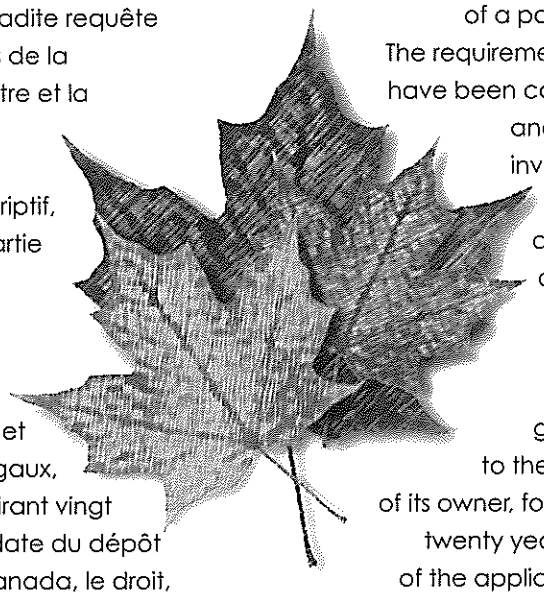
Innovation, Sciences et Développement économique Canada
Office de la propriété intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

Brevet canadien / Canadian Patent

Le commissaire aux brevets a reçu une demande de délivrance de brevet visant une invention. Ladite requête satisfait aux exigences de la *Loi sur les brevets*. Le titre et la description de l'invention figurent dans le mémoire descriptif, dont une copie fait partie intégrante du présent document.



Le présent brevet confère à son titulaire et à ses représentants légaux, pour une période expirant vingt ans à compter de la date du dépôt de la demande au Canada, le droit, la faculté et le privilège exclusif de fabriquer, construire, exploiter et vendre à d'autres, pour qu'ils l'exploitent, l'objet de l'invention, sauf jugement en l'espèce rendu par un tribunal compétent, et sous réserve du paiement des taxes périodiques.

The Commissioner of Patents has received a petition for the grant of a patent for an invention. The requirements of the *Patent Act* have been complied with. The title and a description of the invention are contained in the specification, a copy of which forms an integral part of this document.

The present patent grants to its owner and to the legal representatives of its owner, for a term which expires twenty years from the filing date of the application in Canada, the exclusive right, privilege and liberty of making, constructing and using the invention and selling it to others to be used, subject to adjudication before any court of competent jurisdiction, and subject to the payment of maintenance fees.

BREVET CANADIEN **2,795,085** CANADIAN PATENT

Date à laquelle le brevet a été accordé et délivré	**2019/06/11**	Date on which the patent was granted and issued
Date du dépôt de la demande	**2011/03/29**	Filing date of the application
Date à laquelle la demande est devenue accessible au public pour consultation	**2011/10/13**	Date on which the application was made available for public inspection

Commissaire aux brevets / Commissioner of Patents

(CIPO - 91)
18-12-18

Canada

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Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
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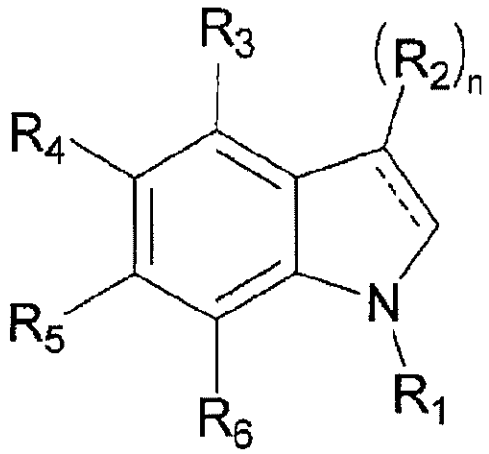
(54) Titre : COMPOSES D'HYDROXAMATE D'INDOLYLE OU D'INDOLINYLE
(54) Title: INDOLYL OR INDOLINYL HYDROXAMATE COMPOUNDS



(I)

(57) Abrégé/Abstract:
Indolyl or indolinyl hydroxamates and pharmaceutical compositions comprising the same, which show histone deacetylase (HDAC) inhibition activity. Method for treating cancer with compounds of Formula (I).

(see formula I).

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(13) C

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INDOLYL OR INDOLINYL HYDROXAMATE COMPOUNDS

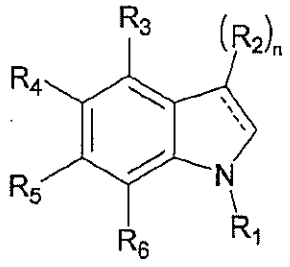
BACKGROUND

Histone deacetylases (HDACs) are a class of enzymes that regulate histone acetylation and thus regulate gene expression. HDAC inhibitors have been known to induce cell growth arrest, differentiation, and apoptosis in tumor cells. They have thus attracted great attention as potent anti-cancer agents.

SUMMARY

This invention is based on the unexpected discovery that certain indolyl or indolinyl hydroxamate compounds are HDAC inhibitors and have potent anticancer activity. Thus, this invention relates to indolyl or indolinyl hydroxamate compounds and their use in cancer treatment.

In one aspect, this invention features an indolyl or indolinyl hydroxamate compound of formula (I):



(I).

In this formula, ---- is a single bond or a double bond; n is 0, 1, or 2; R_1 is H, alkyl optionally substituted with aryl or heteroaryl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, $C(O)R_a$, or SO_2R_a, in which R_a is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; and each of R_2, R_3, R_4, R_5, and R_6, independently is, H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR_b, SR_b, $S(O)R_b$, $CH=CH-C(O)R_b$, $CH=CH-C(O)NR_cR_d$, $NHC(O)-CH=CH-C(O)R_b$, $NHC(O)-CH=CH-C(O)NR_cR_d$, $SO_2NR_cR_d$, $OC(O)R_b$, $C(O)R_b$, $C(O)OR_b$, $C(O)NR_cR_d$, NR_cR_d, $NHC(O)R_b$, $NHC(O)NR_cR_d$, or $NHC(S)R_c$, in which each of R_b, R_c, and R_d, independently, is H, hydroxy, alkoxy, aryloxy,

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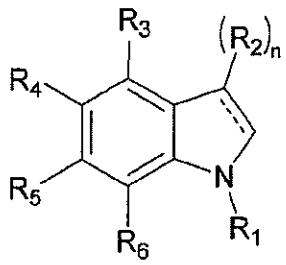
heteroaryloxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; and when R_1 is SO_2R_a, at least one of R_2, R_3, R_5, and R_6 is CH=CH-C(O)NR_cR_d, NHC(O)-CH=CH-C(O)R_b, or NHC(O)-CH=CH-C(O)NR_cR_d, or R_4 is CH=CH-C(O)R_b, CH=CH-C(O)NR_cR_d, NHC(O)-CH=CH-C(O)R_b, or NHC(O)-CH=CH-C(O)NR_cR_d, and when R_1 is aryl, R_4 is CH=CH-C(O)NHR_c.

In a further aspect, there is provided a compound of formula (I):



(I),

wherein

---- is a single bond or a double bond;

n is 0, 1, or 2;

R_1 is SO_2R_a, in which R_a is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, which is optionally substituted with halo, hydroxyl, C_1-C_6alkoxyl, amino, cyano or nitro;

R_2 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR_b, SR_b, S(O)R_b, NHC(O)-CH=CH-C(O)R_b, NHC(O)-CH=CH-C(O)NR_cR_d, $SO_2NR_cR_d$, OC(O)R_b, C(O)NR_cR_d, NR_cR_d, NHC(O)R_b, NHC(O)NR_cR_d, or NHC(S)R_c, in which each of R_b, R_c, and R_d, independently, is H, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

each of R_3, R_4, R_5, and R_6, independently is, H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR_b, SR_b, S(O)R_b, CH=CH-C(O)NR_cR_d, NHC(O)-CH=CH-C(O)R_b, NHC(O)-CH=CH-C(O)NR_cR_d, _____

$SO_2NR_cR_d$, $OC(O)R_b$, $C(O)NR_cR_d$, NR_cR_d, $NHC(O)R_b$, $NHC(O)NR_cR_d$, or $NHC(S)R_c$, in which each of R_b, R_c, and R_d, independently, is H, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; provided that one or more of R_2, R_3, R_4, R_5, and R_6 has the following definitions: R_2 is NHC(O)-CH=CH-$C(O)R_b$ or NHC(O)-CH=CH-$C(O)NR_cR_d$; or R_3, R_5, and R_6 is independently CH=CH-$C(O)NR_cR_d$, NHC(O)-CH=CH-$C(O)R_b$, or NHC(O)-CH=CH-$C(O)NR_cR_d$; or R_4 is C(O)NHOH, CH=CH-$C(O)NR_cR_d$, NHC(O)-CH=CH-$C(O)R_b$, or NHC(O)-CH=CH-$C(O)NR_cR_d$.

One subset of the above-described indolyl or indolinyl hydroxamate compounds includes those in which R_4 is CH=CH-$C(O)R_b$, CH=CH-$C(O)NR_cR_d$, NHC(O)-CH=CH-$C(O)R_b$, or NHC(O)-CH=CH-$C(O)NR_cR_d$. In these compounds, R_4 can be C(O)NHOH, CH=CH-C(O)OH, CH=CH-C(O)NHOH, NHC(O)-CH=CH-C(O)OH, or NHC(O)-CH=CH-C(O)NHOH; R_1 can be SO_2R_a, R_a being aryl or heteroaryl (e.g., phenyl optionally substituted with halo, hydroxyl, alkoxyl, amino, cyano, or nitro); or at least one of R_2, R_3, R_5, and R_6 can be CH=CH-$C(O)NR_cR_d$, NHC(O)-CH=CH-$C(O)R_b$, or NHC(O)-CH=CH-$C(O)NR_cR_d$ (e.g., CH=CH-C(O)NHOH, NHC(O)-CH=CH-C(O)OH, or NHC(O)-CH=CH-C(O)NHOH).

Another subset of the above-described indolyl or indolinyl hydroxamate compounds includes those in which at least one of R_2, R_3, R_5, and R_6 is CH=CH-$C(O)NR_cR_d$, NHC(O)-CH=CH-$C(O)R_b$, or NHC(O)-CH=CH-$C(O)NR_cR_d$. In these compounds, at least one of R_2, R_3, R_5, and R_6 can be CH=CH-C(O)NHOH, NHC(O)-CH=CH-C(O)OH, or NHC(O)-CH=CH-C(O)NHOH. R_1 can be SO_2R_a, R_a being aryl or heteroaryl (e.g., phenyl optionally substituted with halo, hydroxyl, alkoxyl, amino, cyano, or nitro).

Still another subset of the above-described indolyl or indolinyl hydroxamate compounds includes those in which R_1 is SO_2R_a and R_a is aryl or heteroaryl. R_a can be phenyl optionally substituted with halo, hydroxyl, alkoxyl, amino, cyano, or nitro.

The term "alkyl" refers to a straight or branched monovalent hydrocarbon containing, unless otherwise stated, 1-20 carbon atoms (e.g., C_1-C_{10}). Examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, and *t*-butyl. The term "alkenyl" refers to a straight or branched monovalent hydrocarbon containing 2-20 carbon atoms (e.g., C_2-C_{10}) and one or more double bonds. Examples of alkenyl include, but are not limited to, ethenyl, propenyl, allyl, and 1,4-butadienyl. The term "alkynyl" refers to a straight or branched monovalent hydrocarbon containing 2-20 carbon atoms (e.g., C_2-C_{10}) and one or more triple bonds. Examples of alkynyl

include, but are not limited to, ethynyl, 1-propynyl, 1- and 2-butynyl, and 1-methyl-2-butynyl. The term "alkoxy" refers to an -O-alkyl radical. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy. The term "amino" refers to NH_2, alkylamino, or arylamino. The term "alkylamino" refers to an –N(R)-alkyl radical in which R can be H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl.

The term "cycloalkyl" refers to a monovalent saturated hydrocarbon ring system having 3 to 30 carbon atoms (e.g., C_3-C_{12}). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1,4-cyclohexylene, cycloheptyl, cyclooctyl, and adamantyl. The term "cycloalkenyl" refers to a monovalent non-aromatic hydrocarbon ring system having 3 to 30 carbons (e.g., C_3-C_{12}) and one or more double bonds. Examples include cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "heterocycloalkyl" refers to a monovalent nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se). Examples of heterocycloalkyl groups include, but are not limited to, piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, and tetrahydrofuranyl. The term "heterocycloalkenyl" refers to a monovalent nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se) and one or more double bonds.

The term "aryl" refers to a monovalent 6-carbon monocyclic, 10-carbon bicyclic, 14-carbon tricyclic aromatic ring system. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, and anthracenyl. The term "heteroaryl" refers to a monovalent aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se). Examples of heteroaryl groups include pyridyl, furyl, imidazolyl, benzimidazolyl, pyrimidinyl, thienyl, quinolinyl, indolyl, tetrazol, and thiazolyl.

Alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, amino, aryl, and heteroaryl mentioned above include both substituted and unsubstituted moieties. Possible substituents on amino, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, and heteroaryl include, but are not limited to, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{20} cycloalkyl, C_3-C_{20} cycloalkenyl, C_1-C_{20} heterocycloalkyl, C_1-C_{20} heterocycloalkenyl, C_1-C_{10} alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, amino, C_1-C_{10} alkylamino, arylamino, hydroxy, halo, oxo (O=), thioxo (S=), thio, silyl, C_1-C_{10} alkylthio, arylthio, C_1-C_{10} alkylsulfonyl, arylsulfonyl, acylamino, aminoacyl, aminothioacyl, amidino, mercapto, amido, thiourcido, thiocyanato,

sulfonamido, guanidine, ureido, cyano, nitro, acyl, thioacyl, acyloxy, carbamido, carbamyl (-C(O)NH_2), carboxyl (-COOH), and carboxylic ester. On the other hand, possible substituents on alkyl, alkenyl, or alkynyl include all of the above-recited substituents except C_1-C_{10} alkyl. Cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl can also be fused with each other.

The indolyl or indolinyl hydroxamate compounds described herein include the compounds themselves, as well as their salts, their solvates, and their prodrugs, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on an indolyl or indolinyl hydroxamate compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on an indolyl or indolinyl hydroxamate compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The indolyl or indolinyl hydroxamate compounds also include those salts containing quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active indolyl or indolinyl hydroxamate compounds.

In another aspect, this invention relates to a method for inhibiting HDAC activity by contacting a cell with an effective amount of an indolyl or indolinyl hydroxamate compound described above.

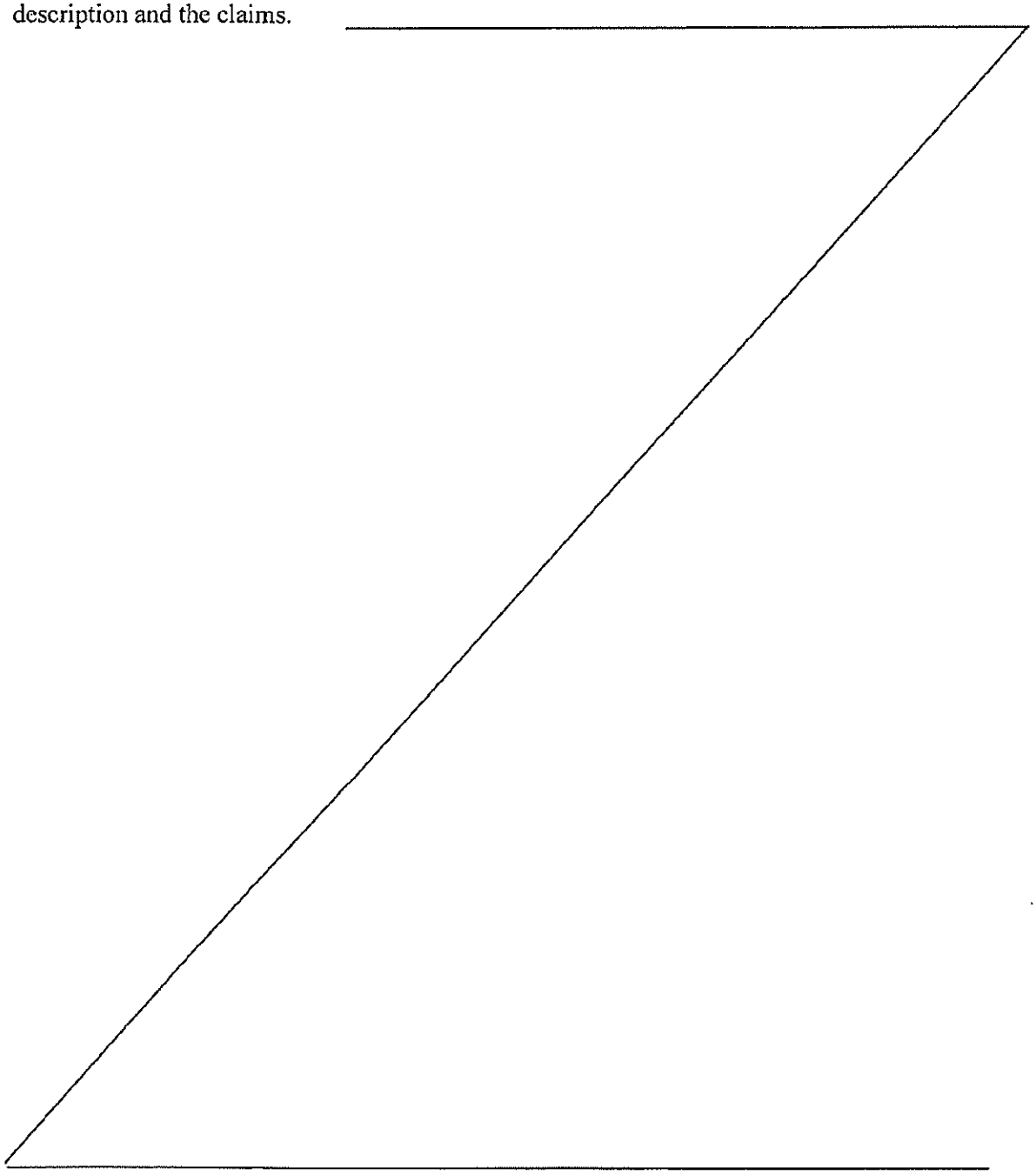
In yet another aspect, this invention relates to a method for treating cancer by administering to a subject in need thereof an effective amount of an indolyl or indolinyl hydroxamate compound described above.

In another aspect, there is provided the use of a compound described herein in the manufacture of a medicament for treating cancer.

Also within the scope of this invention is a pharmaceutical composition containing one or more of the above-described indolyl or indolinyl hydroxamate compounds for use in treating cancer, as well as this therapeutic use and use of the compounds for the manufacture of a medicament for treating cancer.

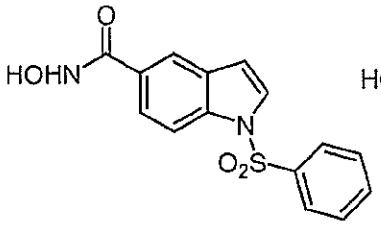
In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and the claims.

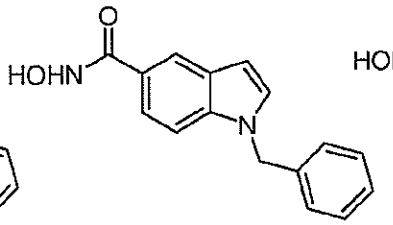


DETAILED DESCRIPTION

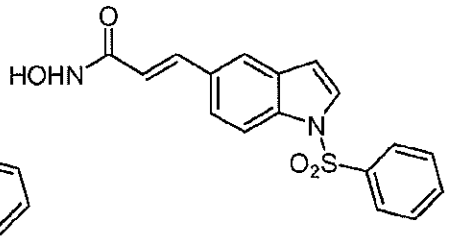
Shown below are exemplary compounds described herein:



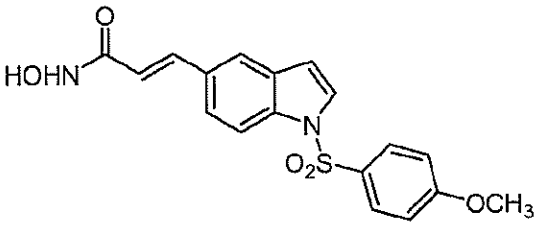
Compound 1



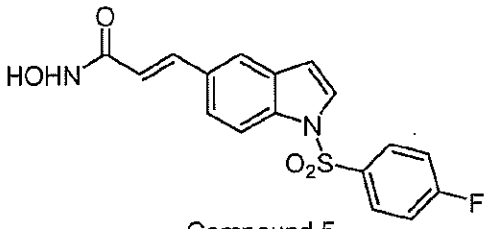
Compound 2



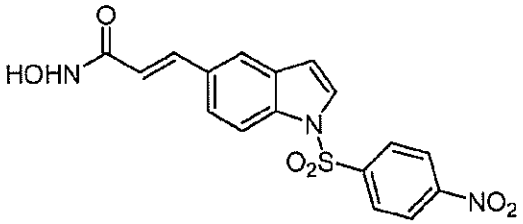
Compound 3



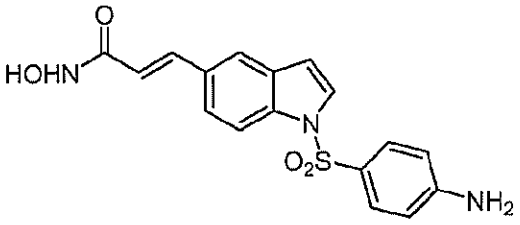
Compound 4



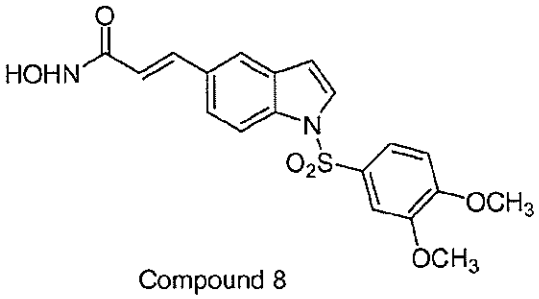
Compound 5



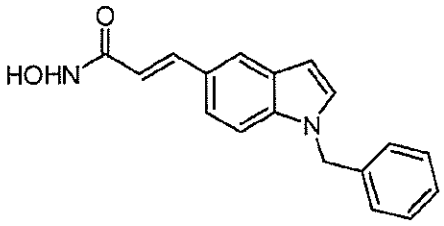
Compound 6



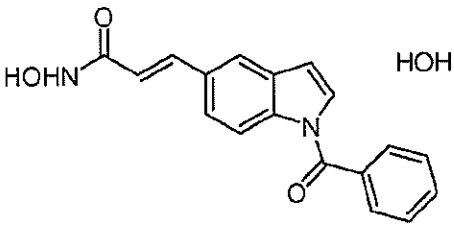
Compound 7



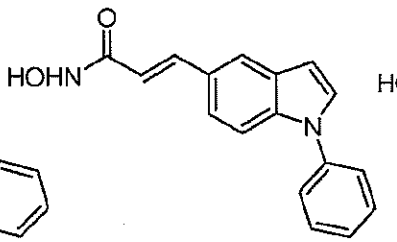
Compound 8



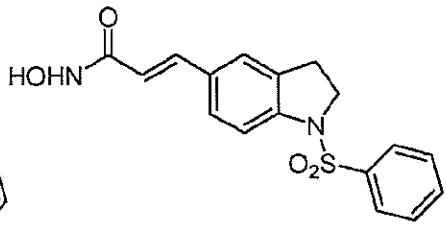
Compound 9



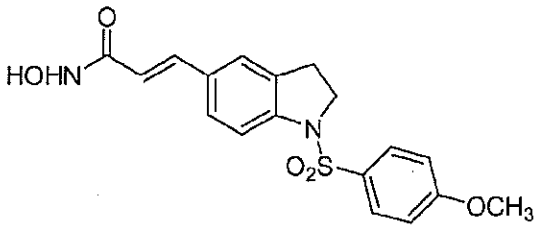
Compound 10



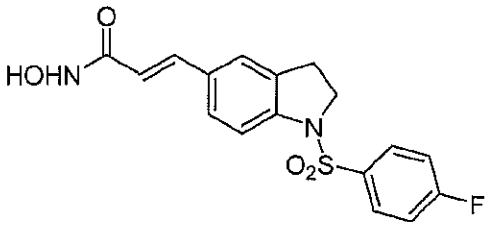
Compound 11



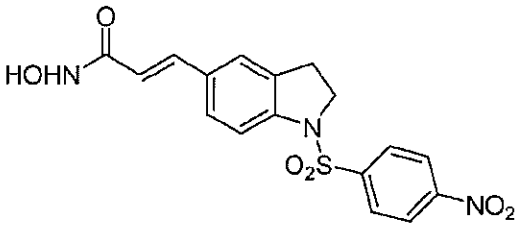
Compound 12



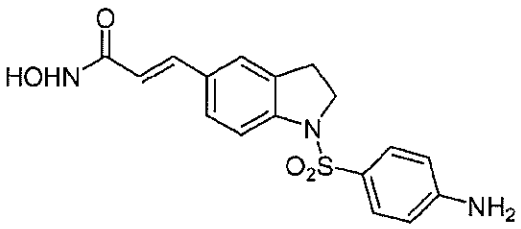
Compound 13



Compound 14



Compound 15



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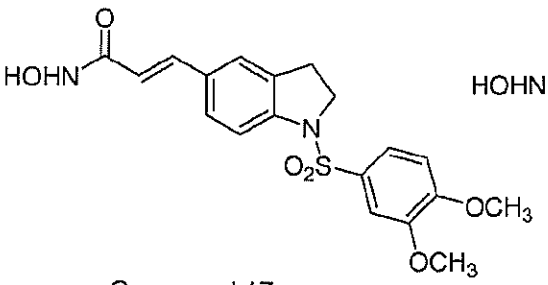
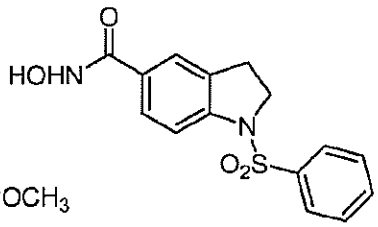


Compound 17



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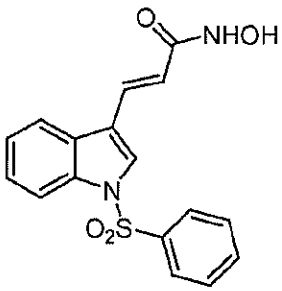
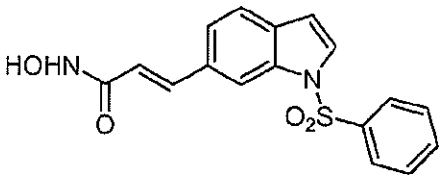
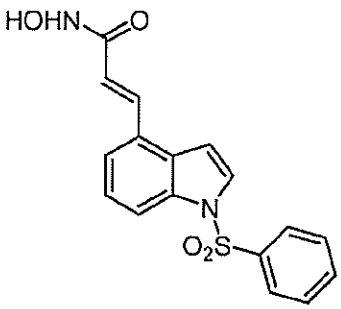


Compound 19



Compound 20



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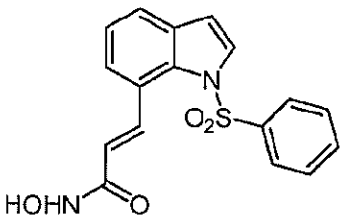
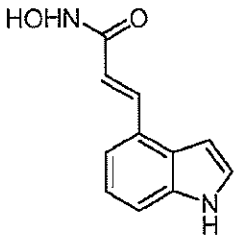


Compound 22



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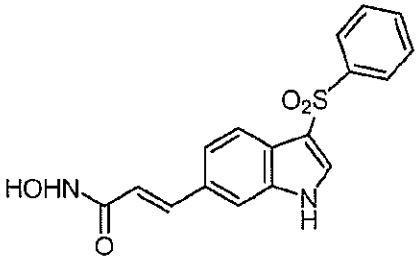
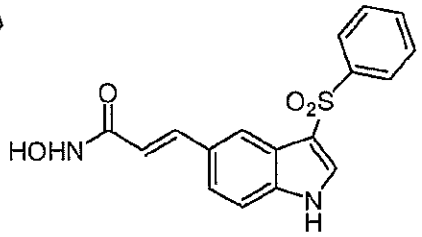
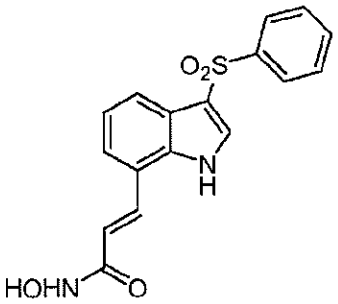


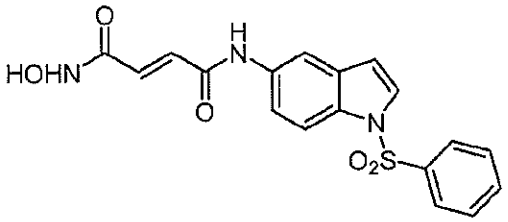
Compound 24



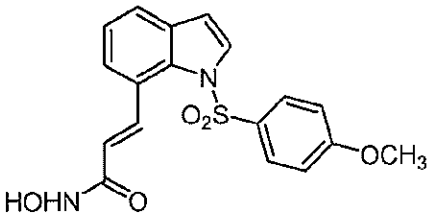
Compound 25



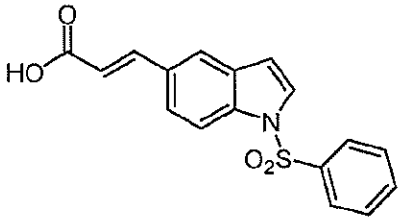
Compound 26



Compound 27



Compound 28



Compound 29

The indolyl or indolinyl hydroxamate compounds described herein can be prepared by conventional chemical transformations (including protecting group methodologies), e.g., those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

An indolyl or indolinyl hydroxamate compound thus synthesized can be further purified by flash column chromatography, high performance liquid chromatography, crystallization, or any other suitable methods.

The indolyl or indolinyl hydroxamate compounds mentioned herein may contain a non-aromatic double bond and one or more asymmetric centers. Thus, they can occur as racemates and racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, and cis- or trans- isomeric forms. All such isomeric forms are contemplated.

Also within the scope of this invention are (1) a pharmaceutical composition that contains an effective amount of at least one of the indolyl or indolinyl hydroxamate compounds of this invention and a pharmaceutically acceptable carrier, and (2) a method for treating cancer by administering to a subject in need of this treatment an effective amount of such an indolyl or indolinyl hydroxamate compound.

As used herein, the term "treating" refers to administering an indolyl or indolinyl hydroxamate compound to a subject that has cancer, or has a symptom of or a predisposition toward it, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, affect, or reduce the risk of the disorder, the symptoms of or the predisposition toward the cancer. The term "an effective amount" refers to the amount of the active agent that is required to confer the intended therapeutic effect in the subject. Effective amounts may vary, as recognized by those skilled in the art, depending on route of administration, excipient usage, and the possibility of co-usage with other agents.

Cancer that can be treated by the methods of the invention includes both solid and haematological tumours of various organs. Examples of solid tumors include pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; hepatocellular cancer; lung cancer, including, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; melanoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; and soft tissue sarcoma. Examples of hematologic malignancy include acute myeloid leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's disease (HD); non-Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma; T-cell

lymphoma; multiple myeloma (MM); Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes.

To practice the method of this invention, the above-described pharmaceutical composition can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

A sterile injectable composition, e.g., a sterile injectable aqueous or oleaginous suspension, can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as polysorbate 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents. Other commonly used surfactants or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

A composition for oral administration can be any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added. A nasal aerosol or inhalation composition can be prepared according

to techniques well known in the art of pharmaceutical formulation. An indolyl or indolinyl hydroxamate compound-containing composition can also be administered in the form of suppositories for rectal administration.

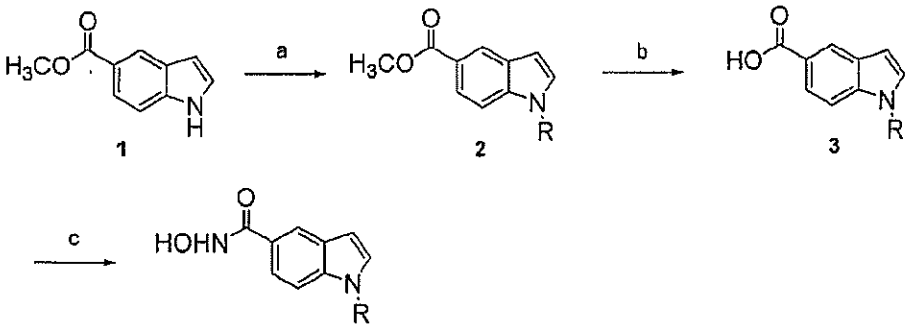
The carrier in the pharmaceutical composition must be "acceptable" in the sense of being compatible with the active ingredient of the formulation (and preferably, capable of stabilizing it) and not deleterious to the subject to be treated. One or more solubilizing agents (e.g., cyclodextrins) which form more soluble complexes with the active indolyl or indolinyl hydroxamate compounds can be utilized as pharmaceutical carriers for delivery of the active compounds. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, sodium lauryl sulfate, and D&C Yellow # 10.

Suitable *in vitro* assays can be used to preliminarily evaluate the efficacy of the indolyl or indolinyl hydroxamate compounds in anticancer activities such as inhibiting growth of tumor cells. The compounds can further be examined for their efficacy in treating cancer. For example, a compound can be administered to an animal (e.g., a mouse model) having cancer and its therapeutic effects are then assessed. Based on the results, an appropriate dosage range and administration route can also be determined.

Without further elaboration, it is believed that the above description has adequately enabled the present invention. The following examples are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Example 1: Synthesis of 1-benzenesulfonyl-1H-indole-5-carboxylic acid hydroxyamide (Compound 1)

Scheme 1



R = -SO_2-Ph (Compound 1)
R = -CH_2-Ph (Compound 2)

Compound 1 was synthesized via the route as shown in Scheme 1 above (reagents and conditions: a) benzyl chloride or benzenesulfonyl chloride, *t*-BuOK, KI, DMF; b) 1M LiOH(aq), dioxane; c) (i) NH_2OTHP, PyBOP, NEt_3, DMF, rt; (ii) TFA, MeOH, rt).

1-Benzenesulfonyl-1H-indole-5-carboxylic acid methyl ester (2): After a suspension of methyl indole-5-carboxylate (1) (0.30 g, 1.71 mmol), TBAHS (0.19 g, 0.26 mmol) and KOH (0.19 g, 3.42 mmol) in CH_2Cl_2 (15 mL) was stirred for 20 min, benzenesulfonyl chloride (0.32 ml, 2.57 mmol) was added. The reaction mixture was stirred at room temperature overnight before it was quenched with water and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue.

1-Benzenesulfonyl-1H-indole-5-carboxylic acid (3): 1M LiOH aqueous solution (3.87 ml, 3.87 mmol) was added to a solution of crude **2** in dioxane (15 mL). The mixture was stirred at 40 °C overnight and then was concentrated under reduced pressure. The residue was dissolved in water. Then concentrated HCl was added into the solution to reach pH <7 to give a precipitation, which was dried under vacuum to afford **3** (0.38 g) as a white solid, yield 74%. ^{1}H NMR (500MHz, CD_3OD): δ 6.83 (d, J = 3.70 Hz, 1H), 7.51-7.54 (m, 2H), 7.60-7.63 (m, 1H), 7.75 (d, J = 3.72 Hz, 1H), 7.95 (d, J = 7.63 Hz, 2H), 7.97 (dd, J = 8.83, 1.49 Hz, 1H), 8.03 (d, J = 8.86 Hz, 1H), 8.25 (d, J = 0.82 Hz, 1H).

1-Benzenesulfonyl-1H-indole-5-carboxylic acid hydroxyamide (Compound 1): NH_2OTHP (0.08 g, 0.72 mmol) was added to a solution of **3** (0.18 g, 0.60 mmol), PyBOP (0.33 g, 0.63 mmol), and triethylamine (0.20 ml, 1.43 mmol) in DMF (1.5 mL). The reaction mixture was stirred at room temperature for 2 h before it was quenched with water and extracted with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2: CH_3OH = 30 : 1 : 1%$NH_{3(aq)}$) to give a white solid, which was treated with TFA (1.70 ml, 22.89 mmol) in the presence of CH_3OH (31 mL). The reaction mixture was stirred overnight at room temperature before it was concentrated under reduced pressure to give a white residue. The residue was recrystallized with CH_3OH to afford Compound 1 (0.10 g). ^{1}H NMR (500MHz, CD_3OD): δ 6.80 (d, J = 3.65 Hz, 1H), 7.49-7.52 (m, 2H), 7.59-7.62 (m, 1H), 7.68 (d, J = 8.53 Hz, 1H), 7.75 (d, J = 3.72 Hz, 1H), 7.93 (d, J = 7.52 Hz, 2H), 7.94-7.97 (m, 1H), 8.04 (d, J = 8.53 Hz, 1H); HRMS (EI) for $C_{15}H_{12}N_2O_4S$ (M^+): calcd, 316.0518; found, 316.0518.

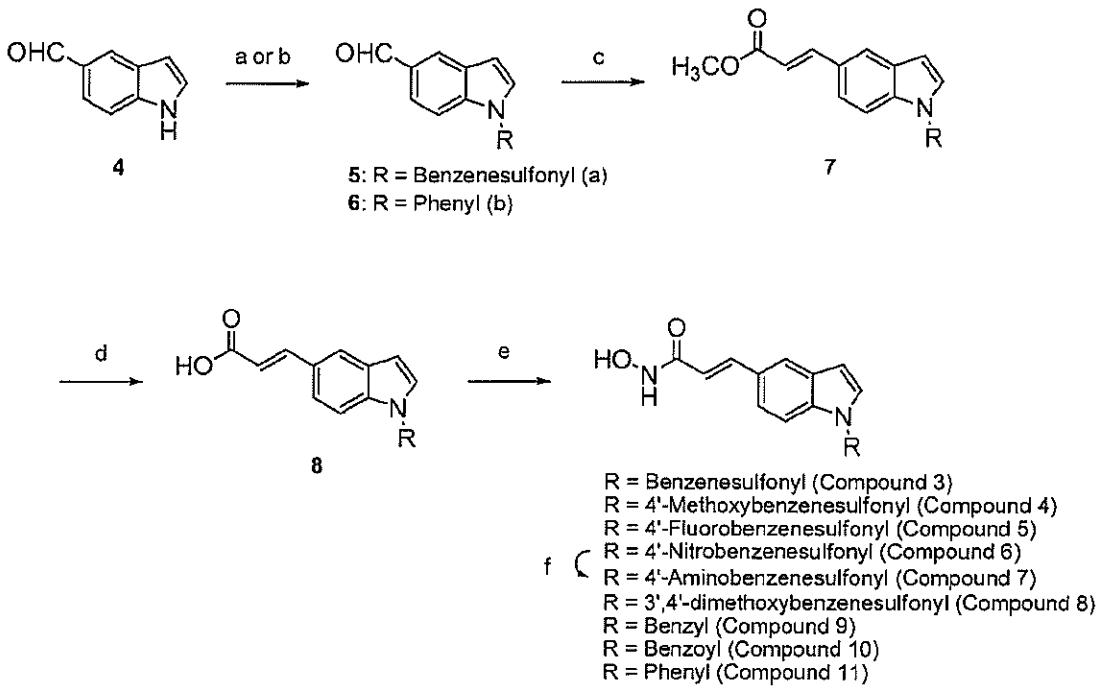
Example 2: Synthesis of 1-benzyl-1H-indole-5-carboxylic acid hydroxyamide (Compound 2)

Compound 2 was prepared in a manner similar to that described in Example 1.

^{1}H NMR (500MHz, CD_3OD): δ 5.40 (s, 2H), 6.60 (d, J = 3.1 Hz, 1H), 7.11 (d, J = 7.2 Hz, 2H), 7.21-7.28 (m, 3H), 7.36-7.38 (m, 2H), 7.50 (dd, J = 8.5, 1.7 Hz, 1H), 8.02 (d, J = 1.1 Hz, 1H). MS (EI) *m/z*: 266. HRMS (EI) for $C_{16}H_{14}N_2O2$ (M^+): calcd, 266.1055; found, 266.1057.

Example 3: Synthesis of 3-(1-benzenesulfonyl-1H-indol-5-yl)-N-hydroxy-acrylamide (Compound 3)

Scheme 2



Compound 3 was synthesized via the route as shown in Scheme 2 above (reagents and conditions: a) benzyl chloride, benzoyl chloride, benzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, or 4-nitrobenzzenesulfonyl chloride, *t*-BuOK, KI, DMF; b) 4-iodobenzene, K_2CO_3, CuO, DMF; c) $Ph_3P{=}CH\text{-}COOCH_3$, CH_2Cl_2; d) 1M LiOH (aq), dioxane; e) (i) NH_2OTHP, PyBOP, NEt_3, DMF; (ii) TFA, MeOH; f) Fe, NH_4Cl, Isopropanol, H_2O).

1-Benzenesulfonyl-1H-indole-5-carbaldehyde (5): After a suspension of methyl indole-5-carboxylate (**4**) (1.00 g, 6.89 mmol), tetrabutylammonium bisulfate (0.35 g, 1.03 mmol) and KOH (0.77 g, 13.78 mmol) in CH_2Cl_2 (30 mL) was stirred for 20 min, benzenesulfonyl chloride (1.32 ml, 10.33 mmol) was added. The reaction mixture was stirred at room temperature overnight before it

was quenched with water and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 2) to afford **5** (1.79 g) as a white solid. ^{1}H NMR (500MHz, $CDCl_3$): δ6.78 (d, J = 3.6 Hz, 1H), 7.45-7.48 (m, 2H), 7.55-7.58 (m, 1H), 7.67 (d, J = 3.7 Hz, 1H), 7.85-7.87 (m, 1H), 7.89 (d, J = 7.6 Hz, 2H), 8.06 (s, 1H), 8.11 (d, J = 8.6 Hz, 1H), 10.03 (s, 1H).

3-(1-Benzenesulfonyl-1H-indol-5-yl)-acrylic acid methyl ester (7): Methyl (triphenylphosphoranylidene) acetate (2.52 g, 7.53 mmol) was added to a solution of **5** (1.79g, 6.27 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at room temperature overnight before it was quenched with water and extracted with CH_2Cl_2 (25 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was then purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 3) to afford **7** (2.08 g) as a white solid.

3-(1-Benzenesulfonyl-1H-indol-5-yl)-acrylic acid (8): 1M LiOH aqueous solution (11.72 ml, 11.72 mmol) was added to a solution of **7** (2.00g, 5.86 mmol) in dioxane (20 mL). The reaction mixture was stirred at 40 °C overnight and was then concentrated under reduced pressure. The residue was dissolved in water. Then concentrated HCl was added to the solution to reach acidic pH to give the precipitation, which was dried by vacuum to afford **8** (1.72 g) as a white solid. ^{1}H NMR (500MHz, $CDCl_3$): δ6.39 (d, J = 16.1 Hz, 1H), 6.71 (d, J = 3.6 Hz, 1H), 7.45-7.48 (m, 2H), 7.52 (dd, J = 8.7, 1.4 Hz, 1H), 7.55-7.58 (m, 1H), 7.61 (d, J = 3.7 Hz, 1H), 7.67-7.72 (m, 2H), 7.89 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.7 Hz, 1H).

3-(1-Benzenesulfonyl-1H-indol-5-yl)-N-hydroxy-acrylamide (Compound 3): NH_2OTHP (0.43 g, 3.67 mmol) was added to a solution of **8** (1.00 g, 3.05 mmol), PyBOP (1.69 g, 3.24 mmol), and triethylamine (1.02 ml, 7.33 mmol) in DMF (1.5 mL). The reaction mixture was stirred at room temperature for 3 h before it was quenched with water and extracted with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2: CH_3OH = 30 : 1 : 1%$NH_{3(aq)}$) to give a white solid, which was treated with TFA (6.90 ml, 92.90 mmol) in the presence of CH_3OH (140 mL). The reaction mixture was stirred overnight at room temperature. Then the mixture was concentrated under reduced pressure to give a white residue, which was recrystallized by CH_3OH to afford Compound 3 (0.85 g) as a red solid. ^{1}H NMR (500MHz, $CDCl_3$): δ6.42 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 3.5 Hz, 1H), 7.49-7.54 (m, 3H), 7.59-7.62 (m, 1H), 7.61 (d, J = 15.5 Hz, 1H), 7.68 (d, J

= 3.6 Hz, 1H), 7.72 (s, 1H), 7.93 (d, J = 7.7 Hz, 2H), 7.98 (d, J = 8.6 Hz, 1H). MS (EI) *m/z*: 327 (100%), 342 (M^+, 3%). HRMS (EI) for $C_{17}H_{14}N_2O_4S$ (M^-): calcd, 342.0674; found, 342.0673.

Example 4: Synthesis of N-hydroxy-3-[1-(4-methoxy-benzenesulfonyl)-1H-indol-5-yl]-acrylamide (Compound 4)

Compound 4 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, CD_3OD): δ 3.79 (s, 3H), 6.43 (d, J = 15.8 Hz, 1H), 6.73 (d, J = 3.5 Hz, 1H), 6.99 (d, J = 9.1 Hz, 2H), 7.52 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 15.7 Hz, 1H), 7.65 (d, J = 3.6 Hz, 1H), 7.71 (s, 1H), 7.86 (d, J = 8.9 Hz, 2H), 7.97 (d, J = 8.6 Hz, 1H). LC/MS *m/z*: 373 (M^-). HRMS (EI) for $C_{18}H_{16}N_2O_5$ (M^+): calcd, 372.0780; found, 372.0779.

Example 5: Synthesis of 3-[1-(4-fluoro-benzenesulfonyl)-1H-indol-5-yl]-N-hydroxy-acrylamide (Compound 5)

Compound 5 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, CD_3OD): δ 6.45 (d, J = 15.9 Hz, 1H), 6.77 (d, J = 3.5 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 15.4 Hz, 1H), 7.67 (d, J = 3.7 Hz, 1H), 7.73 (s, 1H), 7.98-8.02 (m, 3H). LC/MS *m/z*: 361 (M^+). HRMS (EI) for $C_{17}H_{13}FN_2O_4S$ (M^+): calcd, 360.0580; found, 360.0580.

Example 6: Synthesis of N-hydroxy-3-[1-(4-nitro-benzenesulfonyl)-1H-indol-5-yl]-acrylamide (Compound 6)

Compound 6 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, CD_3OD): δ 6.44 (d, J = 15.7 Hz, 1H), 6.81 (d, J = 3.1 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 15.7 Hz, 1H), 7.72 (d, J = 3.5 Hz, 1H), 7.74 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.6 Hz, 2H), 8.33 (d, J = 8.6 Hz, 2H). HRMS (EI) for $C_{17}H_{13}N_3O_6S$ (M^+): calcd, 387.0525; found, 387.0523.

Example 7: Synthesis of 3-[1-(4-Amino-benzenesulfonyl)-1H-indol-5-yl]-N-hydroxy-acrylamide (Compound 7)

Compound 7 was synthesized via the route shown in Scheme 2 in Example 3. A suspension of Compound 6 (0.10 g, 0.26 mmol), iron powder (0.05 g, 0.77 mmol) and ammonium chloride

(0.03 g, 0.52 mmol) in isopropyl alcohol (5 ml) and water (1 ml) was refluxed for 4 h. After the reaction mixture was concentrated under reduced pressure, it was quenched with water and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The reaction mixture was purified by silica gel chromatography (CH_2Cl_2 : CH_3OH= 10 : 1 : 1% $NH_{3(aq)}$) to afford Compound 7 (0.06 g).

^{1}H NMR (500MHz, CD_3OD): δ 6.57 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 15.8 Hz, 1H), 6.69 (d, J = 3.5 Hz, 1H), 7.53 (dd, J = 8.5, 1.4 Hz, 1H), 7.58 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 3.8 Hz, 1H), 7.73 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H). HRMS (EI) for $C_{17}H_{15}N_3O_4S$ (M^+): calcd, 357.0783; found, 357.0785.

Example 8: Synthesis of 3-[1-(3,4-dimethoxy-benzenesulfonyl)-1H-indol-5-yl]-N-hydroxy-acrylamide (Compound 8)

Compound 8 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, CD_3OD): δ 3.78 (s, 3H), 3.81 (s, 3H), 6.42 (d, J = 15.78 Hz, 1H), 6.73 (d, J = 3.57Hz, 1H), 7.00 (d, J = 8.61 Hz, 1H), 7.33 (d, J = 1.99 Hz, 1H), 7.52-7.56 (m, 2H), 7.60 (d, J = 15.75 Hz, 1H), 7.68 (d, J = 3.65 Hz, 1H), 7.72 (s, 1H), 7.99 (d, J = 8.66 Hz, 1H).

Example 9: Synthesis of 3-(1-benzyl-1H-indol-5-yl)-N-hydroxy-acrylamide (Compound 9)

Compound 9 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, $CDCl_3$): δ 5.32 (s, 2H), 6.57 (d, J = 3.1 Hz, 1H), 7.10 (d, J = 7.1 Hz, 2H), 7.14 (d, J = 3.1 Hz, 1H), 7.25-7.32 (m, 5H), 7.37 (d, J = 8.3 Hz, 1H), 7.80 (s, 1H) 7.85 (d, J = 15.4 Hz, 1H). LC/MS m/z: 293 (M^+). HRMS (EI) for $C_{18}H_{16}N_2O_2$ (M^+): calcd, 292.1212; found, 292.1213.

Example 10: Synthesis of 3-(1-benzoyl-1H-indol-5-yl)-N-hydroxy-acrylamide (Compound 10)

Compound 10 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, DMSO): δ 6.48 (d, J = 15.8 Hz, 1H), 6.78 (d, J = 3.6 Hz, 1H), 7.42 (d, J = 3.6 Hz, 1H), 7.54-7.61 (m, 4H), 7.67-7.70 (m, 1H), 7.75 (d, J = 7.3 Hz, 2H), 7.86 (s, 1H), 8.24 (d, J = 8.6 Hz, 1H), 9.00 (s, 1H), 10.73 (s, 1H). MS (EI) m/z: 306. HRMS (EI) for $C_{18}H_{14}N_2O_3$ (M^+): calcd, 306.1004; found, 306.1006.

Example 11: Synthesis of N-hydroxy-3-(1-phenyl-1H-indol-5-yl)-acrylamide (Compound 11)

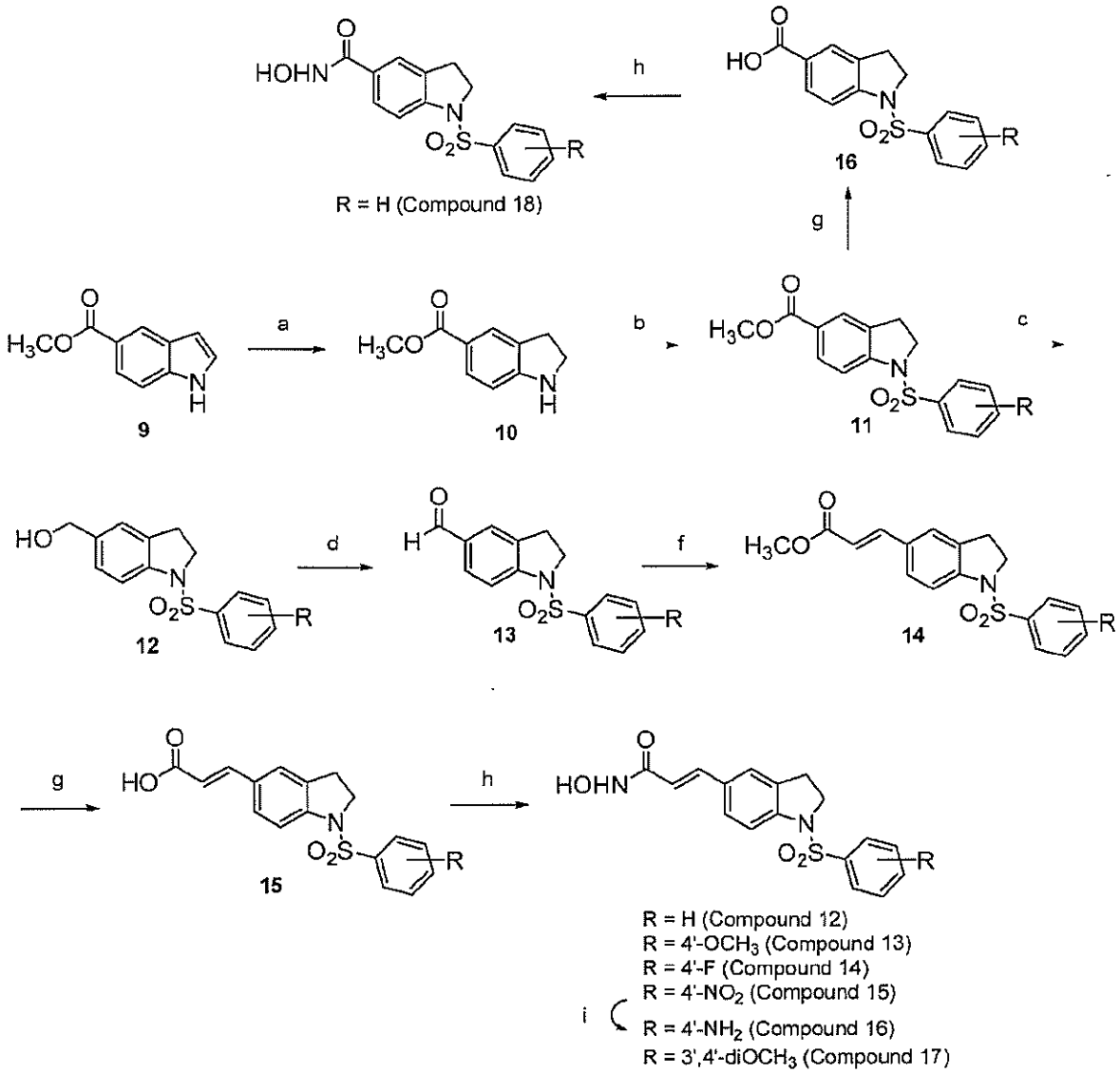
1-Phenyl-1H-indole-5-carbaldehyde (6): The suspension of methyl indole-5-carboxylate (4) (0.70 g, 4.82 mmol), 4-iodobenzene (0.65 mL, 5.79 mmol), K_2CO_3 (0.93 g, 6.75 mmol), CuO (0.04 g, 0.48 mmol) in DMF (2 mL) was refluxed for 2 days. The reaction mixture was quenched with water, followed by extraction with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was purificd by silica gcl chromatography (EtOAc: *n*-hcxanc = 1 : 4) to afford **6** (0.30 g). ^{1}H NMR (500MHz, CD_3OD): δ 6.83 (d, J = 3.2 Hz, 1H), 7.431-7.44 (m, 1H),7.42 (d, J = 3.1 Hz, 1H), 7.49-7.51 (m, 2H), 7.54-7.60 (m, 3H), 7.77 (dd, J = 8.7, 1.1 Hz, 1H), 10.06 (s, 1H).

Compound 11 was prepared in a manner similar to that described in Example 3 using the compound **6** in place of **5**.

^{1}H NMR (500MHz, CD_3OD): δ 7.18 (d, J = 15.7 Hz, 1H), 7.49 (d, J = 3.1 Hz, 1H), 8.15-8.20 (m, 1H), 8.30-8.38 (m, 8H), 8.59 (s, 1H). MS (EI) *m/z*: 278. HRMS (EI) for $C_{17}H_{14}N_2O_2$ (M^+): calcd, 278.1055; found, 278.1055.

Example 12: Synthesis of 3-(1-benzenesulfonyl-2,3-dihydro-1H-indol-5-yl)-N-hydroxy-acrylamide (Compound 12)

Scheme 3



Compound 12 was synthesized via the route as shown in Scheme 3 above (reagents and conditions: (a) $NaBH_3CN$, AcOH; (b) Benzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, or 4-nitrobenzenesulfonyl chloride, pyridine; (c) $LiAlH_4$, THF; (d) PDC, MS, CH_2Cl_2; f) $Ph_3P=CH-COOCH_3$, CH_2Cl_2; (g) 1M LiOH(aq), dioxane; (h) (i) NH_2OTHP, PyBOP, NEt_3, DMF; (ii) TFA, MeOH; (i) Fe, NH_4Cl, Isopropanol, H_2O).

2,3-Dihydro-1H-indole-5-carboxylic acid methyl ester (10): sodium cyanoborohydride (0.16 g, 2.57 mmol) was added to a solution of methyl indole-5-carboxylate (**9**) (0.30 g, 1.71 mmol)

in AcOH (2 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h before it was quenched with water at 0 °C. Concentrated NaOH was added to reach pH=10. The aqueous layer was extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 2) to afford **10** (0.28 g). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.06 (t, *J* = 8.5 Hz, 2H), 3.65 (t, *J* = 8.5 Hz, 2H), 3.84 (s, 3H), 6.53-6.55 (m, 1H), 7.75-7.76 (m, 2H).

1-Benzenesulfonyl-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester (11): To a solution of **10** (0.28 g, 1.58 mmol) in pyridine (2 mL), benzenesulfonyl chloride (0.40 ml, 3.16 mmol) was added. The reaction mixture was refluxed overnight. The mixture was then purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 3) to afford **11** (0.40 g). ^{1}H NMR (500MHz, $CDCl_3$): δ 2.99 (t, *J* = 8.6 Hz, 2H), 3.87 (s, 3H), 3.97 (t, *J* = 8.6 Hz, 2H), 7.45-7.48 (m, 2H), 7.56-7.59 (m, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.75 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 2H), 7.90 (d, *J* = 7.9 Hz, 1H).

(1-Benzenesulfonyl-2,3-dihydro-1H-indol-5-yl)-methanol (12): LAH (0.10 g, 2.52 mmol) was added to a solution of **11** (0.40 g, 1.26 mmol) in THF (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h before it was quenched with water and then extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The reaction mixture was purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 1) to afford **12** (0.24 g). ^{1}H NMR (500MHz, $CDCl_3$): δ 2.83 (t, *J* = 8.4 Hz, 2H), 3.92 (t, *J* = 8.5 Hz, 2H), 4.49 (s, 2H), 7.09 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.46-7.49 (m, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 2H).

1-Benzenesulfonyl-2,3-dihydro-1H-indole-5-carbaldehyde (13): molecular sieves (0.63g) were added to a solution of **12** (0.24 g, 0.83 mmol) in CH_2Cl_2 (10 mL), PDC (0.63 g, 1.66 mmol). The mixture was stirred at room temperature overnight before it was filtered through celite. The organic layer was concentrated under reduced pressure then purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 2) to afford **13** (0.19 g). ^{1}H NMR (500MHz, $CDCl_3$): δ 3.05 (t, *J* = 8.6 Hz, 2H), 4.01 (t, *J* = 8.7 Hz, 2H), 7.46-7,49 (m, 2H), 7.58-7.62 (m, 2H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 9.85 (s, 1H).

3-(1-Benzenesulfonyl-2,3-dihydro-1H-indol-5-yl)-acrylic acid methyl ester (14): Methyl (triphenylphosphoranylidene) acetate (0.27 g, 0.79 mmol) was added to a solution of **13** (0.19g, 0.66 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 3h before it was

quenched with water and then extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was then purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 3) to afford **14** (0.20 g).

3-(1-Benzenesulfonyl-2,3-dihydro-1H-indol-5-yl)-acrylic acid (15): 1M LiOH aqueous solution (1.16 ml, 1.16 mmol) was added to a solution of **14** (0.20g, 0.58 mmol) in dioxane (15 mL). The reaction mixture was stirred at 40 °C overnight before it was concentrated under reduced pressure. The residue was dissolved in water and concentrated HCl was added up to acidic pH to give the precipitation, which was dried by vacuum to afford **15** (0.16 g). ^{1}H NMR (500MHz, CD_3OD): δ 2.92 (t, J = 8.5 Hz, 2H), 3.96 (t, J = 8.5 Hz, 2H), 6.33 (d, J = 15.9 Hz, 1H), 7.38 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.50-7.53 (m, 2H), 7.55 (d, J = 16.1 Hz, 1H), 7.58-7.64 (m, 2H), 7.82 (d, J = 7.6 Hz, 2H).

3-(1-Benzenesulfonyl-2,3-dihydro-1H-indol-5-yl)-N-hydroxy-acrylamide (Compound 12): NH_2OTHP (0.05 g, 0.44 mmol) was added to a solution of **15** (0.12 g, 0.37 mmol), PyBOP (0.20 g, 0.39 mmol), triethylamine (0.12 ml, 0.88 mmol) in DMF (1.5 mL). The reaction mixture was stirred at room temperature for 1 h before it was quenched with water, followed by extraction with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2: CH_3OH = 30 : 1 : 1%$NH_{3(aq)}$) to give a white solid, which was treated with TFA (1.13 ml, 15.21 mmol) in the presence of CH_3OH (25 mL) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to give a white residue, which was recrystallized by CH_3OH to afford Compound 12 (0.12 g). ^{1}H NMR (500MHz, CD_3OD): δ 2.91 (t, J = 8.5 Hz, 2H), 3.96 (t, J = 8.4 Hz, 2H), 6.32 (d, J = 15.8 Hz, 1H), 7.32 (s, 1H), 7.37-7.39 (m, 1H), 7.46 (d, J = 15.7 Hz, 1H), 7.50-7.53 (m, 2H), 7.58-7.64 (m, 2H), 7.82 (d, J = 7.8 Hz, 2H). MS (EI) *m/z*: 170 (100%), 344 (M^+, 3.21%). HRMS (EI) for $C_{17}H_{16}N_2O_4S$ (M^+): calcd, 344.0831; found, 344.0829.

Example 13: Synthesis of N-hydroxy-3-[1-(4-methoxy-benzenesulfonyl)-2,3-dihydro-1H-indol-5-yl]-acrylamide (Compound 13)

Compound 13 was prepared in a manner similar to that described in Example 12.

^{1}H NMR (500MHz, CD_3OD): δ 2.91 (t, J = 8.46 Hz, 2H), 3.81 (s, 3H), 3.92 (t, J = 8.49 Hz, 2H), 6.31 (d, J = 15.78 Hz, 1H), 7.00 (d, J = 8.85 Hz, 2H), 7.32 (s, 1H), 7.37 (d, J = 8.77 Hz, 1H), 7.46 (d, J = 15.78 Hz, 1H), 7.56 (d, J = 8.36 Hz, 1H), 7.74 (d, J = 8.80 Hz, 2H).

Example 14: Synthesis of 3-[1-(4-fluoro-benzenesulfonyl)-2,3-dihydro-1H-indol-5-yl]-N-hydroxy-acrylamide (Compound 14)

Compound 14 was prepared in a manner similar to that described in Example 12.

^{1}H NMR (500MHz, CD_3OD): δ 2.93 (t, J = 8.41 Hz, 2H), 3.95 (t, J = 8.42 Hz, 2H), 6.80 (d, J = 15.40 Hz, 1H), 7.25 (t, J = 8.67 Hz, 2H), 7.33 (s, 1H), 7.37-7.43 (m, 2H), 7.56 (d, J = 8.17 Hz, 1H), 7.86-7.89 (m, 2H).

Example 15: Synthesis of N-hydroxy-3-[1-(4-nitro-benzenesulfonyl)-2,3-dihydro-1H-indol-5-yl]-acrylamide (Compound 15)

Compound 15 was prepared in a manner similar to that described in Example 12.

^{1}H NMR (500MHz, CD_3OD): δ 2.96 (t, J = 8.38 Hz, 2H), 4.02 (t, J = 8.47 Hz, 2H), 6.32 (d, J = 15.78 Hz, 1H), 7.34 (s, 1H), 7.40 (d, J = 8.29 Hz, 1H), 7.45 (d, J = 15.71 Hz, 1H), 7.59 (d, J = 8.34 Hz, 1H), 8.06 (d, J = 8.73 Hz, 2H), 8.34 (d, J = 8.82 Hz, 2H).

Example 16: Synthesis of 3-[1-(4-amino-benzenesulfonyl)-2,3-dihydro-1H-indol-5-yl]-N-hydroxy-acrylamide (Compound 16)

Compound 16 was prepared in a manner similar to that described in Example 7 starting from compound 15.

^{1}H NMR (500MHz, CD_3OD): δ 2.91 (t, J = 8.41 Hz, 2H), 3.87 (t, J = 8.52 Hz, 2H), 6.48 (d, J = 15.75 Hz, 1H), 6.58 (d, J = 8.80 Hz, 2H), 7.34 (s, 1H), 7.37 (d, J = 8.21 Hz, 1H), 7.44 (d, J = 15.78 Hz, 1H), 7.45 (d, J = 8.85 Hz, 2H), 7.53 (d, J = 8.37 Hz, 1H).

Example 17: Synthesis of 3-[1-(3,4-dimethoxy-benzenesulfonyl)-2,3-dihydro-1H-indol-5-yl]-N-hydroxy-acrylamide (Compound 17)

Compound 17 was prepared in a manner similar to that described in Example 12.

^{1}H NMR (500MHz, CD_3OD): δ 2.90 (t, J = 8.39Hz, 2H), 3.72 (s, 3H), 3.85 (s, 3H), 3.93 (t, J = 8.45Hz, 2H), 6.33 (d, J = 15.73 Hz, 1H), 7.06 (d, J = 8.54Hz, 1H), 7.19 (d, J = 1.82 Hz, 1H), 7.36 (s, 1H), 7.41-7.50 (m, 3H), 7.61 (d, J = 8.37 Hz, 1H).

Example 18: Synthesis of 1-benzenesulfonyl-2,3-dihydro-1H-indole-5-carboxylic acid hydroxyamide (Compound 18)

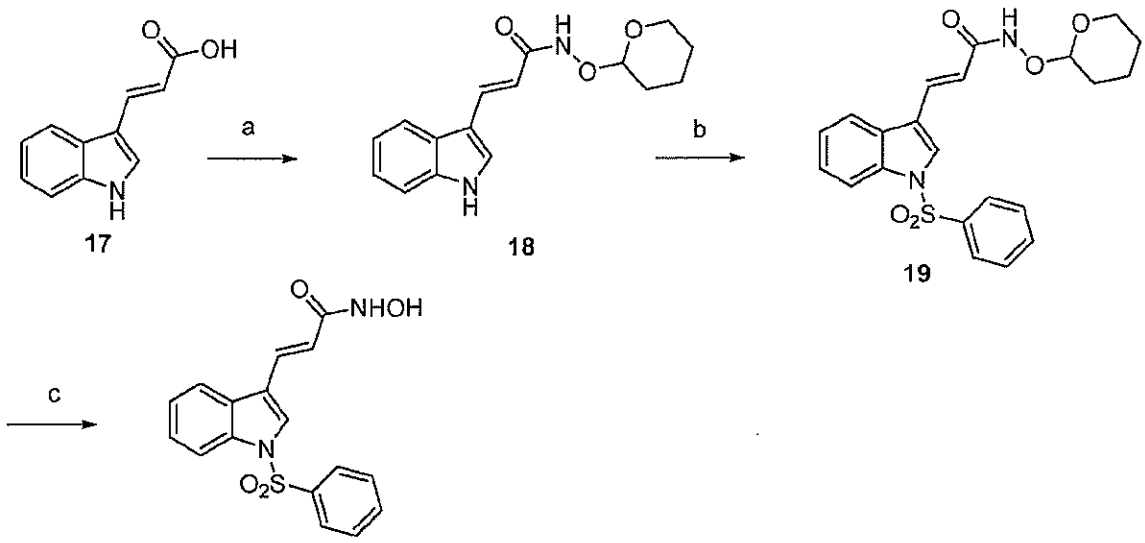
Compound 18 was synthesized via the route as shown in Scheme 3 in Example 12 above.

1-Benzenesulfonyl-2,3-dihydro-1H-indole-5-carboxylic acid (16): 1M LiOH aqueous solution (2.4 ml, 2.40 mmol) was added to a solution of **11** (0.38 g, 1.20 mmol) in dioxane (15 mL). The reaction mixture was stirred at 40 °C overnight and then was concentrated under reduced pressure. The residue was dissolved in water and concentrated HCl was added up to acidic pH to give the precipitation, which was dried by vacuum to afford **16** (0.34 g). ^{1}H NMR (500MHz, CD_3OD): δ 2.97 (t, J = 8.6 Hz, 2H), 3.99 (t, J = 8.6 Hz, 2H), 7.51-7.54 (m, 2H), 7.61-7.64 (m, 2H), 7.74 (s, 1H), 7.84-7.88 (m, 3H).

1-Benzenesulfonyl-2,3-dihydro-1H-indole-5-carboxylic acid hydroxyamide (Compound 18): NH_2OTHP (0.12 g, 0.99 mmol) was added to a solution of **16** (0.25 g, 0.82 mmol), PyBOP (0.46 g, 0.87 mmol), triethylamine (0.28 ml, 1.98 mmol) in DMF (2 mL). The reaction mixture was stirred at room temperature for 1.5 h before it was quenched with water, followed by extraction with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2: CH_3OH = 30 : 1 : 1%$NH_{3(aq)}$) to give a white solid, which was treated with TFA (2.7 ml, 36.35 mmol) in the presence of CH_3OH (52 mL) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to give a white residue, which was recrystallized by CH_3OH to afford Compound 18 (0.25g). ^{1}H NMR (500MHz, CD_3OD): δ 2.95 (d, J = 8.49 Hz, 2H), 3.97 (d, J = 8.52Hz, 2H), 7.48-7.52 (m, 3H), 7.57-7.63 (m, 3H), 7.82 (d, J = 7.71 Hz, 2H). HRMS (EI) for $C_{15}H_{14}N_2O_4S$ (M^+): calcd, 318.0674; found, 318.0672.

Example 19: Synthesis of 3-(1-benzenesulfonyl-1H-indol-3-yl)-N-hydroxy-acrylamide (Compound 19)

Scheme 4



Compound 19

Compound 19 was synthesized via the route as shown in Scheme 4 above (reagents and conditions: a) NH_2OTHP, PyBOP, NEt_3, DMF; b) Benzenesulfonyl chloride, KOH, tetra-*n*-butylammonium bisulfate, CH_2Cl_2; c) TFA, MeOH).

3-(1H-Indol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide (18): NH_2OTHP (0.38 g, 3.21 mmol) was added to a solution of *trans*-3-indoleacrylic acid (**17**) (0.50 g, 2.67 mmol), PyBOP (1.47 g, 2.83 mmol), triethylamine (0.74 ml, 6.41 mmol) in THF (25 mL). The mixture was stirred at room temperature for 2 h and then was concentrated under reduced pressure. The residue was dissolved in EtOAc and quenched with water, followed by extraction with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc: *n*-hexane = 1.5 : 1 : 1%$NH_{3(aq)}$) to afford **18**. ^1H NMR (500MHz, CD_3OD): δ 1.58-1.70 (m, 3H), 1.79-1.90 (m, 3H), 3.63-3.65 (m, 1H), 4.03-4.08 (m, 1H), 4.97-4.98 (m, 1H), 6.47 (d, J = 14.9 Hz, 1H), 7.15-7.21 (m, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.84-7.87 (m, 2H).

3-(1-Benzenesulfonyl-1H-indol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide (19): To a suspension of **18** (0.52 g, 1.82 mmol), tetrabutylammonium bisulfate (0.09 g, 0.27 mmol) and KOH (0.20 g, 3.63 mmol) in CH_2Cl_2 (15 mL) was stirred for 20 min, benzenesulfonyl chloride (0.35 ml, 2.72 mmol) was added and stirred at room temperature overnight. The reaction mixture was quenched with water extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was

dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 2) to afford **19** (0.42 g)

3-(1-Benzenesulfonyl-1H-indol-3-yl)-N-hydroxy-acrylamide (Compound 19): A solution of crude **19** in methanol (50 ml) was treated with TFA (2.2 ml, 29.8 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure to give a yellow residue, which was recrystallized by CH_3OH to afford Compound 19 (0.1 g); ^{1}H NMR (500MHz, CD_3OD): δ 6.61 (d, J = 16.0 Hz, 1H), 7.35-7.43 (m, 2H), 7.55-7.58 (m, 2H), 7.65-7.68 (m, 1H), 6.69 (d, J = 16.0 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 8.00-8.05 (m, 3H), 8.27 (s, 1H). MS (EI) *m/z*: 342. HRMS (EI) for $C_{17}H_{14}N_2O_4S$ (M^+): calcd, 342.0674; found, 342.0673.

Example 20: Synthesis of 3-(1-benzenesulfonyl-1H-indol-6-yl)-N-hydroxy-acrylamide (Compound 20)

Compound 20 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, CD_3OD): δ 6.50 (d, J = 15.8 Hz, 1H), 6.74 (d, J = 3.6 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.50-7.54 (m, 3H), 7.59 (t, J =7.4 Hz, 1H), 8.65 (d, J = 15.8 Hz, 1H), 7.71 (d, J = 3.6 Hz, 1H), 7.93 (d, J = 1.1 Hz, 1H), 7.94 (s, 1H), 8.13 (s, 1H). MS (EI) *m/z*: 342.

Example 21: Synthesis of 3-(1-benzenesulfonyl-1H-indol-4-yl)-N-hydroxy-acrylamide (Compound 21)

Compound 21 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, CD_3OD): δ 6.54 (d, J = 15.8 Hz, 1H), 7.03 (d, J = 3.6 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.55 (s, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 3.8 Hz, 1H), 7.88 (d, J = 15.8 Hz, 1H), 7.92 (d, J =7.7 Hz, 2H), 8.01 (d, J = 8.4 Hz, 1H). MS (EI) *m/z*: 342. HRMS (EI) for $C_{17}H_{14}N_2O_4S$ (M^+): calcd, 342.0674; found, 342.0674.

Example 22: Synthesis of 3-(1-benzenesulfonyl-1H-indol-7-yl)-N-hydroxy-acrylamide (Compound 22)

Compound 22 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, CD_3OD): δ 5.87 (d, J = 15.1 Hz, 1H), 6.62 (d, J = 3.7 Hz, 1H), 7.07-7.10 (m, 1H), 7.15-7.16 (m, 1H), 7.26-7.30 (m, 2H), 7.39-7.43 (m, 2H), 7.61 (d, J =7.9 Hz, 2H),

7.70 (d, J =3.7 Hz, 1H), 8.34 (d, J = 15.2 Hz, 1H). MS (EI) *m/z*: 342. HRMS (EI) for $C_{17}H_{14}N_2O_4S$ (M^+): calcd, 342.0674; found, 342.0672.

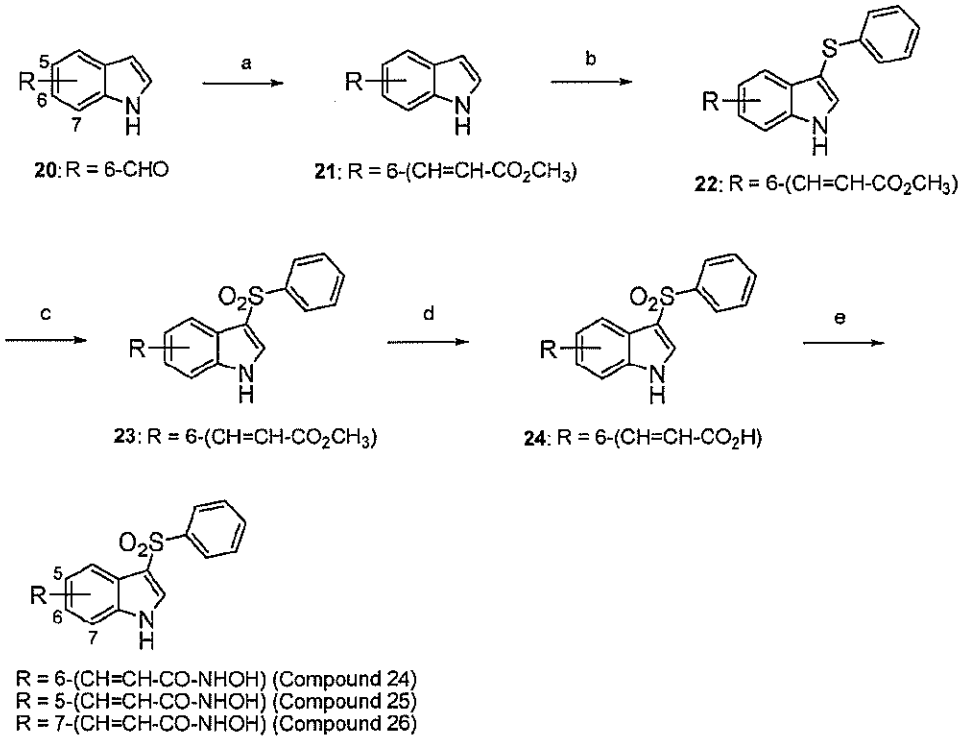
Example 23: Synthesis of N-hydroxy-3-(1H-indol-4-yl)-acrylamide (Compound 23)

Compound 23 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, CD_3OD): δ 6.67 (d, J = 15.6 Hz, 1H), 6.77 (d, J = 2.9 Hz, 1H), 7.11-7.14 (m, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 8.0 (d, J = 15.8 Hz, 1H). LC/MS *m/z*: 203 (M^+ + 1). HRMS (EI) for $C_{11}H_{10}N_2O_2$ (M^+): calcd, 202.0742; found, 202.0742.

Example 24: Synthesis of 3-(3-benzenesulfonyl-1H-indol-6-yl)-N-hydroxy-acrylamide (Compound 24)

Scheme 5



Compound 24 was synthesized via the route as shown in Scheme 5 above (reagents and conditions: (a) Ph_3P=CH-CO_2CH_3, CH_2Cl_2; (b) NaH, Ph-S-S-Ph, DMF; (c) MCPBA, CH_2Cl_2; (d) LiOH, MeOH, H_2O; (e) (i) NH_2OTHP, PyBOP, NEt_3, DMF; (ii) TFA, MeOH).

3-(1H-Indol-6-yl)-acrylic acid methyl ester (21): Methyl (triphenylphosphoranylidene) acetate (1.38 g, 4.13 mmol) was added to a solution of **20** (0.5 g, 3.44 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature overnight before it was quenched with water and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was then purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 4) to afford **21** (0.63 g). ^{1}H NMR (500MHz, CD_3OD): δ 3.81 (s, 3H), 6.43 (d, J = 15.8 Hz, 1H), 6.57 (m, 1H), 7.30 (t, J = 2.7 Hz, 1H), 7.35 (dd, J = 8.2, 1.0 Hz, 1H), 7.55 (s, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 15.9 Hz, 1H), 8.30 (s, 1H).

3-(3-Phenylsulfanyl-1H-indol-6-yl)-acrylic acid methyl ester (22): To a suspension of NaH (0.11 g, 4.70 mmol) in DMF (6 mL), **21** (0.63 g, 3.13 mmol) was added at 0 °C. Then the reaction mixture was warmed up to room temperature. After being stirred for 2 h, phenyl disulfide (0.75 g, 3.44 mmol) was added. The reaction mixture was stirred overnight before it was quenched with water at 0 °C, followed by extraction with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was then purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 3) to afford **22** (0.61g). ^{1}H NMR (500MHz, CD_3OD): δ 3.81 (s, 3H), 6.44 (d, J = 15.8 Hz, 1H), 7.03-7.18 (m, 5H), 7.37-7.39 (m, 1H), 7.56-7.60 (m, 3H), 7.80 (d, J = 15.9 Hz, 1H), 8.53 (s, 1H).

3-(3-Benzenesulfonyl-1H-indol-6-yl)-acrylic acid methyl ester (23): To a solution of **22** (0.61 g, 1.97 mmol) in CH_2Cl_2 (40 mL), 3-chloroperoxybenzoic acid (0.77 g, 4.44 mmol) was added at 0 °C. The reaction mixture was moved to room temperature and stirred overnight. Then it was quenched with saturated $NaHCO_{3(aq)}$ at 0 °C, followed by extraction with CH_2Cl_2 (25 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a green residue, which was then purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 1) to afford **23** (0.36 g). ^{1}H NMR (500MHz, CD_3OD): δ 3.81 (s, 3H), 6.43 (d, J = 16.0 Hz, 1H), 7.03-7.18 (m, 5H), 7.73 (d, J = 16.0 Hz, 1H), 7.56-7.60 (m, 4H), 8.85 (s, 1H).

3-(3-Benzenesulfonyl-1H-indol-6-yl)-acrylic acid (24): To a solution of **23** (0.36 g, 1.05 mmol) in MeOH (10 mL) and water (2 ml), lithium hydroxide (0.05 g, 2.11 mmol) was added. The reaction mixture was refluxed for 6 h and was then concentrated under reduced pressure to provide a residue. The residue was dissolved in water. 3N HCl was added up to acidic pH and the mixture was extracted with EtOAc (20 mL × 3). The combined organic layer was dried over anhydrous

$MgSO_4$ and concentrated under reduced pressure to give a brown residue, which was recrystallized by EtOH to afford **24** (0.2 g). ^{1}H NMR (500MHz, CD_3OD): δ 6.46 (d, J = 15.8 Hz, 1H), 7.62-7.69 (m, 4H), 7.81 (s, 1H), 7.81 (d, J = 16.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 7.3 Hz, 2H), 8.21 (s, 1H).

3-(3-Benzenesulfonyl-1H-indol-6-yl)-N-hydroxy-acrylamide (Compound 24): NH_2OTHP (0.04 g, 0.37 mmol) was added to a solution of **24** (0.10 g, 0.31 mmol), PyBOP (0.17 g, 0.33 mmol), triethylamine (0.1 ml, 0.74 mmol) in DMF (1 mL). The reaction mixture was stirred at room temperature for 1 h before it was quenched with water, followed by extraction with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2: CH_3OH = 30 : 1 : 1%$NH_{3(aq)}$) to give a white solid, which was treated with TFA (0.70 ml, 9.44 mmol) in the presence of CH_3OH (15 mL) and stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to give a white residue, which was recrystallized by CH_3OH to afford Compound 24 (0.08 g). ^{1}H NMR (500MHz, CD_3OD): δ 6.45 (d, J = 15.8 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.50-7.65 (m, 5H), 7.81 (d, J = 8.4 Hz, 1H), 7.98-8.00 (m, 2H), 8.04 (s, 1H). MS (EI) *m/z*: 342. HRMS (EI) for $C_{17}H_{14}N_2O_4S$ (M^+): calcd, 342.0674; found, 342.0674.

Example 25: Synthesis of 3-(3-benzenesulfonyl-1H-indol-5-yl)-N-hydroxy-acrylamide (Compound 25)

Compound 25 was prepared in a manner similar to that described in Example 24.

^{1}H NMR (500MHz, CD_3OD): δ 6.48 (d, J = 16.2 Hz, 1H), 7.52 (s, 2H), 7.56 (d, J = 7.7 Hz, 2H), 7.55-7.59 (m, 1H), 7.67 (d, J = 15.9 Hz, 1H), 8.01 (s, 1H), 8.03 (d, J = 6.9 Hz, 2H), 8.07 (s, 1H). MS (EI) *m/z*: 342.

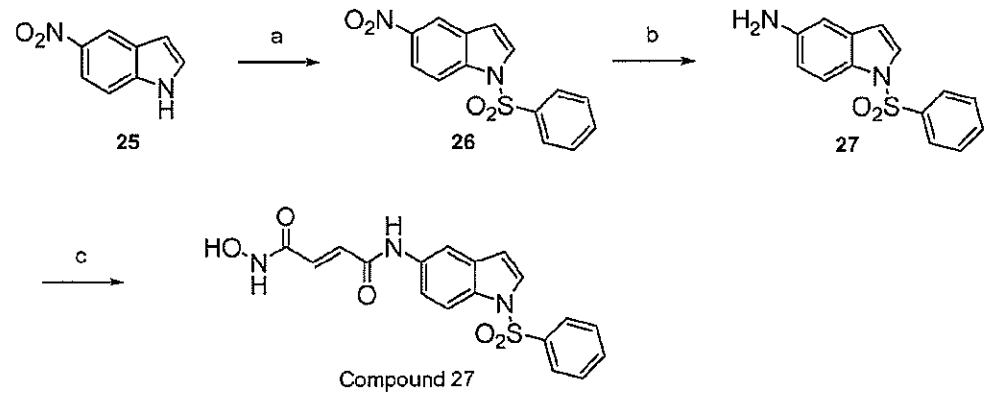
Example 26: Synthesis of 3-(3-benzenesulfonyl-1H-indol-7-yl)-N-hydroxy-acrylamide (Compound 26)

Compound 26 was prepared in a manner similar to that described in Example 24.

^{1}H NMR (500MHz, DMSO): δ 6.58 (d, J = 15.5 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.52-7.58 (m, 4H), 7.86 (d, J =7.9 Hz, 1H), 8.01-8.07 (m, 4H). MS (EI) *m/z*: 342. HRMS (EI) for $C_{17}H_{14}N_2O_4S$ (M^+): calcd, 342.0674; found,342.0673.

Example 27: Synthesis of but-2-enedioic acid (1-benzenesulfonyl-1H-indol-5-yl)-amide hydroxyamide (Compound 27)

Scheme 6



Compound 27 was synthesized via the route as shown in Scheme 6 above (reagents and conditions: (a) benzensulfonyl chloride, KOH, TBAHS, CH_2Cl_2; (b) Fe, NH_4Cl, IPA, H_2O; (c) (i) fumaryl chloride, THF (ii) NH_2OH-HCl, sat. $NaHCO_3$(aq), THF).

1-Benzenesulfonyl-5-nitro-1H-indole (26): After a suspension of 5-nitroindole (**25**) (1.00 g, 6.17 mmol), tetrabutylammonium bisulfate (0.32 g, 0.93 mmol) and KOH (0.69 g, 12.33 mmol) in CH_2Cl_2 (20 mL) was stirred for 30 min, benzenesulfonyl chloride (1.18 ml, 9.25 mmol) was added and stirred at room temperature overnight. The reaction was quenched with water extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 4) to afford **26** (1.72 g). ^{1}H NMR (500MHz, CD_3OD): δ 6.81 (d, J = 3.6 Hz, 1H), 7.48-7.51 (m, 2H), 7.58-7.61 (m, 1H), 7.73 (d, J = 3.69 Hz, 1H), 7.90 (d, J − 7.64 Hz, 2H), 8.09 (d, J − 9.0 Hz, 1H), 8.21 (dd, J − 9.0, 2.0 Hz, 1H), 8.47 (d, J − 2.0 Hz, 1H).

1-Benzenesulfonyl-1H-indol-5-ylamine (27): To the suspension of **2** (1.16 g, 3.84 mmol) in IPA (38 mL) and water (9 mL), iron (0.64 g, 11.51 mmol) and ammonium chloride (0.41 g, 7.67 mmol) were added and refluxed overnight. After the reaction was filtrated with celite, the solvent was concentrated under reduced pressure to give a brown residue, which was dissolved in CH_2Cl_2 and quenched with water, followed by extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a brown residue, which was purified by silica gel chromatography (EtOAc: *n*-hexane = 1 : 2 : 1%$NH_{3(aq)}$) to afford **27** (0.86 g). ^{1}H NMR (500MHz, CD_3OD): δ 3.60 (s, 2H), 6.48 (d, J = 3.6 Hz, 1H), 6.69 (dd,

J = 8.7, 2.1 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 7.39-7.42 (m, 2H), 7.44 (d, J = 3.5 Hz, 1H), 7.49-7.51 (m, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 7.9 Hz, 2H).

But-2-enedioic acid (1-benzenesulfonyl-1H-indol-5-yl)-amide hydroxyamide (Compound 27): A solution of **27** (0.20g, 0.73 mmol) in THF (2 mL) was added dropwise to a solution of fumaryl chloride (0.08 mL, 0.73 mmole) in THF (1 mL). The mixture was stirred at room temperature for 10 min and was then dried under vacuum to provide a residue. The residue was then dissolved in THF (mL). In another vessel, to a suspension of hydroxylamine hydrochloride (0.26 g, 3.77 mmole) in THF (4 mL), a sat. $NaHCO_3$ solution (3 ml) was added, and the reaction mixture was stirred at room temperature for 10 min. The contents of both vessels were combined and stirred at room temperature for 1 h. The mixture was partitioned between EtOAc (15 mL × 3) and water. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow residue, which was purified by silica gel chromatography (CH_2Cl_2: CH_3OH = 10 : 1 : 1% AcOH) to afford Compound 27 (0.12 g). ^{1}H NMR (500MHz, CD_3OD): δ 7.70 (d, J = 3.3 Hz, 1H), 6.86 (d, J = 15.0 Hz, 1H), 7.10 (d, J = 15.0 Hz, 1H), 7.46-7.51 (m, 3H), 7.58-7.61 (m, 1H), 7.65 (d, J = 3.4 Hz, 1H), 7.90-7.97 (m, 4H). HRMS (EI) for $C_{18}H_{15}N_3O_5S$ (M^+): calcd, 385.0732; found, 385.0732.

Example 28: Synthesis of N-hydroxy-3-[1-(4-methoxy-benzenesulfonyl)-1H-indol-7-yl]-acrylamide (Compound 28)

Compound 28 was prepared in a manner similar to that described in Example 3.

Example 29: Synthesis of 3-(1-benzenesulfonyl-1H-indol-5-yl)-acrylic acid (Compound 29)

Compound 29 was prepared in a manner similar to that described in Example 3.

^{1}H NMR (500MHz, $CDCl_3$): δ6.39 (d, J = 16.1 Hz, 1H), 6.71 (d, J = 3.6 Hz, 1H), 7.45-7.48 (m, 2H), 7.52 (dd, J = 8.7, 1.4 Hz, 1H), 7.55-7.58 (m, 1H), 7.61 (d, J = 3.7 Hz, 1H), 7.67-7.72 (m, 2H), 7.89 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.7 Hz, 1H).

Example 30: Cell Viability Assays

i) MTT assay

Human leukemia cell lines K562 (bearing BCR/ABL translocation), NB4 (expressing PML/RARalpha fusion protein), MV4-11 (bearing FLT3-ITD mutation), HL60 (carrying a p53 null mutation), Kasumi-1 (8;21 chromosome translocation; c-kit expression), and U937 (macrophage-like cells) were well-used models for the study of human leukemia cells. Cells were suspended in RPMI 1640 (Life Technologies) containing 10% FCS. 10^4 cells per well were seeded in 96-well culture plates with or without one of the test compounds. Various concentrations for the test compound were examined. Cell viabilities at the various compound concentrations were determined 48 hr or 72 hr after treatment using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay (Sigma, working conc. 0.5mg/ml). The MTT assay is a well-established cytotoxic assay method, which quantitatively detects the cellular mitochondrial reduction activity of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to produce a dark blue formazan product. The values of LC_{50} and GI_{50} for each test compound were determined accordingly. GI_{50} refers to the the compound concentration resulting in a 50% reduction in the net cells increase in control cells. Growth inhibition of 50 % is defined as [(Ti-Tz)/(C-Tz)] x 100 = 50, in which, Tz represents the cell content at time zero (when there is no cell increase), C represents the cell content of the control group (where no test compound is added) and the Ti represents the cell content of the group treated with a test compound at GI_{50}. The drug concentration resulting in total growth inhibition (TGI) is determined when Ti = Tz. LC_{50} refers to the compound concentration resulting in a net cell loss by 50% at the end of the drug treatment as compared to that at the beginning. The net loss of cells following treatment is defined as [(Ti-Tz)/Tz] x 100 = -50.

Cells were seeded in a 96-well flat-bottomed plate (2,500 to 3,000 cells per well). The cells were then treated with a test compound (Compound 3, Compound 12, Ara-C, and SAHA) at various concentrations (i.e. 0, 5, 10, 15 and 20 μM) in RPMI 1640 medium supplemented with 10% FBS at 37°C with a 5% CO_2 supply for 48 or 72 hr. The culture medium was then removed from each well and 150 μL of 0.5 mg/mL of MTT in RPMI 1640 medium were added. After being incubated at 37 °C for 2 h, the supernatant was removed and 200 μL/well of DMSO were added to dissolve the remaining MTT dye. The absorbance at 570 nm in each well was determined using a plate reader. Each compound concentration was tested in 6 duplicates. The MTT assay results obtained are shown in Table 1 below.

Table 1. Comparative Evaluation of the Treatment Efficacy of the present compounds and commercial anti-cancer drugs on Leukemia cells				
NB4				
	Compound 3	Compound 12	Ara-C	SAHA
GI_{50} (nM)	223.1	31.5	448.3	303.3
TGI (nM)	500.9	61.2	2324.0	615.8
LC_{50} (nM)	778.7	91.0	7324.0	928.3
HL60				
	Compound 3	Compound 12	Ara-C	SAHA
GI_{50} (nM)	241.6	32.9	445.4	454.7
TGI (nM)	535.8	65.3	4344.3	811.9
LC_{50} (nM)	829.9	97.8	11487.1	5866.7
U937				
	Compound 3	Compound 12	Ara-C	SAHA
GI_{50} (nM)	162.2	54.7	46.6	589.6
TGI (nM)	440.0	8330.0	109.7	2006.9
LC_{50} (nM)	717.8	>10000	665.2	5853.1
K562				
	Compound 3	Compound 12	Ara-C	SAHA
GI_{50} (nM)	9020	148.7	>10000	>10000
TGI (nM)	>10000	982.0	>10000	>10000
LC_{50} (nM)	>10000	>10000	>10000	>10000
Kasumi-1				
	Compound 3		Ara-C	SAHA
GI_{50} (nM)	96.6		>10000	292.25
TGI (nM)	393.0		>10000	604.75
LC_{50} (nM)	694.2		>10000	917.25
MV4-11				
		Compound 12		
GI_{50} (nM)		13.1		
TGI (nM)		50.2		
LC_{50} (nM)		87.2		

ii) SRB assay

Human cancer A549 (non-small cell lung cancer), MDA-MB-231 (estrogen-independent breast cacner), Hep 3B (hepatoma), and HA22T (hepatoma) cells were seeded in 96-well plates in medium with 5% FBS. After 24 h, cells were fixed with 10 % trichloroacetic acid (TCA) to represent cell population at the time of compound addition (T_0). After additional incubation of

DMSO or test compound for 48 h, cells were fixed with 10 % TCA and SRB at 0.4 % (w/v) in 1 % acetic acid was added to stain cells. Unbound SRB was washed out by 1 % acetic acid and SRB bound cells were solubilized with 10 mM Trizma base. The absorbance was read at a wavelength of 515 nm. Using the absorbance measurements of time zero (T_0), the control group (C), and the cell growth in the presence of the compound (Ti), the percentage growth was calculated at each of the compound concentrations levels. Growth inhibition of 50% is defined as $[(Ti-T_0)/(C-T_0)] \times 100 = 50$ and GI_{50} is defined as the compound concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in the control group during the compound incubation. Results are shown in Table 2 below.

Table 2

Cell lines	A549	MDA-MB-231	Hep-3B	HA22T
	lung	breast	liver	liver
Compound name	GI_{50} (μM)	GI_{50} (μM)	GI_{50} (μM)	GI_{50} (μM)
Compound 13	0.32	0.16	0.14	0.54
Compound 14	0.60	0.37	0.25	1.20
Compound 16	> 10	>10	>10	>10
Compound 15	0.80	0.45	0.28	0.74
Compound 8	0.93	0.37	0.36	0.93
Compound 17	0.32	0.19	0.16	0.62
Compound 4	1.31	0.75	0.55	1.56
Compound 5	1.59	0.66	0.64	2.30
Compound 6	2.12	0.75	0.56	1.98
Compound 7	>10	>10	>10	>10
Compound 3	0.96	0.48	0.41	1.15
Compound 12	0.7	0.25	0.21	0.62
SAHA	2.37	0.97	0.69	2.24

Example 31: Western Blot Analysis

PC-3 cells treated with a test compound at 1, 2.5, or 5 μM in RPMI 1640 supplemented with 10% FBS for 48 hours. The cells were collected and sonicated. Protein concentrations in the resultant lysates were determined by a Bradford protein assay kit (Bio-Rad, Hercules, CA). The protein lysate, containing the same amount of proteins, were subjected to 10% SDS-polyacrylamide gel (10%) electrophoresis. The proteins on the gel were then transferred onto an Immobilon-nitrocellulose membrane (Millipore, Bellerica, MA) in a semi-dry transfer cell. The transblotted

membrane was washed twice with tris-buffered saline containing 0.1% polysorbate 20 (TBST). After being blocked with TBST containing 5% nonfat milk for 40 min, the membrane was incubated with a primary antibody specific to Acetyl-H3 (antibody obtained from Upstate Biotechnology, Inc., Lake Placid, NY), H3 (Upstate Biotechnology), Acetyl α-tubulin (Sigma-Aldrich, St. Louis, MO), phospho-Akt (Serine 473) (Cell Signaling Technologies, Danvers, MA), Akt (Cell Signaling Technologies), Acetyl p53 (Santa Cruz Biotechnology, Santa Cruz, CA), p53 (Santa Cruz Biotechnology), p21 (Santa Cruz Biotechnology), or α-tubulin (Sigma-Aldrich, St. Louis, MO) (1:3000 dilution) in TBST/1% nonfat milk at 4 °C overnight. The membrane was washed three times with TBST for a total of 15 min and then incubated with a goat anti-rabbit or anti-mouse IgG antibody conjugated with horseradish (diluted 1:3000) for 1 h at room temperature. After being washed for at least three times with TBST, the signal intensity for each protein band was determined.

SAHA, Compounds 3, and 12 were tested. The results show that, like SAHA, Compounds 3 and 12 inhibited histone deacetylation and upregulated H3 expression and tubulin acetylation.

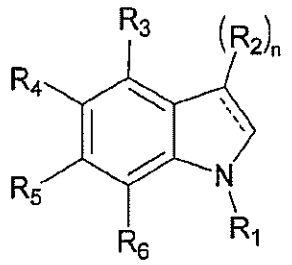
OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I),

wherein

---- is a single bond or a double bond;

n is 0, 1, or 2;

R_1 is SO_2R_a, in which R_a is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, which is optionally substituted with halo, hydroxyl, C_1-C_6alkoxyl, amino, cyano or nitro;

R_2 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR_b, SR_b, $S(O)R_b$, NHC(O)-CH=CH-$C(O)R_b$, NHC(O)-CH=CH-$C(O)NR_cR_d$, $SO_2NR_cR_d$, $OC(O)R_b$, $C(O)NR_cR_d$, NR_cR_d, $NHC(O)R_b$, $NHC(O)NR_cR_d$, or $NHC(S)R_c$, in which each of R_b, R_c, and R_d, independently, is H, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

each of R_3, R_4, R_5, and R_6, independently is, H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR_b, SR_b, $S(O)R_b$, CH=CH-$C(O)NR_cR_d$, NHC(O)-CH=CH-$C(O)R_b$, NHC(O)-CH=CH-$C(O)NR_cR_d$, $SO_2NR_cR_d$, $OC(O)R_b$, $C(O)NR_cR_d$, NR_cR_d, $NHC(O)R_b$, $NHC(O)NR_cR_d$, or $NHC(S)R_c$, in which each of R_b, R_c, and R_d, independently, is H, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

provided that one or more of R_2, R_3, R_4, R_5, and R_6 has the following definitions: R_2 is NHC(O)-CH=CH-$C(O)R_b$ or NHC(O)-CH=CH-$C(O)NR_cR_d$; or R_3, R_5, and R_6 is independently

CH=CH-C(O)NR_cR_d, NHC(O)-CH=CH-C(O)R_b, or NHC(O)-CH=CH-C(O)NR_cR_d; or R_4 is C(O)NHOH, CH=CH-C(O)NR_cR_d, NHC(O)-CH=CH-C(O)R_b, or NHC(O)-CH=CH-C(O)NR_cR_d.

2. The compound of claim 1, wherein R_4 is CH=CH-C(O)NR_cR_d or NHC(O)-CH=CH-C(O)NR_cR_d.

3. The compound of claim 1, wherein R_4 is C(O)NHOH, CH=CH-C(O)NHOH, or NHC(O)-CH=CH-C(O)NHOH.

4. The compound of claim 3, wherein R_4 is CH=CH-C(O)NHOH.

5. The compound of claim 4, wherein R_1 is SO_2R_a and R_a is aryl or heteroaryl.

6. The compound of claim 5, wherein R_a is phenyl optionally substituted with halo, hydroxyl, alkoxyl, amino, cyano, or nitro.

7. The compound of claim 1, wherein R_2 is NHC(O)-CH=CH-C(O)R_b or NHC(O)-CH=CH-C(O)NR_cR_d; or R_3, R_5, and R_6 is independently CH=CH-C(O)NR_cR_d, NHC(O)-CH=CH-C(O)R_b, or NHC(O)-CH=CH-C(O)NR_cR_d.

8. The compound of claim 7, wherein R_2 is NHC(O)-CH=CH-C(O)R_b or NHC(O)-CH=CH-C(O)NHOH; or R_3, R_5, and R_6 is independently CH=CH-C(O)NHOH, NHC(O)-CH=CH-C(O)OH, or NHC(O)-CH=CH-C(O)NHOH.

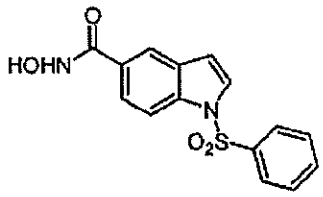
9. The compound of claim 8, wherein R_1 is SO_2R_a and R_a is aryl or heteroaryl.

10. The compound of claim 9, wherein R_a is phenyl optionally substituted with halo, hydroxyl, alkoxyl, amino, cyano, or nitro.

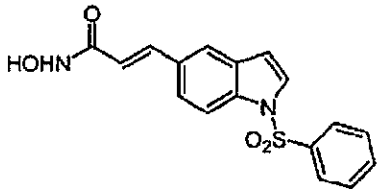
11. The compound of claim 1, wherein R_1 is SO_2R_a and R_a is aryl or heteroaryl.

12. The compound of claim 11, wherein R_a is phenyl optionally substituted with halo, hydroxyl, alkoxyl, amino, cyano, or nitro.

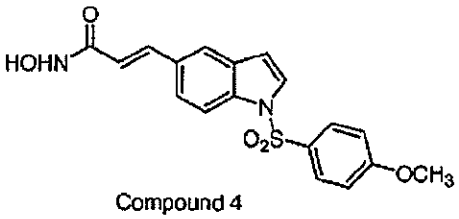
13. The compound of claim 1, wherein the compound is one of the following Compounds 1, 3-8, 12-18, 20-22, 27 and 28:



Compound 1



Compound 3



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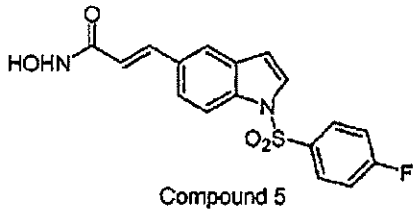

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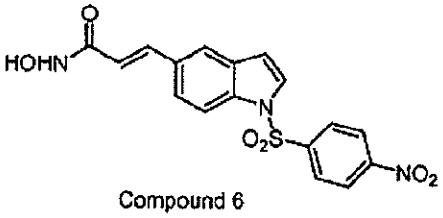

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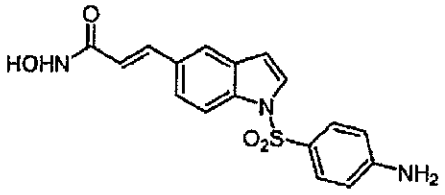
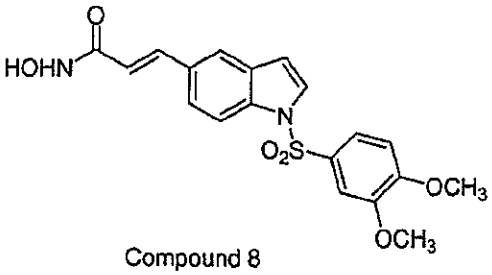


Compound 7



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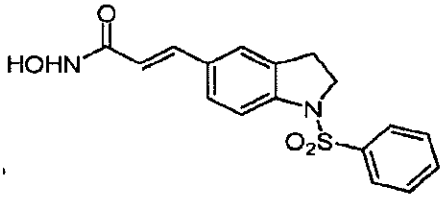

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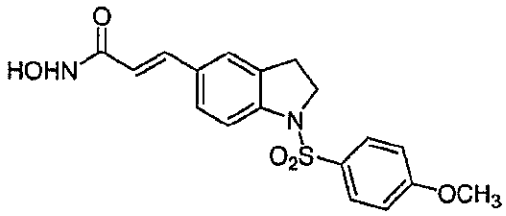
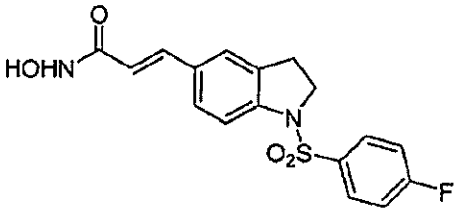
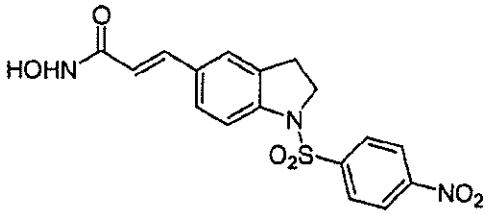


Compound 13



Compound 14



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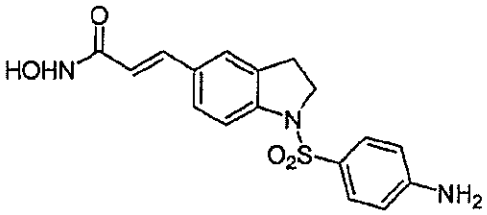
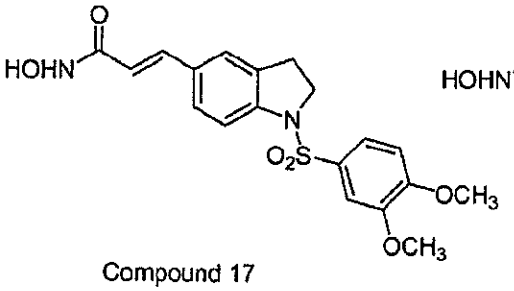


Compound 16



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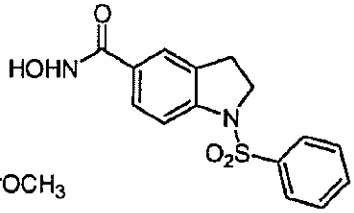
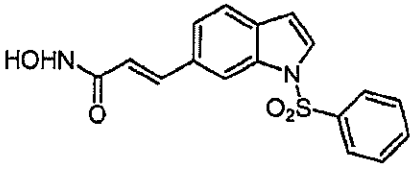
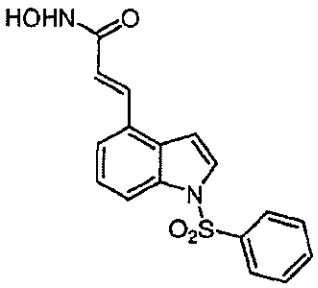


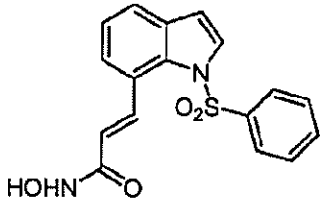
Compound 18



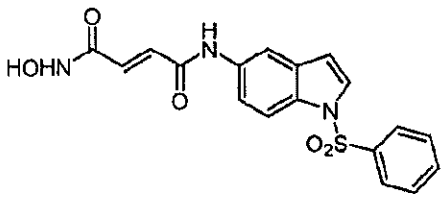
Compound 20



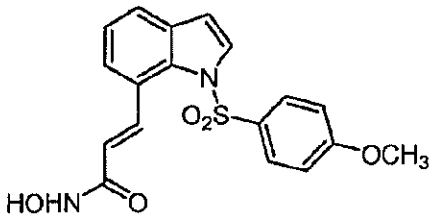
Compound 21



Compound 22



Compound 27



Compound 28

and

14. The compound of claim 13, wherein the compound is 3-(1-benzenesulfonyl-1*H*-indol-5-yl)-*N*-hydroxy-acrylamide or 3-(1-benzenesulfonyl-2,3-dihydro-1*H*-indol-5-yl)-*N*-hydroxy-acrylamide.

15. Use of a compound of any one of claims 1 to 14 in the manufacture of a medicament for treating cancer.

16. A pharmaceutical composition, comprising a compound of any one of claims 1 to 14, and a pharmaceutically acceptable carrier.