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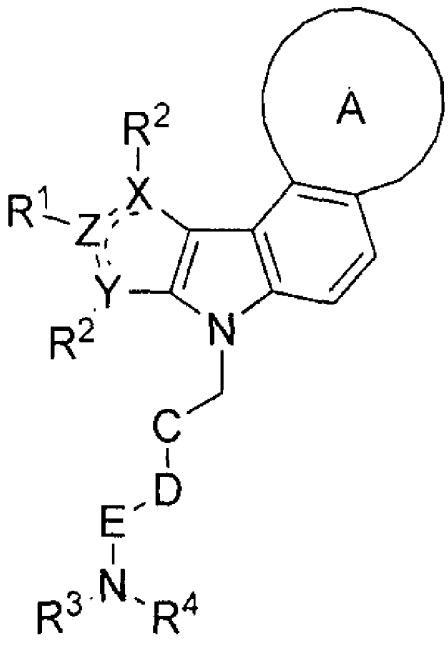

(I)

(57) Abstract: The invention relates to fused indole compounds of formula (I) that can be used for treating microbial infections, in particular, fungal infections, and selectively kill cancer cells.

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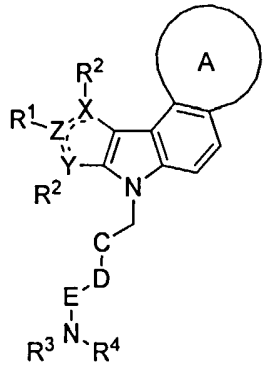
FUSED INDOLE COMPOUNDS AND METHODS OF USING SAME

DETAILED DESCRIPTION OF THE DISCLOSURE

[0001] In an aspect, the present disclosure provides fused indole compounds and fused indole-like compounds. The compounds can be used to treat microbial infections (e.g., fungal infections) and selectively kill cancer cells.

[0002] In an aspect, the present disclosure provides heterocyclic compounds having the following structure (I):



(I),

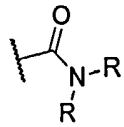
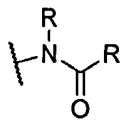
where R^1 is a five or six membered unsubstituted or substituted carbocycle or heterocycle, a ketone group, an amide group, an ester group or a cyano group, or R^1 and X together with the carbon to which they are attached form a five to seven membered carbocyclic or heterocyclic ring; R^2 at each occurrence is independently absent, a hydrogen atom, a fluorine atom, a chlorine atom, a hydroxy group, a cyano group, a substituted or unsubstituted C_1-C_3 alkyl group, or a substituted or unsubstituted C_1-C_3 alkoxy group; R^3 is selected from the group consisting of a hydrogen atom, a substituted or unsubstituted C_1-C_6 alkyl group, cycloalkyl group, heterocycloalkyl group, or taken together with R^4 and the nitrogen atom to which they are attached form a four to eight membered substituted or unsubstituted heterocyclic ring; R^4 is selected from the group consisting of a hydrogen atom, a substituted or unsubstituted C_1-C_6 alkyl group, cycloalkyl group, and heterocycloalkyl group; Z is a carbon atom or nitrogen atom; X and Y are independently a carbon, nitrogen, oxygen or sulfur atom and when Z is a carbon atom there is a double bond between X and Z or Y and Z; C is absent, C=O, or $CH(R^5)$; D is absent or CH_2; E is absent, CH_2, or $CH(C_1$-C_3 alkyl); optionally, E and R^4 taken together with the nitrogen to which they are attached form a four to seven membered heterocyclic ring substituted with one

to twelve R^5's; R^5 at each occurrence is independently selected from the group consisting of a hydrogen atom, a fluorine atom, a hydroxyl group, a cyano group, a substituted or unsubstituted C_1-C_3 alkyl group, and a C_1-C_3 alkoxy group; optionally, C and R^4 taken together with the atoms between them form a four to seven membered heterocyclic ring substituted with one to twelve R^5's, and the A ring is a substituted or unsubstituted 5 to 7 membered carbocyclic or heterocyclic ring.

[0003] As used herein, the term "alkyl group," unless otherwise stated, refers to branched or unbranched hydrocarbons. Examples of such alkyl groups include methyl groups, ethyl groups, propyl groups, butyl groups, isopropyl groups, tert-butyl groups, and the like. For example, the alkyl group can be a C_1 to C_6 alkyl group including all integer numbers of carbons and ranges of numbers of carbons therebetween. Alkyl groups can be substituted with various other functional groups. For example, the alkyl groups can be substituted with groups such as, for example, amines (acyclic and cyclic), alcohol groups, ether groups, and halogen atoms.

[0004] As used herein, the term "halogen atom" refers to a fluorine, chlorine, bromine, or iodine atom.

[0005] As used herein, the term "nitrile" or "cyano group" refers to the following structure:  .

[0006] As used herein, the term "amide," unless otherwise stated, refers to the following structure:  or  where each R independently is a hydrogen atom or substituted or unsubstituted C_1 to C_6 alkyl group, including all integer numbers of carbons and ranges of numbers of carbons therebetween

[0007] As used herein, the term "alkoxy group," unless otherwise stated, refers to the following structure:  , where R is a C_1 to C_3 alkyl group, unless otherwise stated, including all integer numbers of carbons and ranges of numbers of carbons therebetween. The alkoxy groups can be substituted with various other functional groups. For example, the alkyl groups can be unsubstituted or substituted with groups such as, for example, halogen atoms.

[0008] As used herein, the term "cycloalkyl group, " unless otherwise stated, refers to a to a saturated or partially unsaturated carbocyclic group (not aromatic) of from 3 carbons to 11 carbons having a single cyclic ring or multiple condensed rings. For example, the cycloalkyl groups can be cyclopropane, cyclobutane, cyclopentane, cyclohexane, cyclohexene, cycloheptane, cycloheptene, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.3.0]octane, bicyclo[4.4.0]octane, and the like. Cycloalkyl also includes carbocyclic groups to which is fused an aryl or heteroaryl ring, for example indane and tetrahydronaphthalene. The cycloalkyl groups can be unsubstituted or substituted with groups such as, for example, alkyl groups, carbonyl groups, ether groups, or halogen groups.

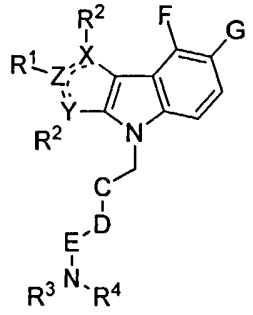
[0009] As used herein, the term "heterocycloalkyl group," unless otherwise stated, refers to a saturated or partially unsaturated group having a single cyclic ring or multiple condensed rings having from 2 to 11 carbon atoms and 1 to 5 heteroatoms, selected from nitrogen, oxygen, sulfur, and combinations thereof. For example, the heterocycloalkyl groups can be, for example, dihydrofuran, tetrahydrofuran, pyrrolidine, dihydropyran, tetrahydropyran, 1,3 dioxane, 1,4-dioxane, dihydropyridinone, piperidine, piperazine, morpholine, thiomorpholine, urazole, 2-aza-bicyclo[2.2.2]oct-5-ane-3-one, and the like. Heteroccycloalkyl also includes heterocyclic groups to which is fused an aryl or heteroaryl ring, for example tetrahydroisoquinoline or indoline. The heterocycloalkyl groups can be unsubstituted or substituted with groups such as, for example, alkyl groups, carbonyl groups, or halogen atoms.

[0010] As used herein, the term "heterocycle" or "heterocyclic ring," unless otherwise stated, refers to a cyclic compound having a ring where at least one or more of the atoms forming the ring is a heteroatom (e.g., oxygen, nitrogen, sulfur, etc.). The heterocyclic ring can be aromatic or nonaromatic, and include compounds that are saturated, partially unsaturated, and fully unsaturated. Examples of such groups include azetidine, pyrrolidine, piperdine, azepane, azocane, dihydropyrdinone, dihydropyridazinone, dihydrooxepinone, dihydroazepinone, pyrazolone, pyrrolone, isoxazolone, pyranone, dihydrodiazepineone, furan, thiophene, oxazole, isoxazole, thiazole, oxadiazole, thiadiazole, triazole, tetrazole, oxazoline, lactam, lactone, dihydrofuran, tetrahydrofuran, furanone, oxazolone, pyridinone, pyrimidinone, dihydropyridazine, pyranone, oxazinone, and the like. For example, the heterocyclic ring can be a 4, 5, 6, 7, or 8 membered ring containing a number of carbon atoms ranging between 1 and 7

and a number of heteroatoms ranging between 1 and 7. The heterocyclic ring can be unsubstituted or substituted with groups such as, for example, alkyl groups, carbonyl groups, or halogen atoms.

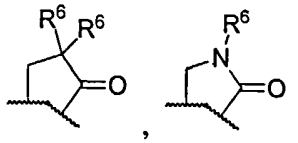
[0011] As used herein, the term "carbocyclic ring," unless otherwise stated, refers to a cyclic compound having a ring where all of the atoms forming the ring are carbon atoms. The carbocyclic ring can be aromatic or nonaromatic, and include compounds that are saturated and partially unsaturated, and fully unsaturated. Examples of such groups include cyclopentane, cyclopentene, cyclohexane, cyclohexene, cyclohexanone, cyclohexenone, cyclopentanone, cyclopentanol, cycloheptenone, indane, indanone, phenyl, naphthyl and the like. For example, the carbocyclic ring is a C_5 to C_7 carbocyclic ring, including all integer numbers of carbons and ranges of numbers of carbons therebetween. The carbocyclic ring can be unsubstituted or substituted with groups such as, for example, alkyl groups, carbonyl groups, or halogen atoms.

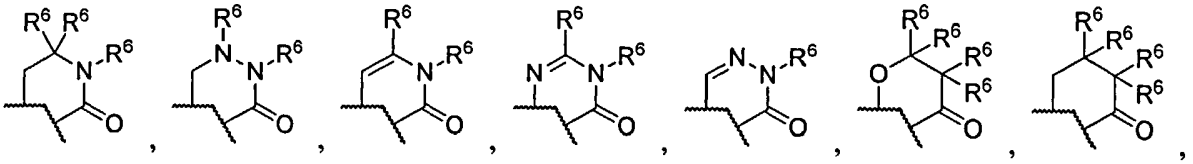
[0012] In an embodiment, the disclosure provides heterocyclic compounds having the following structure (II):

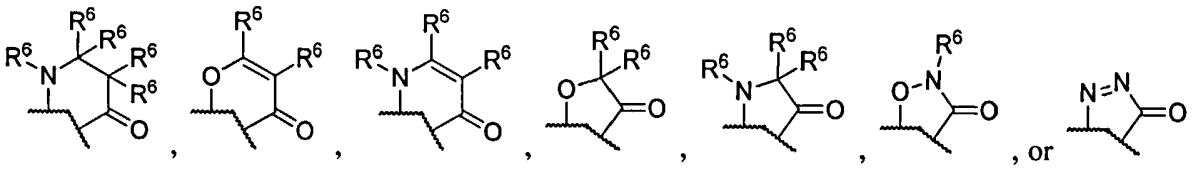


(II),

where F and G are replaced by the atoms of the following structures:

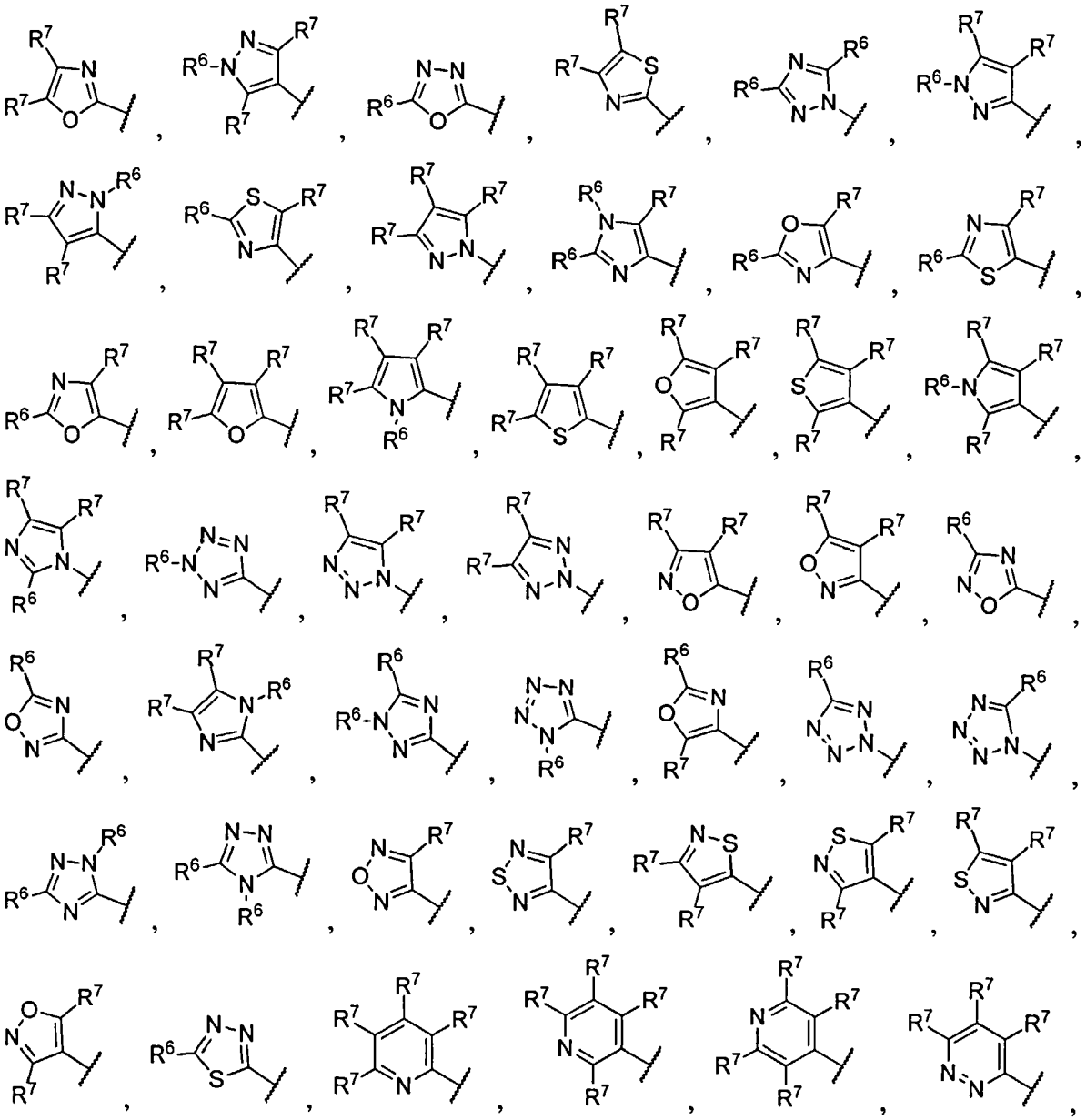


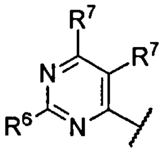
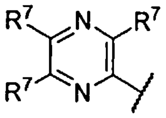
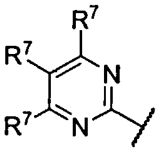
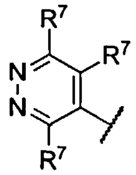
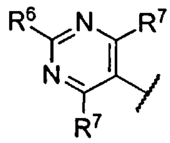
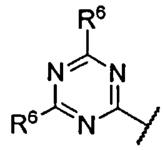
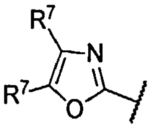
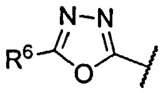
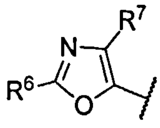
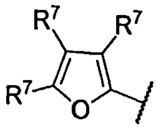
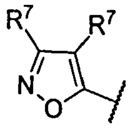
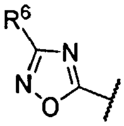


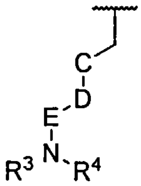
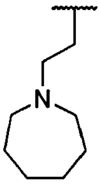
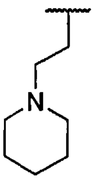
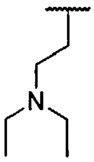
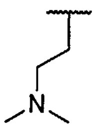
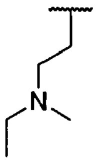
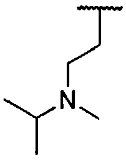
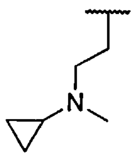
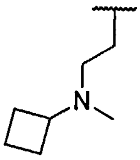
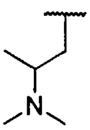
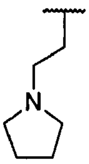
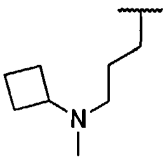
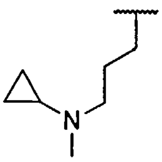
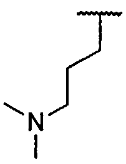
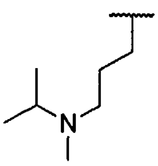
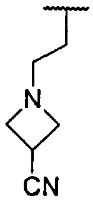
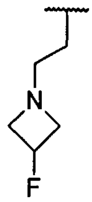
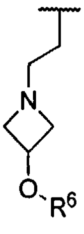
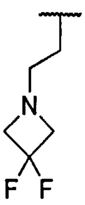
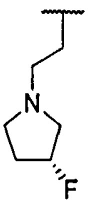
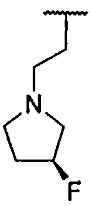
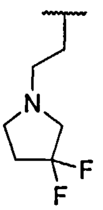
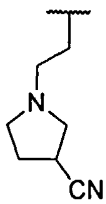
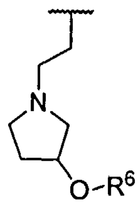
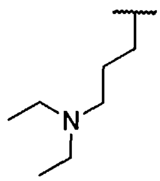


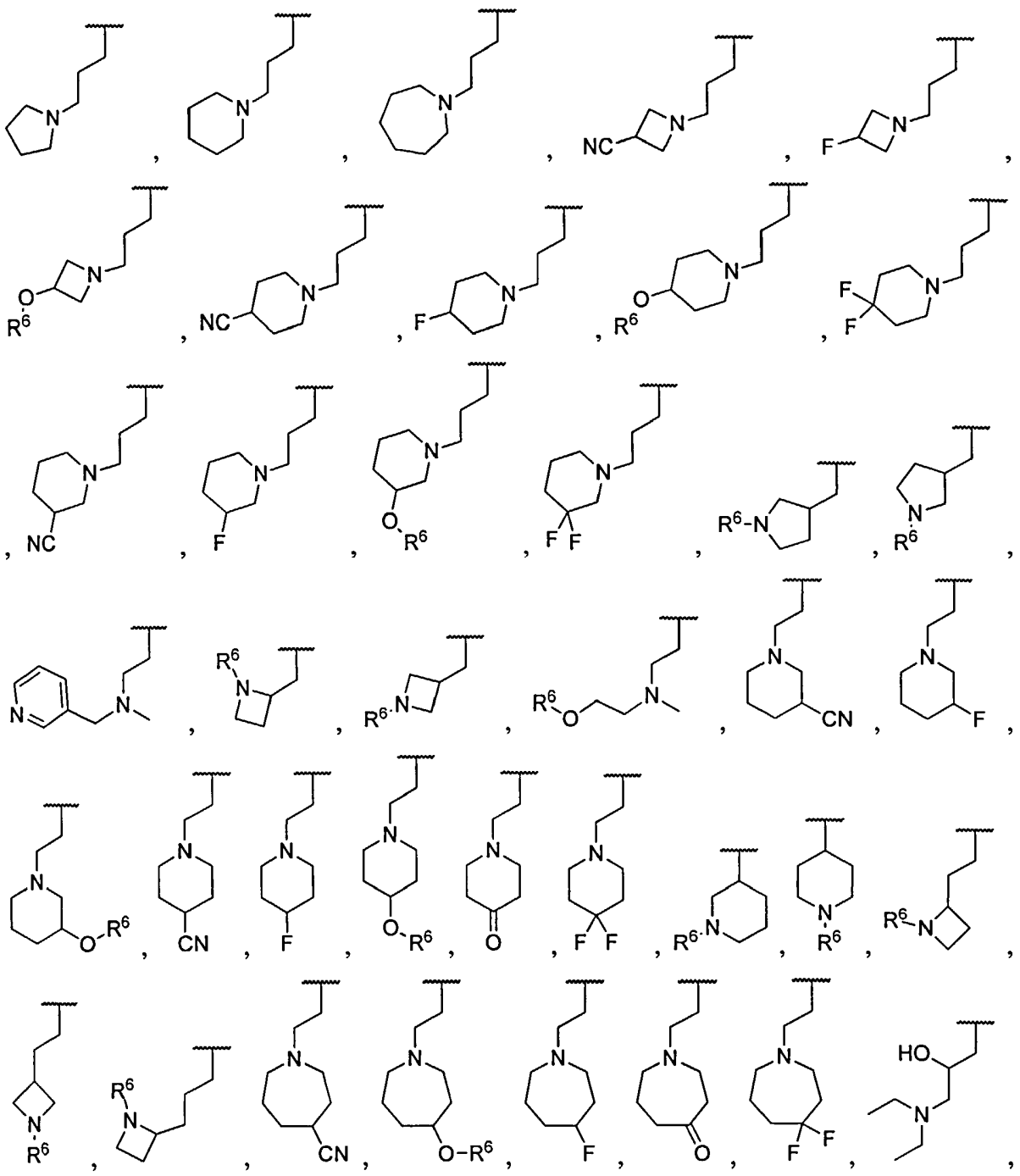
to form a ring; R^6 is hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group; and R^1, R^2, R^3, R^4, X, Y, Z, C, D, and E are as defined herein.

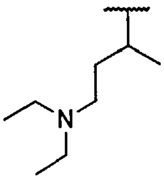
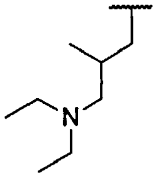
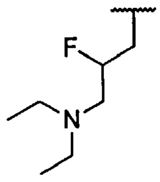
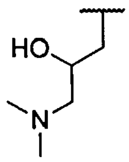
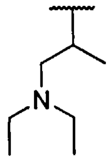
[0013] In an embodiment, R^1 is selected from one of the following structures:

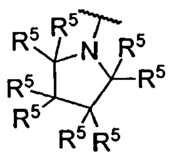
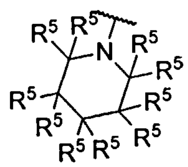
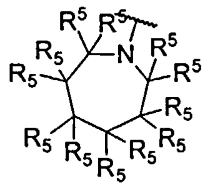


 ,  ,  ,  ,  , and  , where R^6 is a hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group, and R^7 is a hydrogen atom, a fluorine atom, a chlorine atom, a cyano group, a substituted or unsubstituted C_1-C_3 alkyl group or C_1-C_3 alkoxy group. In certain embodiments, R^1 is selected from one of the following structures:  ,  ,  ,  ,  , or  , where R^6 and R^7 are as defined herein.

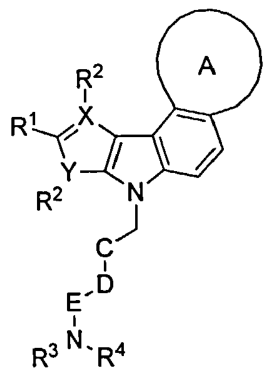
[0014] In an embodiment, the structure  is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,



 ,  ,  ,  , and  , where R^6 is as defined herein.

[0015] In an embodiment, R^3 is $-CH(CH_3)_2$, $-CH_2CH_3$, cyclopropyl, or cyclobutyl; R^4 is -a hydrogen atom, $-CH_3$, $-CH_2CH_3$ or taken together with R^3 and the nitrogen to which they are attached form the following structures:  ,  , or  , where R^5 is as defined herein.

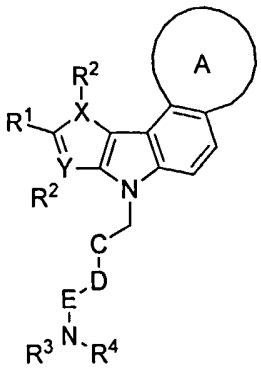
[0016] In an embodiment, the disclosure provides heterocyclic compounds having the following structure (III):



(III),

where X is a carbon or nitrogen atom and R^1, R^2, R^3, R^4, Y, C, D, and E are as defined herein.

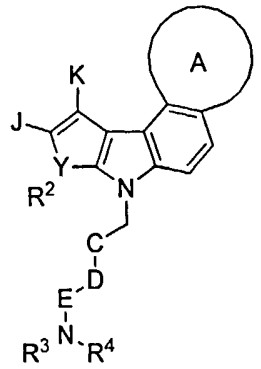
[0017] In an embodiment, the disclosure provides heterocyclic compounds having the following structure (IV):



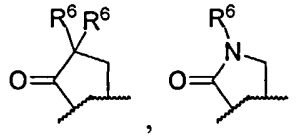
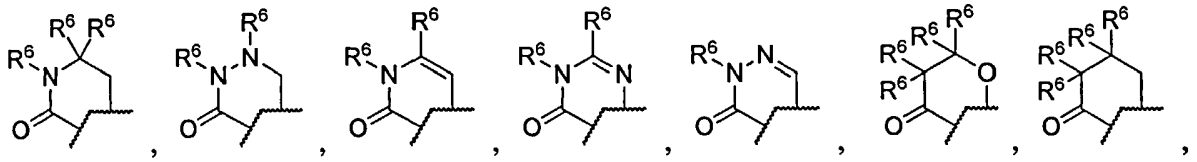
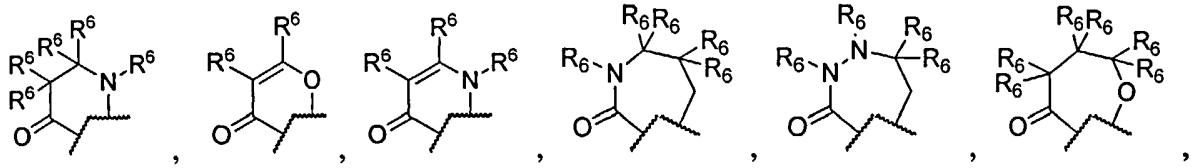
(IV),

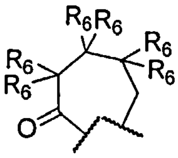
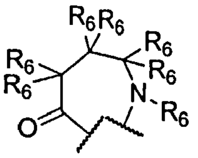
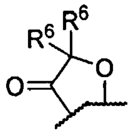
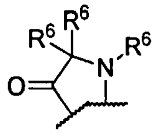
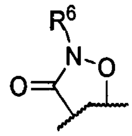
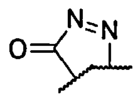
where Y is a carbon or nitrogen atom and R^1, R^2, R^3, R^4, X, C, D, and E are as defined herein.

[0018] In an embodiment, the disclosure provides heterocyclic compounds having the following structure (V):

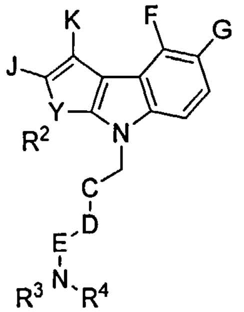


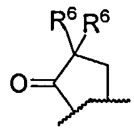
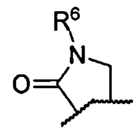
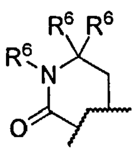
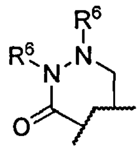
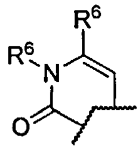
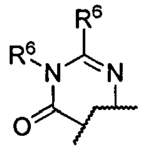
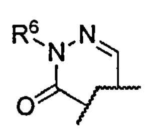
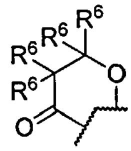
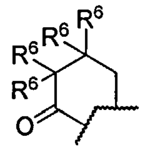
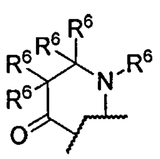
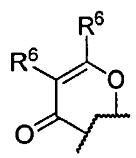
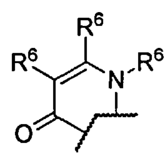
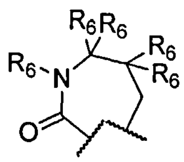
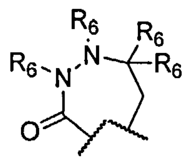
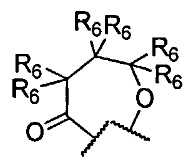
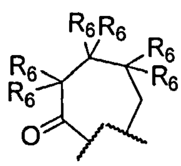
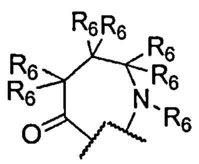
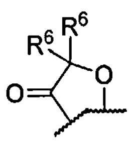
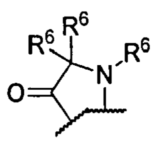
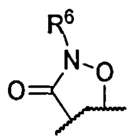
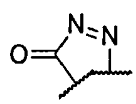
(V),

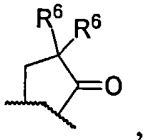
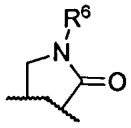
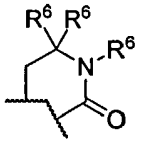
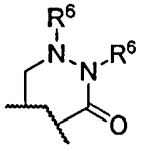
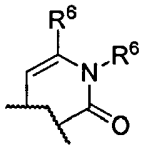
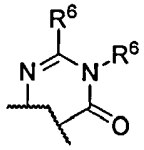
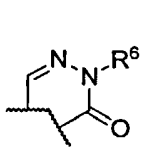
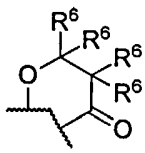
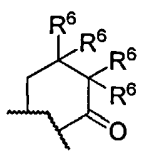
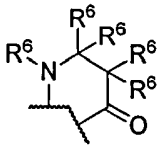
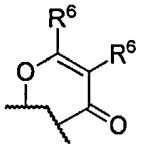
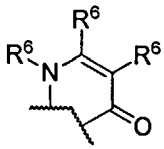
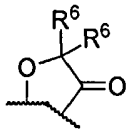
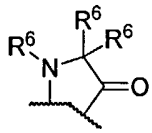
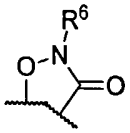
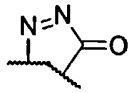
where J and K are replaced by the atoms of the following structures:  ,  ,  ,

 ,  ,  ,  ,  , or  to form a ring; R^6 is a hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group, and R^2, R^3, R^4, Y, C, D, E, and ring A are as defined herein.

[0019] In an embodiment, the disclosure provides heterocyclic compounds having the following structure (VI):

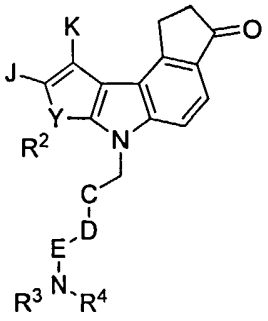

(VI),

where J and K are replaced by the atoms of the following structures:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  to form a

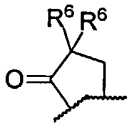
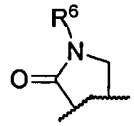
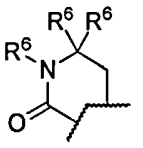
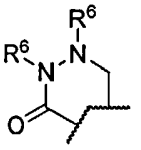
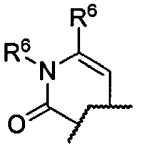
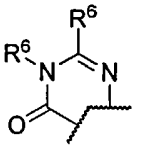
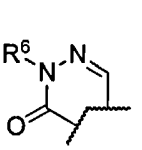
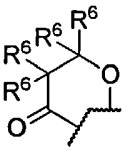
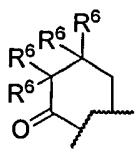
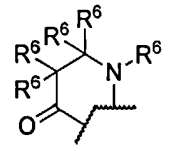
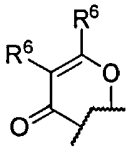
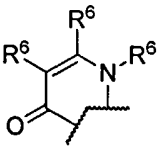
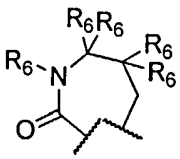
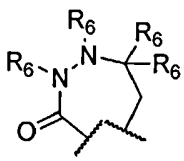
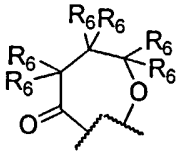
ring and F and G are replaced by the atoms of the following structures:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or 

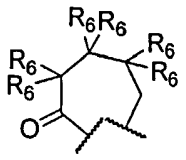
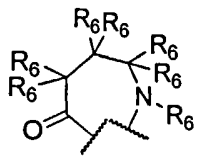
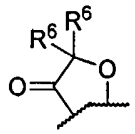
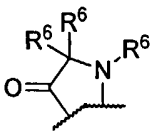
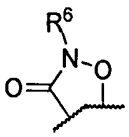
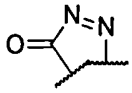
to form a ring; R^6 is a hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group; and R^2, R^3, R^4, Y, C, D, and E are as defined herein.

[0020] In an embodiment, the disclosure provides heterocyclic compounds having the following structure (VII):

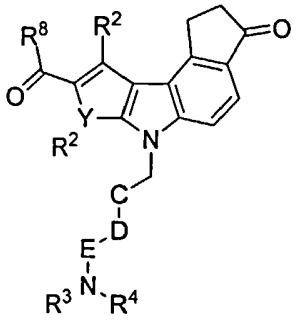


(VII),

where J and K are replaced by the atoms of the following structures:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 

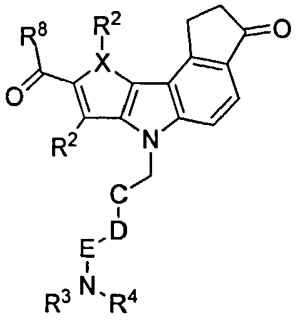






to form a ring; R^6 is a hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group, and R^2, R^3, R^4, Y, C, D, E, are as defined herein.

[0021] In an embodiment, the disclosure provides heterocyclic compounds having the following structure (VIII):


(VIII),

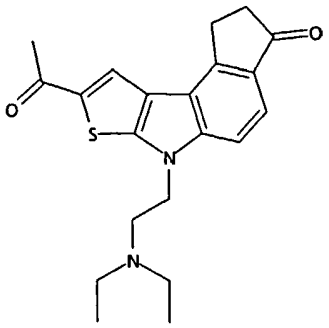
where R^8 is a substituted or unsubstituted C_1-C_3 alkyl group and R^2, R^3, R^4, Y, C, D, and E are as defined herein.

[0022] In an embodiment, the disclosure provides heterocyclic compounds having the following structure (IX):


(IX),

where R^2, R^3, R^4, R^8, X, C, D, and E are as defined herein.

[0023] In various embodiments, the compound of the present disclosure is selected from the following structures:



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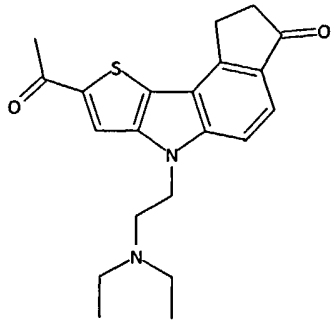

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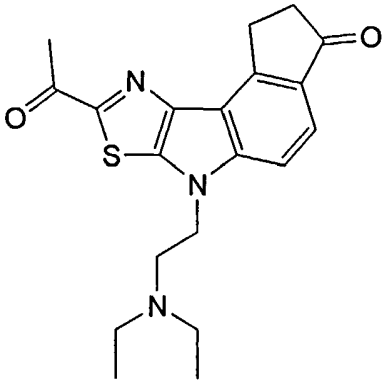

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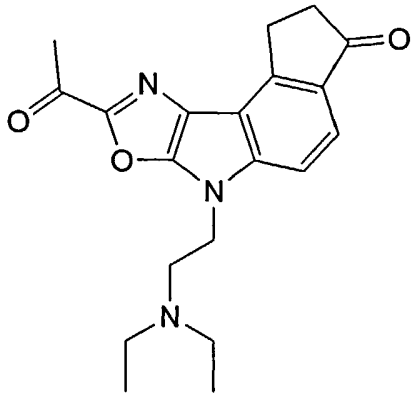

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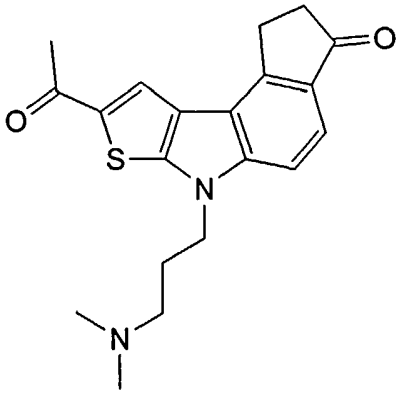

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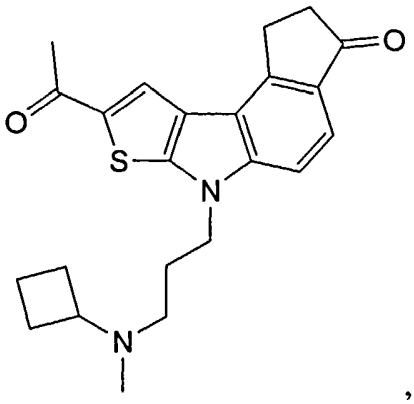

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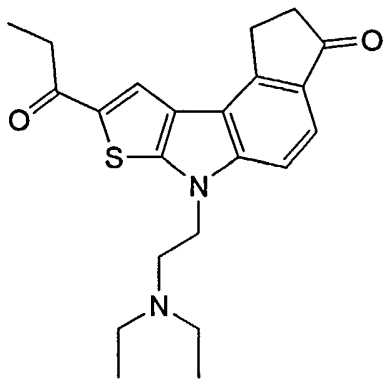
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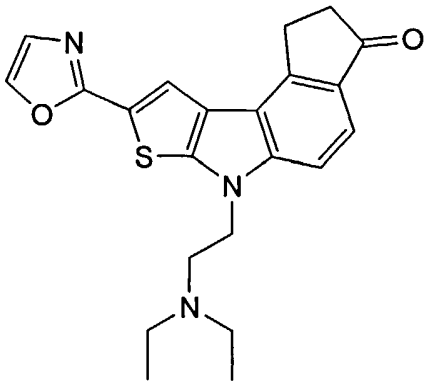
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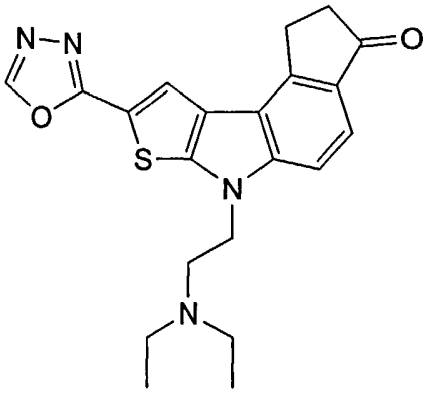
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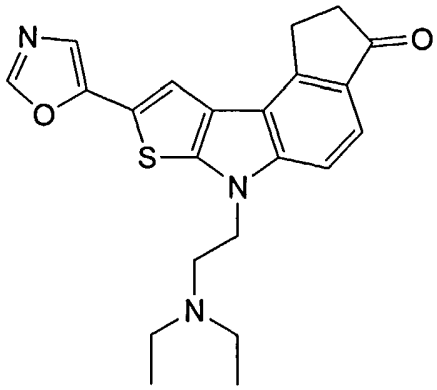
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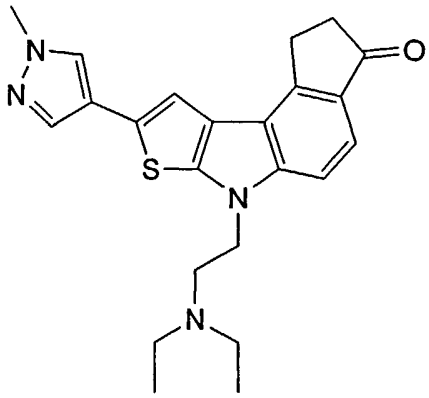
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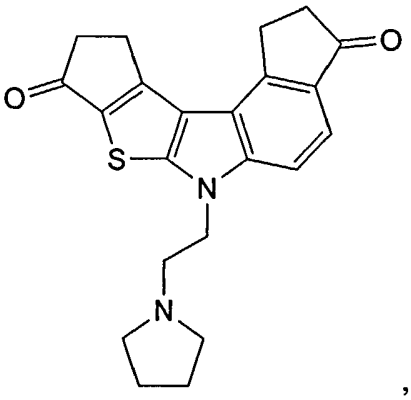
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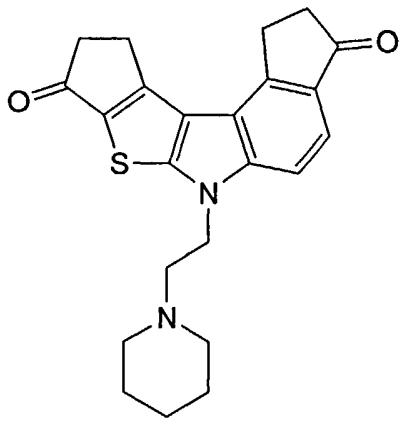
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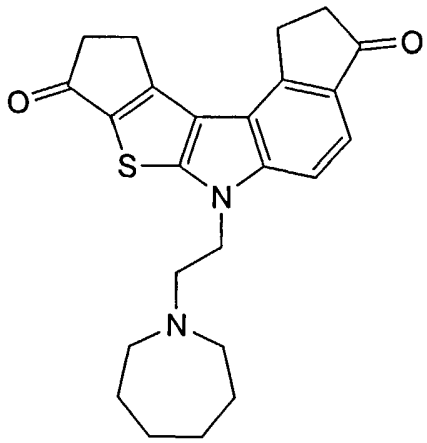
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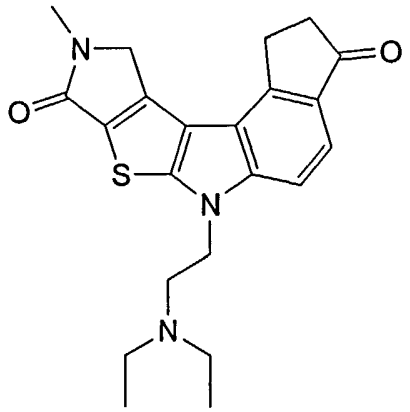
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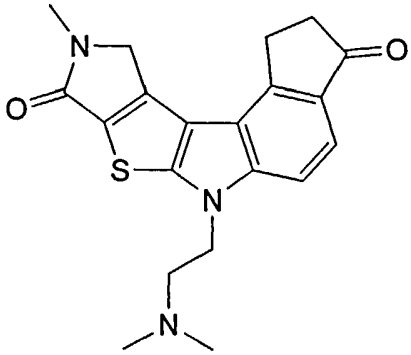
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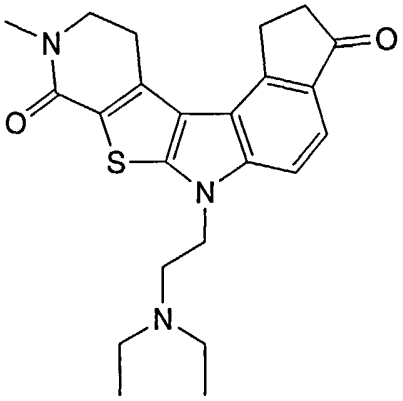
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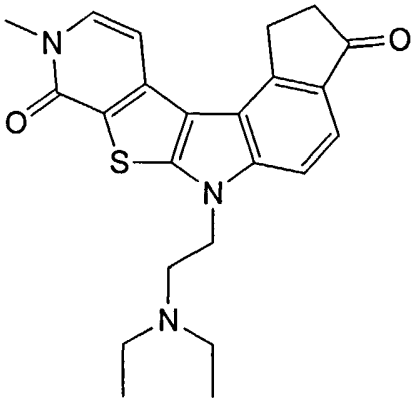
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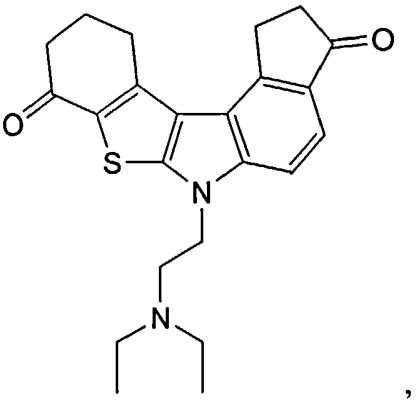
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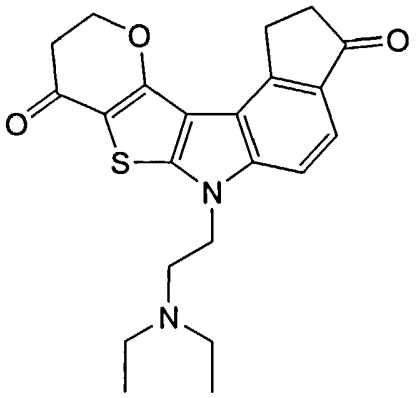
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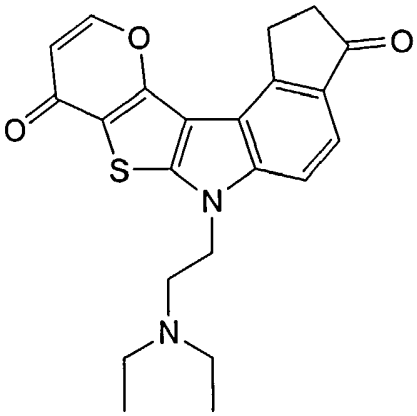
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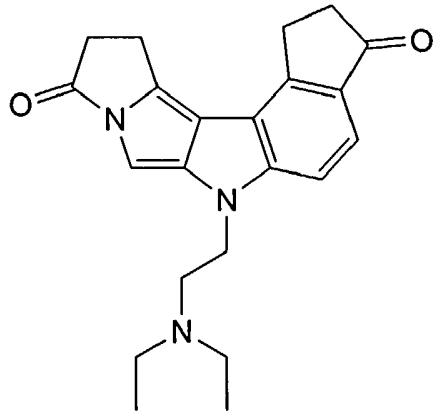
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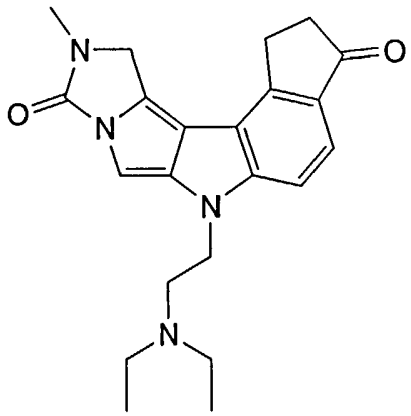
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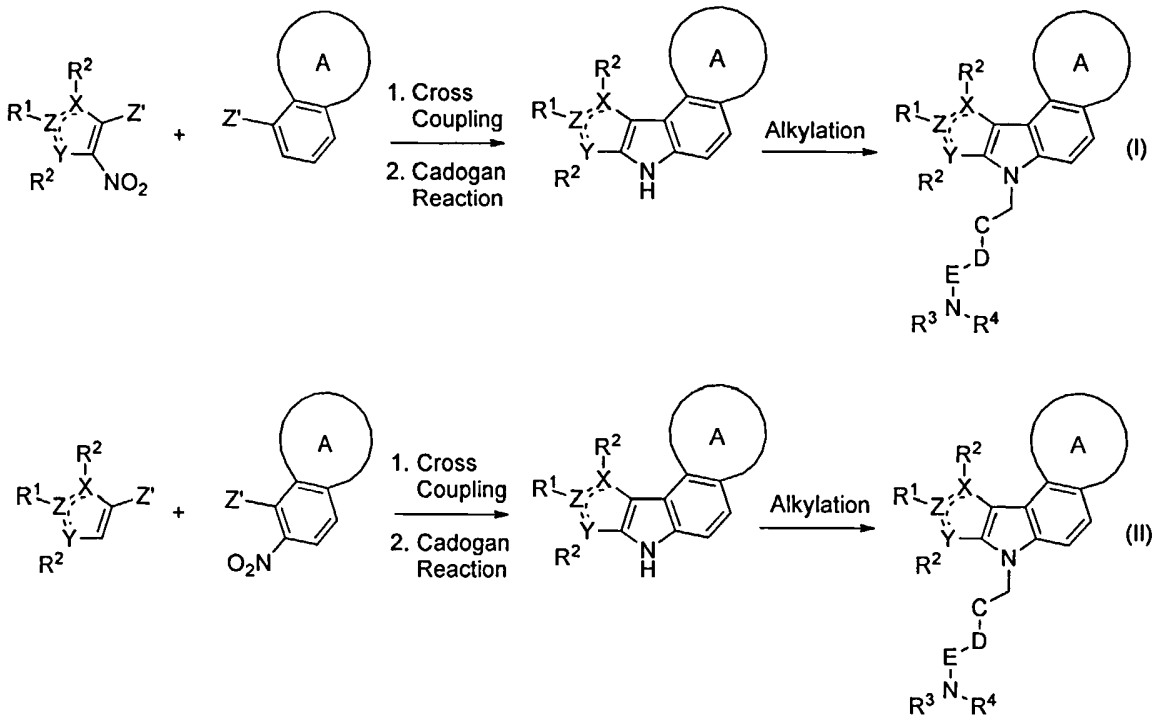
[0024] In an aspect, the disclosure provides a method of treating in an individual diagnosed with or suspected of having a microbial, protozoan, or viral infection comprising administering to the individual a therapeutically effective amount of a compound as described herein.

[0025] Non-limiting examples of general methods for the preparation of the compounds of the present disclosure are provided in the following schemes:



where each Z', independently is a halogen, a trifluoromethanesulfonate, a trialkyltin, a boronic acid, or boronic ester as long as one coupling partner Z' is a halogen and the other coupling partner Z' is not a halogen. Ring A, R^1, R^2, R^3, R^4, X, Y, Z, C, D, and E are as defined herein. The determination of suitable reaction conditions for cross coupling, the Cadogan reaction, alkylation, and other functional group transformations (e.g., metal complex, base, reagents, solvent, reaction time, and reaction temperature) are within the purview of one having skill in the art. In certain circumstances, it may be necessary to form the heterocycles of the present disclosure by well-established condensation reactions. To assemble the coupling partners or further functionalize the aromatic components of the present disclosure it may be necessary to use additional cross-coupling reactions, electrophilic aromatic substitution reactions (e.g., Friedel-Crafts alkylation/acylation), nucleophilic aromatic substitution reactions, anion chemistry, and the like. Alternatively, the ring structure may be assembled by other ring forming reactions such the Fischer indole synthesis and the like. Other oxidation state and functional groups manipulations are within the purview of one having skill in the art.

[0026] More specific, non-limiting, examples of methods to synthesize compounds of the present are illustrated in the examples that follow.

[0027] In an aspect, the present disclosure provides a composition comprising at least one compound of the disclosure. Compositions comprising at least one compound of the disclosure include, for example, pharmaceutical preparations.

[0028] The present disclosure includes all possible stereoisomers and geometric isomers of a compound having the structure (I) to (IX). The present disclosure includes both racemic compounds and optically active isomers. When a compound having the structure (I) to (IX) is desired as a single enantiomer, it can be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or use of a chiral auxiliary reagent, for example, see Z. Ma et al., Tetrahedron: Asymmetry, 8(6), pages 883-888 (1997). Resolution of the final product, an intermediate, or a starting material can be achieved by any suitable method known in the art. Additionally, in situations where tautomers of a compound having the structure (I) to (IX) are possible, the present disclosure is intended to include all tautomeric forms of the compounds.

[0029] Prodrugs of a compound having the structure (I) to (IX) also can be used as the compound in a method of the present disclosure. It is well established that a prodrug approach, wherein a compound is derivatized into a form suitable for formulation and/or administration, then released as a drug in vivo, has been successfully employed to transiently (e.g., bioreversibly) alter the physicochemical properties of the compound (see, H. Bundgaard, Ed., "Design of Prodrugs," Elsevier, Amsterdam, (1985); R.B. Silverman, "The Organic Chemistry of Drug Design and Drug Action," Academic Press, San Diego, chapter 8, (1992); K.M. Hillgren et al., Med. Res. Rev., 15, 83 (1995)).

[0030] Compounds of the present disclosure can contain one or more functional groups. The functional groups, if desired or necessary, can be modified to provide a prodrug. Suitable prodrugs include, for example, acid derivatives, such as amides and esters. It also is appreciated by those skilled in the art that N-oxides can be used as a prodrug.

[0031] Compounds of the disclosure can exist as salts. Pharmaceutically acceptable salts of the compounds of the disclosure generally are preferred in the methods of the disclosure. As used herein, the term "pharmaceutically acceptable salts" refers to salts or zwitterionic forms of a

compound having the structure (I) to (IX). Salts of compounds having the structure (I) to (IX) can be prepared during the final isolation and purification of the compounds or separately by reacting the compound with an acid having a suitable cation. The pharmaceutically acceptable salts of a compound having the structure (I) to (IX) are acid addition salts formed with pharmaceutically acceptable acids. Examples of acids which can be employed to form pharmaceutically acceptable salts include inorganic acids such as nitric, boric, hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Nonlimiting examples of salts of compounds of the disclosure include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphsphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3- phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, paratoluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulphonate, and p-toluenesulfonate salts. In addition, available amino groups present in the compounds of the disclosure can be quatemized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. In light of the foregoing, any reference to compounds of the present disclosure appearing herein is intended to include a compound having the structure (I) to (IX) as well as pharmaceutically acceptable salts, hydrates, or prodrugs thereof.

[0032] A compound having the structure (I) to (IX) also can be conjugated or linked to auxiliary moieties that promote a beneficial property of the compound in a method of therapeutic use. Such conjugates can enhance delivery of the compounds to a particular anatomical site or region of interest (e.g., a tumor), enable sustained therapeutic concentrations of the compounds in target cells, alter pharmacokinetic and pharmacodynamics properties of the compounds, and/or improve the therapeutic index or safety profile of the compounds. Suitable auxiliary moieties include, for example, amino acids, oligopeptides, or polypeptides, e.g., antibodies such

as monoclonal antibodies and other engineered antibodies; and natural or synthetic ligands to receptors in target cells or tissues. Other suitable auxiliaries include fatty acid or lipid moieties that promote biodistribution and/or uptake of the compound by target cells (see, e.g., Bradley et al., Clin. Cancer Res. (2001) 7:3229).

[0033] In an aspect, the present disclosure provides a composition comprising at least one compound of the disclosure. Compositions comprising at least one compound of the disclosure include, for example, pharmaceutical preparations.

[0034] The language "therapeutically effective amount" of a compound of the disclosure refers to an amount of an agent which is effective, upon single or multiple dose administration to the patient, in inhibiting cell proliferation and/or symptoms of a cell proliferative disorder, or in prolonging the survivability of the patient with such a cell proliferative disorder beyond that expected in the absence of such treatment. The exact amount desired or required will vary depending on the particular compound or composition used, its mode of administration, and the like. Appropriate effective amount can be determined by one of ordinary skill in the art informed by the instant disclosure using only routine experimentation.

[0035] Within the meaning of the disclosure, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy.

[0036] Compositions comprising a compound of the disclosure and a pharmaceutical agent can be prepared at a patient's bedside, or by a pharmaceutical manufacture. In the latter case, the compositions can be provided in any suitable container, such as a sealed sterile vial or ampoule, and may be further packaged to include instruction documents for use by a pharmacist, physician or other health care provider. The compositions can be provided as a liquid, or as a lyophilized or powder form that can be reconstituted if necessary when ready for use. In particular, the compositions can be provided in combination with any suitable delivery form or vehicle, examples of which include, for example, liquids, caplets, capsules, tablets, inhalants or aerosol, etc. The delivery devices may comprise components that facilitate release of the pharmaceutical agents over certain time periods and/or intervals, and can include compositions

that enhance delivery of the pharmaceuticals, such as nanoparticle, microsphere or liposome formulations, a variety of which are known in the art and are commercially available. Further, each composition described herein can comprise one or more pharmaceutical agents. The compositions described herein can include one or more standard pharmaceutically acceptable carriers. Some examples of pharmaceutically acceptable carriers can be found in: *Remington: The Science and Practice of Pharmacy* (2005) 21st Edition, Philadelphia, PA. Lippincott Williams & Wilkins.

[0037] Various methods known to those skilled in the art can be used to introduce the compositions of the disclosure to an individual. These methods, for example, of introducing the fused indole compound, or compositions containing the fused indole compound, can be administered in any manner including, but not limited to, orally, parenterally, sublingually, transdermally, rectally, transmucosally, topically, via inhalation, via buccal administration, or combinations thereof. Parenteral administration includes, but is not limited to, intravenous, intraarterial, intracranial, intradermal, subcutaneous, intraperitoneal, subcutaneous, intramuscular, intrathecal, and intraarticular. The fused indole compound also can be administered in the form of an implant, which allows a slow release of the compound, as well as a slow controlled i.v. infusion.

[0038] The dose of the composition comprising a compound of the disclosure and a pharmaceutical agent generally depends upon the needs of the individual to whom the composition of the disclosure is to be administered. These factors include, for example, the weight, age, sex, medical history, and nature and stage of the disease for which a therapeutic or prophylactic effect is desired. The compositions can be used in conjunction with any other conventional treatment modality designed to improve the disorder for which a desired therapeutic or prophylactic effect is intended, non-limiting examples of which include surgical interventions and radiation therapies. The compositions can be administered once, or over a series of administrations at various intervals determined using ordinary skill in the art, and given the benefit of the present disclosure.

[0039] Compositions of the disclosure can comprise more than one pharmaceutical agent. For example, a first composition comprising a compound of the disclosure and a first pharmaceutical agent can be separately prepared from a composition which comprises the same

compound of the disclosure and a second pharmaceutical agent, and such preparations can be mixed to provide a two-pronged (or more) approach to achieving the desired prophylaxis or therapy in an individual. Further, compositions of the disclosure can be prepared using mixed preparations of any of the compounds disclosed herein.

[0040] It is envisioned, therefore, that a compound having the structure (I) to (IX) are useful in the treatment of a variety of conditions and diseases. Thus, the present disclosure concerns the use of a compound having the structure (I) to (IX), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the treatment of such conditions and diseases.

[0041] The compounds of the present disclosure can be therapeutically administered as the neat chemical, but it is preferred to administer a compound having the structure (I) to (IX) as a pharmaceutical composition or formulation. Thus, the present disclosure provides a pharmaceutical composition comprising a compound having the structure (I) to (IX) together with a pharmaceutically acceptable diluent or carrier therefor. Also provided is a process of preparing a pharmaceutical composition comprising admixing a compound having the structure (I) to (IX) with a pharmaceutically acceptable diluent or carrier therefor.

[0042] Accordingly, the present disclosure further provides pharmaceutical formulations comprising a compound having the structure (I) to (IX), or a pharmaceutically acceptable salt, prodrug, or hydrate thereof, together with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients. The carriers are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0043] Examples of pharmaceutically-acceptable carrier include pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ, or portion of the body, to another organ, or portion of the body. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa

butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0044] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0045] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0046] In one embodiment, the pharmaceutically-acceptable formulation is such that it provides sustained delivery of a compound having the structure (I) to (IX) to a subject for at least 12 hours, 24 hours, 36 hours, 48 hours, one week, two weeks, three weeks, or four weeks after the pharmaceutically-acceptable formulation is administered to the subject.

[0047] In certain embodiments, these pharmaceutical compositions are suitable for topical or oral administration to a subject. In other embodiments, as described in detail below, the pharmaceutical compositions of the present disclosure may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the

skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; or (5) aerosol, for example, as an aqueous aerosol, liposomal preparation or solid particles.

[0048] The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of a compound having the structure (I) to (IX) which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, more preferably from about 10 per cent to about 30 per cent.

[0049] Methods of preparing these compositions include the step of bringing into association a compound having the structure (I) to (IX) with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound having the structure (I) to (IX) with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0050] Compositions of the disclosure suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound having the structure (I) to (IX) as an active ingredient. A compound having the structure (I) to (IX) may also be administered as a bolus, electuary or paste.

[0051] In solid dosage forms of the disclosure for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating

agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0052] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent.

[0053] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present disclosure, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The

active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0054] Liquid dosage forms for oral administration of a compound having the structure (I) to (IX) include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0055] In addition to inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0056] Suspensions, in addition to a compound having the structure (I) to (IX) , the composition may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0057] Pharmaceutical compositions of the disclosure for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a compound having the structure (I) to (IX) with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active agent.

[0058] Compositions of the present disclosure which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0059] Dosage forms for the topical or transdermal administration of a compound having the structure (I) to (IX) include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. A compound having a structure (I) to (IX) may be mixed under

sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0060] The ointments, pastes, creams and gels may contain, in addition to a compound having the structure (I) to (IX), excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0061] Powders and sprays can contain, in addition to a compound having a structure (I) to (IX), excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0062] Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of the agent together with conventional pharmaceutically-acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular a compound having the structure (I) to (IX), but typically include nonionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[0063] Transdermal patches have the added advantage of providing controlled delivery of a compound having the structure (I) to (IX) to the body. Such dosage forms can be made by dissolving or dispersing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the active ingredient across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active ingredient in a polymer matrix or gel.

[0064] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of the disclosure.

[0065] Pharmaceutical compositions of the disclosure suitable for parenteral administration comprise a compound having the structure (I) to (IX) in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable

solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0066] Examples of suitable aqueous and nonaqueous carriers, which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0067] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0068] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0069] Injectable depot forms are made by forming microencapsule matrices of a compound having the structure (I) to (IX) in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0070] When a compounds having a structure (I) to (IX) are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically-acceptable carrier.

[0071] Regardless of the route of administration selected, a compound having the structure (I) to (IX), which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present disclosure, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[0072] The pharmaceutical preparations may be given by forms suitable for each administration route. For example, these preparations are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred. The injection can be bolus or can be continuous infusion. Depending on the route of administration, a compound having the structure (I) to (IX) of the present disclosure can be coated with or disposed in a selected material to protect it from natural conditions which may detrimentally affect its ability to perform its intended function. A compound having the structure (I) to (IX) may be administered alone, or in conjunction with either another agent as described above or with a pharmaceutically-acceptable carrier, or both. A compound having the structure (I) to (IX) may be administered prior to the administration of the other agent, simultaneously with the agent, or after the administration of the agent. A compound having the structure (I) to (IX) can also be administered in a pro-drug form which is converted into its active metabolite, or more active metabolite in vivo.

[0073] In certain embodiments, the methods of the disclosure include administering to a subject a therapeutically effective amount of a compound having the structure (I) to (IX) in combination with another pharmaceutically active ingredient. Examples of pharmaceutically active ingredients known to treat cell proliferative disorders, e.g., anticancer agent, antiproliferative agent, chemotherapeutic. Other pharmaceutically active ingredients that may be used can be found in Harrison's Principles of Internal Medicine, Thirteenth Edition, Eds. T.R. Harrison et al. McGraw-Hill N.Y., NY; and the Physicians Desk Reference 50th Edition 1997, Oradell New Jersey, Medical Economics Co., the complete contents of which are expressly

incorporated herein by reference. A compound having the structure (I) to (IX) and the pharmaceutically active ingredient may be administered to the subject in the same pharmaceutical composition or in different pharmaceutical compositions (at the same time or at different times).

[0074] Methods delineated herein include those wherein the subject is identified as in need of a particular stated treatment. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method). In other methods, the subject is prescreened or identified as in need of such treatment by assessment for a relevant marker or indicator of suitability for such treatment.

[0075] A compound having the structure (I) to (IX) determined to be effective for the prevention or treatment of cell proliferative disorders in animals, e.g., dogs, chickens, and rodents, may also be useful in treatment of tumors in humans. Those skilled in the art of treating tumors in humans will know, based upon the data obtained in animal studies, the dosage and route of administration of a compound having the structure (I) to (IX) to humans. In general, the dosage and route of administration in humans is expected to be similar to that in animals.

[0076] The identification of those patients who are in need of prophylactic treatment for cell proliferative disorders is well within the ability and knowledge of one skilled in the art. Certain of the methods for identification of patients which are at risk of developing cell proliferative disorders which can be treated by the subject method are appreciated in the medical arts, such as family history, and the presence of risk factors associated with the development of that disease state in the subject patient. A clinician skilled in the art can readily identify such candidate patients, by the use of, for example, clinical tests, physical examination and medical/family history. The subject may have a cell proliferative disorder, may be at risk of developing a cell proliferative disorder, or may need prophylactic treatment prior to anticipated or unanticipated exposure to a condition(s) capable of increasing susceptibility to a cell proliferative disorder, e.g., exposure to carcinogens or to ionizing radiation.

[0077] In one aspect, a method of monitoring the progress of a subject being treated with a compound having the structure (I) to (IX) includes determining the pre-treatment status (e.g., size, growth rate, or invasiveness of a tumor) of the cell proliferative disorder, administering a

therapeutically effective amount of a compound having the structure (I) to (IX) to the subject, and determining the status (e.g., size, growth rate, or invasiveness of a tumor) of the cell proliferative disorder after an initial period of treatment with a compound having the structure (I) to (IX), wherein the modulation of the status indicates efficacy of the treatment.

[0078] In another aspect, the disclosure provides a packaged composition including a therapeutically effective amount of a compound having the structure (I) to (IX) and a pharmaceutically acceptable carrier or diluent. The composition may be formulated for treating a subject suffering from or susceptible to a cell proliferative disorder, and packaged with instructions to treat a subject suffering from or susceptible to a cell proliferative disorder.

[0079] In one aspect, the disclosure provides a kit for treating a cell proliferative disorder, microbial disease, e.g., fungal disease; protozoan disease; or viral disease in a subject is provided and includes a compound having the structure (I) to (IX), pharmaceutically acceptable esters, salts, and prodrugs thereof, and instructions for use. In further aspects, the disclosure provides kits for inhibiting cell proliferation, assessing the efficacy of an anti-cell proliferative treatment in a subject, monitoring the progress of a subject being treated with a cell proliferation inhibitor, selecting a subject with a cell proliferative disorder for treatment with cell proliferation inhibitor, and/or treating a subject suffering from or susceptible to cancer. In certain embodiments, the disclosure provides: a kit for treating a cell proliferative disorder, microbial disease, e.g., fungal disease; protozoan disease; or viral disease in a subject, the kit comprising a compound having the structure (I) to (IX).

[0080] For veterinary use, a compound having the structure (I) to (IX), or a pharmaceutically acceptable salt or prodrug, is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal. Animals treatable by the present compounds and methods include, but are not limited to, pets, livestock, show animals, and zoo specimens.

[0081] When administered in combination with other therapeutics, a present fused indole compound may be administered at relatively lower dosages. In addition, the use of targeting agents may allow the necessary dosage to be relatively low. Certain compounds may be

administered at relatively high dosages due to factors including, but not limited to, low toxicity and high clearance.

[0082] For human use, a compound having the structure (I) to (IX) can be administered alone, but generally is administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present disclosure can be formulated in a conventional manner using one or more physiologically acceptable carrier comprising excipients and auxiliaries that facilitate processing of a compound having the structure (I) to (IX) into pharmaceutical preparations.

[0083] The present fused indole compounds can be administered simultaneously or metronomically with other anti-cancer treatments, such as chemotherapy and/or radiation therapy. The term "simultaneous" or "simultaneously" means that the other anti-cancer treatment and the fused indole compound are administered within 6 hours, 3 hours or less, of each other. The term "metronomically" means the administration of the other anti-cancer treatments at times different from the anti-cancer treatments and at a certain frequency relative to repeat administration and/or the anti-cancer treatment regimen.

[0084] The fused indole compounds of the present disclosure can be used to treat a variety of diseases and conditions. For example, compounds of the present disclosure can be used in combination with radiation and/or a chemotherapeutic agent in the treatment of cancers. For example, the fused indole compounds can be used to enhance treatment of tumors that are customarily treated with an antimetabolite, e.g., methotrexate or 5-fluorouracil (5-FU).

[0085] Use of fused indole compounds of the present disclosure can result in partial or complete regression of cancer cells, i.e., the partial or complete disappearance of such cells from the cell population. For example, a method of the disclosure can be used to slow the rate of tumor growth, decrease the size or number of tumors, or to induce partial or complete tumor regression.

[0086] A compound having the structure (I) to (IX) can be used for treating a disease or condition in vivo by administration to an individual in need thereof. The disease or condition can be a cancer. A variety of cancers can be treated including, but not limited to: carcinomas, including bladder (including accelerated and metastic bladder cancer), breast, colon (including

colorectal cancer), kidney, liver, lung (including small and non-small cell lung cancer and lung adenocarcinoma), ovary, prostate, testes, genitourinary tract, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, cervix, thyroid, renal, and skin (including squamous cell carcinoma); hematopoietic tumors oflymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, 8-celllymphoma, T-cell lymphoma, Hodgkins lymphoma, nonHodgkins lymphoma, hairy cell lymphoma, histiocytic lymphoma, and Burketts lymphoma, hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, and promyelocytic leukemia; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscarcoma, and osteosarcoma; and other tumors, including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, teratocarcinoma, renal cell carcinoma (RCC), pancreatic cancer, myeloma, myeloid and lymphoblastic leukemia, neuroblastoma, and glioblastoma.

[0087] One method of the present disclosure comprises administration of a therapeutically effective amount of a present fused indole compound in combination with a chemotherapeutic agent that can effect single- or double-strand DNA breaks or that can block DNA replication or cell proliferation. Alternatively, a method of the present disclosure comprises administration of a therapeutically effective amount of at least one present fused indole compound in combination with therapies that include use of an antibody, e.g., herceptin, that has activity in inhibiting the proliferation of cancer cells. Accordingly, cancers, for example, colorectal cancers, head and neck cancers, pancreatic cancers, breast cancers, gastric cancers, bladder cancers, vulvar cancers, leukemias, lymphomas, melanomas, renal cell carcinomas, ovarian cancers, brain tumors, osteosarcomas, and lung carcinomas, are susceptible to enhanced treatment by administration of a present fused indole in combination with a chemotherapeutic agent or an antibody.

[0088] Cancers treatable by the present disclosure also include solid tumors, i.e., carcinomas and sarcomas. Carcinomas include malignant neoplasms derived from epithelial cells which infiltrate (i.e., invade) surrounding tissues and give rise to metastases. Adenocarcinomas are carcinomas derived from glandular tissue, or from tissues that form recognizable glandular

structures. Another broad category of cancers includes sarcomas, which are tumors whose cells are embedded in a fibrillar or homogeneous substance, like embryonic connective tissue. The present disclosure also enables treatment of cancers of the myeloid or lymphoid systems, including leukemias, lymphomas, and other cancers that typically are not present as a tumor mass, but are distributed in the vascular or lymphoreticular systems.

[0089] Additional forms of cancer treatable by the present fused indole compounds include, for example, adult and pediatric oncology, growth of solid tumors/malignancies, myxoid and round cell carcinoma, locally advanced tumors, metastatic cancer, human soft tissue sarcomas, including Ewing's sarcoma, cancer metastases, including lymphatic metastases, squamous cell carcinoma, particularly of the head and neck, esophageal squamous cell carcinoma, oral carcinoma, blood cell malignancies, including multiple myeloma, leukemias, including acute lymphocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, and hairy cell leukemia, effusion lymphomas (body cavity based lymphomas), thymic lymphoma lung cancer (including small cell carcinoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, nonsmall cell cancers, breast cancer, including small cell carcinoma and ductal carcinoma), gastrointestinal cancers (including stomach cancer, colon cancer, colorectal cancer, and polyps associated with colorectal neoplasia), pancreatic cancer, liver cancer, urological cancers (including bladder cancer, such as primary superficial bladder tumors, invasive transitional cell carcinoma of the bladder, and muscleinvasive bladder cancer), prostate cancer, malignancies of the female genital tract (including ovarian carcinoma, primary peritoneal epithelial neoplasms, cervical carcinoma, uterine endometrial cancers, vaginal cancer, cancer of the vulva, uterine cancer and solid tumors in the ovarian follicle), malignancies of the male genital tract (including testicular cancer and penile cancer), kidney cancer (including renal cell carcinoma, brain cancer (including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, and metastatic tumor cell invasion in the central nervous system), bone cancers (including osteomas and osteosarcomas), skin cancers (including malignant melanoma, tumor progression of human skin keratinocytes, and squamous cell cancer), thyroid cancer, retinoblastoma, neuroblastoma, peritoneal effusion, malignant pleural effusion, mesothelioma, Wilms's tumors, gall bladder cancer, trophoblastic neoplasms, hemangiopericytoma, and

Kaposi's sarcoma. Accordingly, administration of a present fused indole compound is expected to enhance treatment regimens.

[0090] In an aspect, a compound having the structure (I) to (IX) exhibit antimicrobial activity, e.g., fungal infection; antiprotozoan activity; and antiviral activity. In certain embodiments, the fungal infection is from the pathogenic fungi from *C. albicans*, *C. glabrata*, *A. fumigatus*, or a combination thereof. In various embodiments, the compounds of the disclosure are those in which show < 40% growth inhibition at 20 μM, >10 μM, 5-10 μM, or <5 μM MIC for 95% inhibition of growth towards three different fungal species (i.e., *C. albicans*, *C. glabrata*, and *A. fumigatus*).

[0091] As appreciated by persons skilled in the art, additional active or ancillary agents can be used in the methods described herein. Reference herein to treatment also extends to prophylaxis, as well as to treatment of established diseases or symptoms.

[0092] The present disclosure can be applied to cell populations *ex vivo*. For example, the present fused indole compounds can be used *ex vivo* to determine the optimal schedule and/or dosing of administration of the present fused indole compound for a given indication, cell type, patient, and other parameter. Information gleaned from such use can be used for experimental purposes or in the clinic to set protocol for in vivo treatment. Other *ex vivo* uses for which the disclosure is suited are apparent to those skilled in the art.

[0093] A present fused indole compound also can be administered in combination with radiation. Diseases that are treatable with electromagnetic radiation include neoplastic diseases, benign and malignant tumors, and cancerous cells.

[0094] Electromagnetic radiation treatment of other diseases not listed herein also is contemplated by the present disclosure. Preferred embodiments of the present disclosure employ the electromagnetic radiation of: gamma-radiation (10-20 to 10- 13 m), X-ray radiation (l0-12 to 10-9 m), ultraviolet light (10 nm to 400 nm), visible light (400 nm to 700 nm), infrared radiation (700 nm to 1 mm), and microwave radiation (l mm to 30 em).

[0095] Many cancer treatment protocols currently employ radiosensitizers activated by electromagnetic radiation, e.g., X-rays. Examples of X-ray-activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, E09, RB 6145,

nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FUdR), hydroxyurea, cis-platin, and therapeutically effective analogs and derivatives of the same.

[0096] Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator of the sensitizing agent. Examples of photodynamic radiosensitizers include the following, but are not limited to: hematoporphyrin derivatives, PHOTOFRINriD, benzoporphyrin derivatives, NPe6, tin etioporphyrin (SnET2), pheoborbide-a, bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

[0097] Radiosensitizers can be administered in conjunction with a therapeutically effective amount of one or more compounds in addition to a present fused indole compound, such compounds including, but not limited to, compounds that promote the incorporation of radiosensitizers to the target cells, compounds that control the flow of therapeutics, nutrients, and/or oxygen to the target cells, chemotherapeutic agents that act on the tumor with or without additional radiation, or other therapeutically effective compounds for treating cancer or other disease. Examples of additional therapeutic agents that can be used in conjunction with radiosensitizers include, but are not limited to, 5-fluorouracil (5-FU), leucovorin, oxygen, carbogen, red cell transfusions, perfluorocarbons (e.g., FLUOSOLW®-DA), 2,3-DPG, BW12C, calcium channel blockers, pentoxifylline, antiangiogenesis compounds, hydralazine, and L-BSO.

[0098] The chemotherapeutic agent can be any pharmacological agent or compound that induces apoptosis. The pharmacological agent or compound can be, for example, a small organic molecule, peptide, polypeptide, nucleic acid, or antibody. Chemotherapeutic agents that can be used include, but are not limited to, alkylating agents, antimetabolites, hormones and antagonists thereof, natural products and their derivatives, radioisotopes, antibodies, as well as natural products, and combinations thereof. For example, a fused indole compound of the present disclosure can be administered with antibiotics, such as doxorubicin and other anthracycline analogs, nitrogen mustards, such as cyclophosphamide, pyrimidine analogs such as 5-fluorouracil, cis-platin, hydroxyurea, taxol and its natural and synthetic derivatives, and the like. As another example, in the case of mixed tumors, such as adenocarcinoma of the breast, where the tumors include gonadotropin-dependent and gonadotropin-independent cells, the compound

can be administered in conjunction with leuprolide or goserelin (synthetic peptide analogs of LH-RH). Other antineoplastic protocols include the use of an inhibitor compound with another treatment modality, e.g., surgery or radiation, also referred to herein as "adjunct anti-neoplastic modalities." Additional chemotherapeutic agents useful in the disclosure include hormones and antagonists thereof, radioisotopes, antibodies, natural products, and combinations thereof.

[0099] A compound having the structure (I) to (IX) of this disclosure can be provided in pharmaceutical compositions. In one embodiment, the pharmaceutical composition comprises one or more compounds having the structure (I) to (IX) of the present disclosure and a pharmaceutically acceptable carrier. In one embodiment, the kits of the disclosure can comprise one or more compounds of the structure (I) to (IX), alone, as pharmaceutical preparations, or separate pharmaceutical preparations with each pharmaceutical preparation comprising a separate compound having the structure (I) to (IX).

[00100] The following specific examples are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

[00101] All synthetic chemistry was performed in standard laboratory glassware unless indicated otherwise in the examples. Commercial reagents were used as received. For reactions generating multiple isomers, pure isomers were isolated whenever feasible. Analytical LC/MS was performed on an Agilent 1200 system with a variable wavelength detector and Agilent 6140 single quadrupole mass spectrometer, alternating positive and negative ion scans. Retention times were determined from the extracted 220 nm UV chromatogram. ^{1}H NMR was performed on a Bruker DRX-400 at 400 MHz or a Bruker Avance DRX 500 at 500 MHz. For complicated splitting patterns, the apparent splitting is tabulated. Microwave reactions were performed in a Biotage Initiator using the instrument software to control heating time and pressure. Silica gel chromatography was performed manually, or with an Isco CombiFlash for gradient elutions.

[00102] Analytical LC/MS method A: HPLC column: Kinetex, 2.6 μm, C18, 50 x 2.1 mm, maintained at 40 °C. HPLC Gradient: 1.0 mL/min, 95:5:0.1 water:acetonitrile:formic acid to 5:95:0.1 water:acetonitrile:formic acid in 2.0 min, maintaining for 0.5 min. Reported retention times are for method A unless indicated otherwise.

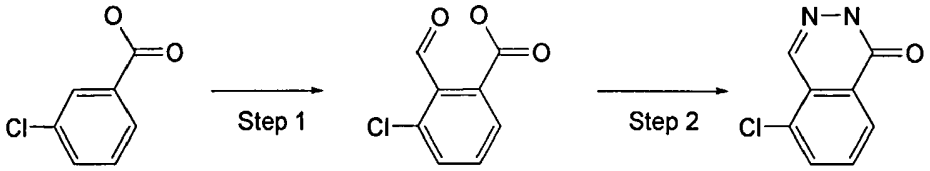
[00103] Analytical LC/MS method B was performed on a Shimadzu system with an attached API 165 single quadrupole mass spectrometer. Retention times were determined from the 220 nm chromatogram. HPLC column: Phenomenex, C18, 2.5 μm, 20 x 2 mm, maintained at 25 °C. HPLC Gradient: 0.5 mL/min, 95:5:0.02 water:acetonitrile:CF_3COOH to 5:95:0.02 water:acetonitrile:CF_3COOH in 2.9 min, maintaining for 0.9 min.

PREPARATIONS

[00104] Preparation 1-1. 8-Bromo-3*H*-quinazolin-4-one.

[00105] A solution of 2-amino-3-bromobenzoic acid (0.96, 4.44 mmol) in formamide (3 mL) was heated at 135 °C for 90 min, then at 175 °C for 90 min. The mixture was cooled to room temperature and poured into water (20 mL). The precipitate was collected and washed with aqueous ammonium hydroxide (0.1 N, 10 mL) to give the title compound (0.87 g, 3.85 mmol, 85%) as a tan powder. LCMS: 97%, Rt 0.969, ESMS m/z 226 $(M+H)^+$.

[00106] Preparation 2-1. 5-Chloro-2*H*-phthalazin-1-one.



[00107] Step 1. To a stirred solution of *n*-butyllithium (1.6 M in hexane, 8.78 mL, 14.05 mmol) under argon at –20°C was added 2,2,6,6-tetramethylpiperidine (2.37 mL, 14.05 mmol) in anhydrous tetrahydrofuran (15 mL). The mixture was cooled to –50 °C and a solution of 3-chlorobenzoic acid (1.0 g, 6.39 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise. The mixture was stirred for 3 h. The mixture was then treated with *N,N*-dimethylformamide (1.97 mL, 25.5 mmol) and allowed to warm to room temperature. The mixture was stirred for 18 h. The reaction was quenched with water (5 mL) and the mixture was evaporated. The residue was diluted with hydrochloric acid (2 M, 25 mL) and extracted with diethyl ether (2 x 25 mL). The combined organic layers were dried over sodium sulfate and

evaporated to give 3-chloro-2-formylbenzoic acid (790 mg, 4.28 mmol, 67%) as a yellow powder. LCMS: 72%, Rt 0.988, ESMS m/z 185 $(M+H)^+$.

[00108] Step 2. To a solution of 3-chloro-2-formylbenzoic acid (Preparation 2a-1, 1.35 g, 7.31 mmol) in water (13.5 mL) was added hydrazine hydrate (1.78 mL, 36.65 mmol), and the mixture was stirred at 95 °C for 4 h. The resulting precipitate was collected, washed with water (5 mL) and dried in air to give the title compound (545 mg, 3.01 mmol, 41%) as a white powder. LCMS: 100%, Rt 1.079, ESMS m/z 181 $(M+H)^+$.

[00109] Preparation 3-1. 5-bromo-3,4-dihydro-2H-isoquinolin-1-one.

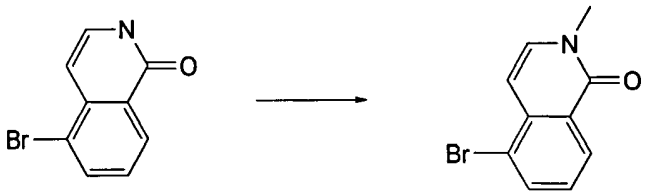
[00110] To a mixture of 4-bromoindan-1-one (4.00g, 18.9 mmol) and methanesulfonic acid (20.2 mL, 310 mmol) in dichloromethane (180 mL) was added sodium azide (2.46 g, 37.9 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was poured into 10% aqueous sodium hydroxide (200 mL) and extracted with dichloromethane (100 mL). The combined organic layers were dried over sodium sulfate and evaporated. The crude product was recrystallized from ethyl acetate (40 mL) to give the title compound (3.98 g, 17.6 mmol, 93%) as a white powder. LCMS: 96%, Rt 1.225, ESMS m/z 226 $(M+H)^+$.

[00111] Preparation 4-1. 5-Bromo-2H-isoquinolin-1-one.

[00112] A mixture of 5-bromo-3,4-dihydro-2H-isoquinolin-1-one (Preparation 3-1, 4.3 g, 18.9 mmol) and 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (8.6 g, 37.9 mmol) in 1,4-dioxane (76 mL) was stirred at 100 °C for 24 h. The reaction mixture was evaporated and the residue was taken up in ethyl acetate (500 mL) and washed with 10% aqueous sodium hydroxide (2 x 500 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (4 x 300 mL). The combined organic layers were dried over sodium sulfate, evaporated and purified by

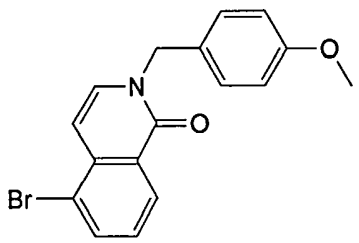
flash chromatography eluting with dichloromethane:methanol (99:1→96:4) to give the title compound (1.49 g, 6.65 mmol, 35%) as a yellow solid. LCMS: 94%, Rt 1.243, ESMS m/z 224 $(M+H)^+$.

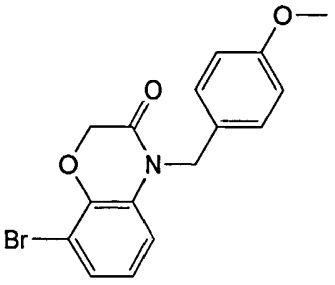
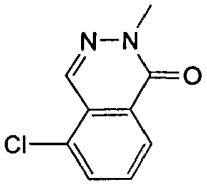
[00113] Preparation 5-1. 5-Bromo-2-methyl-2H-isoquinolin-1-one.



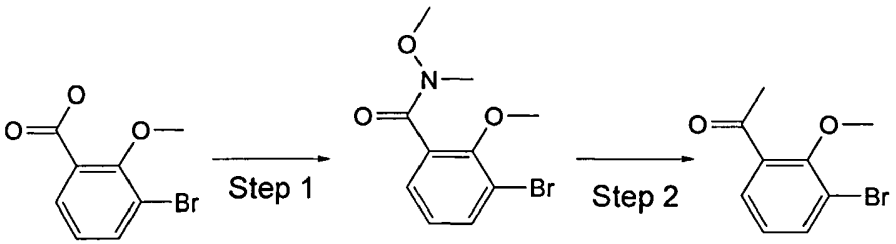
[00114] To a mixture of 5-bromo-2H-isoquinolin-1-one (Preparation 4-1, 615 mg, 2.75 mmol) and cesium carbonate (1.79 g, 5.50 mmol) in *N,N*-dimethylformamide (4.5 mL) and acetonitrile (11 mL) was added methyl iodide (222 µL, 3.57 mmol). The reaction mixture was stirred at 35 °C for 2.5 h and then poured into ice-water (4 mL). The precipitate was collected by filtration and washed with water (3 mL) and diethyl ether (2 x 1 mL) to give the title compound (515 mg, 2.16 mmol, 79%) as a light brown solid. LCMS: 99%, Rt 1.405, ESMS m/z 238 $(M+H)^+$.

[00115] Preparations 5-2 – 4 listed in the table were prepared in a similar manner.

Prep.	Structure	MW	Ion	Rt	Anal. Method	Yield
5-2		344	344	1.800	A	81

5-3		348	348	1.748	A	89
5-4		195	195	1.279	A	97

[00116] Preparation 6-1. 1-(3-Bromo-2-methoxyphenyl)-ethanone.

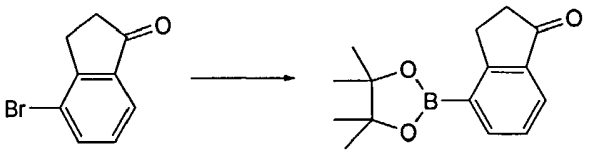


[00117] Step 1. A solution of 3-bromo-2-methoxybenzoic acid (3.0 g, 12.98 mmol) in thionyl chloride (15 mL) was stirred at 50 °C for 2 h and then evaporated. The residue was taken up in dichloromethane (50 mL) and to this solution was added methoxymethylamine hydrochloride (1.27 g, 13.0 mmol) and *N,N*-diisopropylethylamine (4.53 mL, 26.0 mmol). The mixture stirred at room temperature for 16 h. The reaction mixture was washed with water (2 x 20 mL) and the organic layer was dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography eluting with dichloromethane:hexane (50:50 to 100:0) to

give the title compound (2.03 g, 7.41 mmol, 57%) as an off-white powder. LCMS: 94%, Rt 1.327, ESMS m/z 274 $(M+H)^+$.

[00118] Step 2. 3-Bromo-2,*N*-dimethoxy-*N*-methyl-benzamide (Preparation 6a-1, 1.92 g, 7.0 mmol) was dissolved in tetrahydrofuran (6 mL). To this solution was added methylmagnesium bromide (3M in diethyl ether, 4.67 mL, 14.0 mmol) at 0 °C and the mixture stirred for 3 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over sodium sulfate and evaporated to give the title compound (1.5 g, 6.55 mmol, 93%) as a light brown powder. LCMS: 96%, Rt 1.506, ESMS m/z no ionization.

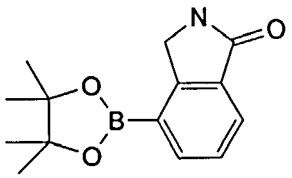
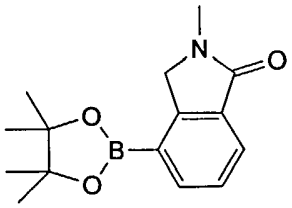
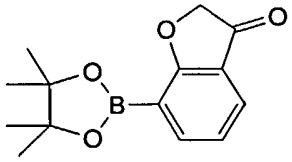
[00119] Preparation 7-1. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-indan-1-one.

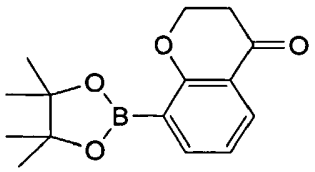
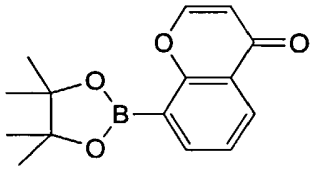
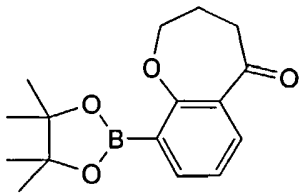


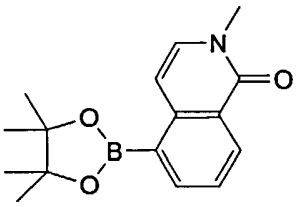
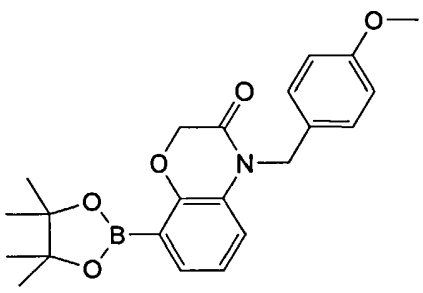
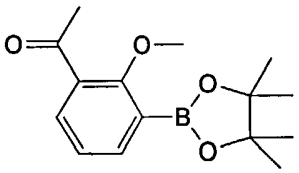
[00120] To a solution of 4-bromo-1-indanone (1.0 g, 4.74 mmol) in *N,N*-dimethylacetamide (25 mL) was added *bis*(pinacolato)diboron (2.41 g, 9.48 mmol), 1,1'-*bis*(diphenylphosphino)ferrocene palladium(II) dichloride (346 mg, 0.47 mmol) and potassium acetate (1.40 g, 14.22 mmol) and the reaction mixture was stirred at 100 °C for 2 h under nitrogen. The mixture was evaporated and the residue was diluted with water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over sodium sulfate and evaporated. The residue was purified by column chromatography eluting with hexane:ethyl acetate (100:0→4:1) to give the title compound (1.8 g, 7.00 mmol, ca. 100%) as an off-white powder. LCMS: 97%, Rt 1.811, ESMS m/z 259 $(M+H-CH_4)^+$.

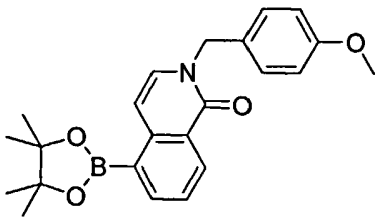
[00121] Preparations 7-2 – 11 listed in the table were prepared in a similar manner.

Prep.	Structure	MW	Ion	Rt	Anal. Method	Yield

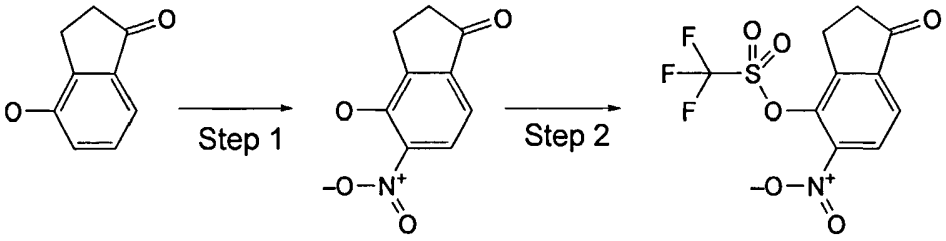
7-2		259	260	1.460	A	65
7-3		273	274	1.582	A	81
7-4		260	260	1.584	A	44

7-5		274	275	1.573	A	71
7-6		272	273	1.524	A	quant
7-7		288	289	1.715	A	quant

7-8		285	286	1.680	A	91
7-9		395	396	1.812	A	89
7-10		276	277	1.737	A	Quant

7-11		391	392	1.981	A	~100

[00122] Preparation 8-1. Trifluoromethanesulfonic acid 5-nitro-1-oxoindan-4-yl ester.

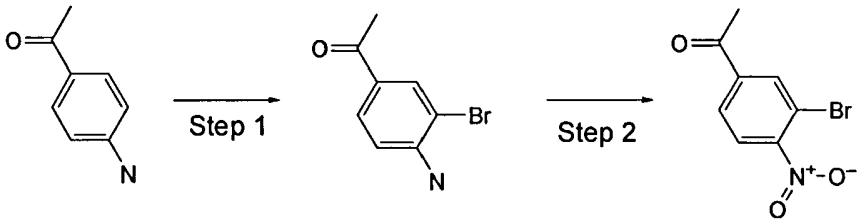


[00123] Step 1. To a suspension of 4-hydroxyindan-1-one (25.0 g, 169 mmol) in concentrated sulfuric acid (250 mL) at –25 °C was added slowly a mixture of fuming nitric acid (8.46 mL) and concentrated sulfuric acid (8.46 mL), maintaining the temperature between –25 °C and –10 °C during the addition. The reaction was monitored by TLC (*n*-hexane:ethyl acetate, 4:1) until complete conversion was achieved (25 min). The reaction mixture was poured onto crushed ice (ca. 1.5 kg) and the yellow precipitate collected by filtration. The crude material was purified by flash chromatography on silica gel, eluting with dichloromethane, to afford the title compound (15.7 g, 81.3 mmol, 48%) as a yellow powder. LCMS: 100%, Rt 1.188, ESMS m/z 192 $(M-H)^-$.

[00124] Step 2. To a solution of 4-hydroxy-5-nitroindan-1-one (Preparation 8a-1, 5.0 g, 25.8 mmol) and triethylamine (3.97 mL, 28.5 mmol) in dichloromethane (50 mL) was added trifluoromethanesulfonic acid anhydride (4.57 mL, 27.2 mmol) dropwise at 0 °C. The mixture was stirred at room temperature for 1 h and washed with water (50 mL), 10% aqueous sodium carbonate (2 x 50 mL) and brine (25 mL). The organic layer was dried over sodium sulfate and

evaporated. The crude product was taken up in dichloromethane, filtered through silica and evaporated to afford the title compound (5.67 g, 17.43 mmol, 67%) as a pale yellow powder. LCMS: 97%, Rt 1.693 min, ESMS (no ionization).

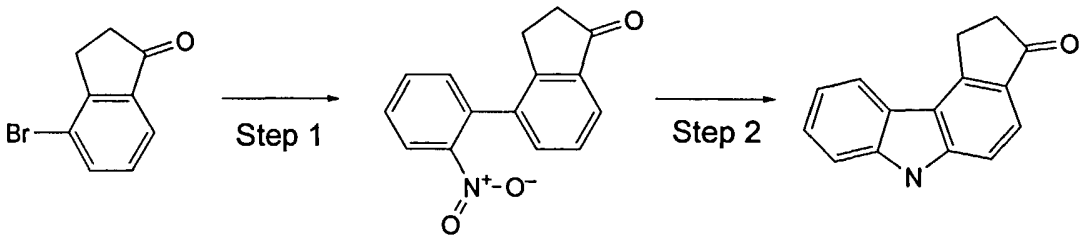
[00125] Preparation 9-1. 1-(3-Bromo-4-nitro-phenyl)-ethanone.



[00126] Step 1. To a suspension of 1-(4-aminophenyl)-ethanone (14.7 g, 109 mmol) in toluene (150 mL) at 40 °C was added *N*-bromosuccinimide (19.4 g, 109 mmol) in several portions over 30 min. After the addition was complete, the mixture was stirred at 40 °C for 15 min. Water (30 mL) was added and the organic layer was separated, washed with water (3 x 30 mL), dried over magnesium sulfate and evaporated to give the title compound (16.5 g, 77 mmol, 71%) as a brown crystalline solid. The crude product was used without further purification. LCMS: 97%, Rt 1.188 min, ESMS m/z 214 $(M+H)^+$.

[00127] Step 2. To a stirred mixture of 1-(4-amino-3-bromophenyl)-ethanone (Preparation 9a-1, 33 g, 154 mmol) in 20% aqueous tetrafluoroboric acid (143 mL) at 0 °C was added sodium nitrite (4M aqueous solution, 60 mL, 240 mmol) over 15 min. The mixture was stirred at 0 °C for 30 min. The resulting yellow foamy suspension was added to a vigorously stirring mixture of copper powder (53 g, 0.83 mol) and sodium nitrite (143 g, 2.07 mol) in water (286 mL) at room temperature. The stirring was continued for 1 h until gas evolved. The mixture was extracted with ethyl acetate (4 x 200 mL) and the combined organic layers dried over magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography eluting with n-hexane:ethyl acetate (4:1). The crude product was recrystallized from ethanol (50 mL) to afford the title compound (10.5 g, 43.0 mmol, 28%) as a yellow powder. LCMS: 100%, Rt 1.482 min, ESMS no ionization; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 2.67 (s, 3H).

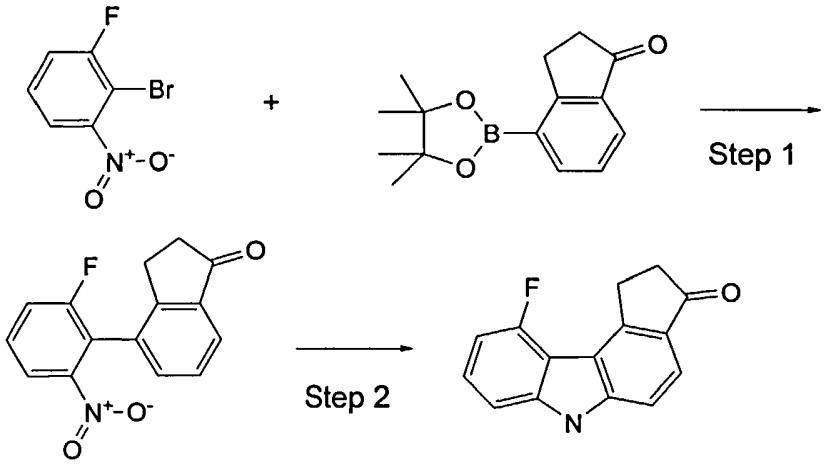
[00128] Preparation 10-1. 1,2-Dihydro-6H-cyclopenta[*c*]carbazol-3-one.



[00129] Step 1. A biphasic mixture of 4-bromo-1-indanone (1.0 g, 4.74 mmol), 2-nitrophenylboronic acid (1.60 g, 9.48 mmol), 1,1'-*bis*(diphenylphosphino)ferrocene palladium(II) dichloride (173 mg, 0.24 mmol) and potassium carbonate (1.31 g, 9.48 mmol) in 1,4-dioxane:water (4:1, 32 mL) was heated at 120 °C for 80 min under microwave irradiation. The mixture was poured into saturated sodium bicarbonate (50 mL), extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and evaporated. The residue was purified by column chromatography eluting with *n*-hexane:ethyl acetate (6:1→3:1) to give the title compound (0.87 g, 3.44 mmol, 73%) as a yellow crystalline solid. LCMS: 98%, Rt 1.546, ESMS m/z 254 $(M+H)^+$.

[00130] Step 2. A mixture of 4-(2-nitrophenyl)-indan-1-one (Preparation 10a-1, 870 mg, 3.44 mmol) and triphenylphosphine (2.25 g, 8.60 mmol) in chlorobenzene (14 mL) was heated at 200 °C for 60 min under microwave irradiation. The mixture was evaporated and the residue purified by column chromatography eluting with dichloromethane:ethyl acetate (98:2→80:20) to give the title compound (1.27 g, >100%; containing triphenylphosphine) as a pale-brown powder. The crude product was used in the next step without further purification. LCMS: 66% (254 nm), Rt 1.430, ESMS m/z 220 $(M-H)^-$.

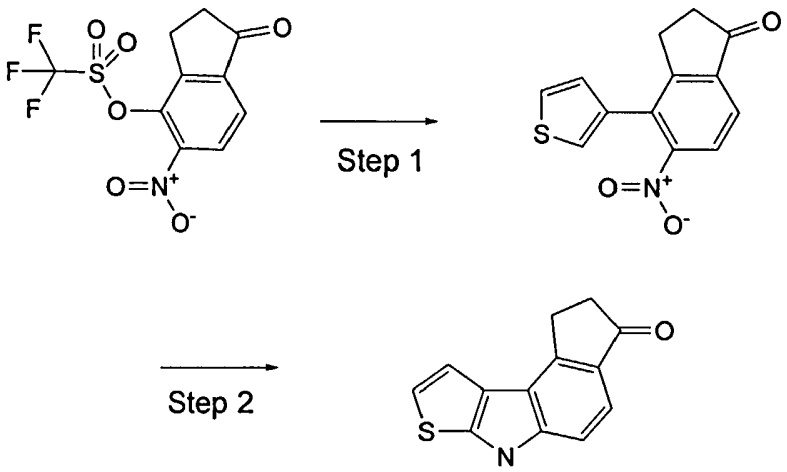
[00131] Preparation 11-1. 10-Fluoro-1,2-dihydro-6H-cyclopenta[c]carbazol-3-one.



[00132] Step 1. A mixture of 2-bromo-1-fluoro-3-nitrobenzene (610 mg, 2.77 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-one (Preparation 7-1, 858 mg, 3.33 mmol), potassium carbonate (2M aq. solution, 2.8 mL, 5.6 mmol) and 1,1'-*bis*(diphenylphosphino)ferrocene palladium(II) dichloride (101 mg, 0.14 mmol) in 1,4-dioxane (12 mL) was irradiated at 100 °C in a microwave reactor for 1 h. The mixture was partitioned between water (15 mL) and ethyl acetate (30 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried over magnesium sulfate and evaporated. The crude product was purified by silica gel column chromatography eluting with *n*-hexane:ethyl acetate (10:1→1:1) to give the title compound (447 mg, 1.65 mmol, 59%) as a yellow solid. LCMS: 100%, Rt 1.548 min, ESMS m/z 272 $(M+H)^+$.

[00133] Step 2. A mixture of 4-(2-fluoro-6-nitrophenyl)-indan-1-one (Preparation 11a-1, 450 mg, 1.65 mmol) and triphenylphosphine (1.08 g, 4.15 mmol) in chlorobenzene (4.5 mL) was irradiated at 200 °C in a microwave reactor for 1 h. The mixture was cooled to room temperature and the precipitate collected by filtration to afford the title compound (376 mg, 1.37 mmol, 67%) as an off-white powder. LCMS: 100%, Rt 1.516 min, ESMS m/z 240 $(M+H)^+$.

[00134] Preparation 12-1. 1,2-Dihydrocyclopenta[e]thieno[2,3-b]indol-3(6H)-one.

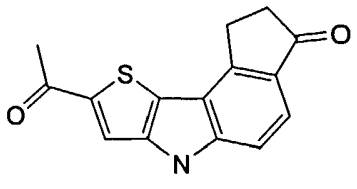


[00135] Step 1. A mixture of trifluoromethanesulfonic acid 5-nitro-1-oxoindan-4-yl ester (Preparation 8-1, 650 mg, 1.99 mmol), thiophene-3-boronic acid (334 mg, 2.60 mmol), potassium carbonate (2 M aqueous solution, 3.2 mL, 6.4 mmol) and 1,1'-bis(diphenylphosphino)ferrocene palladium(II) dichloride (73 mg, 0.10 mmol) in 1,4-dioxane (16 mL) was stirred at 100 °C for 2 h in a sealed vial. The mixture was partitioned between water (10 mL) and ethyl acetate (15 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were dried over sodium sulfate and evaporated. The crude product was purified by column chromatography eluting with hexane:ethyl acetate (7:1) to afford the title compound (345 mg, 1.33 mmol, 66%) as a pale yellow solid. LCMS: 97%, Rt 1.568 min, ESMS m/z 260 (M+H)+.

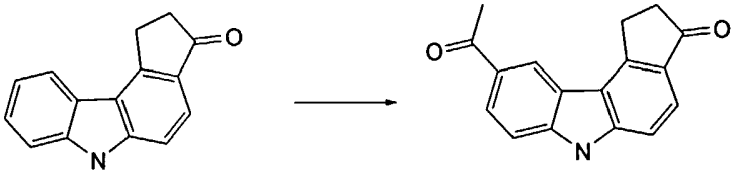
[00136] Step 2. A mixture of 5-nitro-4-thiophen-3-ylindan-1-one (Preparation 12a, 320 mg, 1.23 mmol) and triphenylphosphine (809 mg, 3.08 mmol) in chlorobenzene (10 mL) was irradiated in a microwave reactor at 200 °C for 2 h. The mixture was evaporated onto silica and purified by column chromatography eluting with hexane:ethyl acetate (85:15 to 50:50). The resulting product was triturated with ethyl acetate (3 mL) to give the title compound (76 mg, 0.33 mmol, 27%) as a tan solid. LCMS: 95%, Rt 1.376 min, ESMS m/z 228 $(M+H)^+$.

[00137] Preparation 12-2 listed in the table was prepared in a similar manner.

Prep.	Structure	MW	Ion	Rt	Anal. Method	Yield

12-2		269	270	1.327	A	60

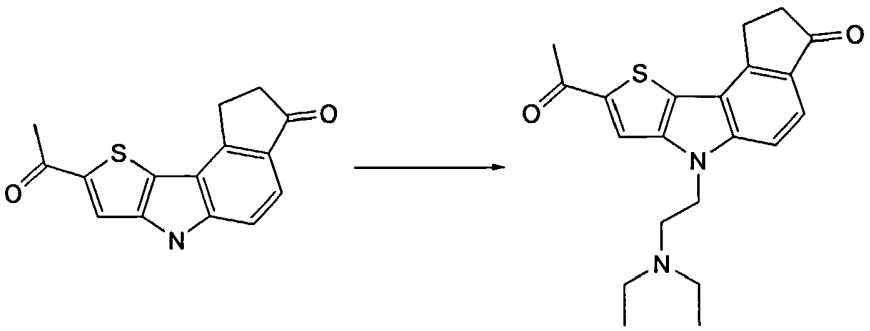
[00138] Preparation 13-1. 9-Acetyl-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one.



[00139] To a suspension of 1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one (Preparation 10-1, 3.00 g, 13.6 mmol) in dichloromethane (60 mL) at 0 °C was added aluminum chloride (7.20 g, 54.4 mmol) and the mixture stirred for 10 min. Acetyl chloride (1.15 mL, 16.3 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 30 min, and poured into ice (150 g). The mixture was allowed to warm to room temperature and the solid was collected to afford the title compound (2.99 g, 11.4 mmol, 84%) as a light brown powder. The product was used without further purification. LCMS: inconclusive due to insufficient solubility; TLC: OK

EXAMPLE 1

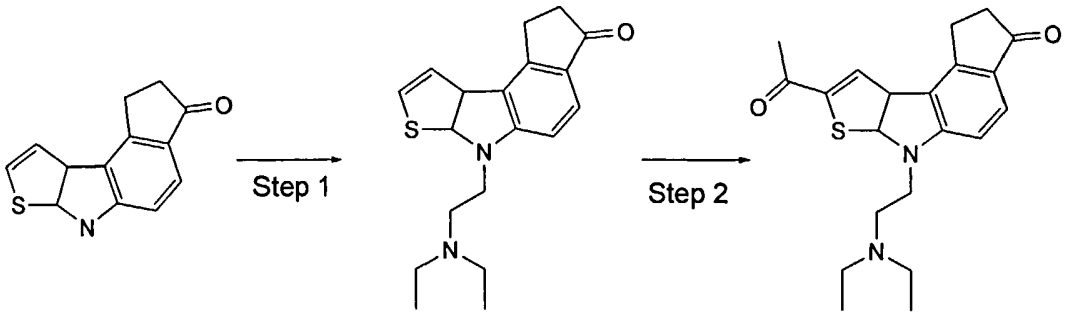
[00140] Compound 1-1. 8-Acetyl-6-(2-(diethylamino)ethyl)-1,2-dihydrocyclopenta[e]thieno[3,2-b]indol-3(6H)-one.



[00141] A mixture of 8-acetyl-1,2-dihydrocyclopenta[e]thieno[3,2-b]indol-3(6H)-one (Preparation 12-2, 70 mg, 0.26 mmol), (2-chloroethyl)diethylamine hydrochloride (58 mg, 0.34 mmol) and cesium carbonate (254 mg, 0.79 mmol) in N,N-dimethylformamide (1.0 mL) was stirred at room temperature for 2 h. Cesium carbonate (85 mg, 0.26 mmol) and (2-chloroethyl)diethylamine hydrochloride (23 mg, 0.13 mmol) were added and the stirring was continued for 14 h. The mixture was evaporated and the residue was taken up in chloroform (7 mL). The organic layer was washed with water (2 x 5 mL), dried over sodium sulfate and evaporated. The crude product was purified by column chromatography eluting with dichloromethane:methanol (10:0.2) to give the title compound as the free base (65 mg, 0.18 mmol, 66%). The product (30 mg) was converted to the hydrochloride salt by treatment with hydrogen chloride in ethyl acetate (0.422 M, 1.0 eq.) to afford the title compound (24 mg, 0.059 mmol, 73 %) as a pale yellow powder. LCMS: 100%, Rt 1.058 min, ESMS m/z 369 $(M+H)^+$; ^1H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.63 (s, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 8.6 Hz, 1H), 5.01 (t, J = 7.6 Hz, 2H), 3.51 (q, J = 6.5 Hz, 2H), 3.41 – 3.33 (m, 2H), 3.23 (dddd, J = 18.8, 13.1, 8.7, 5.9 Hz, 4H), 2.79 – 2.70 (m, 2H), 2.66 (s, 3H), 1.25 (t, J = 7.2 Hz, 6H).

EXAMPLE 2

[00142] Compound 2-1. 8-Acetyl-6-(2-(diethylamino)ethyl)-1,2-dihydrocyclopenta[e]thieno[2,3-b]indol-3(6H)-one.

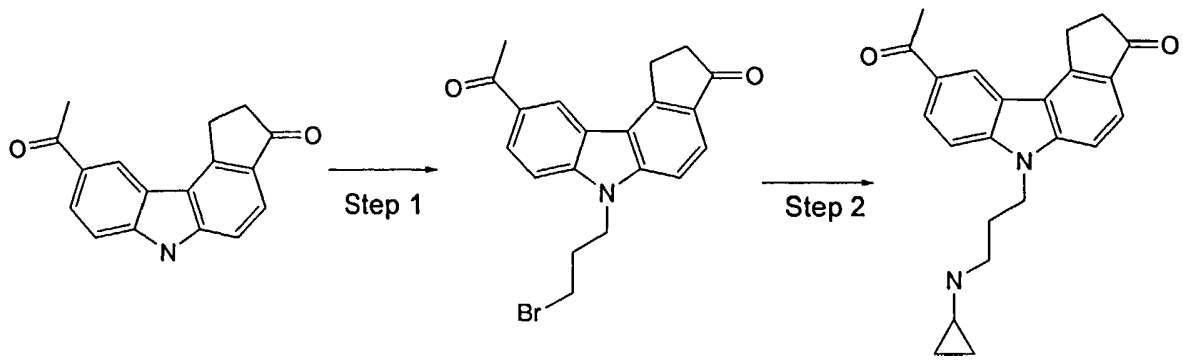


[00143] Step 1. A mixture of 1,2-dihydrocyclopenta[e]thieno[2,3-b]indol-3(6H)-one (76 mg, 0.33 mmol), (2-chloroethyl)diethylamine hydrochloride (86 mg, 0.50 mmol) and cesium carbonate (327 mg, 1.00 mmol) in *N,N*-dimethylformamide (1.5 mL) was stirred at room temperature for 16 h. The mixture was evaporated and the residue taken up in chloroform (6 mL). The organic layer was washed with water (2 x 3 mL), dried over sodium sulfate and evaporated to give the title compound (119 mg, 0.365 mmol, >100 %) as a light brown powder. LCMS: 100%, Rt 1.000 min, ESMS m/z 327 $(M+H)^+$.

[00144] Step 2. To a solution of 6-(2-(diethylamino)ethyl)-1,2-dihydrocyclopenta[e]thieno[2,3-b]indol-3(6H)-one (Compound 2a-1, 90 mg, 0.26 mmol) in dichloromethane (2 mL) at 0 °C was added aluminum chloride (144 mg, 1.08 mmol) and acetyl chloride (38 µL, 0.54 mmol) and the mixture was stirred at room temperature for 1 h. Acetyl chloride (20 µL, 0.27 mmol) was added and the stirring was continued for 16 h. The reaction mixture was partitioned between saturated sodium bicarbonate (10 mL) and dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL) and the combined organic layers were dried over sodium sulfate and evaporated. The crude product was triturated with diethyl ether (3 mL) and recrystallized with acetonitrile (1 mL) to afford the title compound (20 mg, 0.05 mmol, 21 %) as a yellow powder. LCMS: 98%, Rt 1.051 min, ESMS m/z 369 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ δ 8.44 (s, 1H), 7.77 – 7.52 (m, 2H), 4.43 (t, J = 5.7 Hz, 2H), 3.47 (t, J = 5.3 Hz, 2H), 2.91 – 2.67 (m, 4H), 2.43 (q, J = 7.1 Hz, 4H), 0.73 (t, J = 7.1 Hz, 6H).

EXAMPLE 3

[00145] Compound 4-1. 9-Acetyl-6-(3-cyclopropylamino-propyl)-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one hydrochloride.

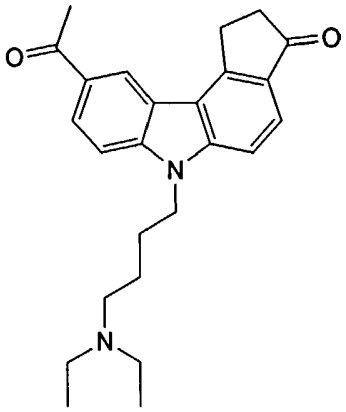
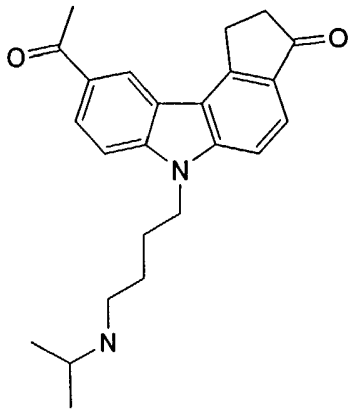
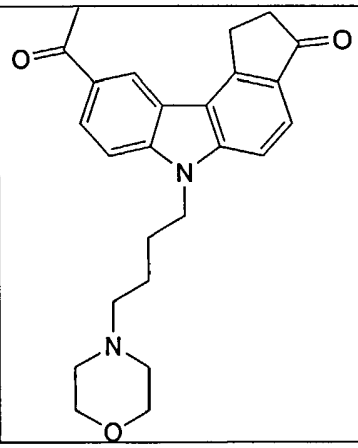


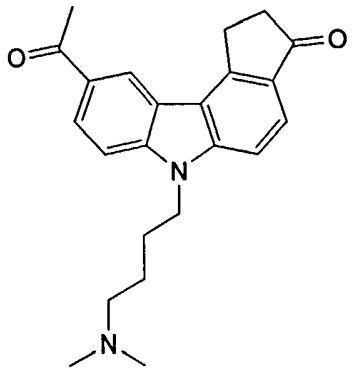
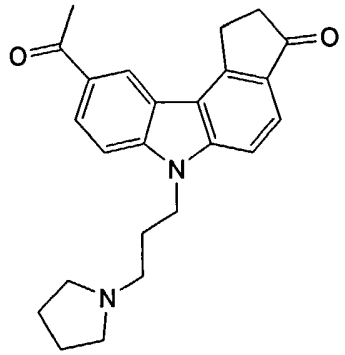
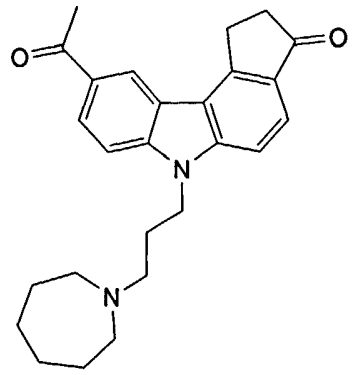
[00146] Step 1. A mixture of 9-acetyl-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one (Preparation 13-1, 500 mg, 1.90 mmol), 1,3-dibromopropane (1.95 mL, 19.0 mmol) and cesium carbonate (2.47 g, 7.60 mmol) in *N,N*-dimethylformamide (25 mL) was stirred at 50 °C for 1 h. The mixture was poured into water (125 mL) and the precipitate collected. The crude material was purified by column chromatography eluting with chloroform:methanol (95:5) to afford the title compound (310 mg, 0.81 mmol, 46%) as an off-white powder. LCMS: 86%, Rt 1.638 min, ESMS m/z 385 $(M+H)^+$.

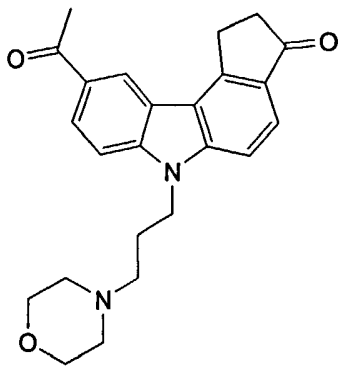
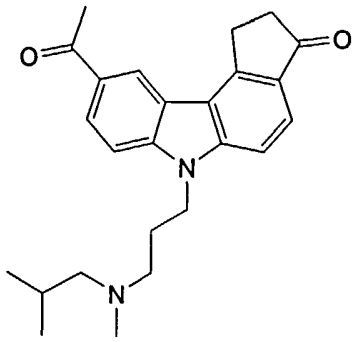
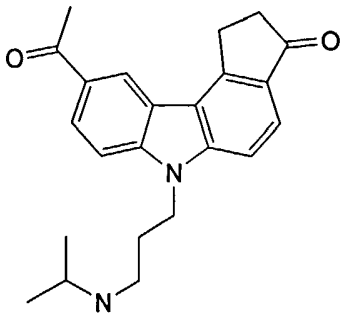
[00147] Step 2. A mixture of 9-acetyl-6-(3-bromo-propyl)-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one (Compound 3a-1, 100 mg, 0.26 mmol), cyclopropylamine (55 µL, 0.78 mmol) and cesium carbonate (338 mg, 1.04 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at 50 °C for 72 h. The mixture was poured into water (10 mL) and the precipitate collected. The crude material was purified by column chromatography eluting with chloroform:methanol (95:5) to afford the title compound as the free base. This material was treated with a solution of hydrogen chloride in ethyl acetate (0.5 M, 1.0 equiv.) to afford the title compound (23 mg, 0.064 mmol, 24%) as a pale yellow powder. LCMS: 97%, Rt 1.067 min, ESMS m/z 361 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (s, 2H), 8.70 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.83 (dd, J = 25.4, 8.5 Hz, 2H), 4.69 (t, J = 7.0 Hz, 2H), 3.653 (t, J = 5.4 Hz, 2H), 3.08 (s, 2H), 2.81 (t, J = 5.4 Hz, 2H), 2.73 (s, 3H), 2.63 (s, 1H), 2.24 – 2.12 (m, 2H), 0.82 – 0.86 (m, 2H), 0.71 (d, J = 6.5 Hz, 2H).

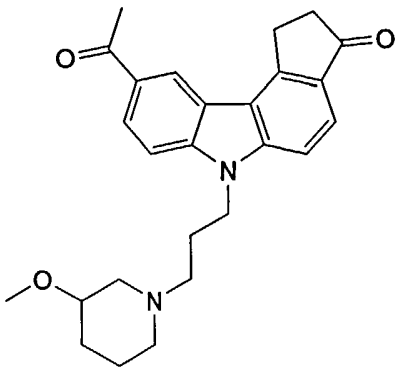
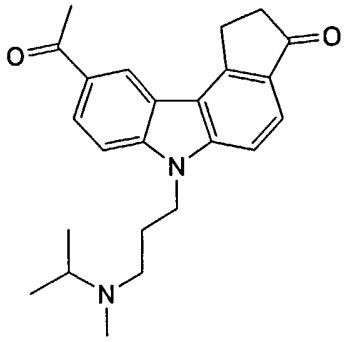
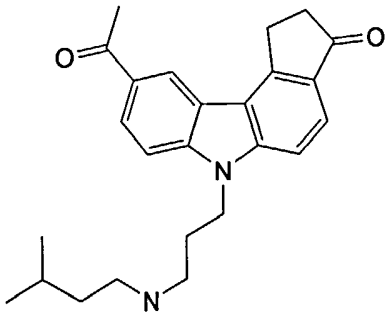
[00148] Compounds 3-2 – 3-17 shown in the table were prepared in a similar manner using the appropriate carbazole/fused indole, dibromoalkyl and amine.

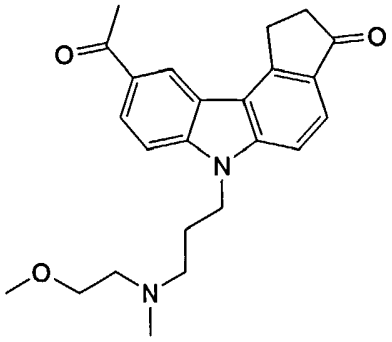
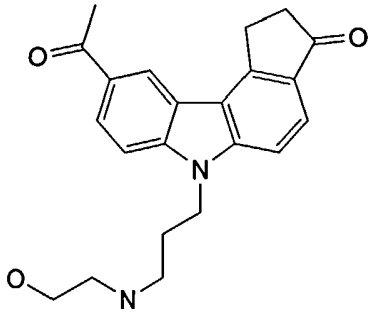
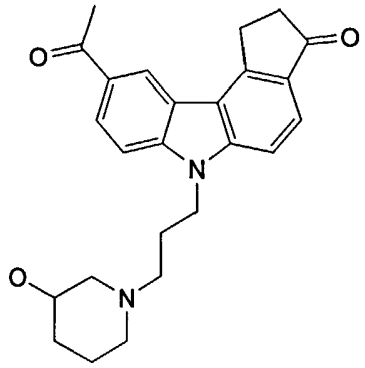
Ex.	Structure	MW	Ion	Rt	Anal. Method	Yield

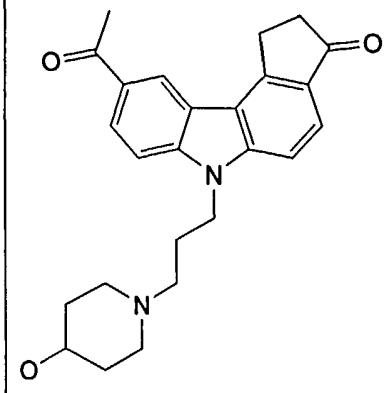
3-2		391	391	1.163	A	22
3-3		376	377	1.154	A	15
3-4		405	405	1.079	A	19

3-5		362	363	1.134	A	32
3-6		374	375	1.083	A	33
3-7		403	403	1.196	A	35

3-8		390	391	1.074	A	18
3-9		391	391	1.156	A	19
3-10		362	363	1.080	A	11

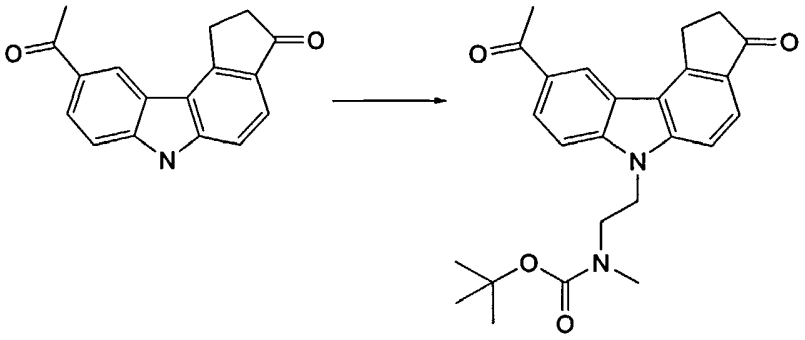
3-11		419	419	1.102	A	9
3-12		376	377	1.083	A	12
3-13		391	391	1.208	A	9

3-14		392	393	1.075	A	12
3-15		364	365	1.031	A	20
3-16		405	405	1.060	A	34

3-17		405	405	1.072	A	27

EXAMPLE 4

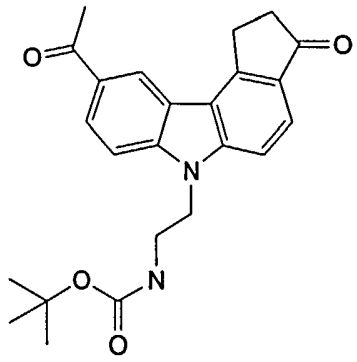
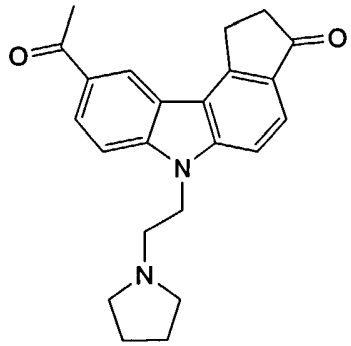
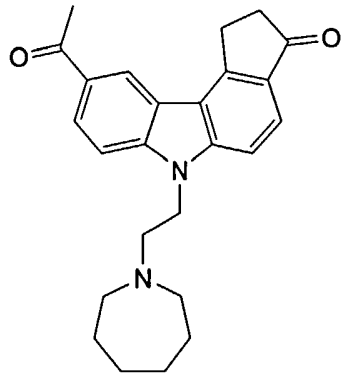
[00149] Compound 4-1. [2-(9-Acetyl-3-oxo-2,3-dihydro-1H-cyclopenta[*c*]carbazol-6-yl)-ethyl]-methylcarbamic acid *tert*-butyl ester.

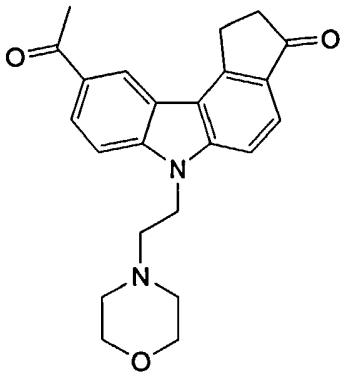
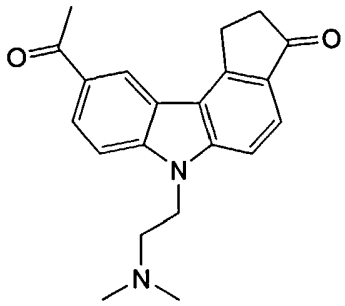
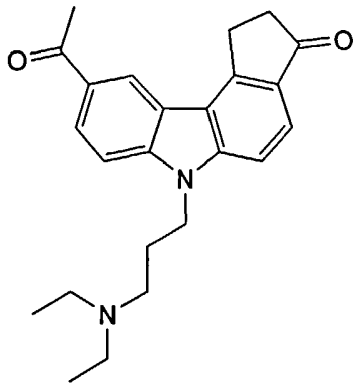


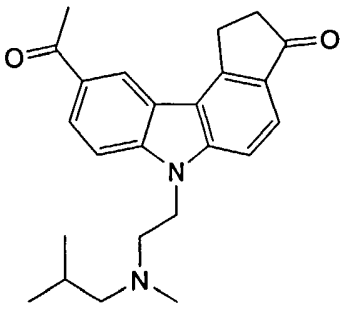
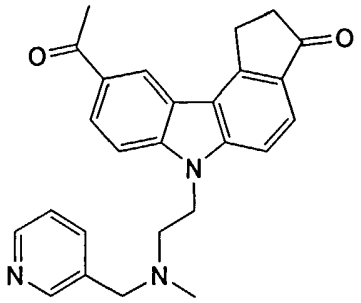
[00150] Step 1. A mixture of 9-acetyl-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one (Preparation 13-1, 281 mg, 1.07 mmol), methanesulfonic acid 2-(*tert*-butoxycarbonyl-methyl-amino)-ethyl ester (541 mg, 2.13 mmol) and cesium carbonate (1.39 g, 4.28 mmol) in *N,N*-dimethylformamide (3 mL) was stirred at 50 °C for 16 h and then at 80 °C for 5 h. The mixture was evaporated and the residue purified by column chromatography eluting with chloroform:methanol (100:0→90:10) to afford the title compound (120 mg, 0.29 mmol, 27%) as a white powder. LCMS: 93%, Rt 1.625 min, ESMS m/z 421 $(M+H)^+$.

[00151] Compounds 4-2 – 4-9 shown in the table were prepared in a similar manner using the appropriate carbazole/fused indole and alkylating agent.

Ex.	Structure	MW	Ion	Rt	Anal. Method	Yield

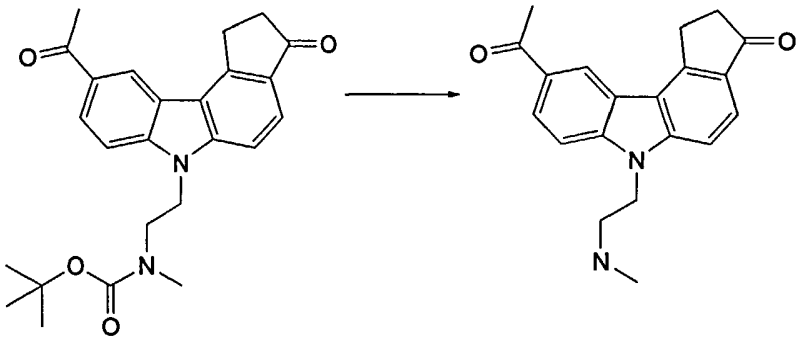
4-2		406	407	1.558	A	88
4-3		360	361	1.084	A	33
4-4		389	389	1.120	A	38

4-5		376	377	1.042	A	32
4-6		334	335	1.009	A	38
4-7		376	377	1.089	A	36

4-8		376	377	1.071	A	27
4-9		412	412	1.057	A	5

EXAMPLE 5

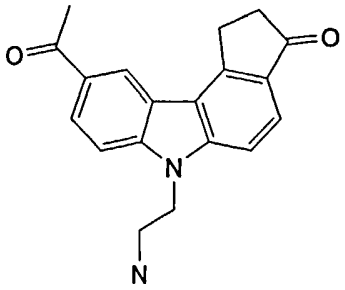
[00152] Compound 5-1. 9-Acetyl-6-(2-methylaminoethyl)-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one hydrochloride.



[00153] To a suspension of [2-(9-acetyl-3-oxo-2,3-dihydro-1H-cyclopenta[*c*]carbazol-6-yl)-ethyl]-methylcarbamic acid *tert*-butyl ester (Compound 4-1, 12 mg, 0.29 mmol) in 1,4-dioxane (1 mL) was added a solution of hydrogen chloride in 1,4-dioxane (4M, 1 mL). The

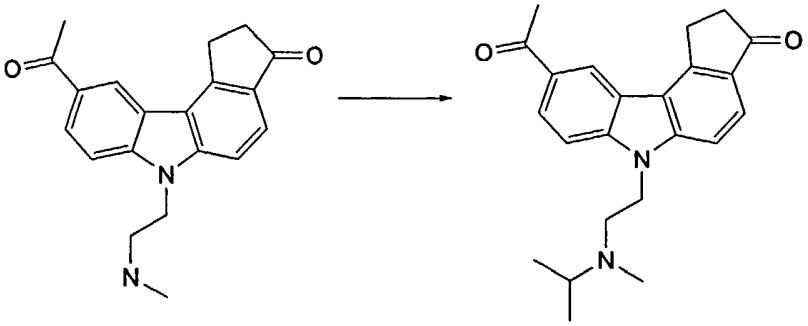
resulting mixture was stirred at 50 °C for 16 h and evaporated. The residue was triturated with diethyl ether (ca. 3 mL). The precipitate was collected and washed with methanol (2 x 1 mL) and diethyl ether (1 mL) to give the title compound (82 mg, 0.23 mmol, 80%) as an off-white powder. LCMS: 99%, Rt 0.983 min, ESMS m/z 321 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.08 (br. s., 2H), 8.70 (s, 1H), 8.21 (d, J = 8.7 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.77 - 7.91 (m, 2H), 4.87 (t, J = 6.4 Hz, 1H), 3.66 (br. s., 2H), 3.35 - 3.43 (m, 2H), 2.83 (qq, 2H), 2.73 (s, 3H), 2.59 (br. s., 3H).

[00154] Compound 5-2 shown in the table was prepared in a similar manner.

Ex.	Structure	MW	Ion	Rt	Anal. Method	Yield
5-2		306	307	0.979	A	94

EXAMPLE 6

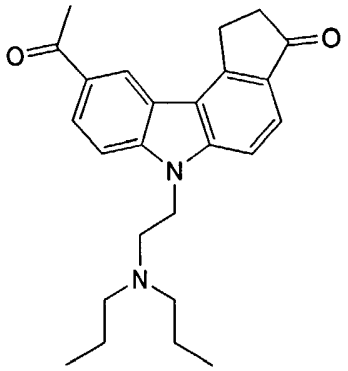
[00155] Compound 6-1. 9-Acetyl-6-[2-(isopropylmethylamino)-ethyl]-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one hydrochloride.

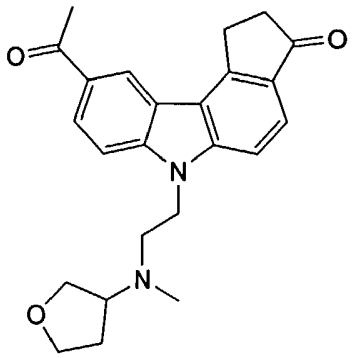
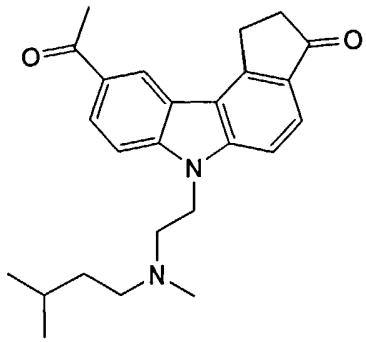


[00156] A mixture of (9-acetyl-6-(2-methylaminoethyl)-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one hydrochloride (Compound 5-1, 40 mg, 0.11 mmol), sodium

triacetoxyborohydride (279 mg, 1.32 mmol) and acetone (129 µL, 1.76 mmol) in dichloromethane (1.6 mL) was stirred at room temperature for 16 h. The reaction mixture was poured into water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate and evaporated. The residue was purified by column chromatography eluting with dichloromethane:methanol (100:0→95:5). The product was converted to its HCl salt by treatment with hydrogen chloride in ethyl acetate (0.5 M, 1.0 eq.) to afford the title compound (16 mg, 0.04 mmol, 36%) as a white powder. LCMS: 97%, Rt 1.037 min, ESMS m/z 363 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 8.70 (s, 1H), 8.21 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 5.13 - 5.00 (m, 2H), 3.66 (t, J = 10.2 Hz, 3H), 3.50 – 3.35 (m, 2H), 2.86 – 2.79 (m, 5H), 2.73 (s, 3H), 1.31 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H).

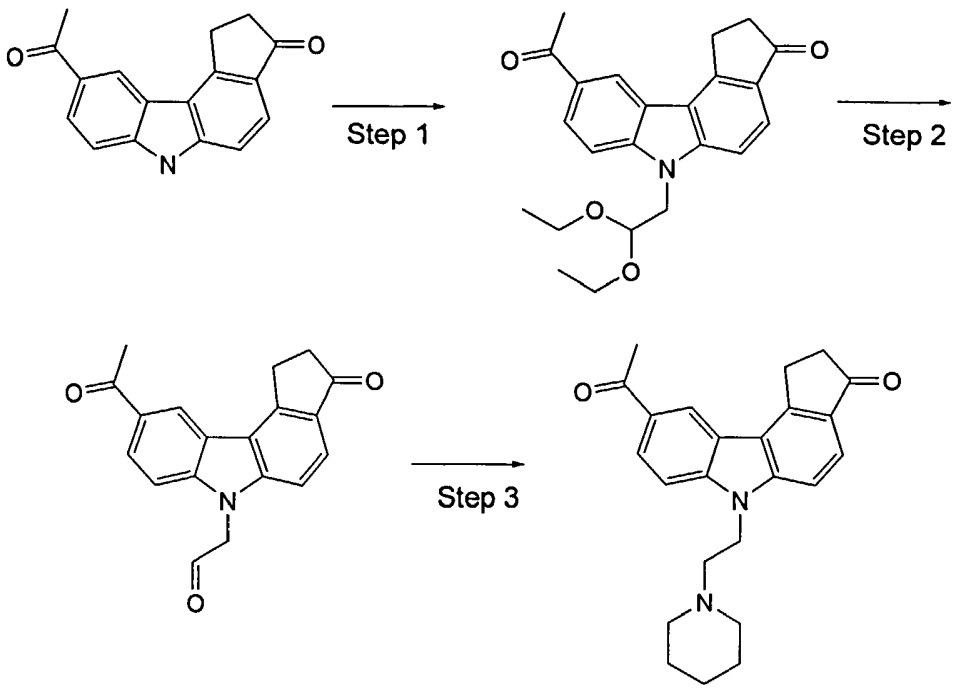
[00157] Compounds 6-2 – 6-4 shown in the table were prepared in a similar manner using the appropriate amine and aldehyde or ketone.

Ex.	Structure	MW	Ion	Rt	Anal. Method	Yield
6-2		391	391	1.107	A	49

6-3		390	391	1.012	A	63
6-4		391	392	1.223	A	61

EXAMPLE 7

[00158] Compound 7-1. 9-Acetyl-6-(2-piperidin-1-ylethyl)-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one.



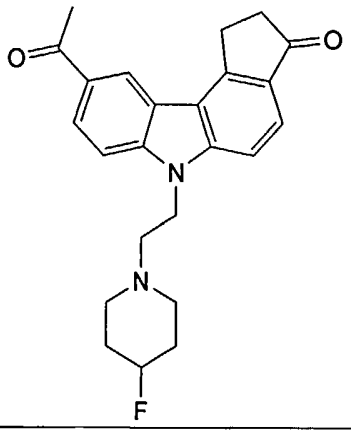
[00159] Step 1. A mixture of 9-acetyl-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one (Preparation 13-1, 1.70 g, 6.46 mmol), 2-bromo-1,1-diethoxyethane (2.65 mL, 19.4 mmol) and cesium carbonate (6.31 g, 19.4 mmol) in *N,N*-dimethylformamide (17 mL) was stirred at 80 °C for 2 h. An additional portion of 2-bromo-1,1-diethoxyethane (2.65 mL, 19.4 mmol) was added and the reaction was stirred at 80 °C for 2 h and poured into water (85 mL). The precipitate was collected and washed with water (20 mL) and diethyl ether (10 mL) to give the title compound (1.24 g, 3.27 mmol, 51%) as a light brown powder. LCMS: 95%, Rt 1.689 min, ESMS m/z 380 $(M+H)^+$.

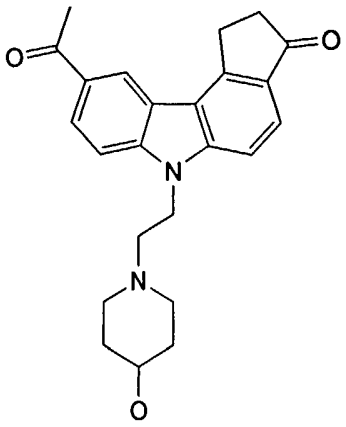
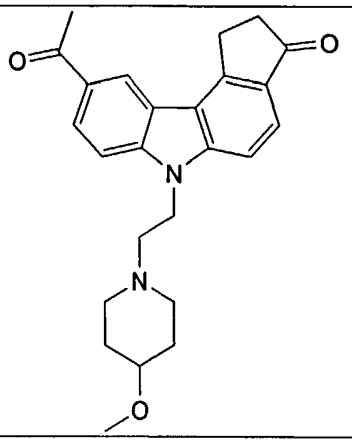
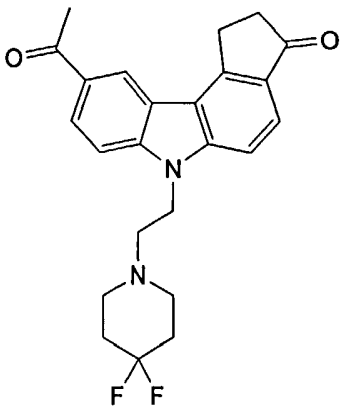
[00160] Step 2. A solution of 9-acetyl-6-(2,2-diethoxyethyl)-1,2-dihydro-6H-cyclopenta[*c*]carbazol-3-one (Compound 7a-1, 1.20 g, 3.16 mmol) in trifluoroacetic acid (11.3 mL) was stirred at room temperature for 1 h. The mixture was evaporated and the residue triturated with water (10 mL). The solid was washed with water (1 x 10 mL) and diethyl ether (1 x 10 mL) to give the title compound (0.75 g, 2.46 mmol, 78%) as an off-white powder. LCMS: inconclusive; hydrate, hemiacetal and aldehyde masses detected, TLC: OK.

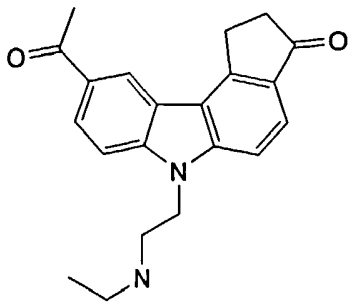
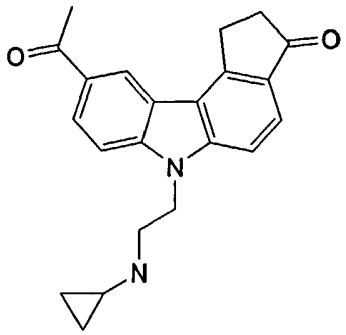
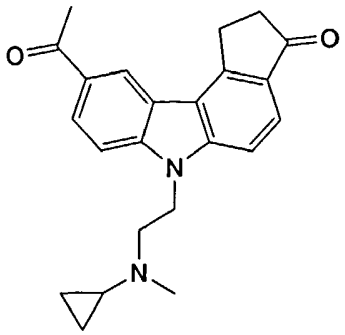
[00161] Step 3. A mixture of (9-acetyl-3-oxo-2,3-dihydro-1H-cyclopenta[*c*]carbazol-6-yl)-acetaldehyde (Compound 7b-1, 100 mg, 0.33 mmol) and piperidine (28 mg, 0.33 mmol) in dichloromethane (2 mL) was stirred at room temperature for 10 min. The mixture was then

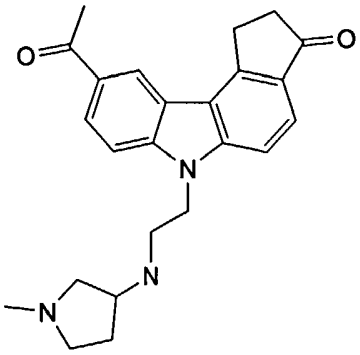
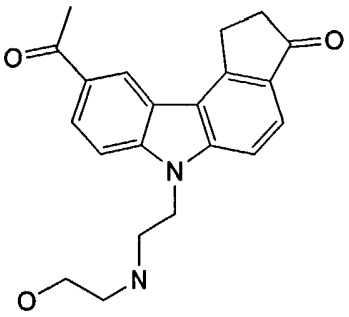
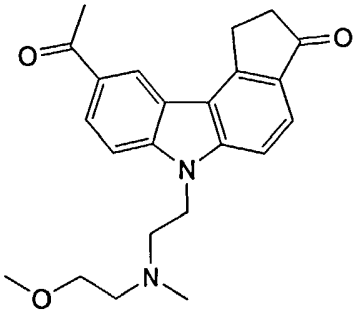
cooled to 0 °C and sodium triacetoxyborohydride (279 mg, 1.32 mmol) was added. The mixture was stirred at 0 °C for 1 h and room temperature for 2 h. The reaction mixture was poured into water (15 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over magnesium sulfate and evaporated. The residue was purified by column chromatography eluting with dichloromethane:methanol (100:0→95:5). The product was triturated with diethyl ether (ca. 1 mL) to afford the title compound (26 mg, 0.07 mmol, 21%) as a white powder. LCMS: 98%, Rt 1.068 min, ESMS m/z 375 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.74 (dd, J = 19.5, 8.5 Hz, 2H), 4.61 (t, J = 6.3 Hz, 2H), 3.64 (t, J = 4.9 Hz, 2H), 2.79 (t, J = 5.1 Hz, 2H), 2.71 (s, 3H), 2.65 (t, J = 6.2 Hz, 2H), 2.42 – 2.36 (m, 4H), 1.43 – 1.27 (m, 6H).

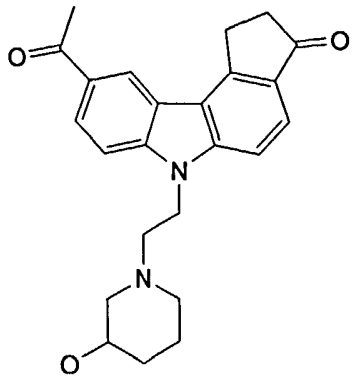
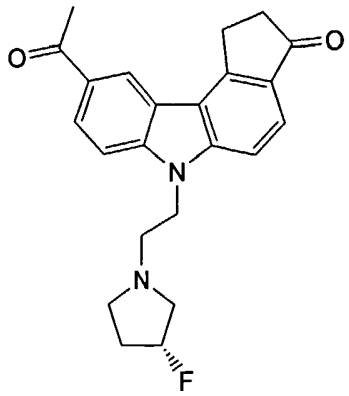
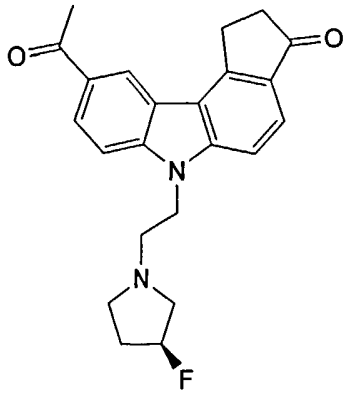
[00162] Compounds 7-2 – 7-18 shown in the table were prepared in a similar manner using the appropriate carbazole-aldehyde or fused indole-aldehyde, and amine.

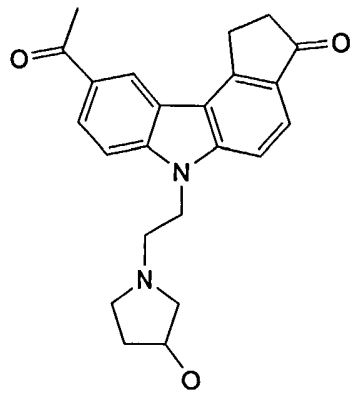
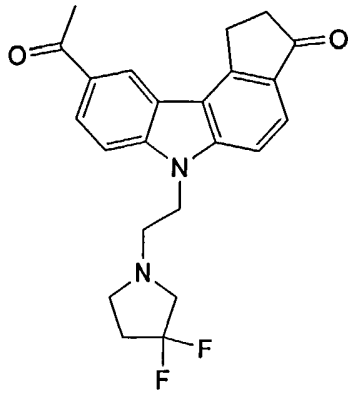
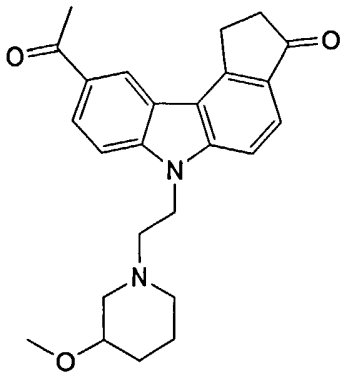
Ex.	Structure	MW	Ion	Rt	Anal. Method	Yield
7-2		392	393	1.083	A	40

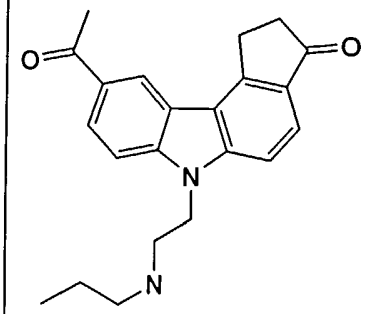
7-3		390	391	1.029	A	30
7-4		405	405	1.087	A	30
7-5		410	411	1.239	A	36

7-6		334	335	1.034	A	15
7-7		346	347	1.073	A	40
7-8		360	361	1.077	A	27

7-9		389	390	0.917	A	39
7-10		350	351	0.999	A	17
7-11		378	379	1.083	A	25

7-12		390	391	1.028	A	19
7-13		378	379	1.015	A	47
7-14		378	379	1.016	A	30

7-15		376	377	1.015	A	37
7-16		396	397	1.439	A	36
7-17		405	405	1.111	A	31

7-18		348	349	1.041	A	16

EXAMPLE 8

[00163] PLX compounds were assessed for anti-fungal activity against a *Candida albicans* strain obtained from ATCC. Assays were carried out according to the protocol provided by the Clinical and Laboratory Standards Institute, USA. Briefly, in a primary toxicity screen the compounds were incubated at 20 μM with *C. albicans* for 24 h. Colonies of *C. albicans* were plated in 100 μM of sterile water to 10^5 CFU/ml in 96 well plates. Compounds were diluted to 100 μM in x2 RPMI 1640 with MOPS and glucose and added to each well. OD readings were taken in a spectrophotometer after 24 hours at $\lambda = 450$ nm. Positive controls were CBL100 at 20 μM and Amphotericin B at 1 mg/ml. The negative control was a 0.2% DMSO solution. Percentage reductions of cells compared to DMSO control (taken as 100%) were calculated after subtraction of background (broth without cells) for each compound. Experiments were performed in quadruplicate and repeated at least twice. Compounds that showed ≥50% average growth inhibition against *C.albicans* were chosen for secondary screening.

[00164] Secondary screening was performed using 8 replicates and with compound doses from 0.08 to 20 μM (10 two fold dilutions). The same compounds were used as positive and negative controls, except that CBL100 was assessed in a dose-dependent manner in parallel with each screening experiment, and Amphotericin B was assessed at four concentrations (2.0, 1.0, 0.5, 0.25 mg/ml) in each plate in quadruplicate. Percentage reductions of cells compared to DMSO control (taken as 100%) were calculated after subtraction of background (broth without cells) for each well. The MIC was calculated as the average dose of compound required to inhibit

95% of *C. albicans* growth after incubation for 24 hours. Averages were calculated from 8 replicates of two separate experiments.

EXAMPLE 9

[00165] This example shows a table of the compounds of the present disclosure and their activity towards three different fungal species (i.e., *C. albicans*, *C. glabrata*, and *A. fumigatus* (48 h incubation)) using the method described in Example 20. The MIC for 95% inhibition of growth is divided into 4 categories: A <5 μM, B 5-10 μM, C >10 μM, D < 40% growth inhibition at 20 μM.

Ex.	C. albicans	C. glabrata	A. fumigatus
1-1	D		
2-1	C		
3-1	B		
3-2	C		
3-3	D		
3-4	C		
3-5	C		
3-6	B		
3-7	A		
3-8	C		
3-9	B		
3-10	C		
3-11	C		
3-12	B		
3-13	D		
3-14	C		
3-15	D		
3-16	D		
3-17	D		
4-3	A		
4-4	A	C	C
4-5	C		
4-6	A		
4-7	A		
4-8	C		
4-9	D		
5-1	C		

5-2	D		
6-1	A	A	C
6-2	D		
6-3	C		
6-4	C		
7-1	A	B	C
7-2	C		
7-3	D		
7-4	C		
7-5	D		
7-6	C		
7-7	C		
7-8	C		
7-9	D		
7-10	D		
7-11	B		
7-12	D		
7-13	C		
7-14	C		
7-15	D		
7-16	D		
7-17	C		
7-18	C		

EXAMPLE 10

[00166] The toxicity of PLX compounds toward non-tumor (MT2 – *in vitro* transformed lymphoblast cells; and NKE-hTERT – immortalized kidney epithelial cells) and tumor (RCC45 – renal cell carcinoma; and RAW264 – leukemia) cell lines was assessed according to SOP 2-18 (Appendix X). These assays were run only for compounds deemed active in the primary screen against *C. albicans*. Briefly, mammalian cells were plated in 96 well plates at 5 x 10^3/well in 100 µl of standard medium. After overnight incubation dilutions of PLX compounds (0.16-40 µM as 10 twofold serial dilutions) were added in 100 µL of medium to cells (Final concentration range 0.08-20 µM). The negative control was 0.2% DMSO; no positive control was used. Background readings were obtained from wells containing standard medium without cells. Cell were incubated for 24 hours and the Cell Titer Blue reagent (Promega) was then added to each well to

assess cell viability according to the manufacturer's protocol. Assays were run in triplicate and experiments were repeated at least twice. Concentrations for 50% inhibition (IC50 or LC50) were calculated for each compound as the average of three readings from two independent experiments.

EXAMPLE 11

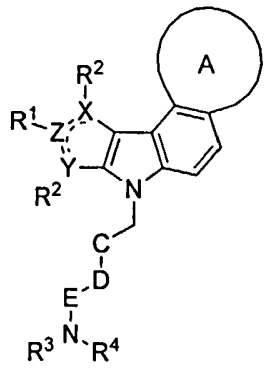
[00167] This example shows a table of the compounds of the present disclosure and their activity towards the cell lines described in Example 22. The LC50 for inhibition of growth is divided into 4 categories: A <1 μM, B 1-5 μM, C 5-20 μM, D >20 μM.

[00168] While the disclosure has been particularly shown and described with reference to specific embodiments (some of which are preferred embodiments), it should be understood by those having skill in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the present disclosure as disclosed herein.

Ex.	NKE	MT2	RAW264	RCC45
3-1		C		
3-6		C		
3-9		C		
3-12		C		
3-14		B		
4-3	D	B		
4-4	D	C	A	A
4-6	D	B		
4-7	B	B		
6-1	D	A		
7-1	B	D		
7-4		C		
7-11		D		
7-17		C		
7-18		C		

Sample claims:

1. A compound having the following structure (I):

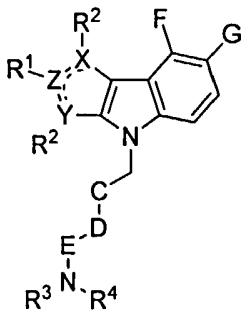


(I)

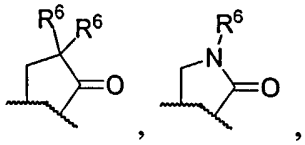
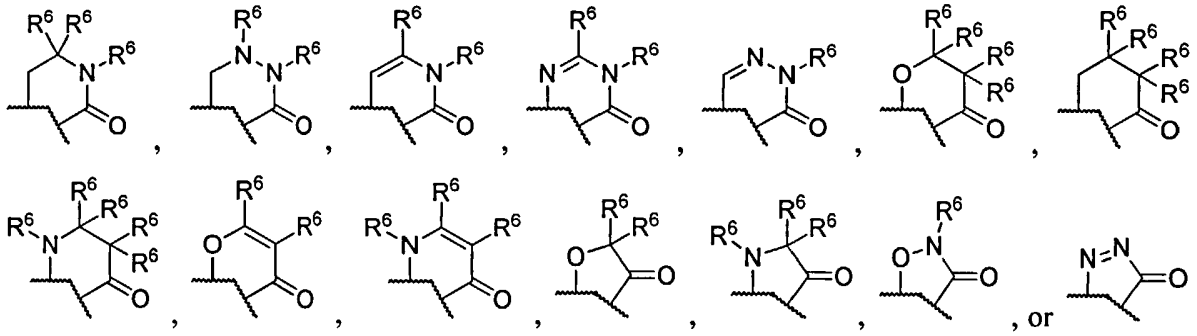
wherein R^1 is a five or six membered unsubstituted or substituted carbocycle or heterocycle, a ketone group, an amide group, an ester group or a cyano group, or R^1 and X together with the carbon to which they are attached form a five to seven membered carbocyclic or heterocyclic ring; R^2 at each occurrence is independently absent, a hydrogen atom, a fluorine atom, a chlorine atom, a hydroxy group, a cyano group, a substituted or unsubstituted C_1-C_3 alkyl group, or a substituted or unsubstituted C_1-C_3 alkoxy group; R^3 is selected from the group consisting of a hydrogen atom, a substituted or unsubstituted C_1-C_6 alkyl group, cycloalkyl group, heterocycloalkyl group, or taken together with R^4 and the nitrogen atom to which they are attached form a four to eight membered substituted or unsubstituted heterocyclic ring; R^4 is selected from the group consisting of a hydrogen atom, a substituted or unsubstituted C_1-C_6 alkyl group, cycloalkyl group, and heterocycloalkyl group; Z is a carbon atom or nitrogen atom; X and Y are independently a carbon, nitrogen, oxygen or sulfur atom and when Z is a carbon atom there is a double bond between X and Z or Y and Z; C is absent, C=O, or CH(R^5); D is absent or CH_2; E is absent, CH_2, or CH(C_1-C_3 alkyl); optionally, E and R^4 taken together with the nitrogen to which they are attached form a four to seven membered heterocyclic ring substituted with one to twelve R^5's; R^5 at each occurrence is independently selected from the group consisting of a hydrogen atom, a fluorine atom, a hydroxyl group, a cyano group, a substituted or unsubstituted C_1-C_3 alkyl group, and a C_1-C_3 alkoxy group; optionally, C and R^4 taken together with the atoms between them form a four to seven membered heterocyclic ring substituted with one to twelve

R^5's, and the A ring is a substituted or unsubstituted 5 to 7 membered carbocyclic or heterocyclic ring.

2. The compound of claim 1, wherein the compound has the following structure (II):

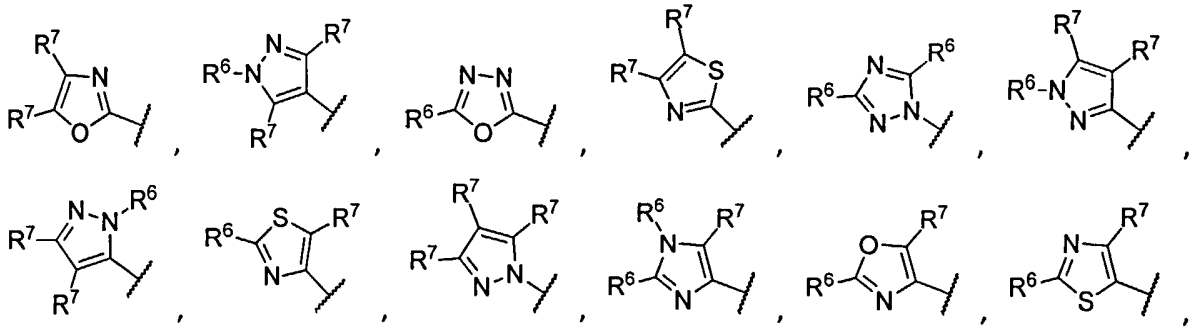


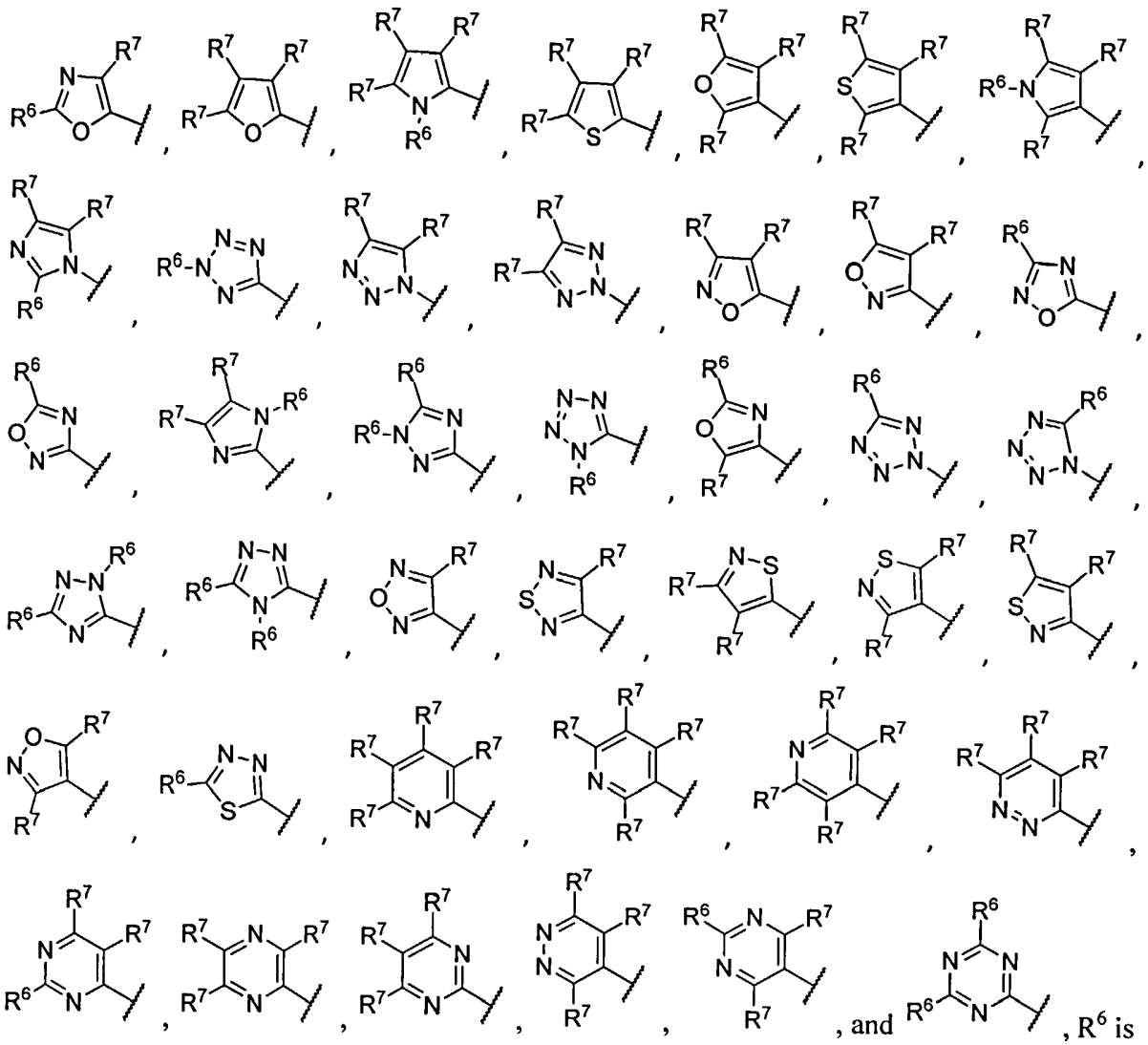
(II)

wherein F and G are replaced by the atoms of the following structures:  ,  , or

to form a ring, and R^6 is hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group.

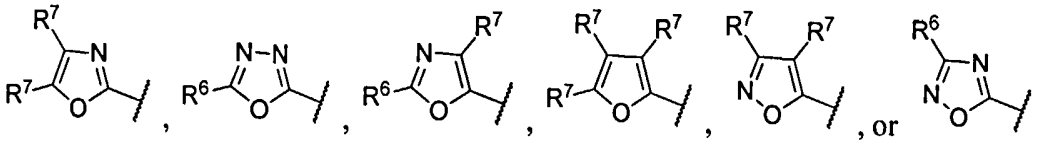
3. The compound of claim 1, wherein R^1 is selected from one of the following structures:



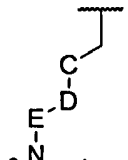


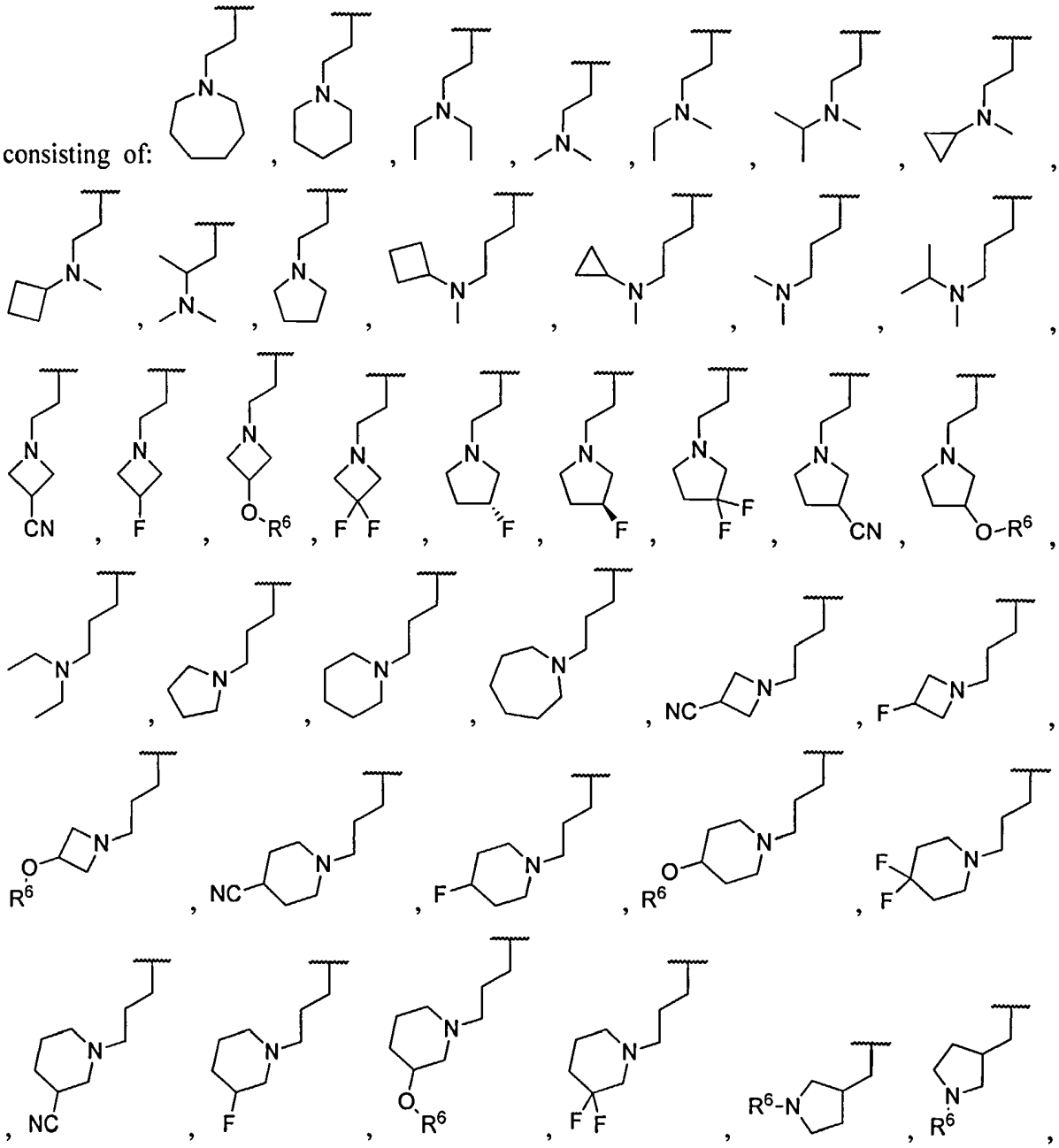
, and , R^6 is a hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group, and R^7 is a hydrogen atom, a fluorine atom, a chlorine atom, a cyano group, a substituted or unsubstituted C_1-C_3 alkyl group or C_1-C_3 alkoxy group.

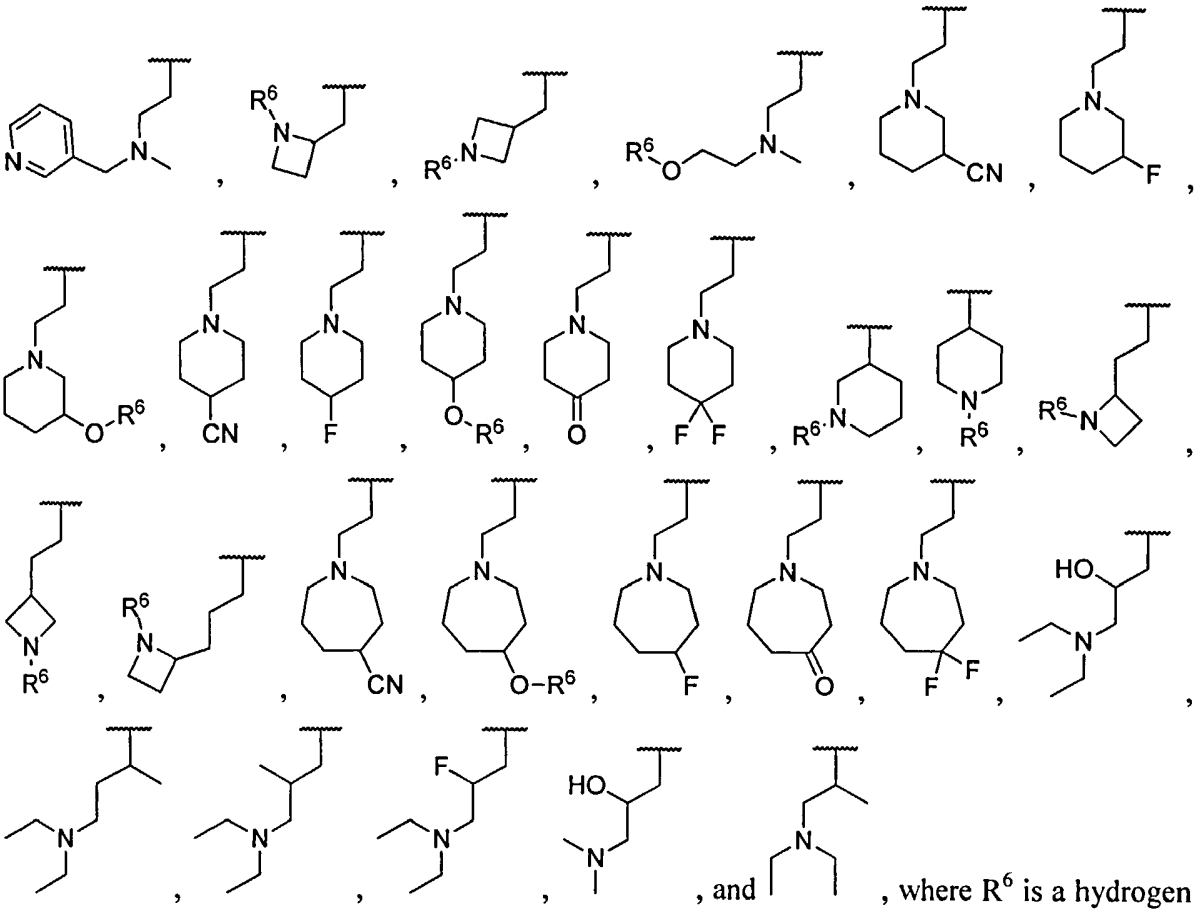
4. The compound of claim 3, wherein R^1 is selected from one of the following structures:



, or .

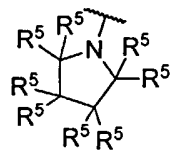
5. The compound of claim 1, wherein the structure  is selected from the group consisting of:





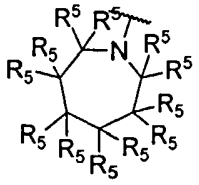
atom or a substituted or unsubstituted C_1-C_3 alkyl group.

6. The compound of claim 1, wherein R^3 is $-CH(CH_3)_2$, $-CH_2CH_3$, cyclopropyl, or cyclobutyl; R^4 is -a hydrogen atom, $-CH_3$, $-CH_2CH_3$ or taken together with R^3 and the nitrogen to which they are attached form the following structures:



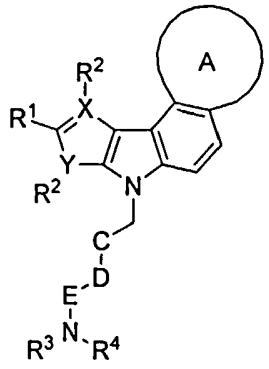
,

, or



.

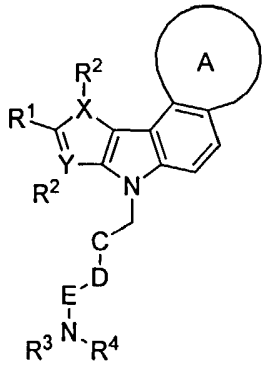
7. The compound of claim 1, wherein the compound has the following structure (III):



(III),

wherein X is a carbon or nitrogen atom.

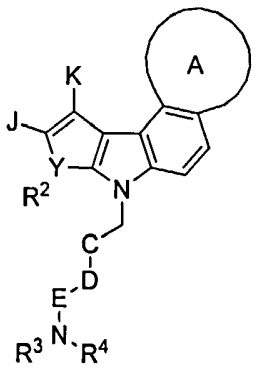
8. The compound of claim 1, wherein the compound has the following structure (IV):



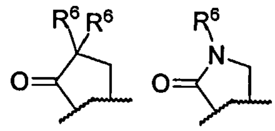
(IV),

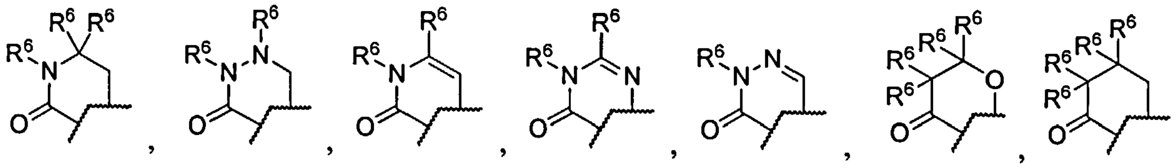
wherein Y is a carbon or nitrogen atom.

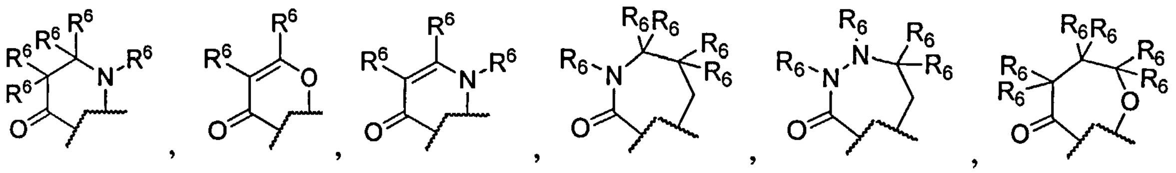
9. The compound of claim 1, wherein the compound has the following structure (V):

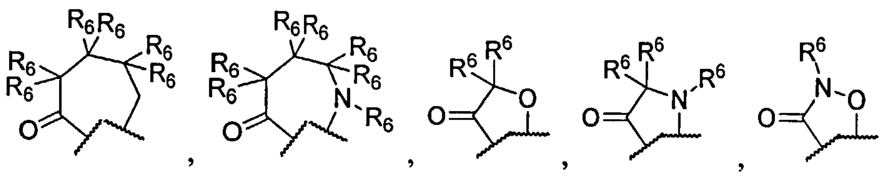
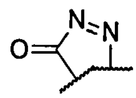


(V),

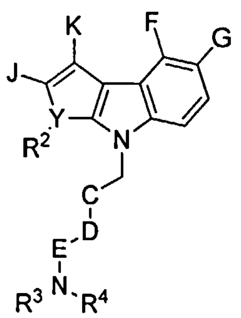
wherein J and K are replaced by the atoms of the following structures: 



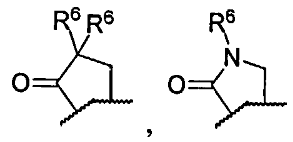


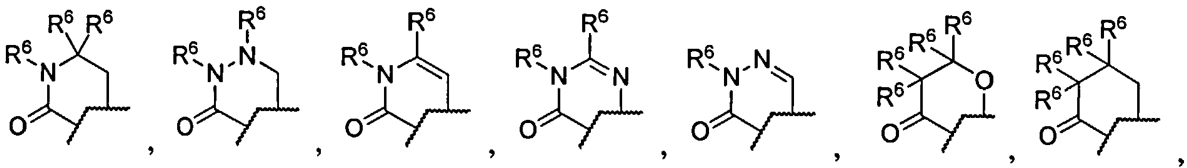
 , or  to form a ring, and R^6 is a hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group.

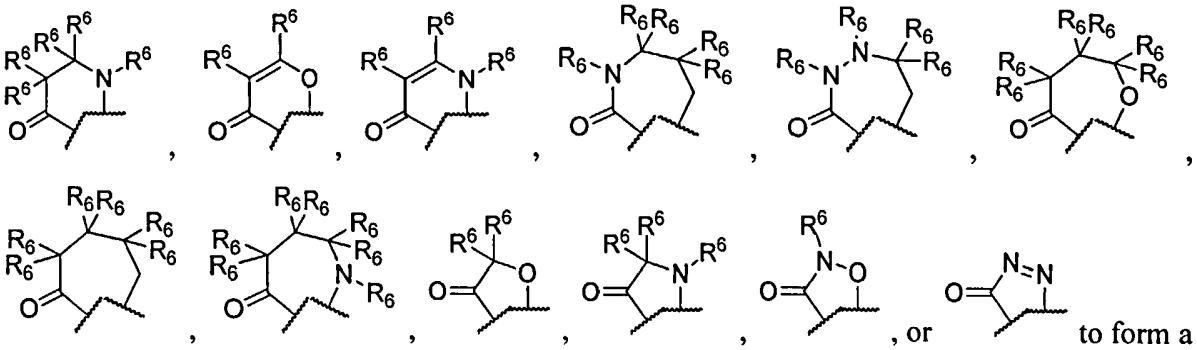
10. The compound of claim 1, wherein the compound has the following structure (VI):



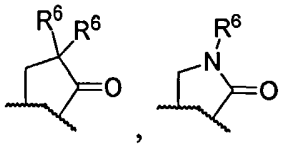
(VI),

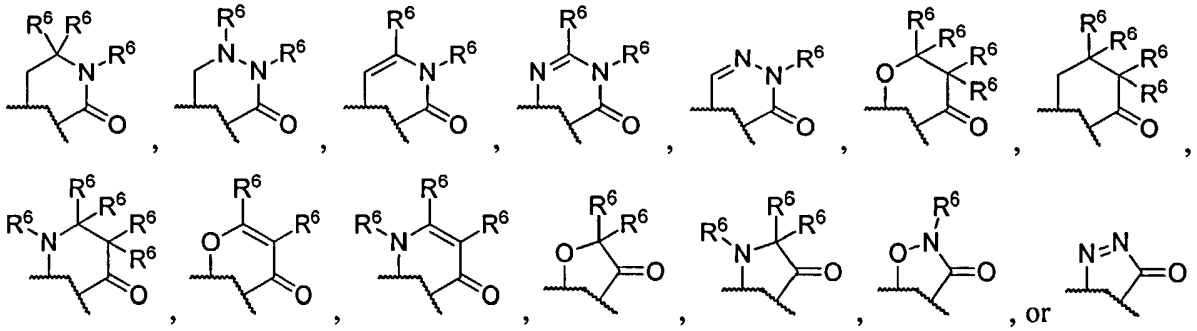
wherein J and K are replaced by the atoms of the following structures: 





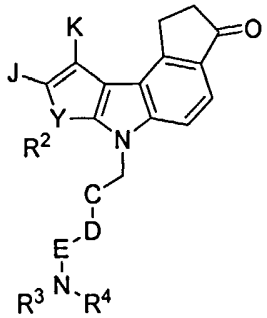
ring and F and G are replaced by the atoms of the following structures:



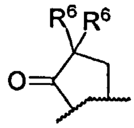
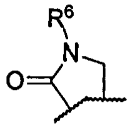
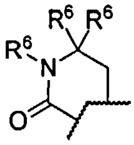
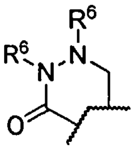
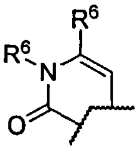
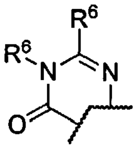
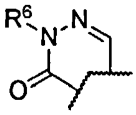
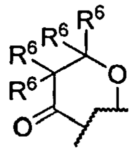
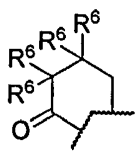
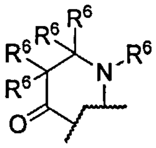
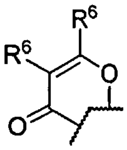
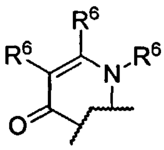
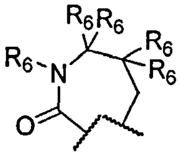
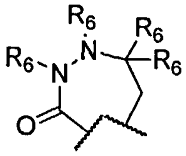
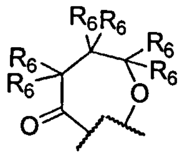
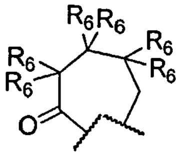
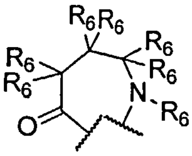
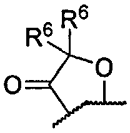
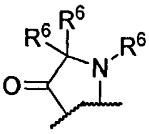
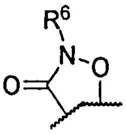
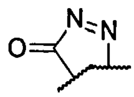


to form a ring, wherein R^6 is a hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group.

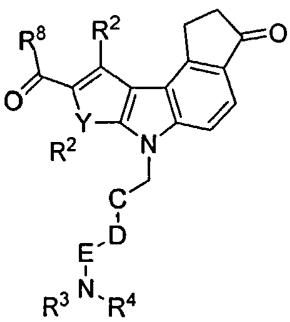
11. The compound of claim 1, wherein the compound has the following structure (VII):



(VII),

wherein J and K are replaced by the atoms of the following structures:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  to form a ring, wherein R^6 is a hydrogen atom or a substituted or unsubstituted C_1-C_3 alkyl group.

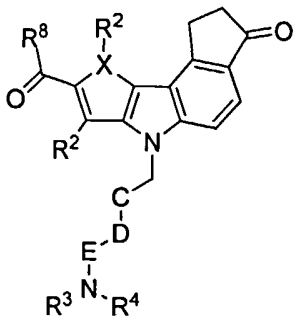
12. The compound of claim 1, wherein the compound has the following structure (VIII):



(VIII),

wherein R^8 is a substituted or unsubstituted C_1-C_3 alkyl group.

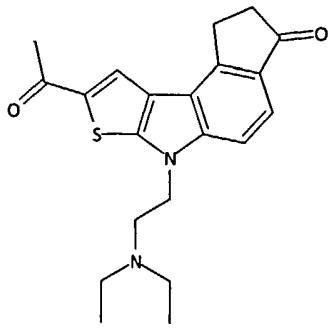
13. The compound of claim 1, wherein the compound has the following structure (IX):



(IX),

wherein R^8 is a substituted or unsubstituted C_1-C_3 alkyl group.

14. The compound of claim 1, wherein the compound is selected from the following structures:



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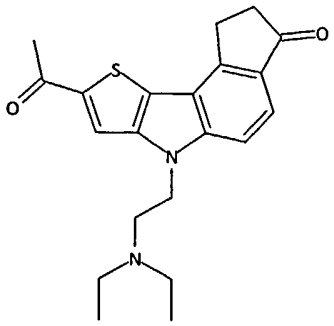

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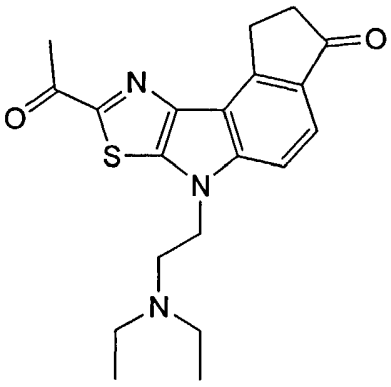

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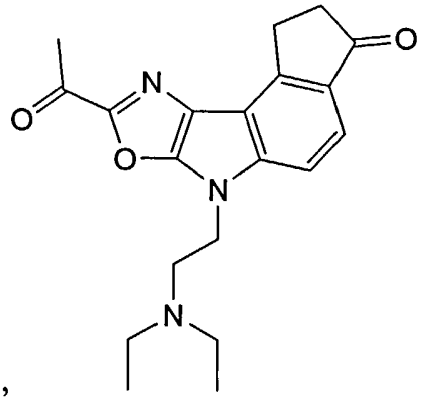

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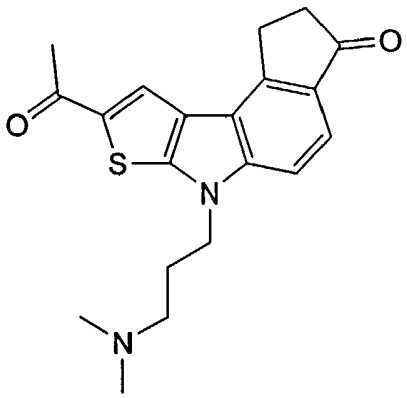
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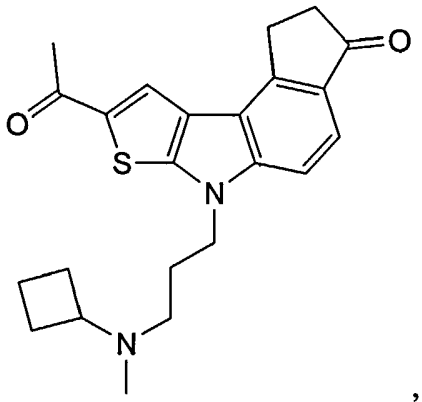
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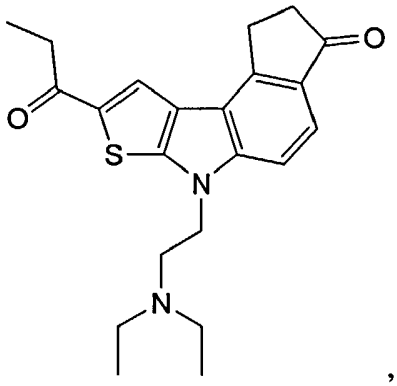
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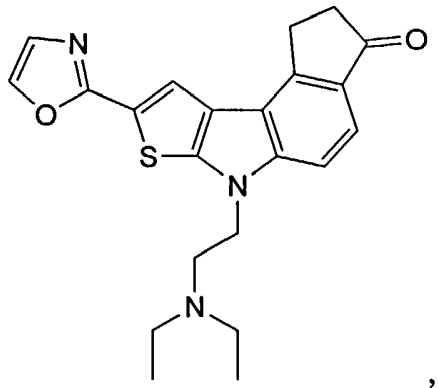
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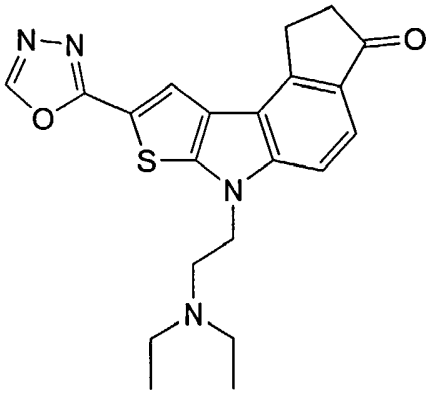
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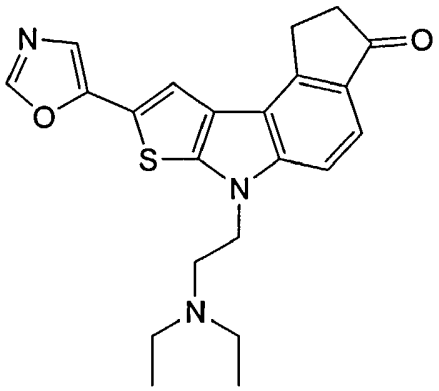
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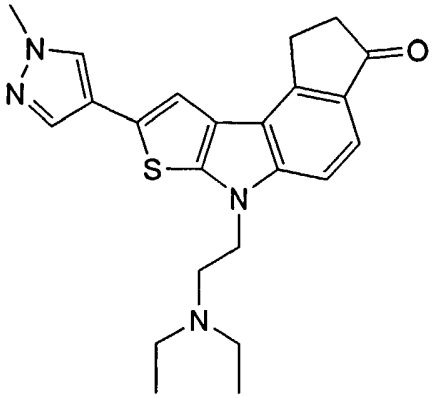
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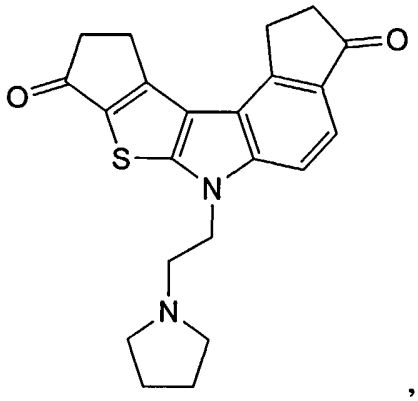
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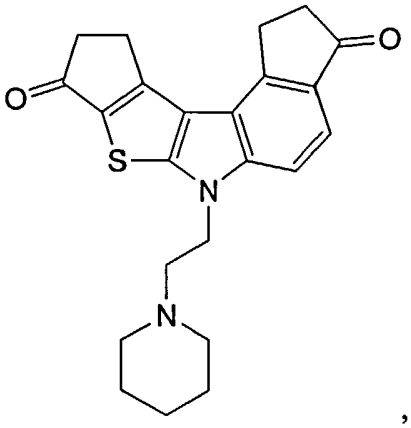
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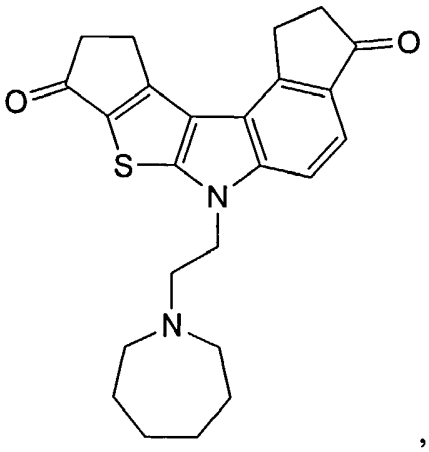
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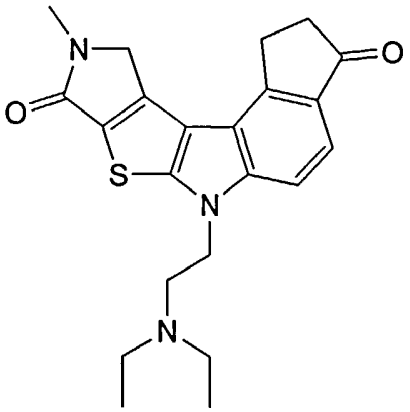
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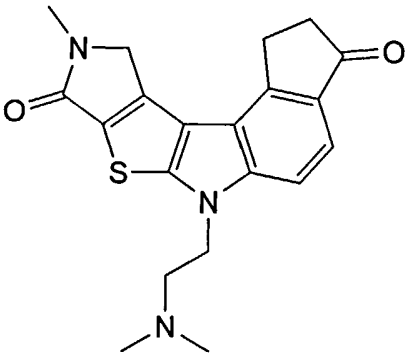
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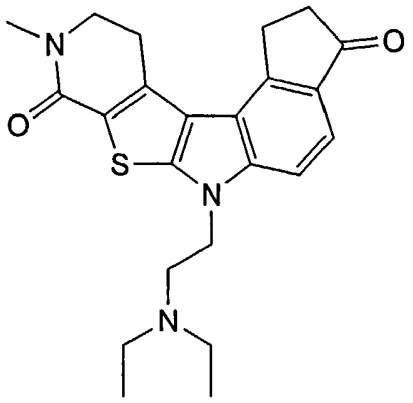
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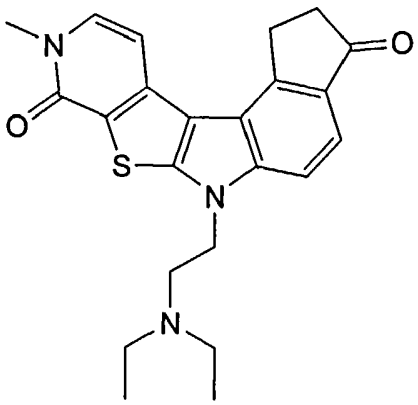
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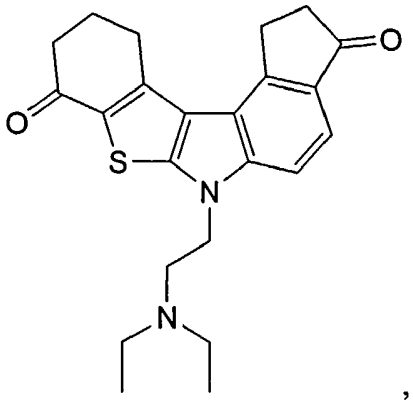
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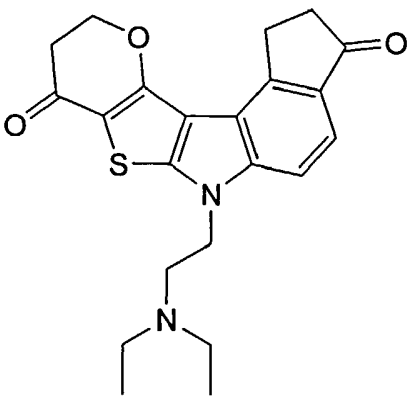
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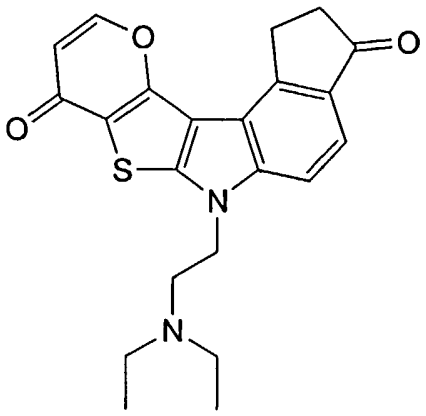

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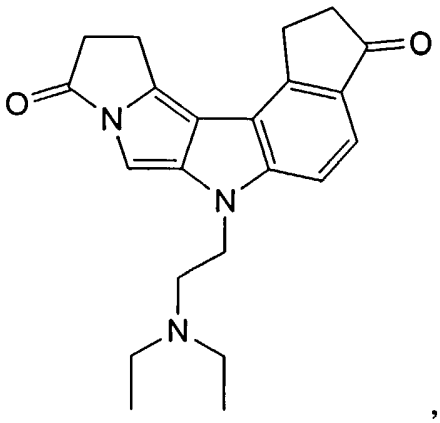

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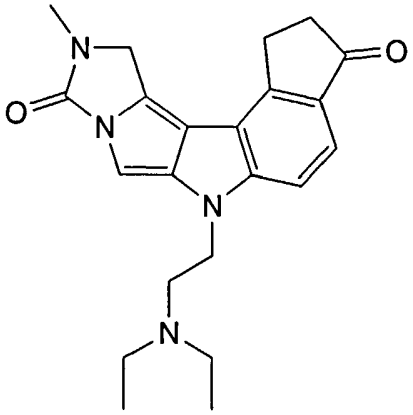

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15. A method of treating an individual diagnosed with or suspected of having a microbial, protozoan, or viral infection comprising administering to the individual a therapeutically effective amount of a compound of claim 1.

16. The method of claim 15, wherein the microbial infection is a fungal infection.

17. The method of claim 16, wherein the fungal infection is from pathogenic fungi from *C. albicans*, *C. glabrata*, *A. fumigatus*, or a combination thereof.

18. A method of treating cancer in an individual diagnosed with or suspected of having cancer comprising administering to the individual a therapeutically effective amount of a compound of claim 1.

19. A composition comprising the compounds of any of claims 1 to 14.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/RU 2013/000867

A. CLASSIFICATION OF SUBJECT MATTER

C07D 209/56 *(2006.01)*
C07D 209/70 *(2006.01)*
C07D 487/04 *(2006.01)*
C07D 495/22 *(2006.01)*
C07D 498/22 *(2006.01)*
C07D 513/22 *(2006.01)*
A61K 31/404 *(2006.01)*
A61P 31/00 *(2006.01)*
A61P 29/00 *(2006.01)*
A61P 35/00 *(2006.01)*

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 209/56, 209/70, 487/04, 495/22, 498/22, 513/22, A61K 31/404, 31/407, A61P 31/00, 29/00, 35/00

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

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

STN, PatSearch (RUPTO internal)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/042445 A1 (CLEVELAND BIOLABS, INC.) 15.04.2010, abstract, paragraphs [0071], [0074], [0076], [0077], [0279], [0360], Table 1on pp. 129-130	1-19
X	RU 2474612 C2 (INCURON LLC et al.) 10.02.2013, abstract, p. 7, claims 1, 4	1-14, 18

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2014 (28.04.2014)	16 July 2014 (16.07.2014)
Name and mailing address of the ISA/RU: FIPS, Russia, 123995, Moscow, G-59, GSP-5, Berezhkovskaya nab., 30-1 Facsimile No. +7 (499) 243-33-37	Authorized officer V. Odintsova Telephone No. 8(495)531-64-81

Form PCT/ISA/210 (second sheet) (July 2009)