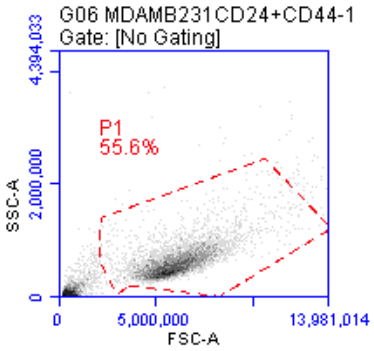


Figure 1A

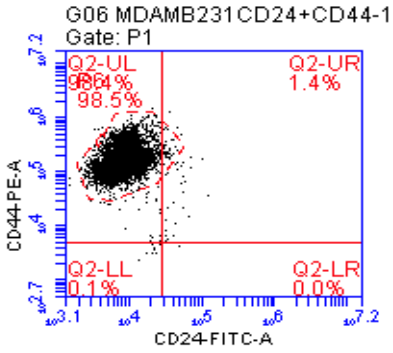


Figure 1B

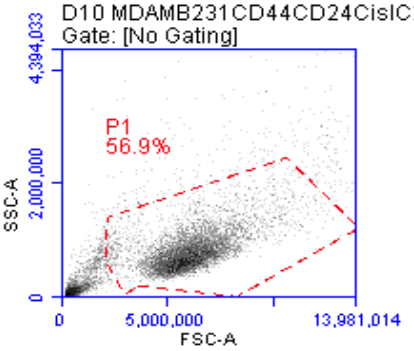


Figure 2A

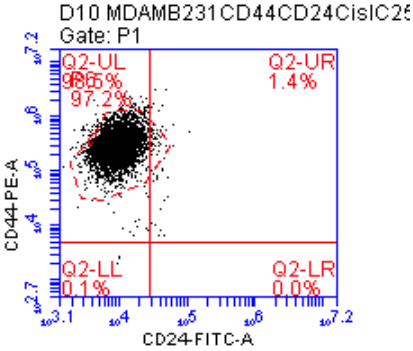


Figure 2B

**(GIRISH VIJAYANAND SHETH)**
**Patent Agent No. IN/PA/1022**
**KRISHNA & SAURASTRI ASSOCIATES**

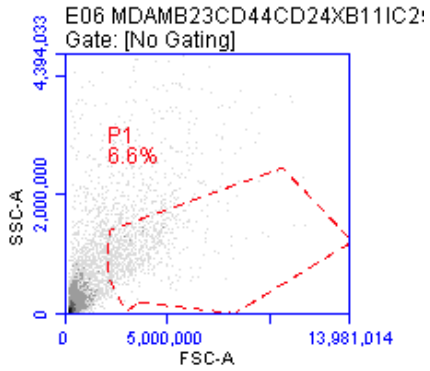


Figure 3A

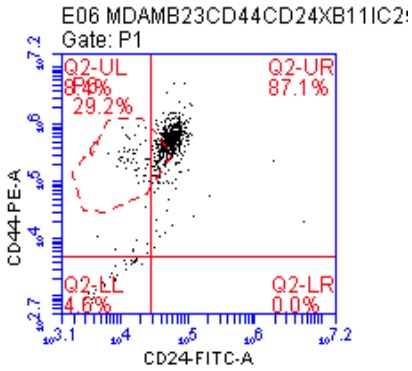


Figure 3B

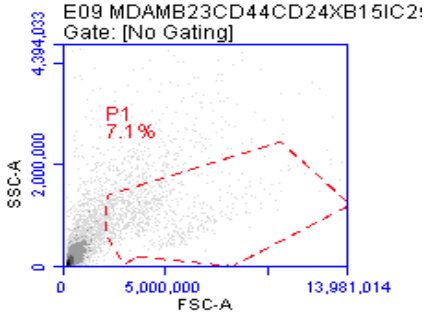


Figure 4A

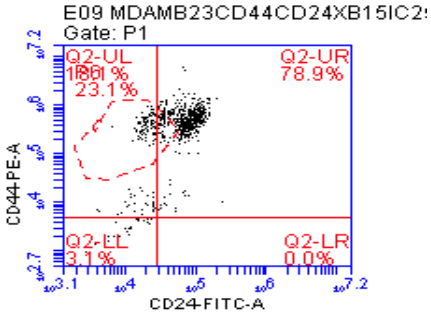


Figure 4B

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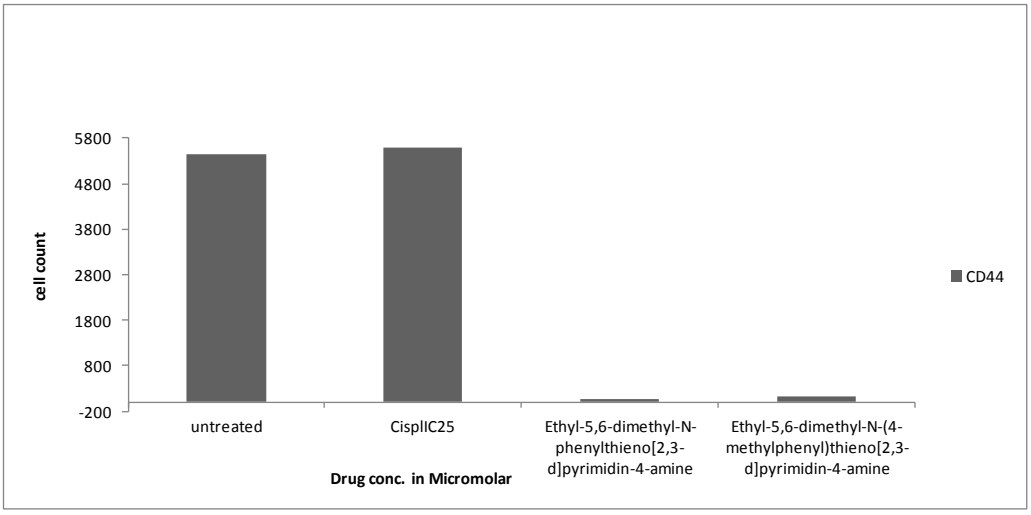


Figure 5

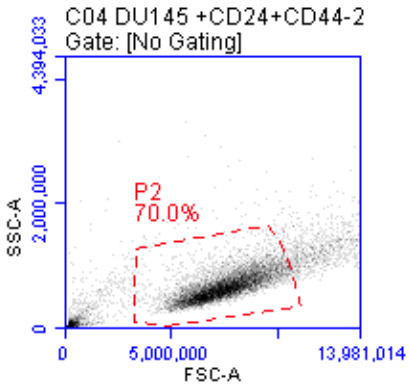


Figure 6A

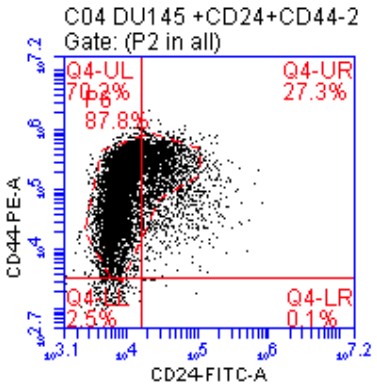


Figure 6B

**(GIRISH VIJAYANAND SHETH)**
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**KRISHNA & SAURASTRI ASSOCIATES**

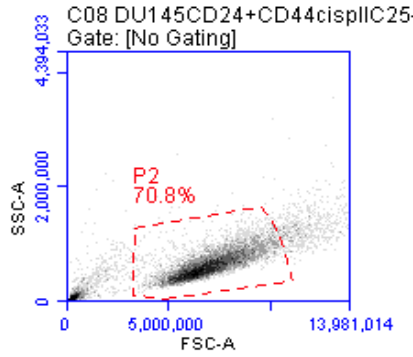


Figure 7A

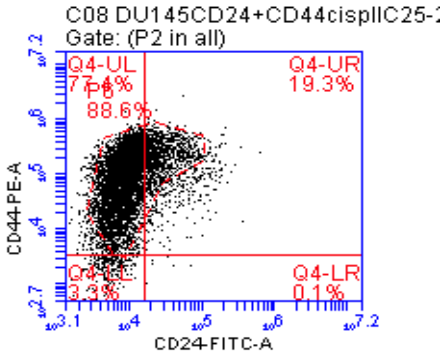


Figure 7B

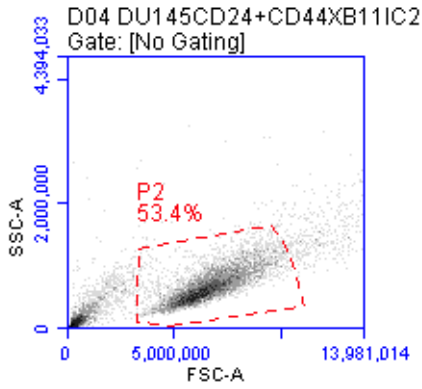


Figure 8A

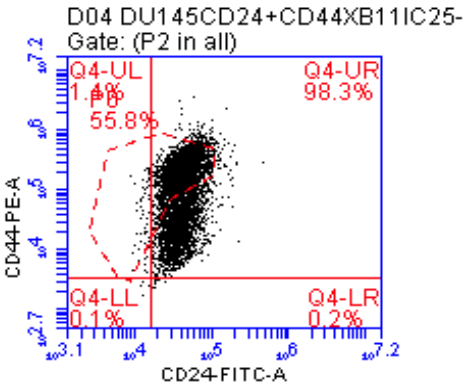


Figure 8B

**(GIRISH VIJAYANAND SHETH)**
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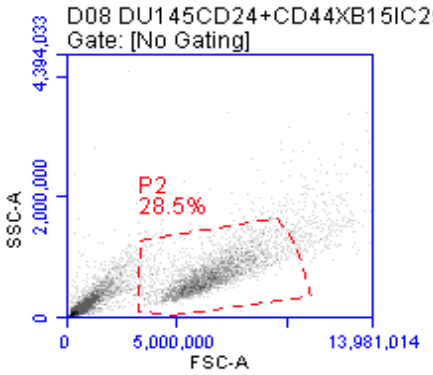



Figure 9A

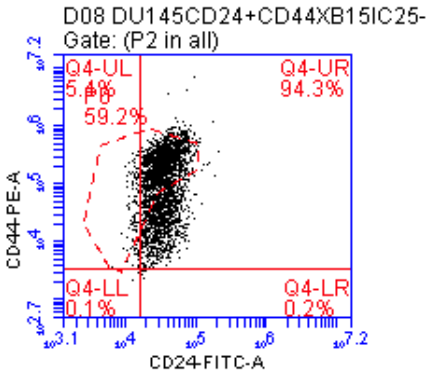



Figure 9B

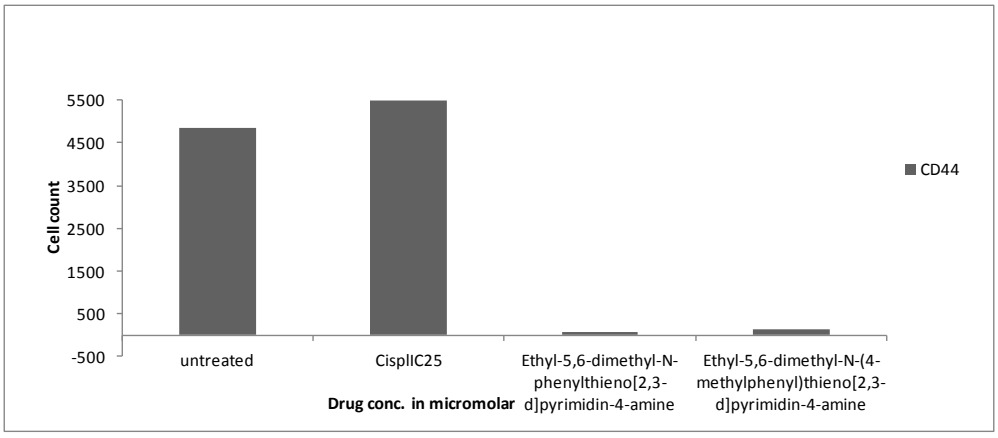



Figure 10

**(GIRISH VIJAYANAND SHETH)**
**Patent Agent No. IN/PA/1022**
**KRISHNA & SAURASTRI ASSOCIATES**

## FIELD OF THE INVENTION

The present invention relates to compounds for eradicating or inhibiting proliferation of cancer stem cells and uses thereof in eradicating or inhibiting proliferation of cancer stem cells. The present invention also relates to a method of eradicating or inhibiting proliferation of cancer stem cells.

## BACKGROUND OF THE INVENTION

Cancer is considered to be the most dreadful disease until today and recurrence or relapse of cancer still remains challenging with the most of the conventional cancer therapies. Radiotherapy is believed to reduce the rate of recurrence to some extent, but it also damages the normal rapidly dividing cells in the area being treated and has never been found to increase overall survival but rather increase mortality. It is also known that though many types of cancer can initially be targeted with chemotherapy using currently available drugs. However, often resistance to treatment with such a drug can occur and recurrence or relapse of cancer is common.

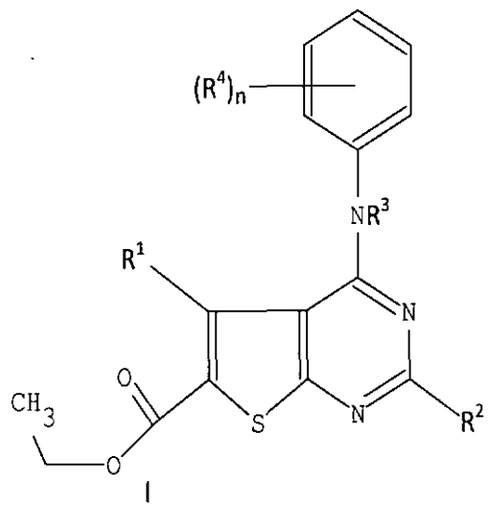
In recent years, a new model for genesis of cancer has gained wide acceptance, it is hypothesized that only a small fraction of cells of the entire tumor mass are responsible for the tumorigenic activities within the tumor. This small fraction of tumorigenic cells, according to the new model, are transformed cells with stem-cell-like qualities and are called "cancer stem cells" (CSCs). In 1990s in vivo presence of CSCs in acute myeloid leukemia (AML) was demonstrated. Later, these CSCs were shown to have the same cellular markers, $CD34^{+}/CD38^{-}$, as that of hematopoietic stem cells. Since then, researchers have conclusively found cancer stem cells in various types of tumors including those of the brain, breast, kidney, skin, prostate, and others.

Studies have demonstrated cancer stem cells to be fundamentally responsible for genesis of cancer, cancer metastasis, and cancer reoccurrence. Cancer stem cells in fact, appear to be resistant to radiotherapy and also refractory to chemotherapeutic and targeted drugs. Normal somatic stem cells appear to be resistant to chemotherapeutic agents as they have various pumps (such as MDR) that pump out drugs, DNA repair proteins and have a slow rate of cell turnover while chemotherapeutic agents target rapidly replicating cells. Cancer stem cells are also believed to have similar mechanisms that allow them to survive drug therapies and radiation treatment, as cancer stem cells are considered to be the mutated counterparts of normal stem cells. It has been postulated that conventional chemotherapies and radiotherapies kill differentiated or differentiating cells, while the population of cancer stem cells that give rise to the differentiated and differentiating cells, could survive and cause a relapse of the disease. Further, it may be likely that chemotherapeutic treatment leaves only chemotherapy-resistant cancer stem cells, and the ensuing recurrent tumor would also be resistant to chemotherapy.

Hence, there is an unmet need of an anti-cancer therapy that can selectively target cancer stem cells to minimize or prevent recurrence or relapse of refractory cancers and tumor metastasis. The same may help to improve survival and the quality of life of cancer patients.

**DESCRIPTION OF THE INVENTION**

The present invention relates to compounds having the general formula I or a pharmaceutically acceptable salts, solvtes, or hydrates thereof for eradicating or inhibiting proliferation of cancer stem cells, wherein:



I

each $R^1$, $R^2$ and $R^3$ is independently selected from halogen, C1-6haloalkyl, -CN, -$NO_2$, -R, -OR, -SR, -$N(R)_2$, -$N(R)NR_2$ , -$C(NR)NR_2$, -$N(R)C(O)R$, $C(O)RN(R)_2$, -$N(R)C(O)N(R)_2$, -$N(R)C(O)OR$, -$OC(O)N(R)$, -$N(R)SO_2R$, - $SO_2RN(R)_2$, $C(O)R$, -$C(O)OR$, -$OC(O)R$, -$C(O)OR$, -$S(O)R$, or -$SO_2R$;

each R is independently selected from H, or an optionally substituted group selected from C1-6 aliphatic, a 3-12 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-12 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

$R^4$ is independently selected from -R, -CN, halogen, C 1-6haloalkyl, -$NO_2$, -SR, -$N(R)_2$, -$N(R)NR_2$ , -$C(NR)NR_2$, -$N(R)C(O)R$, $C(O)RN(R)_2$, -$N(R)C(O)N(R)_2$, -

N(R)C(O)OR, -OC(O)N(R), -N(R)$SO_2$R, - $SO_2RN(R)_2$, C(O)R, -C(O)OR, - -C(O)OR, - S(O)R, or -$SO_2$R;

each R is independently selected from H, or an optionally substituted group selected from C1-6 aliphatic, a 3-12 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-12 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen or sulfur; and

Each n is independently 0-5. In certain embodiments, n is 1-4. In some embodiments, n is 1-3. In yet other embodiments n is 1-2. In some embodiments, n is 0, 1, 2, 3, 4 or 5.

Compounds of the present invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. Various terms and terminology used hereinabove in describing the compounds of the present invention and all technical and scientific terms used herein have the same or would mean or refer to standard definition or meaning or as used in a chemical or technical field or as known or commonly understood by one of ordinary skill in the art to which this invention belongs.

Compounds of the present invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any

given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. *Combinations of substituents envisioned by this invention are* preferably those that result in the formation of stable or chemically feasible compounds.

Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; –CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; –CN; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, SC(S)SR°; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; $SiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene)$O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene)$C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, $C_{1-6}$ aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulphur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^{\bullet}$, $-(haloR^{\bullet})$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; $-O(haloR^{\bullet})$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^{\bullet}$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^{\bullet}$, $-(CH_2)_{0-2}SR^{\bullet}$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, $-C(O)SR^{\bullet}$, $-(C_{1-4}$ straight or branched alkylene)$C(O)OR^{\bullet}$, or $-SSR^{\bullet}$ wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from $C_{1-4}$ aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

*Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following:* =O, =S, $=NNR^{*}_2$, $=NNHC(O)R^{*}$, $=NNHC(O)OR^{*}$, $=NNHS(O)_2R^{*}$, $=NR^{*}$, $=NOR^{*}$, $-O(C(R^{*}_2))_{2-3}O-$, or $-S(C(R^{*}_2))_{2-3}S-$, wherein each independent occurrence of $R^{*}$ is selected from hydrogen, $C_{1-6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^{*}_2)_{2-3}O-$, wherein each independent occurrence of $R^{*}$ is selected from hydrogen, $C_{1-6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of $R^*$ include halogen, $-R^\bullet$, -(halo$R^\bullet$), -OH, $-OR^\bullet$, -O(halo$R^\bullet$), -CN, -C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently $C_{1-4}$ aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, $C_{1-6}$ aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, -(halo$R^\bullet$), –OH, $-OR^\bullet$, -O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently $C_{1-4}$ aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity,

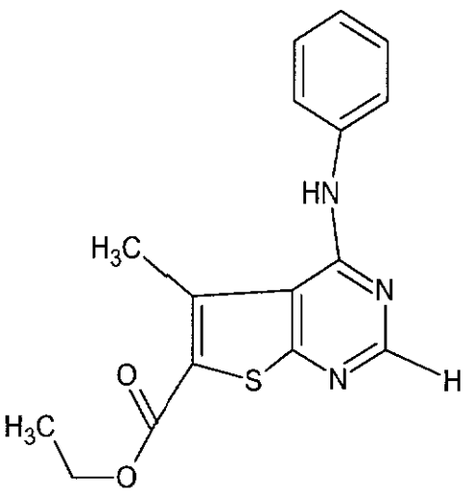
irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Exemplary pharmaceutically acceptable salts include *adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate,* bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

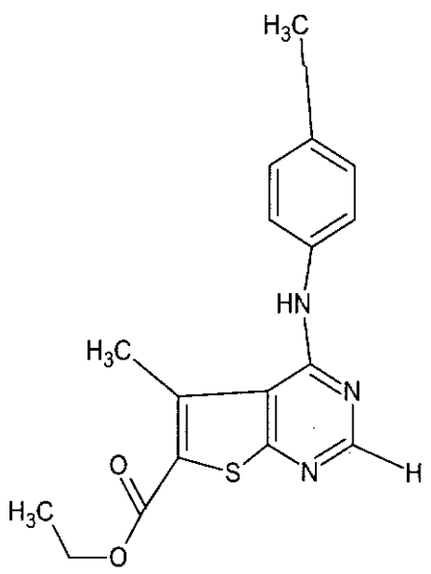
Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational))

forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a $^{13}C$- or $^{14}C$-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In certain embodiments, a warhead moiety, $R^1$, of a provided compound comprises one or more deuterium atoms.

In certain embodiments, the present invention provides a compound of anyone of the formulas II – III, or a pharmaceutically acceptable salts, solvtes, or hydrates thereof for eradicating or inhibiting proliferation of cancer stem cells:



II



III

According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable salt or derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

In certain embodiments, a composition of this invention comprises a compound having the general formula I, or a pharmaceutically acceptable salt or derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

In certain embodiments, a composition of this invention comprises a compound having anyone of the formulas II - III or a pharmaceutically acceptable salt or derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The preferable derivative may be a pharmaceutically acceptable ester, or salt of an ester.

The amount of compound in compositions of this invention may be such that it is effective for in eradicating or inhibiting proliferation of cancer stem cells, in a biological sample or in a subject in the need thereof. In certain embodiments, the amount of compound in compositions of this invention may be such that it is effective to measurably eradicate or inhibit proliferation of cancer stem cells, in a biological sample or in a subject in the need thereof. In certain embodiments, the composition may comprise between the biologically effective dose and the maximum tolerated dose of the compound of the invention or it's pharmaceutically acceptable salt, ester, or salt of an ester.

In certain embodiments, a composition of this invention may be formulated for administration to a subject in the need thereof. In some embodiments, preferably a composition of this invention may be formulated for oral administration to a patient. A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment. The term "subject in the need thereof" refers to a patient suffering from disease, disorder or condition associated with proliferation of cancer stem cells for example any type of cancer or relapse or recurrence of cancer.

The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated.

A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an active metabolite or residue thereof.

Compositions of the present invention may be formulated into a suitable dosage form to be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. Compositions

of the present invention may be formulated into dosage forms including liquid, solid, and semisolid dosage forms. The term "parenteral" as used herein includes subcutaneous, intravenous, intraperitoneal, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intravenously or intraperitoneally.

Sterile injectable forms of the compositions of this invention may be sterile injectable aqueous solution or oleaginous suspension in a non-toxic parenterally acceptable diluent or solvent, or suspension, suitable dispersing or wetting agents and suspending agents.

In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. Depot injectable formulations may also be prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions.

Solid dosage forms for oral administration include but are not limited to capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier, fillers or extenders, binders, humectants, disintegrating agents, solution retarding agents, absorption accelerators, wetting agents, absorbents, lubricants, buffering agents, and/or mixtures thereof.

Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and/or emulsifiers. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Additionally, the present invention contemplates the use of transdermal patches, which may have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a

rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment.

Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in suitable preservatives, absorption promoters to enhance bioavailability, and/or other conventional solubilizing or dispersing agents.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used. Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers.

Most preferably, pharmaceutically acceptable compositions of this invention may be formulated for oral administration. Such formulations may be administered with or without food.

The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the subject to be treated, the particular mode of administration.

Preferably, provided compositions should be formulated so that an effective dosage of the compound of the invention can be administered to a subject receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

In one embodiment compounds of the present invention having the general formula I or a pharmaceutically acceptable salt thereof or compositions thereof may be used for eradicating or inhibiting proliferation of cancer stem cells and thereby treating associated disorders or diseases or conditions. Thus, provided compounds may be useful for treating cancers, including, but not limited to hematological cancers and solid tumors.

In certain embodiments compounds of the present invention having the general formula II or III or a pharmaceutically acceptable salt thereof or compositions thereof may be used for eradicating or inhibiting proliferation of cancer stem cells and thereby treating associated disorders or diseases or conditions. Thus, provided compounds are useful for treating cancers, including, but not limited to hematological cancers and solid tumors.

As used herein, the terms "eradicating or inhibiting proliferation of cancer stem cells" refer to the eradication of cancer stem cells by inhibiting or suppressing growth, division, maturation or viability of cancer stem cells, and/or causing the death of cancer stem cells, individually or in aggregate with other cancer stem cells, by cytotoxicity or the induction of apoptosis. One of skill in the art will

appreciate that by definition, "eradicating or inhibiting proliferation of cancer stem cells" also encompasses the eradication or inhibition of the growth, division, maturation or viability of cancer cells, and/or causing the death of cancer cells, individually or in aggregate with other cancer cells, by cytotoxicity or the induction of apoptosis.

In another embodiment the present invention provides a method of eradicating or inhibiting proliferation of cancer stem cells by administering compounds having the general formula I or a pharmaceutically acceptable salt or derivative thereof or compositions comprising the same in subjects in the need thereof.

In certain embodiments the present invention provides a method of eradicating or inhibiting proliferation of cancer stem cells by administering the compound selected from II or III or a pharmaceutically acceptable salt thereof or compositions comprising the same in subjects in the need thereof.

The activity of a compound utilized in this invention for eradicating or inhibiting proliferation of cancer stem cells or other cancer cells, may be assayed *in vitro* or *in vivo*. An in vivo assessment of the eliminating or cytotoxic activity of the compounds of the invention may be made using an animal model of cancer, e.g., a rodent or primate model. Cell-based assays may be performed using, e.g., a cell line isolated from a tumor or blood-borne cancer. Cell-based assays for activity against a specific protein or nucleic acid component of a cancer cell line. e.g., an enzyme, structural protein, cell surface markers, DNA or RNA, or microarrays, may also be performed. Additionally, biochemical or mechanism-based assays, e.g., transcription assays using a purified protein, Northern blot, RT-PCR, etc., may be performed. *In vitro* assays include assays that determine cell morphology, viability, cell count, or growth inhibition, and/or the cytotoxicity, enzyme inhibitory activity, and/or the subsequent functional consequences of treatment of cancer cells with compounds of the invention.

Alternate *in vitro* assays quantitate the ability of the compounds of the present invention to bind to protein or nucleic acid molecules within the cell.

Examples of cancer cell lines that may be used for testing the inhibition or may be inhibited by the compounds and compositions described herein and against which the methods described herein may be useful include but are not limited to LNCaP, MDA MB 231, MCF7, DU145, PC3, T47D, HeLa, or other cell lines derived from tissues including, but not limited to, breast, prostate, fibroblast, cervical, kidney, colon, pancreas or lung.

According to one embodiment, the invention relates to a method of eradicating or inhibiting proliferation of cancer stem cells in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound. In certain embodiments, the invention relates to a method of killing cancer cells or cancer stem cells in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

The term *"compound of this invention" or "compound of the invention", as used* herein, includes the compounds having the general formula I, II or III, or a pharmaceutically acceptable salt or derivative thereof.

The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Eradicating cancer stem cells in a biological sample may be useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to biological assays, gene expression studies, and biological target identification.

In one more embodiment the present invention provides a method of treatment of disorders or diseases or conditions associated with cancer stem cells by administering compounds of this invention or compositions comprising the same in subjects in the needthereof. According to certain embodiments, the invention relates to a method of eradicating or inhibiting proliferation of cancer stem cells in a patient, leading to remission of the cancer, comprising the step of administering to said patient a compound of this invention or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by cancer stem cells, in a patient in need thereof, comprising the step of administering to said patient a compounds of this invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

In some embodiments the compounds and compositions of the present invention may be used in a method of treating a cancer or other proliferative disorder. In some embodiments the present invention provides a method of treating a cancer or other proliferative disorder, comprising administering a compound or composition of the present invention to a patient with a cancer or other proliferative disorder. In certain embodiments the compounds and compositions of the present invention may be used to treat a cancer in a mammal. In certain embodiments the mammal is a human patient. In certain embodiments the compounds and compositions of the present invention may be used to treat a cancer in a human patient, said cancer occurring in the patient's breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, or stomach.

Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. In some embodiments, a provided compound of this invention, or composition thereof, is administered in combination with one or more other chemotherapeutic agents. Such chemotherapeutic agents include, but are not limited to agents such as kinase inhibitors, alkylating agents, anti-metabolites, tubulin stabilizers, tubulin assembly inhibitors, DNA replication inhibitors, cell cycle inhibitors, topoisomerase inhibitors, cytotoxic antibiotics or nanoparticle or protein conjugates of any of the aforementioned agents.

In certain embodiments, a combination of 2 or more chemotherapeutic agents may be administered together with compounds of the invention. In certain embodiments, a combination of 3 or more chemotherapeutic agents may be administered with compounds of the invention. In some embodiments, the chemotherapeutic agents are selected from alkylating agents or anti-metabolites.

Other examples of agents compounds of this invention may also be combined with include, without limitation: vitamins and nutritional supplements, cancer vaccines, antisense agents, a monoclonal or polyclonal antibody, an siRNA therapeutic or other agents for treatments of conditions, disorders or diseases other than cancer.

Those additional agents may be administered separately from the compound of the invention-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another, normally within five hours from one another. The amount of both, the

compound of this invention and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent.

The amount of additional therapeutic agent present in the compositions of this invention may be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions may range from about 5% to 90% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

Resistance to chemotherapeutic drugs is a major factor limiting the efficacy of therapies against many cancers and other proliferative disorders. The rapid division rate of these cells allows for the development of mutations or upregulation of pumps such as MDR that afford resistance to current first line chemotherapy drugs. The problem of relapse of cancers in a more drug-resistant form is a critical hurdle faced in drug development of new chemotherapeutic drugs to treat cancer patients.

The present invention can address this problem by providing the compounds of this invention and compositions thereof for eradicating or inhibiting proliferation

of cancer stem cells and thereby treating associated disorders or diseases or conditions in particular for avoiding or minimizing problem of relapse of cancers.

The compounds of the invention may be prepared according to the methods of synthesis that may be known to one of ordinary skilled in the art or can be specifically designed to synthesize compounds of the invention or their subclasses or species of each of these compounds, as described herein.

The foregoing description of the invention has been set merely to illustrate the invention and is not intended to be limiting. Since modifications of the disclosed embodiments incorporating the spirit and substance of the invention may occur to person skilled in the art, the invention should be construed to include everything within the scope of the disclosure.

Dated this 11th day of March, 2014

FOR GODAVARI BIOREFINERIES LIMITED
By their Agent

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