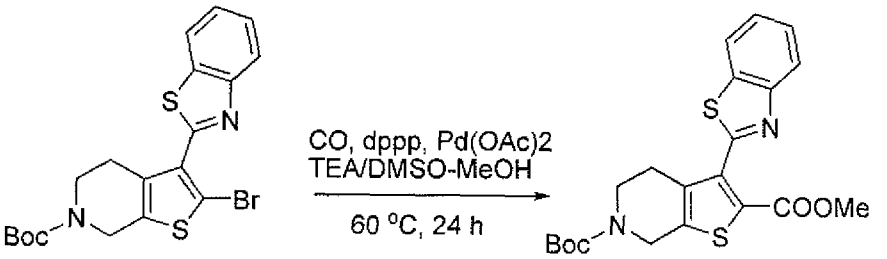
[0213] This Example illustrates a synthesis of a compound in accordance with the invention. A suspension of copper(II) bromide (4.64 g, 20.77 mmol, 1.4 eq) in acetonitrile (100 mL) was added tert-butyl nitrite (2.6 mL, 19.29 mmol, 1.3 eq) slowly and then tert-butyl 2-amino-3-(benzo[d]thiazol-2-yl)-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (5.75 g, 14.84 mmol, 1 eq) was added portion wise at 0 oC. The reaction mixture was warmed to room temperature with stirring over 4 h. The excess solvent was removed under diminished pressure and the crude residue was purified on a Biotage™ silica gel column. Elution with 5% ethyl acetate in hexanes gave the product. Yield: 54 % (3.62 g). LC-MS: rt (min) = 4.13 (4.5 min run); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43 (s, 9 H), 2.87 - 2.92 (m, 2 H), 3.57 - 3.63 (m, 2 H), 4.56 (s, 2 H), 7.48 - 7.63 (m, 2 H) and 8.07 - 8.22 (m, 2 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{19}H_{20}BrN_2O_2S_2$, 451.0152; found 451.0159.



EXAMPLE 21

[0214] This Example illustrates a synthesis of 6-tert-butyl 2-methyl 3-(benzo[d]thiazol-2-yl)-4,5-dihydrothieno[2,3-c]pyridine-2,6(7H)-dicarboxylate (**41a**): A mixture of tert-butyl 3-(benzo[d]thiazol-2-yl)-2-bromo-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (1.25 g, 2.77 mmol, 1 eq) 1,3-bis(diphenylphosphino)propane (0.228 g, 0.554 mmol, 0.2 eq) and TEA (1.54 mL, 11.08 mmol, 4 eq). in MeOH (20.00 mL) and DMSO (20 mL) was bubbled with argon for 10 minutes. Palladium(II) acetate (0.124 g, 0.554 mmol, 0.2 eq) was then added and the reaction mixture was saturated with CO and stirred for 24 h with a supply of CO (CO balloon) at 60 °C. The crude reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, ammonium chloride, and brine, and dried over sodium sulfate.

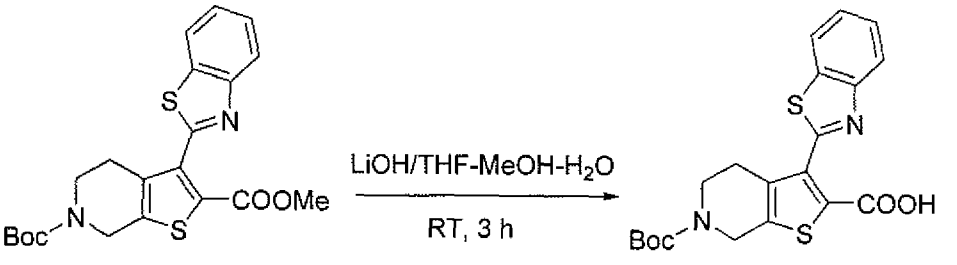
The crude residue obtained after evaporation of the solvent was purified on a Biotage™ silica gel column. Elution with 10% ethyl acetate in hexanes gave the product. Yield: 69 % (0.823 g). LC-MS: rt (min) = 3.39 (4.5 min run); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 - 1.50 (s, 9 H), 3.55 - 3.62 (m, 2 H), 3.67 - 3.74 (m, 5 H), 4.69 (s, 2 H), 7.47 - 7.62 (m, 2 H) and 8.05 - 8.22 (m, 2 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{21}H_{23}N_2O_4S_2$, 431.1108; found 431.1107.



41a

EXAMPLE 22

[0215] This Example illustrates a synthesis of 3-(benzo[d]thiazol-2-yl)-6-(t-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-2-carboxylic acid (**42a**): A solution of 6-tert-butyl 2-methyl 3-(benzo[d]thiazol-2-yl)-4,5-dihydrothieno[2,3-c]pyridine-2,6(7H)-dicarboxylate (1.3 g, 3.02 mmol, 1 eq) in THF/MeOH (3/1, 18 mL) was added lithium hydroxide (0.362 g, 15.10 mmol, 5 eq) in water (2 mL) and stirred at room temperature for 3 h. The reaction mixture was neutralized with 5 % HCl and extracted with ethyl acetate. The organic layer was subsequently washed with water, brine and dried over sodium sulfate. The crude product obtained after evaporation of the solvent was dried under vacuum which is sufficiently pure.



42a

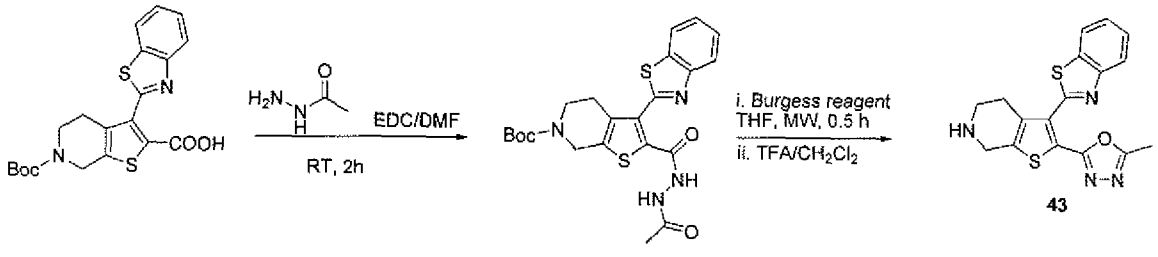
EXAMPLE 23

[0216] This Example illustrates a synthesis of 2-(3-(Benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-5-methyl-1,3,4-oxadiazole (**43**): A mixture of 3-(benzo[d]thiazol-2-yl)-6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-2-

carboxylic acid (0.1820 g, 0.437 mmol, 1 eq), acetylhydrazide (0.039 g, 0.524 mmol, 1 eq), EDC (0.251 g, 1.311 mmol, 3 eq) and DMAP (0.027 g, 0.218 mmol, 0.5 eq) in DMF (1.5 mL) was stirred at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate and washed with water and brine. The organic layer was dried on sodium sulfate and concentrated under reduced pressure. The crude product was further dried under vacuum.

[0217] A mixture of the crude tert-butyl 2-(2-acetylhydrazinecarbonyl)-3-(benzo[d]thiazol-2-yl)-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (0.2 g, 0.423 mmol, 1 eq) and Burgess reagent (0.151 g, 0.635 mmol, 1.5 eq) in THF (2 mL) was heated in a microwave for 30 min at 140 oC. The product was purified in a preparative HPLC, de-protected with TFA following procedure D and again purified in a preparative HPLC.

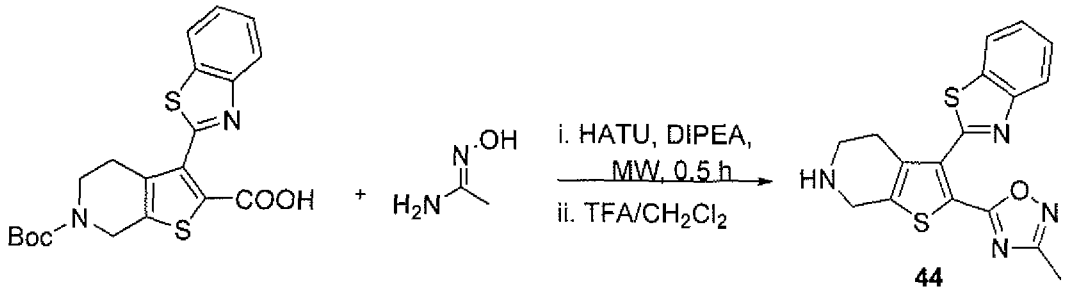
[0218] LC-MS: rt (min) = 3.52; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3 H), 2.95 (t, J = 5.6 Hz, 2 H), 3.41 - 3.51 (m, 2 H), 4.55 (s, 2 H), 7.49 - 7.65 (m, 2 H), 8.10 (d, J = 8.0 Hz, 1 H), 8.15 - 8.24 (m, 1 H) and 9.34 (br, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{15}N_4OS_2$, 355.0693; found 355.0690.



EXAMPLE 24

[0219] This Example illustrates a synthesis of 5-(3-(Benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-3-methyl-1,2,4-oxadiazole (**44**): A mixture of 3-(benzo[d]thiazol-2-yl)-6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-2-carboxylic acid (0.162 g, 0.39 mmol, 1 eq), (Z)-N'-hydroxyacetimidamide (0.036 g, 0.48 mmol, 1.2 eq), HATU (0.163 g, 0.43 mmol, 1.1 eq) and DIPEA (0.18 mL, 1.031 mmol, 2.6 eq) in DMF (2 ml) was heated in MW for 50 oC then 15 min then another 15 min at 150 oC. The product was purified in a preparative HPLC, de-protected with TFA following procedure D and again purified in a preparative HPLC.

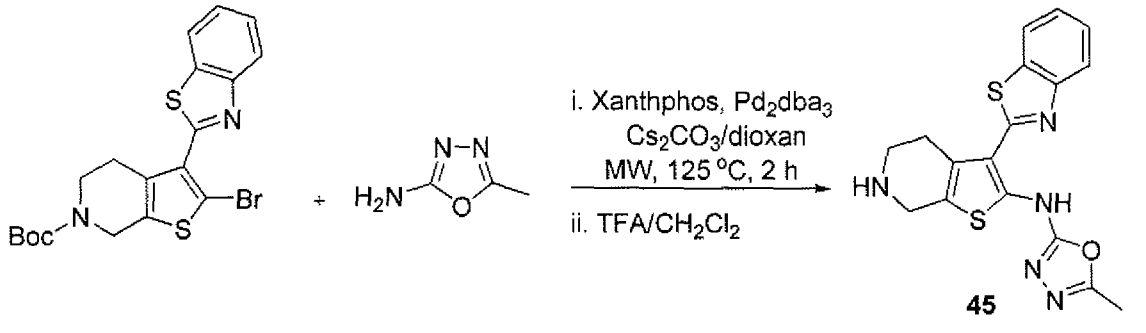
[0220] LC-MS: rt (min) = 3.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 3 H), 2.83 – 2.95 (m, 2 H), 3.34 - 3.44 (m, 2 H), 4.51 (s, 2 H), 7.55 - 7.64 (m, 2 H), 8.12 (d, J = 8.0 Hz, 1 H) and 8.23 (d, J = 8.0 Hz, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{15}N_4OS_2$, 355.0682; found 355.0682.



EXAMPLE 25

[0221] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-5-methyl-1,3,4-oxadiazol-2-amine (**45**): A mixture of tert-butyl 3-(benzo[d]thiazol-2-yl)-2-bromo-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (0.2 g, 0.443 mmol, 1 eq), 5-methyl-1,3,4-oxadiazol-2-amine (0.066 g, 0.665 mmol, 1.5 eq), cesium carbonate (0.289 g, 0.886 mmol, 2 eq) and Xantphos (0.026 g, 0.044 mmol, 0.1 eq) in dioxan (3 mL) was bubbled with argon for 5 min and then Pd2(dba)3 (0.020 g, 0.022 mmol, 0.05 eq) was added and heated in a MW for 2 h at 125 oC. The reaction mixture was diluted with ethyl acetate and filtered through celite pad and concentrated. The crude product was purified on a Biotage™ silica gel column. Elution with 40% ethyl acetate in hexanes gave the product which is further de-protected with TFA following procedure D and purified in a preparative HPLC.

[0222] LC-MS: rt (min) = 3.15; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01 (s, 3 H), 2.94 - 3.03 (m, 2 H), 3.48 - 3.58 (m, 2 H), 4.25 (s, 2 H), 7.59 – 7.71 (m, 2 H), 8.18 (d, J = 8.0 Hz, 1 H), 9.15 - 9.37 (br, 1 H), 9.77 (d, J = 8.4 Hz, 1 H) and 10.13 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{16}N_5OS_2$, 370.0802; found 370.0797.

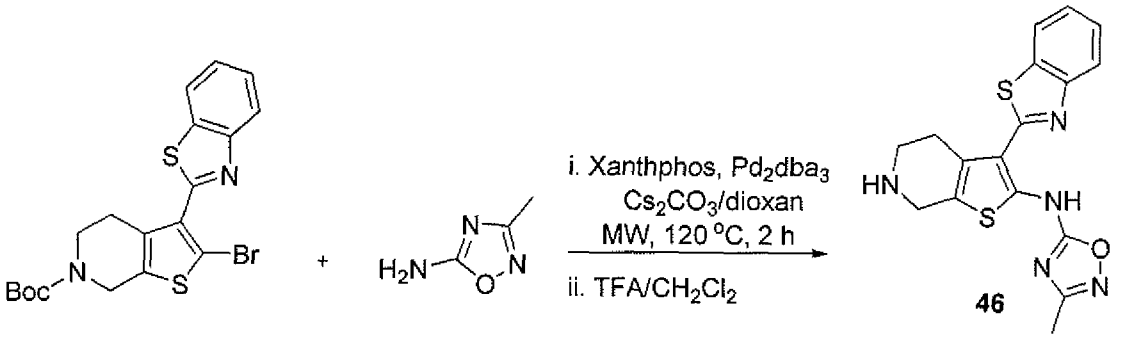


EXAMPLE 26

[0223] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)-3-methyl-1,2,4-oxadiazol-5-amine (**46**): A mixture of tert-butyl 3-(benzo[d]thiazol-2-yl)-2-bromo-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxylate (0.15 g, 0.332 mmol, 1 eq), 3-methyl-1,2,4-oxadiazol-5-amine (0.049 g, 0.498

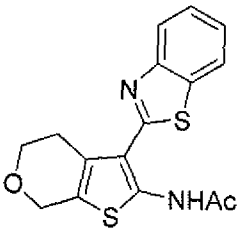
mmol, 1.5 eq), cesium carbonate (0.217 g, 0.665 mmol, 2 eq) and Xantphos (0.019 g, 0.033 mmol, 0.1 eq) in dioxan (3 mL) was bubbled with argon for 5 min and then Pd2(dba)3 (0.015 g, 0.017 mmol, 0.05 eq) was added and heated in a MW for 2 h at 120 oC. The reaction mixture was diluted with ethyl acetate and filtered through celite pad and concentrated. The crude product was purified on a Biotage™ silica gel column. Elution with 25% ethyl acetate in hexanes gave the product which is further de-protected with TFA following procedure D and purified in a preparative HPLC.

[0224] LC-MS: rt (min) = 4.28; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 3 H), 3.22 - 3.35 (m, 2 H), 3.39 - 3.49 (m, 2 H), 4.37 (s, 2 H), 7.41 - 7.61 (m, 2 H), 7.95 - 8.16 (m, 2 H) and 9.19 (br, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{17}H_{16}N_5OS_2$, 370.0803; found 370.0795.



EXAMPLE 27

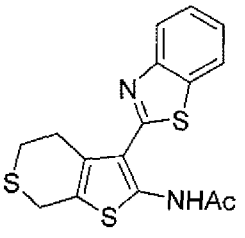
[0225] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-5,7-dihydro-4H-thieno[2,3-c]pyran-2-yl)acetamide (**47**): This compound was prepared following Procedures A-B. LC-MS: rt (min) = 6.63; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3 H), 2.95 (t, J = 5.2 Hz, 2 H), 3.98 (t, J = 5.5 Hz, 2 H), 4.71 (s, 2 H), 7.47 (t, J = 7.7 Hz, 1 H), 7.59 (t, J = 7.6 Hz, 1 H), 8.16 (d, J = 8.2 Hz, 2 H) and 12.56 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{16}H_{15}N_2O_2S_2$, 331.0569; found 331.0572.



EXAMPLE 28

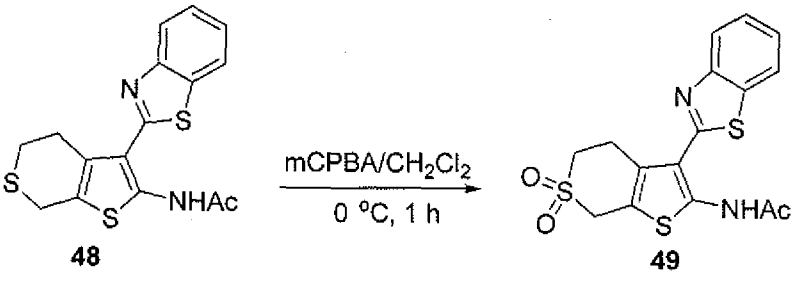
[0226] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-5,7-dihydro-4H-thieno[2,3-c]thiopyran-2-yl)acetamide (**48**): This compound was prepared following

Procedures A-B. LC-MS: rt (min) = 7.17; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 3 H), 3.02 (m, 2 H), 3.06 - 3.12 (m, 2 H), 3.82 (s, 2 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.58 (t, J = 7.6 Hz, 1 H), 8.14 (dd, J = 8.0 Hz and 2.9 Hz, 2 H) and 12.55 (s, 1 H) ; HRMS (ESI) m/z (M+H)+ calcd. for $C_{16}H_{15}N_2OS_3$, 347.0351; found 347.0352.



EXAMPLE 29

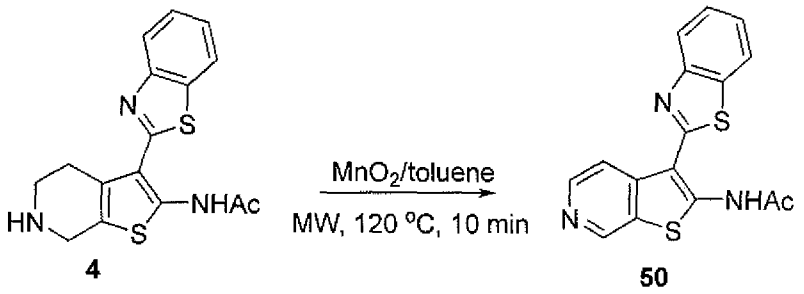
[0227] This Example illustrates a synthesis of N-[3-(1,3-benzothiazol-2-yl)-6,6-dioxido-4,7-dihydro-5H-thieno[2,3-c]thiopyran-2-yl]acetamide (**49**): LC-MS: rt (min) = 5.66; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 3 H), 3.42 (t, J = 5.9 Hz, 2 H), 3.53 (t, J = 6.0 Hz, 2 H), 4.55 (s, 2 H), 7.50 (t, J = 7.6 Hz, 1 H), 7.60 (t, J = 7.6 Hz, 1 H), 8.18 (dd, J = 8.0 and 4.1 Hz, 2 H) and 12.36 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{16}H_{15}N_2O_3S_3$, 379.0234; found 379.0235.



EXAMPLE 30

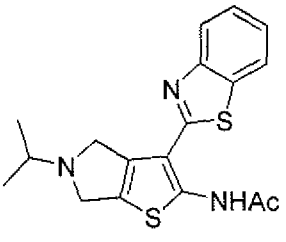
[0228] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)thieno[2,3-c]pyridin-2-yl)acetamide (**50**): A mixture of N-(3-(benzo[d]thiazol-2-yl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-yl)acetamide (0.1 g, 0.304 mmol, 1 eq) and manganese dioxide (0.132 g, 1.518 mmol, 5 eq) in toluene (4.0 mL) was heated in a MW for 10 min at 120 oC. The crude product obtained after filtration and removal of manganese dioxide was purified in a preparative HPLC.

[0229] LC-MS: rt (min) = 4.3; ^{1}H NMR (400 MHz, DMSO-d_6)□ δ 2.43 (s, 3 H), 7.48 - 7.556 (m, 1 H), 7.60 - 7.67 (m, 1 H), 8.09 - 8.28 (m, 3 H), 8.57 – 8.62 (m, 1 H), 9.19 (s, 1 H) and 13.14 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{16}H_{12}N_3OS_2$, 379. 326.0428; found 326.042.



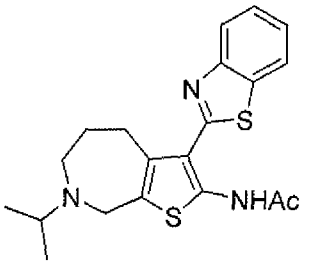
EXAMPLE 31

[0230] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-5-isopropyl-5,6-dihydro-4H-thieno[3,2-c]pyrrol-2-yl)acetamide (**51**): This compound was prepared following Procedures A-D. LC-MS: rt (min) = 4.33; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (d, J = 6.3 Hz, 6 H), 2.36 (s, 3 H), 3.83 (ddd, J = 12.5, 6.2 and 6.0 Hz, 1 H), 4.69 (s, 2 H), 4.84 (s, 2 H), 7.50 (t, J = 7.4 Hz, 1 H), 7.61 (t, J = 7.3 Hz, 1 H), 8.17 (d, J = 8.2 Hz, 2 H) and 12.05 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{18}H_{20}N_3OS_2$, 358.1054; found 358.1054.



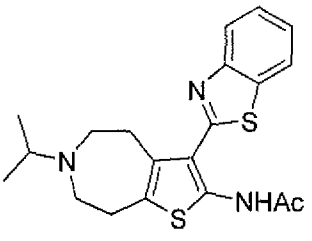
EXAMPLE 32

[0231] This Example illustrates a synthesis of N-(3-(benzo[d]thiazol-2-yl)-7-isopropyl-5,6,7,8-tetrahydro-4H-thieno[2,3-c]azepin-2-yl)acetamide (**54**): This compound was prepared following Procedures A-D (A 50 % mixture of 54 and 55 which were separated in HPLC after Procedure D) . LC-MS: rt (min) = 4.50; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01 (d, J = 6.3 Hz, 6 H), 1.69 - 1.78 (m, 2 H), 2.20 (s, 3 H), 2.82 (t, J = 5.7 Hz, 1 H), 2.96 – 3.42 (m, 4 H), 3.75 (s, 2 H), 7.47 (t, J = 7.5 Hz, 1 H), 7.54 - 7.58 (m, 1 H), 8.10 - 8.17 (m, 2 H) and 11.82 (s, 1 H) ; HRMS (ESI) m/z (M+H)+ $C_{20}H_{24}N_3OS_2$, 386.1372; found 386.1372.



54

[0232] N-(3-(benzo[d]thiazol-2-yl)-6-isopropyl-5,6,7,8-tetrahydro-4H-thieno[3,2-d]azepin-2-yl)acetamide (**55**): LC-MS: rt (min) = 4.38; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (d, J = 6.5 Hz, 6 H), 2.19 (s, 3 H), 2.65 - 2.74 (m, 4 H), 2.79 - 2.86 (m, 2 H), 2.92 - 3.04 (m, 3 H), 7.47 (t, J = 7.5 Hz, 1 H), 7.52 - 7.63 (m, 1 H), 8.13 (t, J = 7.1 Hz, 2 H) and 11.70 (s, 1 H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{20}H_{24}N_3OS_2$, 386.1367; found 386.1360.

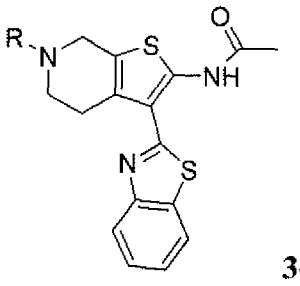


55

EXAMPLE 33

[0233] This Example illustrates the APE1 inhibitory activity of several embodiments of the invention.

[0234] Table 1. Activity of previously reported APE1 inhibitors (**1** and **2**) and SAR of analogs **3-8**.



3-8

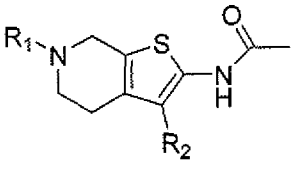
Compound	R	IC_{50}[a] (μM) [± SC (μM)]	Inh. @ 57 μM[b]
1	NA	32[c]	-
2	NA	-	40%
3	$CH(CH_3)_2$	2.0 [0.1]	-
4	H	2.9 [0.1]	
5	Boc	>57	
6	Me	3.8 [0.3]	
7	Bn	_	41%
8	Ac	_	59%

[a]IC_{50} values were determined using the qHTS protocol and represent the average of three separate experiments. [b]For compounds that did not achieve full inhibition (>85%), the % inhibition at the highest tested concentration (57 μM) is noted. Compounds noted as >57 μM are considered inactive. [c]IC_{50} of this compound reflects data from primary screen; follow-up studies with a powder sample were not further pursued.

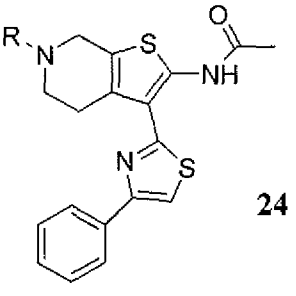
EXAMPLE 34

[0235] This Example illustrates the APE1 inhibitory activity of several embodiments of the invention.

[0236] Table 2. SAR of analogs **9-24**.



9-20, 22, 23



24

Compound	R_1	R_2	IC_{50}[a] (μM) [± SC (μM)]	Inh. @ 57 μM[b]
9	H	COOH	_	29%
10	H	H	_	47%
11	H	Br	_	30%
12	H	1-naphthalene	>57	
13	H	2-furan	_	41%
14	H	2-thiophene	_	34%
15	H	2-benzothiophene	_	23%
16	H	3-benzothiophene	>57	
17	H	2-benzofuran	_	66%
18	H	2-indole	>57	
19	H	2-oxazole	_	45%
20	H	2-thiazole	_	55%
21	$CH(CH_3)_2$	CN	_	31%
22	H	Ph	_	42%

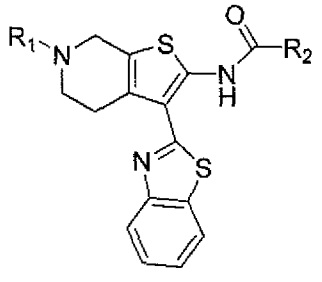
23	$CH(CH_3)_2$	benzoxaole	20.4 [0.1]	
24	$CH(CH_3)_2$	NA	2.9 [0.1]	

[a]IC_{50} values were determined using the qHTS protocol and represent the average of three separate experiments. [b]For compounds that did not achieve full inhibition (>85%), the % inhibition at the highest tested concentration (57 μM) is noted. Compounds noted as >57 μM are considered inactive.

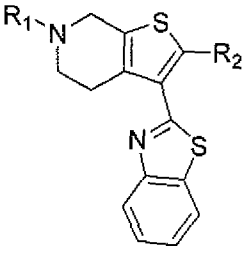
EXAMPLE 35

[0237] This Example illustrates the APE1 inhibitory activity of several embodiments of the invention.

[0238] Table 3. SAR of analogs **25-46.**

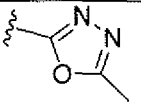
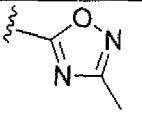
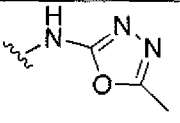
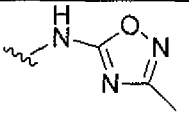


26-39



25, 40-46

Compound	R_1	R_2	IC_{50}[a] (μM) [± SC (μM)]	Inh. @ 57 μM[b]
25	$CH(CH_3)_2$	NH_2	_	40%
26	H	$CH(CH_3)_2$	>57	
27	H	cyclopropyl	6.0 [0.4]	
28	H	cyclopentyl	_	55%
29	$CH(CH_3)_2$	Bn	_	53%
30	H	$(CH_2)_2Ph$	>57	
31	H	CF_3	17.6 [2.4]	
32	H	OMe	11.1 [0.7]	
33	H	CHF_2	3.8 [0.3]	
34	H	$(CH_2)_2C{\equiv}CH$	12.0 [0.8]	
35	$CH(CH_3)_2$	$(CH_2)_2C{\equiv}CH$	_	57%

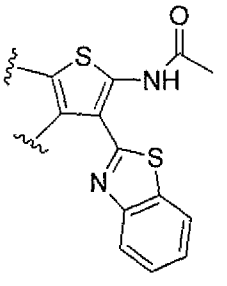
36	$CH(CH_3)_2$	CHF_2	5.3 [0.4]	
37	$CH(CH_3)_2$	cyclohexyl	8.3 [0.1]	
38	$CH(CH_3)_2$	$(CH_2)_3CH_3$	9.1 [0.1]	
39	$CH(CH_3)_2$	Ph	_	57%
40	H	H	25.2 [1.9]	
41	H	C(O)OMe	>57	
42	H	COOH	>57	
43	H		>57	
44	H		>57	
45	H		19.0 [1.3]	
46	H		18.2 [0.1]	

[a]IC_{50} values were determined using the qHTS protocol and represent the average of three separate experiments. [b]For compounds that did not achieve full inhibition (>85%), the % inhibition at the highest tested concentration (57 μM) is noted. Compounds noted as >57 μM are considered inactive.

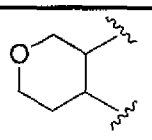
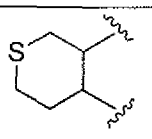
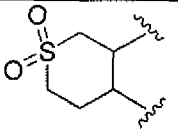
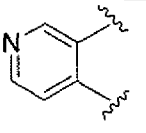
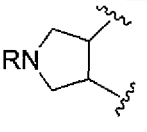
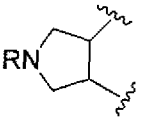
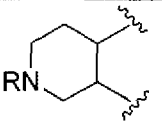
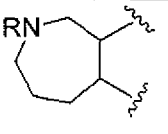
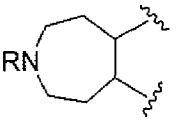
EXAMPLE 36

[0239] This Example illustrates the APE1 inhibitory activity of several embodiments of the invention.

[0240] Table 4. SAR of analogs **47-55**.



47-55

Compound	R	Heterocycle	IC_{50}[a] (μM) [± SC (μM)]	Inh. @ 57 μM[b]
47	NA		–	41%
48	NA		–	56%
49	NA		–	29%
50	NA		>57	
51	$CH(CH_3)_2$		3.1 [0.2]	
52	H		3.3 [0.2]	
53	H		–	31%
54	$CH(CH_3)_2$		12.9 [0.1]	
55	$CH(CH_3)_2$		17.6 [1.1]	

[a]IC_{50} values were determined using the qHTS protocol and represent the average of three separate experiments. [b]For compounds that did not achieve full inhibition (>85%), the % inhibition at the highest tested concentration (57 μM) is noted. Compounds noted as >57 μM are considered inactive.

EXAMPLE 37

[0241] This Example reports studies of the mechanism of APE1 inhibition.

[0242] Encouraged by the potency of compound **52** in the radiotracer incision assay we decided to further investigate mechanism of action studies (MoA) with this compound and our initial lead molecule **3**. To reveal the mode of inhibition, we determined the kinetic parameters for APE1 incision in the absence or presence of 5 μM inhibitor at varying concentrations of DNA substrate. Figure 1 shows the Lineweaver-Burk plots, as well as the K_M and k_{cat} values, of these experiments. These studies indicate that compounds **3** and **52** are largely competitive inhibitors, since K_M values are >2.2-fold higher in the presence of either inhibitor, and there is a less than 1.7-fold change in turnover rate.

[0243] Kinetic parameters without and with **52** or **3**. Ten pg of APE1 (~28 pM) was incubated without or with 5 μM of the indicated inhibitor at room temperature for 15 min. Increasing concentrations of radiolabeled abasic DNA substrate (i.e. 5, 10, 25, 50, or 100 nM) were then added, and the reactions were incubated at 37°C for 5 min before the addition of stop buffer. Intact substrate was separated from incised product on a 15% polyacrylamide denaturing gel, and the percent conversion was determined by standard phosphorimager analysis. Lineweaver – Burk plots of 1/V versus 1/[S] were used to determine K_M and k_{cat} (shown). The plotted data points (averages and standard deviations) were derived from 11 independent values for the no inhibitor reactions, and 5 values for each of the inhibitor points. The Lineweaver-Burk plots are illustrated in Figure 2. The data derived from the plots are set forth in Table 5.

Table 5.

	K_M (nM)	k_{cat} ($min._1$)	k_{cat}/K_M
No inhibitor	31.5	175	3.7
Compound **52**	81.1	282	2.3
Compound **3**	70.2	285	2.7

[0244] Electrophoretic mobility shift assay (EMSA) was performed next to examine the effect of compound **3** and **52** on APE1 and ^{32}P radiolabeled AP-DNA complex formation and stability. The results with **3** and **52** show that the APE1-DNA complex (C) decreased in a dose-dependent manner and was essentially absent when the protein was pre-incubated with 30 μM inhibitor (Figure 3), implying that the inhibitors bind the same site on APE1 as the DNA substrate.

[0245] Figure 3 illustrates the stability of the APE1-DNA substrate complex in the presence of **52** or **3**. (**A**) Representative EMSA. Three hundred ng of APE1 (~0.8 μM) was

incubated without inhibitor ("-", final concentration 1% DMSO) or with the indicated inhibitor (1, 3, 10, 30 or 100 μM) for 10 min on ice. One hundred fmol of abasic DNA substrate (10 nM) was then added, and the binding reaction was incubated on ice for an additional 5 min. At that time, samples were subjected to non-denaturing polyacrylamide gel electrophoresis to separate the APE1-DNA complex (C) from unbound radiolabeled DNA (DNA). Inh = inhibitor. (**B**) Relative complex formation without ("0") or with the indicated inhibitor (in μM). Shown is the average and standard deviation of three independent experimental data points, all relative to the APE1 control, without inhibitor.

EXAMPLE 38

[0246] This Example illustrates the inhibition of HeLa whole cell extract incision activity by embodiments of the invention.

[0247] Since APE1 comprises ≥95% of the total AP endonuclease activity in mammals, most, if not all, the incision observed in human whole cell extracts is the result of APE1-dependent cleavage (Demple and Harrison, Annu Rev Biochem, 1994). Thus, as a means of assessing both the specificity of candidate APE1 inhibitors and their potential biological value, we determined the effect of the most promising actives on total AP site cleavage activity of HeLa whole cell extracts. Inhibitors with specificity for APE1 would be expected to impart a reduced incision capacity relative to the control (no inhibitor, DMSO control) reaction, even amidst all the non-specific proteins in the extract. The results showed that both **3** and **52** potently inhibited HeLa AP site incision activity at 50 and 100 μM concentrations (Figure 4).

[0248] Figure 4 illustrates inhibition of HeLa whole cell extract AP site incision activity with **52** or **3**. Three hundred ng of HeLa whole cell extract was incubated with 0, 1, 3, 10, 30 or 100 μM of the indicated inhibitor at room temperature for 15 min, prior to the addition of 0.5 pmol radiolabeled AP-DNA substrate and subsequent transfer of the reaction mix (final volume of 10 μL) to 37 °C for 5 min to allow for incision. Following addition of stop buffer and heat denaturation, the reaction products were subjected to 15% polyacrylamide denaturing gel electrophoresis. Shown is a bar graph reporting the relative percent incision activity in comparison to the no inhibitor control, arbitrarily set at 100. The values reported represent the averages and standard deviation of three independent experimental data points.

EXAMPLE 39

[0249] This Example shows some in vitro ADME properties of two embodiments of the invention.

[0250] Table 6. In vitro ADME properties of lead molecules 3 and 52.

Compound	aq. kinetic sol. (PBS @ pH 7.4)	CYP2D6 (inh. @ 10 μM)	CYP34A (inh. @ 10 μM)	Caco-2 (P_{app} 10^{-6} m/s @ pH 7.4)	efflux ratio (B→A)/(A→B)
52	51.6	39%	50%	6.8	0.8
3	20.4	0%	53%	5	1.1

hERG inhibition (IC50) patch clamp	mouse liver microsome stability ($T_{1/2}$)	PBS-pH 7.4 Stability: % remaining after 48h	Mouse plasma stability ($T_{1/2}$)
8 μM	7.8 min.	100%	213 min
0.7 μM	80 min.	100%	∞

[0251] As shown in the *in vitro* ADME data, both compounds **3** and **52** have many desirable attributes. Analog **52** exhibits improved kinetic solubility, Caco-2 permeability, plasma stability and 10-fold less inhibition of the hERG channel as compared to the original lead **3**. However, compound **52** appears susceptible to mouse liver microsomes ($T_{1/2}$ = 7.8 min), yet compound **3** shows favorable stability ($T_{1/2}$ = 80 min).

EXAMPLE 40

[0252] This Example shows in vivo PK data for two embodiments of the invention.

[0253] Table 7. In vivo PK data.

Cmpd	$t_{1/2}$ (h) (plasma)	$t_{1/2}$ (h) (brain)	(brain/plasma)	C_{max} (ng/mL) (plasma)	C_{max} (ng/mL) (brain)	t_{max} (h) (plasma)	t_{max} (h) (brain)	cLogP
52	5	2.5	0.74	11330	29000	0.25	0.25	1.02
3	2.1	1	18	5960	80750	0.25	0.25	2.83

[a] IP administration (30 mg/kg), CD1 mice, n =3, monitored at 8 time points (0.25 h, 0.5, 1, 2, 4, 8, 12, 24). Compound **52** formulated as a 50% PEG 200 and 10% Cremophor EL in saline

solution, compound **3** formulated as a 50% PEG 400 and 10% Cremophor EL in saline suspension.

[0254] Compounds **52** and **3** were analyzed for their in vivo PK properties (CD1 mice) via IP administration at 30 mg/kg. Compound **52**, the more hydrophilic analog (cLogP = 1) had a favorable plasma $t_{(1/2)}$ of 5 hours and an drug concentration (ng/mL) which exceeded the IC_{50} for over 12 hours. As expected, this compound did not efficiently cross the blood brain barrier (BBB) with a Brain/Plasma (B/P) ratio of 0.74. In contrast, analog **3**, in which the free amine is capped with an isopropyl group (cLogP = 2.83), crossed the BBB quite readily with a (B/P) ratio of 18. This result correlates which expectations as reduction of hydrogen bond donors and increasing lipophilicity often leads to improved BBB penetration. The ability to easily modulate the BBB penetration ability of these molecules through structural modifications could prove useful depending on the cancer one is targeting. Clearly, for tumors existing outside the brain, a compound which does not efficiently cross the BBB would be useful to avoid potential complications associated with CNS active drugs. However, given that APE1 has been found to be overexpressed in adult and pediatric gliomas (a type of brain cancer), inhibitors such as **3** which efficiently cross the BBB are also desirable.

EXAMPLE 41

[0255] This example shows the effect on total AP site cleavage activity of HeLa whole cell extracts by several embodiments of the invention.

[0256] To prepare protein extracts, HeLa cells maintained in DMEM with 10% fetal bovine serum and 1% penicillin-streptomycin were harvested, washed with 1XPBS, and resuspended in ice cold hypotonic lysis buffer (50 mM Tris, pH 7.4, 1 mM EDTA, 1 mM DTT, 10% glycerol, 0.5 mM PMSF). The suspension was frozen at -80 °C for at least 30 min and then slowly thawed at 4 °C for 1 h. KCl was added to the cell suspension to a final concentration of 222 mM, followed by incubation on ice for 30 min and clarification by centrifugation at 12000g for 15 min at 4 °C. The supernatant (whole cell extract) was retained and the protein concentration determined using the Bio-Rad Bradford reagent. Aliquots were stored until needed at -80 °C. For the incision assays, 300 nm of HeLa whole cell extract was incubated with 0, 1, 3, 10, 30, or 100 μM indicated inhibitor at room temperature for 15 min prior to the addition of 0.5 pmol of 32P radiolabeled AP-DNA substrate (final volume of 10 μL). The reaction mix was then transferred to 37 °C for 5 min

to allow for incision. Following addition of stop buffer and heat denaturation, the reaction products were analyzed as indicated above. The results are set forth in Table 8.

Table 8

Compound	RIA IC_{50}[a] (μM)	HTS IC50 (μM)	HeLa cell extract, % incision activity[b]
3	12	2.0	0.6 ± 0.11
4	5	2.9	1.4 ± 1.1
6	5	3.8	26 ± 3.7
23	13	20.4	12 ± 1.3
24	3	2.9	15 ± 0.5
33	4	3.8	38 ± 7.7
51	4	3.1	15 ± 14
52	1	3.3	0.1 ± 0.03
54	14	12.9	14 ± 2.8
55	13	17.6	1.1 ± 0.3

[a]Assays were run in duplicate at 0, 1, 3, 10, 30, or 100 μM inhibitor concentration.

[b]100 μM of inhibitor was used in these experiments, and the values represent the average and standard deviation of three independent measurements relative to the no inhibitor control.

[0257] As is apparent from the results set forth in Table 8, analogs **3**, **4**, **52**, and **55** exhibited near 100% inhibition of the incision activity of HeLa extracts.

EXAMPLE 42

[0258] This example shows the effect on HeLa cell viability with compounds **3** and **52** alone and in combination with either methyl methanesulfonate or temolozolomide.

[0259] HeLa cells were plated by multichannel pipet of Multidrop Combi dispenser (Thermo) at 6K/25 μL per well in DMEM culture medium with 10% FBS into white solid bottom 384-well cell culture plates. Cells were cultured at 37 °C overnight to allow for cell attachment. The following day, the entire cell medium in the well was replaced with fresh medium containing serial dilutions of the compounds of interest (5-30 μM) in the presence or absence of MMS (0.4 μM) or TMZ (1 mM). The plates were incubated for 24 h at 37 °C. Cell viability was then evaluated via luminescence detection by adding 15 μL of CellTiter

Glo reagent (Promega, Madison, WI) to each well and incubating at room temperature for 30 min and subsequently measuring the luminescence using a ViewLux reader. Percent viability was calculated for each concentration of the tested compounds in duplicate relative to the luminescence of the negative DMSO control. The results are depicted graphically in Figures 5A (for compound **3**) and 5B (for compound **52**).

EXAMPLE 43

[0260] This example illustrates the kinetics of enzyme inhibition exhibited by two embodiments of the present invention.

[0261] An amount of 10 ng of APE1 (28 nM) was incubated without (positive control, 1% DMSO) or with 5, 10, or 20 μM indicated inhibitor at room temperature in RIA buffer for 15 min. Varying concentrations of ^{32}P radiolabeled AP-DNA substrate (i.e., 5, 10, 25, 50, or 100 nM) were then added to a 10 μL final volume. The mixtures were incubated at 37 °C for 5 min and the reactions stopped by adding stop buffer and heating at 95 °C for 10 min. The reaction velocity (nanomolar substrate incised per minute) at each substrate concentration was calculated as described above. Lineweaver-Burk plots of 1/V versus 1/[S] were used to determine Km and k_{cat} and the mode of inhibition. The results are set forth in Tables 9 and 10.

Table 9. Kinetic analysis for compound **52**.

Reaction	k_{cat} (min^{-1})	K_M (nM)	K_{cat}/K_M	R^2 value
No inhibitor	204	28	7.3	0.75
5 μM	169	67	2.5	0.51
10 μM	153	282	0.54	0.75
20 μM	42	175	0.24	0.95

Table 10. Kinetic analysis for compound **3**.

Reaction	k_{cat} (min^{-1})	K_M (nM)	K_{cat}/K_M	R^2 value
No inhibitor	204	28	7.3	0.75
5 μM	251	55	4.6	0.76
10 μM	105	105	1.0	0.97
20 μM	36	58	0.62	0.93

[0262] As is apparent from the results set forth in Tables 9 and 10, in both cases, the k_{cat} decreases less than 6-fold, and only at the high inhibitor concentration. In the case of **52**, K_M increases substantially (up to 10-fold), while the K_M increases less dramatically with 3 (up to 4-fold). Such trends would suggest that these compounds act as competitive inhibitors of APE1 activity and, thus, presumably bind the active site of the enzyme.

[0263] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

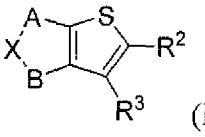
The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0264] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible

variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIM(S):

1. A compound of the formula (I):



(I),

wherein X is NR^1, O, S, or SO_2,

A is $-(CR^5R^6)-(CR^7R^8)_m-$,

B is $-(CR^9R^{10})-(CR^{11}R^{12})_n-$

R^1, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are the same or different and are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when X is NR^1, m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and/or R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond, or when X is NR^1, m is 1 and n is 0, R^5 and R^7 together with the carbon atoms to which they are attached, and/or R^1 and R^9, together with the nitrogen atom and carbon atom to which they are attached, form a bond, R^2 is selected from the group consisting of $-NHCOR^4$, $-NH_2$, heterocyclyl, -NH-heterocyclyl, and -COOH, wherein the heterocyclyl is optionally substituted with an alkyl group,

R^3 is heterocyclyl, wherein the heterocyclyl is optionally substituted with an alkyl group or an aryl group, wherein the aryl group is optionally further substituted with one or more substituents selected from the group consisting of halo, dihaloalkyl, trihaloalkyl, nitro, hydroxy, alkoxy, aryloxy, amino, substituted amino, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, thio, alkylthio, and arylthio,

R^4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkoxy, alkenyl, alkenylalkyl, alkylalkenyl, alkynyl, alkynylalkyl, alkylalkynyl, aryl, arylalkyl, heterocyclyl, and arylheterocyclyl, and

m and n are independently 0, 1, or 2,

with the proviso that when A is CH_2, B is CH_2CH_2, X is NR^1, R^1 is alkyl, alkylcarbonyl, or alkoxycarbonyl, and R^3 is 2-benzothiazolyl, R^2 is not $NHCOR^4$ wherein R^4 is alkyl, arylalkyl, heterocyclyl, or arylheterocyclyl,

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1, wherein R^2 is $NHCOR^4$.

3. The compound or salt of claim 1 or 2, wherein m is 0 and n is 1.

4. The compound or salt of any one of claims 1-3, wherein R^4 is alkyl.

5. The compound or salt of any one of claims 1-4, wherein X is NR^1.

6. The compound or salt of claim 5, wherein R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

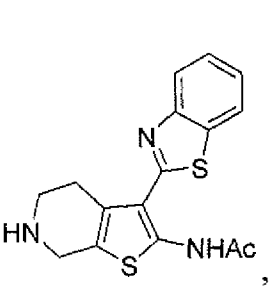
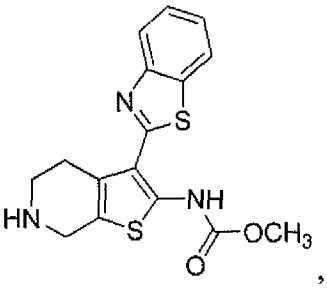
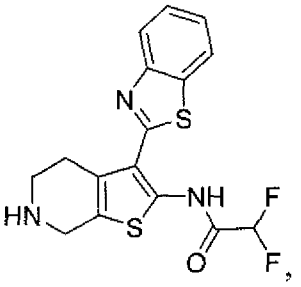
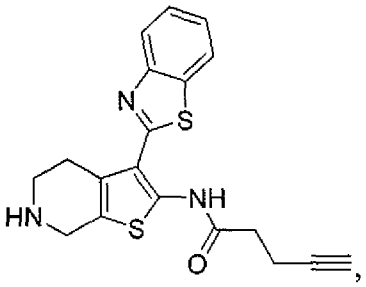
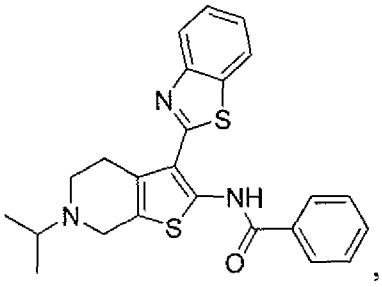
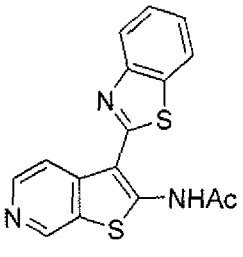
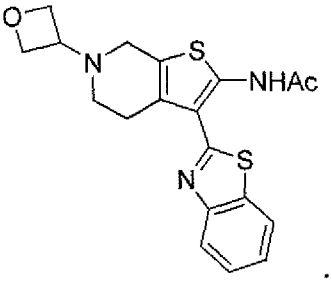
7. The compound or salt of any one of claims 1-6, wherein R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are hydrogen, or, when m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

8. The compound or salt of any one of claims 1-7, wherein R^3 is selected from the group consisting of benzothiazol-2-yl, benzothiophene-2-yl, benzothiophene-3-yl, benzoxazol-2-yl, and indol-2-yl.

9. The compound or salt of claim 8, wherein R^3 is benzothiazol-2-yl.

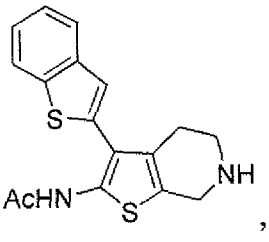
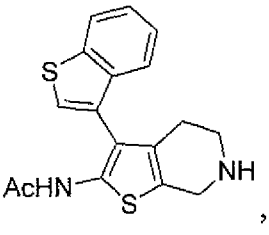
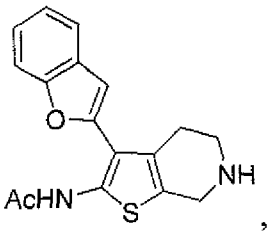
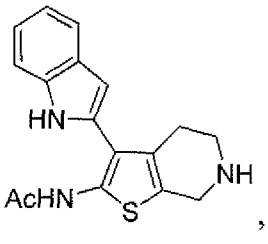
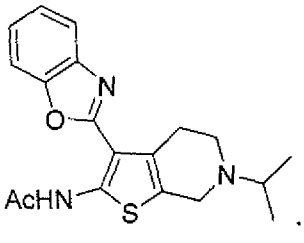
10. The compound or salt of any one of claims 1-7, wherein R^3 is selected from the group consisting of furan-2-yl, tetrazolyl, thiazol-2-yl, arylthiazol-2-yl, and optionally substituted arylthiazol-2-yl.

11. The compound or salt of claim 8 or 9, wherein the compound is selected from the group consisting of:

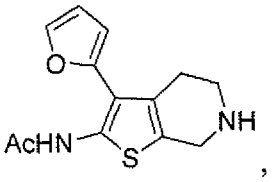
, and .

12. The compound or salt of claim 8, wherein the compound is selected from the group consisting of:

and .

13. The compound or salt of claim 10, wherein the compound is selected from the group consisting of:



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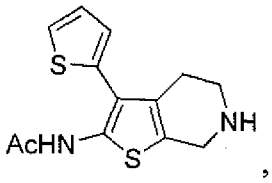

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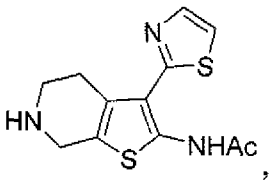
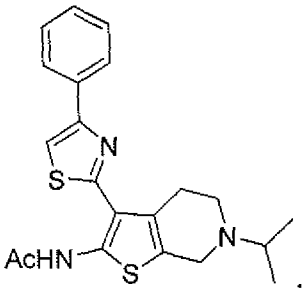


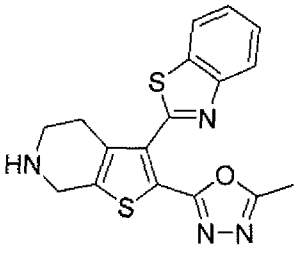
, and


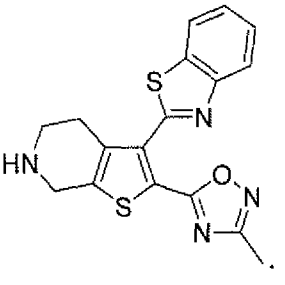
.

14. The compound or salt of any one of claims 5-10, wherein R^2 is heterocyclyl optionally substituted with alkyl.

15. The compound or salt of claim 14, wherein m is 0 and n is 1.

16. The compound or salt of claim 15, wherein the compound is selected from the group consisting of:



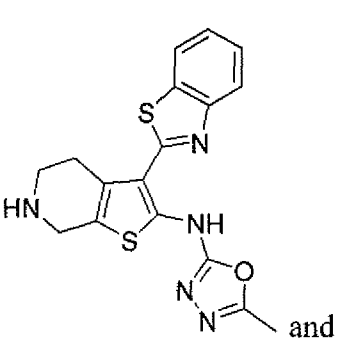
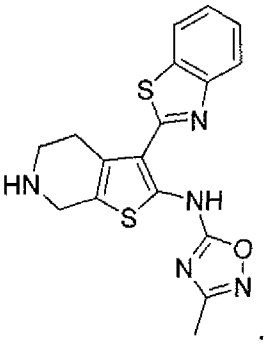
and


.

17. The compound or salt of any one of claims 5-10, wherein R^2 is –NH-heterocyclyl optionally substituted with alkyl.

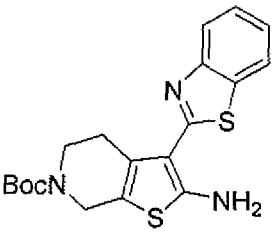
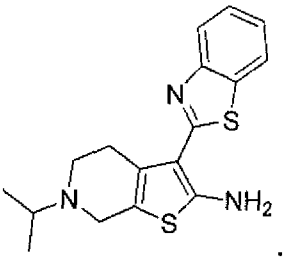
18. The compound or salt of claim 17, wherein m is 0 and n is 1.

19. The compound or salt of claim 18, wherein the compound is selected from the group consisting of:


and

.

20. The compound or salt of any one of claims 5-10, wherein R^2 is $-NH_2$.

21. The compound or salt of claim 20, wherein the compound is selected from the group consisting of:


and

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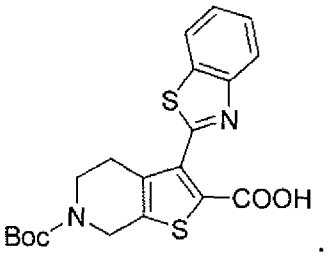
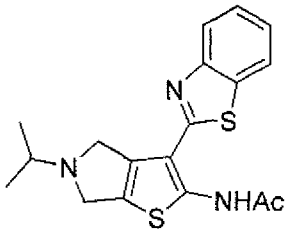
22. The compound or salt of any one of claims 5-10, wherein R^2 is –COOH.

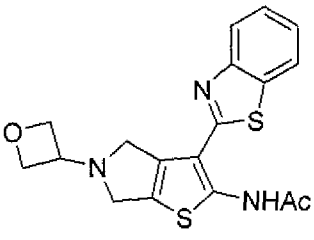
23. The compound or salt of claim 22, wherein the compound is:

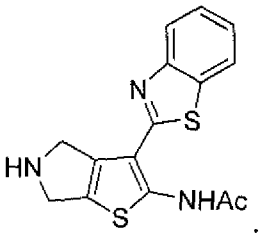

.

24. The compound or salt of any one of claims 1, 2, or 4-10, wherein m and n are both 0.

25. The compound or salt of claim 24, wherein the compound is selected from the group consisting of:



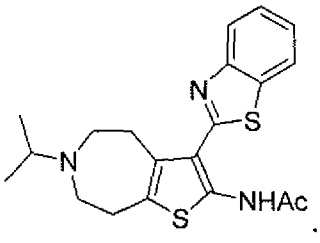
,


, and


.

26. The compound or salt of any one of claims 1, 2, or 4-10, wherein m and n are both 1.

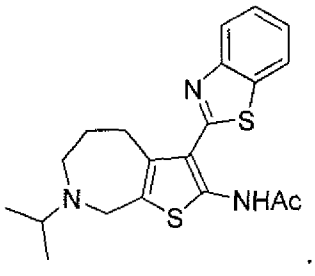
27. The compound or salt of claim 26, wherein the compound is:



.

28. The compound or salt of any one of claims 1, 2, or 4-10, wherein m is 2 and n is 0.

29. The compound or salt of claim 28, wherein the compound is:



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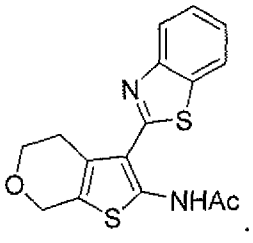
30. The compound or salt of any one of claims 1-4 or 7-10, wherein X is O.

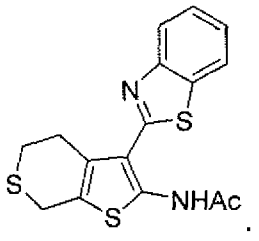
31. The compound or salt of claim 30, wherein the compound is:



.

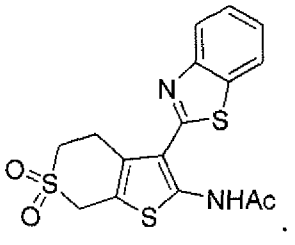
32. The compound or salt of any one of claims 1-4 or 7-10, wherein X is S.

33. The compound or salt of claim 32, wherein the compound is:



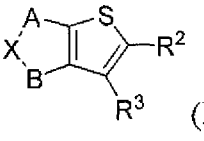
34. The compound or salt of any one of claims 1-4 or 7-10, wherein X is SO_2.

35. The compound or salt of claim 34, wherein the compound is:



36. A pharmaceutical composition comprising a compound or salt according to any of claims 1-35, and a pharmaceutically acceptable carrier.

37. A method for treating cancer, the method comprising administering to a patient in need thereof an effective amount of a compound of the formula (I):



(I),

wherein X is NR^1, O, S, or SO_2,

A is $-(CR^5R^6)-(CR^7R^8)_m-$,

B is $-(CR^9R^{10})-(CR^{11}R^{12})_n-$

R^1, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are the same or different and are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when

X is NR^1, m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and/or R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond, or when X is NR^1, m is 1 and n is 0, R^5 and R^7 together with the carbon atoms to which they are attached, and/or R^1 and R^9, together with the nitrogen atom and carbon atom to which they are attached, form a bond, R^2 is selected from the group consisting of -$NHCOR^4$, -NH_2, heterocyclyl, -NH-heterocyclyl, and -COOH, wherein the heterocyclyl is optionally substituted with an alkyl group,

R^3 is heterocyclyl, wherein the heterocyclyl is optionally substituted with an alkyl group or an aryl group, wherein the aryl group is optionally further substituted with one or more substituents selected from the group consisting of halo, dihaloalkyl, trihaloalkyl, nitro, hydroxy, alkoxy, aryloxy, amino, substituted amino, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, thio, alkylthio, and arylthio,

R^4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkoxy, alkenyl, alkenylalkyl, alkylalkenyl, alkynyl, alkynylalkyl, alkylalkynyl, aryl, arylalkyl, heterocyclyl, and arylheterocyclyl, and

m and n are independently 0, 1, or 2,

or a pharmaceutically acceptable salt thereof.

38. The method of claim 37, wherein R^2 is $NHCOR^4$.

39. The method of claim 37 or 38, wherein m is 0 and n is 1.

40. The method of any one of claims 37-39, wherein R^4 is alkyl.

41. The method of any one of claims 37-40, wherein X is NR^1.

42. The method of claim 41, wherein R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

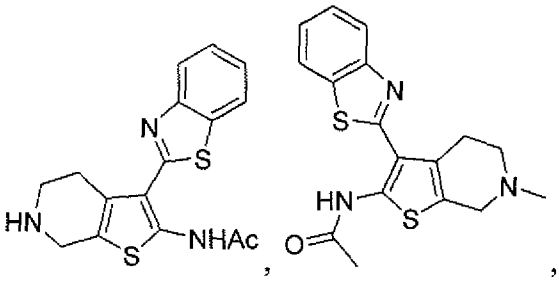
43. The method of any one of claims 37-42, wherein R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are hydrogen, or, when m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

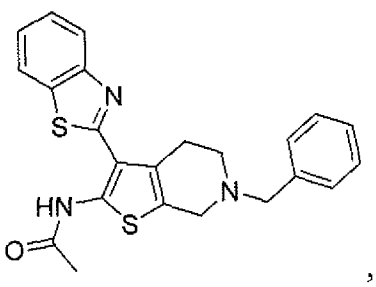
44. The method of any one of claims 37-43, wherein R^3 is selected from the group consisting of benzothiazol-2-yl, benzothiophene-2-yl, benzothiophene-3-yl, benzoxazol-2-yl, and indol-2-yl.

45. The method of claim 44, wherein R^3 is benzothiazol-2-yl.

46. The method of any one of claims 37-43, wherein R^3 is selected from the group consisting of furan-2-yl, tetrazolyl, thiazol-2-yl, arylthiazol-2-yl, and optionally substituted arylthiazol-2-yl.

47. The method of claim 45 or 46, wherein the compound is selected from the group consisting of:

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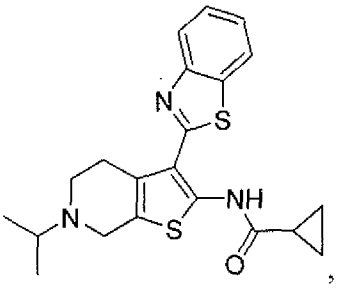
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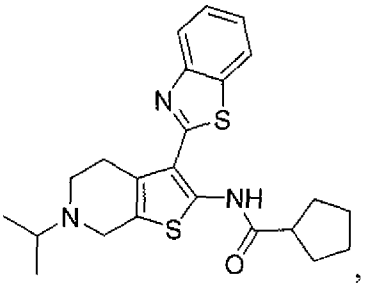
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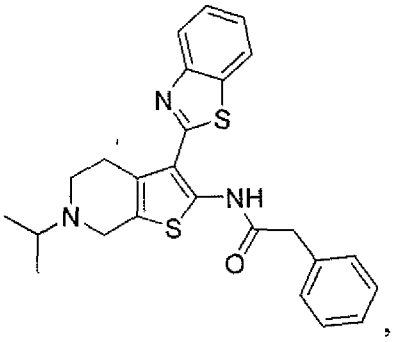
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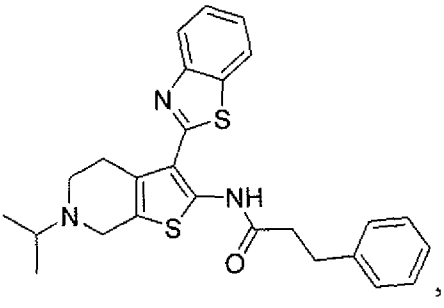
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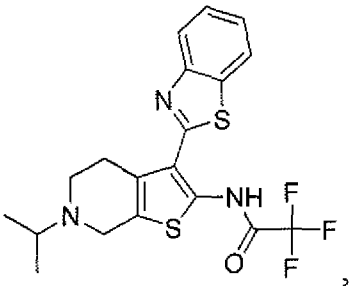
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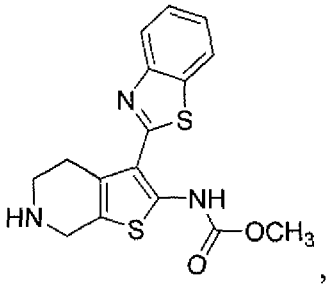
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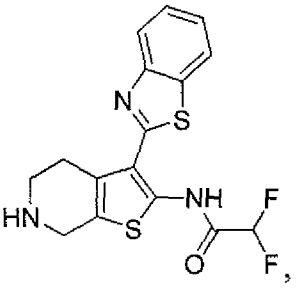
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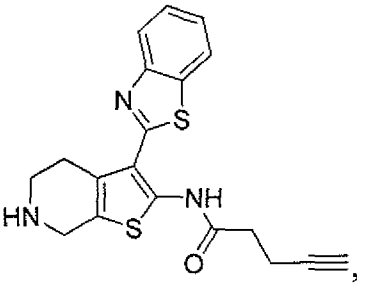
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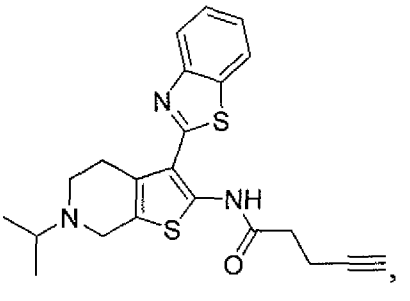
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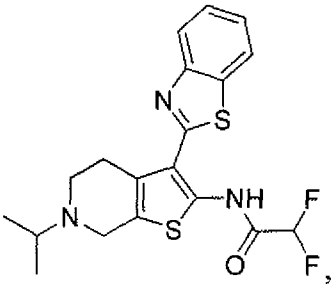
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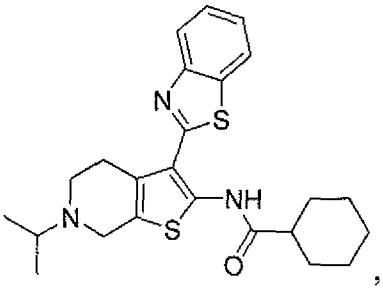
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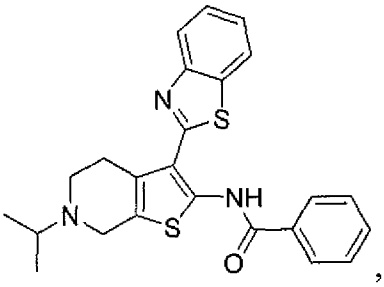
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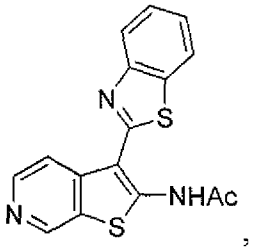
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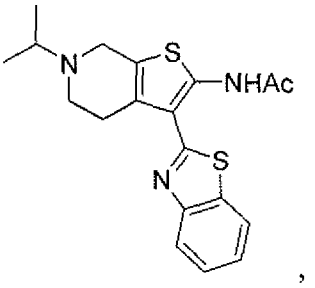
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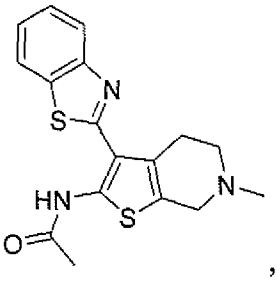
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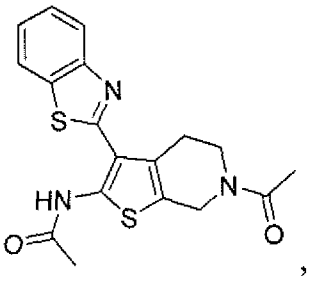
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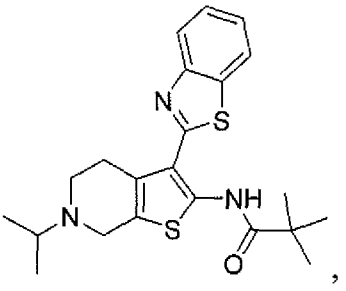
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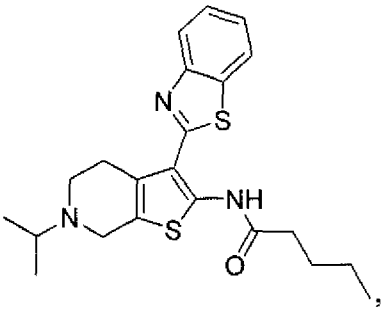
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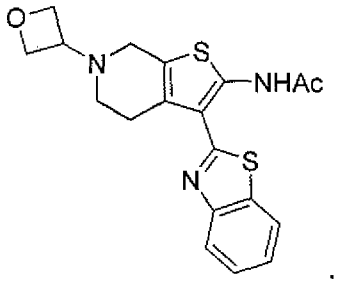
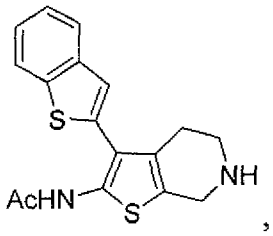
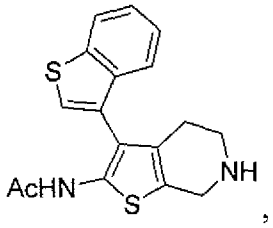
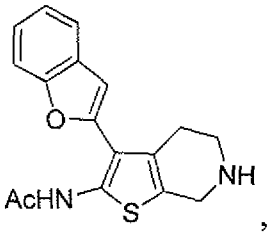
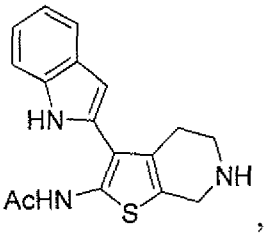
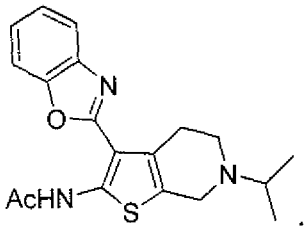


and .

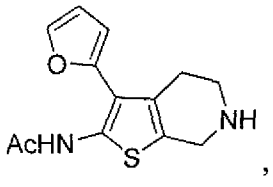
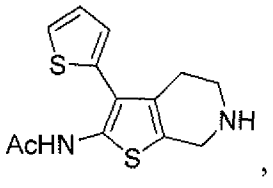
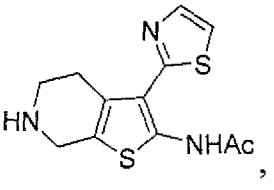
48. The method of claim 45, wherein the compound is selected from the group consisting of:

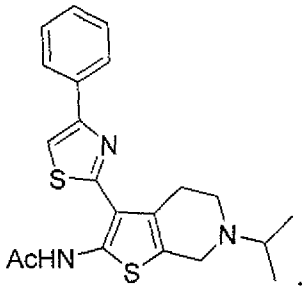
 ,  ,  ,  ,



and .

49. The method of claim 46, wherein the compound is selected from the group consisting of:

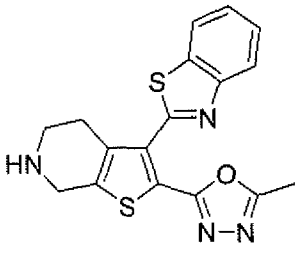
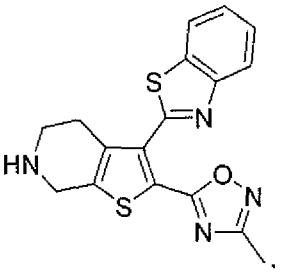
 ,  ,  , and

 .

50. The method of any one of claims 41-46, wherein R^2 is heterocyclyl optionally substituted with alkyl.

51. The method of claim 50, wherein m is 0 and n is 1.

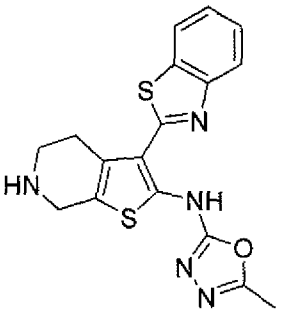
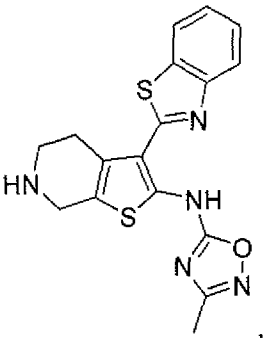
52. The method of claim 51, wherein the compound is selected from the group consisting of:


and


53. The method of any one of claims 41-46, wherein R^2 is –NH-heterocyclyl optionally substituted with alkyl.

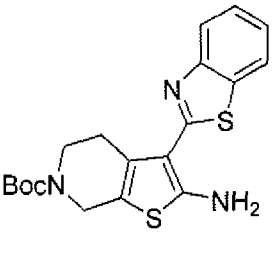
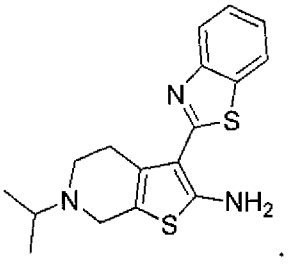
54. The method of claim 53, wherein m is 0 and n is 1.

55. The method of claim 54, wherein the compound is selected from the group consisting of:


and


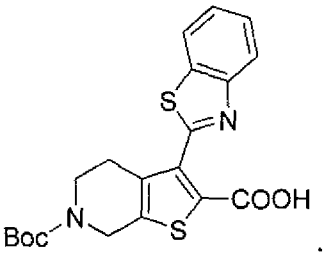
56. The method of any one of claims 41-46, wherein R^2 is $–NH_2$.

57. The method of claim 56, wherein the compound is selected from the group consisting of:


and


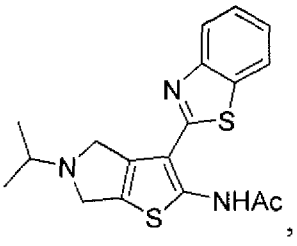
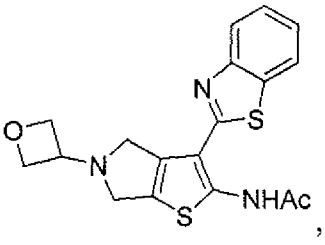
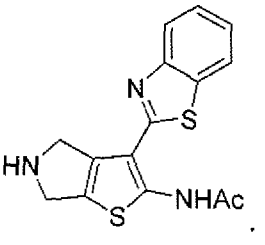
58. The method of any one of claims 41-46, wherein R^2 is –COOH.

59. The method of claim 58, wherein the compound is:



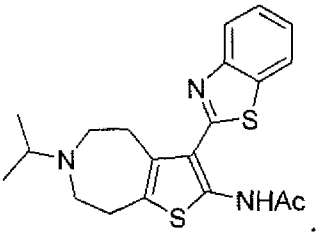
60. The method of any one of claims 37, 38, or 40-46, wherein m and n are both 0.

61. The method of claim 60, wherein the compound is selected from the group consisting of:

 ,  , and  .

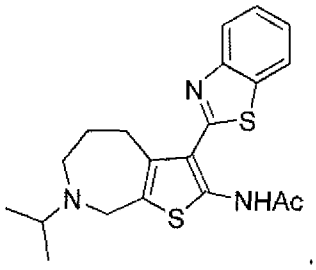
62. The method of any one of claims 37, 38, or 40-46, wherein m and n are both 1.

63. The method of claim 62, wherein the compound is:



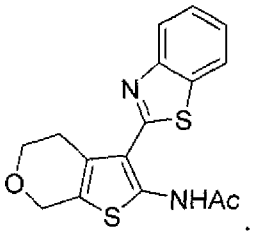
64. The method of any one of claims 37, 38, or 40-46, wherein m is 2 and n is 0.

65. The method of claim 64, wherein the compound is:



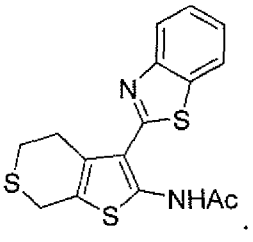
66. The method of any one of claims 37-40, wherein X is O.

67. The method of claim 66, wherein the compound is:



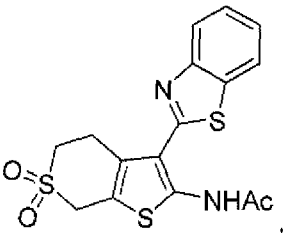
68. The method of any one of claims 37-40, wherein X is S.

69. The method of claim 68, wherein the compound is:



70. The method of any one of claims 37-40, wherein X is SO_2.

71. The method of claim 70, wherein the compound is:

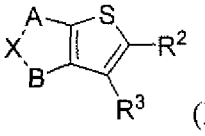


72. The method of any one of claims 37-71, wherein the method further comprises providing the patient with another anticancer agent.

73. The method of claim 72, wherein the another anticancer agent is a DNA damaging agent.

74. The method of claim 73, wherein the DNA damaging agent is methylmethane sulfonate or Temozolomide.

75. A method for potentiating or enhancing anticancer activity of an anticancer agent, the method comprising administering to a patient in need thereof an effective amount of an anticancer agent and a compound of the formula (I):



(I),

wherein X is NR^1, O, S, or SO_2,

A is $-(CR^5R^6)-(CR^7R^8)_m-$,

B is $-(CR^9R^{10})-(CR^{11}R^{12})_n-$

R^1, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are the same or different and are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when X is NR^1, m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and/or R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond, or when X is NR^1, m is 1 and n is 0, R^5 and R^7 together with the carbon atoms to which they are attached, and/or R^1 and R^9, together with the nitrogen atom and carbon atom to which they are attached, form a bond, R^2 is selected from the group consisting of $-NHCOR^4$, $-NH_2$, heterocyclyl, -NH-heterocyclyl, and -COOH, wherein the heterocyclyl is optionally substituted with an alkyl group,

R^3 is heterocyclyl, wherein the heterocyclyl is optionally substituted with an alkyl group or an aryl group, wherein the aryl group is optionally further substituted with one or more substituents selected from the group consisting of halo, dihaloalkyl, trihaloalkyl, nitro,

hydroxy, alkoxy, aryloxy, amino, substituted amino, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, thio, alkylthio, and arylthio,

R^4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, haloalkyl, dihaloalkyl, trihaloalkyl, alkoxy, alkenyl, alkenylalkyl, alkylalkenyl, alkynyl, alkynylalkyl, alkylalkynyl, aryl, arylalkyl, heterocyclyl, and arylheterocyclyl, and

m and n are independently 0, 1, or 2,

or a pharmaceutically acceptable salt thereof.

76. The method of claim 75, wherein R^2 is $NHCOR^4$.

77. The method of claim 75 or 76, wherein m is 0 and n is 1.

78. The method of any one of claims 75-77, wherein R^4 is alkyl.

79. The method of any one of claims 75-78, wherein X is NR^1.

80. The method of claim 79, wherein R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, oxacycloalkyl, alkylcarbonyl, and alkoxycarbonyl, or, when m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

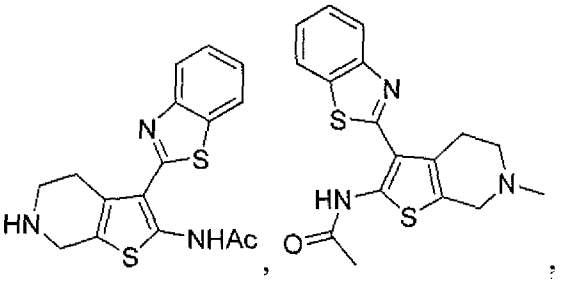
81. The method of any one of claims 75-80, wherein R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are hydrogen, or, when m is 0 and n is 1, R^1 and R^5, together with the nitrogen atom and carbon atom to which they are attached and R^9 and R^{11}, together with the carbon atoms to which they are attached, form a bond.

82. The method of any one of claims 75-81, wherein R^3 is selected from the group consisting of benzothiazol-2-yl, benzothiophene-2-yl, benzothiophene-3-yl, benzoxazol-2-yl, and indol-2-yl.

83. The method of claim 82, wherein R^3 is benzothiazol-2-yl.

84. The method of any one of claims 75-81, wherein R^3 is selected from the group consisting of furan-2-yl, tetrazolyl, thiazol-2-yl, arylthiazol-2-yl, and optionally substituted arylthiazol-2-yl.

85. The method of claim 83 or 84, wherein the compound is selected from the group consisting of:



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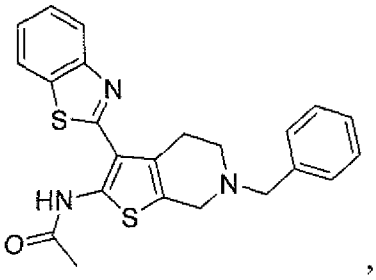

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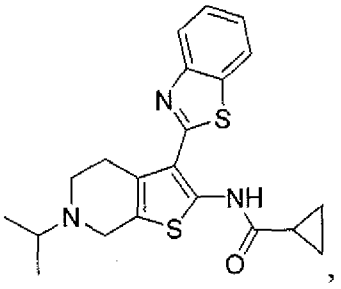

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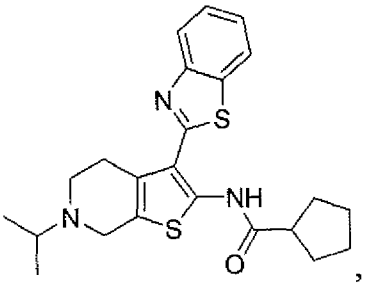

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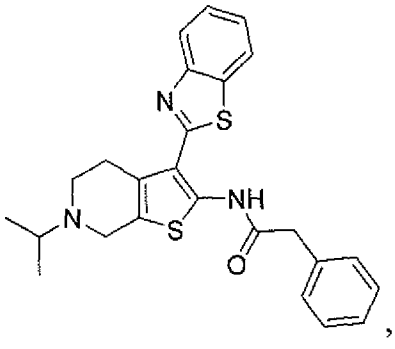

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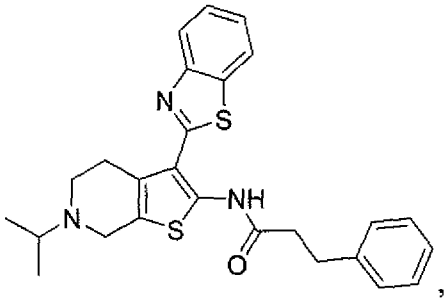

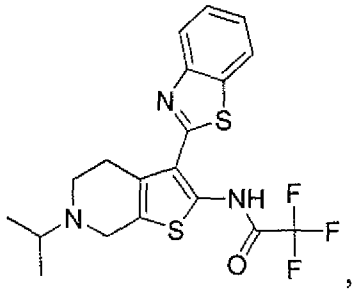

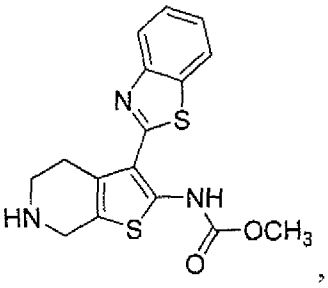

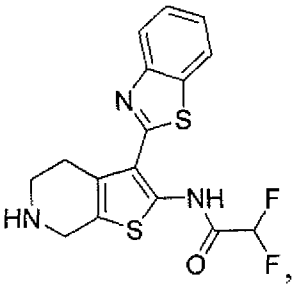

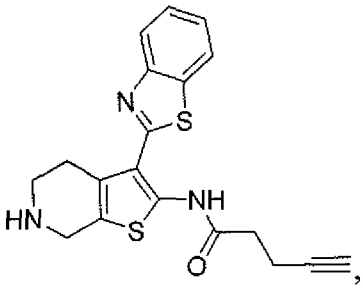

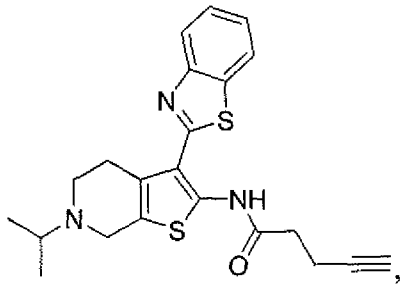

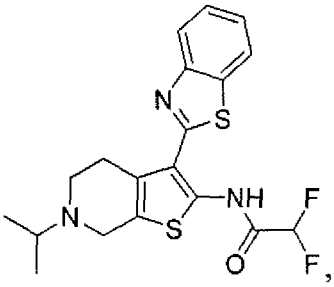
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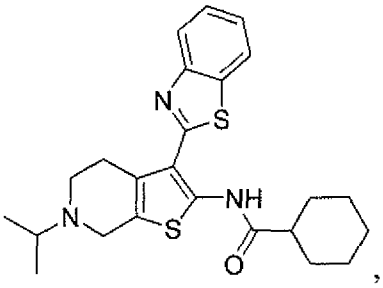
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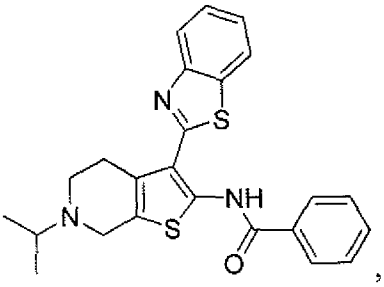
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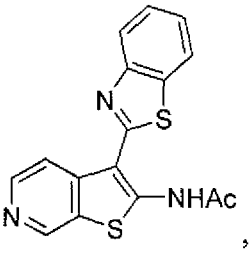
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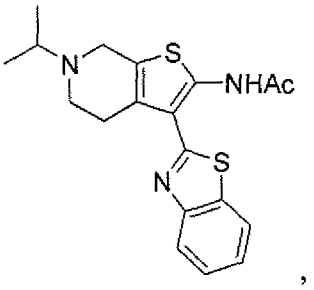
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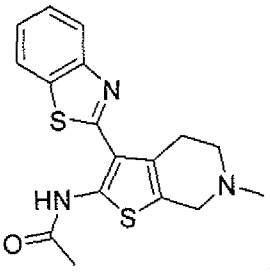
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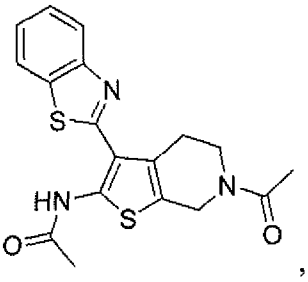
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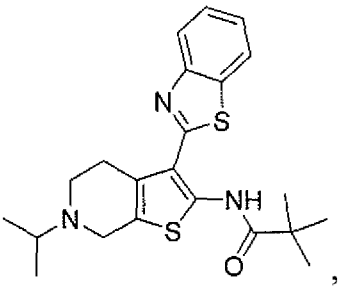
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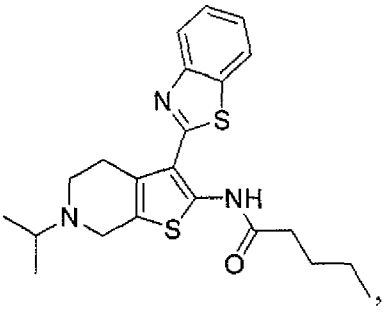
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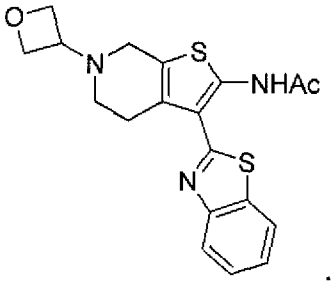
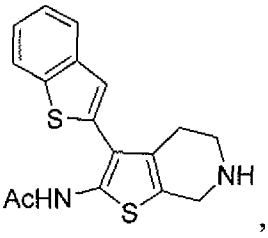
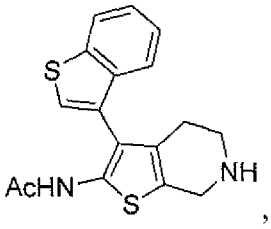
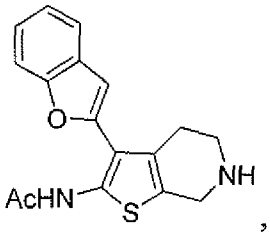
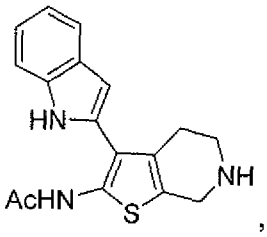
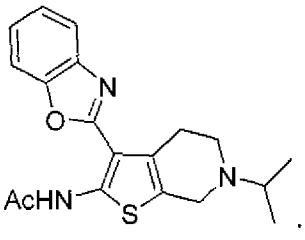


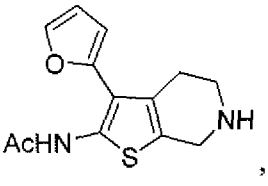
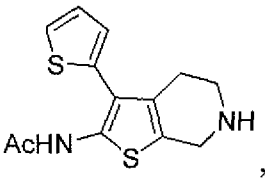
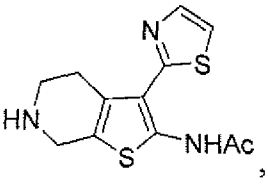
and .

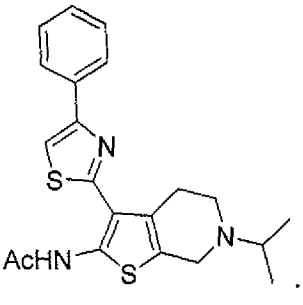
86. The method of claim 83, wherein the compound is selected from the group consisting of:

and  .

87. The method of claim 84, wherein the compound is selected from the group consisting of:

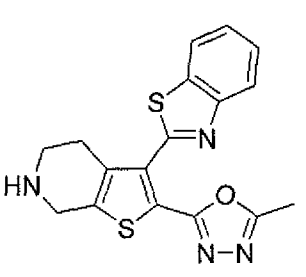
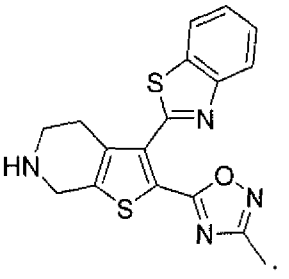


 , and

 .

88. The method of any one of claims 79-84, wherein R^2 is heterocyclyl optionally substituted with alkyl.

89. The method of claim 88, wherein m is 0 and n is 1.

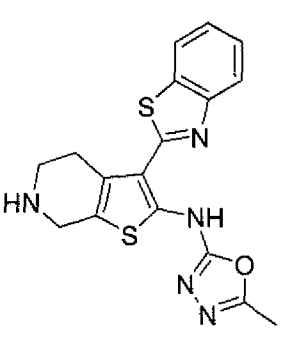
90. The method of claim 89, wherein the compound is selected from the group consisting of:


and

.

91. The method of any one of claims 79-84, wherein R^2 is –NH-heterocyclyl optionally substituted with alkyl.

92. The method of claim 91, wherein m is 0 and n is 1.

93. The method of claim 92, wherein the compound is selected from the group consisting of: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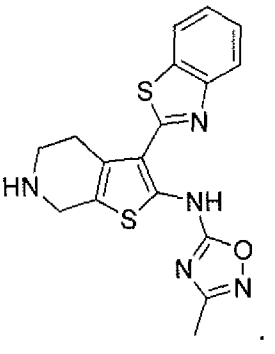
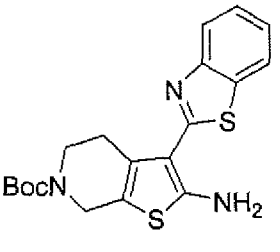
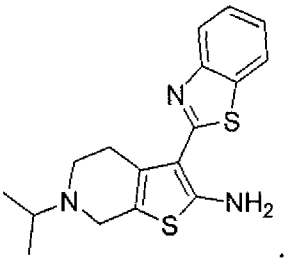

.

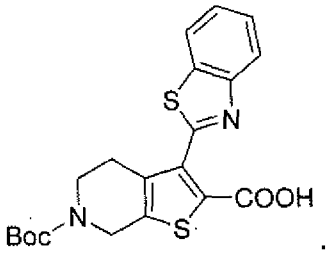
94. The method of any one of claims 79-84, wherein R^2 is $-NH_2$.

95. The method of claim 94, wherein the compound is selected from the group consisting of:


and

.

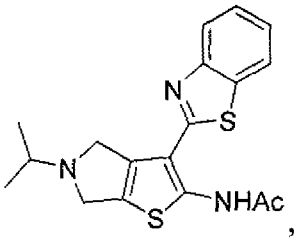
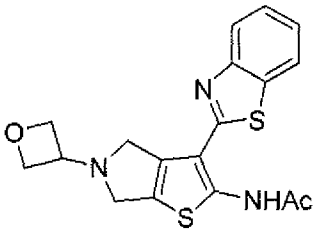
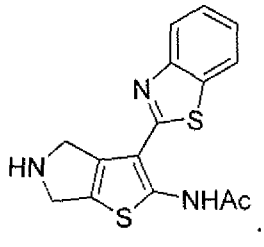
96. The method of any one of claims 79-84, wherein R^2 is –COOH.

97. The method of claim 96, wherein the compound is:



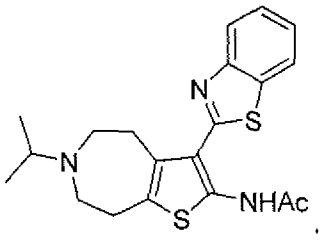
98. The method of any one of claims 75,76, or 78-84, wherein m and n are both 0.

99. The method of claim 98, wherein the compound is selected from the group consisting of:

 ,  , and  .

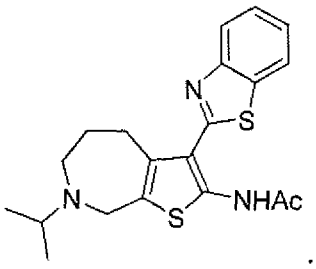
100. The method of any one of claims 75, 76, or 78-84, wherein m and n are both 1.

101. The method of claim 100, wherein the compound is:



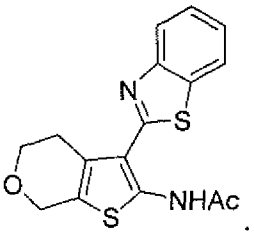
102. The method of any one of claims 75, 76, or 78-84, wherein m is 2 and n is 0.

103. The method of claim 102, wherein the compound is:



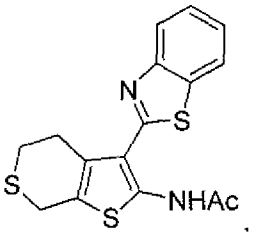
104. The method of any one of claims 75-78, wherein X is O.

105. The method of claim 104, wherein the compound is:



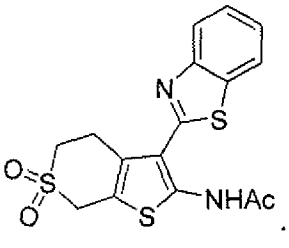
106. The method of any one of claims 75-78, wherein X is S.

107. The method of claim 106, wherein the compound is:



108. The method of any one of claims 75-78, wherein X is SO_2.

109. The method of claim 108, wherein the compound is:



110. The method of any one of claims 75-109, wherein the anticancer agent is a DNA damaging agent.

111. The method of claim 110, wherein the DNA damaging agent is methylmethane sulfonate or Temozolomide.

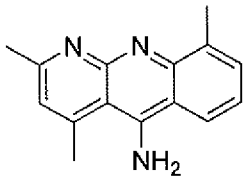
112. The method of any one of claims 75-109, wherein the anticancer agent is a disruptor of DNA replication.

113. The method of claim 112, wherein the disruptor of DNA replication is 5-fluorodeoxyuridine.

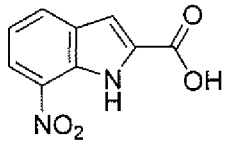
114. The method of any one of claims any one of claims 75-109, wherein co-administering comprises administering the anticancer agent and the compound or salt thereof simultaneously, separately, sequentially, or cyclically.

115. The compound of any of claims 1-35 for use in treating cancer or potentiating the anticancer activity of an anticancer agent.

FIG. 1



1
(AR-03)



2
(CRT-0044876)

FIG. 2

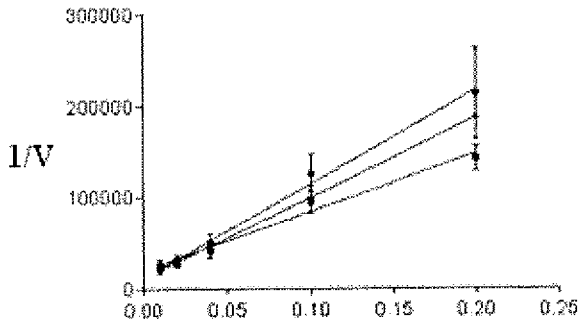


FIG. 3A

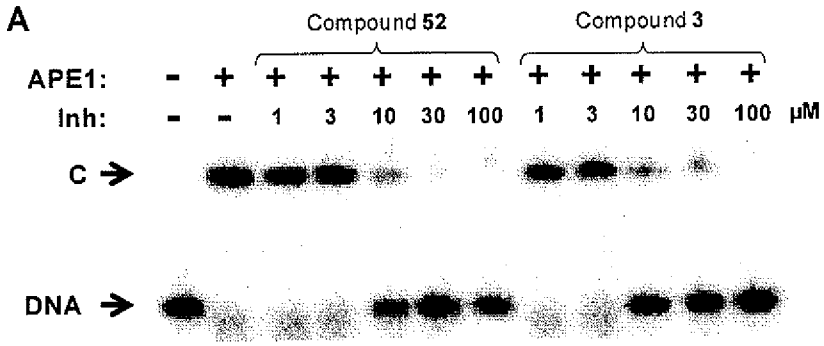

A
Compound 52
Compound 3
APE1: - + + + + + + + + + + +
Inh: - - 1 3 10 30 100 1 3 10 30 100 μM
C
DNA

FIG. 3B

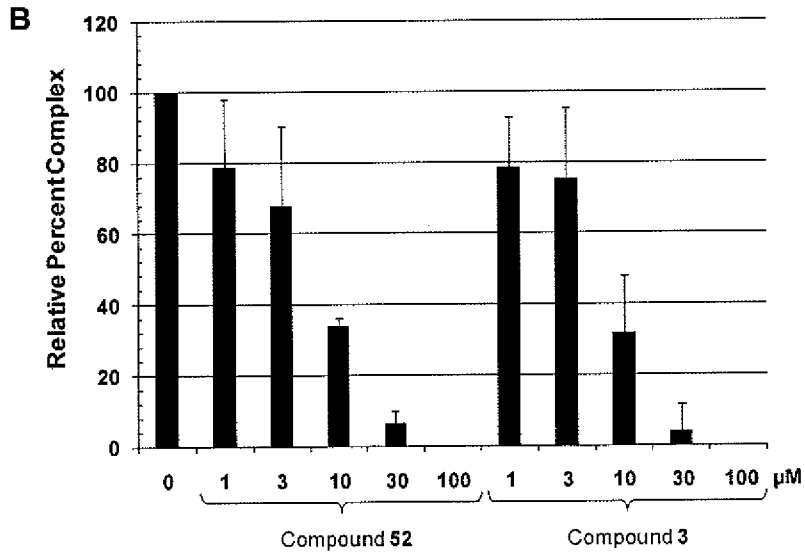
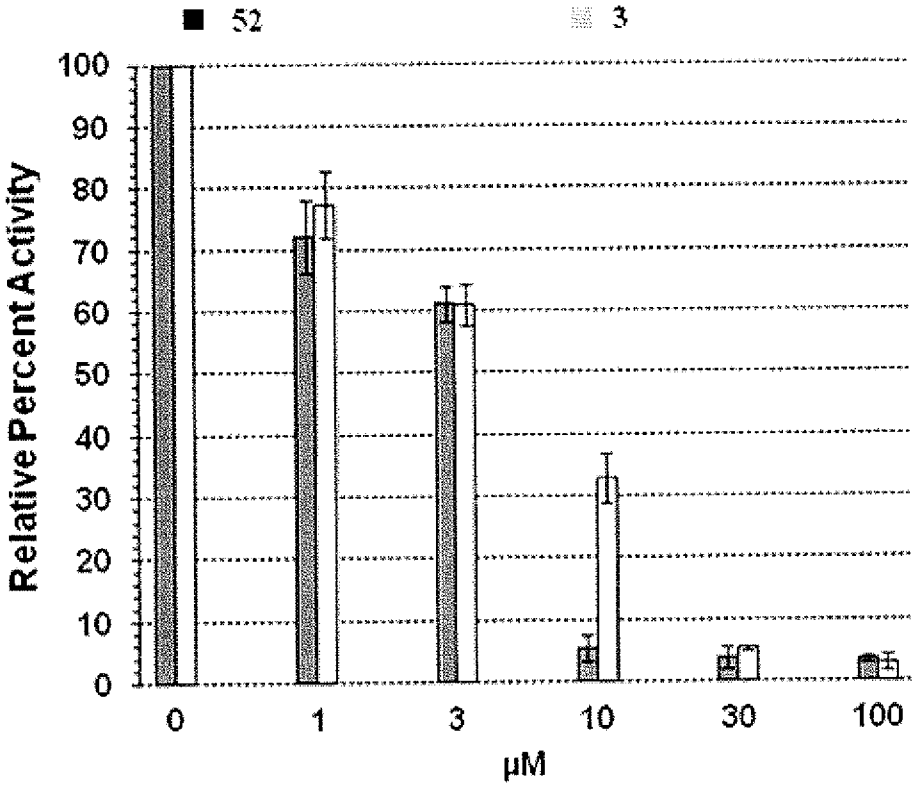

B
Relative Percent Complex
120
100
80
60
40
20
0
0 1 3 10 30 100 1 3 10 30 100 μM
Compound 52
Compound 3

FIG. 4


52
3
Relative Percent Activity
100
90
80
70
60
50
40
30
20
10
0
0
1
3
10
30
100
μM

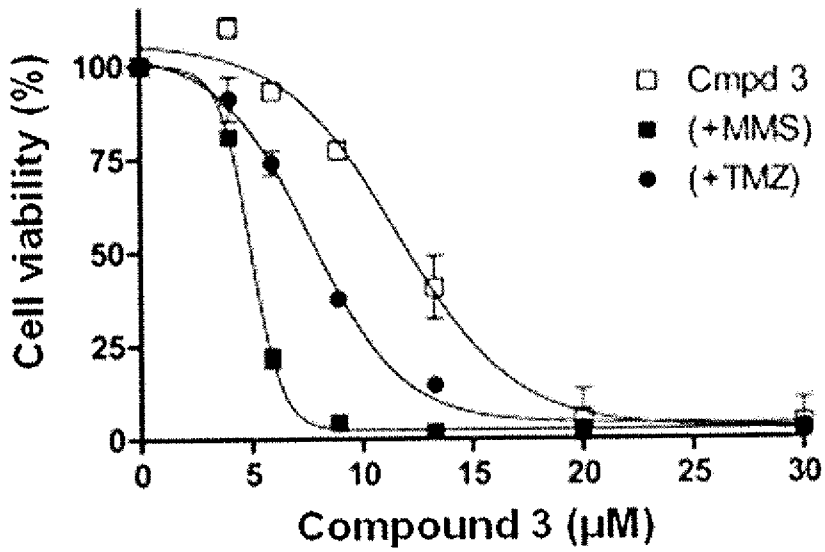

Cell viability (%)
100
75
50
25
0
0
5
10
15
20
25
30
Compound 3 (μM)
Cmpd 3
(+MMS)
(+TMZ)

FIG. 5A

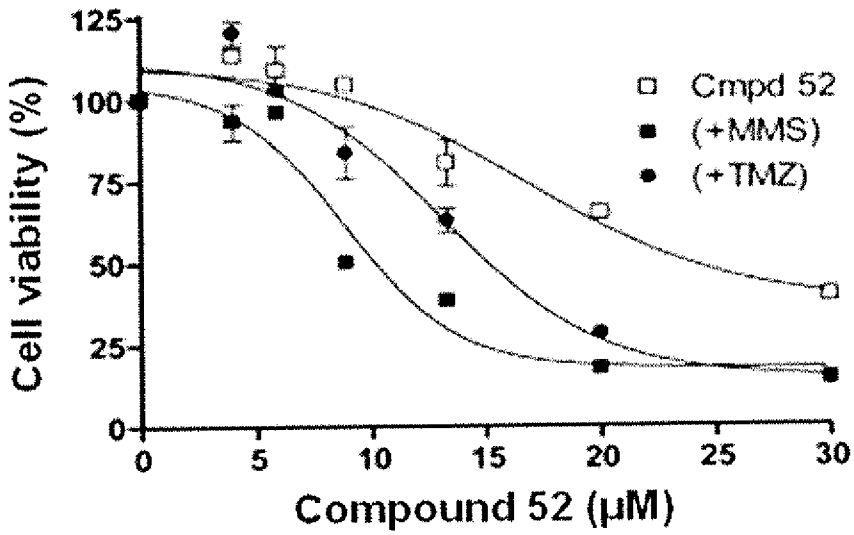

Cell viability (%)
125
100
75
50
25
0
0
5
10
15
20
25
30
Compound 52 (μM)
Cmpd 52
(+MMS)
(+TMZ)

FIG. 5B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/034755

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/55 A61K31/428 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	GANESHA RAI ET AL: "Synthesis, Biological Evaluation, and Structure-Activity Relationships of a Novel Class of Apurinic/Apyrimidinic Endonuclease 1 Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, vol. 55, no. 7, 12 April 2012 (2012-04-12) , pages 3101-3112, XP55033144, ISSN: 0022-2623, DOI: 10.1021/jm201537d the whole document ----- -/--	1-115

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2012	01/08/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Guspanová, Jana

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/053915 A1 (IVASCHENKO ANDREY ALEXANDROVICH [RU] ET AL) 3 March 2011 (2011-03-03) page 1, paragraph 1-3 comppound h2 in Scheme 8 on page 18; compounds VIII-1001,1003,1008,1009,1010, 1016 in Table 10; page 14, paragraph 374-377; claims 8,16; example 10; tables 10,11	1-9,11, 20,21, 36,115
X	WO 2008/020438 A2 (RIMONYX PHARMACEUTICALS LTD [IL]; GREGOR PAUL [IL]; ZHUK REGINA [IL];) 21 February 2008 (2008-02-21) Compounds 9,21,23,26,33,35; page 1, paragraph 1; claims 6,9,16,21; examples 1-6	1-9,11, 20,21, 36,115
X	WO 2004/069149 A2 (RIMONYX PHARMACEUTICALS LTD [IL]; GREGOR PAUL [IL]; HARRIS NICHOLAS [I) 19 August 2004 (2004-08-19) Compound A on page 42. Compounds of Table 1.example 1	1,3,5-9, 20,21
X	WO 2009/033581 A1 (BAYER HEALTHCARE AG [DE]; SCHIROK HARTMUT [DE]; LI-SOMMER YING [DE]; B) 19 March 2009 (2009-03-19) Intermediate compound 50A on page 86	1,3,6,7
X	WO 99/46267 A1 (NOVO NORDISK AS [DK]; ONTOGEN CORP [US]) 16 September 1999 (1999-09-16) Intermediate compound, N- (3- (2H-tetrazol-5-yl)-4,7-dihydro-5H-thieno [2,3-c] pyran-2-yl) formamide in Example 21 on page 74	1-4,7,10
A	ZAHRAH ZAWAHIR ET AL: "Pharmacophore Guided Discovery of Small-Molecule Human Apurinic/Apyrimidinic Endonuclease 1 Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 52, no. 1, 8 January 2009 (2009-01-08), pages 20-32, XP008144539, ISSN: 0022-2623, DOI: 10.1021/JM800739M [retrieved on 2008-12-10] the whole document	1-115

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14 September 2009 (2009-09-14), XP002680377, Database accession no. 1184124-37-5 Compound CAS rn: 1184124-37-5 -----	1,3,5-7, 20
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14 September 2009 (2009-09-14), XP002680378, Database accession no. 1184052-94-5 Compound CAS rn: 1184052-94-5 -----	1,3,5-7, 20
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 September 2009 (2009-09-13), XP002680379, Database accession no. 1183314-71-7 Compound CAS rn: 1183314-71-7 -----	1,3,5-7, 20
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2 September 2009 (2009-09-02), XP002680380, Database accession no. 1179140-58-9 Compound CAS rn: 1179140-58-9 -----	1,3,7, 20,34
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1 September 2009 (2009-09-01), XP002680381, Database accession no. 1178773-12-0 Compound CAS rn: 1178773-12-0 -----	1,3,7, 20,32
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1 September 2009 (2009-09-01), XP002680382, Database accession no. 1178717-08-2 Compound CAS rn: 1178717-08-2 -----	1,3,5-7, 20
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 31 August 2009 (2009-08-31), XP002680383, Database accession no. 1178493-19-0 Compound CAS rn: 1178493-19-0 ----- -/--	1,3,5-7, 20

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 31 August 2009 (2009-08-31), XP002680384, Database accession no. 1178304-26-1 Compound CAS rn: 1178304-26-1 -----	1,3,7, 20,30
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 March 2007 (2007-03-13), XP002680385, Database accession no. 926268-85-1 Compound CAS rn: 926268-85-1 -----	1,3,5-7, 20
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 March 2007 (2007-03-13), XP002680386, Database accession no. 926221-24-1 Compound CAS rn: 926221-24-1 -----	1,3,5-7, 20
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 March 2007 (2007-03-13), XP002680387, Database accession no. 926192-48-5 Compound CAS rn: 926192-48-5 -----	1,3,5-7, 20
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 15 September 2009 (2009-09-15), XP002680388, Database accession no. 1184607-05-3 Compound CAS rn: 1184607-05-3 -----	1,3,8,9, 20,34
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 3 September 2009 (2009-09-03), XP002680389, Database accession no. 1179626-21-1 Compound CAS rn: 1179626-21-1 -----	1,3,8,9, 20,30
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 September 2009 (2009-09-13), XP002680390, Database accession no. 1183238-61-0 Compound CAS rn: 1183238-61-0 -----	1,3,8,9, 20,32

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