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(54) **COMPOUND FOR TREATMENT OF CANCER**

VERBINDUNG ZUR BEHANDLUNG VON KREBS

COMPOSÉ POUR LE TRAITEMENT DU CANCER

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WO-A1-2008/038955 **WO-A2-2005/086902**

- **TUCKER, J. A. ET AL: "Structure-activity relationships of acyloxyamidine cytomegalovirus DNA polymerase inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY, vol. 8, no. 3, 2000, pages 601-615, XP002668129,**

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a novel compound having anti-cancer activity, methods of making these compounds, and its use for treating various forms of cancer.

BACKGROUND OF THE INVENTION

[0002] Cancer is the second most common cause of death in the United States, exceeded only by heart disease. In the United States, cancer accounts for 1 of every 4 deaths. The 5-year relative survival rate for all cancers patients diagnosed in 1996-2003 is 66%, up from 50% in 1975-1977 (Cancer Facts & Figures American Cancer Society: Atlanta, GA (2008)). This improvement in survival reflects progress in diagnosing at an earlier stage and improvements in treatment. Discovering highly effective anticancer agents with low toxicity is a primary goal of cancer research.

[0003] WO 2008/038955 discloses benzophenone derivatives useful for inhibiting the formation of microtubule. 2-arylthiazolidine-4-carboxylic acid amides have been described as potent cytotoxic agents for both prostate cancer and melanoma (Li et al., "Synthesis and Antiproliferative Activity of Thiazolidine Analogs for Melanoma," Bioorg. Med. Chem. Lett. 17:4113-7 (2007); Li et al., "Structure-Activity Relationship Studies of Arylthiazolidine Amides as Selective Cytotoxic Agents for Melanoma," Anticancer Res. 27:883-888 (2007); Lu et al., "Synthesis and Biological Evaluation of 2-Arylthiazolidine-4-Caboxylic Acid Amides for Melanoma and Prostate Cancer," Abstracts of Papers, 234th ACS National Meeting, Boston, MA, United States, August 19-23, 2007, MEDI-304; Gududuru et al., "SAR Studies of 2-Arylthiazolidine-4-Carboxylic Acid Amides: A Novel Class of Cytotoxic Agents for Prostate Cancer," Bioorg. Med. Chem. Lett. 15:4010-4013 (2005); Gududuru et al., "Discovery of 2-Arylthiazolidine-4-Carboxylic Acid Amides as a New Class of Cytotoxic Agents for Prostate Cancer," J. Med. Chem. 48:2584-2588 (2005)). These 2-arylthiazolidine-4-carboxylic acid amides were designed from lysophosphatidic acid (LPA) structure with a lipid chain. This design choice was directed toward inhibition of GPCR (guanine-binding protein-coupled receptor) signaling, which is involved in proliferation and survival of prostate cancer (Raj et al., "Guanosine Phosphate Binding Protein Coupled Receptors in Prostate Cancer: A Review," J. Urol. 167:1458-1463 (2002); Kue et al., "Essential Role for G Proteins in Prostate Cancer Cell Growth and Signaling," J. Urol. 164:2162-7 (2000); Guo et al., "Expression and Function of Lysophosphatidic Acid LPA1 Receptor in Prostate Cancer Cells," Endocrinology 147:4883-4892 (2006); Qi et al., "Lysophosphatidic Acid Stimulates Phospholipase D Activity and Cell Proliferation in PC-3 Human Prostate Cancer Cells," J. Cell. Physiol. 174:261-272 (1998)).

[0004] The most potent of the 2-aryl-thiazolidine-4-carboxylic acid amides could inhibit prostate cancer cells with an average IC_{50} in the range from 0.7 to 1.0 μM and average IC_{50} values against melanoma cells were 1.8~2.6 μM (Li et al., "Synthesis and Antiproliferative Activity of Thiazolidine Analogs for Melanoma," Bioorg. Med. Chem. Lett. 17:4113-7 (2007)). One preferred compound, (*2RS,* 4R)-2-phenyl-thiazolidine-4-carboxylic acid hexadecylamide, was sent to the United States National Cancer Institute 60 human tumor cell line anticancer drug screen (NCI-60). Results from NCI-60 assay showed that this compound could inhibit growth of all nine types of cancer cells with IC_{50} values in the range from 0.124 μM (Leukemia, CCRF-CEM) to 3.81 μM (Non-Small Cell Lung Cancer, NCI-H522). Further improvement in anticancer activity of these compounds, in terms of their IC_{50} values, would be desirable.

[0005] The present invention is directed to overcoming these and other deficiencies in the prior art.

SUMMARY OF THE INVENTION

[0006] A first aspect of the present invention relates to a compound, wherein the compound is (2-(1*H*-indol-3-yl)imidazol-4-yl)(3,4,5-trimethoxyphenyl)methanone. The compound can be provided in the form of pharmaceutically acceptable salts, hydrates, or prodrugs thereof.

[0007] A second aspect of the present invention relates to a pharmaceutical composition including a pharmaceutically acceptable carrier and the compound according to the first aspect of the present invention.

[0008] The invention also provides the compound according to the first aspect of the invention for use as a medicament.

[0009] The invention also provides the compound according to the first aspect of the invention for the preparation of a medicament for treating prostate cancer, breast cancer, ovarian cancer, skin cancer, lung cancer, colon cancer, leukemia, renal cancer or CNS cancer, or a combination thereof in a subject.

[0010] The invention also provides the compound according to the first aspect of the invention for use in treating prostate cancer, breast cancer, ovarian cancer, skin cancer, lung cancer, colon cancer, leukemia, renal cancer or CNS cancer, or a combination thereof in a subject.

[0011] In an embodiment, the compound is administered systemically. In a further embodiment, the compound may be administered orally, topically, transdermally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes.

[0012] In an embodiment, the compound is administered directly to a site where cancer cells are present.

[0013] In an embodiment, the compound is administered at a dosage rate of about 0.01 to about 100 mg of the compound per kg·body weight.

[0014] In an embodiment, the compound is administered periodically.

[0015] In an embodiment, the compound is administered in combination with another cancer therapy.

[0016] The present application discloses a new class of compounds that possess improved potency and selectivity (as compared to prior fatty acid thiazolidine carboxamides) during *in vitro* studies against several different cancer cells lines, including prostate and melanoma cancer cells. Using one preferred member of this class, it is also demonstrated in the accompanying examples that these compounds are inhibitors of tubulin polymerization. One of these compounds is demonstrated to possess significant anti-cancer activity during *in vivo* xenograft studies of melanoma in mice. Based on these data, and the demonstration of their mode of action, it is believed that the compound of the present invention has significant activity against a number of forms of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017]

Figure 1 is ORTEP drawing of compound **8f** with thermal ellipsoids depicted at 50 % probability level. The drawing was generated following X-ray crystallography studies.

Figure 2 illustrates NMR studies measuring the auto-dehydrogenation from thiazoline to thiazole compound **8f.** At 0 day, NMR sample contained thiazoline and thiazole mixtures in $CDCl_3$; ratio is about 3: 2. At 9th day, thiazoline compound was nearly completely converted to thiazole compound **8f.**

Figures 3A-B illustrate the effect of compound **8f** on cell cycle distribution of LNCaP prostate cancer cells. Figures 3A illustrate the effect of various dosages (10 nM, 50 nM, 200 nM, and 500 nM) of compound **8f** relative to control. Amounts in excess of the IC_{50} value illustrate a significant change in cell cycle distribution. Figure 3B graphically illustrates the change in G2/M versus G1 cell cycle distribution.

Figure 4 is a graph illustrating the effect of compound **8f** on tubulin assembly.

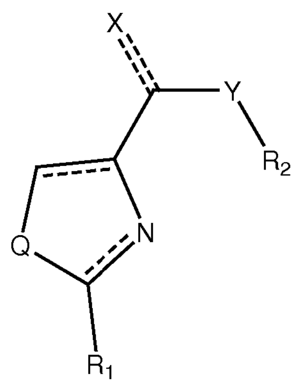
Figures 5A-B are graphs illustrating the ability of compounds **8f** and **8n** significantly to inhibit A375 melanoma colony formation in an *in vitro* assay. At 0.3 μM or above, colony formation is completely inhibited.

Figure 6 is a graph illustrating the ability of compound **8n** (6 mg/kg, IP daily injection) to inhibit B16 melanoma tumor growth *in vivo.*

DETAILED DESCRIPTION OF THE INVENTION

[0018] The present invention relates to a compound, wherein the compound is (2-(1*H*-indol-3-yl)imidazol-4-yl)(3,4,5-trimethoxyphenyl)methanone.

[0019] Also disclosed herein are compounds according to formula (I)

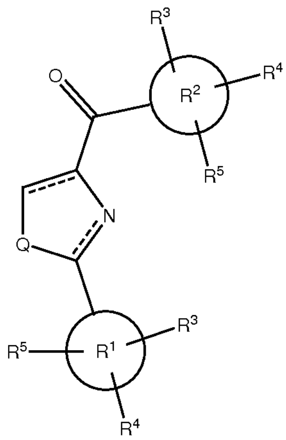


(I)

wherein

Q is S, N, or O;
X is optional, and can be S=, O=, =N-NH_2, =N-OH, or -OH;
Y is optional and can be -N(H)-, O, or C_1 to C_{20} hydrocarbon; and
R_1 and R_2 are each independently substituted or unsubstituted single-, fused- or multiple-ring aryl or (hetero)cyclic ring systems, including saturated and unsaturated N-heterocycles, saturated and unsaturated S-heterocycles, and saturated and unsaturated O-heterocycles, saturated or unsaturated cyclic hydrocarbons, saturated or unsaturated mixed heterocycles, aliphatic straight- or branched-chain C_1 to C_{30} hydrocarbons.

[0020] As disclosed herein, the class of compounds may have a structure according to formula (II):

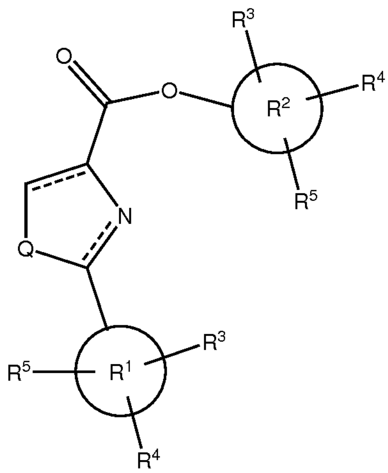


(II)

where X is O=, Y is omitted, and Q and R^1-R^5 are defined as above for formula (I).

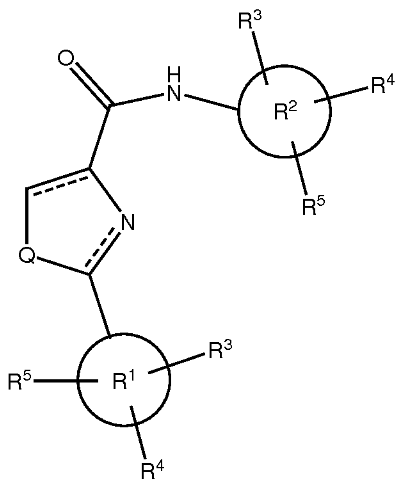
[0021] Exemplary compounds of formula (II) include (2-(*1H*-indol-3-yl)imidazol-4-yl)(3,4,5-trimethoxyphenyl)methanone, which is the compound of the present invention.

[0022] Also disclosed herein are classes of compounds having a structure according to formula (III):



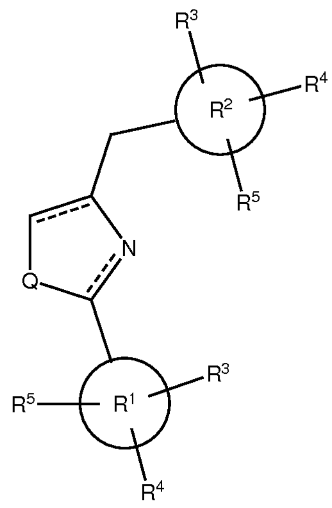
(III)

where X is O=, Y is O, and Q and R^1-R^5 are defined as above for formula (I), or having a structure according to formula (IV):



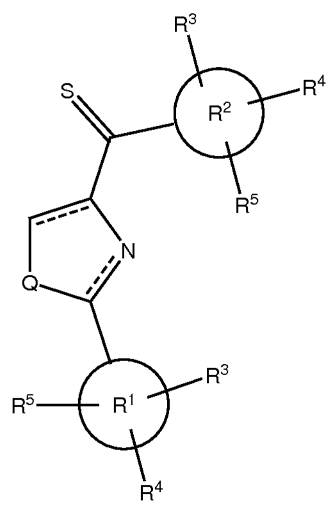
(IV)

where X is O=, Y is -NH-, and Q and R^1-R^5 are defined as above for formula (I), or having a structure according to formula (V):



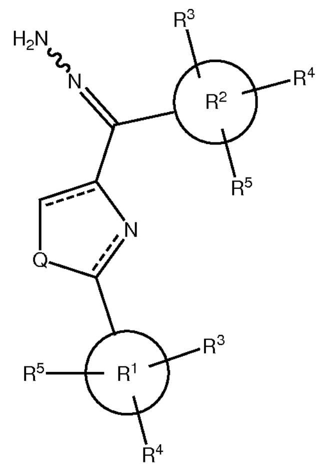
(V)

where X and Y are omitted, and Q and R^1-R^5 are defined as above for formula (I), or having a structure according to formula (VI):



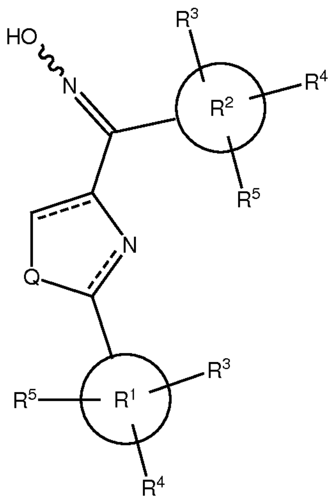
(VI)

where X is S=, Y is omitted, and Q and R^1-R^5 are defined as above for formula (I), or having a structure according to formula (VII):



(VII)

where X is =N-NH_2, Y is omitted, and Q and R^1-R^5 are defined as above for formula (I), or having a structure according to formula (VIII):



(VIII)

where X is =N-OH, Y is omitted, and Q and R^1-R^5 are defined as above for formula (I).

[0023] Certain compounds, particularly those possessing acid or basic groups, can also be in the form of a salt, preferably a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to those salts that retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxylic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcysteine and the like. Other salts are known to those of skill in the art and can readily be adapted for use in accordance with the present invention.

[0024] The compound of the present invention may also be administered as a prodrug. Thus, certain derivatives which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into the compound of the present invention having the desired activity, for example, by hydrolytic cleavage. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (Higuchi and Stella); and Bioreversible Carriers in Drug Design, Pergamon Press (ed. E B Roche, American Pharmaceutical Association) (1987).

[0025] Prodrugs can, for example, be produced by replacing appropriate functionalities present in the compounds of the present invention with certain moieties known to those skilled in the art as pro-moieties. Examples of such prodrugs include, without limitation, replacement of hydrogen in an alcohol functionality (-OH) by a C1 to C6 alkyl to form an ether; and (ii) replacement of hydrogen in a secondary amino functionality with a C1 to C10 alkanoyl to form an amide.

[0026] The compound of the present invention can also be in the form of a hydrate, which means that the compound further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[0027] The compound of the present invention can also be present in the form of a racemic mixture, containing substantially equivalent amounts of stereoisomers. In another embodiment, the compound of the present invention can be prepared or otherwise isolated, using known procedures, to obtain a stereoisomer substantially free of its corresponding stereoisomer (i.e., substantially pure). By substantially pure, it is intended that a stereoisomer is at least about 95% pure, more preferably at least about 98% pure, most preferably at least about 99% pure.

[0028] Also disclosed herein is a method of making the compounds according to formula (I). Furthermore, the present invention discloses synthetic methodologies for the preparation of amide, alkoxyamides, ketone, hydrazine, and oxime derivatives of thiazolidines, thiazolines, thiazoles, imidazolines, imidazoles, oxazolidines, oxazolines, and oxazoles.

[0029] As disclosed herein, to synthesize thiazoline and thiazole series compounds, L- or D-cysteine can be reacted ith substituted or unsubstituted benzonitrile in methanol and pH 6.4 phosphate buffer solution at ambient temperature for several days (Bergeron et al., "Evaluation of Desferrithiocin and its Synthetic Analogs as Orally Effective Iron Chelators," J. Med. Chem. 34:2072-8 (1991); Bergeron et al., "Desazadesmethyldesferrithiocin Analogues as Orally Effective Iron Chelators," J. Med. Chem. 42:95-108 (1999); Zamri et al., "An Improved Stereocontrolled Synthesis of Pyochelin, Siderophore of Pseudomonas aeruginosa and Burkholderia cepacia," Tetrahedron 56:249-256 (2000)). The resulting carboxylic acid intermediates can be easily converted to corresponding Weinreb amides (Nahm et al., "N-Methoxy-N-methylamides as Effective Acylating Agents," Tetrahedron Lett. 22:3815-18 (1981)) using EDCI/HOBt as coupling reagents. Thiazole intermediates can be obtained from $BrCCl_3$/DBU dehydrogenation of the Weinreb amides. The thiazole intermediates can be reacted with appropriate lithium reagents or Grignard reagents (i.e., bearing the corresponding "C" ring, see Scheme 3 *infra*) in anhydrous THF to give the final thiazoles (Nahm et al., "N-Methoxy-N-methylamides as Effective Acylating Agents," Tetrahedron Lett. 22:3815-18 (1981)). Alternatively, the thiazoline Weinreb amides can be reacted directly with appropriate lithium reagents or Grignard reagents, after quenching with saturated NH_4Cl solution, which affords mixtures of thiazoline compounds and the corresponding thiazole compounds.

[0030] As disclosed herein, when thiazoline/thiazole mixtures were placed in the solvent and exposed to air under ambient atmosphere for some time (overnight to several days), the thiazoline ring spontaneously dehydrogenated to thiazoles. As an example, in solution with deuterated chloroform, mixtures of thiazoline/thiazole compounds can be slowly converted to almost pure thiazole compounds after roughly 9 days (*see*, e.g., Figure 2).

[0031] Formation of thiazolidine compounds is described in U.S. Patent No. 7,307,093 to Miller et al. and U.S. Patent Application Publ. No. 2007/0155807 to Miller et al.

[0032] As disclosed herein, oxazoline derivatives (carboxylic acids, carboxamides, methanones) according to the present invention are prepared via condensation of imine derivatives (benzonitrile and 1-phenyl-2-methoxy-ethanimine) with enantioneric (L or D) or racemic cysteine or serine ester while using triethylamine as a base (Meyer et al., Tetrahedron: Asymmetry 14:2229-2238 (2003))

[0033] Imidazoline derivatives, such as the compound of the present invention, are prepared using L-tartaric acid in a condensation reaction with substituted or unsubstituted arylaldehyde to form the imidazoline ring system (Anderson et al., J. Med. Chem. 32(1),119-127 (1989)).

[0034] Syntheses of thiazole, oxazole, and imidazole can be carried out by dehydrogenation of corresponding thiazoline, oxazoline, and imidazoline. Dehydrogenation according to the present invention can be achieved by initial halogenation of these core ring systems (thiazoline, imidazoline, and oxazoline) followed by elimination to yield the desired thiazole, oxazole, and imidazole derivatives.

[0035] Formation of thiocarbonyl linker group (from carbonyl) can be carried out using Lawesson's reagent (Jesberger et al., Synthesis 1929-1958 (2003)). The thioketone structure with conjugated aromatic rings is stable relative to unhindered thioketones.

[0036] The carbonyl linker group can also be reduced to an alcohol using Grignard reaction of an intermediate aldehyde with according Grignard reagents. Alternatively, the carbonyl group can be completely removed with Clemmensen reduction to form the corresponding hydrocarbon (e.g., methylene group). When carbonyl is reduced to an alcohol or methylene, the strong hydrogen acceptor C=O reverses to strong hydrogen donor O-H or hydrocarbon, which totally loses hydrogen bond effects.

[0037] The ester and carboxamide linkages can be prepare from the same intermediate acids used to form the ketone linkage, except that the reactants (acid and "C" ring precursor) are exposed to suitable conditions for formation of the respective ester (DCC, NMM) or amide (EDC1, HOBt, Et_3N) linkages. Carboxamide linkages are also taught in U.S. Patent No. 7,307,093 to Miller et al. and U.S. Patent Application Publ. No. 2007/0155807 to Miller et al.

[0038] It is also appreciated that the compounds and synthetic intermediates disclosed herein can be prepared by synthetic processes known to those skilled in the art. Functional groups of intermediates and compounds of the present invention may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl (t-Boc or Boc), benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R (where R is alkyl, aryl or aralkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or aralkyl esters.

[0039] Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. The use of protecting groups is described in detail in Green et al., Protective Groups in Organic Synthesis, 2nd Ed., Wiley-Interscience (1991).

[0040] Another aspect of the present invention relates to a pharmaceutical composition including a pharmaceutically acceptable carrier and a compound of the present invention. Typically, the pharmaceutical composition of the present invention will include a compound of the present invention or its pharmaceutically acceptable salt, as well as a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to any suitable adjuvants, carriers, excipients, or stabilizers, and can be in solid or liquid form such as, tablets, capsules, powders, solutions, suspensions, or emulsions.

[0041] Typically, the composition will contain from about 0.01 to 99 percent, preferably from about 20 to 75 percent of active compound(s), together with the adjuvants, carriers and/or excipients. While individual needs may vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typical dosages comprise about 0.01 to about 100 mg/kg·body wt. The preferred dosages comprise about 0.1 to about 100 mg/kg·body wt. The most preferred dosages comprise about 1 to about 100 mg/kg·body wt. Treatment regimen for the administration of the compounds of the present invention can also be determined readily by those with ordinary skill in art. That is, the frequency of administration and size of the dose can be established by routine optimization, preferably while minimizing any side effects.

[0042] The solid unit dosage forms can be of the conventional type. The solid form can be a capsule and the like, such as an ordinary gelatin type containing the compounds of the present invention and a carrier, for example, lubricants and inert fillers such as, lactose, sucrose, or cornstarch. In another embodiment, these compounds are tableted with conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders like acacia, cornstarch, or gelatin, disintegrating agents, such as cornstarch, potato starch, or alginic acid, and a lubricant, like stearic acid or magnesium stearate.

[0043] The tablets, capsules, and the like can also contain a binder such as gum tragacanth, acacia, corn starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

[0044] Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets can be coated with shellac, sugar, or both. A syrup can contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor.

[0045] For oral therapeutic administration, these active compounds can be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compound in these compositions can, of course, be varied and can conveniently be between about 2% to about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions according to the present invention are prepared so that an oral dosage unit contains between about 1 mg and 800 mg of active compound.

[0046] The active compound of the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or can be enclosed in hard or soft shell capsules, or can be compressed into tablets, or can be incorporated directly with the food of the diet.

[0047] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

[0048] The compounds or pharmaceutical compositions of the present invention may also be administered in injectable dosages by solution or suspension of these materials in a physiologically acceptable diluent with a pharmaceutical adjuvant, carrier or excipient. Such adjuvants, carriers and/or excipients include, but are not limited to, sterile liquids, such as water and oils, with or without the addition of a surfactant and other pharmaceutically and physiologically acceptable components. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions.

[0049] These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols such as, propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0050] For use as aerosols, the compounds of the present invention in solution or suspension may be packaged in a pressurized aerosol container together with suitable propellants, for example, hydrocarbon propellants like propane, butane, or isobutane with conventional adjuvants. The materials of the present invention also may be administered in a non-pressurized form such as in a nebulizer or atomizer.

[0051] Yet another aspect of the present invention relates to a pharmaceutical composition comprising the compound of the invention and a pharmaceutically acceptable carrier for use in treating prostate cancer, breast cancer, ovarian cancer, skin cancer, lung cancer, colon cancer, leukemia, renal cancer or CNS cancer, or a combination thereof in a subject in need thereof.

[0052] When administering the compounds of the present invention, they can be administered systemically or, alternatively, they can be administered directly to a specific site where cancer cells or precancerous cells are present. Thus, administering can be accomplished in any manner effective for delivering the compounds or the pharmaceutical compositions to the cancer cells or precancerous cells. Exemplary modes of administration include, without limitation, administering the compounds or compositions orally, topically, transdermally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes, such as, that of the nose, throat, and bronchial tubes.

[0053] The compounds of the present invention are useful in the treatment or prevention of various forms of cancer, particularly prostate cancer, breast cancer, ovarian, skin cancer (e.g., melanoma), lung cancer, colon cancer, leukemia, renal cancer, CNS cancer (e.g., glioma, glioblastoma). Treatment of these different cancers is supported by the Examples herein. Moreover, based upon their believed mode of action as tubulin inhibitors, it is believed that other forms of cancer will likewise be treatable or preventable upon administration of the compounds or compositions of the present invention to a patient. Preferred compounds of the present invention are selectively disruptive to cancer cells, causing ablation of cancer cells but preferably not normal cells. Significantly, harm to normal cells is minimized because the cancer cells are susceptible to disruption at much lower concentrations of the compounds of the present invention.

[0054] Thus, a further aspect of the present invention relates to an *ex vivo* method of destroying a cancerous cell that includes: providing a compound of the present invention and then contacting a cancerous cell with the compound under conditions effective to destroy the contacted cancerous cell *ex vivo* (i.e., in culture).

[0055] According to one embodiment, the patient to be treated is characterized by the presence of a precancerous condition, and the administering of the compound is effective to prevent development of the precancerous condition into the cancerous condition. This can occur by destroying the precancerous cell prior to or concurrent with its further development into a cancerous state.

[0056] According to another embodiment, the patient to be treated is characterized by the presence of a cancerous condition, and the administering of the compound is effective either to cause regression of the cancerous condition or to inhibit growth of the cancerous condition, i.e., stopping its growth altogether or reducing its rate of growth. This preferably occurs by destroying cancer cells, regardless of their location in the patient body. That is, whether the cancer cells are located at a primary tumor site or whether the cancer cells have metastasized and created secondary tumors within the patient body.

[0057] As used herein, subject or patient refers to any mammalian patient, including without limitation, humans and other primates, dogs, cats, horses, cows, sheep, pigs, rats, mice, and other rodents.

[0058] When the compounds or pharmaceutical compositions of the present invention are administered to treat or prevent a cancerous condition, the pharmaceutical composition can also contain, or can be administered in conjunction with, other therapeutic agents or treatment regimen presently known or hereafter developed for the treatment of various types of cancer. Examples of other therapeutic agents or treatment regimen include, without limitation, radiation therapy, immunotherapy, chemotherapy, surgical intervention, and combinations thereof.

EXAMPLES

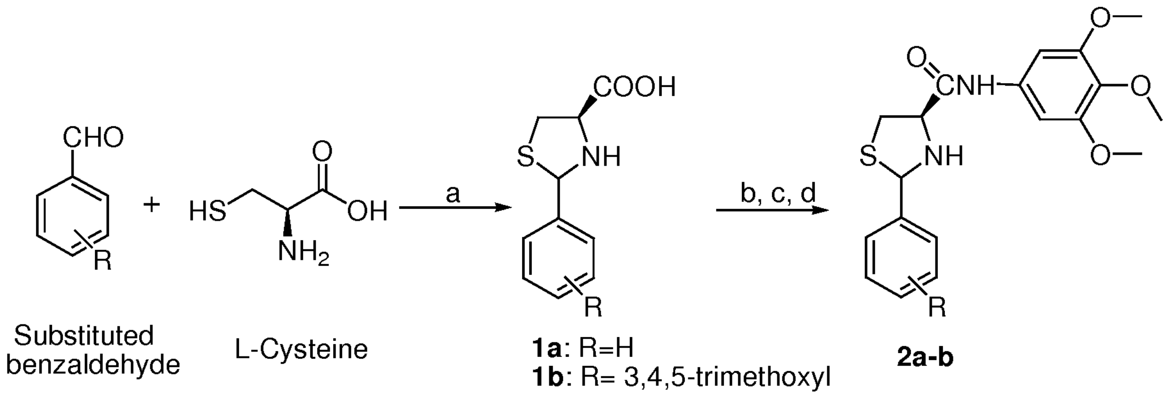
[0059] To the extent that the following examples do not relate to the compound (2-(1*H*-indol-3-yl)imidazol-4-yl)(3,4,5-trimethoxyphenyl)methanone, they are comparative examples.

[0060] All reagents were purchased from Sigma-Aldrich Chemical Co., Fisher Scientific (Pittsburgh, PA), AK Scientific (Mountain View, CA), Oakwood Products (West Columbia, SC), etc. and were used without further purification. Moisturesensitive reactions were carried under an argon atmosphere. Routine thin layer chromatography (TLC) was performed on aluminum backed Uniplates. (Analtech, Newark, DE). Melting points were measured with Fisher-Johns melting point apparatus (uncorrected). NMR spectra were obtained on a Bruker ARX 300 (Billerica, MA) spectrometer or Varian Inova-500 spectrometer. Chemical shifts are reported as parts per million (ppm) relative to TMS in $CDCl_3$. Mass spectral data was collected on a Bruker ESQUIRE electrospray/ion trap instrument in positive and negative ion modes. Elemental analyses were performed by Atlantic Microlab Inc., (Norcross, GA).

Example 1 - Synthesis of Thiazole, Thiazoline, and Thiazolidine Carboxamides

[0061] The synthesis of thiazole and thiazolidine carboxamides is generally disclosed in U.S. Patent No. 7,307,093 to Miller et al. and U.S. Patent Application Publ. No. 2007/0155807 to Miller et al.. The synthesis of various thiazole, dihydrothiazole, and thiazolidine carboxamide compounds is also illustrated in Scheme 1 below.

Scheme 1



Reagents and conditions: (a) C_2H_5OH, H_2O, r.t.; (b) Boc_2O, 1 N NaOH, 1, 4-dioxane, H_2O; (c) EDCI, HOBt, TEA, 3,4,5-trimethoxyaniline; (d) TFA, CH_2Cl_2.

[0062] General Procedure for the preparation of (2RS,4R)-2-Aryl-thiazolidine-4-carboxylic **1:** A mixture of L-cysteine (3.16 g, 26.11 mmol) and appropriate aldehyde (26.15 mmol) in ethanol (300 mL) and water (30 mL) was stirred at room temperature for 6-15h, and the solid that precipitated out was collected, washed with diethyl ether, and dried to afford the according *(2RS,4R)*-2-aryl-thiazolidine-4-carboxylic acid **1** with yields of 70-99%. At 0 °C, **1** (5.95 mmol) was dissolved in 1N NaOH (6 mL) and 1,4-dioxane (15 mL), then di-*tert*-butyldicarbonate (2.80 g, 12.80 mmol) was added slowly and stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuum and washed with ethyl acetate (20 mL). The aqueous phase was adjusted to pH=4 by adding 1N HCl or 5% $KHSO_4$, then extracted with ethyl acetate, dried with magnesium sulfate, filtered and concentrated on vacuum to give corresponding BOC protected acids as white foam-solids, which were used for next step without further purification.

[0063] General Procedure for the preparation of (2RS,4R)-2-Aryl-N-(3,4,5-trimethoxyphenyl)thiazolidine-4-carboxamides **2a,2b:** A mixture of appropriate BOC protected carboxylic acids (0.3-0.5g), EDCI (1.2 equiv) and HOBT (1.05 equiv) in CH_2Cl_2 (20 mL) was stirred at room temperature for 10 min. To this solution, 3,4,5-trimethoxyaniline (1.05 equiv) and Et_3N (1.2 equiv) were added and stirring continued at room temperature for 6-8 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and sequentially washed with water, satd. $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a crude oil, which were stirred with TFA (0.6-1 mL) in 20 mL CH_2Cl_2 at r. t for 1-8 h to cleave the BOC group. The reaction mixture was concentrated, washed with satd. $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed to yield a crude solid, and compounds **2a**-**2b** were purified by column chromatography. Yield was reported as 2 steps yield.

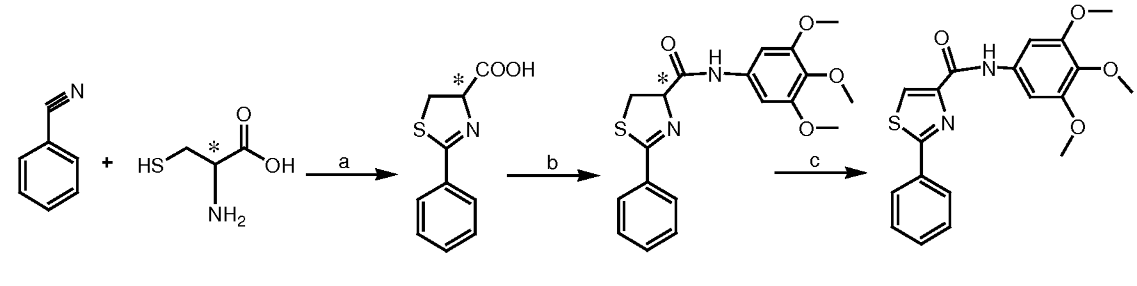
(2RS,4R)-2-Phenyl-N-(3,4,5-trimethoxyphenyl)thiazolidine-4-carboxamide **(compound 2a):** Yield: 69.5 %. M. p. 158-159 °C. ^1H NMR (300MHz, $CDCl_3$) δ 9.14 (s, 0.8 H), 8.61 (s, 0.2 H), 7.58-7.32 (m, 5 H), 6.90 (s, 1.6 H), 6.71 (s, 0.4H), 5.71 (dd, 0.2 H, J = 9.0 Hz), 5.42 (dd, 0.8 H, J = 11.7 Hz), 4.53 (dt, 0.8 H), 4.19 (m, 0.2 H), 3.87, 3.80 (s, s, 6 H), 3.82, 3.78 (s, s, 3 H), 3.80-3.78 (m, 0.4 H), 3.62-3.42 (m, 1.6 H), 2.96 (t, 0.2 H, J = 9.0 Hz), 2.74 (dd, 0.8 H, J = 11.7 Hz). MS (ESI) *m/z* 375.1 $[M + H]^+$, 397.1 $[M + Na]^+$. Anal. ($C_{19}H_{22}N_2O_4S$) C, H, N.

(2RS,4R)-N,2-bis(3,4,5-trimethoxyphenyl)thiazolidine-4-carboxamide **(compound 2b):** Yield: 34.5 %. M. p. 147-149 °C.

^1H NMR (300MHz, $CDCl_3$) δ 9.10 (s, 0.7 H), 8.59 (s, 0.3 H), 6.90 (s, 1.4 H), 6.80 (s, 0.6 H), 6.74 (s, 1.4H), 6.71 (s, 0.6 H), 5.66 (br, 0.3 H), 5.35 (d, br, 0.7 H, J = 7.5 Hz), 4.52 (br, 0.7 H), 4.21 (br, 0.3 H), 3.90, 3.87, 3.86, 3.84, 3.82, 3.81, 3.79, 3.78 (all s, 18 H), 3.66-3.61, 3.54-3.38 (m, 1.6 H), 2.98, 2.72 (br, 1 H). MS (ESI) *m/z* 465.1 $[M + H]^+$, 487.1 $[M + Na]^+$. Anal. ($C_{22}H_{28}N_2O_7S$) C, H, N.

[0064] To enhance the activity and to develop more selective agents, this synthesis was extended and, as discussed in the subsequent examples, biological studies were performed to examine the nature of the substituents attached to the carbonyl at the 4 position. The synthesis of these additional compounds is shown in Scheme 2 below.

Scheme 2



Benzonitrile L- or D- Cysteine **3a-b** **4a-b** **5**

a: R-isomer
b: S-isomer

Reagents and conditions: (a) MeOH / pH=6.4 phosphate buffer, r.t.; (b) EDCI, HOBt, TEA, 3, 4, 5-trimethoxyaniline; (c) $CBrCl_3$, DBU.

[0065] *Synthesis of 2-Phenyl-N-(3,4,5-trimethoxyphenyl)-4,5-dihydrothiazole-4-carboxamides* ***4a-4b***, *5*: Substituted benzonitrile (40 mmol) was combined with L- or D-Cysteine (45mmol) in 100 mL of 1:1 MeOH/pH6.4 phosphate buffer solution. The reaction was stirred at 40°C for 3 days (Bergeron et al., "Evaluation of Desferrithiocin and its Synthetic Analogs as Orally Effective Iron Chelators," J. Med. Chem. 34:2072-8 (1991)). Precipitate was removed through filtration, and MeOH was removed using rotary evaporation. The remaining solution was added 1M HCl to adjust pH=4 under 0 °C. The resulting precipitate was extracted into CH_2Cl_2, dried and concentrated (Scheme 2). The carboxylic acids **3a,3b** were reacted with 3,4,5-trimethoxyaniline using the same procedures as described for preparation of compounds **2a,2b,** thereby forming compounds **4a,4b.** Conversion of the dihydrothiazoles **4a,4b** to the thiazolidine **5** was carried out by oxidation with $BrCCl_3$/DBU (Williams et al., "Studies of Mild Dehydrogenations in Heterocyclic Systems," Tetrahedron Lett. 38:331-334 (1997)).

(4R)-2-Phenyl-4,5-dihydrothiazole-4-carboxylic acid **(compound 3a):** Yield: 58.3 %. ^1H NMR (300MHz, $CDCl_3$) δ 9.31 (br, 1 H), 7.88-7.85 (m, 2 H), 7.55-7.41 (m, 3 H), 5.38 (t, 1 H, J = 9.6 Hz), 3.75 (dt, 2 H, J = 9.6 Hz, 2.7 Hz). MS (ESI) *m/z* 162.0 $[M - COOH]^-$.

(4S)-2-Phenyl-4,5-dihydrothiazole-4-carboxylic acid **(compound 3b):** Yield: 53.9 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.89-7.85 (m, 2 H), 7.55-7.41 (m, 3 H), 5.38 (t, 1 H, J = 9.3 Hz), 3.75 (dt, 2 H, J = 9.3 Hz, 2.7 Hz). MS (ESI) *m/z* 162.0 $[M - COOH]^-$.

(4R)-2-Phenyl-N-(3,4,5-trimethoxyphenyl)-4,5-dihydrothiazole-4-carboxamide **(compound 4a):** Yield: 98.7 %. M. p. 121-122 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.98 (s, 1 H), 8.02-7.94, 7.62-7.48 (m, 5 H), 6.93 (s, 2 H), 5.38 (t, 1 H, J = 9.6 Hz), 3.92-3.85 (m, 2 H), 3.87 (s, 6 H), 3.82 (s, 3 H). MS (ESI) *m/z* 373.1 $[M + H]^+$. Anal. ($C_{19}H_{20}N_2O_4S$) C, H, N.

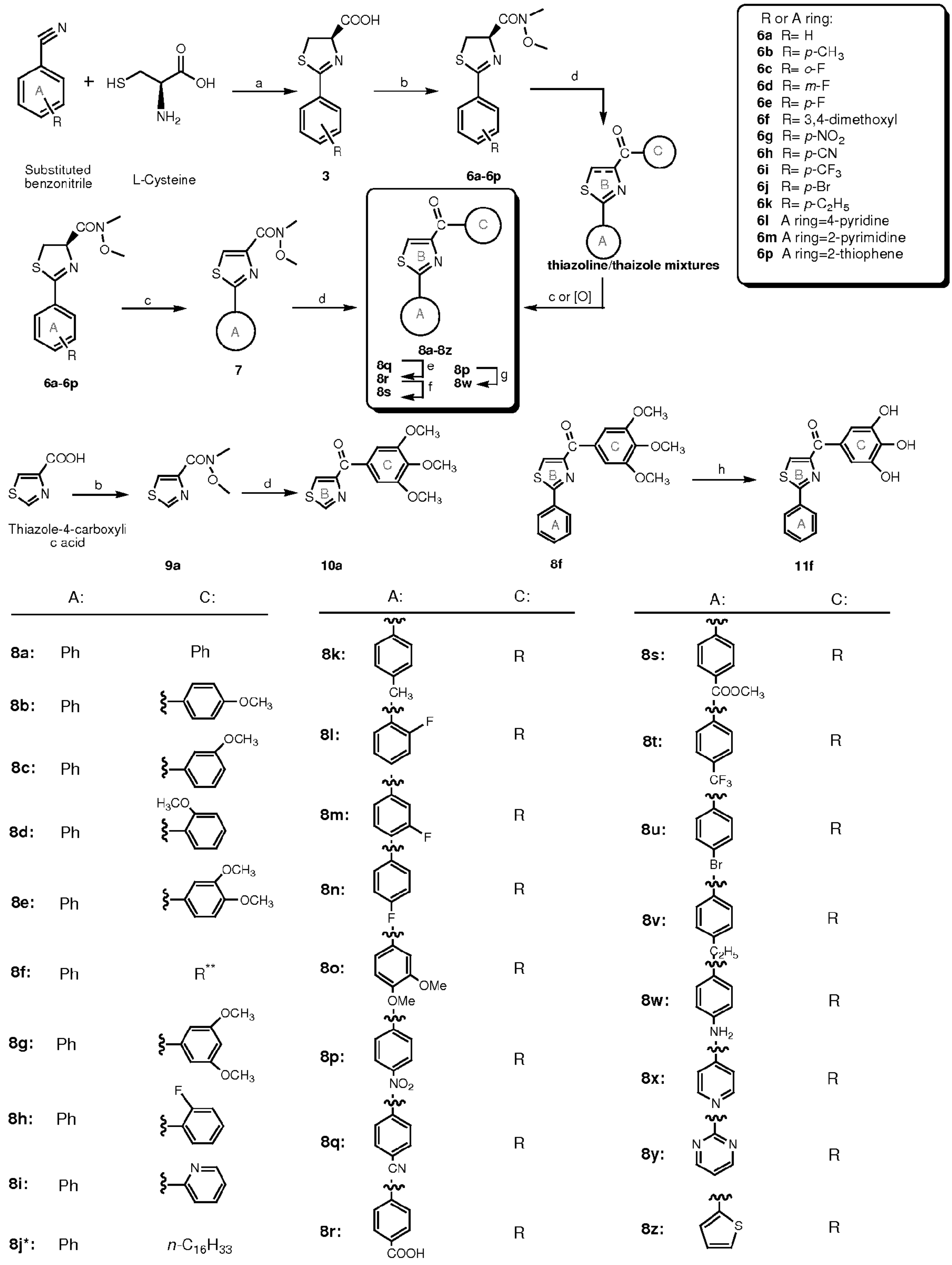
(4R)-2-Phenyl-N-(3,4,5-trimethoxyphenyl)-4,5-dihydrothiazole-4-carboxamide **(compound 4b):** Yield: 70.7 %. M. p. 122-123 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.62 (s, 1 H), 7.93-7.90 (m, 2 H), 7.55-7.45 (m, 3 H), 6.88 (s, 2 H), 5.31 (t, 1 H, J = 9.6 Hz), 3.86 (s, 6 H), 3.79 (s, 3 H), 3.83-3.70 (m, 2 H). MS (ESI) *m/z* 395.1 $[M + Na]^+$, 370.9 $[M - 1]^-$. Anal. ($C_{19}H_{20}N_2O_4S$) C, H, N.

2-Phenyl-N-(3,4,5-trimethoxyphenyl)thiazole-4-carboxamide **(compound 5):** Yield: 89.7 %. M. p. 157-158 °C. ^1H NMR (300MHz, $CDCl_3$) δ 9.30 (s, 1 H), 8.20 (s, 1 H), 8.04-8.01 (m, 2 H), 7.53-7.51 (m, 3 H), 7.08 (s, 2 H), 3.92 (s, 6 H), 3.86 (s, 3 H). MS (ESI) *m/z* 393.1 $[M + Na]^+$. Anal. ($C_{19}H_{18}N_2O_4S$) C, H, N.

Example 2 - Synthesis of Thiazole and Thiazolidine Methanone Derivatives

[0066] *2-(substituted-phenyl)-4, 5-dihydrothiazole-4-carboxylic acid methoxymethylamide intermediates:* As shown in Scheme 3 below, 2-(substituted-phenyl)-and unsubstituted 2-phenyl-4, 5-dihydrothiazole-4-carboxylic acids **3** were prepared from appropriate nitriles (e.g., benzonitrile, pyridinyl-nitrile, pyrimidinyl-nitrile, thiophene-yl-nitrile) and L-Cysteine as described above. The obtained carboxylic acids were then used for the synthesis of the methoxymethylamide intermediates. A mixture of appropriate the appropriate carboxylic acid **3** (5mmol), EDCI (6 mmol) and HOBt (5 mmol) in CH_2Cl_2 (50mL) was stirred for 10 min. To this solution, NMM (5 mmol) and $HNCH_3OCH_3$ (5 mmol) was added and stirring continued at room temperature for 6-8 hours. The reaction mixture was diluted with CH_2Cl_2 (100mL) and sequentially washed with water, Satd. $NaHCO_3$, Brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a crude product **2,** which was purified by column chromatography.

Scheme 3



* Compound **8j** contains a lipid at "C" position
** R=3,4,5-trimethoxyphenyl

Reagents and conditions: (a) MeOH/pH=6.4 phosphate buffer, r. t.; (b) EDCI, HOBt, NMM, $HNCH_3OCH_3$; (c) $CBrCl_3$, DBU; (d) ArBr/BuLi or ArMgBr, THF; (e) HCl/HOAc; (f) $MeOH/CH_3COCl$; (g) Fe/HOAc; (h) BBr_3, CH_2Cl_2.

[0067] *(R)-N-Methoxy-N-methyl-2-phenyl-4,5-dihydrothiazole-4-carboxamide* **(compound 6a).** Yield: 92.0 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.85-7.83 (m, 2 H), 7.48-7.36 (m, 3 H), 5.66 (t, 1 H, J = 9.0 Hz), 3.90 (s, 3 H), 3.88-3.80 (br, 1 H), 3.55-3.47 (dd, 1 H, J = 10.8 Hz, 9.0 Hz), 3.30 (s, 3 H). MS (ESI) *m/z* 251.0 $[M + H]^+$, 273.0 $[M + Na]^+$.

(R)-N-methoxy-N-methyl-2-p-tolyl-4,5-dihydrothiazole-4-carboxamide **(compound 6b).** Yield: 55.8 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.79 (d, 2 H, J = 7.8 Hz), 7.22 (d, 2 H, J = 7.8 Hz), 5.68 (t, 1 H, J = 8.7 Hz), 3.91 (s, 3 H), 3.80 (t, 1 H, J = 9.3 Hz), 3.55 (t, 1 H, J = 9.3 Hz), 3.30 (s, 3 H), 2.93 (s, 3 H). MS (ESI) *m/z* 265.0 $[M + H]^+$, 287.0 $[M + Na]^+$.

(R)-2-(2-fluorophenyl)-N-methoxy-N-methyl-4,5-dihydrothiazole-4-carboxamide **(compound 6c).** Yield: 39.6 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.91 (dt, 1 H, J = 7.5 Hz, 1.8 Hz), 7.43 (m, 1 H), 7.19-7.09 (m, 2 H), 5.63 (t, 1 H), 3.88 (s, 3 H), 3.83 (br, 1 H), 3.48 (dd, 1 H, J = 11.1 Hz, 9.6 Hz), 3.30 (s, 3 H). MS (ESI) *m/z* 291.0 $[M + Na]^+$.

(R)-2-(3-fluorophenyl)-N-methoxy-N-methyl-4,5-dihydrothiazole-4-carboxamide **(compound 6d).** Yield: 84.3 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.60-7.56 (m, 2 H), 7.38 (dt, 1 H, J = 8.1 Hz, 6.0 Hz), 7.16 (dt, 1 H, J = 8.1 Hz, 2.4 Hz), 5.67 (t, 1 H), 3.90 (s, 3 H), 3.86-3.83 (br, 1 H), 3.52 (dd, 1 H, J = 10.8 Hz, 9.3 Hz), 3.30 (s, 3 H). MS (ESI) *m/z* 291.0 $[M + Na]^+$.

(R)-2-(4-fluorophenyl)-N-methoxy-N-methyl-4,5-dihydrothiazole-4-carboxamide **(compound 6e).** Yield: 66.0 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.90 (d, 2 H), 7.13 (d, 2 H), 5.63 (t, 1 H), 3.88 (s, 3 H), 3.83 (br, 1 H), 3.46 (dd, 1 H), 3.31 (s, 3 H). MS (ESI) *m/z* 269.0 $[M + H]^+$.

(R)-2-(3,4-dimethoxyphenyl)-N-methoxy-N-methyl-4,5-dihydrothiazole-4-carboxamide **(compound 6f).** Yield: 36.7 %. ^1H NMR (300MHz, $CDCl_3$) δ 8.11 (d, 1 H), 7.93 (s, 1 H), 7.19-7.09 (d, 1H), 5.41 (t, 1 H), 3.97 (s, 6H), 3.89 (s, 3 H), 3.73 (br, 1 H), 3.39 (dd, 1 H), 3.31 (s, 3 H). MS (ESI) *m/z* 333.1 $[M + Na]^+$.

(R)-N-methoxy-N-methyl-2-(4-nitrophenyl)-4,5-dihydrothiazole-4-carboxamide **(compound 6g).** Yield: 53.7 %. ^1H NMR (300MHz, $CDCl_3$) δ 8.25(d, 2 H, J = 9.0 Hz), 8.01 (d, 2 H, J = 9.0 Hz), 5.73 (t, 1 H), 3.90 (s, 3 H), 3.87 (br, 1 H), 3.59 (dd, 1 H, J = 11.1 Hz, 9.3 Hz), 3.31 (s, 3 H). MS (ESI) *m/z* 318.1 $[M + Na]^+$.

(R)-2-(4-cyanophenyl)-N-methoxy-N-methyl-4,5-dihydrothiazole-4-carboxamide **(compound 6h).** Yield: 26.7 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.94(d, 2 H, J = 8.1 Hz), 7.69 (d, 2 H, J = 8.1 Hz), 5.71 (t, 1 H, J = 9.3 Hz), 3.89 (s, 3 H), 3.87 (br, 1 H), 3.56 (dd, 1 H, J = 10.8 Hz, 9.3 Hz), 3.30 (s, 3 H). MS (ESI) *m/z* 298.0 $[M + Na]^+$.

(R)-N-methoxy-N-methyl-2-(4-trifluoromethylphenyl)-4,5-dihydrothiazole-4-carboxamide **(compound 6i).** Yield: 62.0 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.95 (d, 2 H, J = 8.1 Hz), 7.65 (d, 2 H, J = 8.1 Hz), 5.70 (t, 1 H, J = 9.6 Hz), 3.89 (s, 3 H), 3.85 (br, 1 H), 3.55 (dd, 1 H, J = 10.8 Hz, 9.6 Hz), 3.30 (s, 3 H). MS (ESI) *m/z* 341.0 $[M + Na]^+$.

(R)-2-(4-bromophenyl)-N-methoxy-N-methyl-4,5-dihydrothiazole-4-carboxamide **(compound 6j).** Yield: 20.0 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.71, 7.53 (d, d, 4 H, J = 8.4 Hz), 5.63 (t, 1 H, J = 9.6 Hz), 3.88 (s, 3 H), 3.84 (t, 1 H, J = 9.6 Hz), 3.52 (dd, 1 H, J = 10.8 Hz, 9.6 Hz), 3.30 (s, 3 H). MS (ESI) *m/z* 351.0 $[M + Na]^+$.

(R)-N-methoxy-N-methyl-2-(4-ethyl)-4,5-dihydrothiazole-4-carboxamide **(compound 6k).** Yield: 77.7 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.75(d, 2 H, J = 8.4 Hz), 7.21 (d, 2 H, J = 8.4 Hz), 5.64 (t, 1 H), 3.89 (s, 3 H), 3.81 (m, 1 H), 3.48 (dd, 1 H, J = 10.8 Hz, 9.3 Hz), 3.29 (s, 3 H), 2.67 (q, 2 H), 1.24 (t, 3 H). MS (ESI) *m/z* 301.0 $[M + Na]^+$.

(R)-N-methoxy-N-methyl-2-(pyridin-4-yl)-4,5-dihydrothiazole-4-carboxamide **(compound 61).** Yield: 66.6 %. ^1H NMR (300MHz, $CDCl_3$) δ 8.70 (d, 2 H, J = 9.0 Hz), 7.67 (d, 2 H, J = 9.0 Hz), 5.71 (t, 1 H, J = 9.6 Hz), 3.90 (s, 3 H), 3.73 (t, 1 H), 3.55 (dd, 1 H, J = 10.8 Hz, 9.6 Hz), 3.30 (s, 3 H). MS (ESI) *m/z* 252.1 $[M + H]^+$, 274.0 $[M + Na]^+$.

(R)-N-methoxy-N-methyl-2-(pyrimidin-2-yl)-4,5-dihydrothiazole-4-carboxamide **(compound 6m).** Yield: 32.5 %. ^1H NMR (300MHz, $CDCl_3$) δ 8.88 (d, 2 H, J = 4.8 Hz), 7.38 (t, 1 H, J = 4.8 Hz), 5.83 (t, 1 H, J = 9.0 Hz), 3.87 (s, 3 H), 3.56 (dd, 2 H, J = 9.0 Hz), 3.30 (s, 3 H). MS (ESI) *m/z* 275.0 $[M + Na]^+$.

(R)-N-methoxy-N-methyl-2-(thiophen-2-yl)-4,5-dihydrothiazole-4-carboxamide **(compound 6p).** Yield: 58.5 %. ^1H NMR (300MHz, $CDCl_3$) δ 7.57 (br, 1 H), 7.49 (d, 1 H, J = 4.8 Hz), 7.09 (dd, 1 H, J = 3.6 Hz, 4.8 Hz), 5.64 (t, 1 H, J = 9.0 Hz), 3.90 (s, 3 H), 3.85 (br, 1 H), 3.57 (dd, 1 H, J = 9.9, 9.0Hz), 3.29 (s, 3 H). MS (ESI) *m/z* 279.0 $[M + Na]^+$.

N-methoxy-N-methylthiazole-4-carboxamide **(compound 9a)***:* Yield: 58.7 %. ^1H NMR (300MHz, $CDCl_3$) δ 8.82 (d, 1 H, J = 2.1 Hz), 8.10 (d, 1 H, J = 2.1 Hz), 3.79 (s, 3 H), 3.45 (s, 3 H). MS (ESI) *m/z* 194.9 $[M + Na]^+$.

[0068] *2-(Substituted-phenyl)-thiazole-4-carboxylic acid methoxymethylamides* **7a-p:** A solution of the resulting dihydrothiazole-4-carboxylic acid methoxymethylamides **6a-6p** (1 equiv) in CH_2Cl_2 was cooled to 0°C, and distilled DBU (2 equiv) was added. Bromotrichloromethane (1.7 equiv) was then introduced dropwise via syringe over 10 min. The reaction mixtures were allowed to warm to room temperature and stirred overnight. Upon washing with satd. aqueous NH_4Cl (2 x 50 mL), the aqueous phase was extracted with EtOAc (3x 50 mL). The combined organic layers were dried on $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by flash chromatography as needed providing compounds **7a-p**.

2-Phenyl-thiazole-4-carboxylic acid methoxymethylamide **(compound 7a):** Yield: 73.6 %. ^1H NMR (300MHz, $CDCl_3$) δ 8.01 (s, 1 H), 7.99-7.96 (m, 2 H), 7.47-7.44 (m, 3 H), 3.88 (s, 3 H), 3.49 (s, 3 H). MS (ESI) *m/z* 271.0 $[M + Na]^+$.

[0069] *(2-(substituted-phenyl)-thiazol-4-yl)-(substituted-phenyl)-methanones:* As shown in Scheme 3 above, three different methods were utilized for the synthesis of the methanones **8a-8z.**

Method 1: To a solution of *n*-BuLi (1.6M, 0.713 mL) in 8 mL THF was added a solution of 3,4,5-trimethoxybromobenzene (1.09 mmol) in 3 mL THF under -78°C. The mixture was stirred for 2h and a solution of amides **6** or **7** (1.14

mmol) in 3 mL THF was charged. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with satd. NH_4Cl, extracted with ethyl ether, dried with $MgSO_4$, and exposed in air atmosphere overnight. The solvent was removed under reduced pressure to yield a crude product, which was purified by column chromatography to obtain pure compounds **8a-8z.**

Method 2: To a solution of corresponding Grignard reagents (0.5M, 3 mL) in 2 mL THF was charged a solution of amides **6** or **7** (1 mmol) in 3 mL THF at 0 °C. The mixtures were stirred for 30 min to 2 hours until amides disappeared on TLC plates. The reaction mixture was quenched with satd. NH_4Cl, extracted with ethyl ether, dried with $MgSO_4$ and to set in air atmosphere overnight to yield **6** as starting material. The solvent was removed under reduced pressure to yield a crude product, which was purified by column chromatography to obtain pure compound **8a-8z.** Hydrochloride salts of compounds **8i, 8x,** and **8w** were also prepared. At 0 °C, to a solution of 10 mL HCl in ethyl ether (2 M) solution was added **8i, 8x** or **8w** (100 mg) in 5 mL CH_2Cl_2 (5 mL) and stirred overnight. The hydrochloride precipitate was filtered and washed with ethyl ether. Dying under high vacuum yielded the corresponding salts.

Phenyl (2-phenylthiazol-4-yl)-methanone **(compound 8a)***:* Yield: 76.3 %. M. p. 65-66 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.32-8.29 (m, 2 H), 8.24 (s, 1 H), 8.04-8.00 (m, 2 H), 7.64-7.52 (m, 3 H), 7.50-7.46 (m, 3 H). MS (ESI) *m/z* 288.0 $[M + Na]^+$. Anal. ($C_{16}H_{11}NOS$) C, H, N.

(4-Methoxyphenyl)(2-phenylthiazol-4-yl)-methanone **(compound 8b)***:* Yield: 74.8 %. M. p. 105-106 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.41 (d, 2 H), 8.22 (s, 1 H), 8.02 (dd, 2 H), 7.47 (m, 3 H), 7.01 (d, 2 H), 3.80 (s, 3 H). MS (ESI) *m/z* 318.1 $[M + Na]^+$. Anal. ($C_{17}H_{13}NO_2S$) C, H, N.

(3-Methoxyphenyl)(2-phenylthiazol-4-yl)-methanone **(compound 8c)***:* Yield: 58.8 %. M. p. 43-44 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.23 (s, 1 H), 8.05-8.01 (m, 2 H), 7.93 (d, 1 H), 7.84 (m, 1 H), 7.49-7.40 (m, 4 H), 7.16-7.15 (m, 1 H), 3.89 (s, 3 H). MS (ESI) *m/z* 318.1 $[M + Na]^+$. Anal. ($C_{17}H_{13}NO_2S$) C, H, N.

(2-Methoxyphenyl)(2-phenylthiazol-4-yl)-methanone **(compound 8d)***:* Yield: 57.4 %. Colorless oil. ^1H NMR (300MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.98-7.95 (m, 2 H), 7.57-7.47 (m, 2 H), 7.47-7.42 (m, 3 H), 7.08-7.01 (m, 2 H), 3.78 (s, 3 H). MS (ESI) *m/z* 318.1 $[M + Na]^+$. Anal. ($C_{17}H_{13}NO_2S$) C, H, N.

(3, 4-Dimethoxyphenyl)(2-phenylthiazol-4-yl)-methanone **(compound 8e)***:* Yield: 15.3 %. M. p. 89-91 °C. ^1H NMR (500MHz, $CDCl_3$) δ 8.24 (s, 1 H), 8.22 (dd, 1 H, J = 8.5 Hz, 2.0 Hz), 8.04-8.02 (m, 2 H), 7.99 (d, 1 H, J = 2.0 Hz), 7.49-7.47 (m, 3 H), 6.98 (d, 1 H, J = 8.5 Hz), 3.99 (s, 6 H). MS (ESI) *m/z* 348.0 $[M + Na]^+$. Anal. ($C_{18}H_{15}NO_3S$) C, H, N.

(2-Phenyl-thiazol-4-yl)-(3,4,5-trimethoxy-phenyl)-methanone **(compound 8f)***:* Yield: 27.3 %. M. p. 133-135 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.29 (s, 1 H), 8.03 (q, 2 H), 7.80 (s, 2 H), 7.49-7.47 (m, 3 H), 3.96 (s, 6 H), 3.97 (s, 3 H). MS (ESI) *m/z* 378.1 $[M + Na]^+$. Anal. ($C_{19}H_{17}NO_4S$) C, H, N.

(3,5-Dimethoxyphenyl)(2-phenylthiazol-4-yl)-methanone **(compound 8g)***:* Yield: 41.5 %. M. p. 84-85 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.23 (s, 1 H), 8.04-8.01 (m, 2 H), 7.99 (d, 2 H, J = 2.4 Hz), 7.49-7.43 (m, 3 H), 6.72 (t, 1 H, J = 2.4 Hz), 3.87 (s, 6 H). MS (ESI) *m/z* 348.3 $[M + Na]^+$. Anal. ($C_{18}H_{15}NO_3S$) C, H, N.

(2-Fluorophenyl)(2-phenylthiazol-4-yl)-methanone **(compound 8h)***:* Yield: 66.4 %. M. p. 77-79°C. ^1H NMR (300MHz, $CDCl_3$) δ 8.48-8.41 (m, 2 H), 8.28 (s, 2 H), 8.04-7.98 (m, 2 H), 7.50-7.46 (m, 3 H), 7.26-7.16 (m, 2 H). MS (ESI) *m/z* 306.0 $[M + Na]^+$, 283.9 $[M - H]^-$. Anal. ($C_{16}H_{10}FNOS$) C, H, N.

(2-Phenylthiazol-4-yl)-(pyridin-2-yl)-methanone **(compound 8i)***:* Yield: 20.7 %. M. p. 95-97°C. ^1H NMR (300MHz, $CDCl_3$) δ 9.01 (s, 1 H), 8.77 (d, 1 H, J = 4.8 Hz), 8.28 (d, 1 H, J = 7.8 Hz), 8.08-8.05 (m, 2 H), 7.92 (dt, 1 H, J = 7.8 Hz, 1.2 Hz), 7.52 (ddd, 1 H, J = 7.8 Hz, 4.8 Hz, 1.2 Hz), 7.48-7.46 (m, 3 H). **(compound 8i·HCl salt):** Yield: 70.6 %. M. p. 105-107°C. ^1H NMR (300MHz, DMSO-d_6) δ 9.03 (s, 1 H), 8.79 (d, 1 H, J = 4.8 Hz), 8.10 (br, 1 H), 8.08 (br, 1 H), 8.03-8.00 (m, 2 H), 7.73-7.69 (m, 1 H), 7.56-7.54 (m, 3 H). MS (ESI) *m/z* 267.0 $[M + H]^+$. Anal. ($C_{15}H_{10}N_2OS$, $C_{15}H_{10}N_2OS{\cdot}HCl$) C, H, N.

1-(2-phenylthiazol-4-yl)-heptadecan-1-one **(compound 8j)***:* Yield: 66.4 %. M. p. 63-64 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.12 (s, 1 H), 8.02-7.99 (m, 2 H), 7.49-7.47 (m, 3 H), 3.16 (t, 2 H, J = 7.5 Hz), 1.82-1.72 (m, 2 H), 1.26 (s, 26 H), 0.88 (t, 3 H, J = 6.9 Hz). MS (ESI) *m/z* 414.4 $[M + H]^+$. Anal. ($C_{26}H_{39}NOS$) C, H, N.

(2-p-Tolylthiazol-4-yl)-(3,4,5-trimethoxyphenyl)-methanone **(compound 8k):** Yield: 53.2 %. M. p. 116-119 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.25 (s, 1 H), 7.91 (d, 2 H, J = 8.1 Hz), 7.80 (s, 2 H), 7.28 (d, 2 H, J= 8.1 Hz), 3.96 (s, 3 H), 3.95 (s, 6 H). MS (ESI) *m/z* 392.1 $[M + Na]^+$. Anal. ($C_{20}H_{19}NO_4S$) C, H, N.

[2-(2-Fluorophenyl)-thiazol-4-yl]-(3,4,5-trimethoxyphenyl)-methanone **(compound 81)***:* Yield: 39.6 %. M. p. 90-102 °C. ^1H NMR (500MHz, $CDCl_3$) δ 8.40 (s, 1 H), 8.33 (dt, 1 H, J = 1.5 Hz, 8.0 Hz), 7.78 (s, 2 H), 7.49-7.44 (m, 1 H), 7.30-7.23 (m, 2 H), 3.97 (s, 3 H), 3.95 (s, 6 H). MS (ESI) *m/z* 396.1 $[M + Na]^+$. Anal. ($C_{19}H_{16}FNO_4S$) C, H, N.

[2-(3-Fluorophenyl)-thiazol-4-yl](3,4,5-trimethoxyphenyl)-methanone **(compound 8m)***:* Yield: 14.1 %. M. p. 122-124 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.31 (s, 1 H), 7.79 (s, 2 H), 7.76-7.74 (m, 2 H), 7.45 (dt, 1 H, J = 6.0 Hz, 8.4 Hz), 7.18 (dt, 1 H, J = 1.8 Hz, 8.4 Hz), 3.97 (s, 3 H), 3.96 (s, 6 H). MS (ESI) *m/z* 396.1 $[M + Na]^+$. Anal. ($C_{19}H_{16}FNO_4S$) C, H, N.

[2-(4-Fluorophenyl)-thiazol-4-yl]-(3,4,5-trimethoxyphenyl)-methanone **(compound 8n)***:* Yield: 40.2 %. M. p. 153-155 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.27 (s, 1 H), 8.04-8.00 (dd, 2 H, J = 8.4 Hz, 5.7 Hz), 7.75 (s, 2 H), 7.21-7.15 (t, 3

H, J = 8.4 Hz), 3.97 (s, 3 H), 3.95 (s, 6 H). MS (ESI) *m/z* 396.1 [M + Na]+. Anal. ($C_{19}H_{16}FNO_4S$) C, H, N.

[2-(3,4-Dimethoxyphenyl)-thiazol-4-yl]-(3,4,5-trimethoxyphenyl)-methanone **(compound 8o)*:*** Yield: 46.6 %. M. p. 145-147 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.20 (s, 1 H), 7.76 (s, 2 H), 7.58-7.54 (m, 2 H), 6.94 (d, 2 H, J = 8.1 Hz), 3.96 (s, 6 H), 3.95 (s, s, 9H). MS (ESI) *m/z* 438.1 [M + Na]+. Anal. ($C_{21}H_{21}NO_6S{\cdot}1/4H_2O$) C, H, N.

[2-(4-Nitrophenyl)-thiazol-4-yl]-(3,4,5-trimethoxyphenyl)-methanone **(compound 8p)*:*** Yield: 46.4 %. M. p. 199-200 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.38 (d, 2 H, J = 8.7 Hz), 8.34 (s, 1 H), 8.20 (d, 2 H, J = 8.7 Hz), 7.73 (s, 2 H), 3.98 (s, 3 H), 3.95 (s, 6 H). MS (ESI) *m/z* 423.1 [M + Na]+. Anal. ($C_{19}H_{16}N_2O_6S$) C, H, N.

4-[4-(3,4,5-Trimethoxybenzoyl)-thiazol-2-yl]-benzonitrile **(compound 8q):** Yield: 45.9 %. M. p. 181-182 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.37 (s, 1 H), 8.13 (d, 2 H, J = 8.4 Hz), 7.78 (d, 2 H, J = 8.4 Hz), 7.72 (s, 2 H), 3.97 (s, 3 H), 3.94 (s, 6 H). MS (ESI) *m/z* 403.1 [M + Na]+. Anal. ($C_{20}H_{16}N_2O_4S$) C, H, N.

4-[4-(3,4,5-Trimethoxybenzoyl)-thiazol-2-yl]-benzoic acid **(compound 8r)*:*** Yield: 61.9 %. M. p. >220 °C (dec.). ^{1}H NMR (300MHz, $CDCl_3$) δ 8.65 (s, 1 H), 8.00 (d, d, 4 H), 7.65 (s, 2 H), 3.88 (s, 6 H), 3.80 (s, 3 H). MS (ESI) *m/z* 397.9 [M - H]-, 353.9 [M - COOH]-,. Anal. ($C_{20}H_{17}NO_6S$) C, H, N.

Methyl-4-[4-(3,4,5-trimethoxybenzoyl)-thiazol-2-yl]-benzoate **(compound 8s)*:*** Yield: 72.5 %. M. p. 172-174 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.35 (s, 1 H), 8.12 (dd, 4 H, J = 8.4 Hz), 7.78 (s, 2 H), 3.97 (s, 3 H), 3.96 (s, 3H), 3.95 (s, 6 H). MS (ESI) *m/z* 436.1 [M + Na]+. Anal. ($C_{21}H_{19}NO_6S$) C, H, N.

(2-(4-(Trifluoromethyl)-phenyl)-thiazol-4-yl)(3,4,5-trimethoxyphenyl)-methanone **(compound 8t)*:*** Yield: 45.5 %. M. p. 144-145 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.35 (s, 1 H), 8.14, 7.65 (d, d, 4 H, J = 8.1 Hz), 7.76 (s, 2 H), 3.97 (s, 3 H), 3.95 (s, 6 H). MS (ESI) *m/z* 446.1 [M + Na]+. Anal. ($C_{20}H_{16}F_3NO_4S$) C, H, N.

[2-(4-Bromophenyl)-thiazol-4-yl]-(3,4,5-trimethoxyphenyl)-methanone **(compound 8u)*:*** Yield: 51.8 %. M. p. 149-150 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.28 (s, 1 H), 7.89, 7.62 (d, d, 4 H, J = 8.1 Hz), 7.75 (s, 2 H), 3.97 (s, 3 H), 3.94 (s, 6 H). MS (ESI) *m/z* 456.0, 458.0 [M + Na]+. Anal. ($C_{19}H_{16}BrNO_4S$) C, H, N.

[2-(4-Ethyl-phenyl)-thiazol-4-yl]-(3,4,5-trimethoxy-phenyl)-methanone **(compound 8v)*:*** Yield: 40.0 %. M. p. 86-87 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.25 (s, 1 H), 7.93, 7.31 (d, d, 4 H, J = 8.4 Hz), 7.81 (s, 2 H), 3.97 (s, 3 H), 3.95 (s, 6 H). MS (ESI) *m/z* 406.1 [M + Na]+. Anal. ($C_{21}H_{21}NO_4S$) C, H, N.

[2-(4-Amino-phenyl)-thiazol-4-yl]-(3,4,5-trimethoxy-phenyl)-methanone **(compound 8w)*:*** Yield: 61.8 %. M. p. 177-179 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.14 (s, 1 H), 7.82, 7.65 (d, d, 4 H, J = 8.4 Hz), 7.78 (s, 2 H), 3.96 (s, 3 H), 3.94 (s, 6 H). **(compound 8w·HCl salt):** Yield: 50.1 %. M. p. 166-169 °C. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.49 (s, 1 H), 7.84, 6.94 (d, d, 4 H, J = 8.4 Hz), 7.62 (s, 2 H), 3.86 (s, 3 H), 3.79 (s, 6 H). MS (ESI) *m/z* 393.1 [M + Na]+. Anal. ($C_{19}H_{18}N_2O_4S$, $C_{19}H_{18}N_2O_4S{\cdot}HCl$) C, H, N.

[2-(Pyridin-4-yl)-thiazol-4-yl]-(3,4,5-trimethoxyphenyl)-methanone **(compound 8x)*:*** Yield: 29.3 %. M. p. 178-180 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.77 (dd, 2 H, J = 6.0 Hz, 1.5 Hz), 8.40 (s, 1 H), 7.87 (dd, 2 H, J = 6.0 Hz, 1.8 Hz), 7.75 (s, 2 H), 3.98 (s, 3 H), 3.95 (s, 6 H). **(compound 8x·HCl salt):** Yield: 92.7 %. M. p. 182-184 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.85 (br, 2 H), 8.52 (s, 1 H), 8.22 (br, 2 H), 7.66 (s, 2 H), 3.98 (s, 3 H), 3.94 (s, 6 H). MS (ESI) *m/z* 379.1 [M + Na]+. Anal. ($C_{18}H_{16}N_2O_4S$, $C_{18}H_{16}N_2O_4S{\cdot}HCl$) C, H, N.

[2-(Pyrimidin-2-yl)-thiazol-4-yl]-(3,4,5-trimethoxyphenyl)-methanone **(compound 8y)*:*** Yield: 51.9 %. M. p. 190-191 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.88 (d, 2 H, J = 4.8 Hz), 8.44 (s, 1 H), 7.73 (s, 2 H), 7.37 (t, 1 H, J = 4.8 Hz), 3.95 (s, 3 H), 3.94 (s, 6 H). MS (ESI) *m/z* 380.1 [M + Na]+. Anal. ($C_{17}H_{15}N_3O_4S$) C, H, N.

[2-(Thiophen-2-yl)-thiazol-4-yl]-(3,4,5-trimethoxyphenyl)-methanone **(compound 8z):** Yield: 30.5 %. M. p. 111-113 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.25 (s, 1 H), 7.90 (s, 2 H), 7.58 (dd, 1 H, J = 3.6, 0.9 Hz), 7.46 (dd, 1 H, J = 5.4, 0.9 Hz), 7.12 (dd, 1 H, J = 5.4, 3.6 Hz), 3.98 (s, 6 H), 3.97 (s, 3 H). MS (ESI) *m/z* 384.1 [M + Na]+. Anal. ($C_{17}H_{15}NO_4S_2$) C, H, N.

Thiazol-4-yl-(3,4,5-trimethoxy-phenyl)-methanone **(compound 10a)*:*** Yield: 49.4 %. M. p. 106-108 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.92 (d, 1 H, J = 2.1 Hz), 8.34 (d, 1 H, J = 2.1 Hz), 7.61 (s, 2 H), 3.94 (s, 3 H), 3.93 (s, 6 H). MS (ESI) *m/z* 302.0 [M + Na]+. Anal. ($C_{13}H_{13}NO_4S$) C, H, N.

Method 3: *(2-Phenyl-thiazol-4-yl)-(3,4,5-trihydroxy-phenyl)-methanone* **(11f)** was synthesized beginning with compound **8f.** To a solution of compound **8f** (123 mg, 0.35 mmol) in 5 mL anh. CH_2Cl_2 was added BBr_3 (1M solution in CH_2Cl_2, 1.75 mL, 5 mmol) under -78°C. The mixture was stirred for 2h and a solution of amide 7 (1.14 mmol) in 3 mL THF was charged. The mixture was allowed to warm to room temperature slowly and stirred overnight. The reaction mixture was quenched with satd. NH_4Cl, extracted with ethyl acetate, dried with $MgSO_4$. The solvent was removed under reduced pressure to yield a crude product, which was purified by column chromatography to obtain pure compound as red crystalline solid. Yield: 50.9 %. M. p. 175-176 °C. ^{1}H NMR (300MHz, DMSO-d6) δ 8.44 (d, 1 H), 8.07-8.04 (m, 2 H), 7.57-7.55 (m, 3 H), 7.33 (s, 2 H). MS (ESI) *m/z* 336.1 [M + Na]+. Anal. ($C_{16}H_{11}NO_4S$) C, H, N.

Example 3 - X-ray Crystallography Structure Determination for Compound 8f

[0070] Compound **8f** was recrystallized from hexane and ethyl acetate, and single colorless crystals suitable for X-ray diffraction were obtained. X-ray crystallographic data for **8f** were collected from a single crystal mounted with paratone oil on a nylon cryoloop. Data were collected at 100K on a Bruker Proteum CCD area detector, controlled by Proteum2 software (Proteum2, Bruker AXS Inc., Madison, Wisconsin, USA (2005)), using a rotating-anode generator and Osmic mirrors to generate Cu radiation (λ=1.54178Å). The data were reduced using SAINT (SAINT, Bruker AXS Inc., Madison, Wisconsin, USA. (1998)), with an absorption correction applied using SADABS (SADABS, Bruker AXS Inc., Madison, Wisconsin, USA. (2000)) based on redundant reflections; this correction included a spherical component. The structure was solved using direct methods (SHELXS^{x4}), which revealed all of the heavy atoms. Structure refinement with SHELXL (SHELXL-97, G.M. Sheldrick, University of Göttingen, Germany (1997)) was carried out using full-matrix methods based on F^2, and proceeded smoothly. Hydrogen atoms were added to the structural model assuming ideal C-H distances and isotropic ADPs constrained to be similar to that of the bonded carbon atom. In the final model, anisotropic ADPs were refined for all heavy atoms, and isotropic ADPs for chemically-similar hydrogens (e.g. methyl H) were constrained to be identical. The final refinement parameters are: wR2=0.084 for 228 parameters and 3066 independent observations, R1=0.031, S (goodness-of-fit)=1.057.

[0071] An ORTEP drawing of **8f** with the atom labeling scheme is shown in Figure 1. The X-ray structure showed that **8f** molecule contained a conjugated system composed of three aromatic rings and a carbonyl group linker between "B" and "C" ring as expected ("A" ring = phenyl; "B" ring = thiazole; "C" ring = 3, 4, 5-trimethoxyphenyl). As a result, two C-C bonds adjacent to C=O and C-C- bond between "A" phenyl and "B" thiazole ring display (C1-C7 = 1.496(2) Å; C7-C8 = 1.492(2) Å; C10-C11 = 1.471(2) Å) shorter bond lengths than normal C-C single bond (1.54 Å) and longer than normal C=C double bond (1.34 Å) (*see* Table 1 below). Thus, conjugation of the π system is possible for "A", "B", "C" rings and carbonyl group. The carbonyl group is nearly coplanar with the adjacent "B" thiazole ring (O-C7-C1-C6 16.2(2)°, O-C7-C8-C9 9.7(2)°).

Table 1: Selected Geometric Parameters of Compound 8f (A, °)

C1-C7	1.496(2)	O-C7-C1	120.1(2)
C7-O	1.224(2)	C8-C7-C1	121.9(2)
	1.492(2)	C9-C8-N	115.1(2)
	1.371(2)	C9-C8-C7	121.7(2)
C8-N	1.380(2)	N-C8-C7	123.0(2)
C9-S	1.711(2)	C8-C9-S	110.0(1)
S-C10	1.747(2)	C9-S-C10	89.6(1)
C10-N	1.303(2)	N-C10-C11	123.5(2)
C10-C11	1.471(2)	N-C10-S	113.9(1)
C2-C1-C6	121.2(2)	C11-C10-S	122.6(1)
C2-C1-C7	122.3(2)	C10-N-C8	111.4(2)
C6-C1-C7	116.4(2)	C12-C11-C10	122.3(2)
O-C7-C8	118.0(2)	C16-C11-C10	118.5(2)

Example 4 - *In vitro* Assays for Anti-cancer Cytotoxicity

[0072] *In vitro* assays were tested against both melanoma cell lines and prostate cancer cells lines. In each case, standard sulforhodamine B assay was used. Cells were seeded into 96-well plates at 1000 to 5000 cells/well depending on growth rates. After 12 hours, media were changed and serial dilutions of compounds were added. Cells were incubated with each compound for 48 hours. Fresh media containing the test compound were changed ever 24 hours. Thereafter, total cell protein corresponding to cell numbers (both viable and non-viable cells) were measured using the sulforhodamine B (SRB) assay according to manufacturer's protocol (Sigma-Aldrich, Inc.) (Rubinstein et al., "Comparison of in vitro Anticancer Drug-screening Data Generated with a Tetrazolium Assay Versus a Protein Assay Against a Diverse Panel of Human Tumor Cell Lines," J. Natl. Cancer Inst. 82:1113-1118 (1990); Dothager et al., "Synthesis and Identification of Small Molecules that Potently Induce Apoptosis in Melanoma Cells Through G1 Cell Cycle Arrest," J. Am. Chem. Soc. 127:8686-8696 (2005)).

[0073] For melanoma assays, one human melanoma cell line (A375) and one mouse melanoma cell line (B16-F1) were used. A375 cells and B16-F1 cells were purchased from ATCC (American Type Culture Collection, Manassas, VA, USA). Fibroblast cells were used as a control to determine the selectivity of these compounds against melanoma. Human dermal fibroblast cells were purchased from Cascade Biologics, Inc., Portland, OR, USA. All cell lines were cultured in DMEM (Cellgro Mediatech, Inc., Herndon, VA, USA), supplemented with 5% FBS (Cellgro Mediatech), 1% antibiotic/antimycotic mixture (Sigma-Aldrich, Inc., St. Louis, MO, USA) and bovine insulin (5 μg/ml; Sigma-Aldrich).

Cultures were maintained at 37°C in a humidified atmosphere containing 5% CO_2. Cells were exposed to a wide range of concentrations for 48 h in round-bottomed 96-well plates. Cells were fixed with 10% trichloroacetic acid and washed five times with water. After cells were air-dried overnight and stained with SRB solution, total proteins were measured at 560 nm with a plate reader. IC_{50} (i.e., concentration which inhibited cell growth by 50% of no treatment controls) values were obtained by nonlinear regression analysis with GraphPad Prism (GraphPad Software, San Diego,CA).

[0074] For prostate cancer assays, four human prostate cancer cell lines (LNCaP, DU 145, PC-3, and PPC-1) were selected. LNCaP, PC-3 and DU 145 cells were purchased from ATCC (American Type Culture Collection, Manassas,VA, USA). Dr. Mitchell Steiner at University of Tennessee Health Science Center kindly provided PPC-1cells. All prostate cancer cell lines were cultured in RPMI 1640 (Cellgro Mediatech, Inc., Herndon, VA, USA), supplemented with 10% FBS (Cellgro Mediatech). Cultures were maintained at 37°C in a humidified atmosphere containing 5% CO_2. 1000 to 5000 cells were plated into each well of 96-well plates depending on growth rate and exposed to different concentrations of a test compound for 96 h in three to five replicates. Cell numbers at the end of the drug treatment were measured by the SRB assay. Briefly, the cells were fixed with 10% of trichloroacetic acid and stained with 0.4% SRB, and the absorbances at 540 nm were measured using a plate reader (DYNEX Technologies, Chantilly, VA). Percentages of cell survival versus drug concentrations were plotted and the IC_{50} (concentration that inhibited cell growth by 50% of untreated control) values were obtained by nonlinear regression analysis using WinNonlin (Pharsight Corporation, Mountain View, CA).

[0075] The results of these assays are provided in Tables 2-4 below.

[0076] Modifications of the "B" ring from a thiazolidine to thiazole system and the linker from an amide to a ketone. In prior ATCAA compounds, the thiazolidine ring, which contained a free NH at its 3-position, was shown to be important for cytotoxicity. Once the "B" ring thiazolidine moiety was replaced by a thiazoline ring, the antiproliferative activity decreased sharply from 0.6 μM to over 50 μM on WM-164 cell lines (Li et al., "Synthesis and Antiproliferative Activity of Thiazolidine Analogs for Melanoma," Bioorg. Med. Chem. Lett. 17:4113-7 (2007)). The ATCAA-1 fatty amide derivative that was most effective against melanoma and prostate cancer cell lines were examined and shown to have an IC_{50} 0.4-2.2 μM (*see* Table 2). Replacement of the long fatty chain with a certain aromatic bulky subsistent such as fluorene (ATCAA-2) showed inhibitory activity on both cancer cell lines (IC_{50} = 1.6 - 3.9 μM). The fluorene group in 4-carboxylic amide position was also replaced by 3,4,5-trimethoxylphenyl group (**2a** and **2b**), but the potency against both cancer cell lines was lost. The subsequent "B" ring modification from saturated thiazolidine compound **2a** to unsaturated thiazole **5** did not show any cytotoxicity against either cancer cell line tested. But thiazoline enantiomers **4a** and **4b** (*R*-isomer and *S*-isomer, with similar antiproliferative activities) showed improved activity (IC_{50} = 3.4 - 38.3 μM) compared with **2a, 2b** and **5.** When the amide CONH linkage between "B" ring and "C" ring was replaced by a carbonyl linker, the mixtures of thiazoline/thiazole ketone **8f** were obtained instead of desired thiazoline ketone, because the auto-dehydrogenation between thiazoline and thiazole occurred (the conversion was shown in Figure 2). Surprisingly, introduction of the carbonyl group linker and thiazole "B" ring led to a significant enhancement of growth inhibition of examined cancer cell lines with a low nanomolar level (**8f**, IC_{50} = 0.021 - 0.071 μM) that is comparable to the natural anticancer agent Colchicine. Consequently, a series of the related compounds with "B" as a thiazole ring were designed and synthesized based on the discovery of **8f.** Their anticancer activity was also evaluated against melanoma and prostate cancer.

[0077] Modifications of the "C" ring also had significant effects. Variation of the phenyl substituents has a remarkable change in effect on potency. The *in vitro* assay results shown in Table 3 provide interesting results, but only the 3,4,5-trimethoxylphenyl "C" ring (**8f**) showed excellent inhibition against all cancer cells (IC_{50}= 21 -71 nM, average IC_{50}= 41 nM). Compound **8g,** with a 3,5-dimethoxyphenyl group, showed 6-fold average cytotoxicity lower than **8f** against six different cell lines (IC_{50} = 170-424 nM, calcd. average IC_{50}= 261 nM). Modifications of **8f** by removal of one methoxy at *meta*-position (**8e**) or two methoxy groups (**8b, 8c** and **8d**) from **8f** led to a dramatic loss in activity (IC_{50} >20 μM). Although *ortho-* substituted monomethoxy compound **8d** exhibited weak activity against a certain cell lines compared with *meta-/para*-MeO substituted **8c/8b** and dimethoxyphenyl compound **8e,** none of them showed significant potency in inhibition compared with **8f.** Similar trends were also seen in **8h** and **8j** with 2-fluorophenyl and hexadecyl in "C" ring modifications.

[0078] Modifications of the "A" ring using different para-substituted electron withdrawing groups (EWG) and electron donor groups (EDG) did not show clear influence on antiproliferative activity. Introduction of a weak EWG (4-F in **8n,** IC_{50} values: 6 - 43 nM) or weak EDG (4-CH_3 in **8k,** IC_{50}s: 5 - 21 nM), both increased the potency compared with **8f** (see Table 4). The replacement of para-position with strong EWG such as NO_2 (**8p**), CN (**8q**), CF_3 (**8t**) or introducing strong EDG (3, 4-dimethoxy) to "A" phenyl ring (**8o**) exhibited comparable antiproliferative activity.

[0079] To compare the effects of *ortho-*, *meta-* and *para-* substitutions, a fluoro atom was introduced to different positions of "A" phenyl ring (**8l, 8m,** and **8n**). The various *o-*, *m-*, *p-* substituents did not exhibit equal activities. *p*-Fluoro substituted **8n** has the best activity for examined prostate cancer cells (6-13 nM) while *o*-fluoro substituted **8l** showed the lowest IC_{50} values (27 - 30 nM) against melanoma cells. **8n** has similar average IC_{50} values (33 - 43 nM) against melanoma compared with **8l.** But *o*-fluoro substituted **8l** has lowest potency (IC_{50} values: 52-114 nM) among the three substituted compounds on prostate cancer cells. *Meta*-substituted compound **8m** showed lowest activity on melanoma cells (IC_{50} values: 287-304 nM) but showed moderate inhibition on prostate cancer cells (IC_{50} values: 23-46 nM).

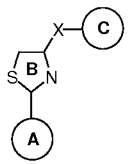
[0080] Turning to the effects of steric hindrance group on the "A" phenyl ring substituents, it was found that *p*-bromo (**8u**, IC_{50} values: 18-44 nM) caused a decrease in antiproliferative activity relative to *p*-fluoro position (**8n,** IC_{50} values: 6-12 nM) but only against prostate cancer cells. Reduced activity against both cancer cell lines occurred when *p*-methyl (**8k,** IC_{50} values: 5-21 nM) was replaced with a *p*-ethyl group (**8v,** IC_{50} values: 17-70 nM).

[0081] To investigate if the phenyl ring played an essential role at the "A" ring site, phenyl at 2-thiazole position was removed and compound **10** was obtained. This modification caused a total loss of activity compared with **8f.** The replacement of the "A" ring by pyridine (compound **8x**) had the same effect. Moreover, substituting 2-pyrimidine in "A" ring (compound **8y**) also caused a significant loss of activity (IC_{50}s: 11.8 - 41.0 μM). However, introducing the thiophene replacement of phenyl (**8z**) into "A" position improved the potency calcd. 1-3 folds on all examined cell lines (IC_{50}s: 9-38 nM) compared to **8f** (IC_{50}s: 21-71 nM).

[0082] Because many of the compounds show poor water-solubility, three watersoluble salts were prepared after introducing a hydrophilic group such as NH_2 (**8w**) and COOH (**8r**) into "A" ring to form HCl or sodium salts. Another modification is replacing "A" / "C" rings in **8a** with pyridine (**8i, 8x, 8y**) or pyrimidine rings, which could also be converted into HCl salts. These modifications reduced the calculated LogP values (LogP = 2.74 - 3.90) compared with **8a** and **8f** (LogP = 4.46 and 4.08; *see* Table 5). Introducing *p*-amino to "A" phenyl (**8w**) is the only case to increase the antiproliferative activity (HCl salt, IC_{50} values: 11-29 nM) compared with **8f** against all cell lines. Although replacing phenyl with pyrimidine (**8y**) kept partial activity against both cancer cells, the potency range was markedly reduced from nM to μM compared with **8f.** Unfortunately, introducing COOH to *para-* phenyl "A" ring and pyridine to "A" or "C" rings (**8i, 8r, 8x**) all resulted in the total loss of the anti-cancer activity. A total loss of potency was seen in the methyl ester **8s** of acid **8r** against both cancer cell lines. Demethylation of compound **8f** afforded water soluble 3,4,5-trihydroxyphenyl at "C" ring compound **11f**, but this demethylation results in complete loss of antiproliferative activity against all tested cancer cells, which also points out the importance of 3, 4, 5-trimethoxyphenyl at "C" position of the methanones.

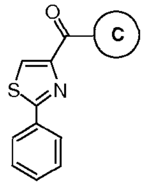
[0083] Given these results, compound **8f** was also subjected to *in vitro* testing in an NCI-60 screening assay, which measures the ability of the compound to act against six leukemia cell lines, eight non-small cell lung cancer cell lines, seven colon cancer cell lines, six CNS cancer (e.g., glioma/glioblastoma) cell lines, eight melanoma cell lines, six ovarian cancer cell lines, seven renal cancer cell lines, two prostate cancer cell lines, and eight breast cancer cell lines. The results of the NCI-60 assay showed broad activity against all of these cancers, with GI_{50} values in the nanomolar range ($< 1.0 \times 10^{-8}$) against most cell lines and TGI values in the micromolar range against most cell lines. TGI values in the nanomolar range were obtained against several leukemia cell lines, one lung cancer cell line, several colon cancer cell lines, several ovarian cancer cell lines, and several breast cancer cell lines.

Table 2: *In Vitro* Inhibitory Effects of Modificated ATCAA Compounds against the Proliferation of Melanoma (A375, B16-F1) and Prostate Cancer Cells (DU145, PC-3, LNCaP, PPC-1)

	A ring	B ring[a]	C ring[b]	X	IC_{50} ± SEM (μM)					
					B16-F1	A375	DU 145	PC-3	LNCaP	PPC-1
ATCAA-1	p-NHAc-Ph	TZD	$C_{16}H_{33}$	CONH	2.2±0.3	2.1±0.2	1.7 ± 0.1	1.2 ± 0.1	1.0±0.1	0.4±0.1
ATCAA-2	p-NHAc-Ph	TZD	9H-fluoren-l-yl	CONH	3.9±0.3	2.1±0.1	1.9 ± 0.3	2.1 ± 0.1	3.5±0.7	1.6±0.1
2a	Ph	TZD	3,4,5-triMeO-Ph	CONH	>100	>100	>20	>20	>20	>20
2b	3,4,5-triMeO-Ph	TZD	3,4,5-triMeO-Ph	CONH	>100	>100	>20	>20	>20	>20
4a*(4R)*	Ph	TZL	3,4,5-triMeO-Ph	CONH	38.3± 3.2	22.8±1.6	>20	>20	>20	5.3±0.3
4b*(4S)*	Ph	TZL	3,4,5-triMeO-Ph	CONH	30.4±2.8	13.6±1.2	>20	13.2± 2.1	16.8±1.8	3.4±0.2
5	Ph	TZ	3,4,5-triMeO-Ph	CONH	>100	>100	>20	>20	>20	>20
8f	Ph	TZ	3,4,5-triMeO-Ph	CO	0.055± 0.005	0.028± 0.005	0.071±0.004		0.028±0.004	0.043±0.005
Colchicine					0.029± 0.005	0.020± 0.003	0.010±0.002	0.011± 0.001	0.016±0.004	0.020±0.001

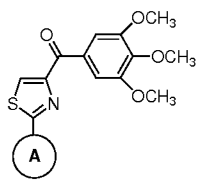
[a]. TZD=Thiazolidine, TZL=Thiazoline, TZ= Thiazole; [b]For **ATCAA-1,** "C" position contains a lipid chain. **ATCAA-1** and **ATCAA-2** were prepared using appropriate starting materials according to Scheme 1 of Example 1 (*see also* Li et al., "Synthesis and Antiproliferative Activity of Thiazolidine Analogs for Melanoma," Bioorg. Med. Chem. Lett. 17:4113-7 (2007); Gududuru et al., "Discovery of 2-Arylthiazolidine-4-Carboxylic Acid Amides as a New Class of Cytotoxic Agents for Prostate Cancer," J. Med. Chem. 48:2584-2588 (2005)).

Table 3: *In Vitro* Growth Inhibitory Effects of Compounds 8a-8j with Different "C" Rings against Proliferation of Melanoma (A 375, B16-F1) and Prostate Cancer Cells (DU145, PC-3, LNCaP, PPC-1)

Compounds **8**		C Ring	IC_{50} ± SEM (μM)					
			B16-F1	A375	DU 145	PC-3	LNCaP	PPC-1
	**8a**	Ph	>100	>100	>20	>20	>20	>20
	8b	4-MeO-Ph	>100	>100	>20	>20	>20	>20
	8c	3-MeO-Ph	>100	>100	>20	>20	>20	>20
	8d	2-MeO-Ph	59.4 ± 21.2	70.3 ± 32.5	>20	>20	>20	>20
	8e	3,4-diMeO-Ph	>100	>100	>20	>20	>20	>20
	8f	3,4,5-triMeO-Ph	0.055 ± 0.005	0.028 ± 0.005	0.071 ± 0.004	0.021 ± 0.001	0.028 ± 0.004	0.043 ± 0.005
	8g	3,5-diMeO-Ph	0.350 ± 0.2	0.170 ± 0.1	0.424 ± 0.098	0.301 ± 0.030	0.323 ± 0.041	0.242 ± 0.014
	8h	2-Fluoro-Ph	>100	>100	>20	>20	>20	>20
	8j	Hexadecyl[a]	18.6±17.5	16.0 ± 15.2	>20	>20	>20	>20

[a] Compound **8j** has a lipid chain at "C" ring position.

Table 4: *In Vitro* Growth Inhibitory Effects of Compounds 8f, 8k-8q, 8t-v, 8x-z, and 10 with different "A" Rings against the Proliferation of Melanoma (A 375, B16-F1) and Prostate Cancer Cells (DU145, PC-3, LNCaP, PPC-1)



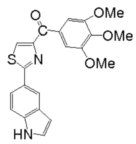
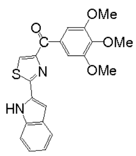
Compounds **8**		A Ring	IC_{50} ± SEM (nM)					
			B16-F1	A375	DU 145	PC-3	LNCaP	PPC-1
	8f	Ph	55 ± 5	28 ± 5	71 ± 4	21 ± 1	28 ± 4	43 ± 5
	8k	4-Methyl-Ph	21 ± 10	11 ± 5	7 ± 1	5± 1	6 ± 1	6 ± 1
	8l	2-Fluoro-Ph	27 ± 11	30 ± 9	114 ± 3	82 ±9	53 ± 4	52 ± 3
	8m	3-Fluoro-Ph	287 ± 36	304 ± 25	35 ± 3	24 ± 2	11 ± 2	21 ± 1
	8n	4-Fluoro-Ph	43 ± 21	33 ± 14	12 ± 1	13 ± 1	6 ± 1	8 ± 1
	8o	3, 4-diMeO-Ph	161 ± 29	34 ± 10	102 ± 2	69 ± 3	38 ± 6	56 ± 2
	8p	4-Nitro-Ph	56 ± 12	38 ± 9	95 ± 5	56 ± 1	39 ± 4	34 ±1
	8q	4-Cyano-Ph	53 ± 16	59 ± 24	52 ± 2	30 ± 7	15 ±4	19 ± 2
	8t	4-Trifluoromethyl-Ph	92 ± 16	23 ± 5	50 ± 5	58 ± 4	94 ± 1	76 ± 1
	8u	4-Bromo-Ph	32 ± 5	13 ± 2	21 ± 4	18 ± 3	44 ± 3	21 ± 5
	8v	4-Ethyl-Ph	70 ± 8	17 ± 2	31 ± 4	27 ± 4	60 ± 5	22 ± 3
	8x	4-Pyridine	>100000	>100000	>20000	>20000	>20000	>20000
	8y	2-Pyrimidine	2300 ± 860	4100 ± 740	2813 ± 92	2657 ± 40	2370 ± 85	1186 ± 22
	8z	2-Thienyl	38 ± 15	20 ± 7	22+1	17 ± 2	9 ± 1	13 ± 1
	10	H[a]	>100000	>100000	>20000	>20000	>20000	>20000

[a]. Compound **10** has a proton at "A" ring position.

Example 5 - Synthesis and *in vitro* Cytotoxicity of Additional Methanone Compounds

[0084] The A ring indole of compounds **31** and **32** was synthesized using the same approach as **8f** described in Scheme 3 above from 1H-indole-5-carbonitrile or 1H-indole-2-carbonitrile as starting material. Crude product was purified by column chromatography.
(2-(1H-indol-5-yl)thiazol-4-yl)(3,4,5-trimethoxyphenyl)methanone **(Compound 31):** Yield: 36.3 %. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.36 (br, 1H), 8.31 (br, 1H), 8.21 (s, 1H), 7.92-7.89 (dd, 1H), 7.83 (s, 2H), 7.47 (d, 1H), 7.29 (t, 1H), 6.64 (t, br, 1H), 3.98 (s, 3 H), 3.97 (m, 6 H). MS (ESI) *m/z* 417.1 $[M + Na]^+$, 392.9 $[M - H]^-$.
(2-(1H-indol-2-yl)thiazol-4-yl)(3,4,5-trimethoxyphenyl)methanone **(Compound 32):** Yield: 45.8 %. ^{1}H NMR (500MHz, $CDCl_3$) δ 9.26 (br, 1H), 8.11 (s, 1H), 7.67 (d, 2H), 7.46 (s, 2H), 7.42 (d, 1H), 7.29 (t, 1H), 7.16 (t, 1H), 7.10 (s, 1H), 3.97 (s, 3 H), 3.93 (m, 6 H). MS (ESI) *m/z* 417.1 $[M + Na]^+$, 392.9 $[M - H]^-$.
[0085] The activity of compound **31** was assessed by *in vitro* cytotoxicity assay as described in Example 4 above. It was determined that compound **31** exhibited enhanced activity against the PC-3, A375, and B16 cell lines.

Table 5: *In Vitro* Growth Inhibitory Effects of Compounds 31-32 Against Proliferation of Prostate and Melanoma Cancer Cells

Compound	Structure	IC_{50} (nM)						
		RH7777	DU 145	PC-3	LNCaP	PPC-1	A375	B16
31	 $C_{21}H_{18}N_2O_4S$ Mol. Wt.: 394.44 C, 63.94; H, 4.60; N, 7.10; O, 16.22; S, 8.13	ND	ND	7.6	ND	ND	25.0	8.3
32	 $C_{21}H_{18}N_2O_4S$ Mol. Wt.: 394.44 C, 63.94; H, 4.60; N, 7.10; O, 16.22; S, 8.13	ND	ND	ND	ND	ND	ND	ND

ND = not determined.

Example 6 - Determining Mechanism of Action for Compound 8f

[0086] To understand the target for these highly potent compounds, cell cycle analysis was performed using compound **8f.** LNCaP prostate cancer cells were exquisitely sensitive to compound **8f** (IC_{50}= 29 nM). LNCaP cells were treated with compound **8f** (10 to 500 nM) for 24 h prior to staining with propidium iodide and performing cell cycle analysis. Although compound **8f** had no effect on cell cycle distribution at a 10 nM (below the IC_{50}), the proportion of cells in G2/M phase increased in proportion to the concentration of compound **8f** at higher concentrations. About 10% of untreated cells were observed in G2/M phase, whereas the cells treated with more than 50 nM showed a greater proportion of cells in G2/M phase (57, 63, and 49%, respectively, for 50, 200, and 500 nM). The results are shown in Figures 3A-B. The increase in G2/M phase cells was accompanied by a decrease in G1 populations, relative to control. These data indicate that compound **8f** may inhibit tubulin action in a manner similar to paclitaxel, the vinca alkaloids, and cochicine (Margolis et al., "Addition of Colchicine--Tubulin Complex to Microtubule Ends: The Mechanism of Substoichiometric Colchicine Poisoning," Proc. Nat'l Acad. Sci. USA 74:3466-70 (1977)).

[0087] Based on these results, an *in vitro* microtubule polymerization assay was performed. Bovine brain tubulin (0.4 mg) (Cytoskeleton, Denver, CO) was mixed with various concentrations(0.625-20 μM) of compound **8f** and incubated in 120 μl of general tubulin buffer (80 mM PIPES, 2.0 mM $MgCl_2$, 0.5 mM EGTA, pH 6.9 and 1 mM GTP). The absorbance of wavelength at 340 nm was monitored every 60s for 20 min by the SYNERGY 4 Microplate Reader (Bio-Tek Instruments, Winooski, VT). The spectrophotometer was set at 37 °C for tubulin polymerization. The IC_{50} value was defined as the concentration which can inhibit 50% of microtubule polymerization. The results are shown in Figure 4. Compared with non-treated control, compound **8f** inhibits tubulin polymerization. The effect of **8f** on tubulin assembly was examined at concentrations from 0.625 μM to 20 μM. The observed results demonstrate that compound **8f** inhibited tubulin polymerization in a dose-dependent manner with an IC_{50} value of 4.23 μM.

Example 7 - *In vitro* Cytotoxicity of Compounds 8f and 8n Against A375 Melanoma Cell Line

[0088] Human A375 malignant melanoma cells were plated at a colony-forming density (200 cells per well on six well plates). Cells were grown in DMEM medium (GIBCO, Invitrogen Corp., Carlsbad, CA) supplemented with charcoal-stripped fetal bovine serum (HyClone, Logan, UT) and an antibiotic-antimycotic solution (Sigma, St. Louis, MO) at 37°C in an atmosphere of 95% air and 5% CO_2. Cells were treated with compounds **8f** and 8n at different concentrations (0, 0.03, 0.3, and 3 μM). Cells were grown for 10 days and colonies were fixed with 4% paraformaldehyde in PBS at 4°C. The fixed colonies were washed with distilled water, stained with 0.1% crystalline blue for 30min and rinsed with distilled water to remove excess of the dye. Plates were photographed and colony formations were examined by eye and under the microscope. Both of compounds **8f** and **8n** significantly inhibit melanoma colony formation at 0.03 μM. At the two higher concentrations tested (0.3 and 3 μM), colony formations were completely inhibited, with no colonies visible under the microscope (Figures 5A-B).

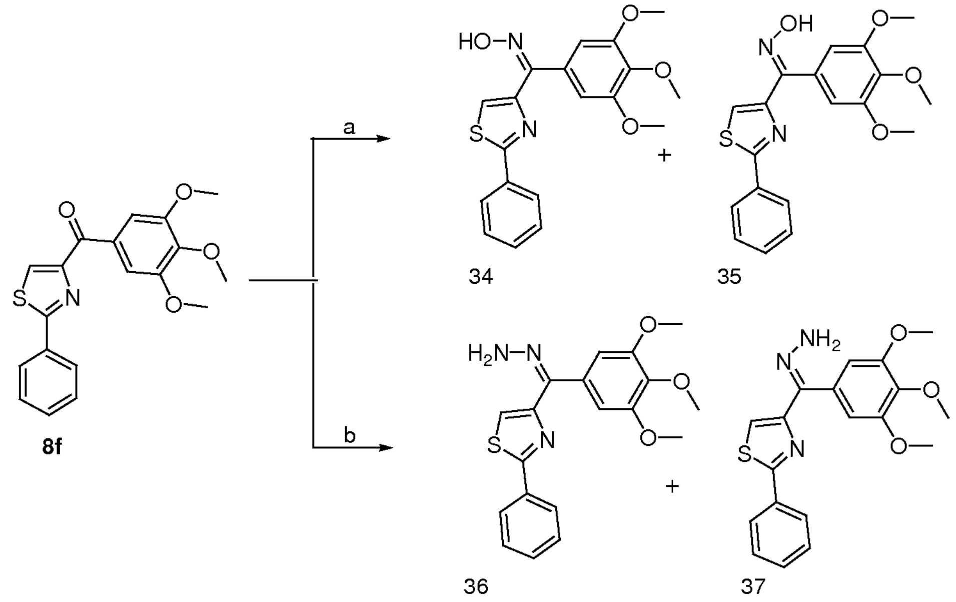
Example 8 - *In vivo* Cytotoxicity of Compound 8n Against Melanoma Xenograft Tumor

[0089] The efficacy of compound **8n** was assessed using B16-F1 mouse melanoma cells injected in C57 black mice. B16 tumors will grow in a fully immunocompetent host, in which case the tumor progression may more accurately replicate melanoma growth. Logarithmic growth phase B16-F1 (3.8×10^5) cells were injected s.c. into the right dorsal flank of C57BL/6 mice. When tumors were palpable, mice were randomized into a control and a treatment group (n = 9). Mice were dosed by daily i.p. injection with 30 μl of vehicle (control group) or **8n** solution (treatment group, 6 mg/kg). Tumor volume was measured once daily with a Traceable® electronic digital caliper and calculated by using the formula $a\times b^2\times 0.5$, where a and b represented the larger and smaller diameters, respectively. Body weights were also recorded. Tumor volume was expressed as cubic millimeters. Data were expressed as Mean±SE for each group and plotted as a function of time. At the end of treatment, all mice were euthanized by CO_2 inhalation followed by cervical dislocation. Compound **8n** showed significant tumor growth inhibition at this relatively low dose (6 mg/kg) as shown in Figure 6. There was no significant body weight loss (<5%), and all mice had normal activities during the experiments.

Example 9 - Synthesis of Compound 8f Derivatives with Hydrazine or Oxime

[0090] Carbonyl group linkers were modified into oxime and hydrazine linkers (compounds **33-36**) as illustrated in Scheme 4. Compound **8f** was used as starting material.

Scheme 4



Reagents (a) NH_2OH. HCl, C_2H_5OH, H_2O, NaOH, 51%; (b) NH_2NH_2 xH_2O, CH_2Cl_2, C_2H_5OH, 57%.

[0091] To a suspension of 50 mg **8f** in 2 mL ethyl alcohol was added a 0.5 mL aqueous solution of 34 mg hydroxylamine hydrochloride. Then 13 mg sodium hydroxide in 0.5 mL H_2O was added and stirred at room temperature for 10 min. Then heating to 60 °C and stirred for 3h. Oxime isomers **33** and **34** were separated from the reaction mixtures by flash chromatograph as white crystals with a 50% overall yield.

(Z)-(2-phenylthiazol-4-yl)(3,4,5-trimethoxyphenyl)methanone oxime **(compound 33):** M.p 150-153°C. ^1H NMR (300MHz, $CDCl_3$) δ 11.94 (br, 1H), 8.35 (br, 1H), 7.91-7.89 (m, 2H), 7.81-7.75 (d, 1H), 7.50-7.49 (m, 3H), 6.85 (s, 2H), 3.73 (s, 6 H), 3.71 (s, 3 H). MS (ESI) *m/z* 393.3 $[M + Na]^+$, 368.9 $[M - H]^-$.

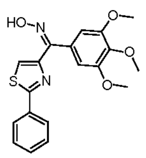
*(E)-(*2-phenylthiazol-4-*yl)(3,4,5-trimethoxyphenyl)methanone oxime* **(compound 34):** M.p 176-177°C. ^1H NMR (500MHz, DMSO-d_6) δ 11.48 (br, 1H), 7.92-7.90 (m, 2H), 7.64 (br, 1H), 7.52-7.48 (d, 1H), 7.52-7.48 (m, 3H), 6.75 (s, 2H), 3.75 (s, 6 H), 3.72 (s, 3 H). MS (ESI) *m/z* 393.1 $[M + Na]^+$, 368.9 $[M-H]^-$.

[0092] To a solution of 2 mL hydrazine in 6 mL ethyl alcohol was added a solution of 230 mg **8f** in 2 mL methylene chloride. The mixtures was refluxed overnight and absorbed on silicon gel. Hydrazone isomers **35** and **36** was separated from the flash chromatograph as white crystals with a 56.9% overall yield.

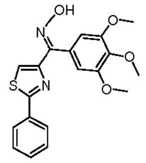
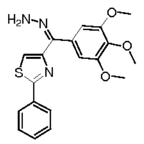
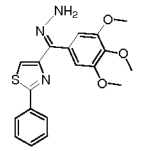
(Z)-4-(hydrazono(3,4,5-trimethoxyphenyl)methyl)-2-phenylthiazole **(compound 35):** M.p 117-119 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.01-7.98 (m, 2H), 7.49-7.46 (m, 5H), 7.33 (s, 1H), 6.82 (s, 2H), 3.87 (s, 3 H), 3.85 (s, 6 H). MS (ESI) *m/z* 370.1 $[M + H]^+$.

(E)-4-(hydrazono*(3,4,5-trimethoxyphenyl)methyl)-2-phenylthiazole* **(compound 36):** M.p 65-66 °C. ^1H NMR (300MHz, $CDCl_3$) δ 8.04-8.00 (m, 2H), 7.44-7.40 (m, 3H), 6.95 (s, 1H), 6.62 (s, 2H), 5.62 (s, 2H), 3.93 (s, 3 H), 3.87 (s, 6 H). MS (ESI) *m/z* 370.1 $[M + H]^+$.

Table 6: Antiproliferative effects of compounds 33-36

Compound		IC_{50} (μM)						
		B16	A375	Fibroblast	DU145	PC-3	LNCaP	PPC-1
33		0.32	0.18	0.36	0.10	0.12	0.19	0.16

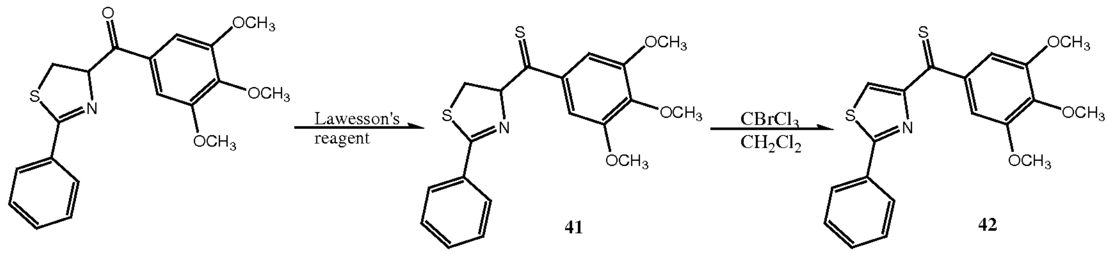
(continued)

Compound		IC50 (μM)						
		B16	A375	Fibroblast	DU145	PC-3	LNCaP	PPC-1
34		11.4	7.8	10.1	>1	>1	>1	>1
35		2.0	0.9	1.9	1.21	1.12	1.80	0.87
36		1.8	0.6	1.0	1.21	1.04	1.30	0.97

Example 10 - Design of Additional Derivatives

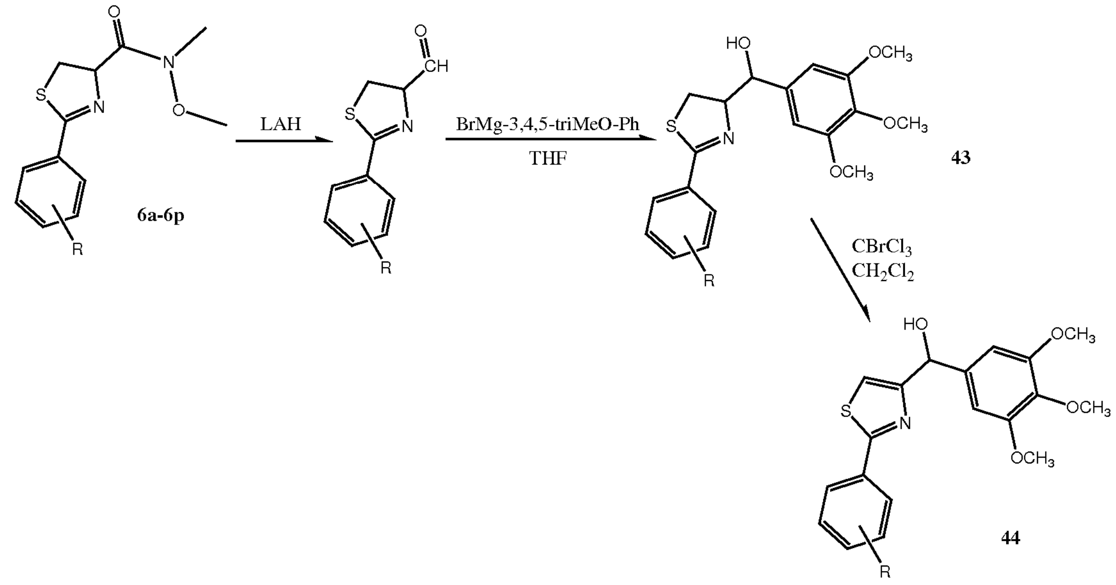
[0093] Compound **8f** will be further modified to thioketone analogs **41** and **42** (Scheme 5 below). Compounds **8a-z** will be similarly modified. The carbonyl group can be converted into a thiocarbonyl group by the action of Lawesson's reagent (Jesberger et al., Synthesis 1929-1958 (2003)). The thioketone structure with conjugated aromatic rings is stable relative to unhindered thioketones. The thiazole compound can be obtained after dehydronation. (Riedrich et al., Angewandte Chemie, International Edition, 46(15):2701-2703 (2007)). This conversion will decrease the hydrogen bond acceptor ability from O···H in ketone to S··· H in thione. It will be helpful to examine the importance of hydrogen acceptor position in these molecules.

Scheme 5

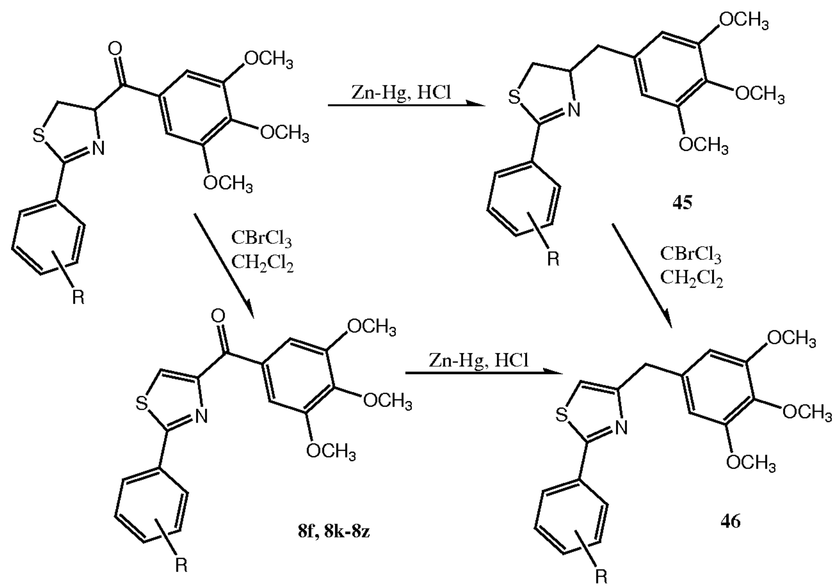


[0094] New analogs in which the carbonyl has been reduced to an alcohol (**43** and **44,** Scheme 6A below) or reduced to methylene (**45** and **46,** Scheme 6B below) will be synthesized. The alcohol **43** and **44** can be obtained using Grignard reaction of intermediate aldehyde with according Grignard reagents. Analogs **45** and **46** can be prepared with Clemmensen reduction of ketone function group to produce the corresponding hydrocarbon. When carbonyl is reduced to an alcohol or methylene, the strong hydrogen acceptor C=O reverses to strong hydrogen donor O-H or hydrocarbon, which totally loses hydrogen bond effects. This modification will provide insight as to the importance of carbonyl group and if it has a specific function in the anti-cancer activity.

Scheme 6A

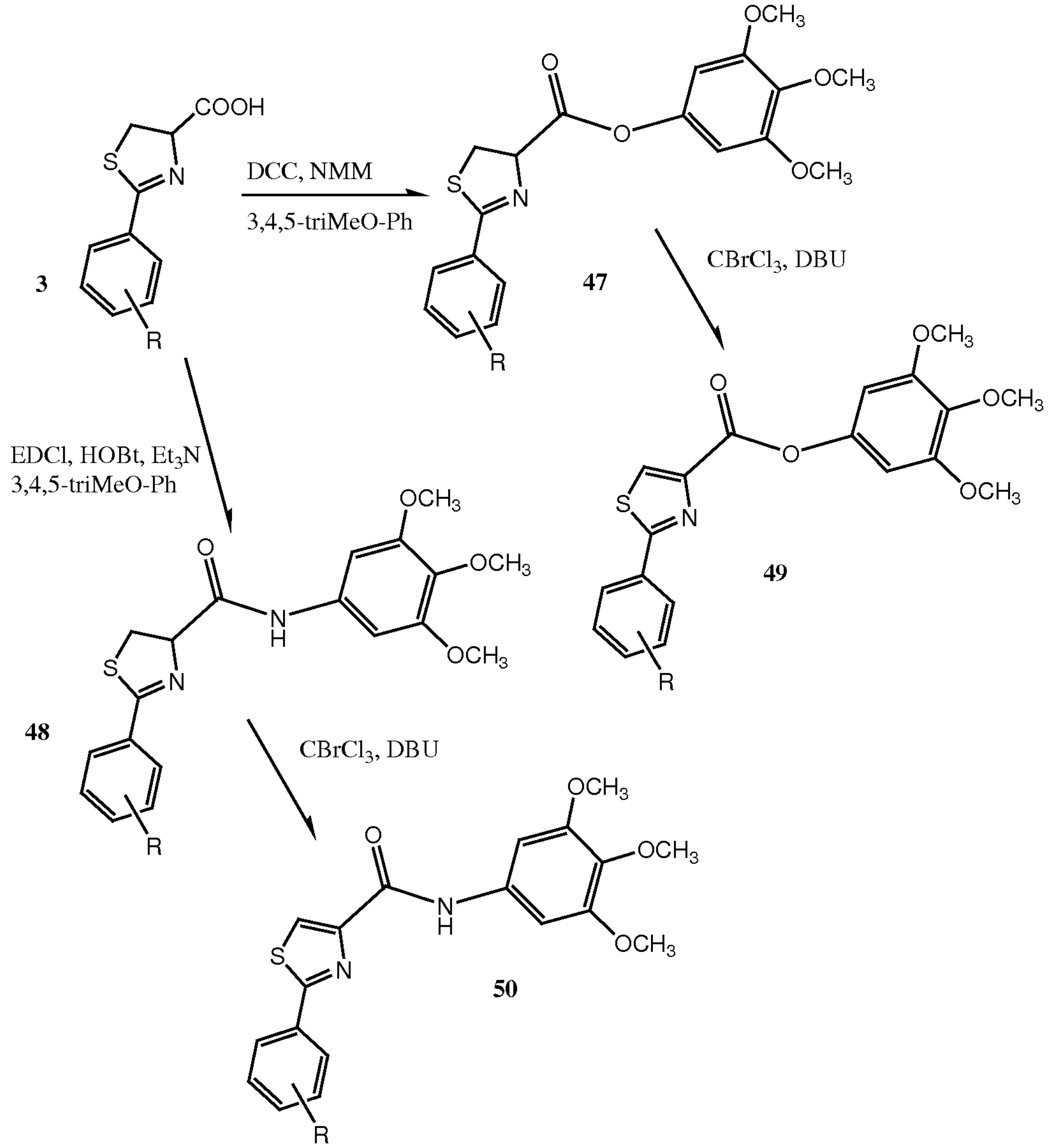


Scheme 6B



[0095] To examine the importance of ketone on antiproliferation in cancer cells, this linker will be converted into amide and ester analogs **(47-50,** Scheme 7 below). Finding activity in any of these series of analogs, the different linkages between the rings optimized to enhance activity and metabolic stability. As Scheme 7 below shows, consistent with the results demonstrated in the preceding examples, thiazoline and thiazole rings will be obtained from reaction of benzonitrile (including substituted benzonitrile) and cysteine (Bergeron et al., J. Med. Chem. 48:821-831 (2005)). The resulting acid intermediates will be used to prepare the ester and amide linkages. These analogs will be compared for antiproliferation activity on prostate cancer cells and/or melanoma cells, and control cells, and compared to Compounds **8f** and **8n.**

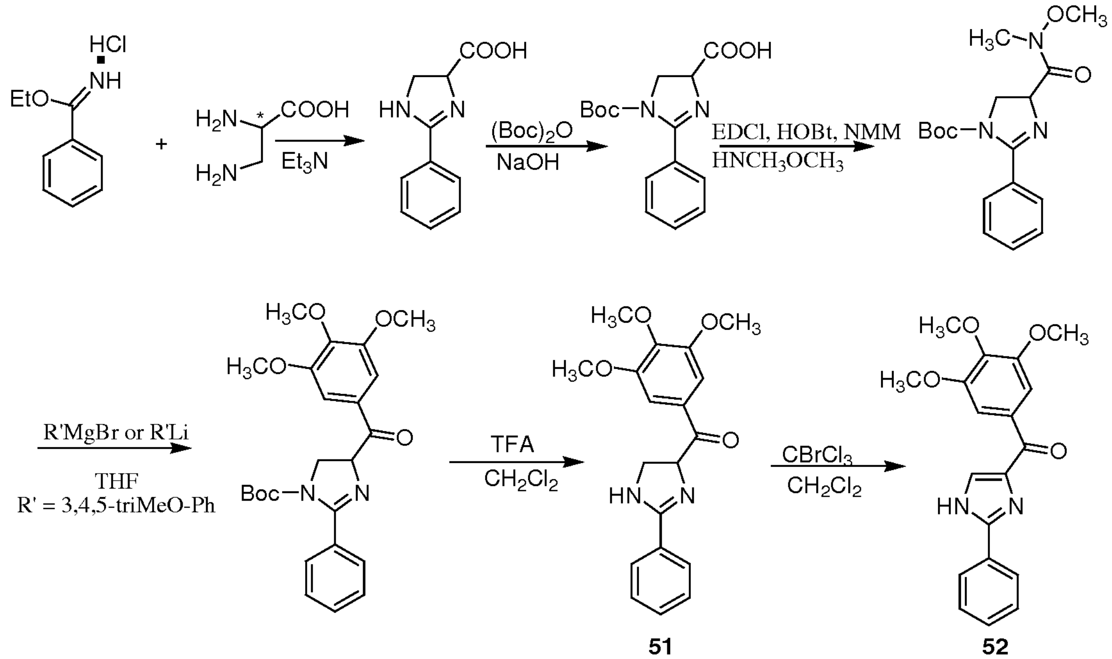
Scheme 7



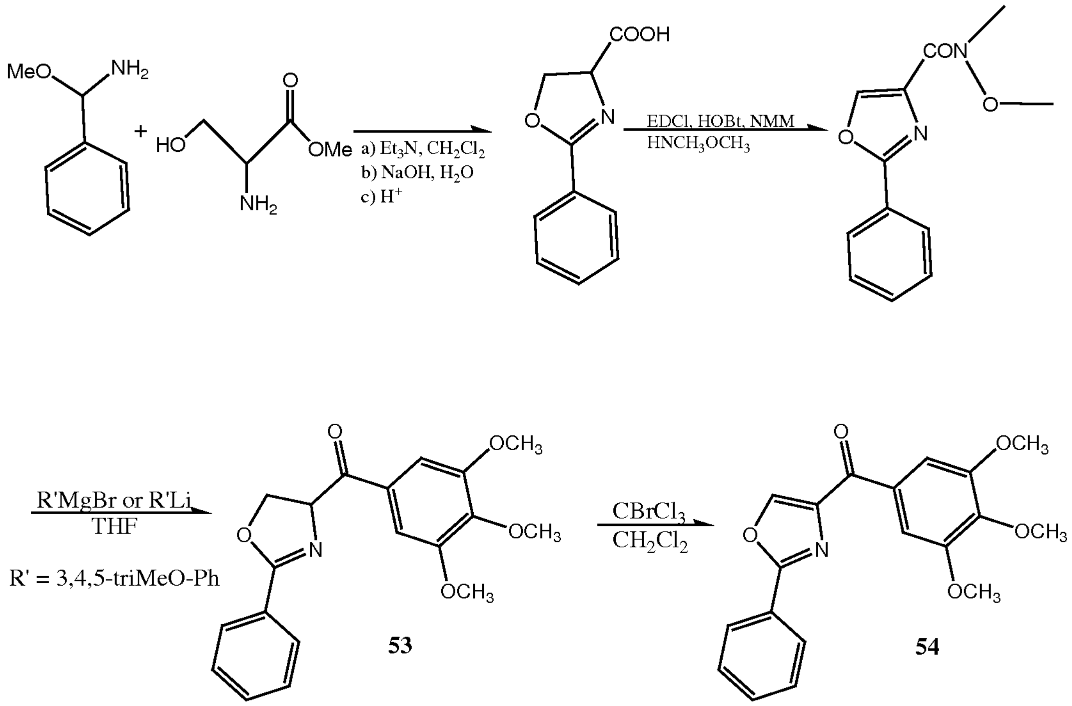
[0096] Compounds will also be prepared with the trimethoxylphenyl group replaced with different substituted aromatic rings, saturated or unsaturated alkyls and various heterocyclic groups as defined herein. This can be accomplished by using different Grignard reagents. These analogs will allow for optimization of the "C" ring with best activities, lowest toxicity, and best metabolic stability for prostate cancer, melanoma, and other cancers.

[0097] Replacement of the central thiazoline and thiazole rings with corresponding imidazoline **(51),** imidazole **(52),** oxazoline **(53)** and oxazole **(54)** ring systems will also be performed. Ethyl benzimidate hydrochloride salt reacted with 2,3-diaminopropanoic acid to give imidazoline ring system (*see* Scheme 8A below). (Hsu et al., J. Med. Chem. 23(11), 1232-1235 (1980)). Dehydrogenation of imidazolines will afford desired imidazole compounds. Oxazolines can be prepared according to the classical condensation of phenyl imino ether with serine ester using triethylamine as a base (*see* Scheme 8B below) (Meyer et al., Tetrahedron: Asymmetry 14:2229-2238 (2003)). Dehydrogenation of oxazolines will give the desired oxazole compounds.

Scheme 8A



Scheme 8B



[0098] Optically pure isomers of compounds **8a-8z** will also be prepared to investigate the importance of chirality at 4-position of thiazoline. This will be carried out using D- or L-Cysteine to synthesize the chiral intermediate ketones from protected D- or L-Cysteine. Condensation of the intermediate ketones with benzonitrile will afford R- or S-thiazoline isomers. Thiazoles can be prepared by dehydrogenation.

[0099] From previous studies on structure-relationship of thiazolidine carboxylic acid amides, reversed electronic effects of substituents on phenyl in C-2 position of thiazolidine ring resulted in significant different activity on prostate cancer cell lines. Derivatives with different aromatic ring substitutions from various substituted benzonitrile reactants will also be prepared (e.g., 4-dimethylamino-benzonitrile, 3-hydroxybenzonitrile, 4-methoxybenzonitrile, 3,4-dimethoxybenzonitrile, 3,4,5-trimethoxybenzonitrile, 4-acetamidobenzonitrile, 4-fluorobenzonitrile, 4-bromobenzonitrile, 4-nitrobenzonitrile, 4-cyanobenzonitrile, 3,5-difluorobenzonitrile, 4-methylbenzonitrile, 3-bromo-4-fluorobenzonitrile, 2,6-dichlorobenzonitrile, phenylbenzonitrile, indolenitrile and substituted indolylnitriles, pyridine-nitrile and substituted pyridinylnitriles, furan-nitrile and substituted furanylnitriles) to induce both electron withdrawing and electron donating substituents in ring substituent of C-2 position in thiazoline ring. It is believed that the best substituents of C-2 phenyl, indolyl, furanyl, thiophen-yl, and pyridinyl groups can be found after screening the resulting analogs.

Claims

1. A compound, wherein the compound is (2-(1*H*-indol-3-yl)imidazol-4-yl)(3,4,5-trimethoxyphenyl)methanone.

2. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

3. A compound according to claim 1 for use as a medicament.

4. Use of a compound of claim 1, for the preparation of a medicament for treating prostate cancer, breast cancer, ovarian cancer, skin cancer, lung cancer, colon cancer, leukemia, renal cancer or CNS cancer, or a combination thereof.

5. The use according to claim 4, wherein the medicament is administered systemically.

6. The use according to claim 4, wherein the medicament is administered orally, topically, transdermally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes.

7. The use according to claim 4, wherein the medicament is administered directly to a site where cancer cells are present.

8. The use according to claim 4, wherein the medicament is administered at a dosage rate of about 0.01 to about 100 mg of the compound per kg·body weight.

9. The use according to claim 4, wherein the medicament is administered periodically.

10. The use according to claim 4, wherein the medicament is administered in combination with another cancer therapy.

11. The compound of claim 1 for use in treating prostate cancer, breast cancer, ovarian cancer, skin cancer, lung cancer, colon cancer, leukemia, renal cancer or CNS cancer, or a combination thereof.

12. The compound for use according to claim 11, wherein the compound is administered systemically.

13. The compound for use according to claim 11, wherein the compound is administered orally, topically, transdermally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitary or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes.

14. The compound for use according to claim 11, wherein the compound is administered directly to a site where cancer cells are present.

15. The compound for use according to claim 11, wherein the compound is administered at a dosage rate of about 0.01 to about 100 mg/kg·body weight.

16. The compound for use according to claim 11, wherein the compound is administered periodically.

17. The compound for use according to claim 11, wherein the compound is administered in combination with another cancer therapy.

Patentansprüche

1. Verbindung, wobei die Verbindung (2-(1*H*-Indol-3-yl)Imidazol-4-yl(3,4,5-Trimethoxyphenyl)Methanon ist.

2. Pharmazeutische Zusammensetzung, die eine Verbindung gemäß Anspruch 1 und eine pharmazeutisch zulässige Trägersubstanz aufweist.

3. Verbindung gemäß Anspruch 1 zur Verwendung als Medikament.

4. Verwendung einer Verbindung von Anspruch 1 für die Herstellung eines Medikaments zur Behandlung von Prostatakrebs, Brustkrebs, Eierstockkrebs, Hautkrebs, Lungenkrebs, Dickdarmkrebs, Leukämie, Nierenkrebs oder ZNS-Tumoren oder eine Kombination derselben.

5. Verwendung gemäß Anspruch 4, wobei das Medikament systemisch verabreicht wird.

6. Verwendung gemäß Anspruch 4, wobei das Medikament oral, lokal, transkutan, parenteral, subkutan, intravenös, intramuskulär, intraperitoneal, durch intranasale Instillation, durch intrakavitäre oder intraveskilare Instillation, intraokular, intraarteriell, intraläsional oder durch Applikation auf Schleimhäute verabreicht wird.

7. Verwendung gemäß Anspruch 4, wobei das Medikament direkt an einer Stelle verabreicht wird, an der Krebszellen vorhanden sind.

8. Verwendung gemäß Anspruch 4, wobei das Medikament mit einer Dosierung von etwa 0,01 bis etwa 100 mg der Verbindung pro kg Körpergewicht verabreicht wird.

9. Verwendung gemäß Anspruch 4, wobei das Medikament periodisch verabreicht wird.

10. Verwendung gemäß Anspruch 4, wobei das Medikament zusammen mit einer anderen Krebstherapie verabreicht wird.

11. Verbindung gemäß Anspruch 1 zur Verwendung für die Behandlung von Prostatakrebs, Brustkrebs, Eierstockkrebs, Hautkrebs, Lungenkrebs, Dickdarmkrebs, Leukämie, Nierenkrebs oder ZNS-Tumoren oder eine Kombination derselben.

12. Verbindung zur Verwendung gemäß Anspruch 11, wobei die Verbindung systemisch verabreicht wird.

13. Verbindung zur Verwendung gemäß Anspruch 11, wobei die Verbindung oral, lokal, transdermal, parenteral, subkutan, intravenös, intramuskulär, intraperitoneal, durch intranasale Instillation, durch intrakavitäre oder intraveskilare Instillation, intraokular, intraarteriell, intraläsional oder durch Applikation auf Schleimhäute verabreicht wird.

14. Verbindung zur Verwendung gemäß Anspruch 11, wobei die Verbindung direkt an einer Stelle verabreicht wird, an der Krebszellen vorhanden sind.

15. Verbindung zur Verwendung gemäß Anspruch 11, wobei die Verbindung mit einer Dosierung von etwa 0,01 bis etwa 100 mg der Verbindung pro kg Körpergewicht verabreicht wird.

16. Verbindung zur Verwendung gemäß Anspruch 11, wobei die Verbindung periodisch verabreicht wird.

17. Verbindung zur Verwendung gemäß Anspruch 11, wobei die Verbindung zusammen mit einer anderen Krebstherapie verabreicht wird.

Revendications

1. Composé, le composé étant la (2-(1*H*-indol-3-yl)imidazol-4-yl)(3,4,5-triméthoxyphényl)méthanone.

2. Composition pharmaceutique comprenant un composé selon la revendication 1 et un support acceptable sur le plan pharmaceutique.

3. Composé selon la revendication 1, pour une utilisation en tant que médicament.

4. Utilisation d'un composé selon la revendication 1, pour la préparation d'un médicament destiné au traitement du cancer de la prostate, du cancer du sein, du cancer des ovaires, du cancer de la peau, du cancer du poumon, du cancer du côlon, de la leucémie, du cancer rénal ou du cancer du système nerveux central, ou une combinaison de ceux-ci.

5. Utilisation selon la revendication 4, dans laquelle le médicament est administré de manière systémique.

6. Utilisation selon la revendication 4, dans laquelle le médicament est administré par voie orale, localement, par voie transcutanée, par voie parentérale, par voie sous-cutanée, par voie intraveineuse, par voie intramusculaire, par voie intrapéritonéale, par instillation intranasale, par instillation intracavitaire ou intravésicale, par voie intraoculaire, par voie intra-artérielle, par voie intralésionnelle, ou par application aux membranes muqueuses.

7. Utilisation selon la revendication 4, dans laquelle le médicament est administré directement à un site où des cellules cancéreuses sont présentes.

8. Utilisation selon la revendication 4, dans laquelle le médicament est administré à un taux de dose d'environ 0,01 à environ 100 mg du composé par kg de poids corporel.

9. Utilisation selon la revendication 4, dans laquelle le médicament est administré de manière périodique.

10. Utilisation selon la revendication 4, dans laquelle le médicament est administré en combinaison avec une autre thérapie du cancer.

11. Composé selon la revendication 1, destiné à être utilisé dans le traitement du cancer de la prostate, du cancer du sein, du cancer des ovaires, du cancer de la peau, du cancer du poumon, du cancer du côlon, de la leucémie, du cancer rénal ou du cancer du système nerveux central, ou une combinaison de ceux-ci.

12. Composé utilisable selon la revendication 11, le composé étant administré de manière systémique.

13. Composé utilisable selon la revendication 11, le composé étant administré par voie orale, localement, par voie transcutanée, par voie parentérale, par voie sous-cutanée, par voie intraveineuse, par voie intramusculaire, par voie intrapéritonéale, par instillation intranasale, par instillation intracavitaire or intravésicale, par voie intraoculaire, par voie intra-artérielle, par voie intralésionnelle, ou par application aux membranes muqueuses.

14. Composé utilisable selon la revendication 11, le composé étant administré directement à un site où des cellules cancéreuses sont présentes.

15. Composé utilisable selon la revendication 11, le composé étant administré à un taux de dose d'environ 0,01 à environ 100 mg/kg de poids corporel.

16. Composé utilisable selon la revendication 11, le composé étant administré de manière périodique.

17. Composé utilisable selon la revendication 11, le composé étant administré en combinaison avec une autre thérapie du cancer.

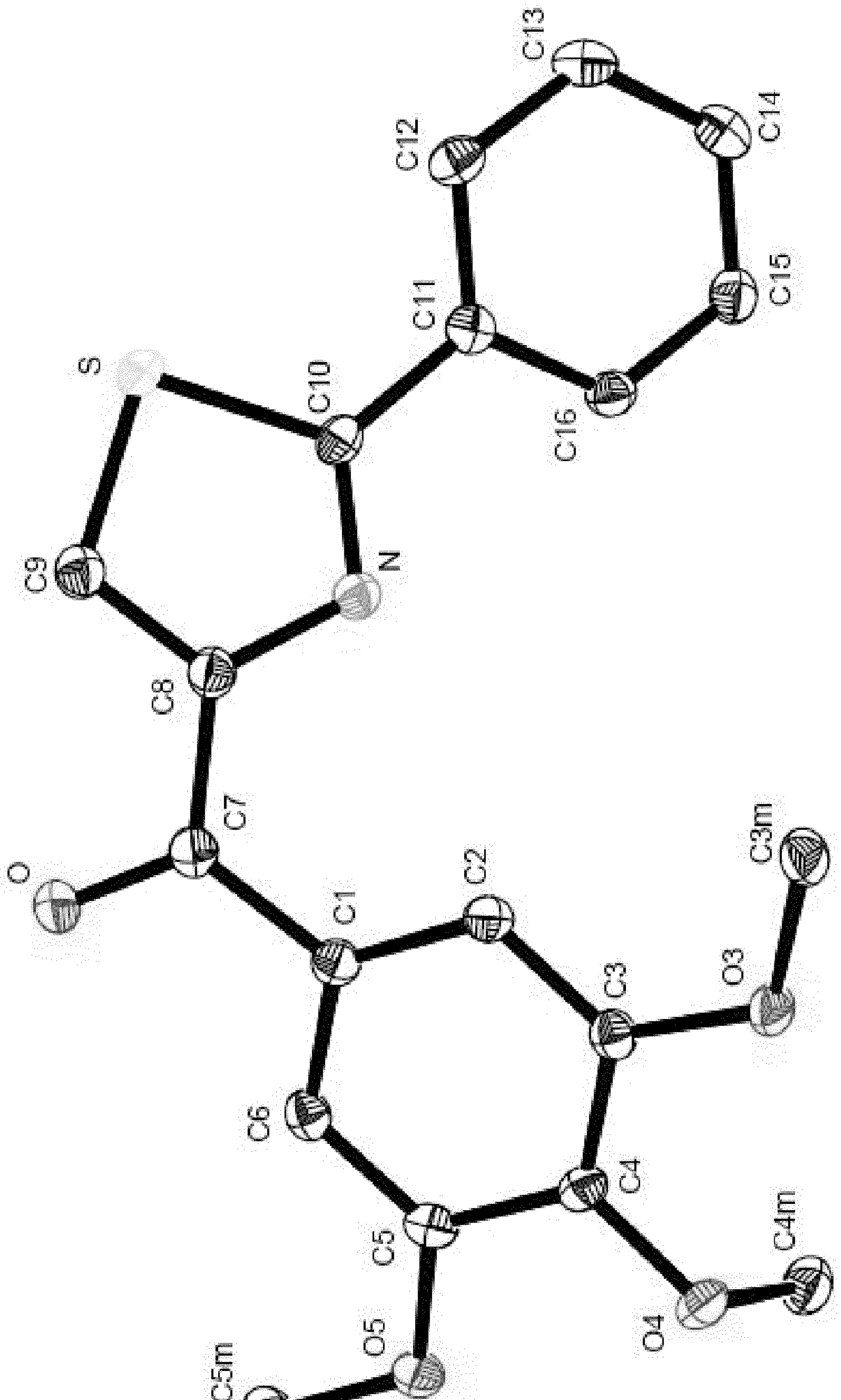

C13
C12
C14
C15
C11
S
C10
C16
C9
N
C8
C7
O
C1
C2
C3m
C6
C3
O3
C4
C5
C4m
O5
O4
C5m

Figure 1

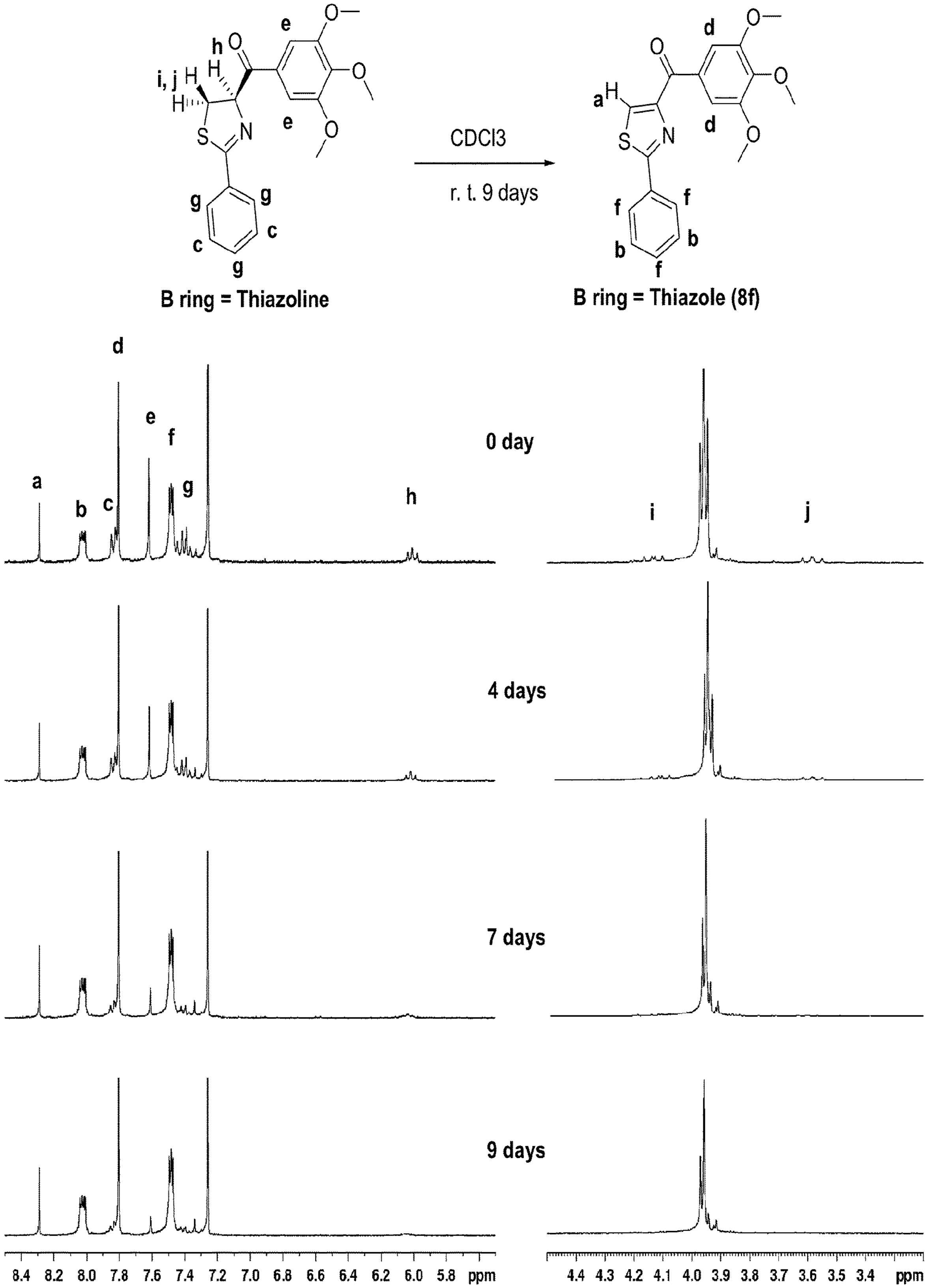

CDCl3
r. t. 9 days
B ring = Thiazoline
B ring = Thiazole (8f)
0 day
4 days
7 days
9 days
ppm
ppm

Figure 2

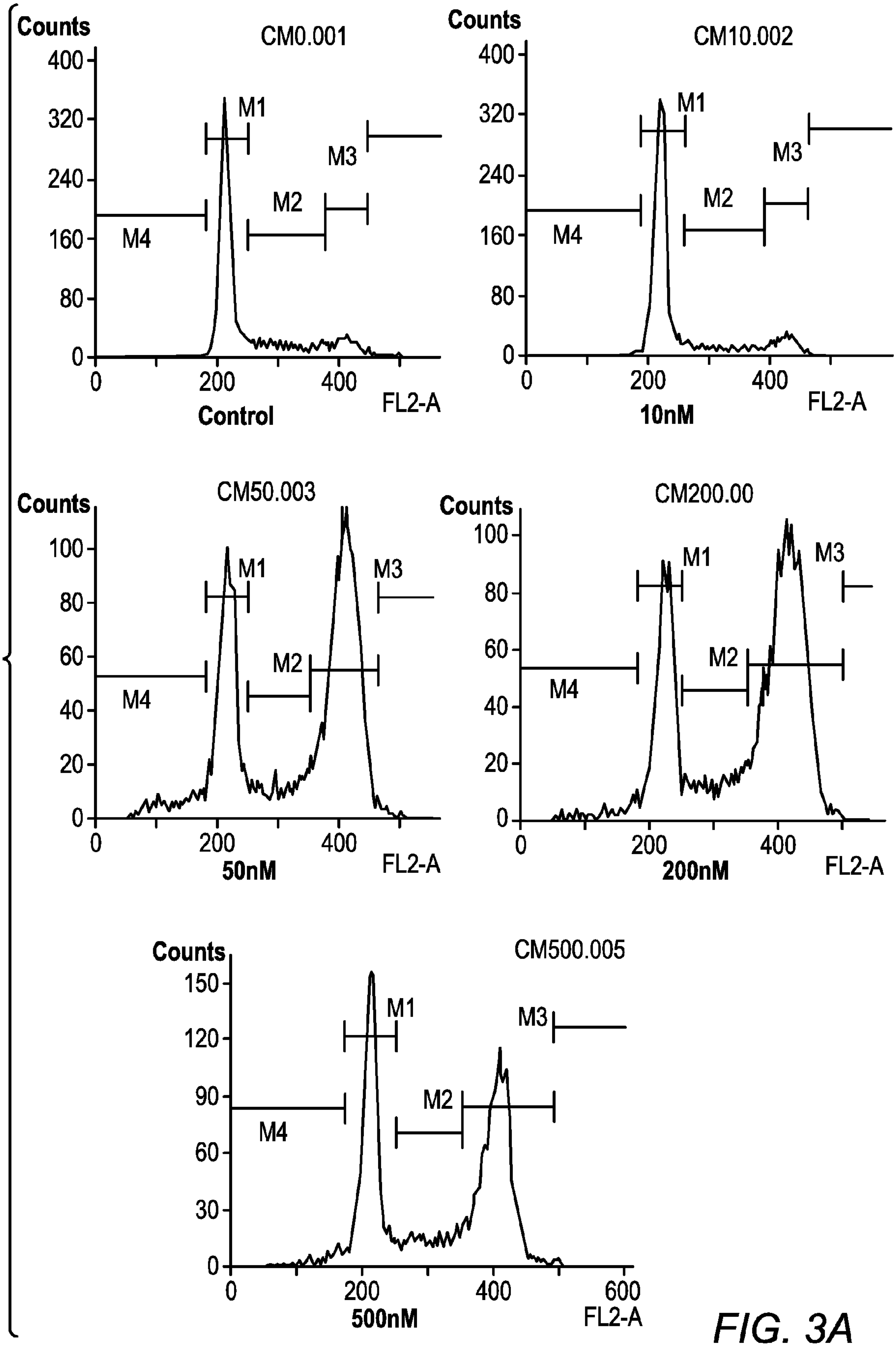

Counts
CM0.001
400
320
240
160
80
0
M1
M2
M3
M4
0
200
400
FL2-A
Control
Counts
CM10.002
10nM
Counts
CM50.003
100
80
60
40
20
50nM
Counts
CM200.00
200nM
Counts
CM500.005
150
120
90
60
30
600
500nM

FIG. 3A

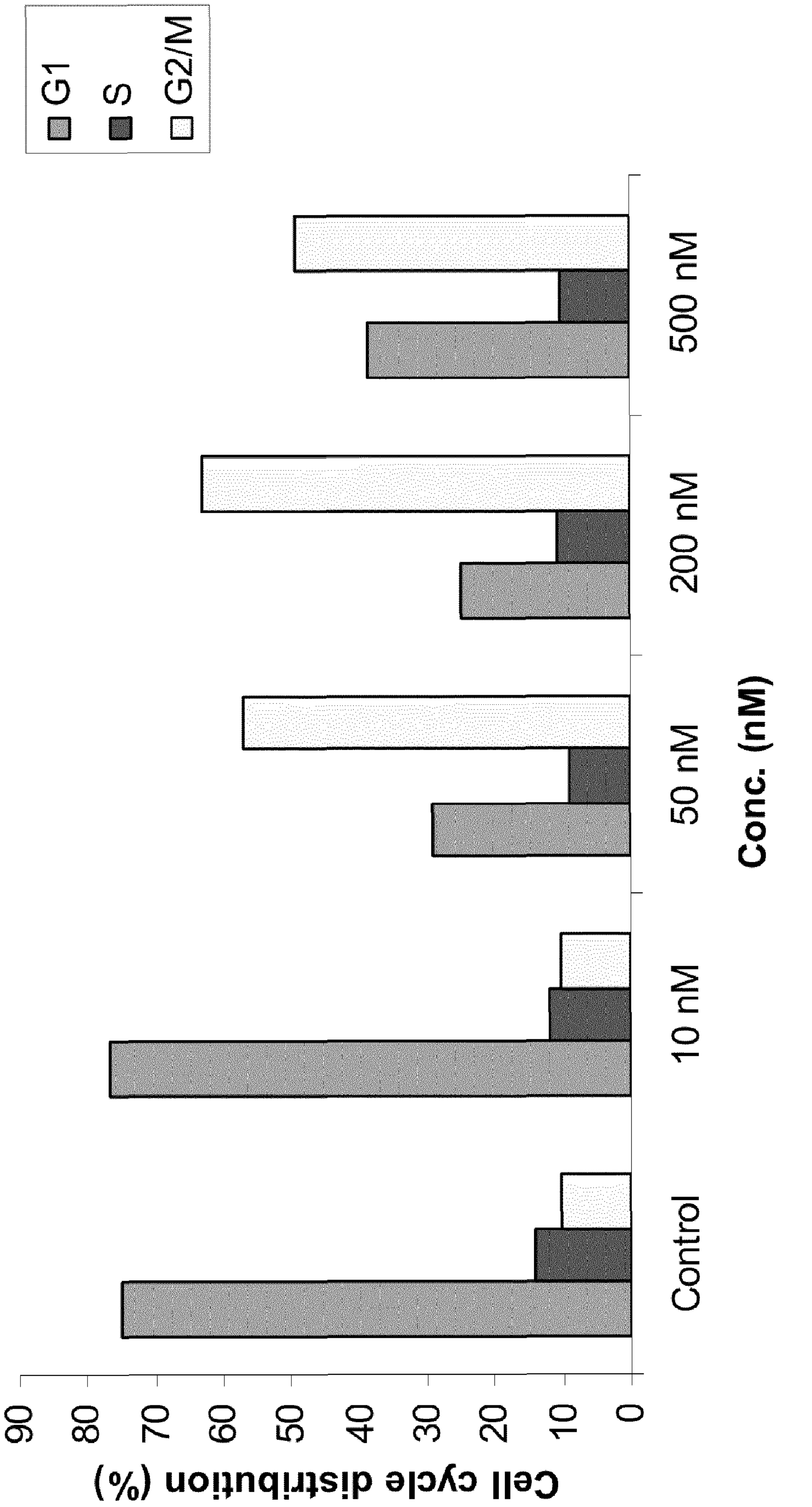

G1
S
G2/M
Cell cycle distribution (%)
90
80
70
60
50
40
30
20
10
0
Control
10 nM
50 nM
200 nM
500 nM
Conc. (nM)

Figure 3B

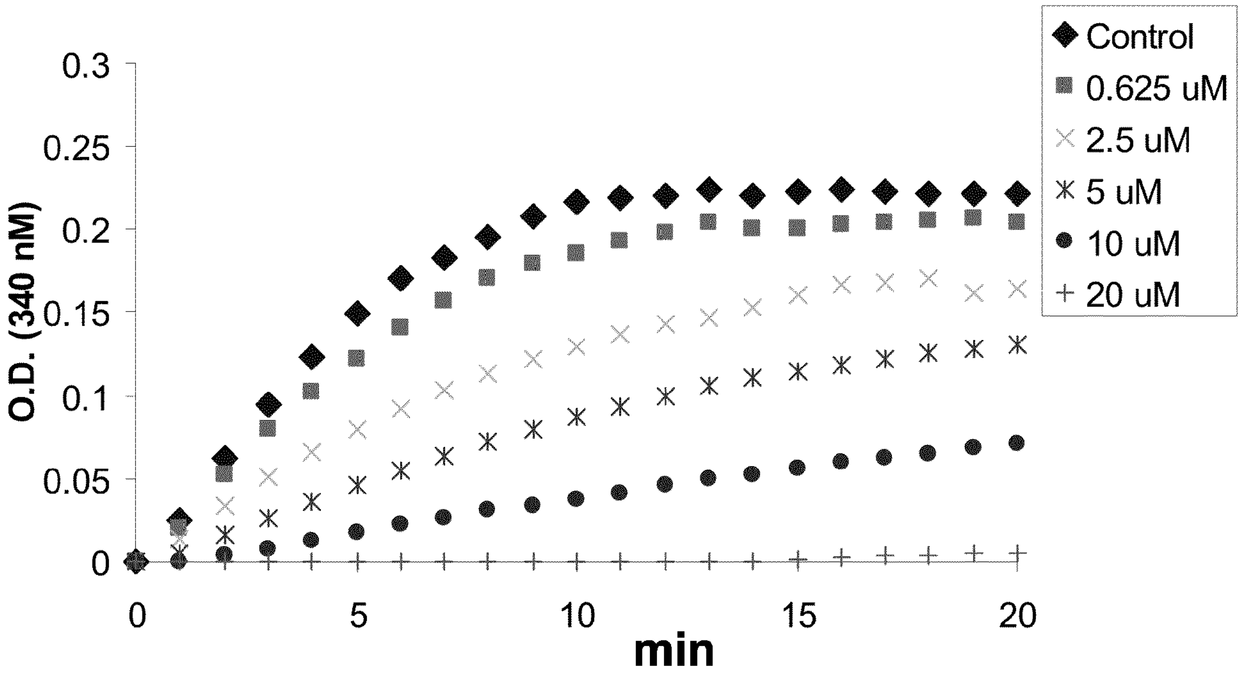


Figure 4

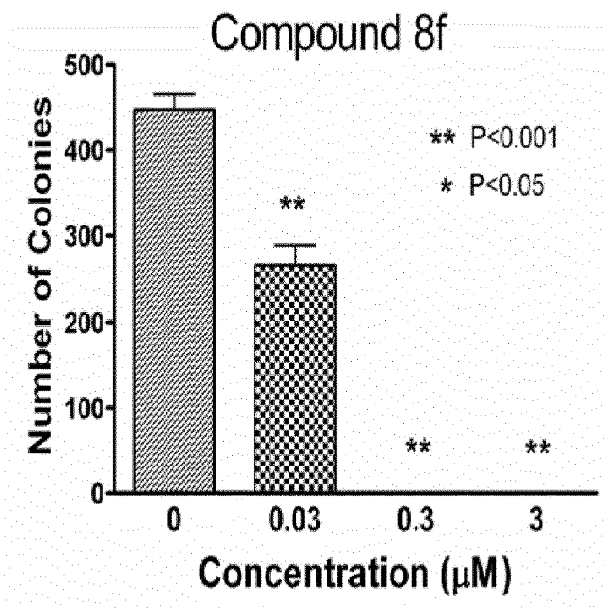


Figure 5A

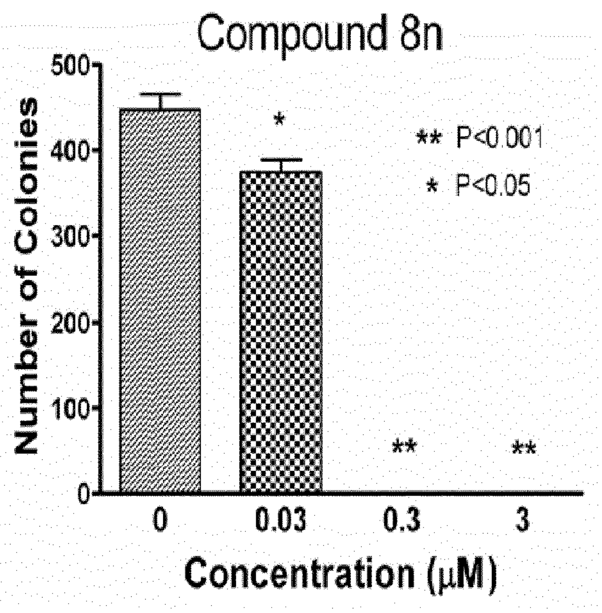


Figure 5B

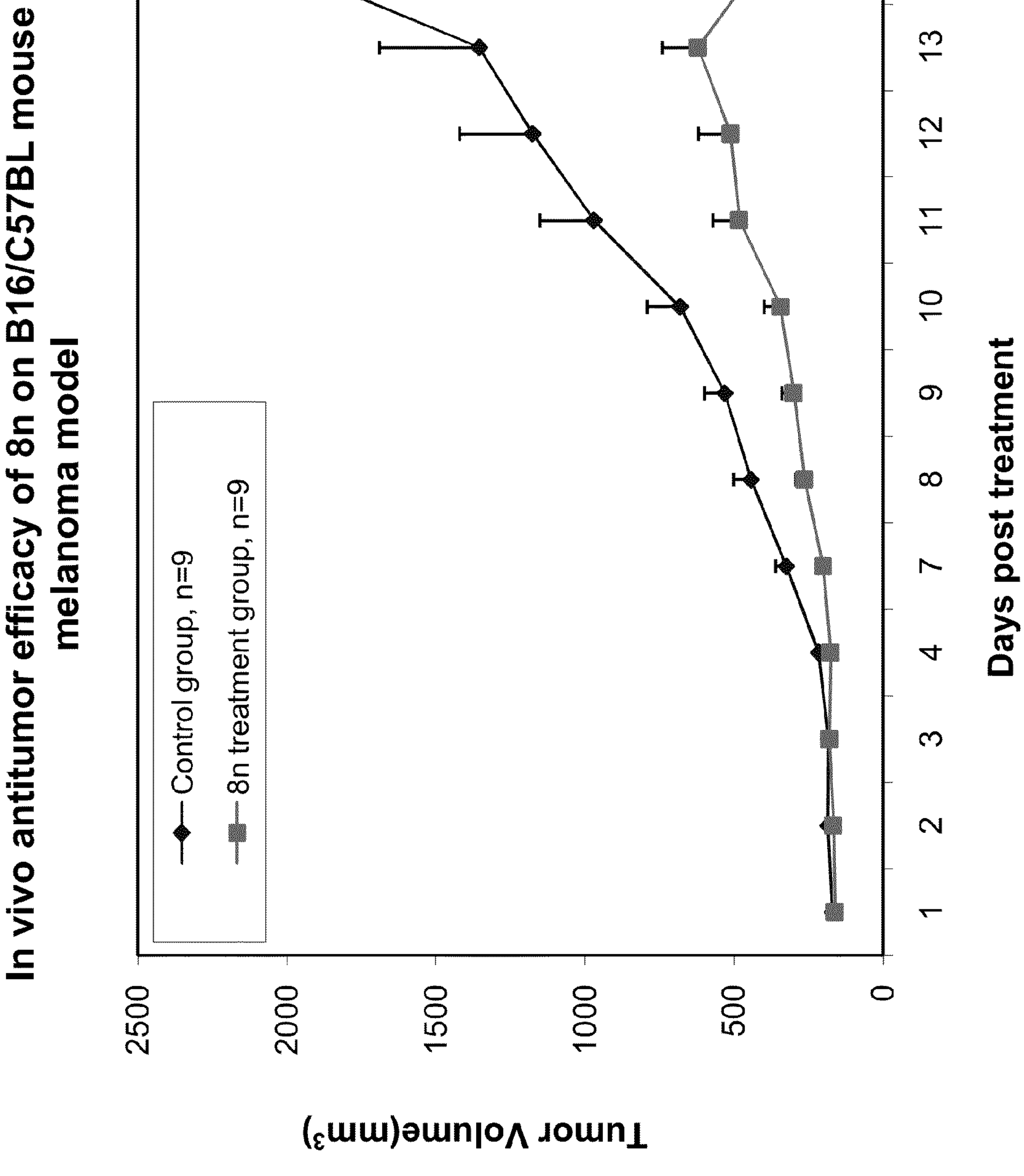

In vivo antitumor efficacy of 8n on B16/C57BL mouse melanoma model
Control group, n=9
8n treatment group, n=9
Tumor Volume(mm3)
0
500
1000
1500
2000
2500
Days post treatment
1
2
3
4
7
8
9
10
11
12
13
14
15

Figure 6

REFERENCES CITED IN THE DESCRIPTION

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- US 7307093 B, Miller **[0031] [0037] [0061]**
- US 20070155807 A, Miller **[0031] [0037] [0061]**

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- **LI et al.** Structure-Activity Relationship Studies of Arylthiazolidine Amides as Selective Cytotoxic Agents for Melanoma. *Anticancer Res.,* 2007, vol. 27, 883-888 **[0003]**
- Synthesis and Biological Evaluation of 2-Arylthiazolidine-4-Caboxylic Acid Amides for Melanoma and Prostate Cancer. **LU et al.** Abstracts of Papers. ACS National Meeting, 19 August 2007 **[0003]**
- **GUDUDURU et al.** SAR Studies of 2-Arylthiazolidine-4-Carboxylic Acid Amides: A Novel Class of Cytotoxic Agents for Prostate Cancer. *Bioorg. Med. Chem. Lett.,* 2005, vol. 15, 4010-4013 **[0003]**
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Vegyület rák kezelésére

Szabadalmi igénypontok

1. Vegyület, ahol a vegyület (2-(1H-indol-3-il)imidazol-4-il)(3,4,5-trimetoxifenil)metanon.

2. Gyógyászati készítmény, mely egy 1. igénypont szerinti vegyületet és egy gyógyászatilag elfogadható hordozót tartalmaz.

3. Egy 1. igénypont szerinti vegyület gyógyszerként történő alkalmazásra.

4. Egy 1. igénypont szerinti vegyület alkalmazása prosztatarák, tüdőrák, végbélrák, leukémia, veserák vagy központi idegrendszeri rák, vagy ezek kombinációi kezelésére szolgáló gyógyszer előállítására.

5. A 4. igénypont szerinti alkalmazás, ahol a gyógyszert systemásan adagoljuk.

6. A 4. igénypont szerinti alkalmazás, ahol a gyógyszert orálisan, transzdermálisan, parenterálisan, szubkután, intravénásan, intramuszkulárisan, intraperitoneálisan, orrba csepegtetve, intracavitárisan vagy intravesikálisan csepegtetve, intraokulárisan, intraarteriálisan, intralezionálisan vagy a nyálkahártyára történő felvitellel adagoljuk.

7. A 4. igénypont szerinti alkalmazás, ahol a gyógyszert közvetlenül a rákos sejtek jelenlétének helyére adagoljuk.

8. A 4. igénypont szerinti alkalmazás, ahol a gyógyszert körülbelül 0.01 és körülbelül 100 mg vegyület/testsúly kg közötti dózisban adagoljuk.

9. A 4. igénypont szerinti alkalmazás, ahol a gyógyszert periodikusan adagoljuk.

10. A 4. igénypont szerinti alkalmazás, ahol a gyógyszert egy másik rákterápiával kombinálva adagoljuk.

11. Az 1. igénypont szerinti vegyület prosztatarák, tüdőrák, végbélrák, leukémia, veserák vagy központi idegrendszeri rák, vagy ezek kombinációi kezelésében történő alkalmazásra.

12. A vegyület a 11. igénypont szerinti alkalmazásra, ahol a vegyületet systemásan adagoljuk.

13. A vegyület a 11. igénypont szerinti alkalmazásra, ahol a vegyületet orálisan, transzdermálisan, parenterálisan, szubkután, intravénásan, intramuszkulárisan, intraperitoneálisan, orrba csepegtetve, intracavitárisan vagy intravesikálisan csepegtetve, intraokulárisan, intraarteriálisan, intralezionálisan vagy a nyálkahártyára történő felvitellel adagoljuk.

14. A vegyület a 11. igénypont szerinti alkalmazásra, ahol a vegyületet közvetlenül a rákos sejtek jelenlétének helyére adagoljuk.

15. A vegyület a 11. igénypont szerinti alkalmazásra, ahol a vegyületet körülbelül 0.01 és körülbelül 100 mg vegyület/testsúly kg közötti dózisban adagoljuk.

16. A vegyület a 11. igénypont szerinti alkalmazásra, ahol a vegyületet periodikusan adagoljuk.

17. A vegyület a 11. igénypont szerinti alkalmazásra, ahol a vegyületet egy másik rákterápiával kombinálva adagoljuk.