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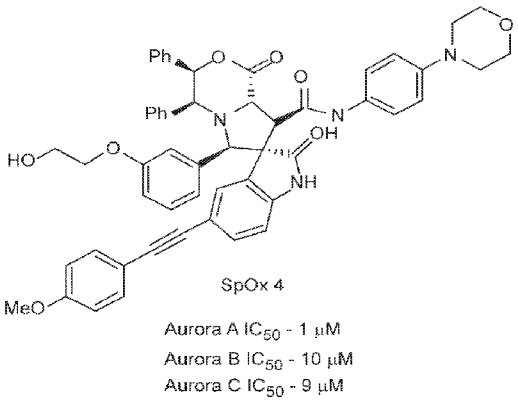
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(54) Title: SPIROOXINDOLE INHIBITORS OF AURORA KINASE



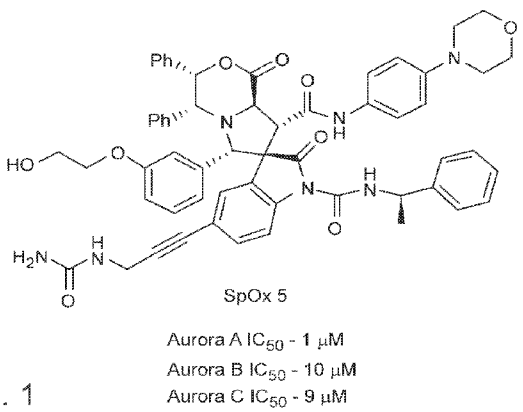


FIG. 1

(57) Abstract: Aurora kinases have been found to be overexpressed in many tumors including breast, colon, and pancreatic cancers. The present invention provides novel inhibitors and/or binders of Aurora kinases. Certain of the spirooxindole compounds are specific inhibitors or binders of Aurora A, B, or C kinases. The compounds are useful in both the diagnosis and treatment of proliferative diseases such as cancer. Pharmaceutical compositions and method of using the compounds to treat proliferative diseases are also provided.

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SPIROOXINDOLE INHIBITORS OF AURORA KINASE

Related Applications

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, USSN 60/938,362, filed May 16, 2007, which is incorporated herein by reference.

Government Support

[0001] This invention was made with U.S. Government support from the Initiative for Chemical Genetics (20XS139A) and National Institute of General Medical Sciences (GM38627). The U.S.Government has certain rights in the invention.

Background of the Invention

[0001] The members of the Aurora kinase family are serine/threonine kinases which are involved in mitosis (Keen *et al.*, *Nat. Rev. Cancer*, 4:927, 2004; incorporated herein by reference). These kinases have been found to regulate multiple steps in mitosis including centrosome duplication, formation of bipolar mitotic spindles, and chromosome alignment on the mitotic spindle. Centrosomes act as mitotic spindle pole bodies during mitosis. Abnormal centrosome numbers are frequently detected in human solid tumors and are a hallmark of genomically unstable cells.

[0002] Three Aurora kinases, A, B, and C, are known. Aurora A kinase localizes to the duplicated centrosomes and to the spindle poles during mitosis and assists with centrosome maturation and separation. Aurora B kinase is a chromosomal passenger protein which is localized to the centromeric regions of the chromosomes in the early stages of mitosis and accumulates in the spindle midzone and midbody. The role of Aurora C kinase is unknown currently.

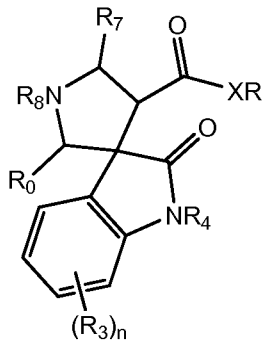
[0003] Both Aurora A and Aurora B kinases are overexpressed in many tumors including breast, colon, and pancreatic cancers. Numerous literature reports have shown that small molecule Aurora kinase inhibitors may be useful in the teatment of cancer. The activity of these compounds has been demonstrated both *in vitro* and *in vivo*. Examples of such compounds include VX-680 from Vertex (*Nature Med.* 10:262, 2004; incorporated herein by

reference); hesperadin (*J. Cell. Biol.* 161:281, 2003; incorporated herein by reference); and ZN447439 from AstraZeneca (*J. Cell. Biol.* 161:267, 2003; incorporated herein by reference.

Summary of the Invention

[0004] The present invention stems from the recognition that small molecule inhibitors and/or binders of Aurora kinases may be useful in the diagnosis and treatment of proliferative diseases such as cancer since these kinases have been found to be overexpressed in many tumors. The present invention provides a novel class of spirooxindole compounds shown to be inhibitors and/or binders of Aurora kinases. The inventive compounds have been found to inhibit Aurora kinases *in vitro* and have been found to be cytotoxic to cancer cell lines (*e.g.*, colorectal cancer cells) in cell culture. Fluorescent derivatives of the inventive compounds have been found to be useful in imaging cells to identify cells undergoing mitosis such as malignant cells. Therefore, the present invention represents an important advance in the field of Aurora kinase inhibitors by providing a novel class of compounds that bind to and/or inhibit Aurora kinases.

[0005] Inventive compounds are of the formula:



wherein

n is an integer between 1 and 5, inclusive;

X is O, S, or NR_2;

R_0 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_A$; $-C(=O)R_A$; $-C(=O)N(R_A)_2$; $-CO_2R_A$; -CN; -SCN; $-SR_A$; $-SOR_A$; $-SO_2R_A$; $-NO_2$; $-N(R_A)_2$; $-NHC(O)R_A$; or $-C(R_A)_3$; wherein each occurrence of R_A is

independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_2 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_B$; $-C(=O)R_B$; $-C(=O)N(R_B)_2$; $-CO_2R_B$; -CN; -SCN; $-SR_B$; $-SOR_B$; $-SO_2R_B$; $-NO_2$; $-N(R_B)_2$; $-NHC(O)R_B$; or $-C(R_B)_3$; wherein each occurrence of R_B is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_3 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_C$; $-C(=O)R_C$; $-C(=O)N(R_C)_2$;$-CO_2R_C$; -CN; -SCN; $-SR_C$; $-SOR_C$; $-SO_2R_C$; $-NO_2$; $-N(R_C)_2$; $-NHC(O)R_C$; or $-C(R_C)_3$; wherein each occurrence of R_C is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

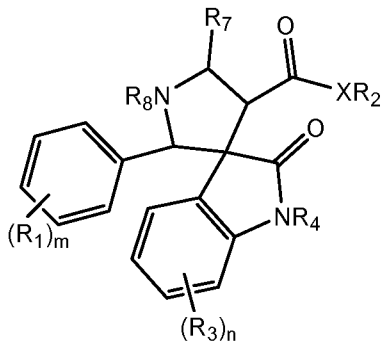
each occurrence of R_4 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_D$; $-C(=O)R_D$; $-C(=O)N(R_D)_2$; $-CO_2R_D$; -CN; -SCN; $-SR_D$; $-SOR_D$; $-SO_2R_D$; $-NO_2$; $-N(R_D)_2$; $-NHC(O)R_D$; or $-C(R_D)_3$; wherein each occurrence of R_D is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino,

heteroaryloxy; or heteroarylthio moiety;

R_7 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_G$; $-C(=O)R_G$; $-N(R_G)_2$; $-CO_2R_G$; -CN; -SCN; $-SR_G$; $-SOR_G$; $-SO_2R_G$; $-NO_2$; $-N(R_G)_2$; $-NHC(O)R_G$; or $-C(R_G)_3$; wherein each occurrence of R_G is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_8 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_H$; $-C(=O)R_H$; $-C(=O)N(R_H)_2$; $-CO_2R_H$; -CN; -SCN; $-SR_H$; $-SOR_H$; $-SO_2R_H$; $-NO_2$; $-N(R_H)_2$; $-NHC(O)R_H$; or $-C(R_H)_3$; wherein each occurrence of R_H is independently a hydrogen, halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; wherein R_7 and R_8 may be taken together to form a cyclic moiety.

[0006] In certiain embodiments, R_0 is an optionally substituted phenyl moiety leading to inventive compounds of the formula:



wherein

n is an integer between 1 and 5, inclusive;

m is an integer between 1 and 4, inclusive;

X is O, S, or NR_2;

R_1 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_A$; $-C(=O)R_A$; $-C(=O)N(R_A)_2$; $-CO_2R_A$; -CN; -SCN; $-SR_A$; $-SOR_A$; $-SO_2R_A$; $-NO_2$; $-N(R_A)_2$; $-NHC(O)R_A$; or $-C(R_A)_3$; wherein each occurrence of R_A is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_2 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_B$; $-C(=O)R_B$; $-C(=O)N(R_B)_2$; $-CO_2R_B$; -CN; -SCN; $-SR_B$; $-SOR_B$; $-SO_2R_B$; $-NO_2$; $-N(R_B)_2$; $-NHC(O)R_B$; or $-C(R_B)_3$; wherein each occurrence of R_B is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

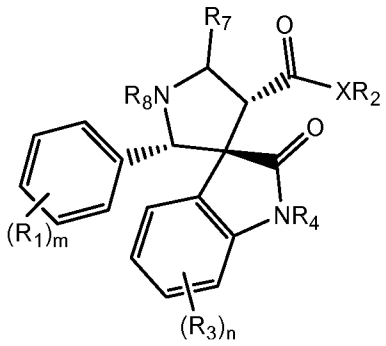
each occurrence of R_3 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_C$; $-C(=O)R_C$; $-C(=O)N(R_C)_2$;$-CO_2R_C$; -CN; -SCN; $-SR_C$; $-SOR_C$; $-SO_2R_C$; $-NO_2$; $-N(R_C)_2$; $-NHC(O)R_C$; or $-C(R_C)_3$; wherein each occurrence of R_C is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

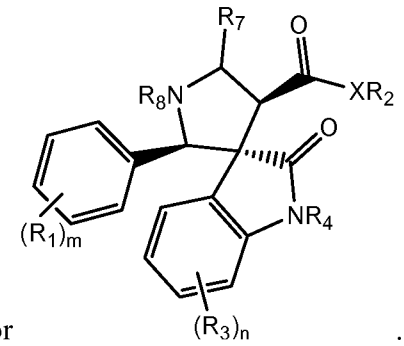
each occurrence of R_4 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted,

branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_D$; $-C(=O)R_D$; $-C(=O)N(R_D)_2$; $-CO_2R_D$; -CN; -SCN; $-SR_D$; $-SOR_D$; $-SO_2R_D$; $-NO_2$; $-N(R_D)_2$; $-NHC(O)R_D$; or $-C(R_D)_3$; wherein each occurrence of R_D is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_7 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_G$; $-C(=O)R_G$; $-N(R_G)_2$; $-CO_2R_G$; -CN; -SCN; $-SR_G$; $-SOR_G$; $-SO_2R_G$; $-NO_2$; $-N(R_G)_2$; $-NHC(O)R_G$; or $-C(R_G)_3$; wherein each occurrence of R_G is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

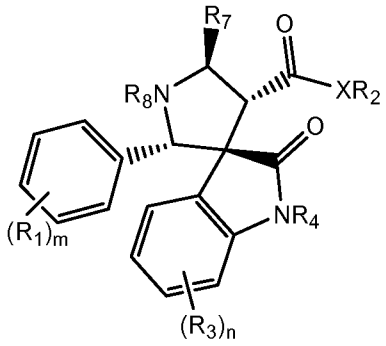
R_8 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_H$; $-C(=O)R_H$; $-C(=O)N(R_H)_2$; $-CO_2R_H$; -CN; -SCN; $-SR_H$; $-SOR_H$; $-SO_2R_H$; $-NO_2$; $-N(R_H)_2$; $-NHC(O)R_H$; or $-C(R_H)_3$; wherein each occurrence of R_H is independently a hydrogen, halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; wherein R_7 and R_8 may be taken together to form a cyclic moiety. The invention also includes stereoisomers, tautomers, enantiomers, diastereomers, racemates, pro-drugs, protected forms, salts, hydrates, solvates, and derivatives (*e.g.*, fluorescent derivatives) of the inventive compounds. Certain stereoisomers of the inventive compounds include compounds of the formula:

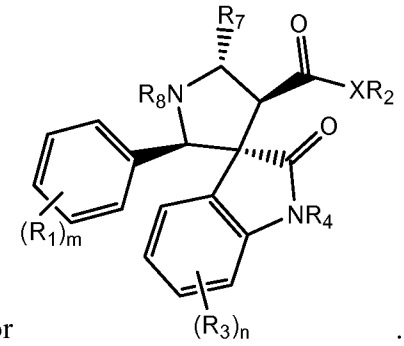


or


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Other stereoisomers of the inventive compounds include compounds of the formula:

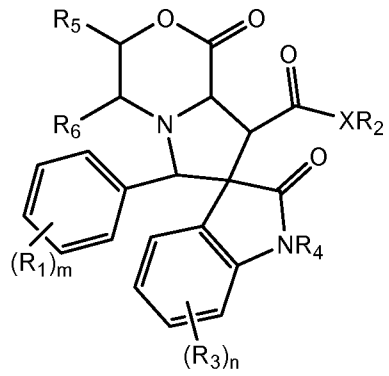


or


.

Other stereoisomers including other enantiomers and diastereomers are also contemplated by the present invention. In certain embodiments, the inventive compound is a specific inhibitor and/or binder of Aurora A kinase, Aurora B kinase, or Aurora C kinase.

[0007] A subclass of the inventive compounds wherein R_7 and R_8 form a heterocyclic ring system is represented by compounds of the formula:



wherein

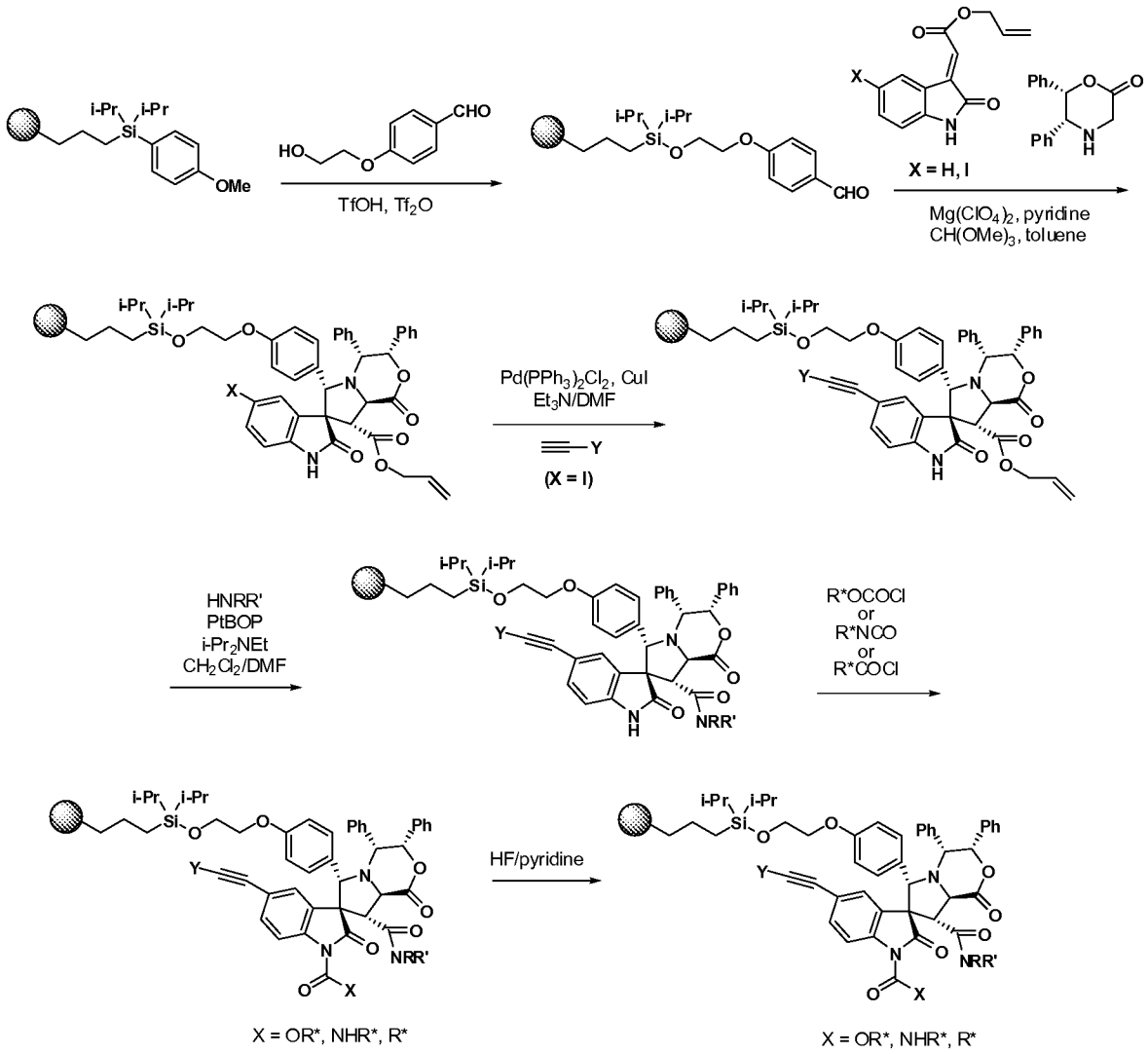
n, m, X, R_1, R_2, R_3, and R_4 are as defined above;

R_5 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or

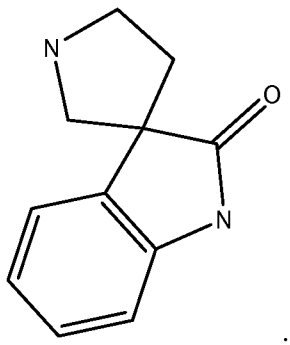
unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_E$; $-C(=O)R_E$; $-C(=O)N(R_E)_2$; $-CO_2R_E$; -CN; -SCN; $-SR_E$; $-SOR_E$; $-SO_2R_E$; $-NO_2$; $-N(R_E)_2$; $-NHC(O)R_E$; or $-C(R_E)_3$; wherein each occurrence of R_E is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; and

R_6 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_F$; $-C(=O)R_F$; $-C(=O)N(R_F)_2$; $-CO_2R_F$; -CN; -SCN; $-SR_F$; $-SOR_F$; $-SO_2R_F$; $-NO_2$; $-N(R_F)_2$; $-NHC(O)R_F$; or $-C(R_F)_3$; wherein each occurrence of R_F is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety.

[0008] The compounds of the present invention may be prepared based on synthetic methods described in *J. Am. Chem. Soc.* 126:16077, 2004; which is incorporated herein by reference. In certain embodiments, the synthesis of the inventive compounds is performed on a solid phase such as a functionalized silicon resin. The compound may also be prepared using similar methodology by replacing the linker and resin with a silyl protecting group such as a trialkylsilyl protecting group. An exemplary solid phase synthesis is shown below:



[0009] The present invention also includes all intermediates useful in the synthesis of compounds of the present invention. In certain embodiments, the intermediates include the spirooxindole core structure:



The intermediates include various substituted forms, isomers, stereoisomers, salts, protected forms, and derivatives thereof.

[0010] In another aspect, the present invention provides methods of treatment, methods of diagnosis, and pharmaceutical compositions comprising the inventive compounds. The pharmaceutical compositions may optionally include a pharmaceutically acceptable excipient. The methods and pharmaceutical compositions may be used to diagnose or treat any disease including proliferative diseases such as cancer, benign neoplasms, autoimmune diseases, inflammatory diseases, and diabetic retinopathy. The inventive compounds are particularly useful in treating colorectal cancer, cervical cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, bone cancer, prostate cancer, renal cancer, liver cancer, stomach cancer, and brain cancer. The methods and compositions may be used to treat disease in humans and other animals including domesticated animals. Any mode of administration including oral and parenteral administration of the pharmaceutical composition may be used. The inventive compounds may also be prepared in extended release formulations or controlled release formulations.

[0011] The inventive compounds, particularly labeled compounds, are also useful in identifying dividing cells, for example, in the diagnosis of cancer. In certain embodiments, inventive compounds tagged with a fluorescent moiety (*e.g.*, fluorescein) are useful in the diagnosis of cancer. A biological sample (*e.g.*, a biopsy, Pap smear) may be contacted with a fluorescent derivative in order to identify dividing and/or malignant cells. The identification may be performed by computer-assisted analysis or human eye. Such compounds may be useful in identifying the centrosome or centromeric regions of the chromosomes. Labeled compounds may also be useful for research purposes in studying mitosis. Such compounds are particularly useful in studying the localization of Aurora kinases.

Definitions

[0012] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell,

University Science Books, Sausalito: 1999, the entire contents of which are incorporated herein by reference.

[0013] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0014] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

[0015] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0016] One of ordinary skill in the art will appreciate that the synthetic methods, as described herein, utilize a variety of protecting groups. By the term "protecting group", as used herein, it is meant that a particular functional moiety, *e.g.*, O, S, or N, is temporarily blocked so that a reaction can be carried out selectively at another reactive site in a multifunctional compound. In preferred embodiments, a protecting group reacts selectively in good yield to give a protected substrate that is stable to the projected reactions; the protecting group should be selectively removable in good yield by readily available, preferably non-toxic reagents that do not attack the other functional groups; the protecting group forms an easily separable derivative (more preferably without the generation of new

stereogenic centers); and the protecting group has a minimum of additional functionality to avoid further sites of reaction. As detailed herein, oxygen, sulfur, nitrogen, and carbon protecting groups may be utilized. Hydroxyl protecting groups include methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate,

triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl *p*-nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*-methoxybenzyl carbonate, alkyl 3,4-dimethoxybenzyl carbonate, alkyl *o*-nitrobenzyl carbonate, alkyl *p*-nitrobenzyl carbonate, alkyl *S*-benzyl thiocarbonate, 4-ethoxy-1-napththyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenoate, *o*-(methoxycarbonyl)benzoate, α-naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). For protecting 1,2- or 1,3-diols, the protecting groups include methylene acetal, ethylidene acetal, 1-*t*-butylethylidene ketal, 1-phenylethylidene ketal, (4-methoxyphenyl)ethylidene acetal, 2,2,2-trichloroethylidene acetal, acetonide, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal, benzylidene acetal, *p*-methoxybenzylidene acetal, 2,4-dimethoxybenzylidene ketal, 3,4-dimethoxybenzylidene acetal, 2-nitrobenzylidene acetal, methoxymethylene acetal, ethoxymethylene acetal, dimethoxymethylene ortho ester, 1-methoxyethylidene ortho ester, 1-ethoxyethylidine ortho ester, 1,2-dimethoxyethylidene ortho ester, α-methoxybenzylidene ortho ester, 1-(*N,N*-dimethylamino)ethylidene derivative, α-(*N,N'*-dimethylamino)benzylidene derivative, 2-oxacyclopentylidene ortho ester, di-*t*-butylsilylene group (DTBS), 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) derivative (TIPDS), tetra-*t*-butoxydisiloxane-1,3-diylidene derivative (TBDS), cyclic carbonates, cyclic boronates, ethyl boronate, and phenyl boronate. Amino-protecting groups include methyl carbamate, ethyl carbamante, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl

carbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-*t*-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc), 1-(3,5-di-*t*-butylphenyl)-1-methylethyl carbamate (*t*-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(*N,N*-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, phenothiazinyl-(10)-carbonyl derivative, *N'-p*-toluenesulfonylaminocarbonyl derivative, *N'*-phenylaminothiocarbonyl derivative, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxycarbonylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p'*-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-

dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, 2,4,6-trimethylbenzyl carbamate, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N'*-dithiobenzyloxycarbonylamino)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine derivative, *o*-nitrobenzamide, *o*-(benzoyloxymethyl)benzamide, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypropylamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N',N'*-dimethylaminomethylene)amine, *N,N'*-isopropylidenediamine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentacarbonylchromium- or tungsten)carbonyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-

dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, 3-nitropyridinesulfenamide (Npys), *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide. Exemplary protecting groups are detailed herein, however, it will be appreciated that the present invention is not intended to be limited to these protecting groups; rather, a variety of additional equivalent protecting groups can be readily identified using the above criteria and utilized in the method of the present invention. Additionally, a variety of protecting groups are described in *Protective Groups in Organic Synthesis,* Third Ed. Greene, T.W. and Wuts, P.G., Eds., John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference.

[0017] It will be appreciated that the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted" whether preceded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those

that result in the formation of stable compounds useful in the treatment, for example, of infectious diseases or proliferative disorders. The term "stable", as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

[0018] The term "aliphatic", as used herein, includes both saturated and unsaturated, straight chain (*i.e.*, unbranched), branched, acyclic, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties. Thus, as used herein, the term "alkyl" includes straight, branched and cyclic alkyl groups. An analogous convention applies to other generic terms such as "alkenyl", "alkynyl", and the like. Furthermore, as used herein, the terms "alkyl", "alkenyl", "alkynyl", and the like encompass both substituted and unsubstituted groups. In certain embodiments, as used herein, "lower alkyl" is used to indicate those alkyl groups (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-6 carbon atoms.

[0019] In certain embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-4 carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, -CH_2-cyclopropyl, vinyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, -CH_2-cyclobutyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, cyclopentyl, -CH_2-cyclopentyl, n-hexyl, sec-hexyl, cyclohexyl, -CH_2-cyclohexyl moieties and the like, which again, may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl, and the like.

[0020] The term "alkoxy", or "thioalkyl" as used herein refers to an alkyl group, as

previously defined, attached to the parent molecule through an oxygen atom or through a sulfur atom. In certain embodiments, the alkyl, alkenyl, and alkynyl groups contain 1-20 alipahtic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups contain 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups contain 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups contain 1-4 aliphatic carbon atoms. Examples of alkoxy, include but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, neopentoxy, and n-hexoxy. Examples of thioalkyl include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, and the like.

[0021] The term "alkylamino" refers to a group having the structure -NHR′, wherein R′ is aliphatic, as defined herein. In certain embodiments, the aliphatic group contains 1-20 aliphatic carbon atoms. In certain other embodiments, the aliphatic group contains 1-10 aliphatic carbon atoms. In yet other embodiments, the aliphatic group employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the aliphatic group contains 1-6 aliphatic carbon atoms. In yet other embodiments, the aliphatic group contains 1-4 aliphatic carbon atoms. Examples of alkylamino groups include, but are not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, cyclopropylamino, n-butylamino, tert-butylamino, neopentylamino, n-pentylamino, hexylamino, cyclohexylamino, and the like.

[0022] The term "dialkylamino" refers to a group having the structure -NRR′, wherein R and R′ are each an aliphatic group, as defined herein. R and R′ may be the same or different in an dialkyamino moiety. In certain embodiments, the aliphatic groups contains 1-20 aliphatic carbon atoms. In certain other embodiments, the aliphatic groups contains 1-10 aliphatic carbon atoms. In yet other embodiments, the aliphatic groups employed in the invention contain 1-8 aliphatic carbon atoms. In still other embodiments, the aliphatic groups contains 1-6 aliphatic carbon atoms. In yet other embodiments, the aliphatic groups contains 1-4 aliphatic carbon atoms. Examples of dialkylamino groups include, but are not limited to, dimethylamino, methyl ethylamino, diethylamino, methylpropylamino, di(n-propyl)amino, di(iso-propyl)amino, di(cyclopropyl)amino, di(n-butyl)amino, di(tert-butyl)amino, di(neopentyl)amino, di(n-pentyl)amino, di(hexyl)amino, di(cyclohexyl)amino, and the like.

In certain embodiments, R and R′ are linked to form a cyclic structure. The resulting cyclic structure may be aromatic or non-aromatic. Examples of cyclic diaminoalkyl groups include, but are not limted to, aziridinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrrolyl, imidazolyl, 1,3,4-trianolyl, and tetrazolyl.

[0023] Some examples of substituents of the above-described aliphatic (and other) moieties of compounds of the invention include, but are not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; arylalkyl; heteroarylalkyl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; F; Cl; Br; I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$ wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0024] In general, the terms "aryl" and "heteroaryl", as used herein, refer to stable mono- or polycyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated moieties having preferably 3-14 carbon atoms, each of which may be substituted or unsubstituted. Substituents include, but are not limited to, any of the previously mentioned substitutents, *i.e.*, the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound. In certain embodiments of the present invention, "aryl" refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, and the like. In certain embodiments of the present invention, the term "heteroaryl", as used herein, refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O, and N; zero, one, or two ring atoms are additional heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl,

oxazolyl, isooxazolyl, thiadiazolyl,oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

[0025] It will be appreciated that aryl and heteroaryl groups can be unsubstituted or substituted, wherein substitution includes replacement of one, two, three, or more of the hydrogen atoms thereon independently with any one or more of the following moieties including, but not limited to: aliphatic; heteroaliphatic; aryl; heteroaryl; arylalkyl; heteroarylalkyl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; -F; -Cl; -Br; -I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$, wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substitutents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0026] The term "cycloalkyl", as used herein, refers specifically to groups having three to seven, preferably three to ten carbon atoms. Suitable cycloalkyls include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like, which, as in the case of other aliphatic, heteroaliphatic, or hetercyclic moieties, may optionally be substituted with substituents including, but not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; arylalkyl; heteroarylalkyl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; -F; -Cl; -Br; -I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$, wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substitutents are illustrated by the specific

embodiments shown in the Examples that are described herein.

[0027] The term "heteroaliphatic", as used herein, refers to aliphatic moieties that contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms, *e.g.*, in place of carbon atoms. Heteroaliphatic moieties may be branched, unbranched, cyclic or acyclic and include saturated and unsaturated heterocycles such as morpholino, pyrrolidinyl, *etc.* In certain embodiments, heteroaliphatic moieties are substituted by independent replacement of one or more of the hydrogen atoms thereon with one or more moieties including, but not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; arylalkyl; heteroarylalkyl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; -F; -Cl; -Br; -I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$, wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substitutents are illustrated by the specific embodiments shown in the Examples that are described herein.

[0028] The terms "halo" and "halogen" as used herein refer to an atom selected from fluorine, chlorine, bromine, and iodine.

[0029] The term "haloalkyl" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

[0030] The term "heterocycloalkyl" or "heterocycle", as used herein, refers to a non-aromatic 5-, 6-, or 7- membered ring or a polycyclic group, including, but not limited to a bi- or tri-cyclic group comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally be oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to a benzene ring. Representative heterocycles include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl,

piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl. In certain embodiments, a "substituted heterocycloalkyl or heterocycle" group is utilized and as used herein, refers to a heterocycloalkyl or heterocycle group, as defined above, substituted by the independent replacement of one, two or three of the hydrogen atoms thereon with but are not limited to aliphatic; heteroaliphatic; aryl; heteroaryl; arylalkyl; heteroarylalkyl; alkoxy; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; heteroalkylthio; heteroarylthio; -F; -Cl; -Br; -I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$, wherein each occurrence of R_x independently includes, but is not limited to, aliphatic, heteroaliphatic, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the aryl or heteroaryl substituents described above and herein may be substituted or unsubstituted. Additional examples of generally applicable substitutents are illustrated by the specific embodiments shown in the Examples which are described herein.

[0031] "Carbocycle": The term "carbocycle", as used herein, refers to an aromatic or non-aromatic ring in which each atom of the ring is a carbon atom.

[0032] "Independently selected": The term "independently selected" is used herein to indicate that the R groups can be identical or different.

[0033] "Labeled": As used herein, the term "labeled" is intended to mean that a compound has at least one element, isotope, or chemical compound attached to enable the detection of the compound. In general, labels typically fall into three classes: a) isotopic labels, which may be radioactive or heavy isotopes, including, but not limited to, ^{2}H, ^{3}H, ^{32}P, ^{35}S, ^{67}Ga, ^{99m}Tc (Tc-99m), ^{111}In, ^{123}I, ^{125}I, ^{169}Yb and ^{186}Re; b) immune labels, which may be antibodies or antigens, which may be bound to enzymes (such as horseradish peroxidase) that produce detectable agents; and c) colored, luminescent, phosphorescent, or fluorescent dyes. It will be appreciated that the labels may be incorporated into the compound at any position that does not interfere with the biological activity or characteristic of the compound that is being detected. In certain embodiments of the invention, photoaffinity labeling is utilized for the direct elucidation of intermolecular interactions in biological systems. A variety of known photophores can be employed, most relying on photoconversion of diazo compounds,

azides, or diazirines to nitrenes or carbenes (*See*, Bayley, H., *Photogenerated Reagents in Biochemistry and Molecular Biology* (1983), Elsevier, Amsterdam.), the entire contents of which are hereby incorporated by reference. In certain embodiments of the invention, the photoaffinity labels employed are o-, m- and p-azidobenzoyls, substituted with one or more halogen moieties, including, but not limited to 4-azido-2,3,5,6-tetrafluorobenzoic acid.

[0034] "Tautomers": As used herein, the term "tautomers" are particular isomers of a compound in which a hydrogen and double bond have changed position with respect to the other atoms of the molecule. For a pair of tautomers to exist there must be a mechanism for interconversion. Examples of tautomers include keto-enol forms, imine-enamine forms, amide-imino alcohol forms, amidine-aminidine forms, nitroso-oxime forms, thio ketone-enethiol forms, *N*-nitroso-hydroxyazo forms, nitro-*aci*-nitro forms, and pyridione-hydroxypyridine forms.

[0035] Definitions of non-chemical terms used throughout the specification include:

[0036] "Animal": The term animal, as used herein, refers to humans as well as non-human animals, at any stage of development, including, for example, mammals, birds, reptiles, amphibians, fish, worms, and single cell organisms. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a primate, or a pig). A non-human animal may be a transgenic animal or clone.

[0037] "Biological sample": As used herein the term "biological sample" includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from an animal (*e.g.*, mammal) or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. For example, the term "biological sample" refers to any solid or fluid sample obtained from, excreted by or secreted by any living organism, including single-celled micro-organisms (such as bacteria and yeasts) and multicellular organisms (such as plants and animals, for instance a vertebrate or a mammal, and in particular a healthy or apparently healthy human subject or a human patient affected by a condition or disease to be diagnosed or investigated). The biological sample can be in any form, including a solid material such as a tissue, cells, a cell pellet, a cell extract, cell homogenates, or cell fractions; or a biopsy; or a smear; or a biological fluid. The biological fluid may be obtained from any site (*e.g.* blood, saliva (or a mouth wash containing buccal cells), tears, plasma, serum, urine, bile, cerebrospinal fluid, amniotic fluid, peritoneal fluid, and pleural fluid, or cells therefrom,

aqueous or vitreous humor, or any bodily secretion), a transudate, an exudate (*e.g.* fluid obtained from an abscess or any other site of infection or inflammation), or fluid obtained from a joint (*e.g.* a normal joint or a joint affected by disease such as rheumatoid arthritis, osteoarthritis, gout or septic arthritis). The biological sample can be obtained from any organ or tissue (including a biopsy or autopsy specimen) or may comprise cells (whether primary cells or cultured cells) or medium conditioned by any cell, tissue, or organ. Biological samples may also include sections of tissues such as frozen sections taken for histological purposes. Biological samples also include mixtures of biological molecules including proteins, lipids, carbohydrates and nucleic acids generated by partial or complete fractionation of cell or tissue homogenates. Although the sample is preferably taken from a human subject, biological samples may be from any animal, plant, bacteria, virus, yeast, *etc.* If desired, the biological sample may be subjected to preliminary processing, including preliminary separation techniques.

[0038] "Effective amount": In general, the "effective amount" of a compound or composition refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the patient. For example, the effective amount of an inventive compound is the amount that results in a sufficient concentration at the site of the neoplasms to kill the undesired, neoplastic cells. In another example, the effective amount of an inventive compound is the amount sufficient to reverse clinicals signs and symptoms of the cancer or other neoplasm.

[0039] "Small Molecule": As used herein, the term "small molecule" refers to a non-peptidic, non-oligomeric organic compound either synthesized in the laboratory or found in nature. Small molecules, as used herein, can refer to compounds that are natural product-like, however, the term "small molecule" is not limited to natural product-like compounds. Rather, a small molecule is typically characterized in that it contains several carbon-carbon bonds, and has a molecular weight of less than 2000 g/mol although this characterization is not intended to be limiting for the purposes of the present invention. In certain embodiments, the molecular weight of the compound is less than 1500 g/mol.

Brief Description of the Drawing

[0040] *Figure 1* shows the chemical structures of SpOx-4 and SpOx-5 with IC_{50}s for Aurora A, B, and C kinases for each compound.

[0041] *Figure 2A-D* show the inhibition of Aurora A, B, and C kinases by SpOx-4 and SpOx-5.

[0042] *Figure 3A-D* show cell viability data for colorectal cancer cell lines, COLO205 and HCT116, using AlamarBlue as a detection agent. Cells were incubated with SpOx-4 or SpOx-5 for 48 hours or 75 hours as indicated. SpOx-5 was found to decrease the viability of colorectal cancer cells to 30% at 50 μM in 72 hours.

[0043] *Figure 4* is a scheme showing an exemplary synthesis of a fluorescein-labeled derivative of SpOx-5 (SpOx-5-FITC).

[0044] *Figure 5* shows the Aurora A inhibitory activity of SpOx-5 and SpOx-5-FITC. The inhibitory activity is similar for both compounds. The structures of the compounds SpOx-5 and SpOx-5-FITC are shown in *Figure 4*.

[0045] *Figure 6* includes images from an imaging experiment with HeLa cells. The top right panel shows cells treated with tagged SpOx-5-FITC. The bottom left shows cells treated with differentially tagged Aurora A antibody. And the bottom right is a merged image. Similar images have been obtained using U20S and MCF7 cells.

[0046] *Figure 7* demonstrates the selectivity of SpOx-5 for Aurora A kinase.

[0047] *Figure 8* includes the cellular activity of three Aurora A kinase inhibitors at different concentrations. The known ATP competitive Aurora kinase inhibitor VX-680 loses much of its activity in the cellular assay due to high concentrations of ATP in the cells.

[0048] *Figure 9* is a Lineweaver-Burke plot of 4XADF inhibition.

Detailed Description of Certain Embodiments of the Invention

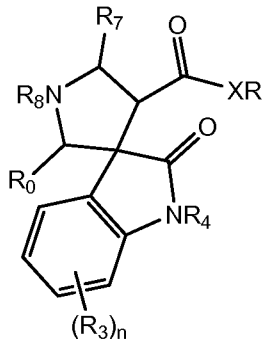
[0049] The present invention provides novel compounds that bind to and/or inhibit Aurora kinases such as Aurora A, B, or C kinase. In certain embodiments, the inventive compound specifically inhibits one or more Aurora kinases and does not substantially affect the activity of other kinases. The compounds include a spirooxindole core as shown herein. The compounds are particularly useful in the treatment and diagnosis of proliferative diseases such as cancer or benign neoplasms. The present invention also provides pharmaceutical compositions and methods of using the inventive compounds for the treatment of proliferative diseases. The compounds may be tagged with identifiable tags such as

fluorescent tags for use in identifying cells undergoing mitosis such as malignant cells. Such derivatives may also be used for research purposes in studying mitosis and the localization of Aurora kinases in cells. Methods are provided for using the tagged derivatives for these diagnostic and research applications. The present invention also provides synthetic methodology and intermediates for preparing the inventive compounds.

Compounds

[0050] Compounds of the present invention include spirooxindoles. Particularly useful spirooxindoles of the present invention include those with biological activity, particularly the ability to inhibit kinases (*e.g.*, threonine/serine kinases, tyrosine kinases). In certain embodiments, the compounds of the invention inhibit Aurora kinases. In certain embodiments, the compounds inhibit one or more of Aurora A, B, or C kinases. The inhibition may be specific for one or a subset of A, B, and C. In other embodiments, the compounds may bind to but not inhibit kinases. In certain embodiments, the compound have an IC_{50} of less than 10 μM, preferably less than 5 μM, more preferably less than 1 μM, and most preferably less than 0.1 μM. The compounds are particularly useful in the treatment of proliferative diseases such as cancer and other neoplasms. The compounds may also be useful in treating inflammatory diseases or autoimmune diseases. In certain embodiments, the compounds may be useful in the treatment of diabetic retinopathy. Tagged and labeled derivatives of the inventive compounds are useful for diagnostic and research purposes.

[0051] In certain embodiments, the compounds of the present invention are represented by the formula:



wherein

n is an integer between 1 and 5, inclusive;

X is O, S, or NR_2;

R_0 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_A$; $-C(=O)R_A$; $-C(=O)N(R_A)_2$; $-CO_2R_A$; -CN; -SCN; $-SR_A$; $-SOR_A$; $-SO_2R_A$; $-NO_2$; $-N(R_A)_2$; $-NHC(O)R_A$; or $-C(R_A)_3$; wherein each occurrence of R_A is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_2 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_B$; $-C(=O)R_B$; $-C(=O)N(R_B)_2$; $-CO_2R_B$; -CN; -SCN; $-SR_B$; $-SOR_B$; $-SO_2R_B$; $-NO_2$; $-N(R_B)_2$; $-NHC(O)R_B$; or $-C(R_B)_3$; wherein each occurrence of R_B is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_3 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_C$; $-C(=O)R_C$; $-C(=O)N(R_C)_2$;$-CO_2R_C$; -CN; -SCN; $-SR_C$; $-SOR_C$; $-SO_2R_C$; $-NO_2$; $-N(R_C)_2$; $-NHC(O)R_C$; or $-C(R_C)_3$; wherein each occurrence of R_C is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_4 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted,

branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_D$; $-C(=O)R_D$; $-C(=O)N(R_D)_2$; $-CO_2R_D$; -CN; -SCN; $-SR_D$; $-SOR_D$; $-SO_2R_D$; $-NO_2$; $-N(R_D)_2$; $-NHC(O)R_D$; or $-C(R_D)_3$; wherein each occurrence of R_D is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

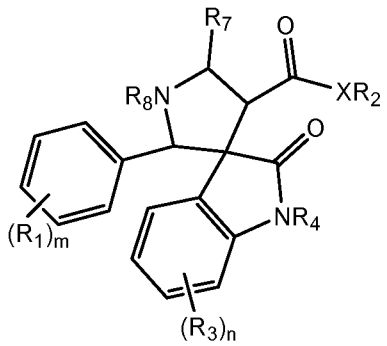
R_7 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_G$; $-C(=O)R_G$; $-N(R_G)_2$; $-CO_2R_G$; -CN; -SCN; $-SR_G$; $-SOR_G$; $-SO_2R_G$; $-NO_2$; $-N(R_G)_2$; $-NHC(O)R_G$; or $-C(R_G)_3$; wherein each occurrence of R_G is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_8 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_H$; $-C(=O)R_H$; $-C(=O)N(R_H)_2$; $-CO_2R_H$; -CN; -SCN; $-SR_H$; $-SOR_H$; $-SO_2R_H$; $-NO_2$; $-N(R_H)_2$; $-NHC(O)R_H$; or $-C(R_H)_3$; wherein each occurrence of R_H is independently a hydrogen, halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; wherein R_7 and R_8 may be taken together to form a cyclic moiety; and stereoisomers, tautomers, enantiomers, diastereomers, racemates, pro-drugs, protected forms, salts, hydrates, solvates, and derivatives thereof..

[0052] In certain embodiments, R_0 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety. In certain embodiments, R_0 is alkyl. In certain embodiments, R_0 is C_1-C_6 alkyl. In certain embodiments, R_0 is methyl, ethyl, propyl, or iso-propyl. In certain embodiments, R_0 is a cyclic or acyclic, substituted or unsubstituted,

branched or unbranched heteroaliphatic moiety. In certain embodiments, R_0 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, R_0 is a substituted or unsubstituted aryl moiety. In certain embodiments, R_0 is a substituted or unsubstituted phenyl moiety. In certain embodiments, R_0 is a substituted or unsubstituted heteroaryl moiety.

[0053] In certain embodiments, the compounds of the present invention are represented by the formula:



wherein

n is an integer between 0 and 5, inclusive;

m is an integer between 0 and 4, inclusive;

X is O, S, or NR_2;

R_1 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_A$; $-C(=O)R_A$; $-C(=O)N(R_A)_2$; $-CO_2R_A$; -CN; -SCN; $-SR_A$; $-SOR_A$; $-SO_2R_A$; $-NO_2$; $-N(R_A)_2$; $-NHC(O)R_A$; or $-C(R_A)_3$; wherein each occurrence of R_A is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_2 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_B$; $-C(=O)R_B$; $-C(=O)N(R_B)_2$; $-CO_2R_B$; -CN; -SCN; $-SR_B$; $-SOR_B$; $-SO_2R_B$; $-NO_2$; $-N(R_B)_2$; $-NHC(O)R_B$; or -

$C(R_B)_3$; wherein each occurrence of R_B is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_3 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_C$; $-C(=O)R_C$; $-C(=O)N(R_C)_2$; $-CO_2R_C$; -CN; -SCN; $-SR_C$; $-SOR_C$; $-SO_2R_C$; $-NO_2$; $-N(R_C)_2$; $-NHC(O)R_C$; or $-C(R_C)_3$; wherein each occurrence of R_C is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_4 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_D$; $-C(=O)R_D$; $-C(=O)N(R_D)_2$; $-CO_2R_D$; -CN; -SCN; $-SR_D$; $-SOR_D$; $-SO_2R_D$; $-NO_2$; $-N(R_D)_2$; $-NHC(O)R_D$; or $-C(R_D)_3$; wherein each occurrence of R_D is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_7 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_G$; $-C(=O)R_G$; $-C(=O)N(R_G)_2$; $-CO_2R_G$; -CN; -SCN; $-SR_G$; $-SOR_G$; $-SO_2R_G$; $-NO_2$; $-N(R_G)_2$; $-NHC(O)R_G$; or $-C(R_G)_3$; wherein each occurrence of R_G is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy;

alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_8 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_H$; $-C(=O)R_H$; $-C(=O)N(R_H)_2$; $-CO_2R_H$; -CN; -SCN; $-SR_H$; $-SOR_H$; $-SO_2R_H$; $-NO_2$; $-N(R_H)_2$; $-NHC(O)R_H$; or $-C(R_H)_3$; wherein each occurrence of R_H is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; wherein R_7 and R_8 may be taken together to form a cyclic moiety; and stereoisomers, tautomers, enantiomers, diastereomers, racemates, pro-drugs, protected forms, salts, hydrates, solvates, and derivatives thereof.

[0054] In certain embodiments, n is 0. In certain embodiments, n is 1. In other embodiments, n is 2. In other embodiments, n is 3. In yet other embodiments, n is 4. In certain embodiments, n is at least 2.

[0055] In certain embodiments, m is 0. In certain embodiments, m is 1. In other embodiments, m is 2. In other embodiments, m is 3. In yet other embodiments, m is 4. In still other embodiments, m is 5.

[0056] In certain embodiments, both n and m are 0. In certain embodiments, n is 0, and m is 1. In certain embodiments, n is 1, and m is 0. In certain embodiments, both n and m are 1. In certain embodiments, n is 1, and m is 2. In certain embodiments, n is 1, and m is 3. In certain embodiments, n is 2, and m is 1. In certain embodiments, n is 2, and m is 2. In certain embodiments, n is 2, and m is 3.

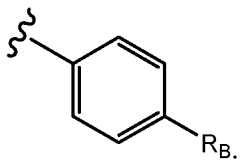
[0057] In certain embodiments, X is O. In other embodiments, X is S. In other embodiments, X is NR_2. In yet other embodiments, X is NH.

[0058] In certain embodiments, at least one of R_1 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic aliphatic moiety. In certain embodiments, at least one of R_1 is C_1-C_6 alkyl. In certain embodiments, at least one of R_1 is C_1-C_6 alkenyl. In certain embodiments, at least one of R_1 is C_1-C_6 alkynyl. In certain embodiments, at least one of R_1 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic heteroaliphatic moiety. In certain embodiments, at least one of R_1 is $-OR_A$. In certain

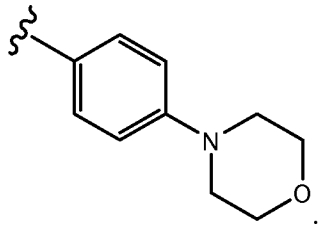
embodiments, at least one of R_1 is –OH. In certain embodiments, at least one of R_1 is –$OCH_2CH_2OR_A$. In certain particular embodiments, at least one of R_1 is –OCH_2CH_2OH. In certain embodiments, at least one of R_1 is –SR_A. In certain embodiments, at least one of R_1 is –$N(R_A)_2$. In certain embodiments, at least one of R_1 is –NHR_A. In certain embodiments, at least one of R_1 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, at least one of R_1 is a substituted or unsubstituted aryl moiety. In other embodiments, at least one of R_1 is a substituted or unsubstituted heteroaryl moiety. In certain embodiments, at least one of R_1 is a halogen.

[0059] In certain embodiments, at least one of R_2 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic aliphatic moiety. In certain embodiments, at least one of R_2 is C_1-C_6 alkyl. In certain embodiments, at least one of R_2 is methyl, ethyl, or propyl. In certain embodiments, at least one of R_2 is C_1-C_6 alkenyl. In certain embodiments, at least one of R_2 is vinyl. In certain embodiments, at least one of R_2 is allyl. In certain embodiments, at least one of R_2 is C_1-C_6 alkynyl. In certain embodiments, at least one of R_1 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic heteroaliphatic moiety. In certain embodiments, at least one of R_2 is –OR_A. In certain embodiments, at least one of R_2 is –OH. In certain embodiments, at least one of R_2 is –$N(R_B)_2$. In certain embodiments, at least one of R_2 is –NHR_B. In certain embodiments, at least one of R_2 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, at least one of R_2 is acetyl. In certain embodiments, at least one of R_2 is a substituted or unsubstituted aryl moiety. In certain embodiments, at least one of R_2 is a substituted or unsubstituted phenyl moiety. In certain embodiments, at least one of R_2 is a substituted phenyl moiety. In certain embodiments, at least one of R_2 is an unsubstituted phenyl moiety. In other embodiments, at least one of R_2 is a substituted or unsubstituted heteroaryl moiety.

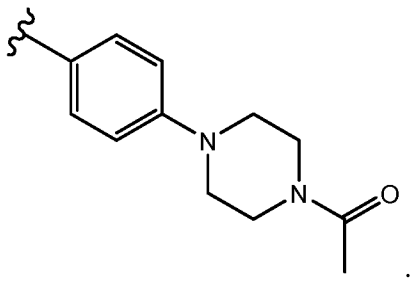
[0060] In certain embodiments, X is NH, and R_2 is a substituted or unsubstituted aryl moiety. In certain embodiments, X is NH, and R_2 is a substituted or unsubstituted phenyl moiety. In certain embodiments, X is NH, and R_2 is a substituted phenyl moiety. In certain embodiments, X is NH, and R_2 is of the formula:



In certain embodiments, X is NH, and R_2 is of the formula:

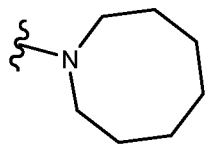
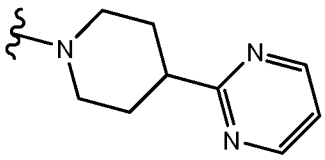


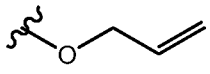
In certain embodiments, X is NH, and R_2 is of the formula:



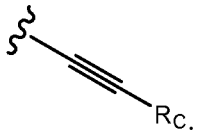
In certain embodiments, X is NH, and R_2 is a substituted or unsubstituted heteroaryl moiety.

[0061] In certain embodiments, X is O, and R_2 is H. In certain embodiments, X isO, and R_2 is a carboxylic acid protecting group. In certain embodiments, X is O, and R_2 is C_{1-6} alkyl.

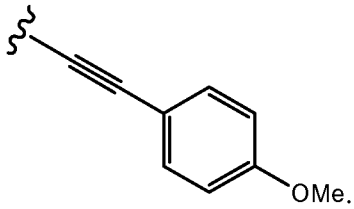
[0062] In certain embodiments, $-XR_2$ is . In certain embodiments, $-XR_2$ is .

[0063] In certain embodiments, $-XR_2$ is .

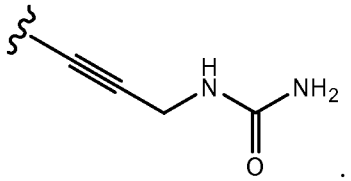
[0064] In certain embodiments, at least one of R_3 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic aliphatic moiety. In certain embodiments, at least one of R_3 is alkyl. In certain embodiments, at least one of R_3 is C_1-C_6 alkyl. In certain embodiments, at least one of R_3 is alkenyl. In certain embodiments, at least one of R_3 is C_1-C_6 alkenyl. In certain embodiments, at least one of R_3 is alkynyl. In certain embodiments, at least one of R_3 is of the formula:



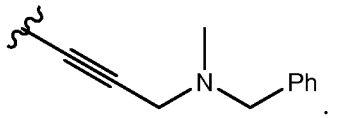
In certain embodiments, at least one of R_3 is of the formula:



In certain embodiments, at least one of R_3 is of the formula:

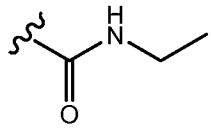
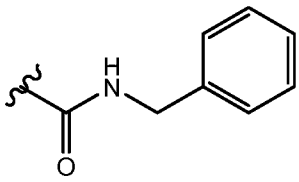
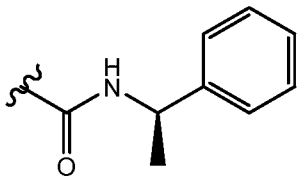
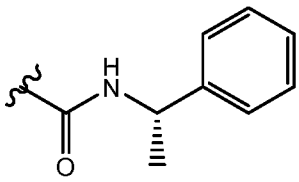
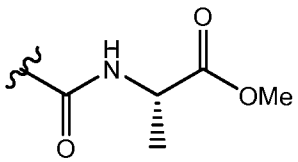
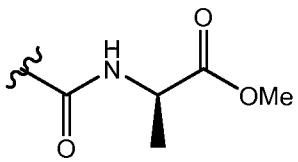


In certain embodiments, at least one of R_3 is of the formula:



In certain embodiments, at least one of R_3 is C_1-C_6 alkynyl. In certain embodiments, at least one of R_3 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic heteroaliphatic moiety. In certain embodiments, at least one of R_3 is halogen. In certain embodiments, at least one of R_3 is –F. In certain embodiments, at least one of R_3 is –Cl. In certain embodiments, at least one of R_3 is –Br. In certain embodiments, at least one of R_3 is –I. In certain embodiments, at least one of R_3 is $-OR_C$. In certain embodiments, at least one of R_3 is –OH. In certain embodiments, at least one of R_3 is $-SR_C$. In certain embodiments, at least one of R_3 is $-N(R_C)_2$. In certain embodiments, at least one of R_3 is $-NHR_C$. In certain embodiments, at least one of R_3 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, at least one of R_3 is a substituted or unsubstituted aryl moiety. In other embodiments, at least one of R_3 is a substituted or unsubstituted heteroaryl moiety. In certain embodiments, at least one of R_3 is a halogen.

[0065] In certain embodiments, R_4 is hydrogen. In certain embodiments, R_4 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic aliphatic moiety. In certain embodiments, R_4 is C_1-C_6 alkyl. In certain embodiments, R_4 is methyl, ethyl, or propyl. In certain embodiments, R_4 is C_1-C_6 alkenyl. In certain embodiments, R_4 is vinyl. In certain embodiments, R_4 is allyl. In certain embodiments, R_4 is C_1-C_6 alkynyl. In certain embodiments, R_4 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic heteroaliphatic moiety. In certain embodiments, at least one of R_4 is $-OR_D$. In certain

embodiments, at least one of R_4 is –OH. In certain embodiments, at least one of R_4 is –$N(R_D)_2$. In certain embodiments, at least one of R_4 is –NHR_D. In certain embodiments, R_4 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, R_4 is acetyl. In certain embodiments, R_4 is –$C(=O)R_D$. In certain embodiments, R_4 is –$C(=O)OR_D$. In certain embodiments, R_4 is –$C(=O)N(R_D)_2$. In certain embodiments, R_4 is –$C(=O)NHR_D$. In certain embodiments, R_4 is a substituted or unsubstituted aryl moiety. In certain embodiments, R_4 is a substituted or unsubstituted phenyl moiety. In certain embodiments, R_4 is a substituted phenyl moiety. In certain embodiments, R_4 is an unsubstituted phenyl moiety. In other embodiments, R_4 is a substituted or unsubstituted heteroaryl moiety. In certain embodiments, R_4 is . In certain embodiments, R_4 is . In certain embodiments, R_4 is . In certain embodiments, R_4 is . In certain embodiments, R_4 is . In certain embodiments, R_4 is .

[0066] In certain embodiments, R_7 is hydrogen. In certain embodiments, R_7 is a halogen. In certain embodiments, R_7 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic aliphatic moiety. In certain embodiments, R_7 is alkyl. In certain embodiments, R_7 is C_1-C_6 alkyl. In certain embodiments, R_7 is alkenyl. In certain embodiments, R_7 is C_1-C_6 alkenyl. In certain embodiments, R_7 is alkynyl. In certain embodiments, R_7 is C_1-C_6 alkynyl. In certain embodiments, R_7 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic heteroaliphatic moiety. In certain embodiments, R_7 is a substituted or unsubstituted, branched or unbranched acyl moiety. In

certain embodiments, R_7 is $-OR_G$. In certain embodiments, R_7 is –OH. In certain embodiments, R_7 is $-C(=O)R_G$. In certain embodiments, R_7 is $-C(=O)N(R_G)_2$. In certain embodiments, R_7 is $-C(=O)NHR_G$. In certain embodiments, R_7 is $-C(=O)NH_2$. In certain embodiments, R_7 is $-CO_2R_G$. In certain embodiments, R_7 is $-CO_2H$. In certain embodiments, R_7 is $-SR_G$. In certain embodiments, R_7 is –SH. In certain embodiments, R_7 is $-N(R_G)_2$. In certain embodiments, R_7 is $-NHR_G$. In certain embodiments, R_7 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, R_7 is a substituted or unsubstituted aryl moiety. In other embodiments, R_7 is a substituted or unsubstituted heteroaryl moiety.

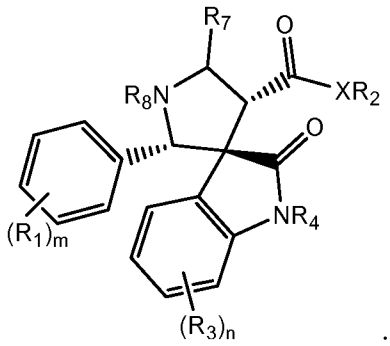
[0067] In certain embodiments, R_8 is hydrogen. In certain embodiments, R_8 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic aliphatic moiety. In certain embodiments, R_8 is C_1-C_6 alkyl. In certain embodiments, R_8 is methyl, ethyl, or propyl. In certain embodiments, R_8 is C_1-C_6 alkenyl. In certain embodiments, R_8 is vinyl. In certain embodiments, R_8 is allyl. In certain embodiments, R_8 is C_1-C_6 alkynyl. In certain embodiments, R_8 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic heteroaliphatic moiety. In certain embodiments, at least one of R_8 is $-OR_H$. In certain embodiments, at least one of R_8 is –OH. In certain embodiments, at least one of R_8 is $-N(R_H)_2$. In certain embodiments, at least one of R_8 is $-NHR_H$. In certain embodiments, R_4 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, R_8 is acetyl. In certain embodiments, R_8 is $-C(=O)R_H$. In certain embodiments, R_8 is $-C(=O)OR_H$. In certain embodiments, R_8 is $-C(=O)N(R_H)_2$. In certain embodiments, R_8 is $-C(=O)NHR_H$. In certain embodiments, R_8 is a substituted or unsubstituted aryl moiety. In certain embodiments, R_8 is a substituted or unsubstituted phenyl moiety. In certain embodiments, R_8 is a substituted phenyl moiety. In certain embodiments, R_8 is an unsubstituted phenyl moiety. In other embodiments, R_8 is a substituted or unsubstituted heteroaryl moiety.

[0068] In certain embodiments, R_7 and R_8 are not taken together to form a cyclic moiety.

[0069] In certain embodiments, R_7 and R_8 are taken together to form a substituted or unsubstituted heterocyclic moiety. In certain embodiments, R_7 and R_8 are taken together to form a substituted or unsubstituted 5-membered heterocyclic moiety. In certain embodiments, R_7 and R_8 are taken together to form a substituted or unsubstituted 6-

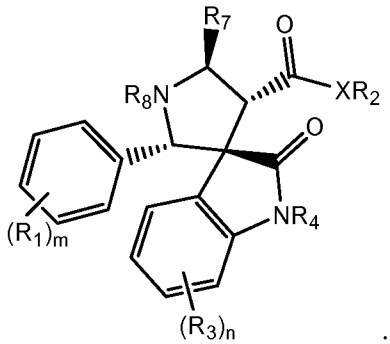
membered heterocyclic moiety. In certain embodiments, R_7 and R_8 are taken together to form a substituted or unsubstituted 7-membered heterocyclic moiety. In certain embodiments, the heterocyclic moiety is aromatic. In certain embodiments, the heterocyclic moiety is non-aromatic.

[0070] In certain embodiments, the compounds has the stereochemistry as shown in the formula:



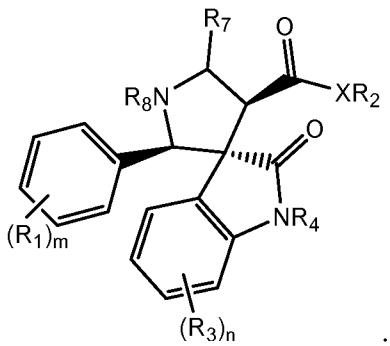
.

[0071] In certain embodiments, the compounds has the stereochemistry as shown in the formula:



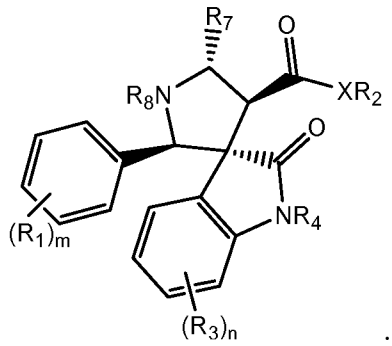
.

[0072] In certain embodiments, the compounds has the stereochemistry as shown in the formula:

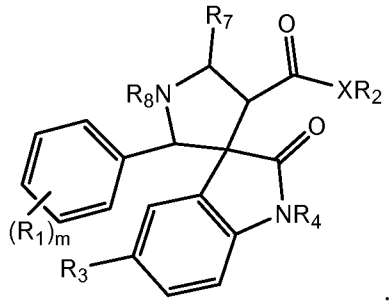


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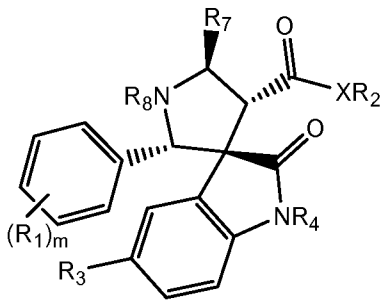
[0073] In certain embodiments, the compounds has the stereochemistry as shown in the formula:



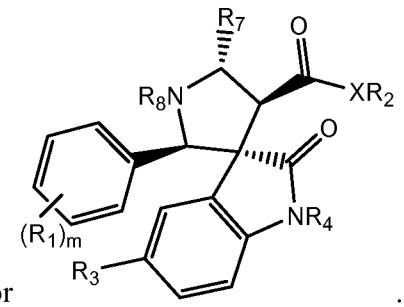
[0074] In certain embodiments, the compound is of the formula:



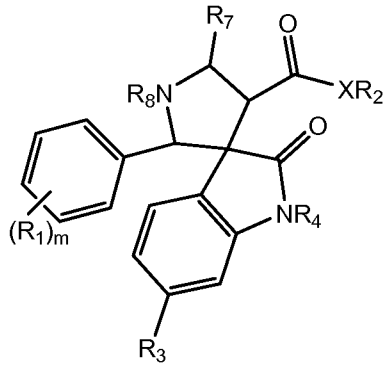
In certain embodiments, the compound has the stereochemistry as shown in either of the formulae below:



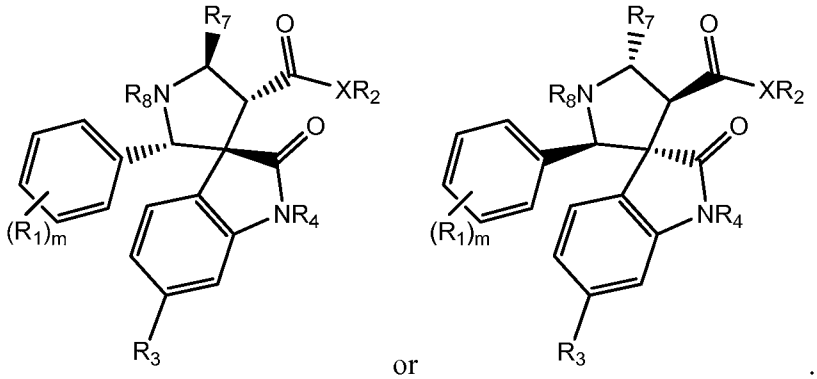
or



[0075] In certain embodiments, the compound is of the formula:

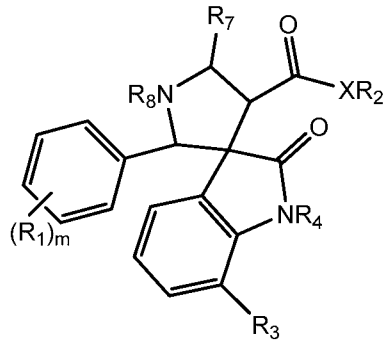


In certain embodiments, the compound has the stereochemistry as shown in either of the formulae below:

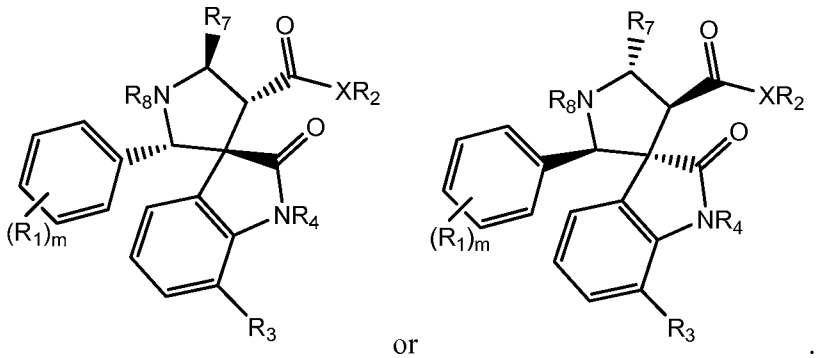


or

[0076] In certain embodiments, the compound is of the formula:

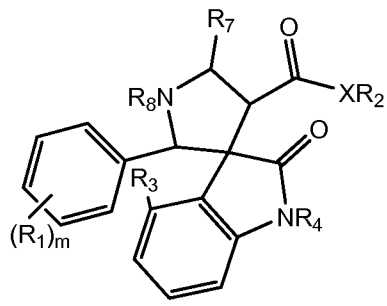


In certain embodiments, the compound has the stereochemistry as shown in either of the formulae below:

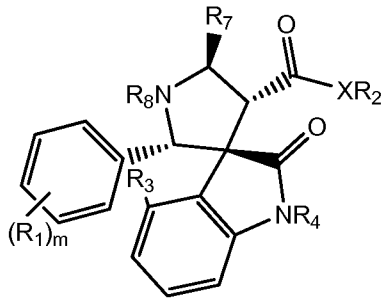


or

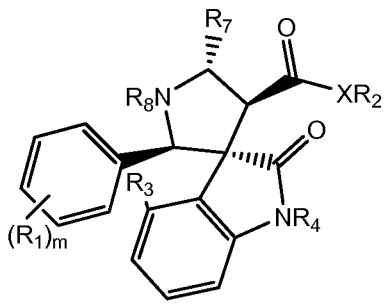
[0077] In certain embodiments, the compound is of the formula:



In certain embodiments, the compound has the stereochemistry as shown in either of the formulae below:

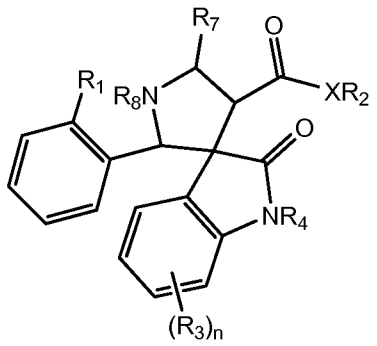


or



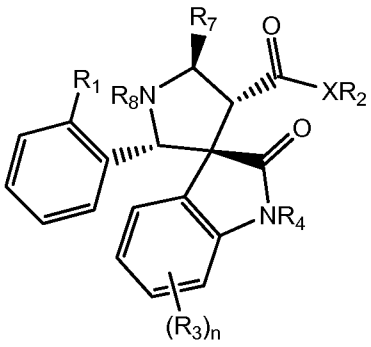
.

[0078] In certain embodiments, the compound is of the formula:

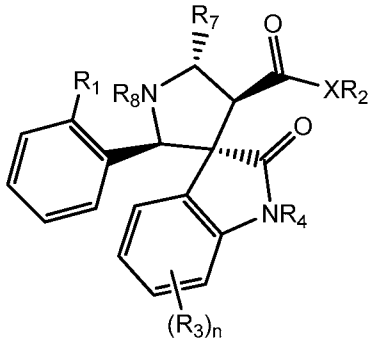


.

In certain embodiments, the compound has the stereochemistry as shown in either of the formulae below:

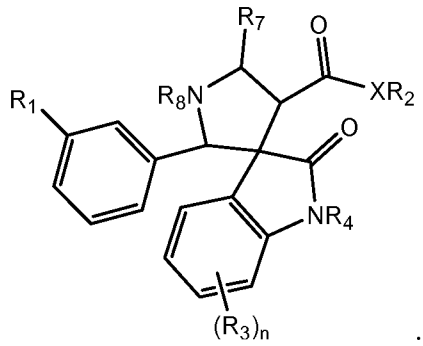


or

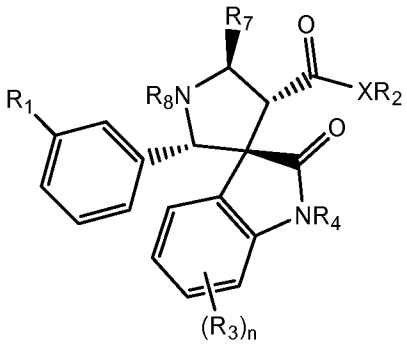


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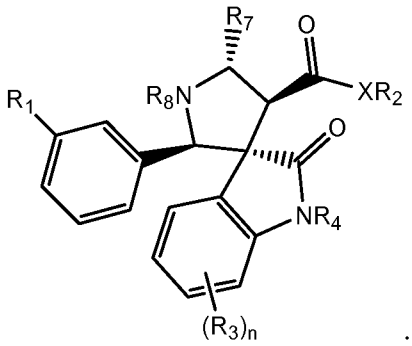
[0079] In certain embodiments, the compound is of the formula:



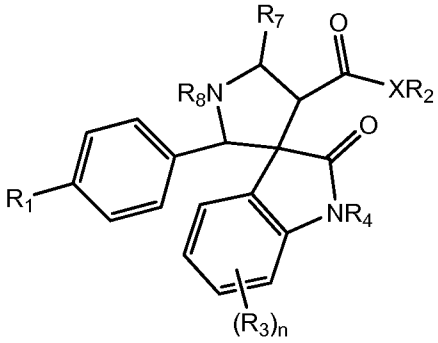
In certain embodiments, the compound has the stereochemistry as shown in either of the formulae below:



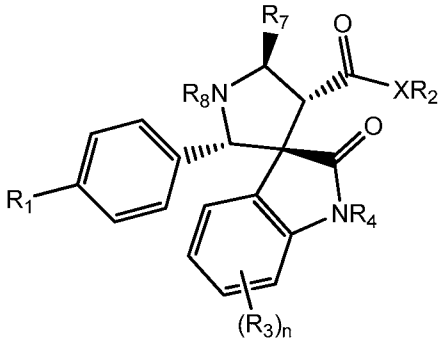
or



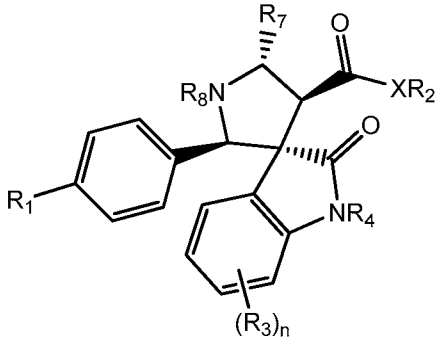
[0080] In certain embodiments, the compound is of the formula:



In certain embodiments, the compound has the stereochemistry as shown in either of the formulae below:

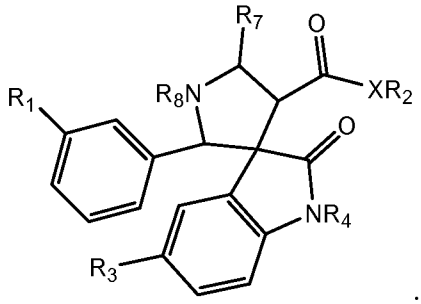


or



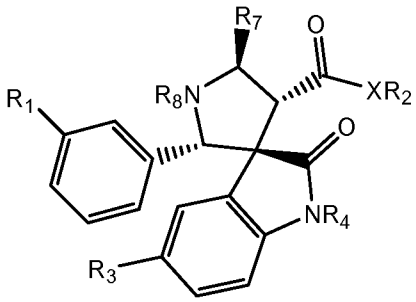
.

[0081] In certain embodiments, the compound is of the formula:

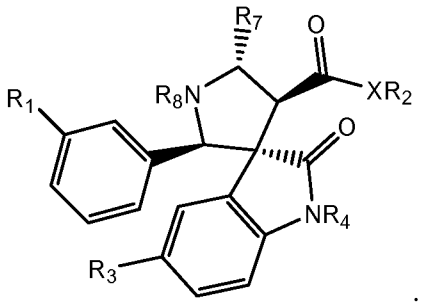


.

In certain embodiments, the compound has the stereochemistry as shown in either of the formulae below:

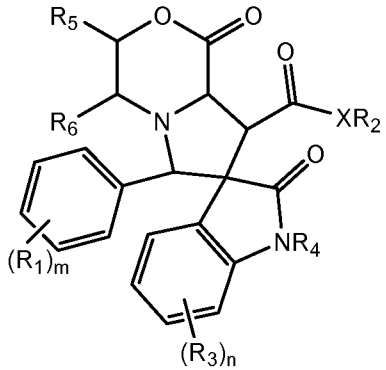


or



.

[0082] In certain embodiments, the compound is of formula:



wherein

n, m, X, R_1, R_2, R_3, and R_4 are as defined herein;

R_5 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_E$; $-C(=O)R_E$; $-C(=O)N(R_E)_2$; $-CO_2R_E$; -CN; -SCN; $-SR_E$; $-SOR_E$; $-SO_2R_E$; $-NO_2$; $-N(R_E)_2$; $-NHC(O)R_E$; or $-C(R_E)_3$; wherein each occurrence of R_E is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; and

R_6 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_F$; $-C(=O)R_F$; $-C(=O)N(R_F)_2$; $-CO_2R_F$; -CN; -SCN; $-SR_F$; $-SOR_F$; $-SO_2R_F$; $-NO_2$; $-N(R_F)_2$; $-NHC(O)R_F$; or $-C(R_F)_3$; wherein each occurrence of R_F is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety.

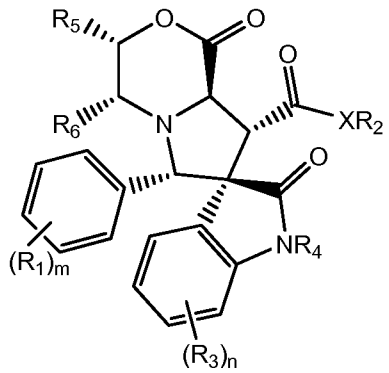
[0083] In certain embodiments, R_5 is hydrogen. In certain embodiments, R_5 is a halogen. In certain embodiments, R_5 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic aliphatic moiety. In certain embodiments, R_5 is alkyl. In certain embodiments, R_5 is C_1-C_6 alkyl. In certain embodiments, R_5 is alkenyl. In certain embodiments, R_5 is C_1-C_6 alkenyl. In certain embodiments, R_5 is alkynyl. In certain embodiments, R_5 is C_1-C_6 alkynyl. In certain embodiments, R_5 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic heteroaliphatic moiety. In certain embodiments, R_5 is $-OR_E$. In certain embodiments, R_5 is –OH. In certain embodiments, at least one of R_5 is $-SR_E$. In certain embodiments, at least one of R_5 is –SH. In certain embodiments, R_5 is $-N(R_E)_2$. In certain embodiments, R_5 is $-NHR_E$. In certain embodiments, R_5 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, R_5 is a substituted or unsubstituted aryl moiety. In certain embodiments, R_5 is a substituted or unsubstituted phenyl moiety. In certain embodiments, R_5

is a substituted phenyl moiety. In certain embodiments, R_5 is an unsubstituted phenyl moiety. In other embodiments, R_5 is a substituted or unsubstituted heteroaryl moiety.

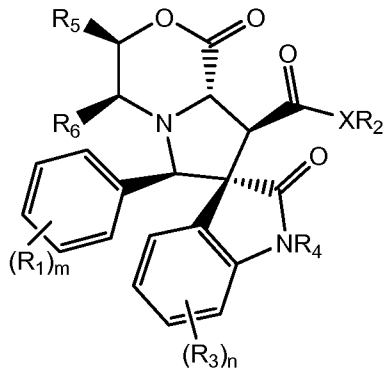
[0084] In certain embodiments, R_6 is hydrogen. In certain embodiments, R_6 is a halogen. In certain embodiments, R_6 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic aliphatic moiety. In certain embodiments, R_6 is alkyl. In certain embodiments, R_6 is C_1-C_6 alkyl. In certain embodiments, R_6 is alkenyl. In certain embodiments, R_6 is C_1-C_6 alkenyl. In certain embodiments, R_6 is alkynyl. In certain embodiments, R_6 is C_1-C_6 alkynyl. In certain embodiments, R_6 is a substituted or unsubstituted, branched or unbranched, cyclic or acyclic heteroaliphatic moiety. In certain embodiments, R_6 is $-OR_F$. In certain embodiments, R_6 is –OH. In certain embodiments, at least one of R_6 is $-SR_F$. In certain embodiments, R_6 is –SH. In certain embodiments, R_6 is $-N(R_F)_2$. In certain embodiments, R_6 is $-NHR_F$. In certain embodiments, R_6 is a substituted or unsubstituted, branched or unbranched acyl moiety. In certain embodiments, at least one of R_6 is a substituted or unsubstituted aryl moiety. In certain embodiments, R_6 is a substituted or unsubstituted phenyl moiety. In certain embodiments, R_6 is a substituted phenyl moiety. In certain embodiments, R_6 is an unsubstituted phenyl moiety. In other embodiments, R_6 is a substituted or unsubstituted heteroaryl moiety.

[0085] In certain embodiments, at least one of R_5 and R_6 is a substituted or unsubstituted phenyl moiety. In certain embodiments, at least one of R_5 and R_6 is not a substituted or unsubstituted phenyl moiety. In certain embodiments, at least one of R_5 and R_6 is an unsubstituted phenyl moiety. In certain embodiments, both R_5 and R_6 are substituted or unsubstituted phenyl moieties. In certain embodiments, both R_5 and R_6 are unsubstituted phenyl moieties. In certain embodiments, both R_5 and R_6 are substituted phenyl moieties. In certain embodiments, both R_5 and R_6 are not unsubstituted phenyl moieties.

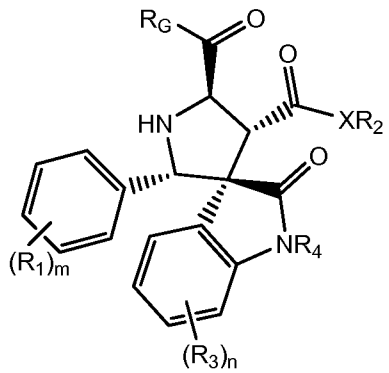
[0086] In certain embodiments, the compound has the stereochemistry shown in the formula:



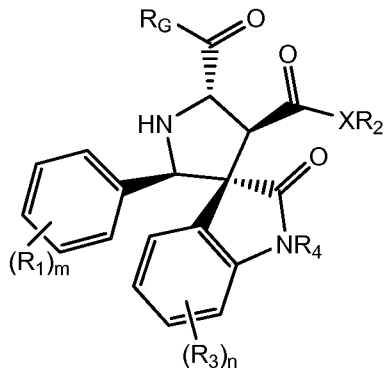
[0087] In other embodiments, the compound has the stereochemisty shown in the formula:



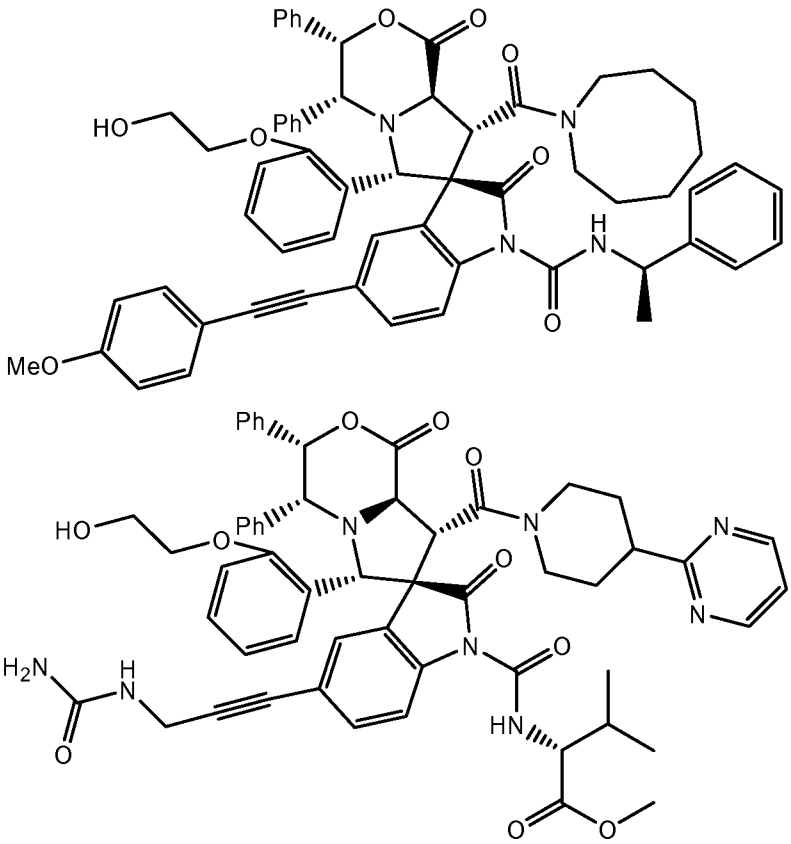
[0088] In certain embodiments, the compound has the stereochemistry shown in the formula:

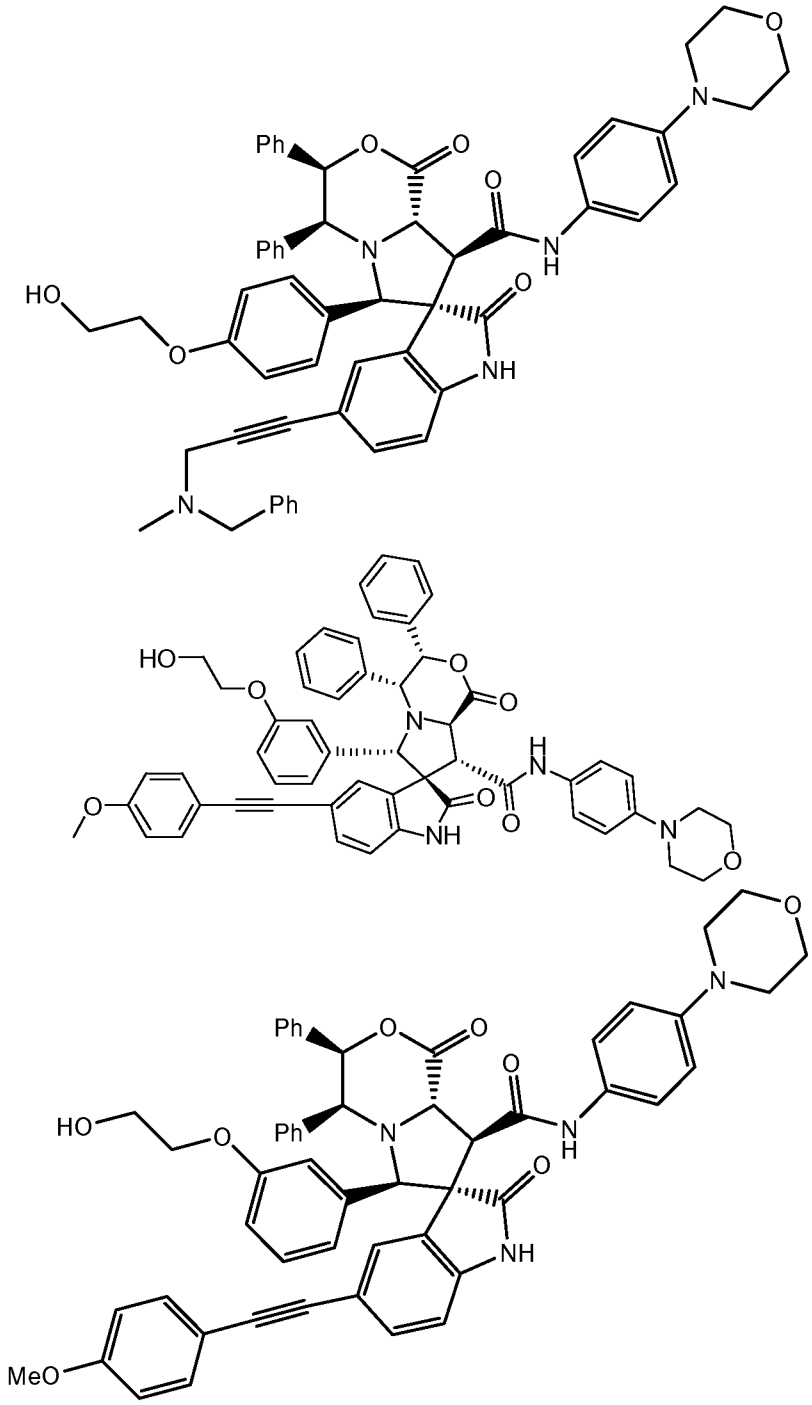


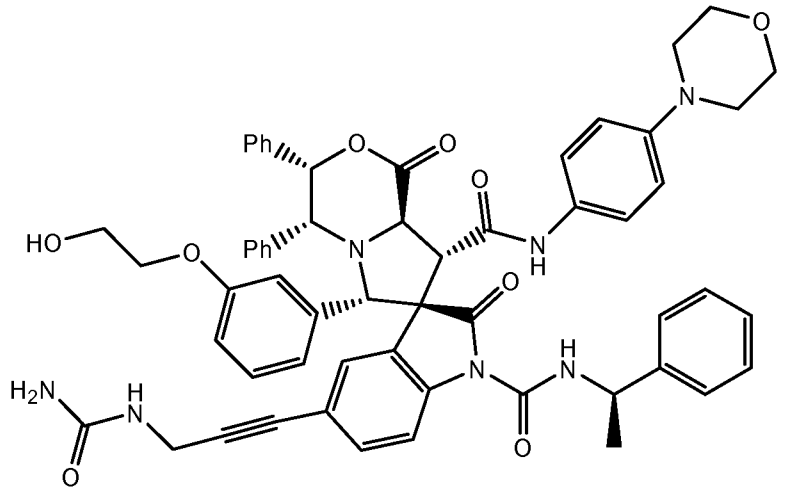
[0089] In other embodiments, the compound has the stereochemisty shown in the formula:

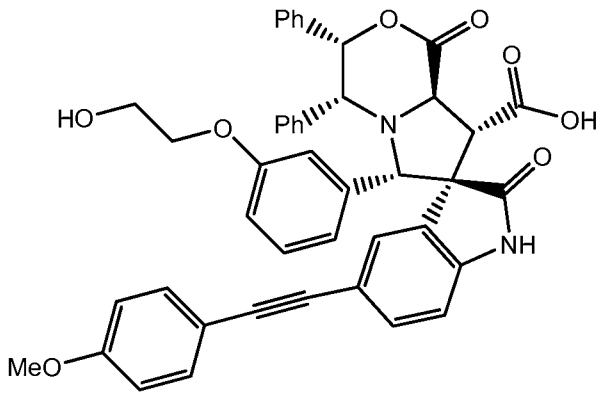


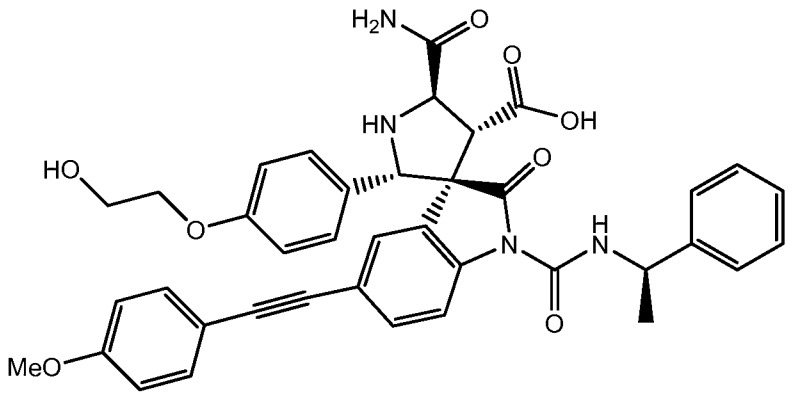
[0090] Exemplary compounds of the invention include:

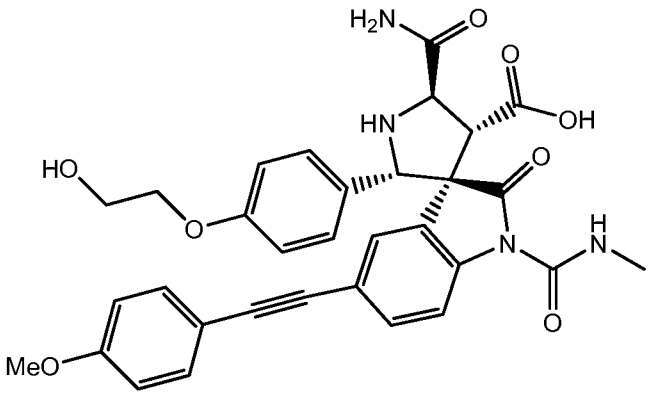


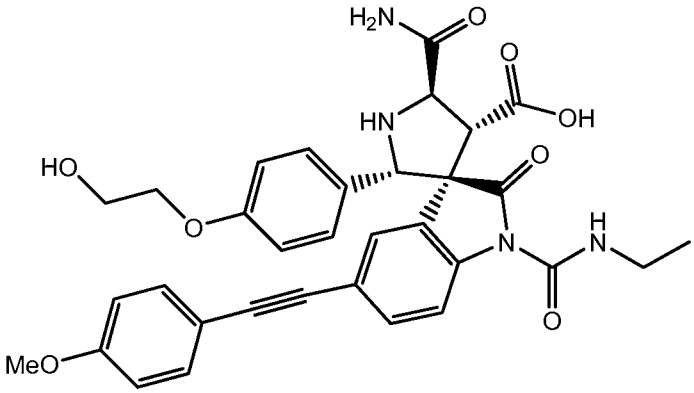


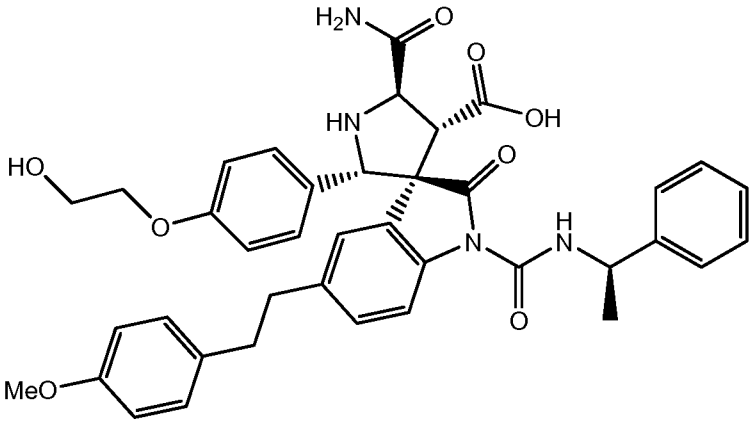


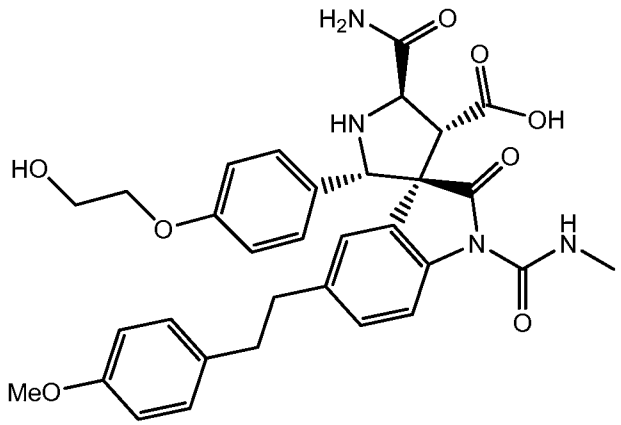


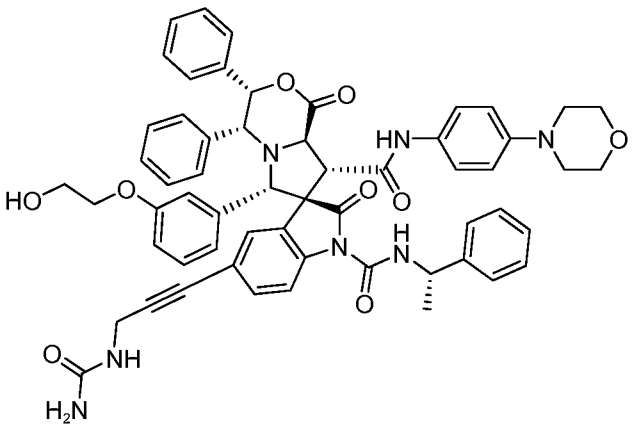


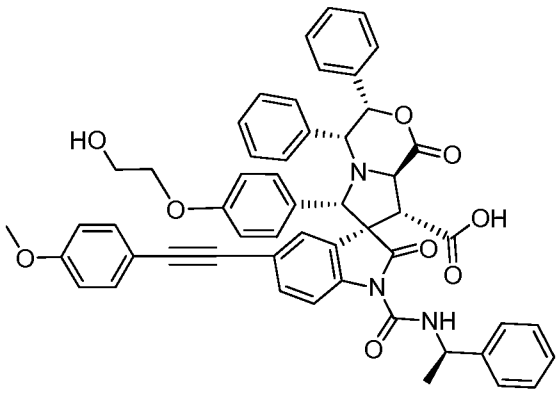


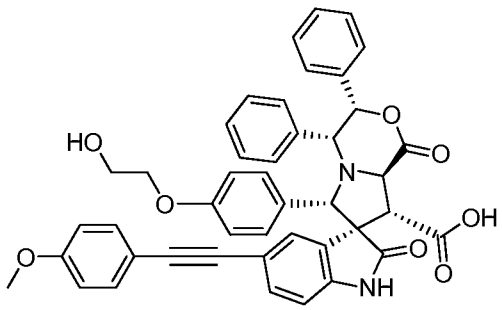


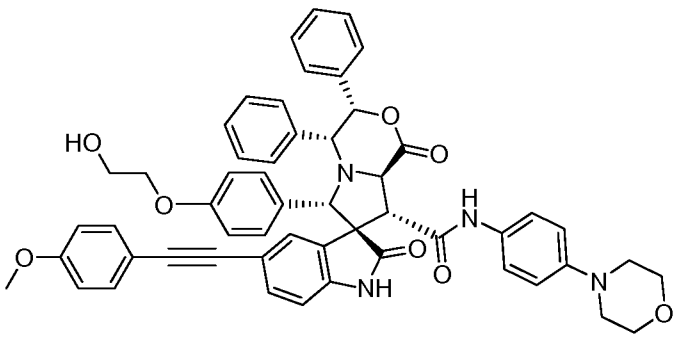


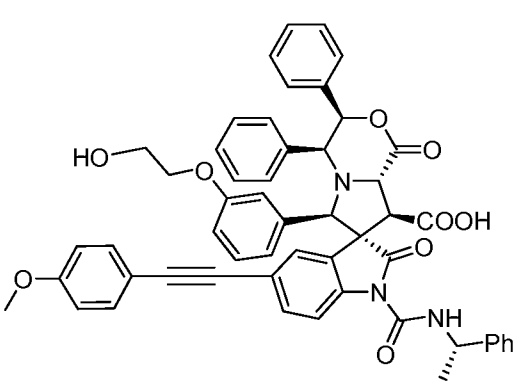


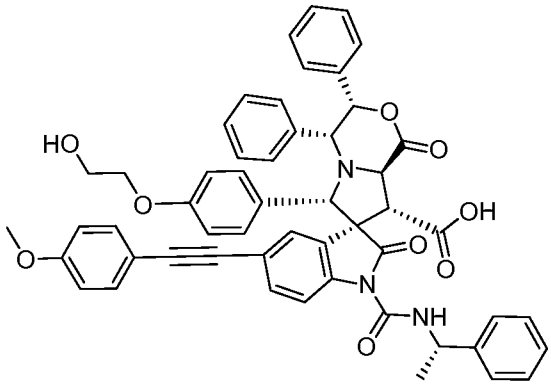


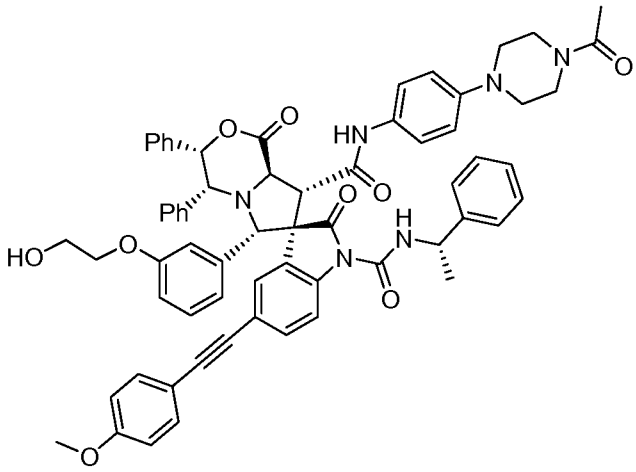


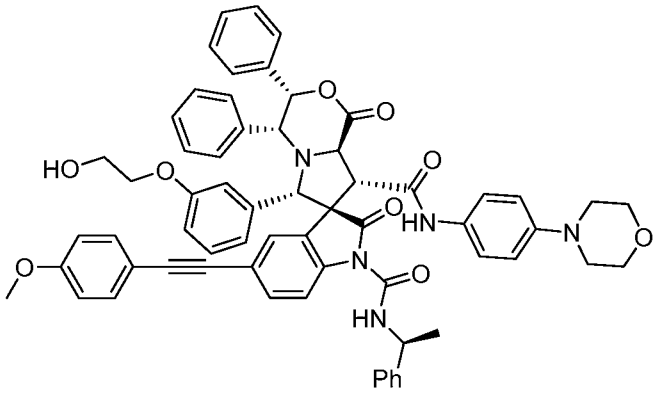


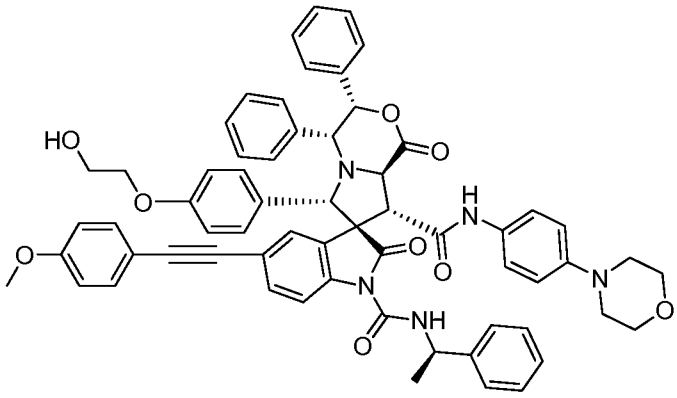


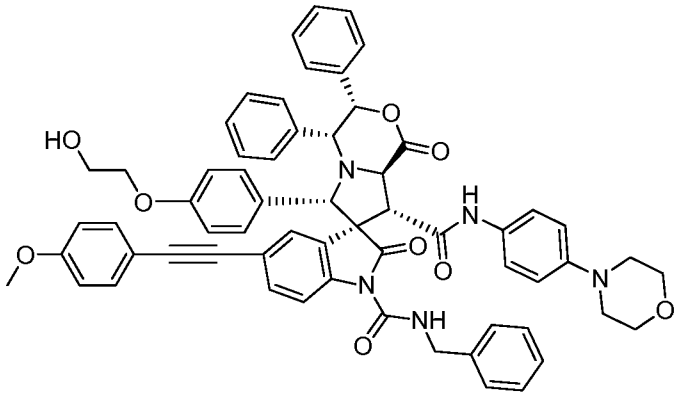


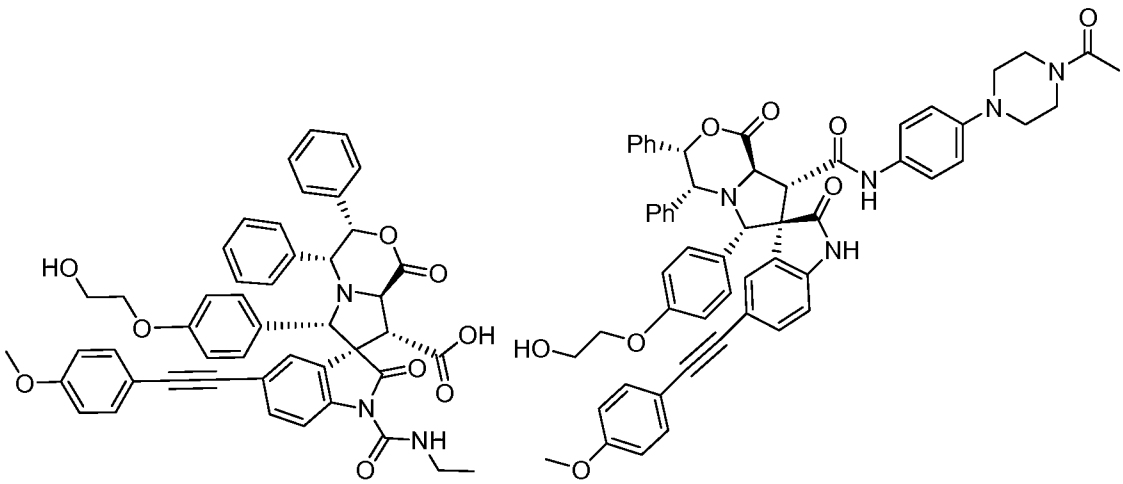


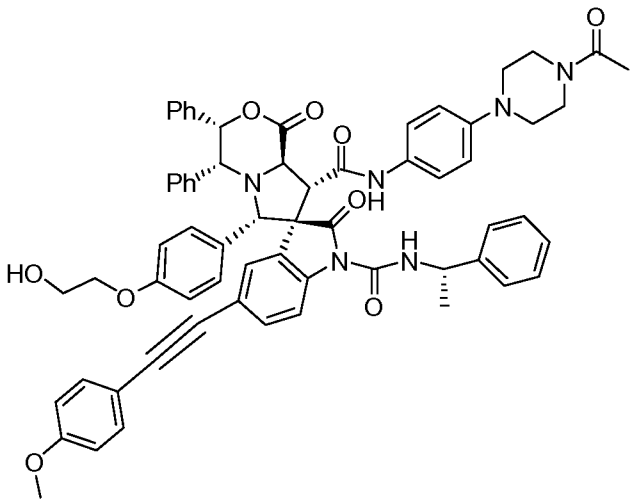


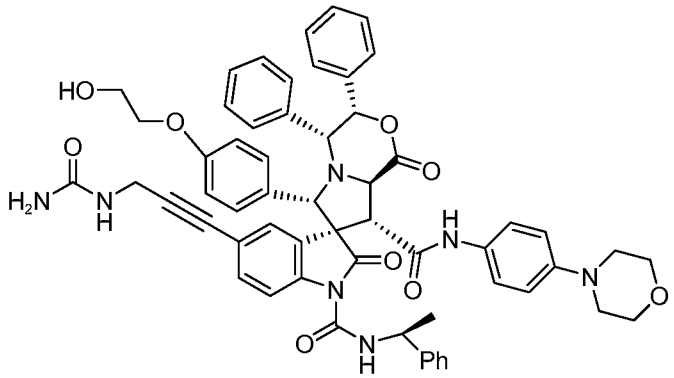


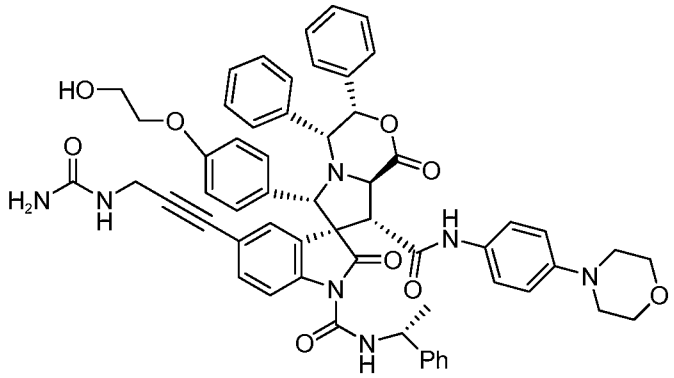


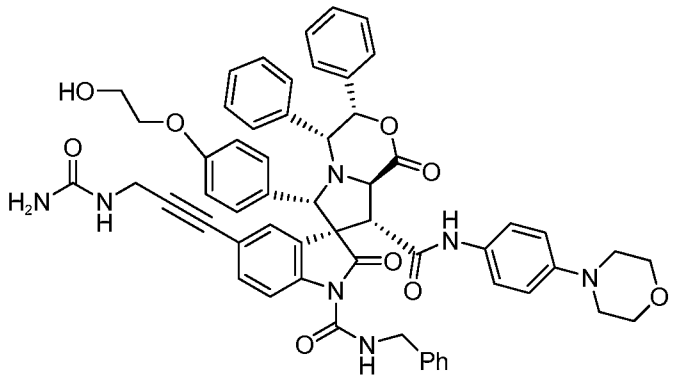


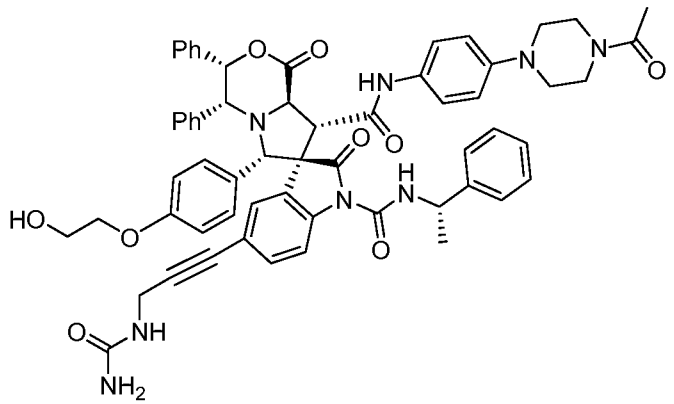


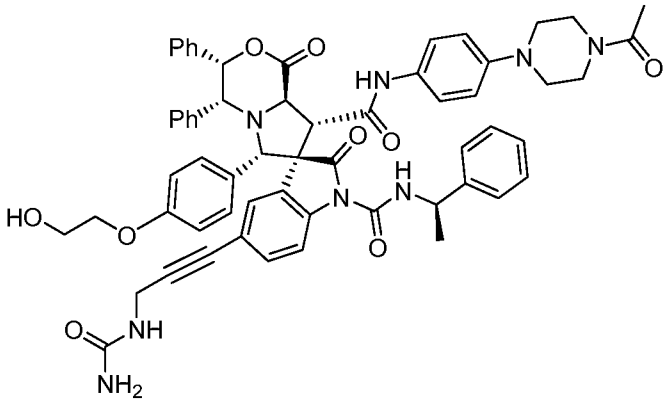


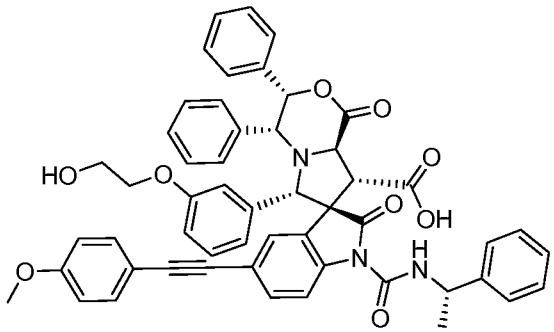


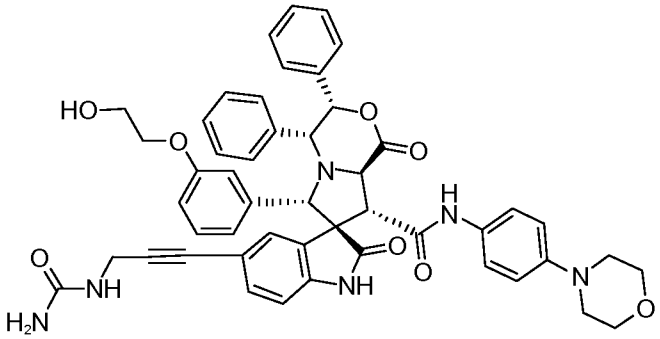


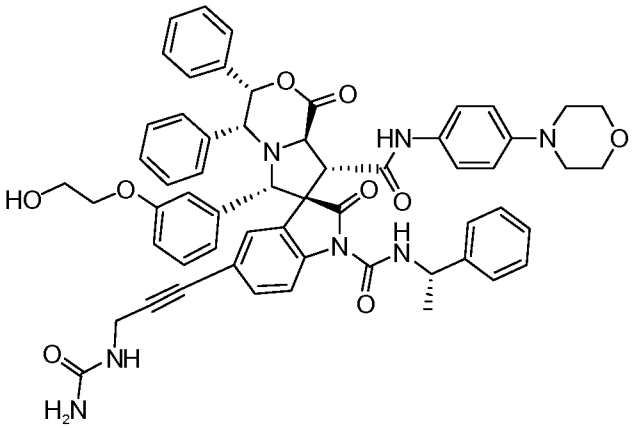


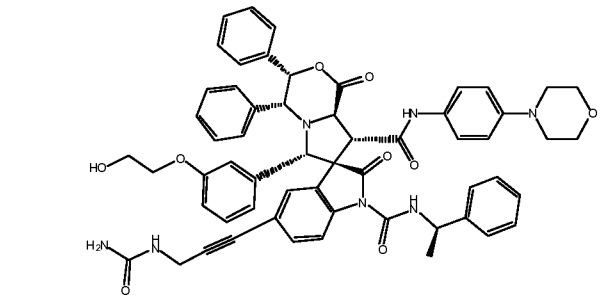


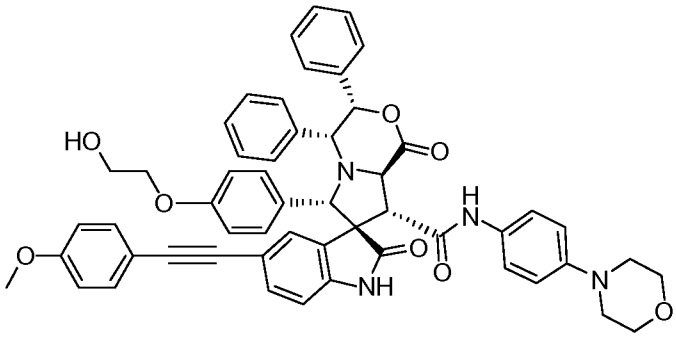


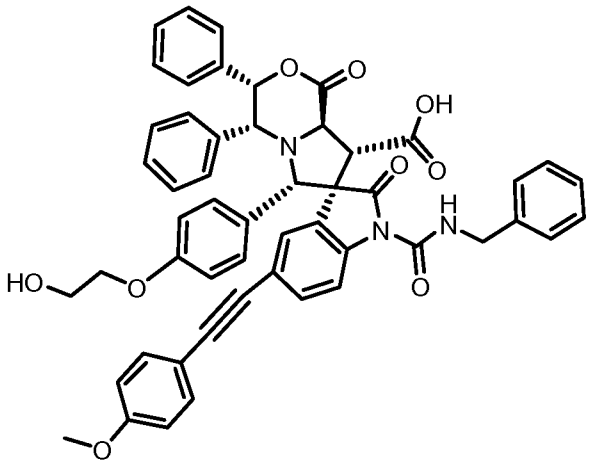


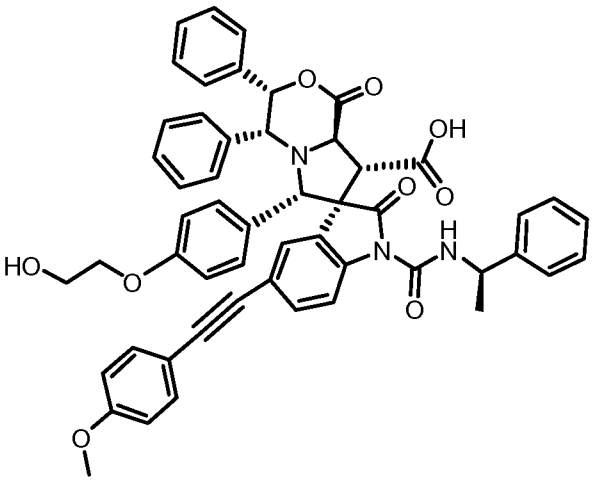


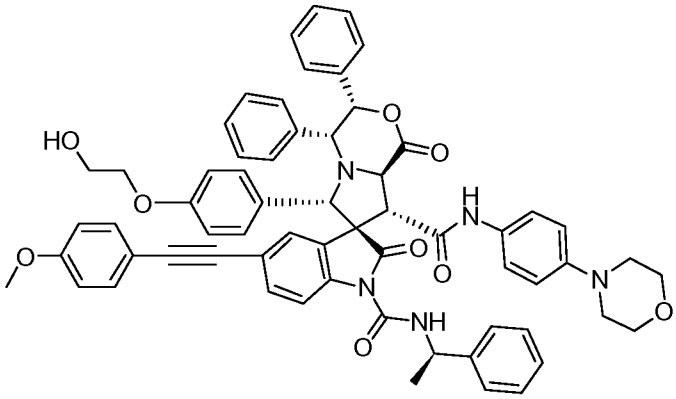


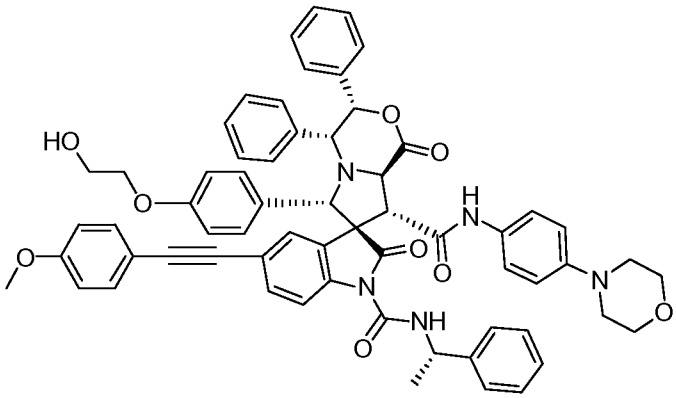


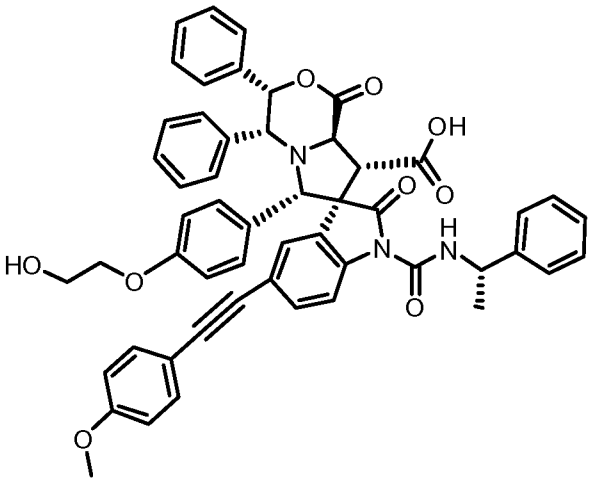


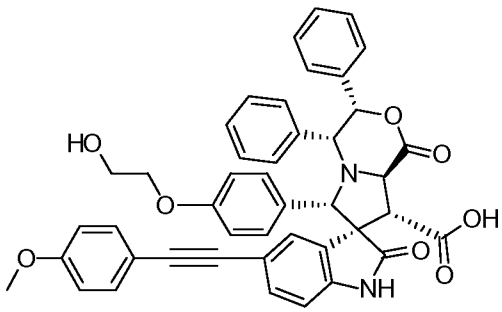


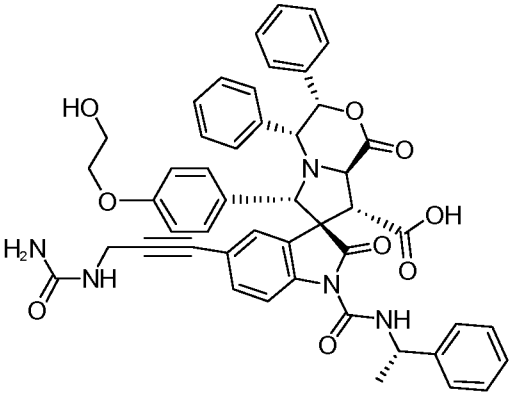


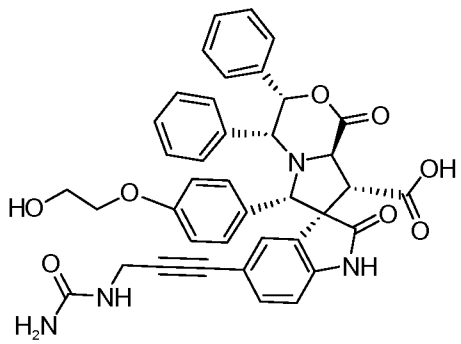


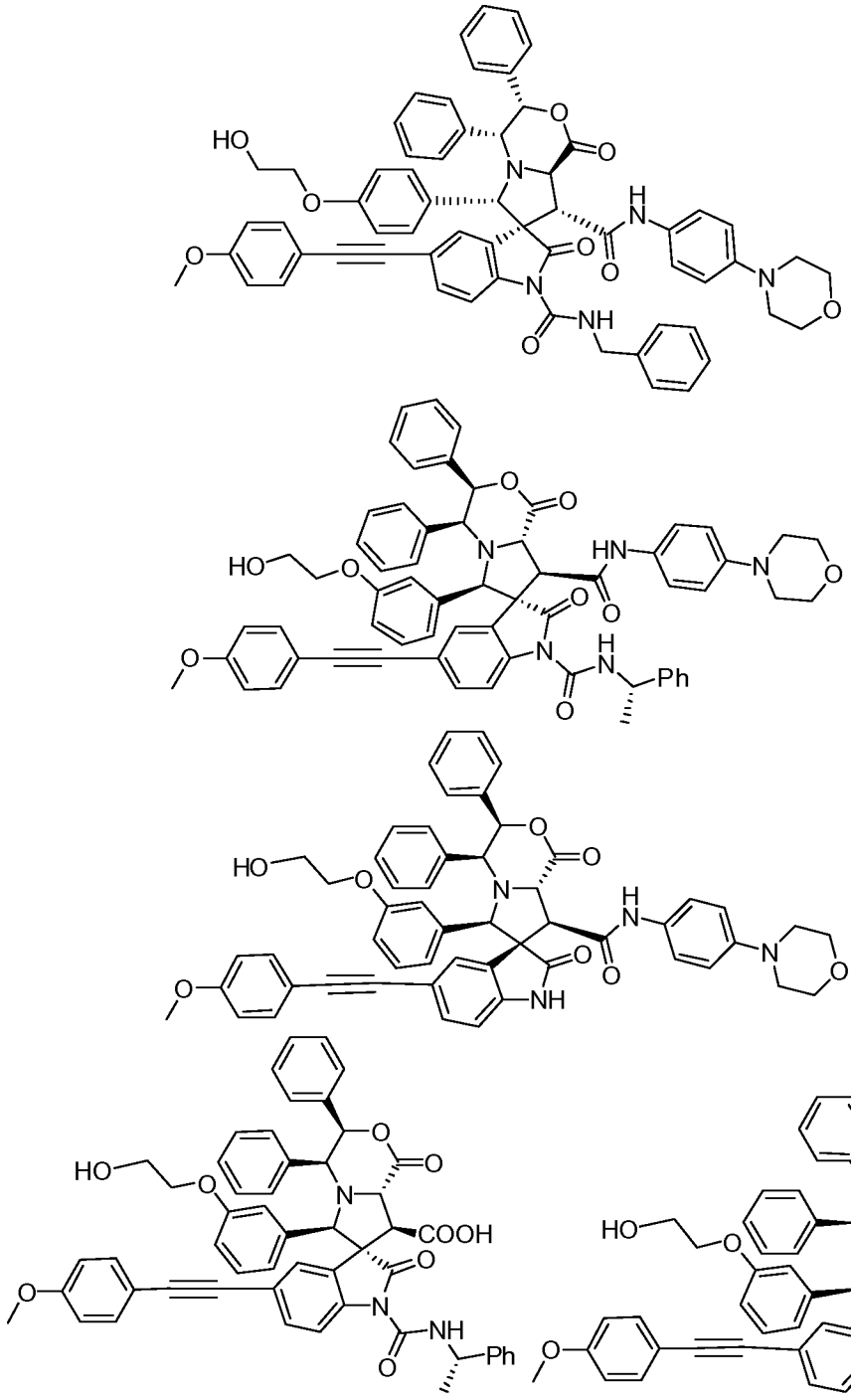


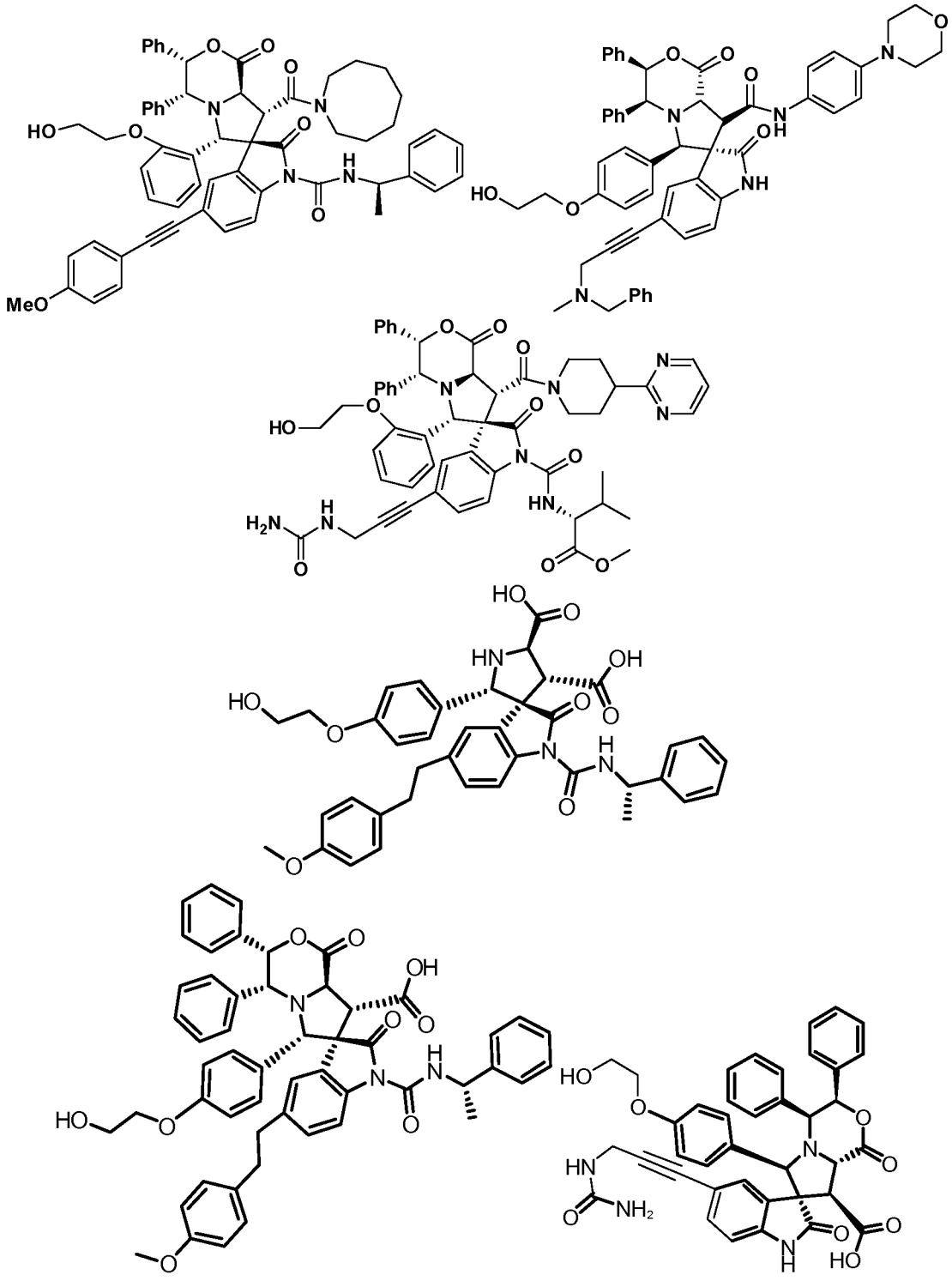


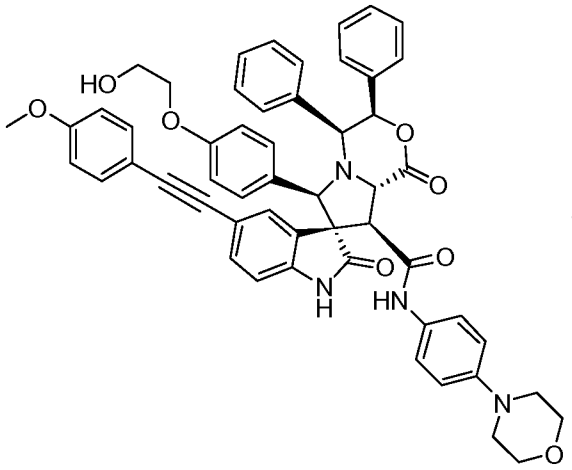


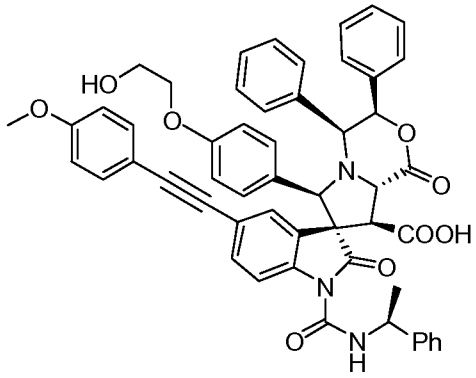


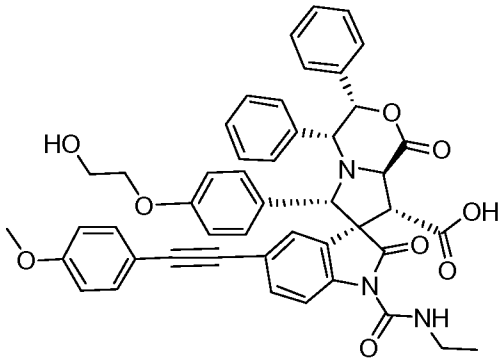


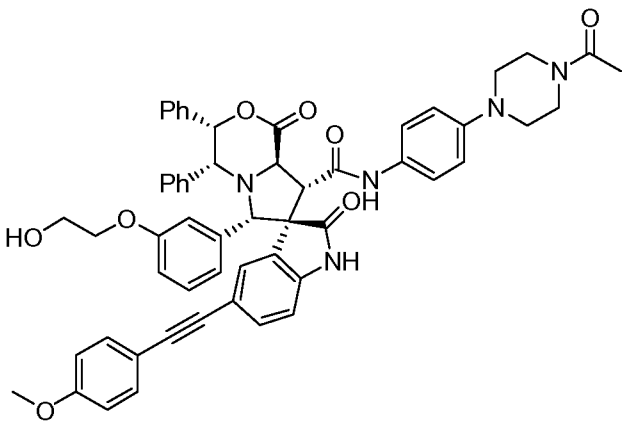


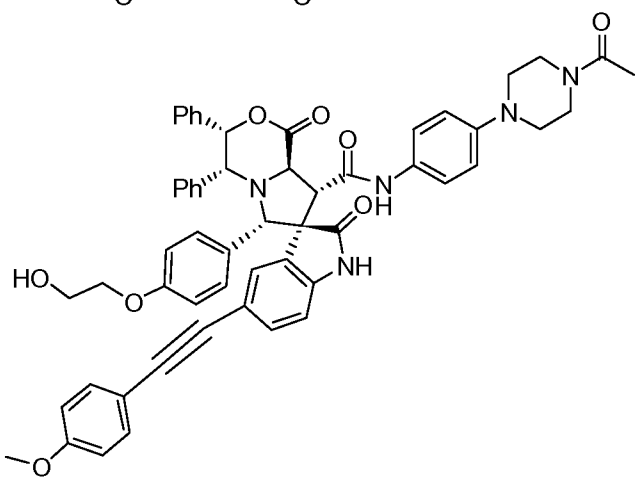


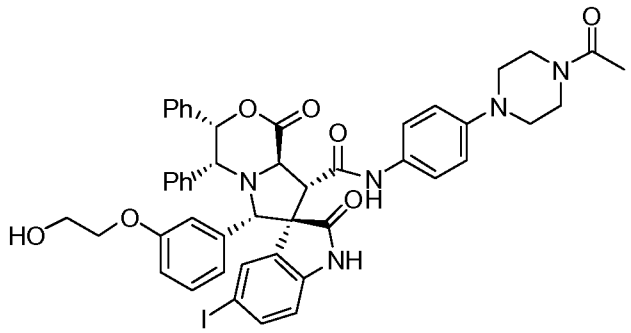


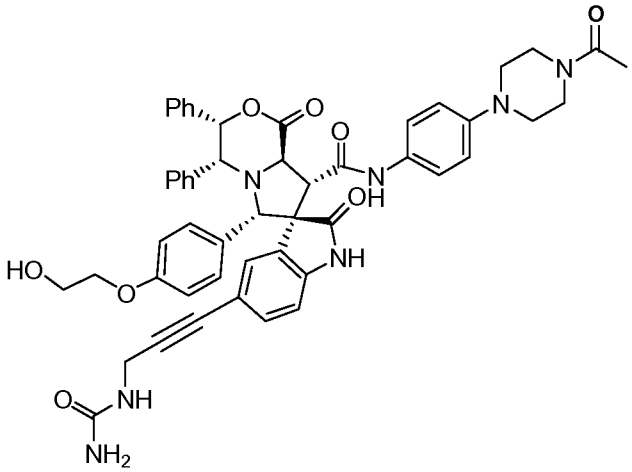


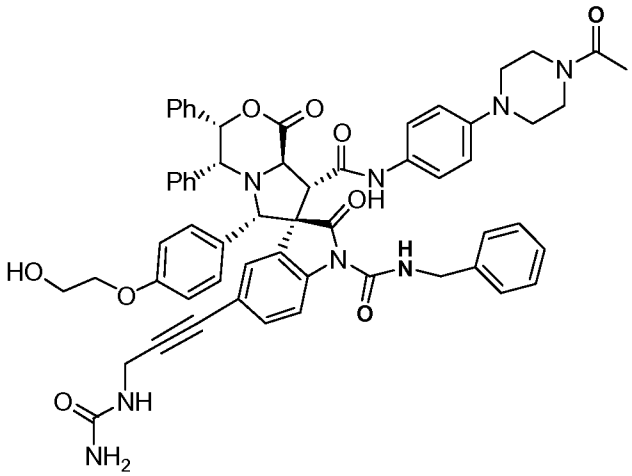


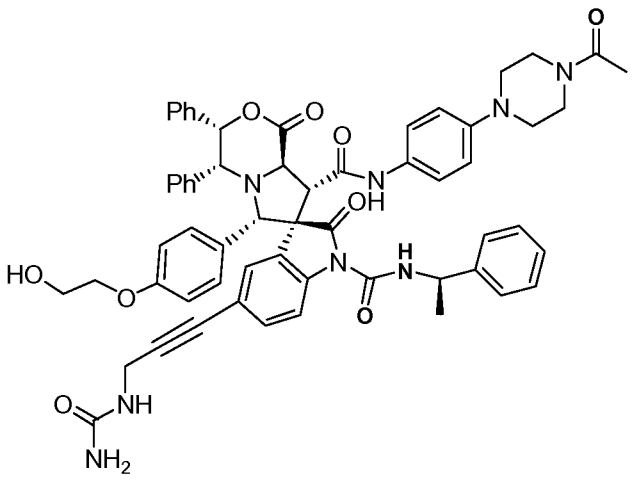


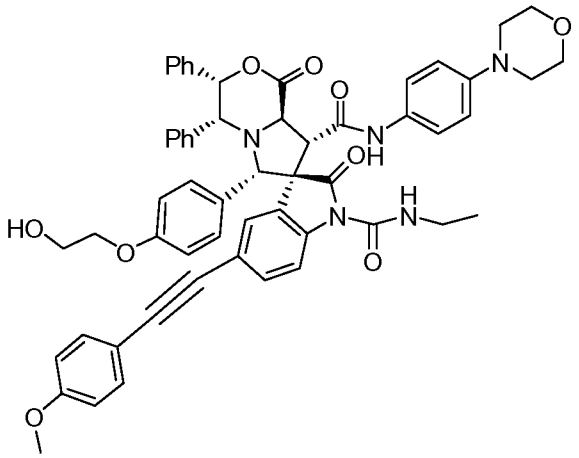


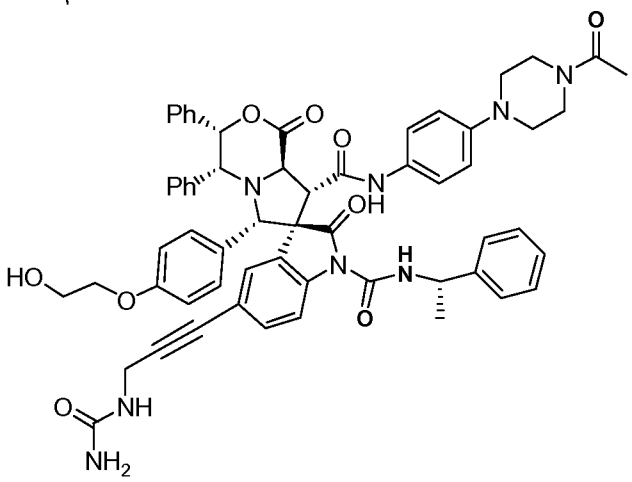


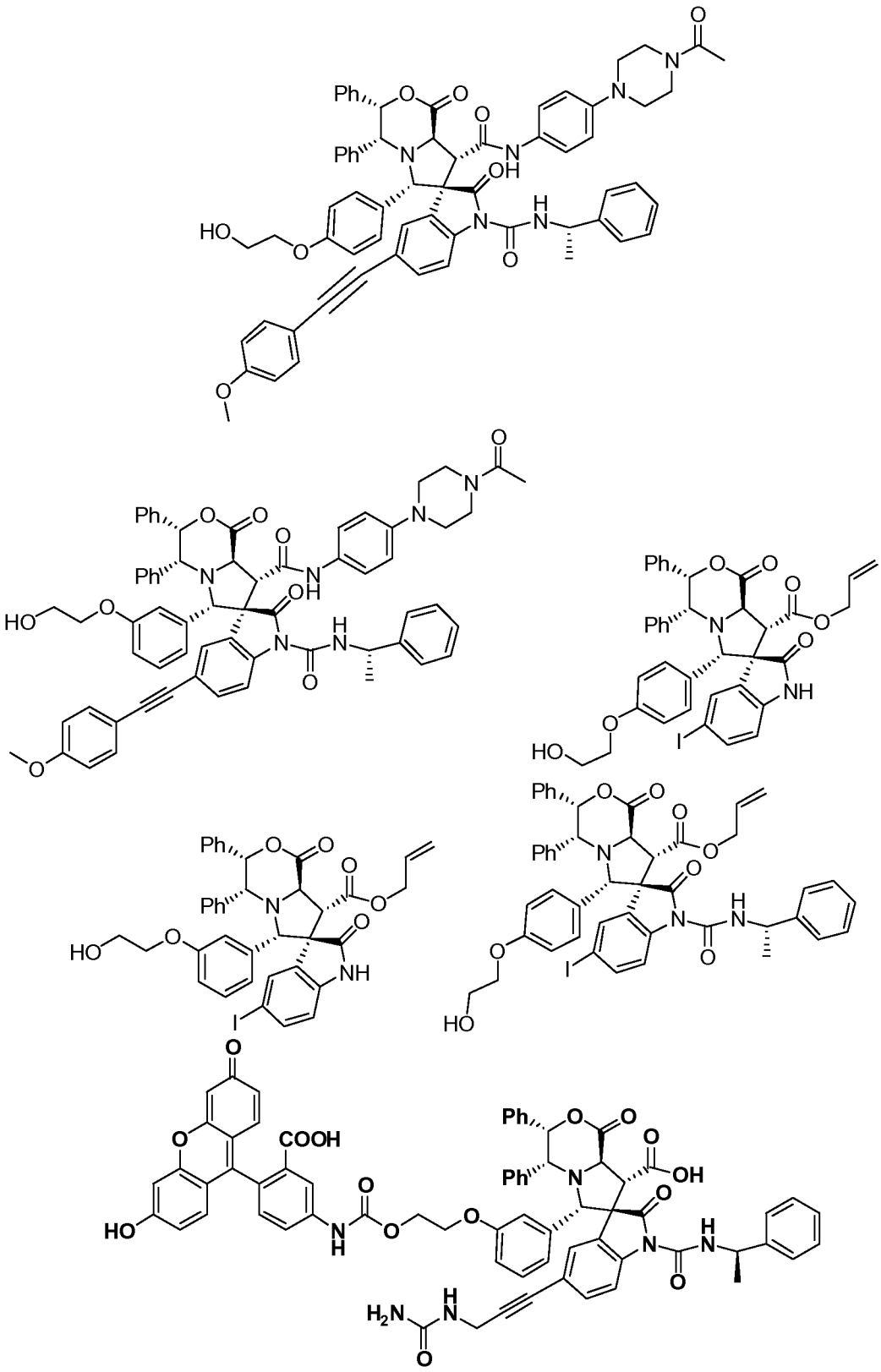


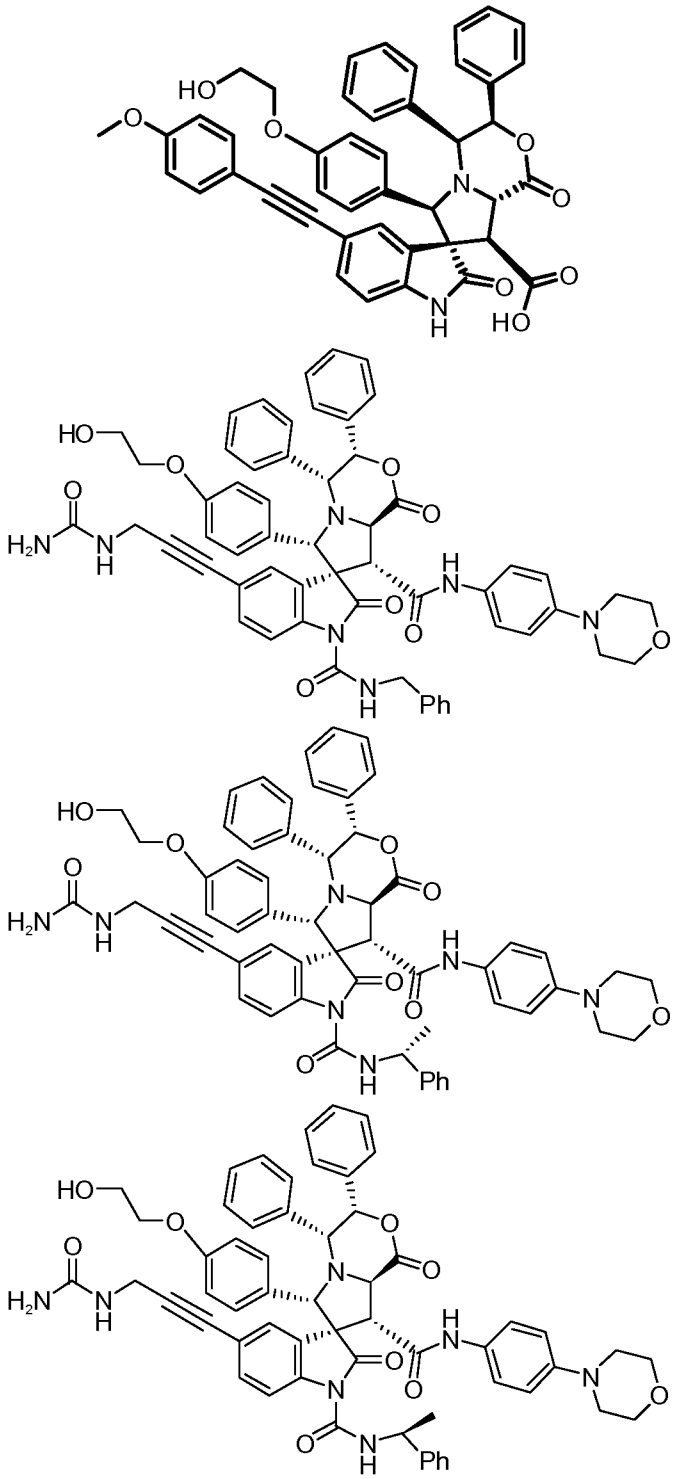


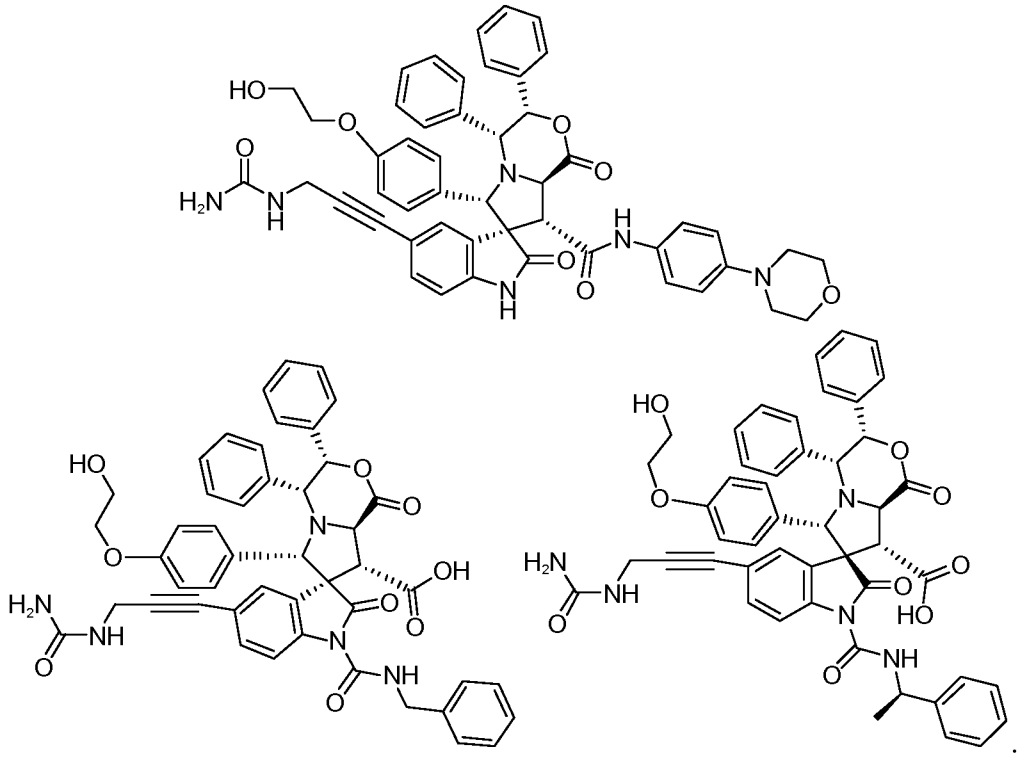






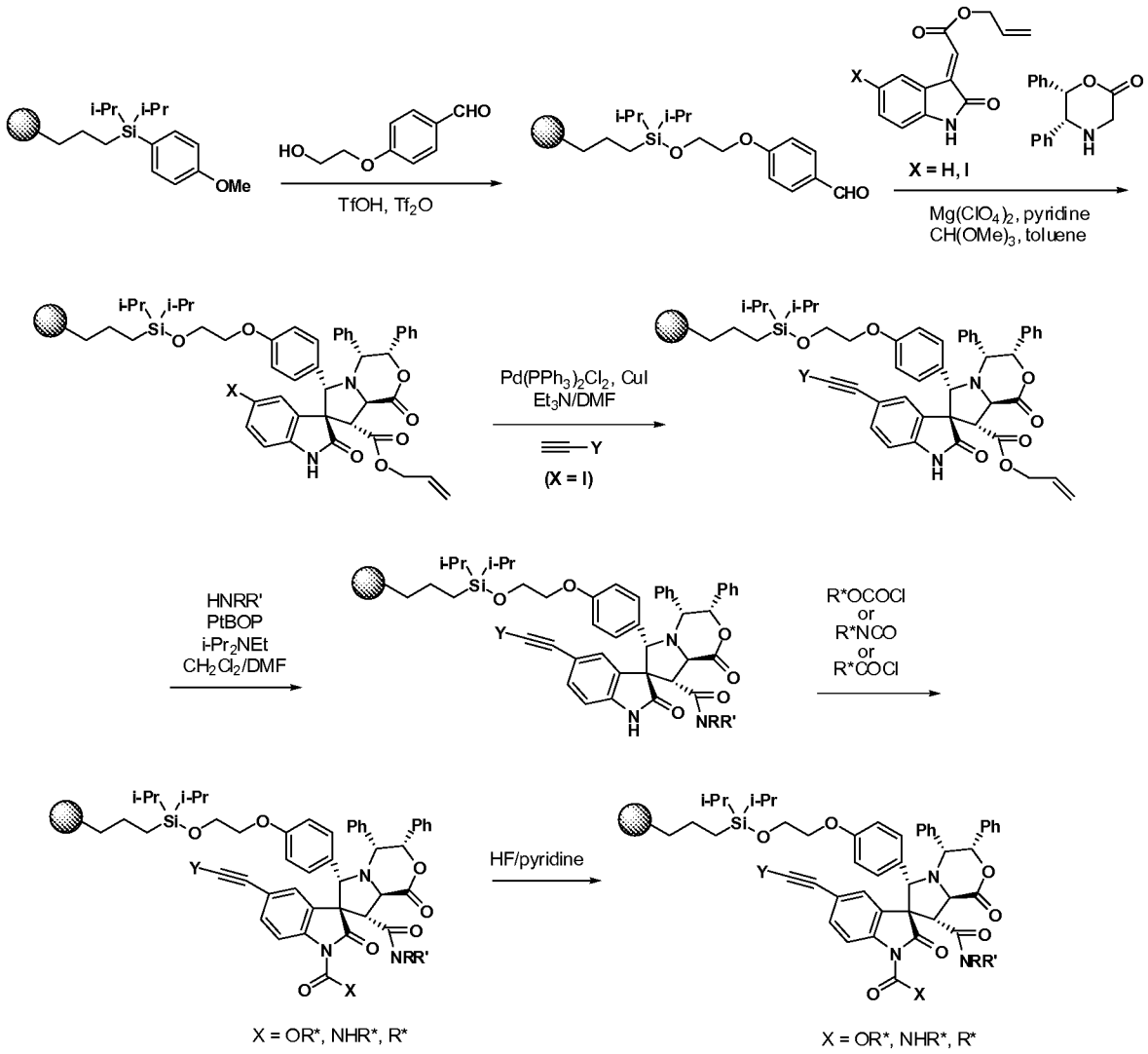






Methods of Synthesis

[0091] The present invention also includes all steps and methodologies used in preparing the compounds of the invention as well as intermediates along the synthetic route. An exemplary synthesis of the inventive compounds is shown below:



[0092] As would be appreciated by one of skill in the art, the synthetic methodology may be used to include a label (*e.g.*, an isotopic or radioactive label) into an inventive compound. Such labeled compounds are useful in diagnostic and research applications.

[0093] In certain embodiments, the present invention provides a synthetic method for covalently attaching a fluorescent moiety (*e.g.*, fluorescein) or other tag to an inventive compound. An examplary reaction is shown in *Figure 4*. In certain embodiments, the fluorescent moiety or other tag is attached to the compound at a position that does not interfere with the biological activity of the compound.

[0094] As will be appreciated by one of skill in the art, various isolation and purification techniques including flash chromatography, crystallization, distillation, HPLC,

thin layer chromatography, extraction, filtration, *etc.* may be used in the course of synthesizing compounds of the invention. These techniques may be used in the preparation or purification of intermediates, reagents, products, starting materials, or solvents.

Uses of Compounds and Pharmaceutical Compositions

[0095] The invention provides methods of using the inventive compounds. The compounds may be used for therapeutic purposes, diagnostic purposes, or research purposes. The ability of the inventive compounds to inhibit and/or bind Aurora kinases makes them useful for all three purposes.

[0096] In certain embodiments, the invention provides methods of using the inventive compounds, particularly labeled or tagged compounds, to identify dividing cells. The identification of dividing cells is useful in identifying cells that are malignant. A biological sample is contacted with a labeled or tagged inventive compound and the cells of the biological sample are visualized. The images of the cells may be analysed by computer-assisted analysis. In certain embodiments, a biological sample is take from a tissue suspected of being cancerous. In certain embodiments, the biological sample is a Pap smear. In other embodiments, the biological sample is derived from a biopsy. The method may be combined with other technqiues known in the art for staining cells and/or identifying cell undegoing division.

[0097] The present invention also provides methods of localizing Aurora kinase in a cell. Since the tagged or labeled compounds bind Aurora kinase, the localization of Aurora kinase in a cell at various times or under various conditions may be determined. Any type of cell may be analysed using the inventive method. In certain embodiments, the cell is a human cell. In certain embodiments, the cell is mammalian cell. Inventive compounds that specifically bind Aurora A, B, or C kinase are particularly useful in such methods because the localization of each kinase may be determined.

[0098] The invention further provides a method of inhibiting tumor growth. The method involves the administration of a therapeutically effective amount of the compound or a pharmaceutically acceptable derivative thereof to a subject (including, but not limited to a human or animal) in need thereof.

[0099] The compounds and pharmaceutical compositions of the present invention may be used in treating or preventing any disease or conditions including proliferative

diseases (*e.g.*, cancer or benign neoplams), inflammatory diseases, autoimmune diseases (*e.g.*, rheumatoid arthritis, lupus), and diabetic retinopathy. The compounds and pharmaceutical compositions may be administered to animals, preferably mammals (*e.g.*, domesticated animals, cats, dogs, mice, rats), and more preferably humans. Any method of administration may be used to deliver the compound of pharmaceutical compositions to the animal. In certain embodiments, the compound or pharmaceutical composition is administered orally. In other embodiments, the compound or pharmaceutical composition is administered parenterally.

[00100] This invention also provides a pharmaceutical preparation comprising at least one of the compounds as described above and herein, or a pharmaceutically acceptable derivative thereof, which compounds inhibit the growth of or kill neoplastic cells. In yet other embodiments, the compounds inhibit the growth of or kill rapidly dividing cells such as stimulated inflammatory cells.

[00101] As discussed above, the present invention provides novel compounds having antiproliferative activity, and thus the inventive compounds are useful for the treatment of a variety of medical conditions including cancer, autoimmune diseases, inflammatory diseases, and diabetic retinopathy. Accordingly, in another aspect of the present invention, pharmaceutical compositions are provided, wherein these compositions comprise any one of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents, *e.g.*, another anti-proliferative agent. In other embodiments, these compositions further comprise an anti-inflammatory agent such as aspirin, ibuprofen, acetaminophen, *etc.*, pain reliever, anti-nause agents, or anti-pyretic.

[00102] In yet another aspect, according to the methods of treatment of the present invention, malignant cells are killed, or their growth is inhibited by contacting the cells with an inventive compound or composition, as described herein. Thus, in still another aspect of the invention, a method for the treatment of cancer is provided comprising administering a therapeutically effective amount of an inventive compound, or a pharmaceutical composition comprising an inventive compound to a subject in need thereof, in such amounts and for such time as is necessary to achieve the desired result. In certain embodiments of the present invention a "therapeutically effective amount" of the inventive compound or pharmaceutical composition is that amount effective for killing or inhibiting the growth of the malignant

cells. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for killing or inhibiting the growth of the undesired cells. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular compound, its mode of administration, its mode of activity, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[00103] Furthermore, after formulation with an appropriate pharmaceutically acceptable carrier in a desired dosage, the pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be

delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00104] It will also be appreciated that certain of the compounds of the present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof, *e.g.*, a prodrug.

[00105] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1-19, 1977; incorporated herein by reference. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base functionality with a suitable organic or inorganic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hernisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium,

calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate, and aryl sulfonate.

[00106] Additionally, as used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates. In certain embodiments, the esters are cleaved by enzymes such as esterases.

[00107] Furthermore, the term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[00108] Liquid dosage forms for oral and parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters

of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the compounds of the invention are mixed with solubilizing agents such an Cremophor, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and combinations thereof.

[00109] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00110] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00111] In order to prolong the effect of a drug, it is often 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 with 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. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon 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 tissues.

[00112] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00113] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00114] 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 sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. 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 sugar as well as high molecular weight polethylene glycols and the like.

[00115] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release

controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[00116] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00117] It will also be appreciated that the compounds and pharmaceutical compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutical compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another anticancer agent), or they may achieve different effects (*e.g.*, control of any adverse effects).

[00118] In still another aspect, the present invention also provides a pharmaceutical

pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention, and in certain embodiments, includes an additional approved therapeutic agent for use as a combination therapy. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Screening of Inventive Compounds

[00119] The compounds described herein may be screened for any biological activity. In certain embodiments, the compounds are screened using known assays in the art. In certain embodiments, the compounds are screened for anti-proliferative activity. For example, assays may be used to determined the concentration of the compound necessary to inhibit growth of cells (*e.g.*, cells derived from a cancer cell line) by 50%. Compounds with anti-proliferative activity may be useful for treating diseases such as cancer, inflammation, autoimmune diseases, benign neoplasms, and diabetic retinopathy. In certain other embodiments, the compounds are tested for their ability to bind Aurora kinases. In yet other embodiments, the compounds are tested for their ability to inhibit Aurora kinases.

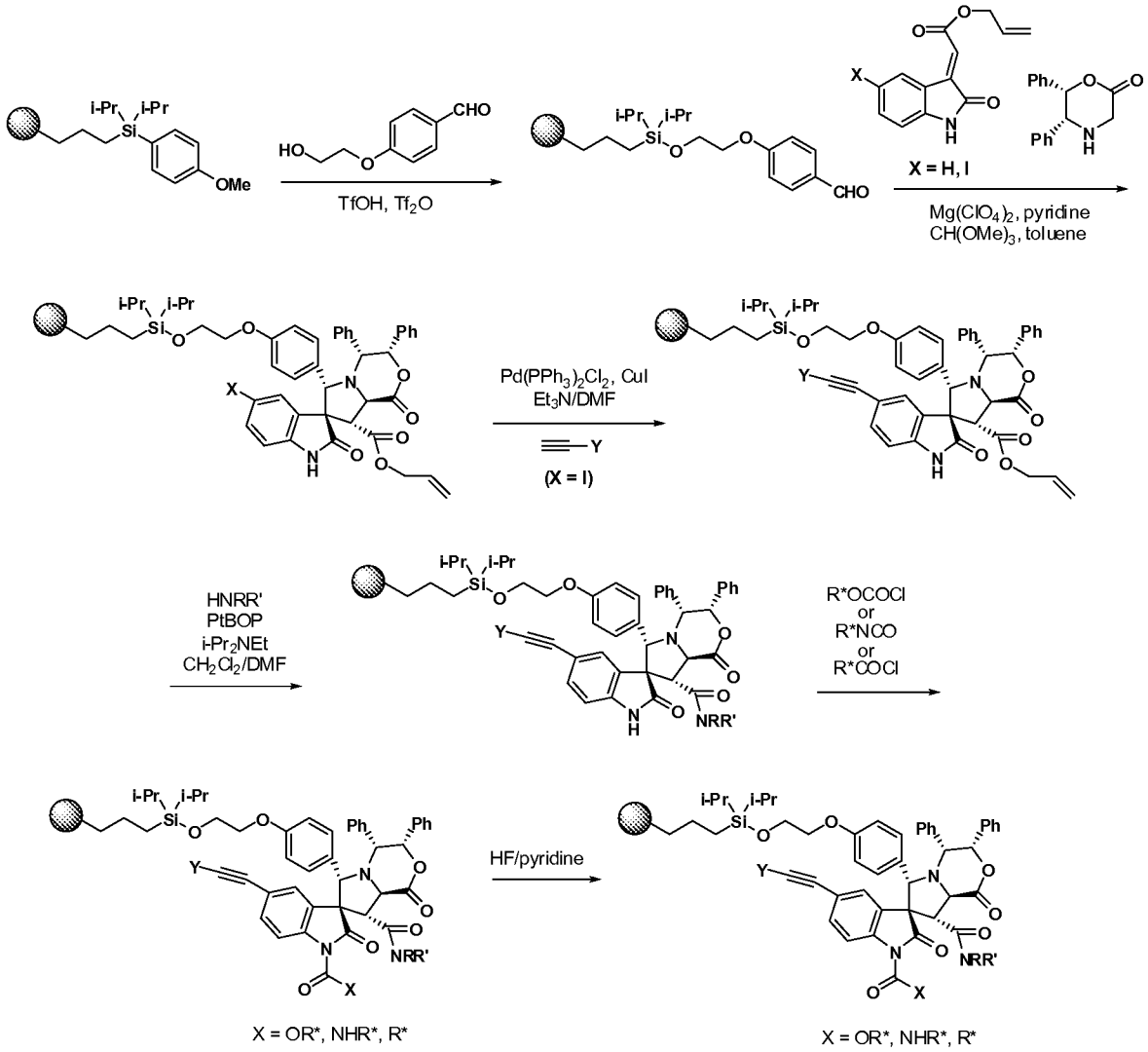
[00120] These and other aspects of the present invention will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the invention but are not intended to limit its scope, as defined by the claims.

Examples

Example 1

Chemical synthesis

[00121] Synthesis of the inventive compounds was performed as described (*J. Amer. Chem. Soc.* **2004**, *126,* 16077). Library synthesis was done on a silicon functionalized resin, or individual compounds can be made using the same route replacing the resin with a trialkylsilyl protecting group. By modifying the described procedures, one skilled in the art is able to make any analogs described in this application.



Biological Activity

Small-Molecule Microarray Assays

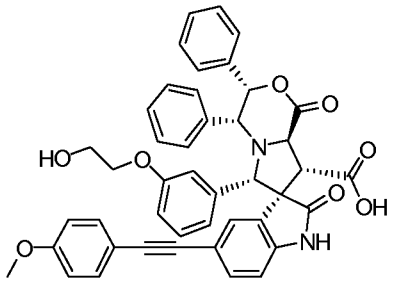
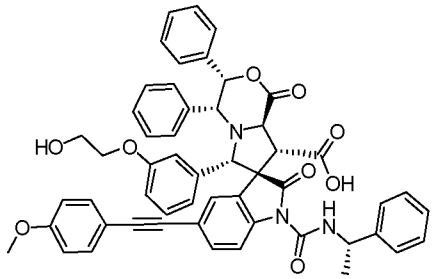
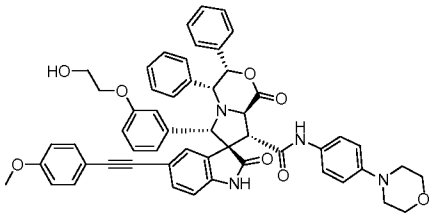
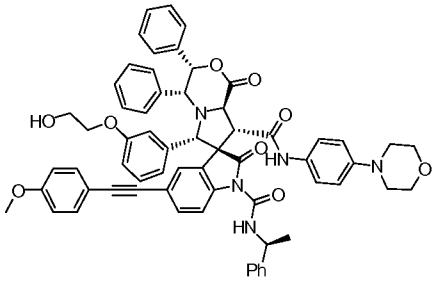
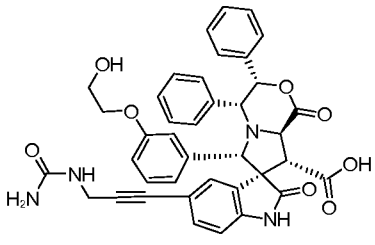
[00122] Recombinant Aurora A was expressed in *E. coli* BL21(DE3)pLysS cells (Novagen) as a C-terminal RGS-6xHis-tagged protein and was purified using Ni-NTA agarose affinity chromatography according to the standard protocols. Small-molecule microarrays were incubated in triplicate with 400 µl of a 10 µg/ml solution of purified Aurora A-RGS-6xHis in TBST buffer for 30 min at room temperature. The arrays were washed three times in TBST (1 min for each wash) on an orbital platform shaker. Arrays were then incubated with 300 µl of a 0.2 µg/ml solution of Cy5-labeled anti-5xHis antibody (Qiagen) in

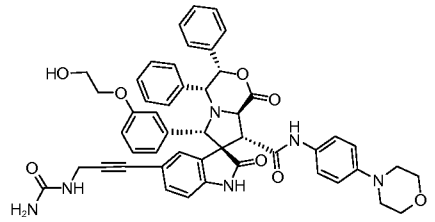
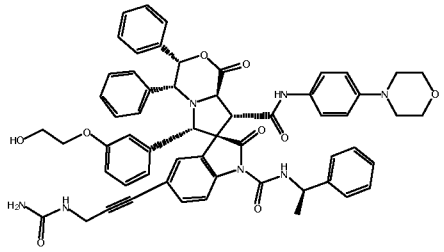
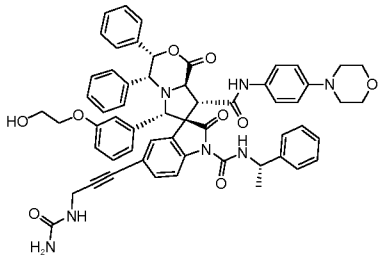
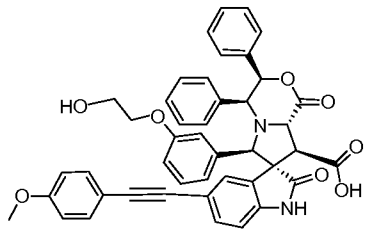
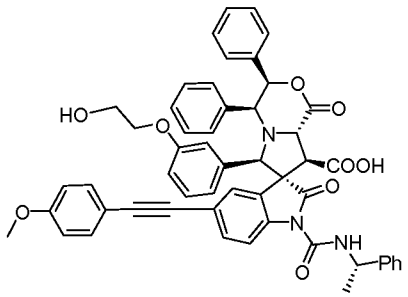
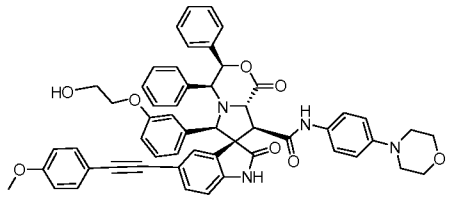
TBST for 30 min at room temperature. The probed arrays were washed three times in TBST (5 min for each wash), followed by doubly distilled water for 3 min on an orbital platform shaker. Arrays were dried by centrifugation and scanned for fluorescence at 635 nm using a Genepix 4000B microarray scanner.

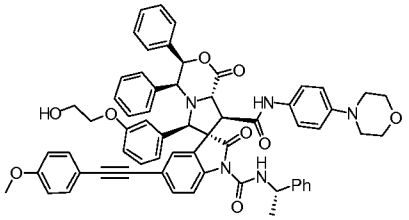
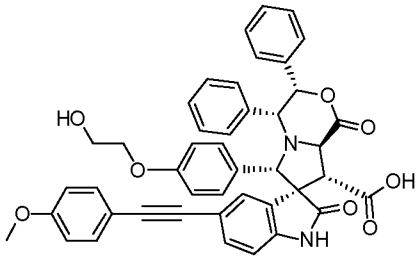
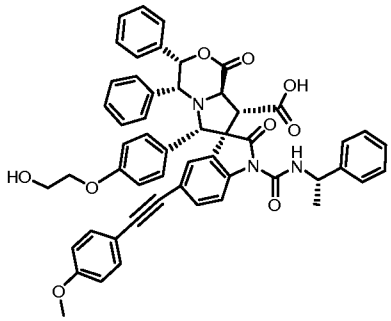
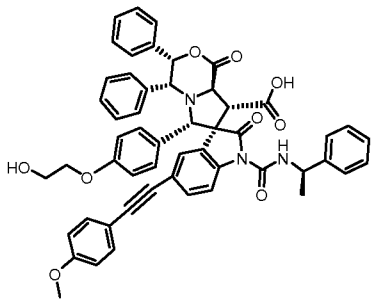
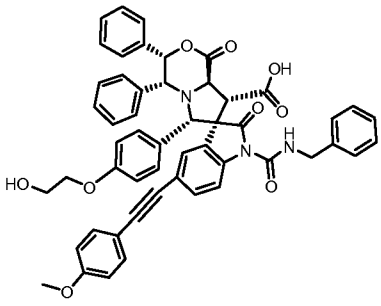
Enzyme Inhibition Assays

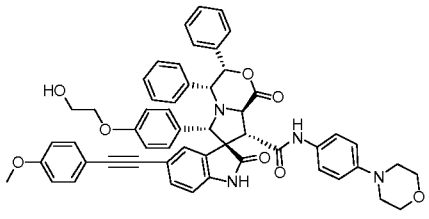
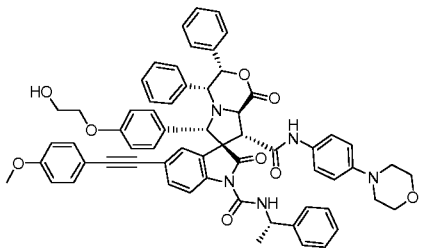
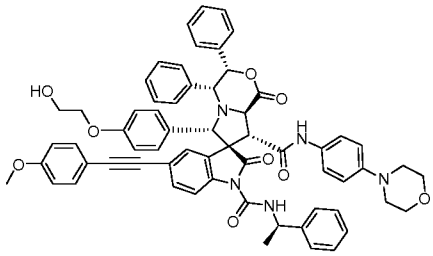
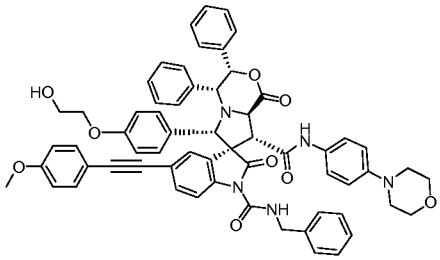
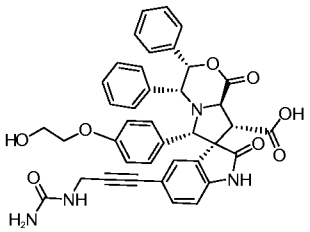
[00123] Enzyme inhibition assays were run with a commercially available Aurora A Kinase Assay/Inhibitor Screening Kit, CycLex Co., Ltd., (cat. no. CY-1165) as instructed. Aurora B kinase inhibitory activity was determined using CY1174 CycLex® Aurora Family Kinase Assay/Inhibitor Screening Kit using Aurora B Positive Control (CY-E1174-1) and Aurora C Positive Control (CY-E1174-2). These reagents were obtained from MBL International (Woburn, MA). Briefly, test compounds at various concentrations were incubated with Aurora A kinase positive control (CycLex Co., Ltd., cat. no. CY-E1165) and ATP in kinase reaction buffer in microtiter wells at 30 °C for 45 minutes. Wells were washed with wash buffer (5x200 µl). 100 µl of anti-phospho-Lats2-S83 antibody solution (supplied with the kit) was added to each well and incubated at room temperature for 30 min. Wells were washed with wash buffer (5x200 µl - supplied with the kit). 100 µl of HRP-conjugated anti-mouse IgG solution was added per well and incubated at room temperature for 30 min. Wells were washed with wash buffer (5x200 µl), and 100 µl of substrate reagent (supplied with the kit) was added and incubated at room temperature for 10 min. Reactions were stopped by adding 100 µl of stop solution (supplied with the kit) and absorbance was measured in each well using a spectrophotomeric plate reader (Molecular Devices, Spectra MAX 190) at dual wavelengths of 450 and 540 nm.

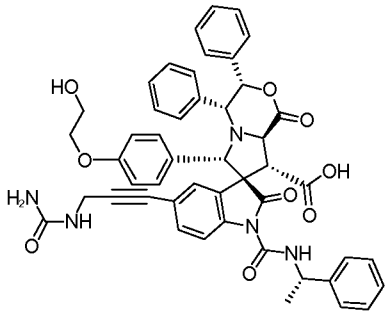
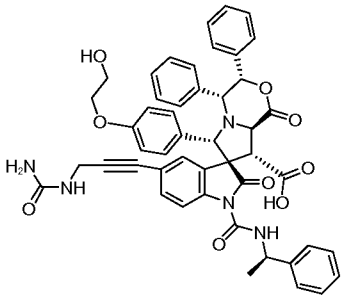
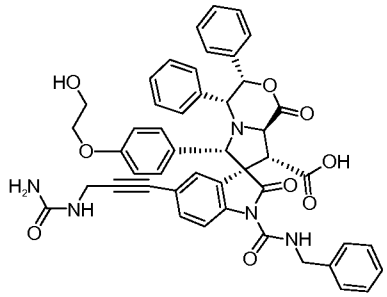
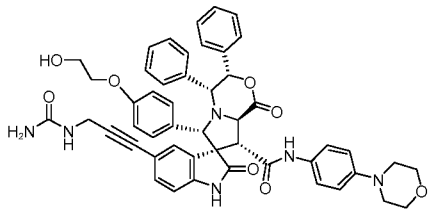
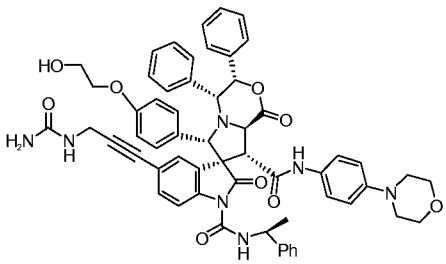
[00124] SpOx-4 inhibited Aurora-A kinase activity by 75% at 5 µM and by 97% at 50 µM, whereas SpOx-5 inhibited by 53% at 5 µM and by 74% at 20 µM. *See Figure2A-B.* The other Aurora kinase family members, Aurora-B and C, were inhibited by SpOx-4 by 75% and 71%, respectively at 50 µM. *See Figure2C-D.* SpOx-5 inhibited Aurora-B and -C by 72% and 55%, respectively at 50 µM. *See Figure2C-D.* The Aurora A and B kinase inhibitory activity of other spirooxindoles is shown in the tables below.

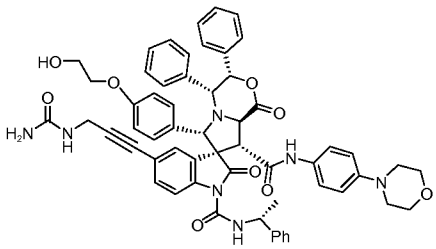
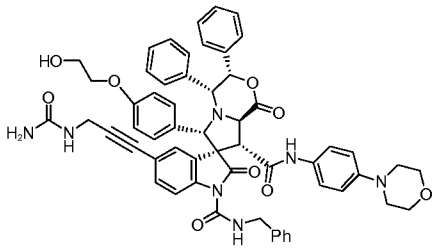
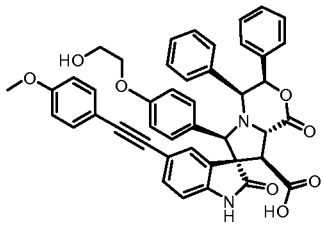
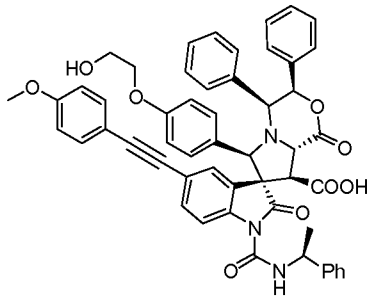
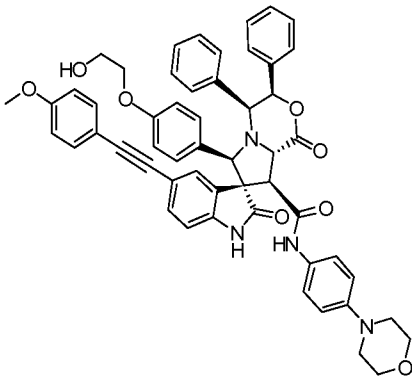
Compound	Structure	*In Vitro* Aurora A Kinase Activity				
		IC_{50}	10 uM	3 uM	1 uM	300 nM	100 nM
3XAD		28.1				
3XADF		2.1	9.7	26.5	52.6	
3XAC		33				
3XACF		12	37.9	29.9	62.4	
3XBD		34.8				

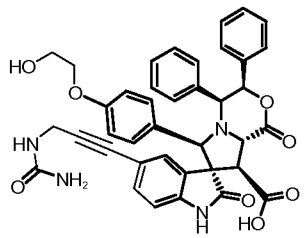
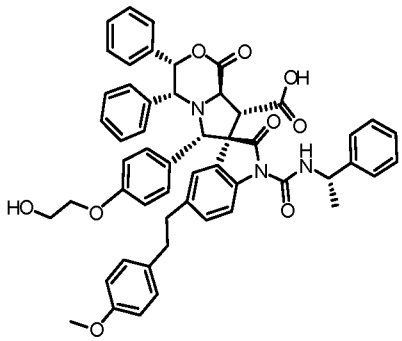
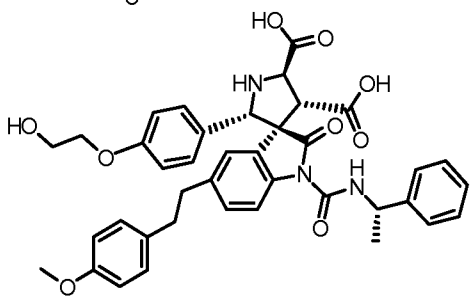
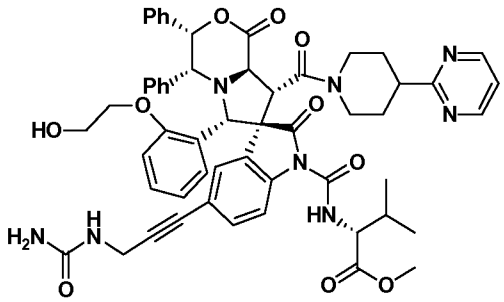
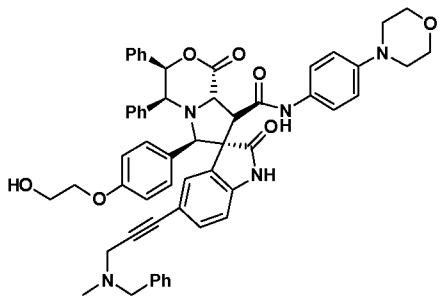
3XBC			63.7			
3XBCG (1296-D11 SpOx-5)		3 uM	30.0	67.6	83.3	93.2
3XBCF						
3X'AD				43		
3X'ADF				5.2		
3X'AC				84.3		

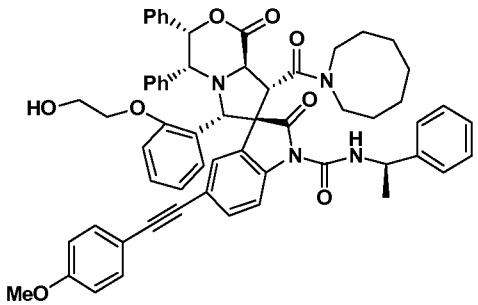
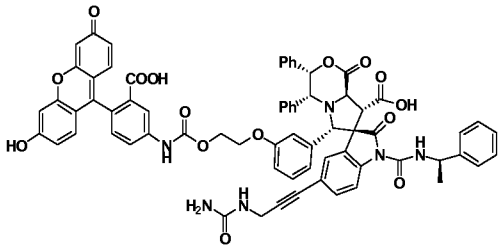
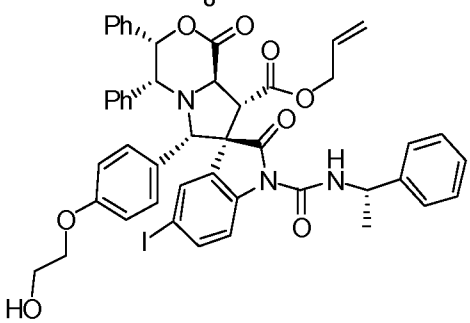
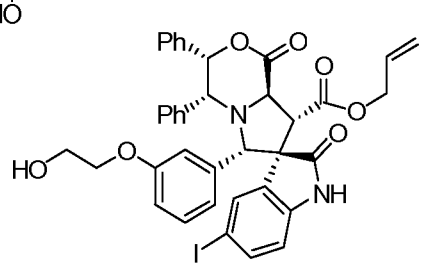
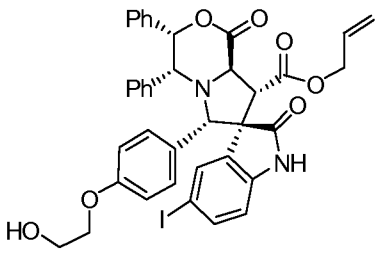
3X'ACF			76.4				
4XAD		3 uM	17.9	41.7			
4XADF		296 nM	4.3	0.9	8.0	55.5	90.8
4XADG		221 nM	-	0.9	2.9	36.7	81.1
4XADH		255 nM	-	1.3	8.0	50.4	80.4

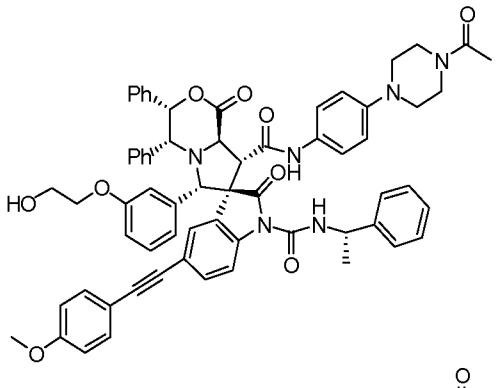
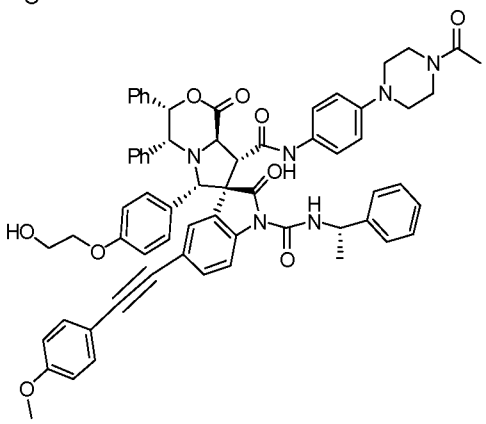
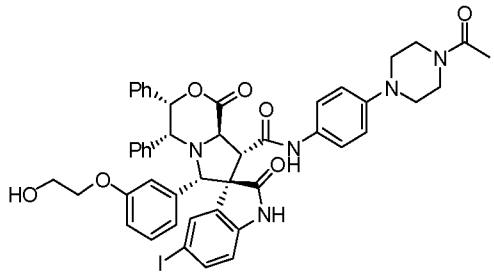
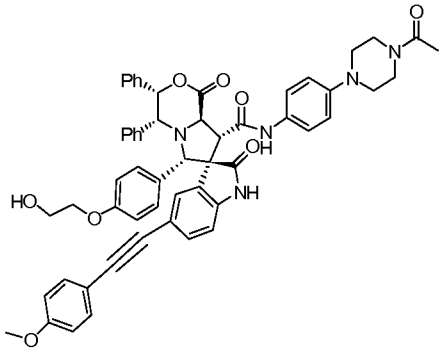
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4XACF		18	42.8
4XACG			34.6
4XACH			13.8
4XBD		71.9	70.2

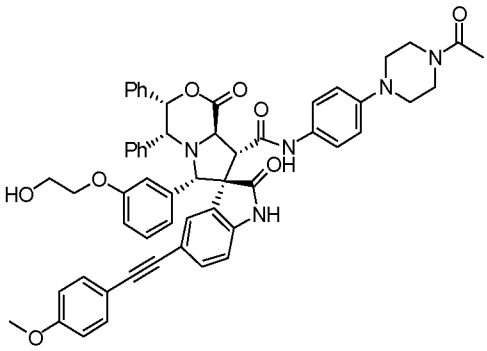
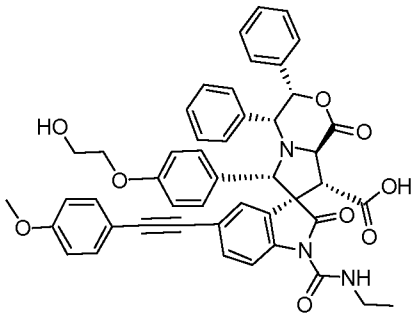
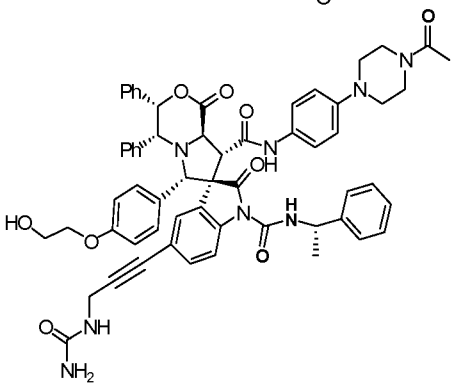
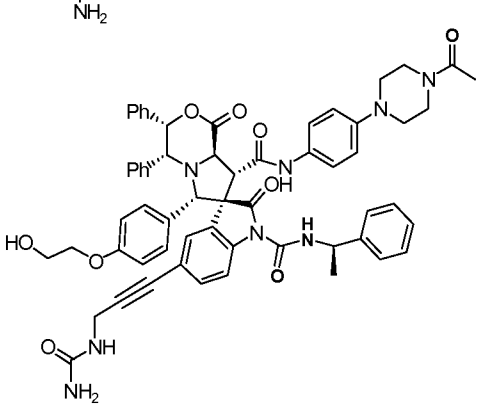
4XBDF		16.2
4XBDG		18.8
4XBDH		10.2
4XBC		42.7
4XBCF		24.8

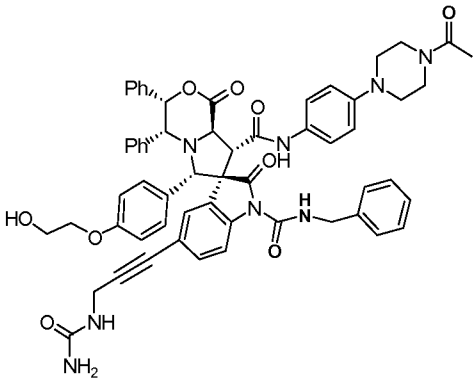
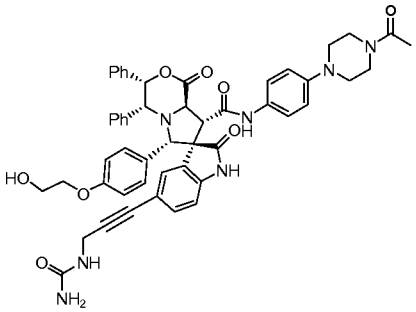
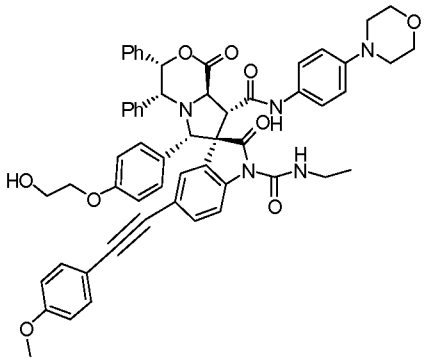
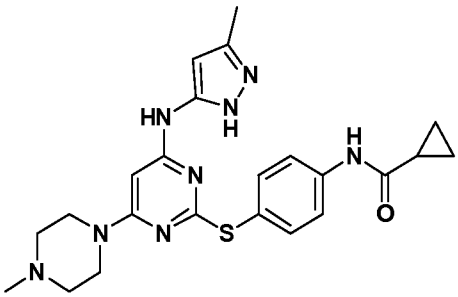
4XBCG			32.9
4XBCH			20.6
4X'AD			19
4X'ADF			4.2
4X'AC (1281-I04 SpOx-4)		1 uM	17.8

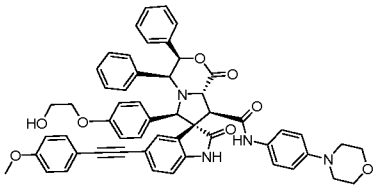
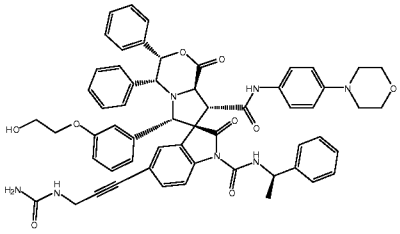
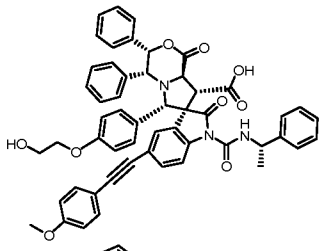
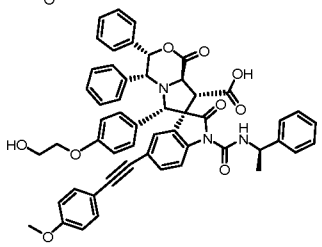
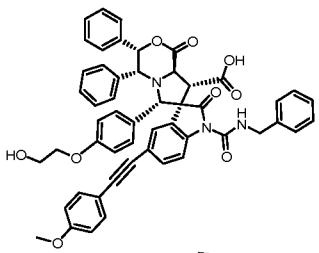
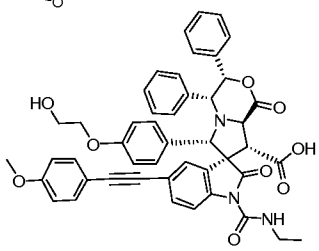
4X'BD				75.6			
TL 199		543 nM	-	3.5	18.3	56.0	91.2
TL 214		827 nM	0.0	5.3	25.4	73.9	74.7
SpOx-1 (1293-K01)			31.1^				
SpOx-2 (1281-G13)			37.7^				

SpOx-3 (1297-P11)			67.8	
SpOx-5-FITC		4 uM	34.5	85.1
4XF			53.2	
3X			53.6	
4X			51.1	

3XAEF		12.9	53.6	69.2	80.6
4XAEF		20.9	61.1	70.9	81.5
3XE		75.1			
4XAE		14.3	67.5		

3XAE		27.3					
4XADK		670 nM	-	3.5	23.4	79.5	93.3
4XBEF				33.8			
4XBEG				23.2			

4XBEH					29.7	
4XBE					25.9	
4XACK					53.7	
					1 nM	.5 nM
VX-680		0.61 nM	1.2		30.5	51.6

Compound	a.k.a	Structure	*In vitro* Aurora B Kinase Activity 600 nM	300 nM	IC_{50}
4X'AC	1281-I04 SpOx-4				5 μM
3XBCG	1296-D11 SpOx-5				1 μM
4XADF			56.1	48.8	
4XADG			55.5	54.4	
4XADH			57.1	61.1	
4XADK			70.5	69.9	

Cell Viability Assays

[00125] Cell viability assays were run using colorectal cancer cell lines, colon cancer cell line COLO205, colon cancer cell line HCT116, breast cancer cell line MCF10A, and breast cell line MCF7 (see tables below), using AlamarBlue (BioSource, cat. no. DAL-1100) as a detection agent. Cells were harvested and resuspended in growth medium at $1x10^4$ cells/ml. 250 µl of cell suspension was added to each well of a 96-well plate and cells were incubated at 37 °C in 5% CO_2 atmosphere for three days. SpOx-4 and SpOx-5 dissolved in DMSO was mixed with growth media at various concentrations. Old media was removed from the wells and 200 µl of each dilution of SpOx-4 or SpOx-5 compound in media was added to the wells. Cells were incubated at 37 °C in 5% CO_2 atmosphere for 48 or 75 hours. After incubation, 20 µl of AlamarBlue reagent was added to each well, and plates were incubated for an additional 3 hours. Plates were scanned by a spectrophotomeric plate reader (Molecular Devices, Spectra MAX 190) at dual wavelength of 570 and 600 nm. Cell viability was calculated by using the equations shown in the product manual. SpOx-5 decreased the viability of colorectal cancer cells to 30% at 50 µM in 72 hours. *See Figure 3.*

COLO-205 Cell Activity (% living)

Compound	a.k.a	ED_{50}	500 nM	1 uM	2 uM	3 uM	5 uM	10 uM	30 uM	50 uM
3XBCG	SpOx-5						102	94		63
4XADF		5.5 uM	-	108.6	-	89.7	62.3	46.3	19.5	-
4X'AC	SpOx-4						>100	>100		>100
SpOx 1	1293-K01						>100	>100		
SpOx 2	1281-G13						>100	>100		
SpOx 3	1297-P11						103	99		
VX-680			101.8	-	25.2	23.2	21.7	-	9.3	8.9

HCT-116 Cell Activity (% living)

Compound	a.k.a	ED_{50}	500 nM	1 uM	3 uM	5 uM	10 uM	30 uM	50 uM	100 uM
3XADF						81.9	66.5	53.2	33.2	
3XACF									95	
3XBCG	SpOx-5	50 uM				95	86		47	

3X'ADF						102.1	96.8		48.9	
3X'ACF									80.6	
4XADF		6.0 uM	110.8	112.2	97.4	71.2	30.3	9.6	-	8.9
4XADG		13.3 uM	101.9	116.7	120.7	99.1	80.1	30.0		13.9
4XADH		33.4 uM	107.0	124.0	132.0	128.2	109.1	58.8	32.2	6.4
4XACF									99.6	
4XACH							100.4		99.1	
4XBD									97.3	
4XBDF							97.3		102.7	
4XBDG							98.6		105.6	
4XBDH							105.7		104.4	
4X'ADF						109.7	100.5		50.7	
4X'AC	SpOx-4					100	103		99	
TL 199		10.1 uM	-	70.6	78.9	78.8	44.6	3.1	-	-
SpOx-1	1293-K01					>100	>100			
SpOx-2	1281-G13					>100	>100			
SpOx-3	1297-P11					89	102			
VX-680		9.7 uM	79.4	86.9	68.8	56.1	-	20.0	22.6	-
4XADK		70.5 uM	108.5	116.3	125.1	119.9	122.08	111.2	-	30.7

Cellular viability of MCF7 cells (% living)

Compound	ED_{50}	500 nM	1 uM	3 uM	5 uM	10 uM	30 uM	50 uM	100 uM
3XADF						56.5		55.1	
3XACF								72.8	
3X'ADF						84.3		76.1	
3X'ACF								81.3	
4XADF	15.9 uM	115.4	121.4	126.9	121.3	91.4	56.3	-	35.7
4XADG	33.3 uM	-	-	161.9	160.4	149.4	111.7	-	56.0
4XADH	55.1 uM	-	127.2	136.1	157.6	165.0	139.6	-	64.0
4XACF								85.7	
4XBD								70.2	

4X'ADF						82.2		81.0	
VX-680	13.8 uM	117.6	122.6	103.8	96.6	67.5	21.6	1.9	-2.1

Cellular activity of MCF10A cells (% living)

Compound	ED_{50}	500 nM	1 uM	3 uM	5 uM	10 uM	30 uM	50 uM	100 uM
4XADF	19.7 uM	-	117.8	116.5	118.7	96.7	34.6	-	9.5
VX-680	5.2 uM	87.9	88.2	70.4	58.1	37.8	22.7	11.2	1.2

Tagging Experiments

[00126] SpOx-5 was reacted with fluorescein-5-carbonyl azide diacetate at high temperatures and then with hydroxylamine as shown in *Figure 4* to give the tagged derivative. The fluorescent derivative was tested for Aurora A activity along with the parent compound as described above. As seen in *Figure 5*, the activities are similar.

Imaging Experiments

[00127] U2OS (osteosarcoma), HeLa (cervix cancer), and MCF7 (breast cancer) cells were used for immunofluorescence analyses. Cells were grown on glass coverslips, pre-extracted at room temperature with CSK buffer (100 mM NaCl, 300 mM sucrose, 10 mM PIPES-pH6.8, and 3 mM $MgCl_2$) with 0.1% Tritin-X100 and rinsed with CSK buffer. Cells were then fixed and permeabilized in cold methanol for 10 min at -20 C, followed by rehydrated with PBS for 5 min. Normal goat serum (Jackson ImmunoResearch) was used for blocking samples at the concentrations of 10% in SNBP buffer (BSA (5g/L), saponin (0.1 g/L), sodium azide (0.25 g/L) in PBS) for 1 h at room temperature. FITC-labeled SpOx-5 was incubated at the concentrations of 2.2 μM in the presence of polyclonal antibody against Aurora-A (Abcam, cat. #ab13408) at a dilution of 1:1000 for 30 min at 37 C, followed by additional 30 min at room temperature. Samples were washed with SNBP buffer and incubated with Alexa Fluor 647 goat anti-rabbit IgG antibody (Molecular Probes, cat. #A21244) at a dilution of 1:1000 for 1 h at room temperature. Nuclei were stained with Hoechst 33258 DNA dye. Confocal images were acquired by using a PCM2000 (Nikon) coupled to a Zeiss microscope using SIMPLE 32 software (Nikon). Green and far-red channels were used for the imaging.

[00128] The images in *Figure 6* are from an imaging experiment with HeLa cells. Similar images have been obtained with U2OS and MCF7 cells.

Example 2 – Synthesis of Spirooxindoles

[00129] **General Procedures.** All reactions were run under inert atmosphere. Starting materials and reagents were purchased from commercial suppliers and used without further purification with the exceptions CH_2Cl_2 and THF which were passed through two activated alumina columns to remove impurities. Brominated polystyrene macrobeads (500-600 μm) were purchased from Polymer Labs. Silyl-functionalized macrobeads were prepared and loading levels were determined according to a published procedure (*J. Comb. Chem.* **2001**, *3*, 312).

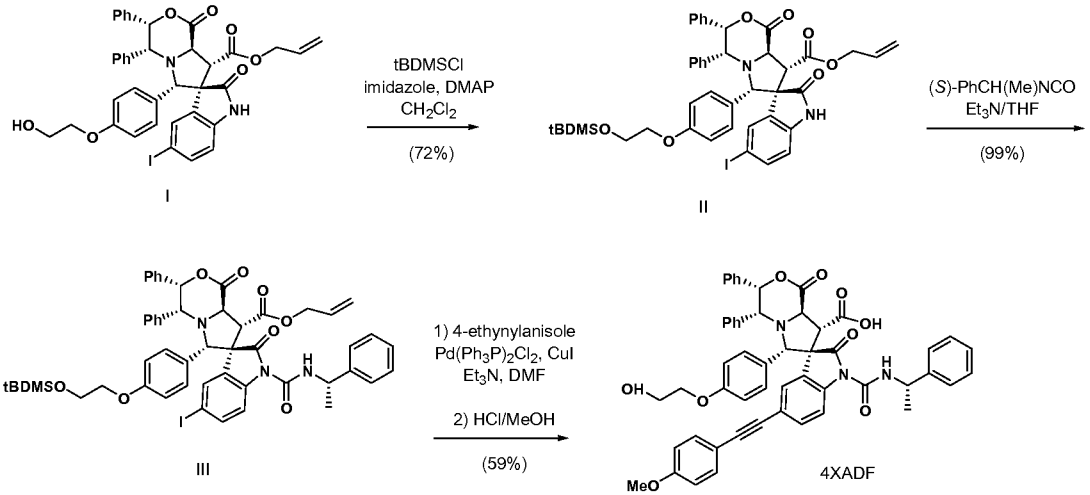
[00130] Purification of reaction products was carried out by flash chromatography using E. Merck silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on E. Merck 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous cerium ammonium molybdate (CAM) solution followed by heating. Analytical LC/MS chromatography was performed on Waters Alliance 2690 HPLC system with a Waters Symmetry C18 column (3.5 μm, 4.6 × 100 mm) with a gradient of 20-80% CH_3CN in water with constant 0.1% formic acid, with diode array UV detection and a Micromass LCZ (ESI) spectrometer. ^1H NMR spectra were recorded on a Varian 500 MHz spectrometer or a Bruker 300 MHz spectrometer and are reported in ppm and referenced to residual protons in the NMR solvent. Data are reported as shift, splitting (s = singlet, d = doublet, t = triplet, m = multiplet; br = broad), coupling constant in Hz; integration. ^{13}C NMR spectra were recorded at 125 MHz on a Varian spectrometer, ^{13}C shifts are reported in ppm and referenced to carbon resonances in the NMR solvent.

[00131] **Solid Phase Chemistry**. Small-scale solid phase reactions (5-10 mg resin) were performed in 1 mL fritted polyacrylamide Bio-Spin® chromatography columns (Bio-Rad Laboratories, Hercules, CA; 732-6008) or Wheaton glass vials, fitted with Teflon-coated caps with gentle mixing provided by Thermoline Vari-Mix shaker or a Vortex Genie-2 vortexer. Larger-scale solid phase reactions (> 500 mg resin) were performed in 10-50 mL Amersham columns or silanized 50 or 100 mL fritted glass tubes equipped for vacuum filtration and N_2 bubbling. Resin samples were washed as indicated and solvent was

removed under argon flow and/or in vacuum on a Vac-Man® laboratory vacuum manifold (Promega, Madison, WI; A7231) fitted with nylon 3-way stopcocks (Biorad 732-8107).

[00132] All compounds were cleaved from macrobeads using the following standard procedure: to resin in a polypropylene Eppendorf tube was added a freshly prepared solution of 85:10:5 THF/pyridine/HF·pyridine. The resulting mixture was then agitated at room temperature for 3 hours before quenching with 10:1 (v:v) TMSOEt/THF. The resulting mixture was agitated at room temperature for 30 min, then transferred to an Eppendorf vial and evaporated on a Speedvac. Resin was washed twice with THF, and the wash solutions were combined, concentrated, and analyzed by LC/MS. Compounds were then purified by silica gel column chromatography and were determined to be >95% pure by LC with UV detection.

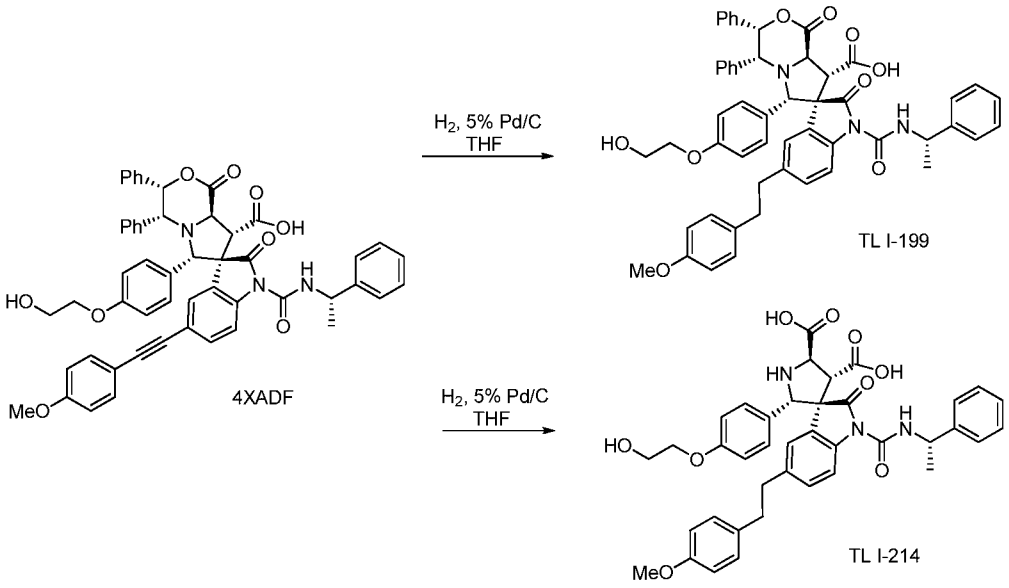
[00133] **Solution Phase Chemistry.**



[00134] **Compound II**. To a solution of 530 mg (0.70 mmol) of compound **I** (*J. Am. Chem. Soc. 126*:16077, **2004**) in 5 mL of CH_2Cl_2 was added 102 mg of imidazole (1.5 mmol), 157 mg of tBDMSCl (0.105 mmol), and a pinch of 4-dimethylaminopyridine, and the solution becomes cloudy with stirring overnight. The next day more CH_2Cl_2 is added and the CH_2Cl_2 is rinsed with $NaHCO_3$ (aq) and brine before drying, concentrating, and chromatography with 1:1 EtOAc:hexane to give 501 mg of product (82%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (s, 1H), 7.50 (d, J = 1.46 Hz, 1H), 7.37 (dd, J = 1.68, 8.19 Hz, 1H), 7.01-7.15 (m, 11H), 6.65 (d, J = 8.69 Hz, 2H), 6.34 (d, J = 8.18 Hz, 1H), 6.15 (d, J = 3.02 Hz, 1H), 5.16-5.23 (m, 1H), 4.90-4.98 (m, 3H), 4.27 (s, 1H), 4.10-4.27 (m, 3H), 4.06 (d, J = 7.68 Hz, 1H), 3.82-3.90 (m, 4H), 0.82 (s, 9H), 0.02 (s, 6H).

[00135] **Compound III**. To a solution of 501 mg of compound **II** in 10 mL of THF was added 0.16 mL of Et_3N (1.2 mmol) and 0.17 mL of (*S*)-α-methylbenzylisocyanate (0.25 mmol) and the solution was stirred overnight. The reaction was concentrated and chromatographed with 10% then 25% EtOAc in hexane to yield 513 mg of product (88%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.91 (d, J = 7.36 Hz, 1H), 7.75 (d, *J* = 8.65 Hz, 1H), 7.62 (d, *J* = 1.53 Hz, 1H), 7.50 (dd, *J* = 1.64, 8.67 Hz, 1H), 7.36-7.42 (m, 5H), 7.29-7.32 (m, 1H), 7.15-7.22 (m, 6H), 7.11-7.19 (m, 3H), 6.99 (d, *J* = 8.63 Hz, 2H), 6.63 (d, *J* = 8.64 Hz, 2H), 6.20 (d, *J* = 2.84 Hz, 1H), 5.25-5.30 (m, 1H), 5.01-5.09 (m, 4H), 4.96 (s, 1H), 4.30 (d, *J* = 3.18 Hz, 1H), 4.17-4.26 (m, 3H), 3.89 (s br, 4H), 1.59 (d, *J* = 6.90 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C δ ($CDCl_3$, 125 MHz) 176.95, 170.49, 166.93, 159.37, 149.92, 142.94, 139.93, 137.96, 135.42, 134.90, 133.92, 130.12, 128.62, 128.61, 128.43, 128.18, 127.83, 127.68, 127.29, 126.42, 125.66, 125.12, 123.74, 119.55, 117.85, 114.49, 87.21, 75.84, 74.60, 68.88, 66.21, 61.66, 61.53, 57.92, 56.20, 54.33, 49.89, 28.87, 25.75, 22.57, 18.20, -5.37.

[00136] **4XADF**. To a solution of 204 mg of compound III (0.20 mmol) in 5 mL of DMF was added several drops of Et_3N, 0.52 mL of 4-ethynylanisole (0.40 mmol), and 76 mg of CuI (0.40 mmol) and the mixture was purged with nitrogen gas. Then 140 mg of $Pd(PPh_3)_2Cl_2$ was added and the mixture was stirred overnight. The next day another 2.0 mL of 4-ethynylanisole, 300 mg of CuI, and 700 mg of $Pd(PPh_3)_2Cl_2$ was added and the mixture was stirred overnight before heating to 80 °C for 30 minutes. The mixture was concentrated and chromatographed with CH_2Cl_2 and 10% MeOH in CH_2Cl_2 which eluted impure silylated product which was added to a basic resin (Isolute, 1 g PEAX column, International Sorbent Technology). The resin was flushed with MeOH and then with HCl(aq)/MeOH which removes the silyl protecting group to give 103 mg of 4XADF (59%) as a white solid; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.94 (d, *J* = 7.16 Hz, 1H), 7.90 (d, *J* = 8.46 Hz, 1H), 7.47 (d, *J* = 8.45 Hz, 2H), 7.33-7.43 (m, 8H), 7.22-7.26 (m, 5H), 7.12-7.16 (m, 4H), 6.99 (d, *J* = 8.50 Hz, 2H), 6.90 (d, *J* = 8.44 Hz, 2H), 6.61 (d, *J* = 8.41 Hz, 2H), 6.24 (s, 1H), 5.13 (d, *J* = 8.37 Hz, 1H), 5.06 (t, *J* = 7.14 Hz, 1H), 4.98 (s, 1H), 4.25 (s, 1H), 4.20 (d, *J* = 8.23 Hz, 1H), 3.92 (d, *J* = 3.63 Hz, 2H), 3.88 (d, *J* = 2H, 3.92 Hz, 2H),3.86 (s, 3H), 1.60 (d, *J* = 6.85 Hz, 3H); ^{13}C δ ($CDCl_3$, 125 MHz) 177.54, 171.19, 159.53, 159.01, 150.54, 143.13, 139.51, 135.36, 134.98, 132.93, 132.85, 128.82, 128.76, 128.67, 128.64, 128.63, 128.46, 128.27, 127.89, 127.82, 127.34, 125.75, 125.28, 124.57, 124.15, 119.51, 115.93, 115.11, 114.53, 113.98, 89.50, 87.73, 76.62, 75.43, 69.13, 61.73, 61.54, 59.09, 57.00, 55.58, 54.73, 50.42, 23.09.

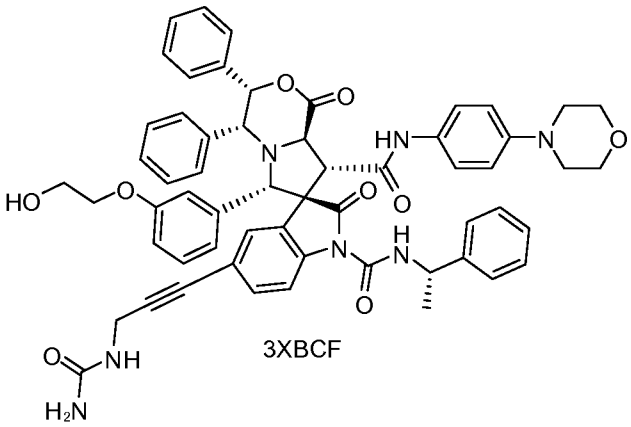


[00137] **TL I-199**. A mixture of 3 mg of 5% Pd on carbon in 1 mL was purged with hydrogen gas before addition of 2.1 mg of 4XADF in 1 mL of THF. After 2.5 hours, the mixture was filtered and concentrated to give 2.0 mg of alkane as a white solid after lyophilization from benzene. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.95 (d, J = 8.29 Hz, 1H), 7.83 (d, J = 8.27 Hz, 2H), 7.33-7.44 (m, 4H), 7.22-7.31 (m, 1H), 7.13 (d, J = 7.53 Hz, 1H), 7.08 (s, 1H), 7.03 (d, J = 8.21 Hz, 2H), 6.97 (d, J = 8.29 Hz, 1H), 6.91 (d, J = 8.13 Hz, 2H), 6.82 (d, J = 8.21 Hz, 2H), 6.49 (d, J = 7.93 Hz, 2H), 6.23 (d, J = 1.90 Hz, 1H), 5.06-5.09 (m, 1H), 4.99 (d, J = 8.34 Hz, 1H), 4.94 (s, 1H), 4.23 (d, J = 2.58 Hz, 1H), 4.20 (d, J = 8.35 Hz, 1H), 3.87-3.91 (m, 4H), 3.80 (s, 3H), 2.85-2.89 (m, 2H), 2.74-2.82 (m, 2H), 1.61 (d, J = 6.75 Hz, 3H).

[00138] **TL I-214**. A mixture of 41 mg of 5% Pd on carbon in 5 mL of THF was purged with hydrogen gas before addition of 27 mg of 4XADF in 5 mL of THF (*J. Org. Chem.* *57*, 6527:**1992**; *J. Org. Chem.* *55*, 3723:**1990**). The reaction flask was then fitted with a balloon containing hydrogen gas and was stirred vigorously. After 8 hours, the mixture was filtered and concentrated. This procedure was then repeated twice, the reaction was monitored by LC until no more product formation was detected. Purification by reverse phase HPLC yielded 3.5 mg of product as a white solid. HPLC conditions: Waters semi-preparative LCMS autopurification system with MS based fractions collection. MassLynx software was used to control the system and for data acquisition and processing, column: XTerra, prep MS, C18, OBD, 10 μm, 19x50mm, flow rate: 40 mL/min, mobile phase: 0.1% FA in water/acetonitrile gradient, method: 25-65% over 5 min. ^{1}H NMR (DMSO-d_6, 500

MHz) δ 8.60 (d, *J* = 7.50 Hz, 1H), 7.62 (d, *J* = 8.21 Hz, 1H), 7.49 (s, 1H), 7.25-7.40 (m, 7H), 7.13 (d, *J* = 8.43 Hz, 2H), 6.82 (d, *J* = 8.49 Hz, 2H), 6.74 (d, *J* = 8.29 Hz, 2H), 6.60 (d, *J* = 8.59 Hz, 2H), 4.85-5.02 (m, 1H), 4.81 (s, 1H), 4.60 (d, *J* = 7.49 Hz, 1H), 4.30 (m, 1H), 3.60-3.78 (m, 2H), 3.48-3.55 (m, 2H), 3.69 (s, 3H), 2.59-2.80 (m, 4H), 1.34 (d, J = 6.86 Hz, 3H).

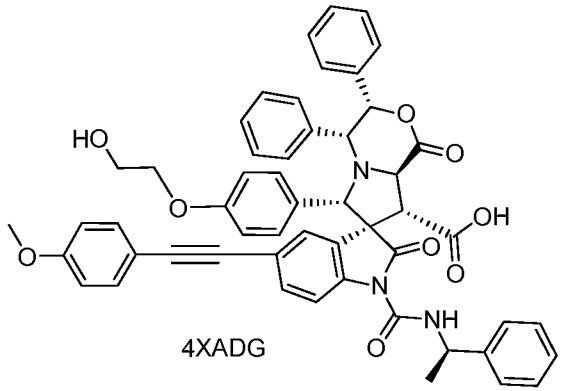
[00139] **Compounds synthesized via solid phase synthesis.**



3XBCF

[00140]

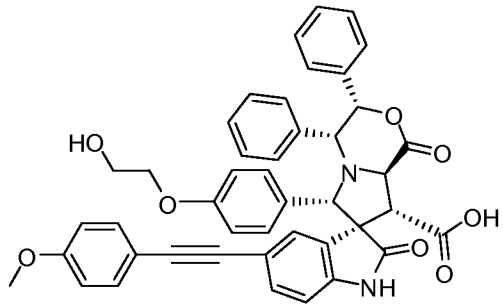
[00141] **3XBCF**. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.90 (d, *J* = 7.38 Hz, 1H), 7.83 (d, *J* = 8.52 Hz, 1H), 7.31-7.34 (m, 4H), 7.16-7.26 (m, 11H), 7.07 (dd, *J*=1.53, 8.51 Hz, 1H), 7.01-7.06 (m, 2H), 6.83-6.88 (m, 4 H), 6.71 (d, *J* = 9.02 Hz, 1H), 6.48-6.52 (m, 3H), 6.25 (d, *J* = 2.75 Hz, 1H), 5.59 (s br, 1H), 5.20 (d, *J* = 10.81 Hz, 1H), 5.02 (dq, *J* = 7.33, 7.08 Hz, 1H), 4.97 (s, 1H), 4.62 (s br, 2H), 4.32 (d, *J* = 10.86 Hz, 1H), 4.09 (d, *J* = 2.81 Hz, 1H), 3.99 (d, *J* = 5.04 Hz, 2H), 3.74 (t, *J* = 4.73 Hz , 4H), 3.42-3.60 (m, 4H), 2.98 (t, *J* = 4.72 Hz , 4H), 1.51 (d, *J* = 6.93 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.78, 173.06, 163.99, 158.53, 150.36, 148.46, 143.40, 140.59, 134.91, 134.83, 134.47, 132.70, 129.76, 129.48, 129.46, 128.71, 128.50, 128.42, 128.27, 128.13, 127.30, 127.12, 125.68, 125.54, 121.59, 119.29, 118.10, 116.13, 115.96, 86.05, 82.30, 77.73, 73.86, 68.99, 66.71, 61.13, 61.04, 60.62, 57.48, 57.17, 49.97, 49.47, 30.56, 22.84.



4XADG

[00142]

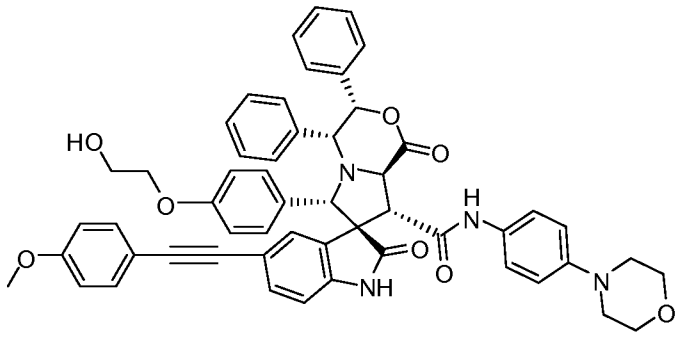
[00143] **4XADG**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.96 (d, J = 7.10 Hz, 1H), 7.85 (d, J = 8.23, 1H), 7.45-7.48 (m, 3H), 7.37-38 (m, 4H), 7.20-7.28 (m, 8H), 7.12-7.17 (m, 4H), 7.07 (d, J = 8.68 Hz, 2H), 6.90 (d, J = 8.74, 2H), 6.71 (d, J = 8.59Hz, 2H), 6.25 (d, J = 2.70, 1H), 5.02-5.09 (m, 2H), 5.00 (s, 1H), 4.24 (d, J = 3.07, 1H), 4.15-4.19 (m, 1H), 3.96 (d, J = 4.14 Hz, 2H), 3.90 (d, J = 4.35 Hz, 2H), 3.85 (s, 3H), 1.60 (d, J = 6.87 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.73, 171.29, 159.26, 159.25, 150.53, 142.86, 135.53, 135.18, 133.03, 132.89, 128.98, 128.98, 128.84, 128.55, 128.38, 128.03, 128.01, 127.97, 127.50, 125.92, 125.44, 125.00, 119.59, 115.99, 115.32, 114.76, 114.08, 100.01, 89.54, 87.88, 77.21, 76.33, 69.02, 61.32, 58.82, 58.80, 55.33, 54.77, 50.28, 22.90.



4XAD

[00144]

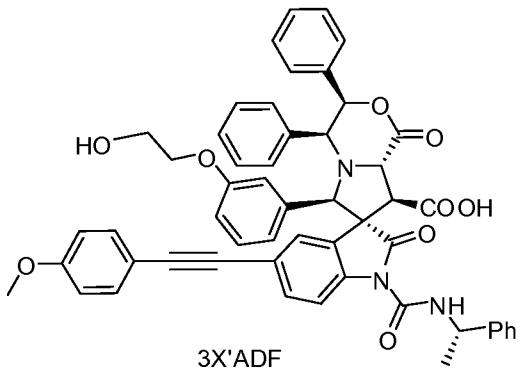
[00145] **4XAD**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s br, 1H), 7.40-7.46 (m, 4H), 7.05-7.24 (m, 9H), 6.88 (d, J = 8.80 Hz, 2H), 6.65 (d, J = 8.40 Hz, 2H), 6.53 (d, J = 8.01 Hz, 1H), 6.26 (s br, 1H), 5.17 (d, J = 8.71 Hz, 1H), 5.02 (s, 1H), 4.16 (d, J = 2.72 Hz, 1H), 4.11 (d, J = 8.56 Hz, 1H), 3.90 (d, J = 4.14 Hz, 2H), 3.81-3.85 (m, 2H), 3.84 (s, 3H).



4XAC

[00146]

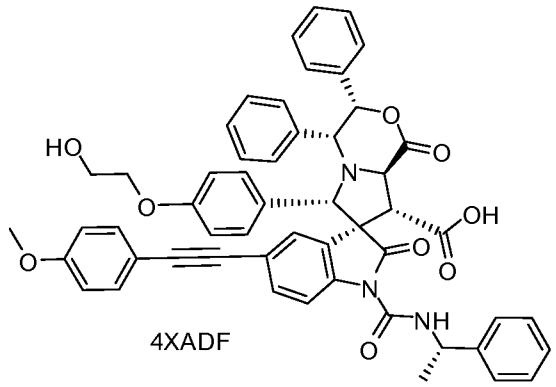
[00147] **4XAC**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.62 (s br, 1H), 7.45 (d, *J* = 8.80 Hz, 2H), 7.25-7.32 (m, 2H), 7.21-7.23 (m, 8H), 7.07-7.13 (m, 4H), 7.02-7.06 (m, 2H), 6.89 (d, *J* = 8.84 Hz, 2H), 6.78 (d, *J* = 9.00 Hz, 2H), 6.69 (d, *J* = 8.41 Hz, 2H), 6.61 (d, *J* = 8.01 Hz, 1H), 6.41 (d, *J* = 2.42 Hz, 1H), 5.19 (d, *J* = 10.43 Hz, 1H), 5.02 (s, 1H), 4.30 (d, *J* = 10.44, 1H), 4.23 (d, *J* = 2.83, 1H), 3.85-3.93 (m, 4H), 3.82 (s, 3H), 3.79-3.84 (m, 4H), 3.04 (t, *J* = 4.75, 4H).



3X'ADF

[00148]

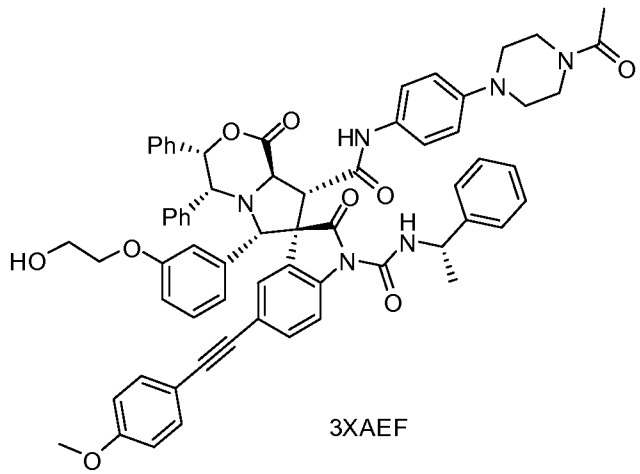
[00149] **3X'ADF**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (d, *J* = 7.17 Hz, 1H), 7.78 (d, *J* = 8.52 Hz, 1H), 7.27-7.36 (m, 8H), 7.18-7.25 (m, 8H), 7.04-7.10 (m, 4H), 6.80 (d, *J* = 8.58 Hz, 2H), 6.72-6.68 (m, 3H), 6.18 (d, *J* = 2.48, 1H), 5.07 (d, *J* = 8.39 Hz, 1H), 4.95-5.01 (m, 1H), 4.97 (s, 1H), 4.27 (t, *J* = 6.70 Hz, 1H), 4.16 (d, *J* = 3.15 Hz, 1H), 4.10 (d, *J* = 8.31 Hz, 1H), 3.82 (s, 3H), 3.71-3.80 (m, 4H), 1.50 (d, *J* = 6.85 Hz, 3H).



4XADF

[00150]

[00151] **4XADF**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.94 (d, J = 7.16 Hz, 1H), 7.90 (d, J = 8.46 Hz, 1H), 7.47 (d, J = 8.45 Hz, 2H), 7.33-7.43 (m, 8H), 7.22-7.26 (m, 5H), 7.12-7.16 (m, 4H), 6.99 (d, J = 8.50 Hz, 2H), 6.90 (d, J = 8.44 Hz, 2H), 6.61 (d, J = 8.41 Hz, 2H), 6.24 (s, 1H), 5.13 (d, J = 8.37 Hz, 1H), 5.06 (t, J = 7.14 Hz, 1H), 4.98 (s, 1H), 4.25 (s, 1H), 4.20 (d, J = 8.23 Hz, 1H), 3.92 (d, J = 3.63 Hz, 2H), 3.88 (d, J = 2H, 3.92 Hz, 2H),3.86 (s, 3H), 1.60 (d, J = 6.85 Hz, 3H); ^{13}C δ ($CDCl_3$, 125 MHz) δ 177.54, 171.19, 159.53, 159.01, 150.54, 143.13, 139.51, 135.36, 134.98, 132.93, 132.85, 128.82, 128.76, 128.67, 128.64, 128.63, 128.46, 128.27, 127.89, 127.82, 127.34, 125.75, 125.28, 124.57, 124.15, 119.51, 115.93, 115.11, 114.53, 113.98, 89.50, 87.73, 76.62, 75.43, 69.13, 61.73, 61.54, 59.09, 57.00, 55.58, 54.73, 50.42, 23.09

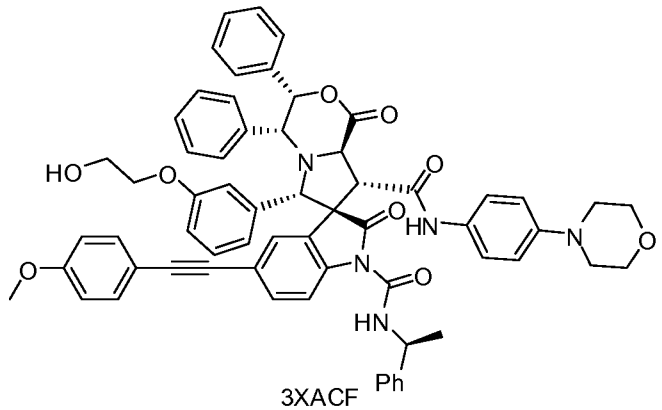


3XAEF

[00152]

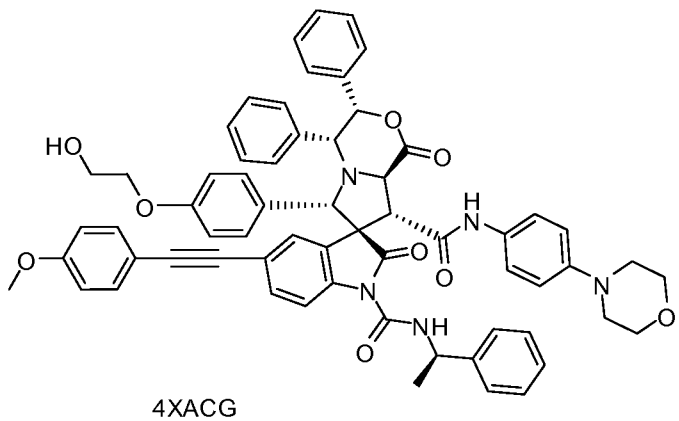
[00153] **3XAEF**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.85 (s, 1H), 8.98 (d, J = 7.45 Hz, 1H), 7.99 (d, J = 8.53 Hz, 1H), 7.39-7.49 (m, 8H), 7.32-7.34 (m, 12H), 7.13-7.15 (m, 3H), 7.04 (d, J = 7.09 Hz, 2H), 6.91-6.97 (m, 2H), 6.88 (d, J = 8.71 Hz, 2H), 6.82 (d, J = 8.94 Hz, 2H), 6.68 (d, J = 7.97 Hz, 2H), 6.61 (s, 1H), 5.20 (d, J = 10.68 Hz, 1H), 5.13 (t, J = 7.15 Hz,

1H), 5.03 (s, 1H), 3.84-3.86 (m, 1H), 3.83 (s, 3H), 3.74-3.76 (m, 2H), 3.58-3.66 (m, 4H), 3.09 (t, J = 5.08, 2H), 3.07 (d, J = 5.13 Hz, 2H), 2.13 (s, 3H), 1.61 (d, J = 6.95 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.03, 173.74, 169.23, 164.31, 158.84, 143.73, 133.12, 129.04, 128.84, 128.79, 128.74, 126.06, 125.91, 121.78, 117.40, 114.40, 114.36, 114.35, 114.329, 109.989, 87.608, 82.289, 77.846, 74.161, 69.391, 61.378, 61.322, 55.566, 50.29, 50.28, 50.25, 49.94, 46.40, 41.52, 23.25, 21.57.



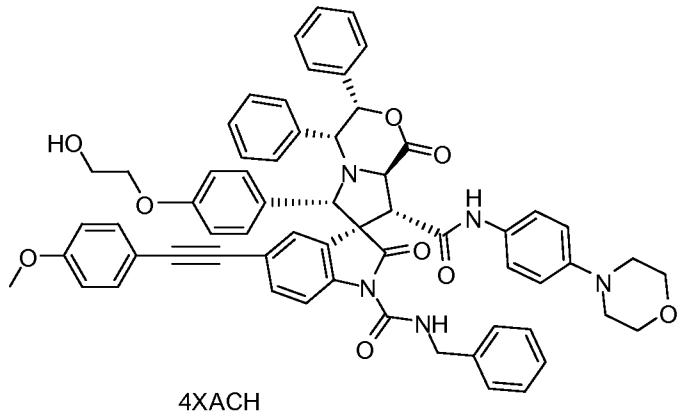
[00154] 3XACF

[00155] **4XACF**. ($CDCl_3$, 500 MHz) δ 9.82 (s, 1H), 9.00 (d, J = 7.37 Hz, 1H), 8.00 (d, J = 8.53 Hz, 1H), 7.41-7.49 (m, 11H), 7.28-7.36 (m, 8H), 7.12-7.13 (m, 2H), 7.05 (d, J = 7.39 Hz, 2H), 6.99 (d, J = 8.45 Hz, 2H), 6.88 (d, J = 8.51 Hz, 2H), 6.80 (d, J = 8.83 Hz, 2H), 6.57 (d, J = 8.42 Hz, 2H), 6.38 (d, J = 1.84 Hz, 1H), 5.15 (d, J = 10.48 Hz, 1H), 5.10 (t, J = 7.02 Hz, 1H), 4.99 (s, 1H), 4.36 (d, J = 10.51 Hz, 1H), 4.24 (d, J = 2.40 Hz, 1H), 3.80-3.90 (m 11H), 3.07 (t, J = 4.58 Hz, 4H), 1.60 (d, J = 6.95 Hz, 3H).



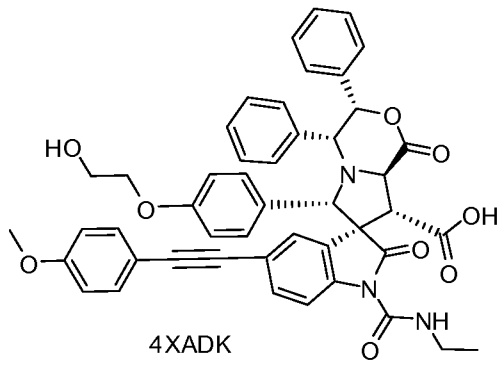
[00156] 4XACG

[00157] **4XACG**. ($CDCl_3$, 500MHz) δ 9.71 (s, 1H), 8.93 (d, *J* = 7.11 Hz, 1H), 8.00 (d, *J* = 8.56 Hz, 1H), 7.43 (d, *J* = 8.71 Hz, 2H) 7.33-7.38 (m, 7H), 7.22-7.29 (m, 8H), 7.10-7.11 (m, 2H), 7.02-7.05 (m, 4H), 6.86 (d, *J* = 8.75 Hz, 2H), 6.75 (d, *J* = 8.98 Hz, 2H), 6.68 (d, *J* = 8.00 Hz, 2H), 6.35 (d, *J* = 2.38 Hz, 1H), 5.10 (d, *J* = 10.47 Hz, 1H), 5.06 (t, *J* = 6.96 Hz, 1H), 4.97 (s, 1H), 4.29 (d, *J* = 10.41 Hz, 1H), 4.23 (d, *J* = 2.74 Hz, 1H), 3.96 (t, *J* = 4.30 Hz, 2H), 3.89 (t, *J* = 4.29 Hz, 2H), 3.81 (s, 3H), 3.79-3.83 (m, 4H), 3.03 (t, *J* = 4.75 Hz, 4H), 1.60 (d, *J* = 6.85 Hz, 3H).



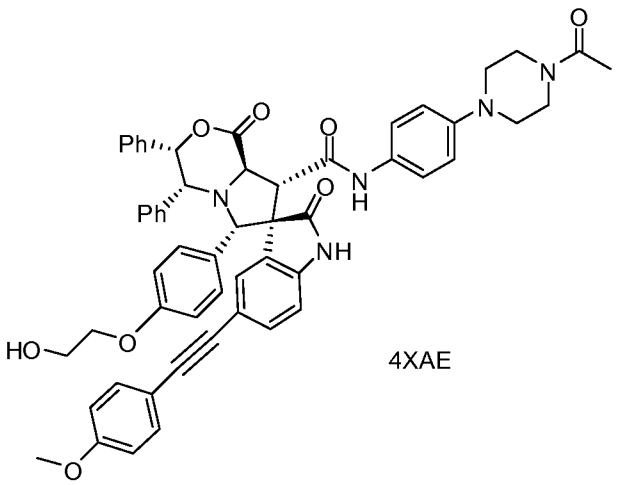
[00158] 4XACH

[00159] **4XACH**. (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.91 (t, J = 5.63 Hz, 1H), 8.04 (d, *J* = 8.50 Hz, 1H), 7.39-7.44 (m, 4H), 7.34-7.37 (m, 5H), 7.24-7.29 (m, 8H), 7.07-7.11 (m, 2H), 6.99-7.04 (m, 4H), 6.86 (d, *J* = 8.78 Hz, 2H), 6.75 (d, *J* = 9.00 Hz, 2H), 6.63 (d, *J* = 8.43 Hz, 2H), 6.32 (d, *J* = 2.49 Hz, 1H), 5.11 (d, *J* = 10.53 Hz, 1H), 4.95 (s, 1H), 4.64 (dd, *J* = 6.01, 15.12 Hz, 1H,), 4.47 (dd, *J* = 5.26, 15.15 Hz, 1H), 4.29 (d, *J* = 10.55 Hz, 1H), 4.20 (d, *J* = 2.8 Hz, 1H), 3.92 (t, *J* = 3.92 Hz, 2H), 3.87 (t, *J* = 3.84 Hz, 2H), 3.80 (s, 3H), 3.79-3.82 (m, 4H), 3.02-3.04 (m, 4H).



[00160] 4XADK

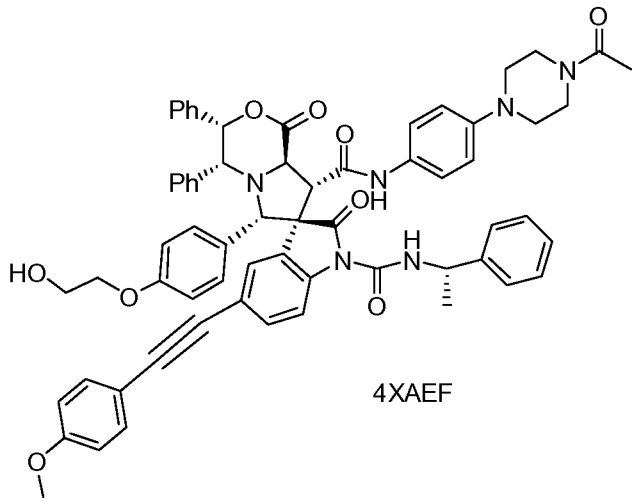
[00161] **4XACK**. (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.49 (t, *J* = 5.34 Hz, 1H), 8.03 (d, *J* = 8.52 Hz, 1H), 7.34-7.45 (m, 6H), 7.23-7.28 (m, 6H), 7.09-7.11 (m, 2H), 7.00-7.03 (m, 4H), 6.86 (d, *J* = 8.68 Hz, 2H), 6.75 (d, *J* = 8.98 Hz, 2H), 6.64-6.68 (m, 2H), 6.36 (d, *J* = 2.43 Hz, 1H), 5.12 (d, *J* = 10.50 Hz, 1H), 4.95 (s, 1H), 4.29 (d, *J* = 10.51 Hz, 1H), 4.22 (d, *J* = 2.95 Hz, 1H), 3.93-3.95 (m, 2H), 3.85-3.87 (m, 2H), 3.81 (s, 3H), 3.78-3.83 (m, 4H), 3.38-3.41 (m, 2H), 3.02-3.08 (m, 4H), 1.25 (t, *J* = 7.21, 3H).



4XAE

[00162]

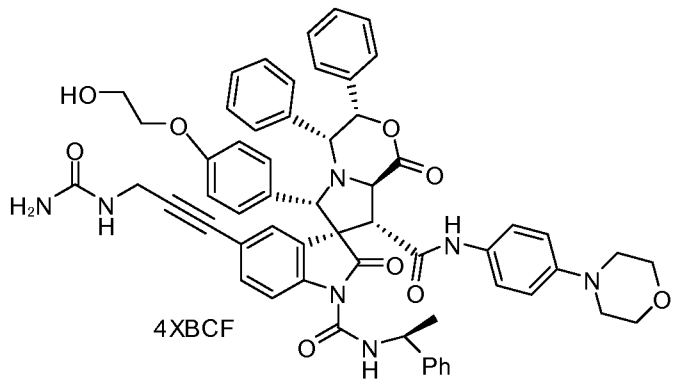
[00163] **4XAE**. (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.41 (s br, 1H), 7.41-7.47 (m, 3H), 7.20-7.25 (m, 5H), 7.11-7.14 (m, 4H), 7.02 (d, *J* = 7.07 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 6.75 (d, *J* = 8.72 Hz, 2H), 6.65 (d, *J* = 8.05, 2H), 6.54 (d, *J* = 7.94 Hz, 1H), 6.44 (s br, 1H), 5.20 (d, *J* = 10.42 Hz, 1H), 5.07 (s, 1H), 4.31 (d, *J* = 10.28 Hz, 1H), 4.22 (d, *J* = 1.72 Hz, 1H), 3.85-3.91 (m, 4H), 3.84 (s, 3H), 3.79 (s br, 2H), 3.56 (s br, 2H), 3.00-3.05 (m, 4H), 2.11 (s, 3H).



4XAEF

[00164]

[00165] **4XAEF**. (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.95 (d, *J* = 7.40 Hz, 1H), 7.96 (d, *J* = 7.55 Hz, 1H), 7.36-7.46 (m, 9H), 7.26-7.35 (m, 4H), 7.09-7.11 (m, 2H), 7.02 (d, *J* = 7.47 Hz, 2H), 6.96 (d, *J* = 8.33 Hz, 2H), 6.85 (d, *J* = 8.60 Hz, 2H), 6.79 (d, *J* = 8.67 Hz, 2H), 6.55 (d, *J* = 8.22 Hz, 2H), 6.34 (d, *J* = 2.29 Hz, 1H), 5.11 (d, *J* = 10.39 Hz, 1H), 5.08 (t, *J* = 7.14 Hz, 1H), 4.95 (s, 1H), 4.22 (d, *J* = 2.36 Hz, 1H), 3.87-3.88 (m, 2H), 3.85-3.86 (m, 2H), 3.81 (s, 3H), 3.72 (t, *J* = 4.96 Hz, 2H), 3.56 (t, *J* = 4.88 Hz, 2H), 3.06 (t, *J* = 4.98 Hz, 2H), 3.03 (t, *J* = 5.06 Hz, 2H), 2.10 (s, 3H), 1.57 (d, *J* = 6.87 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.03, 173.75, 169.23, 164.31, 158.85, 143.73, 133.13, 129.04, 128.84, 128.79, 128.74, 126.06, 125.91, 121.78, 117.40, 114.40, 114.36, 114.35, 114.33, 109.99, 87.61, 82.29, 77.85, 74.16, 69.39, 61.38, 61.32, 55.56, 50.29, 50.27, 50.25, 49.94, 46.40, 41.52, 23.25, 21.57.

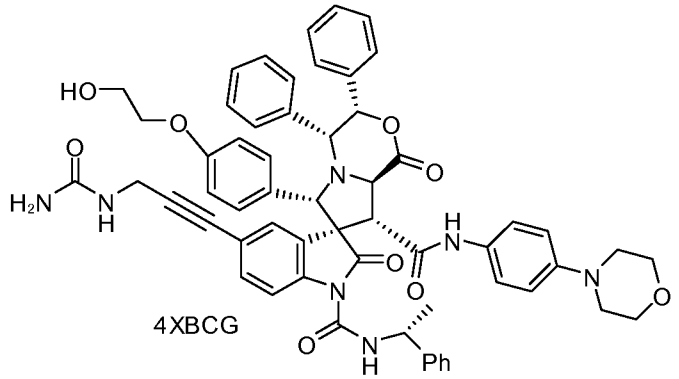


4XBCF

[00166]

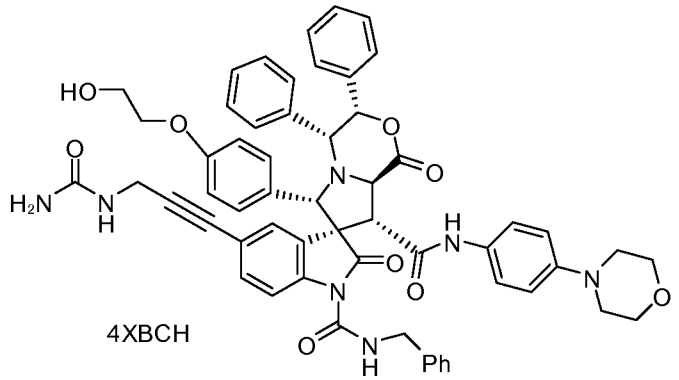
[00167] **4XBCF**. (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.94 (d, *J* = 7.26 Hz, 1H), 7.84 (d, *J* = 8.45 Hz, 1H), 7.35-7.41 (m, 7H), 7.32-7.36 (m, 3H), 7.21-7.25 (m, 1H), 7.05-7.12 (m, 4H), 6.97 (d, *J* = 6.40 Hz, 2H), 6.90 (d, *J* = 8.40 Hz, 2H), 6.74 (d, *J* = 8.49 Hz, 2H), 6.46 (d, *J*

= 8.19 Hz, 2H), 6.33 (s br, 1H), 5.34 (s br, 1H), 5.22 (d, *J* = 10.46 Hz, 1H), 5.05 (dt, *J* = 6.89, 6.95 Hz, 1H), 4.95 (s, 1H), 4.60 (s br, 1H), 4.32 (d, *J* = 11.27 Hz, 1H), 4.16 (d, *J* = 2.27 Hz, 1H), 4.00 (s br, 2H), 3.70-3.79 (m, 10H), 3.02 (t, *J* = 4.35 Hz, 4H), 1.56 (d, *J* = 6.84 Hz, 3H).^{13}C (125 MHz, $CDCl_3$) δ 178.20, 173.64, 173.62, 159.31, 150.71, 150.70, 149.16, 148.76, 143.82, 134.99, 133.09, 130.08, 129.05, 129.03, 128.87, 128.85, 128.78, 128.73, 127.64, 126.04, 126.02, 125.84, 121.94, 116.31, 116.29, 116.27, 114.80, 114.74, 101.98, 92.37, 74.30, 69.27, 68.76, 67.04, 61.50, 61.34, 61.32, 60.67, 57.20, 50.35, 49.80, 31.18, 29.96.



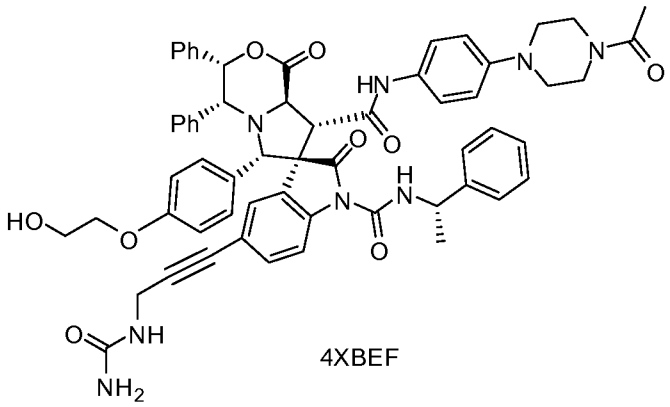
[00168]

[00169] **4XBCG**. (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.91 (d, *J* = 7.09 Hz, 1H), 7.91 (d, *J* = 8.50 Hz, 1H), 7.30-7.42 (m, 5H), 7.21-7.25 (m, 4H), 7.12-7.17 (m, 4H), 7.04-7.07 (m, 3H), 6.97-6.99 (m, 4H), 6.72 (d, *J* = 8.81 Hz, 2H), 6.61 (d, *J* = 7.37 Hz, 2H), 6.33 (d, *J* = 2.05 Hz, 1H), 5.16 (d, *J* = 10.25 Hz, 1H), 5.03 (dt, *J* = 6.93, 6.95 Hz, 1H), 4.97 (s, 1H), 4.51 (s br, 1H), 4.27 (d, *J* = 10.41 Hz, 1H), 4.17 (d, *J* = 2.60 Hz, 1H), 4.04 (d, *J* = 5.04 Hz, 2H), 3.85-3.99 (m, 5H), 3.78 (t, *J* = 4.61 Hz, 4H), 3.01 (t, *J* = 4.64 Hz, 4H), 1.59 (d, *J* = 6.82 Hz, 3H).



[00170]

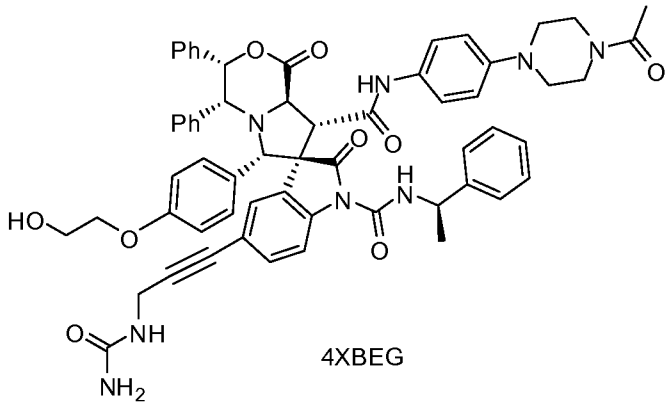
[00171] **4XBCH**. (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.91 (t, *J* = 5.56 Hz, 1H), 7.93 (d, *J* = 8.50 Hz, 1H), 7.32-7.39 (m, 7H), 7.22-7.25 (m, 3H), 7.14-7.18 (m, 4H), 7.04-7.05 (m, 3H), 6.94-6.97 (m, 4H), 6.72 (d, *J* = 8.95 Hz, 2H), 6.54 (d, *J* = 7.53 Hz, 2H), 6.31 (d, *J* = 1.86 Hz, 1H), 5.35 (s br, 1H), 5.21 (d, *J* = 10.47 Hz, 1H), 4.95 (s, 1H), 4.61 (dd, *J* = 5.9, 15.0 Hz, 1H), 4.54 (s, 1H), 4.47 (dd, *J* = 5.26, 15.02 Hz, 1H), 4.28 (d, *J* = 10.54Hz, 1H), 4.15 (d, *J* = 2.5 Hz, 1H), 4.00 (d, *J* = 5.3 Hz, 1H), 3.83-3.84 (m, 2H), 3.76-3.79 (m, 8H), 3.01 (t, *J* = 4.67 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.86, 173.26, 164.22, 159.09, 158.35, 151.42, 151.41, 140.59, 137.66, 134.78, 134.73, 132.91, 128.77, 128.59, 128.53, 128.46, 128.13, 127.55, 127.37, 125.70, 125.56, 125.07, 121.687, 118.41, 116.04, 115.98, 114.56, 85.93, 82.62, 73.97, 69.05, 66.76, 63.72, 61.22, 61.12, 60.42, 57.33, 57.18, 49.50, 43.91, 30.74.



4XBEF

[00172]

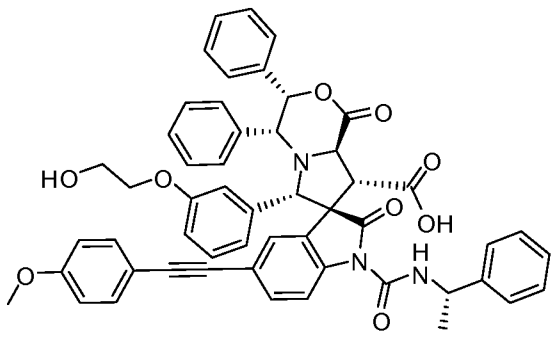
[00173] **4XBEF**. (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.94 (d, *J* = 7.18 Hz, 1H), 7.81 (d, *J* = 8.43 Hz, 1H), 7.34-7.40 (m, 4H), 7.30-7.32 (m, 2H), 7.21-7.25 (m, 4H), 7.04-7.09 (m, 3H), 6.95-6.96 (m, 2H), 6.89 (d, *J* = 4.40 Hz, 2H), 6.72 (d, *J* = 8.47 Hz, 2H), 6.44 (d, *J* = 7.93 Hz, 2H), 6.31 (s br, 1H), 5.42 (s br, 1H), 5.22 (d, *J* = 10.36 Hz, 1H), 5.03 (t, *J* = 6.90 Hz, 1H), 4.94 (s, 1H), 4.58 (s br, 2H), 4.31 (d, *J* = 10.53 Hz, 1H), 4.15 (s, 1H), 3.93-4.01 (m, 2H), 3.78 (s br, 4H), 3.66 (s br, 2H), 3.49 (s br, 2H), 2.97-3.01 (m, 4H), 2.05 (s, 3H), 1.55 (d, *J* = 7.20 Hz, 3H).



4XBEG

[00174]

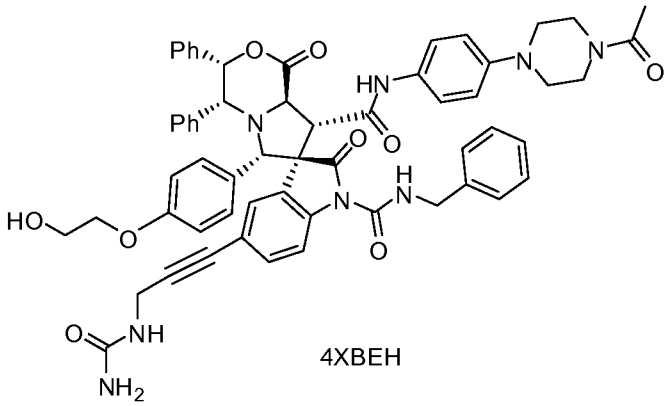
[00175] **4XBEG**. (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.90 (d, *J* = 7.03 Hz, 1H), 7.88 (d, *J* = 8.55 Hz, 1H), 7.29-7.41 (m, 5H), 7.22-7.25 (m, 3H), 7.11-7.13 (m, 3H), 7.05-7.07 (m, 2H), 6.98 (d, *J* = 7.71 Hz, 4H), 6.68 (d, *J* = 8.67 Hz, 2H), 6.60 (d, *J* = 7.73 Hz, 2H), 6.32 (s br, 1H), 5.46 (s br, 1H), 5.19 (d, *J* = 10.36 Hz, 1H), 5.04 (t, *J* = 6.84 Hz, 1H), 4.97 (s, 1H), 4.62 (s br, 2H), 4.26 (d, *J* = 10.32 Hz, 1H), 4.16 (d, *J* = 2.30 Hz, 1H), 3.99-4.01 (m, 2H), 3.78-3.88 (m, 4H), 3.65 (s br, 2H), 3.48 (s br, 2H), 2.95-2.98 (m, 4H), 2.05 (s, 3H), 1.59 (d, *J* = 6.86 Hz, 3H).



3XADF

[00176]

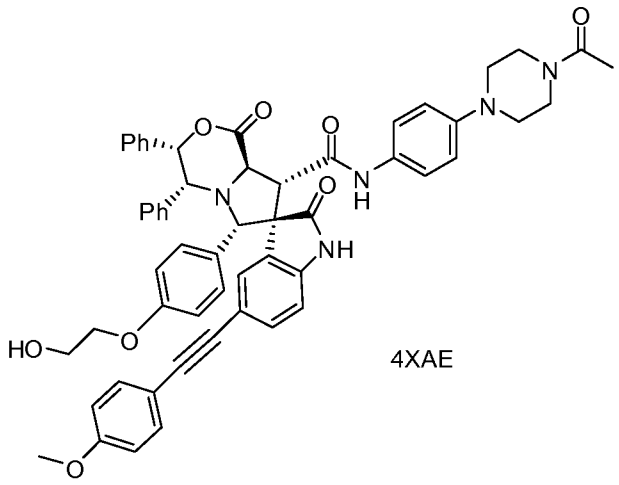
[00177] **3XADF**. ($CDCl_3$, 500 MHz) δ 9.01 (d, *J* = 7.15 Hz, 1H), 7.89 (d, *J* = 8.55 Hz, 1H), 7.26-7.37 (m, 8H), 7.22-7.26 (m, 3H), 7.12-7.24 (m, 8H), 7.00-7.04 (m, 4H), 6.90 (d, *J* = 7.97 Hz, 2H), 6.80 (d, *J* = 8.00 Hz, 2H), 6.51 (d, *J* = 7.63 Hz, 2H), 6.14 (s, 1H), 5.03 (d, *J* = 8.37 Hz, 1H), 4.96 (t, 7.14 Hz, 1H), 4.88 (s, 1H), 4.10-4.12 (m, 2H), 3.78-3.83 (m, 4H), 3.76 (s, 3H), 1.51 (d, *J* = 6.96).



4XBEH

[00178]

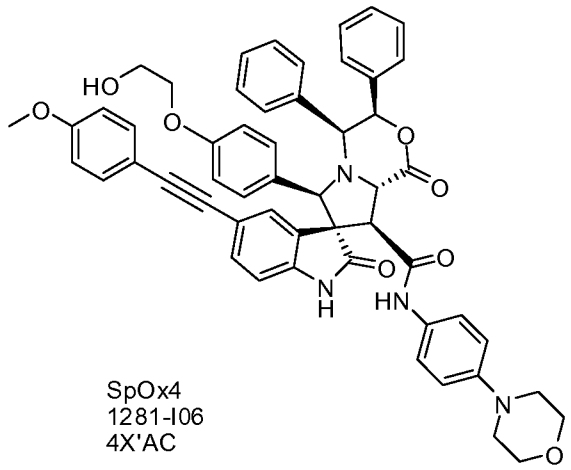
[00179] **4XBEH**. (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.86 (t, *J* = 9.93 Hz, 1H), 7.86 (d, *J* = 8.46 Hz, 1H), 7.09-7.30 (m, 14H), 6.94-7.02 (m, 4H), 6.87-6.91 (m 4H), 6.63 (d, *J* = 8.43 Hz, 2H), 6.49 (d, *J* = 7.11 Hz, 2H), 6.24 (s, 1H), 5.50 (s br, 1H), 5.15 (d, *J* = 10.14 Hz, 1H), 4.89 (s, 1H), 4.67 (s br, 2H), 4.55 (dd, *J* = 5.43, 14.91Hz, 1H), 4.41 (dd, *J* = 4.82, 14.82 Hz, 1H), 4.22 (d, *J* = 10.21 Hz, 1H), 4.09 (s, 1H), 3.95 (s, 2H), 3.72-3.80 (m, 4H), 3.59 (s br, 2H), 3.43 (s br, 2H), 2.89-2.93 (m, 4H), 2.00 (s, 3H).



4XAE

[00180]

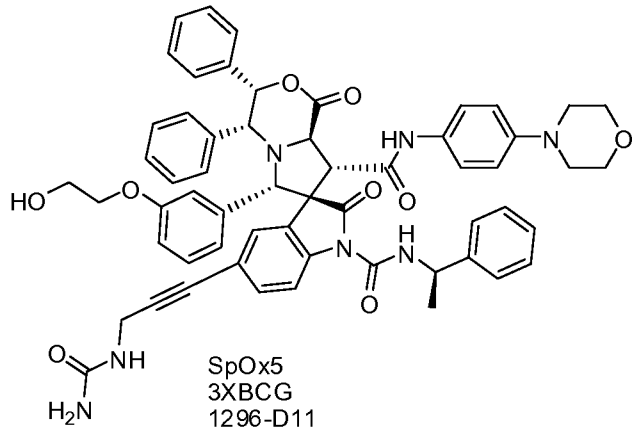
[00181] **4XAE**. (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.40 (s br, 1H), 7.41-7.47 (m, 4H), 7.21-7.25 (m, 6H), 7.10-7.15 (m, 6H), 7.01 (d, *J* = 7.07 Hz, 2H), 6.88 (d, *J* = 8.59 Hz, 2H), 7.75 (d, *J* = 8.72 Hz, 2H), 6.64 (d, *J* = 8.05 Hz, 2H), 6.54 (d, *J* = 7.94 Hz, 1H), 6.44 (s br, 1H), 5.20 (d, *J* = 10.42 Hz, 1H), 5.07 (s, 1H), 4.32 (d, *J* = 10.28 Hz, 1H), 3.88-3.92 (m, 2H), 3.85-3.88 (m, 2H), 3.83 (s, 3H), 3.70-3.74 (m, 2H), 3.48-3.53 (m, 2H), 3.00-3.05 (m, 4H), 2.10 (s, 3H).



SpOx4
1281-I06
4X'AC

[00182]

[00183] **4X'AC.** (SpOx-4). (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.62-7.64 (m, 1H), 7.38-7.45 (m, 4H), 7.23-7.29 (m, 6H), 7.07-7.12 (m, 5H), 7.01 (d, *J* = 6.92 Hz, 2H), 6.86 (d, *J* = 8.68 Hz, 2H), 6.75 (d, *J* = 8.94 Hz, 2H), 6.66 (d, *J* = 8.18 Hz, 2H), 6.58 (d, *J* = 8.05 Hz, 1H), 6.37 (d, *J* = 2.27 Hz, 1H), 5.16 (d, *J* = 10.48 Hz, 1H), 4.98 (s, 1H), 4.26 (d, *J* = 10.51 Hz, 1H), 4.20 (d, *J* = 2.60 Hz, 1H), 3.92-3.93 (m, 2H), 3.86-3.88 (m 2H), 3.82 (s, 3H), 3.79-3.84 (m, 4H), 3.03-3.05 (m, 4H).



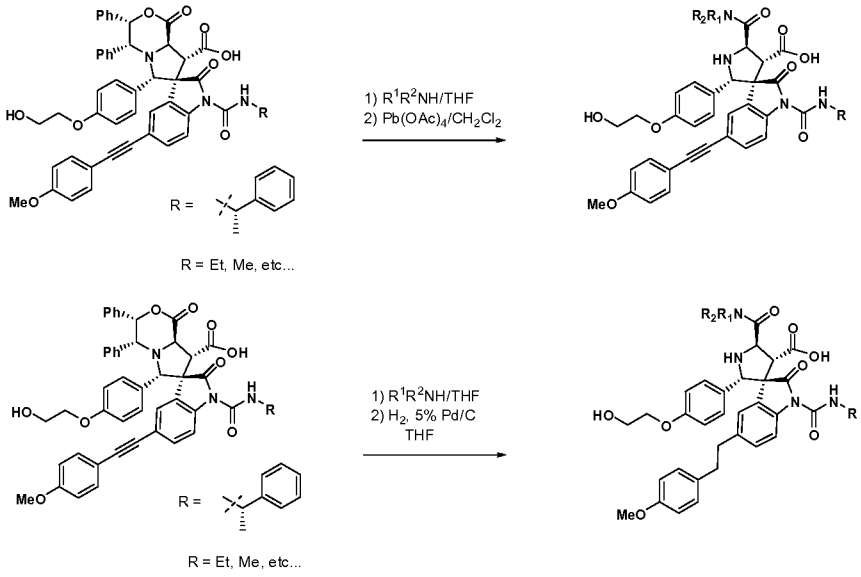
SpOx5
3XBCG
1296-D11

[00184]

[00185] **3XBCG**. (SpOx-5) (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.86 (d, *J* = 6.89 Hz, 1H), 7.88 (d, *J* = 8.53 Hz, 1H), 7.80-7.81 (m, 3H), 7.69-7.70 (m, 3H), 7.42-7.49 (m, 2H), 7.25-7.40 (m, 6H), 6.98-7.03 (m, 4H), 6.87 (d, *J* = 7.30 Hz, 2H), 6.70 (d, *J* = 8.92 Hz, 2H), 6.57-6.60 (m, 2H), 6.25 (d, *J* = 1.42 Hz, 1H), 5.19 (d, *J* = 11.03 Hz, 1H), 5.12-5.18 (m, 1H), 5.03-5.04 (m, 1H), 5.00 (s, 1H), 4.40 (s br, 2H), 4.29 (d, *J* = 10.68 Hz, 1H), 4.09 (d, *J* = 1.25 Hz, 1H), 4.06 (d, *J* = 4.83 Hz, 2H), 3.79 (t, *J* = 4.48 Hz , 4H), 3.58-3.64 (m, 4H), 2.99 (t, *J* = 4.51 Hz , 4H), 1.56 (d, *J* = 7.00 Hz, 3H).

Example 3 – Synthesis of Spirooxindoles without Chiral Auxilliary

[00186] Dicarboxylic acids, *e.g.*, **TL I-214**, often have poor permeability due to their being ionized in plasma, resulting in poor cellular activity (EC_{50} >50 μM (HCT-116)). Analogous monocarboxylic acids (*e.g.*, **4XADF**, EC_{50} 6 μM (HCT-116)) should be more permeable. The literature has examples of the lactone ring of these spirooxindoles being opened by amines (*J. Am. Chem. Soc. 127*:10130, **2005**). Ring opening of the lactone spirooxindoles followed by removal of the diphenylethyl chiral auxiliary under reduction or oxidative (*J. Am. Chem. Soc. 127*:10130, **2005**) conditions will produce monocarboxylic acid analogs of **TL I-214**. The 4XADF analog where the α-methylbenzyl group is replaced with an ethyl group has a slight decrease in activity against Aurora A (IC_{50} 300 vs. 670 nM) but its lower molecular weight and clogP may enhance its pharmacokinetic properties.



Example 4 – Biological Activity of Spirooxindoles

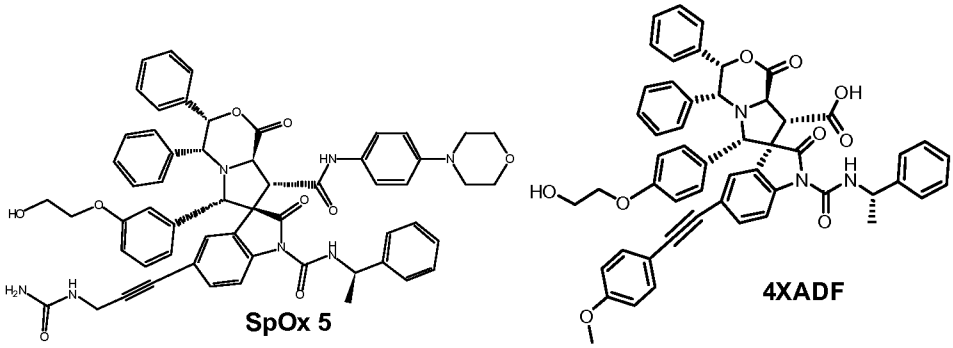
[00187] Many kinase inhibitors interact at the ATP binding site of the kinase. This often leads to two effects: 1. the inhibitors are non-selective as the ATP binding site is conserved amongst kinases; and 2. the inhibitors are far more active *in vitro* than *in vivo* due to high concentrations of ATP in cells (1-10 mM).

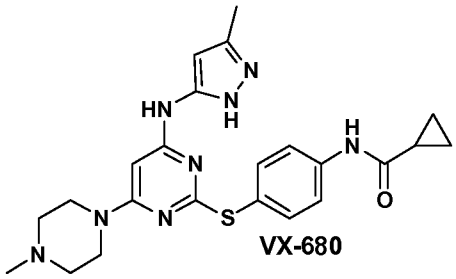
[00188] Kinase Selectivity of SpOx-5. SpOx-5 was sent to Upstate Biotechnology (Lake Placid, NY, now part of Millipore) for kinase profiling (*Figure 7*). The activity of SpOx-5 was measured across a panel of 50 different kinases at a SpOx-5 concentration of 20 μM. A standard assay is performed as follows. In a final reaction volume of 25 μL, Aurora-A (human) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 200 mM LRRASLG (Kemptide), 10 mM $Mg(OAc)_2$, and [γ–^{33}P-ATP]. The reaction is initiated by the addition of the MgATP mix. After incubating for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μL of a 3% phosphoric acid solution. 10 μL of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 50 mM phosphoric acid and once in methanol prior to drying and scintillation counting. The results were as follows:

Kinase	**Activity % at 20 μM**
Abl(m)	87
AMPK(r)	85
ASK1(h)	119
Aurora-A(h)	28
CDK1/cyclinB(h)	111
CDK2/cyclinA(h)	104
CDK6/cyclinD3(h)	130
CDK7/cyclinH/MAT1(h)	61
CDK9/cyclinT1(h)	116
CHK1(h)	126
CK1γ1(h)	70
CK2α2(h)	102
c-RAF(h)	99
eEF-2K(h)	95
EGFR(h)	93
EphA5(h)	100
ErbB4(h)	99
FAK(h)	105
FGFR1(h)	109

Flt1(h)	103
Flt4(h)	63
GSK3β(h)	64
IGF-1R(h)	143
IKKα(h)	131
IR(h)	112
JAK2(h)	95
Lyn(h)	96
MAPKAP-K2(h)	104
MEK1(h)	108
MELK(h)	105
MKK6(h)	104
MKK7β(h)	95
MLCK(h)	95
MSK2(h)	69
MST1(h)	105
NEK2(h)	90
p70S6K(h)	102
PAK2(h)	110
PDGFRβ(h)	146
Pim-1(h)	120
PKA(h)	81
PKBα(h)	98
PKBβ(h)	113
PKCα(h)	95
PKCθ(h)	144
Plk3(h)	95
PRAK(h)	59
ROCK-I(h)	101
Rsk1(h)	128
SRPK1(h)	43

[00189] ***In vitro* vs. cellular activity.** *Figure 8* shows the cellular activity of three Aurora A kinase inhibitors at different concentrations. The *in vitro* IC_{50}s are 3 μM for SpOx-5, 296 nM for 4XADF. The known ATP competitive Aurora inhibitor VX-680, IC_{50} of 0.6 nM, loses much of its activity in the cellular assay due to high concentration of ATP in the cells. 4XADF has been found to be non-competitive with ATP.





[00190] **Lineweaver Burke Analysis.** ATP competitiveness can be determined by running a Lineweaver Burke experiment where the enzyme inhibition is determined varying the concentration of ATP and of inhibitor while holding the enzyme concentration constant. An ATP competitive inhibitor will not affect V_{max}, whereas a noncompetitive inhibitor will have an affect on V_{max}. The changes in V_{max} across the compound concentrations suggest that the inhibition is not competitive with ATP. All the curves in *Figure 9* would intersect at a position on the Y axis if 4XADF were ATP competitive. However, the changes in K_m across the compound concentrations suggest that 4XADF is indirectly competitive with ATP. Such inhibitors, termed Type II (Liu and Gray, *Nature Chemical Biology* **2006**, *2*, 358) may bind to an allosteric site near the ATP binding site or may bind to the enzyme and lock it in an inactive conformation.

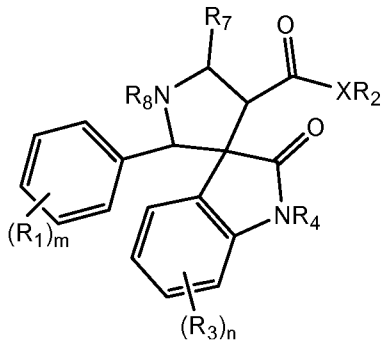
Other Embodiments

[00191] The foregoing has been a description of certain non-limiting preferred embodiments of the invention. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

Claims

What is claimed is:

1. A compound of the formula:



wherein

n is an integer between 1 and 5, inclusive;

m is an integer between 1 and 4, inclusive;

X is O, S, or NR_2;

R_1 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_A$; $-C(=O)R_A$; $-C(=O)N(R_A)_2$; $-CO_2R_A$; -CN; -SCN; $-SR_A$; $-SOR_A$; $-SO_2R_A$; $-NO_2$; $-N(R_A)_2$; $-NHC(O)R_A$; or $-C(R_A)_3$; wherein each occurrence of R_A is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_2 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_B$; $-C(=O)R_B$; $-C(=O)N(R_B)_2$; $-CO_2R_B$; -CN; -SCN; $-SR_B$; $-SOR_B$; $-SO_2R_B$; $-NO_2$; $-N(R_B)_2$; $-NHC(O)R_B$; or $-C(R_B)_3$; wherein each occurrence of R_B is independently a hydrogen, halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a

heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_3 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_C$; $-C(=O)R_C$; $-C(=O)N(R_C)_2$; $-CO_2R_C$; -CN; -SCN; $-SR_C$; $-SOR_C$; $-SO_2R_C$; $-NO_2$; $-N(R_C)_2$; $-NHC(O)R_C$; or $-C(R_C)_3$; wherein each occurrence of R_C is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

each occurrence of R_4 is independently hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_D$; $-C(=O)R_D$; $-C(=O)N(R_D)_2$; $-CO_2R_D$; -CN; -SCN; $-SR_D$; $-SOR_D$; $-SO_2R_D$; $-NO_2$; $-N(R_D)_2$; $-NHC(O)R_D$; or $-C(R_D)_3$; wherein each occurrence of R_D is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

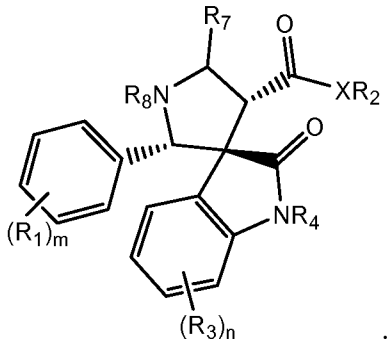
R_7 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_G$; $-C(=O)R_G$; $-C(=O)N(R_G)_2$; $-CO_2R_G$; -CN; -SCN; $-SR_G$; $-SOR_G$; $-SO_2R_G$; $-NO_2$; $-N(R_G)_2$; $-NHC(O)R_G$; or $-C(R_G)_3$; wherein each occurrence of R_G is independently a hydrogen, halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety;

R_8 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or

unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_H$; $-C(=O)R_H$; $-C(=O)N(R_H)_2$; $-CO_2R_H$; -CN; -SCN; $-SR_H$; $-SOR_H$; $-SO_2R_H$; $-NO_2$; $-N(R_H)_2$; $-NHC(O)R_H$; or $-C(R_H)_3$; wherein each occurrence of R_H is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; wherein R_7 and R_8 may be taken together to form a cyclic moiety; and stereoisomers, tautomers, enantiomers, diastereomers, racemates, pro-drugs, protected forms, salts, hydrates, solvates, and derivatives thereof.

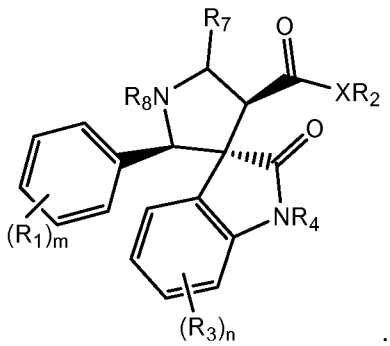
2. The compound of claim 1, wherein R_7 and R_8 are not taken together to form a cyclic moiety.

3. The compound of claim 1 with the stereochemistry of formula:



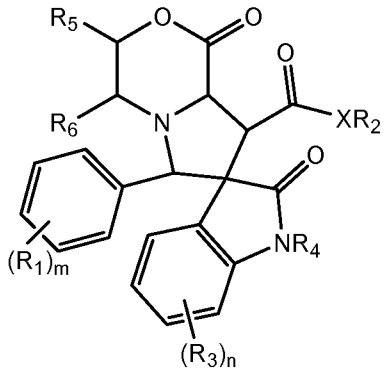
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4. The compound of claim 1 with the stereochemistry of formula:



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5. The compound of claim 1 of the formula:

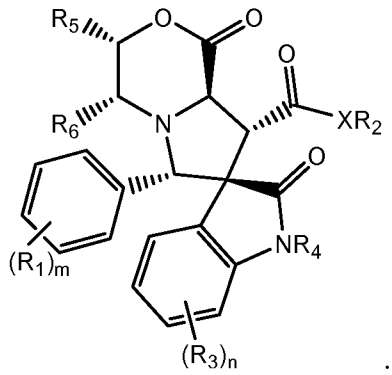


wherein

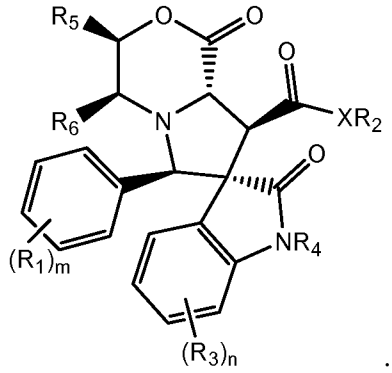
R_5 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_E$; $-C(=O)R_E$; $-C(=O)N(R_E)_2$; $-CO_2R_E$; -CN; -SCN; $-SR_E$; $-SOR_E$; $-SO_2R_E$; $-NO_2$; $-N(R_E)_2$; $-NHC(O)R_E$; or $-C(R_E)_3$; wherein each occurrence of R_E is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety; and

R_6 is hydrogen; halogen; cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; substituted or unsubstituted, branched or unbranched acyl; substituted or unsubstituted, branched or unbranched aryl; substituted or unsubstituted, branched or unbranched heteroaryl; $-OR_F$; $-C(=O)R_F$; $-C(=O)N(R_F)_2$; $-CO_2R_F$; -CN; -SCN; $-SR_F$; $-SOR_F$; $-SO_2R_F$; $-NO_2$; $-N(R_F)_2$; $-NHC(O)R_F$; or $-C(R_F)_3$; wherein each occurrence of R_F is independently a hydrogen, a halogen, a protecting group, an aliphatic moiety, a heteroaliphatic moiety, an acyl moiety; an aryl moiety; a heteroaryl moiety; alkoxy; aryloxy; alkylthio; arylthio; amino, alkylamino, dialkylamino, heteroaryloxy; or heteroarylthio moiety.

6. The compound of claim 5 with the stereochemistry of formula:



7. The compound of claim 5 with the stereochemistry of formula:



8. The compound of claim 5, 6, or 7, wherein at least one of R_5 and R_6 is a substituted or unsubstituted phenyl moiety.

9. The compound of claim 5, 6, or 7, wherein at least one of R_5 and R_6 is an unsubstituted phenyl moiety.

10. The compound of claim 5, 6, or 7, wherein both R_5 and R_6 are substituted or unsubstituted phenyl moieties.

11. The compound of claim 5, 6, or 7, wherein both R_5 and R_6 are unsubstituted phenyl moieties.

12. The compound of claim 5, 6, or 7, wherein both R_5 and R_6 are not unsubstituted phenyl moieties.

13. The compound of any one of claims 1-12, wherein n is 1.

14. The compound of any one of claims 1-12, wherein n is 2.

15. The compound of any one of claims 1-12, wherein n is 3.

16. The compound of any one of claims 1-12, wherein m is 1.

17. The compound of any one of claims 1-12, wherein m is 2.

18. The compound of any one of claims 1-12, wherein m is 3.

19. The compound of any one of claims 1-12, wherein X is O.

20. The compound of any one of claims 1-12, wherein X is NR_2.

21. The compound of any one of claims 1-12, wherein X is NH.

22. The compound of any one of claim 1-12, wherein at least one occurrence of R_1 is $-OR_A$.

23. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is –OH.

24. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is $-OCH_2CH_2OH$.

25. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is $-N(R_A)_2$.

26. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is a halogen.

27. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety.

28. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is a C_{1-6} alkyl moiety.

29. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic moiety.

30. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is a substituted or unsubstituted aryl moiety.

31. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is a substituted or unsubstituted heteroaryl moiety.

32. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is an acyl moiety.

33. The compound of any one of claims 1-12, wherein at least one occurrence of R_2 is hydrogen.

34. The compound of any one of claims 1-12, wherein at least one occurrence of R_2 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety.

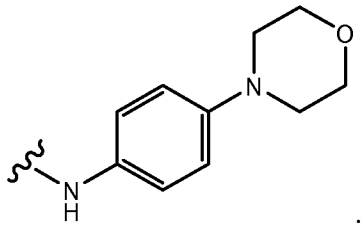
35. The compound of any one of claim 1-12, wherein at least one occurrence of R_2 is a C_{1-6} alkyl moiety.

36. The compound of any one of claims 1-12, wherein at least one occurrence of R_2 is allyl.

37. The compound of any one of claims 1-12, wherein at least one occurrence of R_2 is a substituted or unsubstituted aryl moiety.

38. The compound of any one of claims 1-12, wherein at least one occurrence of R_2 is a substituted or unsubstituted phenyl moiety.

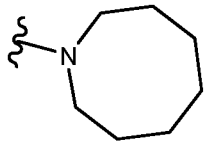
39. The compound of any one of claims 1-12, wherein $-XR_2$ is of the formula:



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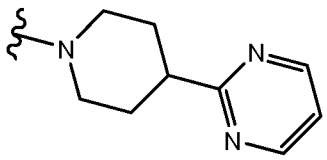
40. The compound of any one of claims 1-12, wherein at least one occurrence of R_2 is a substituted or unsubstituted heteoaryl moiety.

41. The compound of any one of claims 1-12, wherein $-XR_2$ is of the formula:



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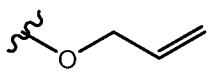
42. The compound of any one of claims 1-12, wherein $-XR_2$ is of the formula:



.

43. The compound of any one of claims 1-12, wherein $-XR_2$ is –OH.

44. The compound of any one of claims 1-12, wherein $-XR_2$ is of the formula:



.

45. The compound of any one of claim 1-12, wherein at least one occurrence of R_3 is $-OR_A$.

46. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is $-N(R_A)_2$.

47. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is a halogen.

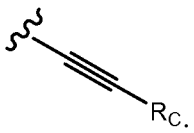
48. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety.

49. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is a substituted or unsubstituted alkyl moiety.

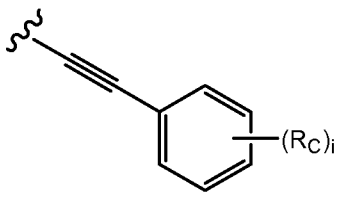
50. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is a substituted or unsubstituted alkenyl moiety.

51. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is a substituted or unsubstituted alkynyl moiety.

52. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is of the formula:

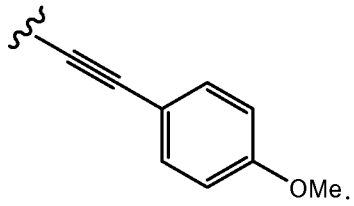


53. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is of the formula:

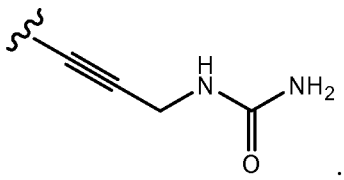


wherein i is an integer between 1 and 5, inclusive.

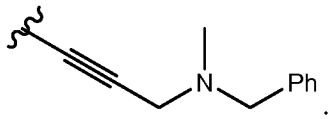
54. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is of the formula:



55. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is of the formula:



56. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is of the formula:



57. The compound of any one of claims 1-12, wherein at least one occurrence of R_1 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic moiety.

58. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is a substituted or unsubstituted aryl moiety.

59. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is a substituted or unsubstituted heteroaryl moiety.

60. The compound of any one of claims 1-12, wherein at least one occurrence of R_3 is an

acyl moiety.

61. The compound of any one of claims 1-12, wherein R_4 is hydrogen.

62. The compound of any one of claims 1-12, wherein R_4 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety.

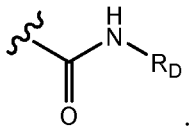
63. The compound of any one of claims 1-12, wherein R_4 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic moiety.

64. The compound of any one of claim 1-12, wherein R_4 is an acyl moiety.

65. The compound of any one of claims 1-12, wherein R_4 is a substituted or unsubstituted aryl moiety.

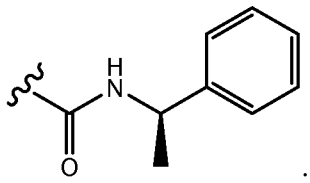
66. The compound of any one of claims 1-12, wherein R_4 is a substituted or unsubstituted heteroaryl moiety.

67. The compound of any one of claims 1-12, wherein R_4 is of the formula:



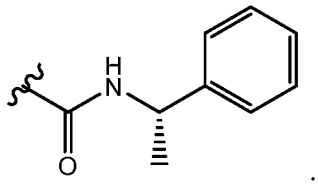
.

68. The compound of any one of claims 1-12, wherein R_4 is of the formula:



.

69. The compound of any one of claims 1-12, wherein R_4 is of the formula:



70. The compound of any one of claims 1-4, wherein R_7 is hydrogen.

71. The compound of any one of claims 1-4, wherein R_7 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety.

72. The compound of any one of claims 1-4, wherein R_7 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic moiety.

73. The compound of any one of claim 1-4, wherein R_7 is an acyl moiety.

74. The compound of any one of claims 1-4, wherein R_7 is a substituted or unsubstituted aryl moiety.

75. The compound of any one of claims 1-4, wherein R_7 is a substituted or unsubstituted heteroaryl moiety.

76. The compound of any one of claims 1-4, wherein R_8 is hydrogen.

77. The compound of any one of claims 1-4, wherein R_8 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety.

78. The compound of any one of claims 1-4, wherein R_8 is a cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic moiety.

79. The compound of any one of claim 1-4, wherein R_8 is an acyl moiety.

80. The compound of any one of claims 1-4, wherein R_8 is a substituted or unsubstituted aryl moiety.

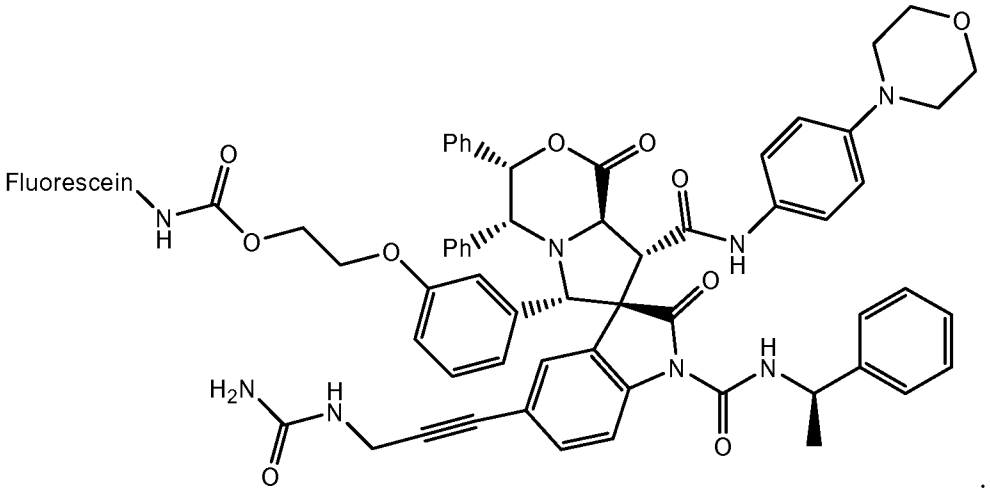
81. The compound of any one of claims 1-4, wherein R_8 is a substituted or unsubstituted heteroaryl moiety.

82. The compound of any one of claims 1-4, wherein R_7 and R_8 taken together form a heterocyclic moiety.

83. The compound of any one of claims 1-4, wherein R_1, R_2, R_3, R_4, R_7 or R_8 comprises a fluorescent, phosphorescent, or chemiluminescent moiety.

84. The compound of claim 83, wherein the fluorescent moiety comprises fluorescein.

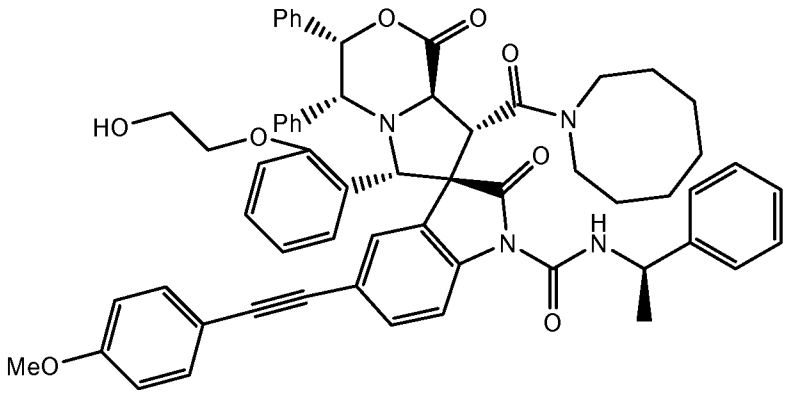
85. The compound of claim 84 of the formula:

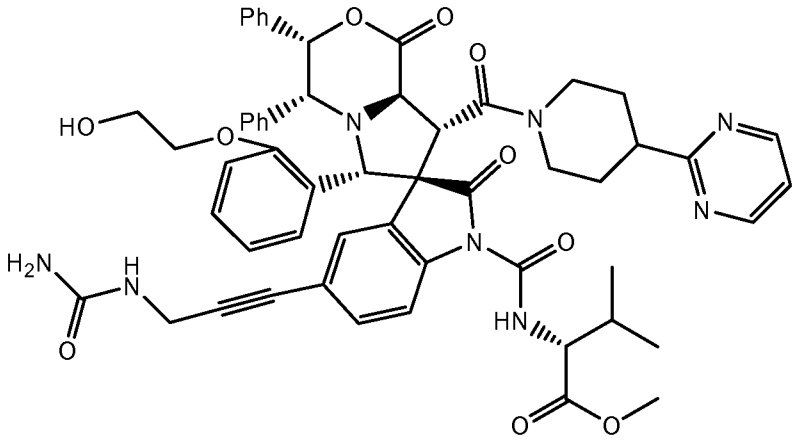


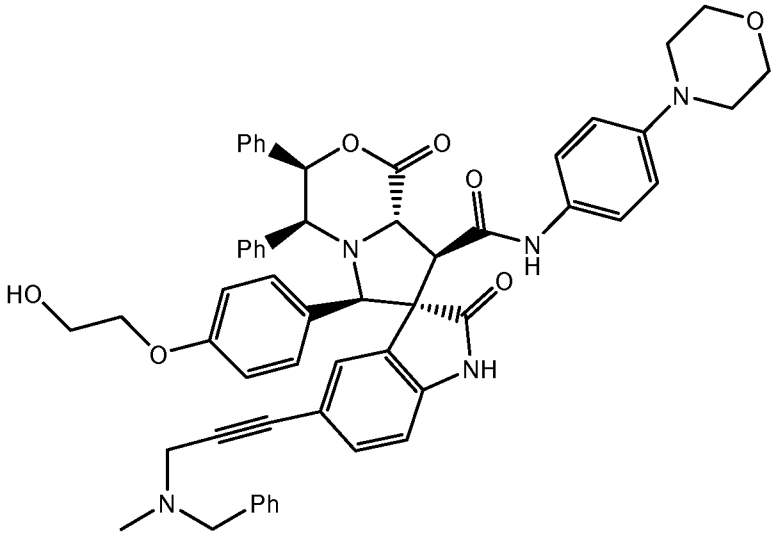
86. The compound of claim 83, wherein the fluorescent moiety comprises green fluorescent protein.

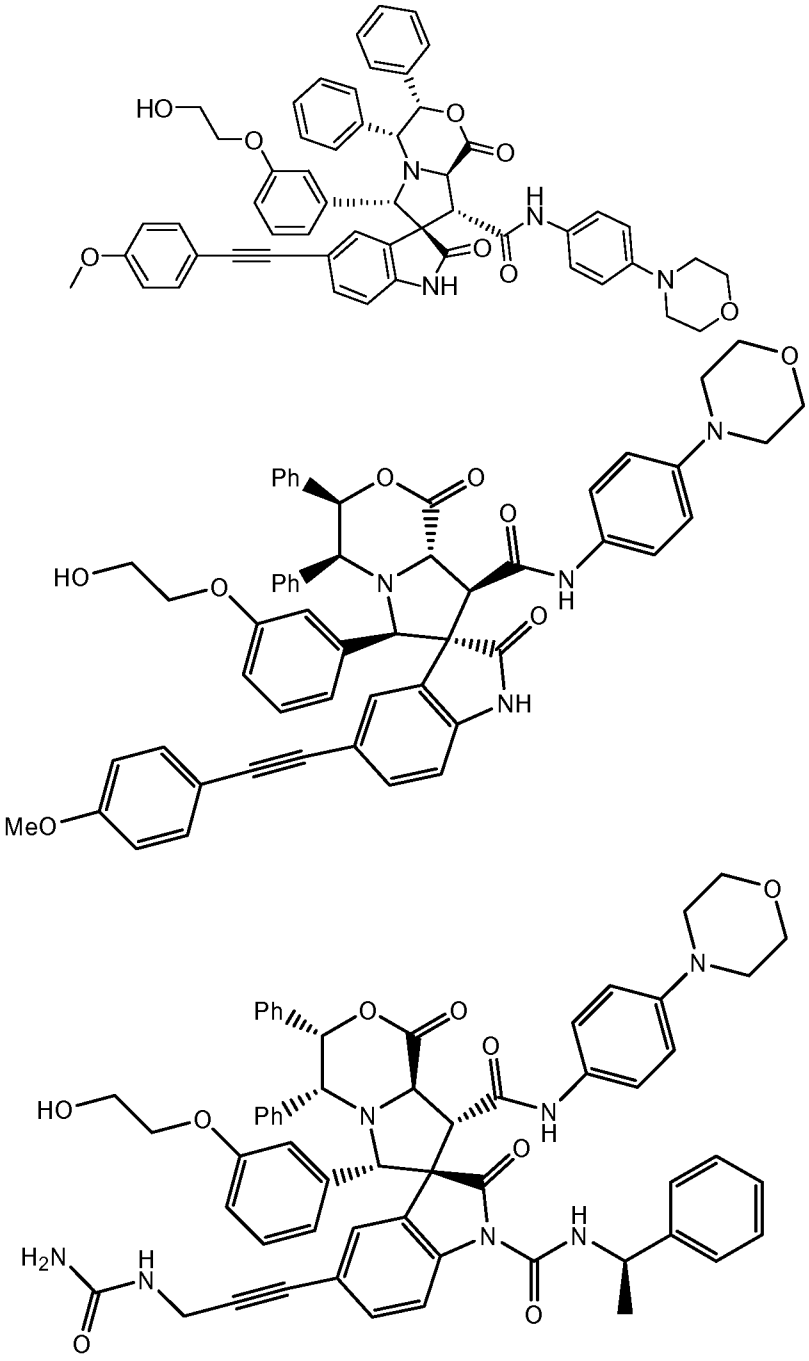
87. The compound of any one of claims 1-4, wherein R_1, R_2, R_3, R_4, R_7 or R_8 comprises a radioactive atom.

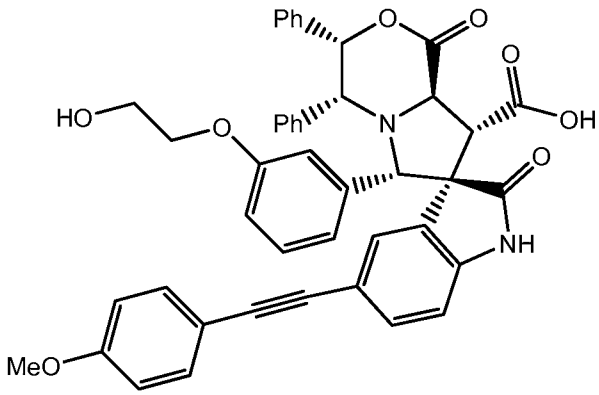
88. The compound of claim 1 of one of the formula:

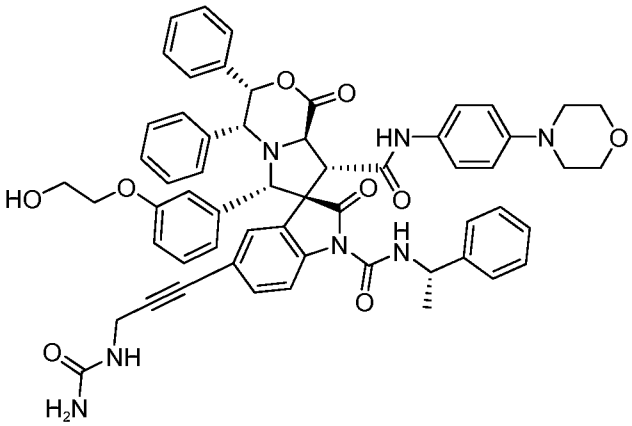


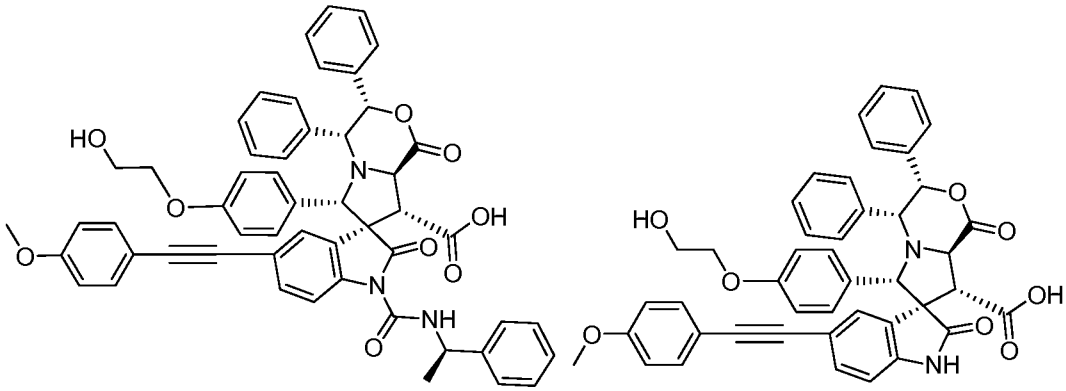


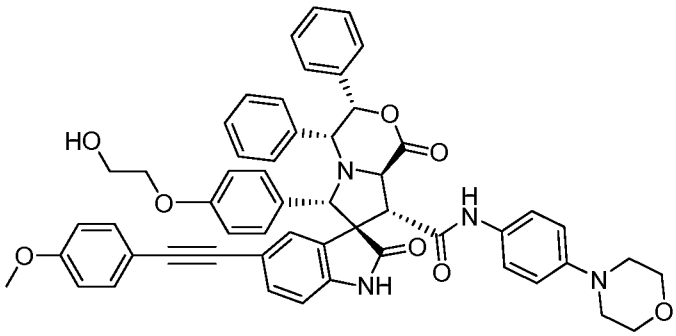


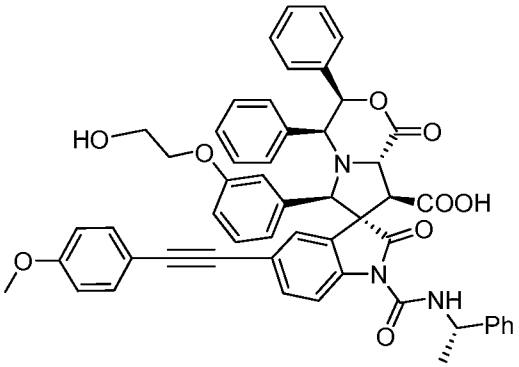


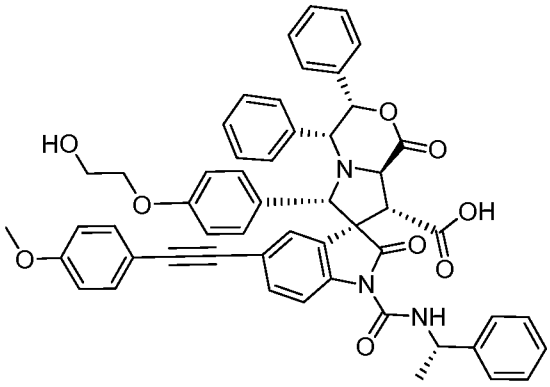

Ph
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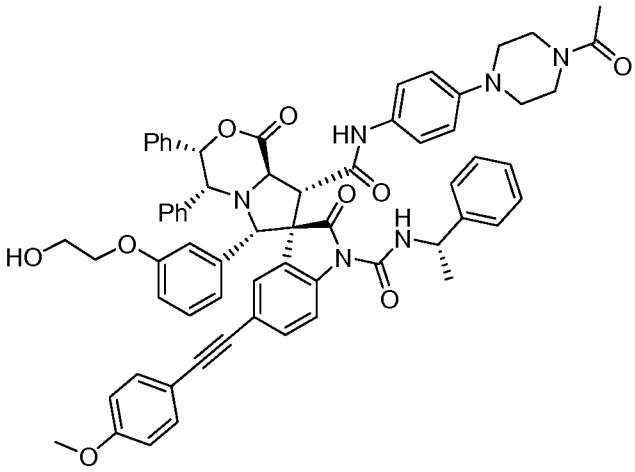

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NH
H2N

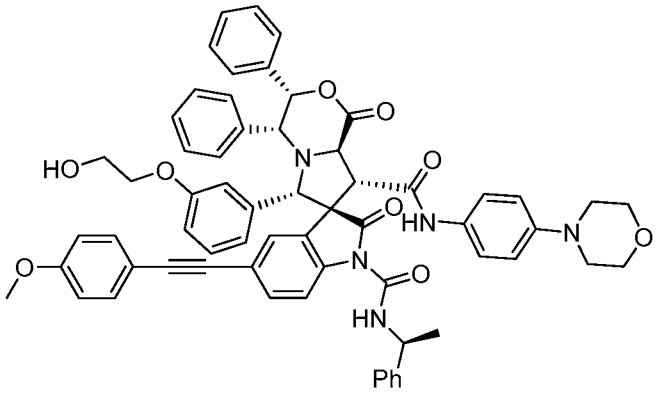

HO
O
O
N
O
OH
O
O
O
N
NH
HO
O
O
N
O
OH
O
O
NH

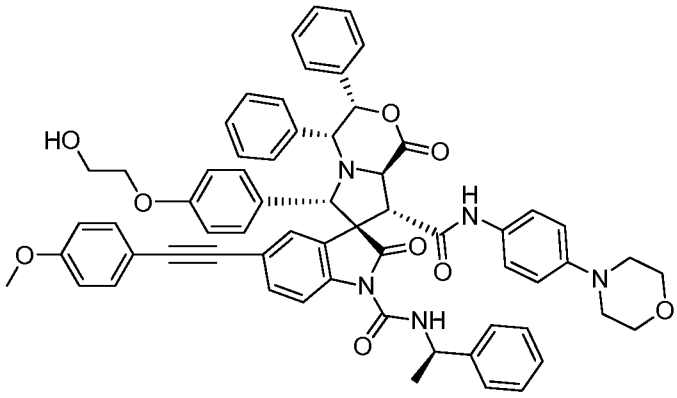

HO
O
O
N
O
H
N
O
O
NH
N
O

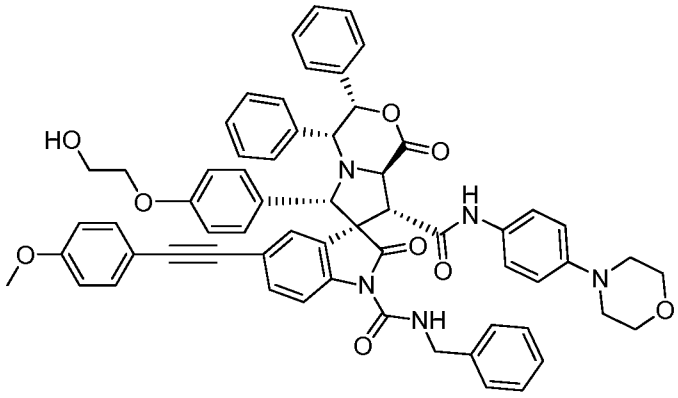


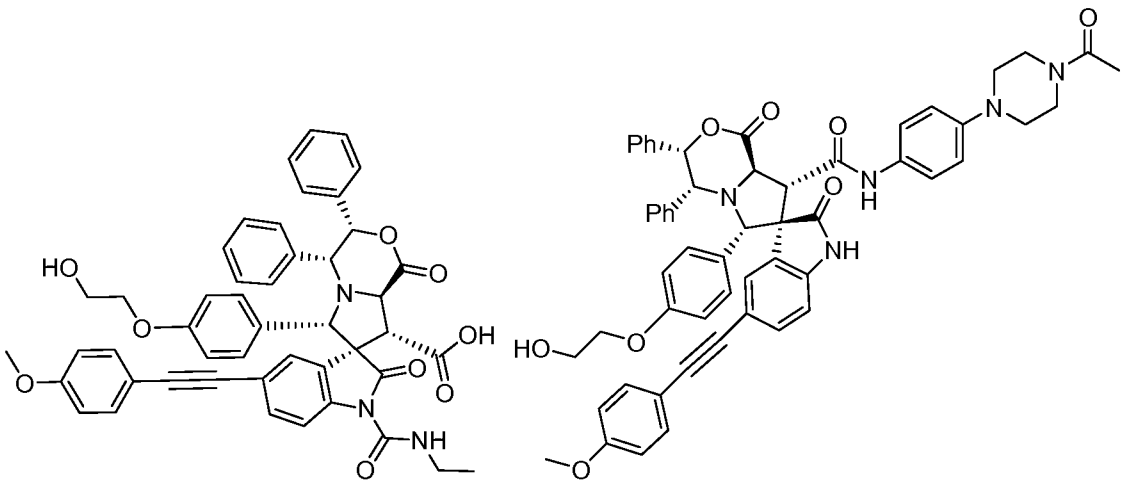


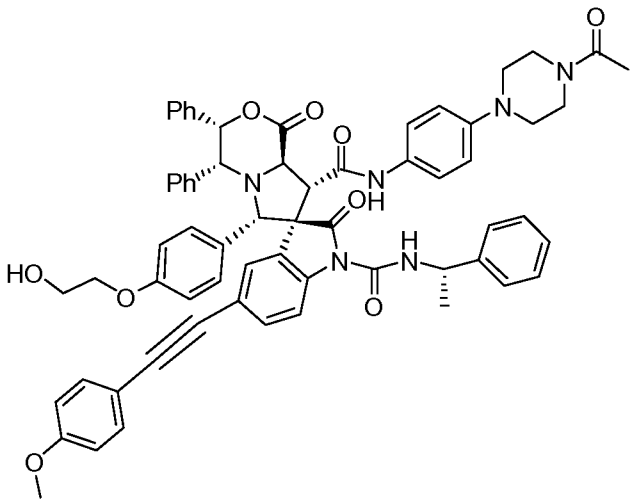


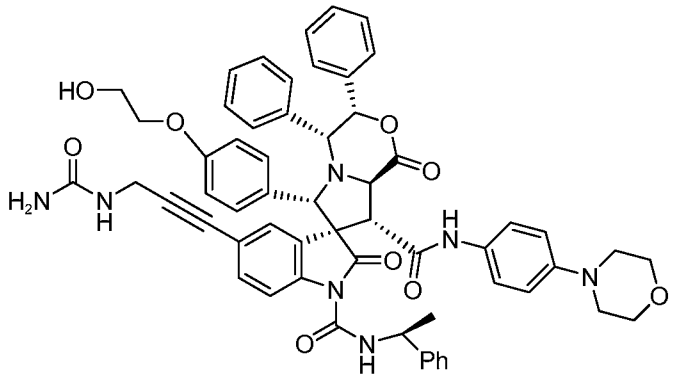


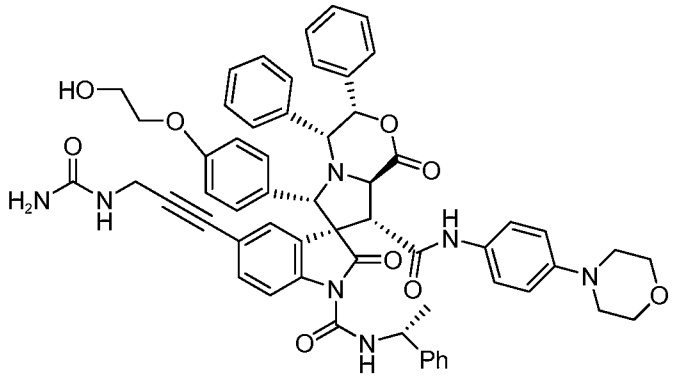


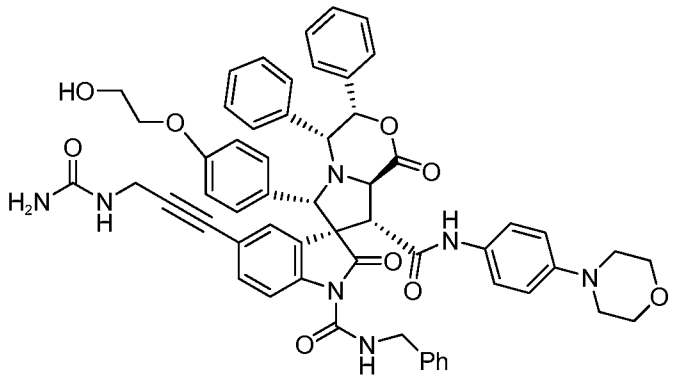


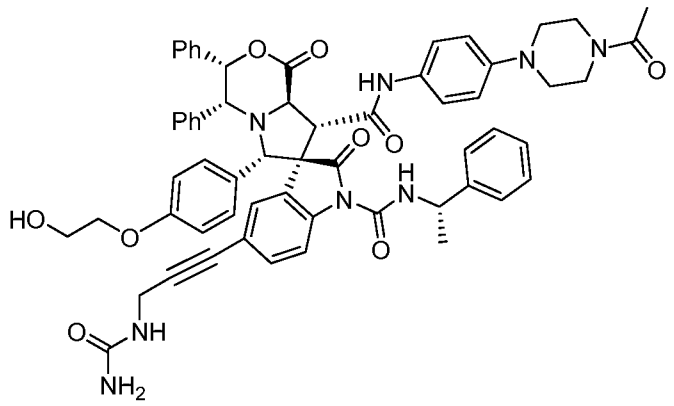


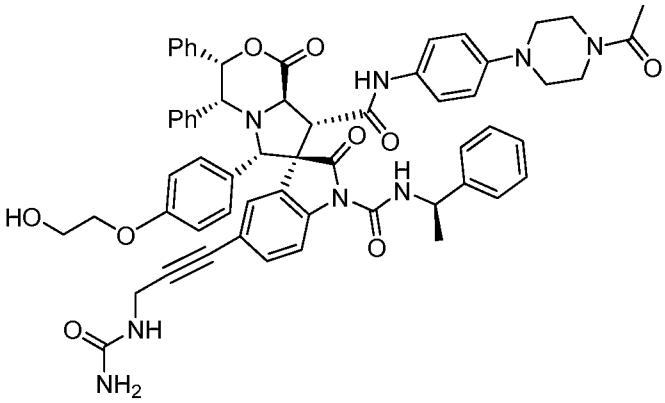


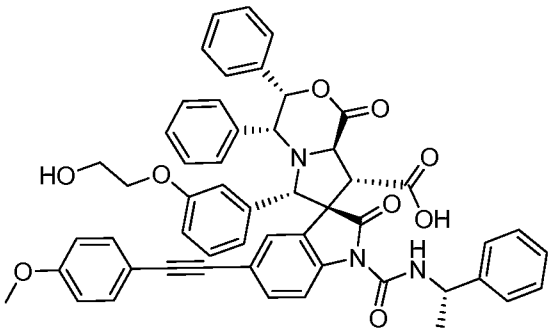


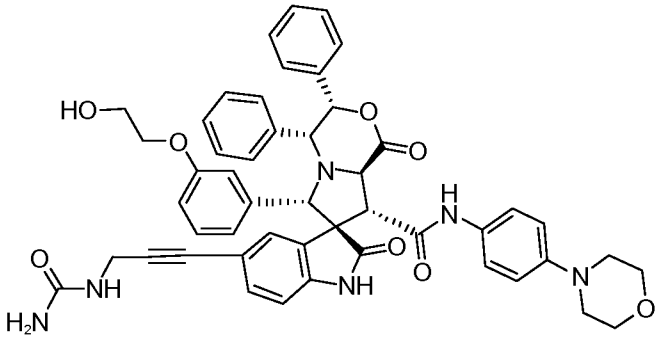


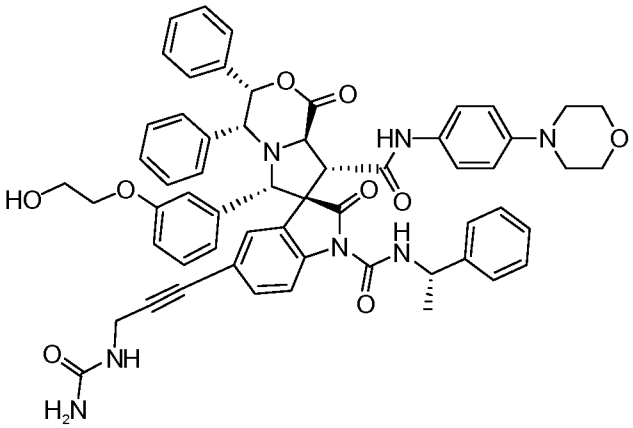


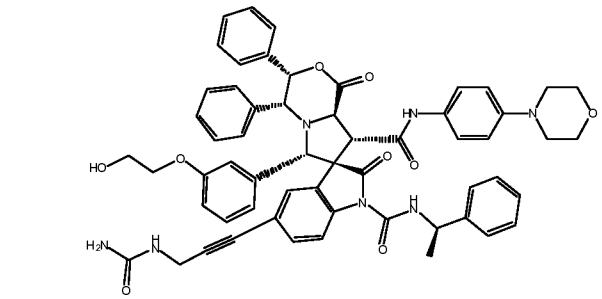


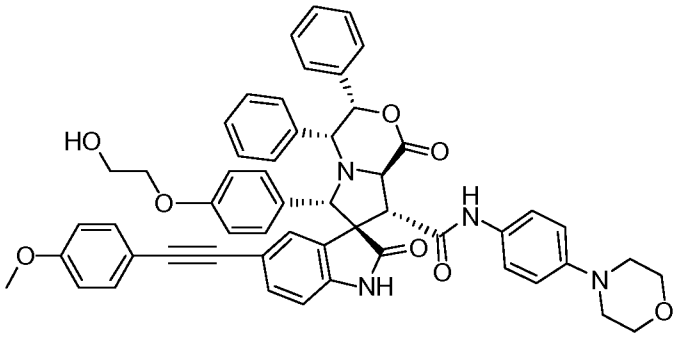


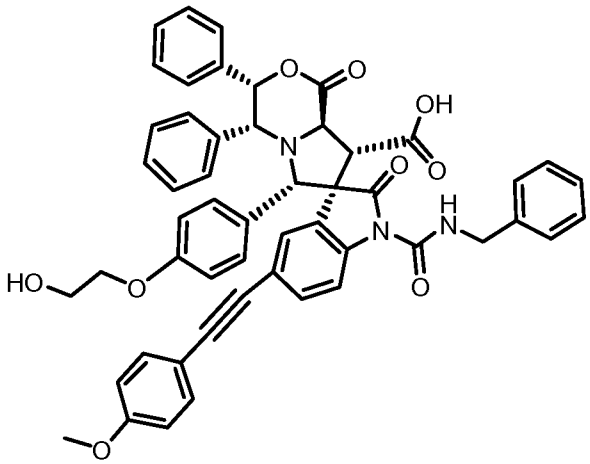


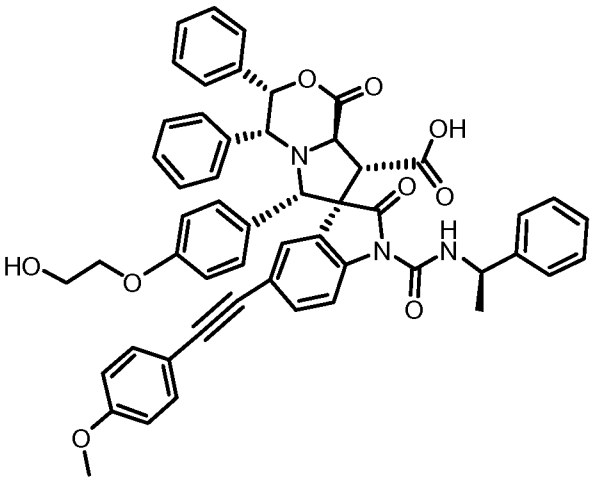


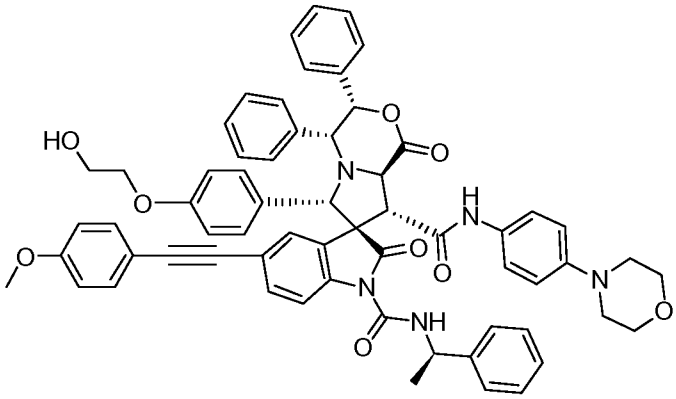


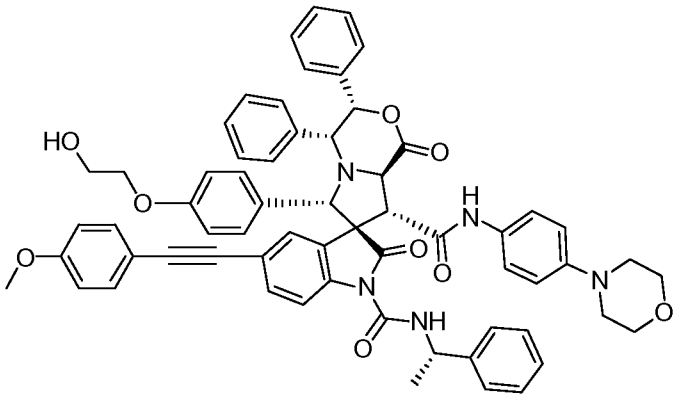


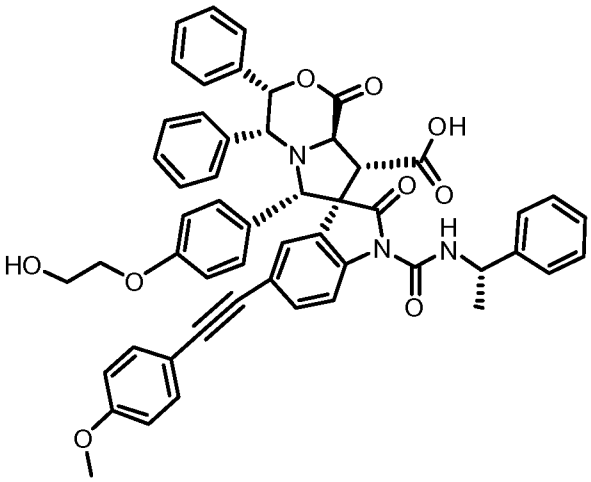


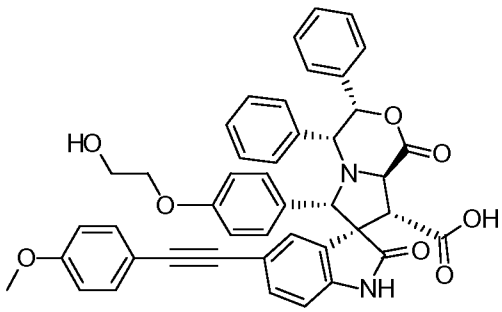


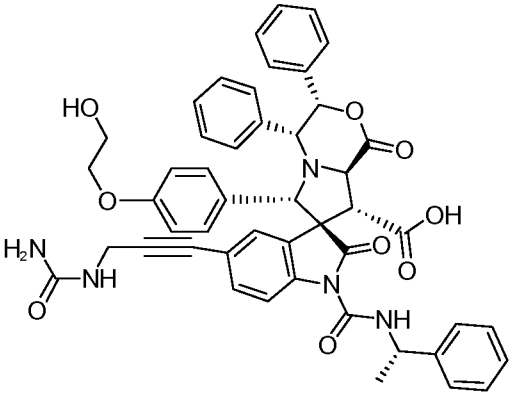


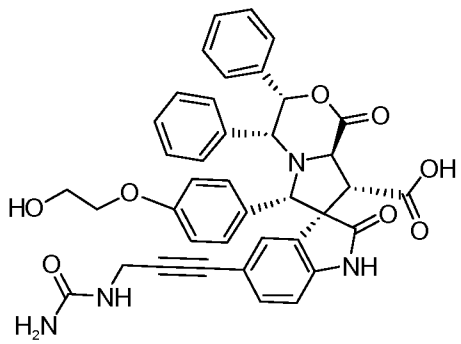


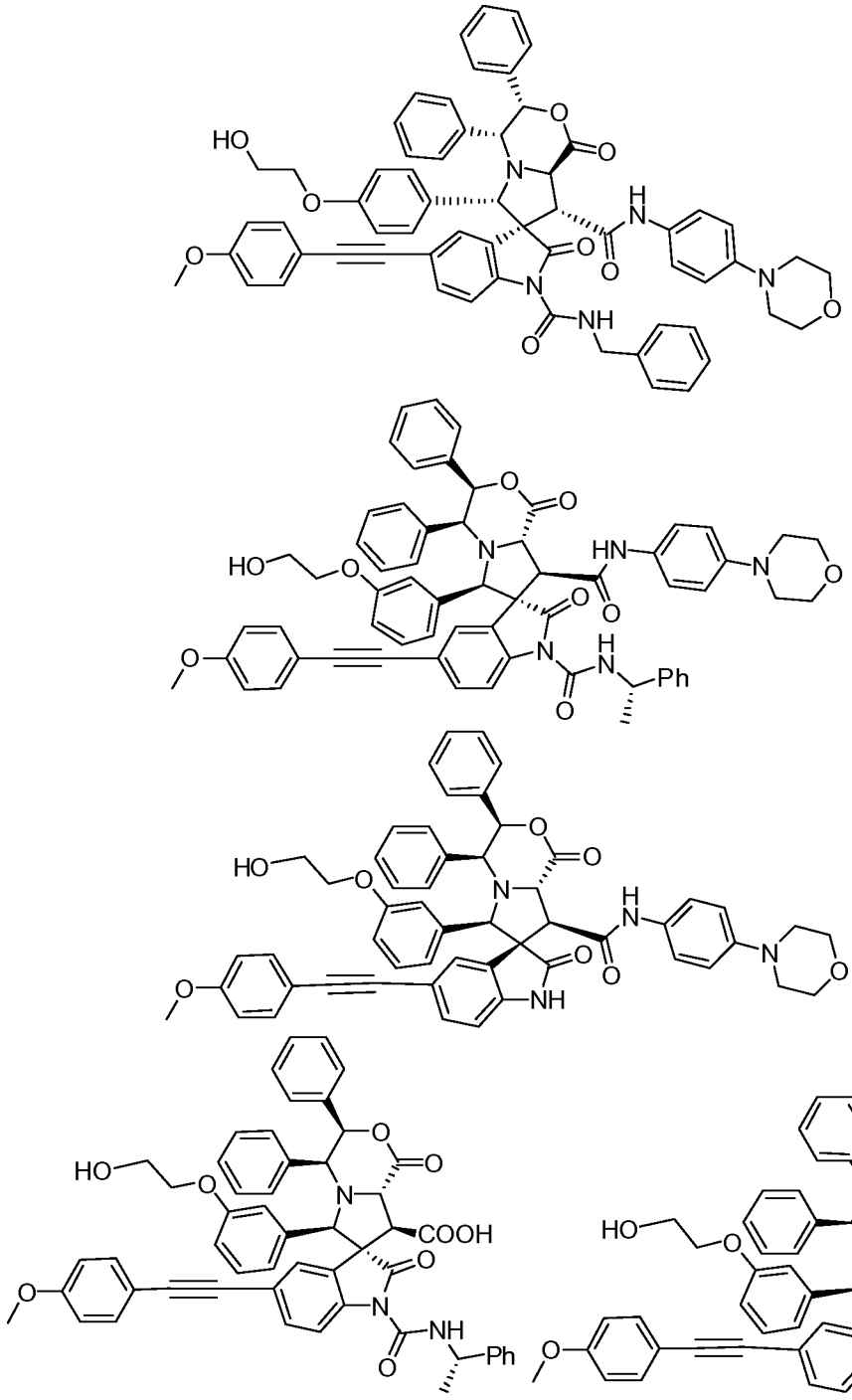


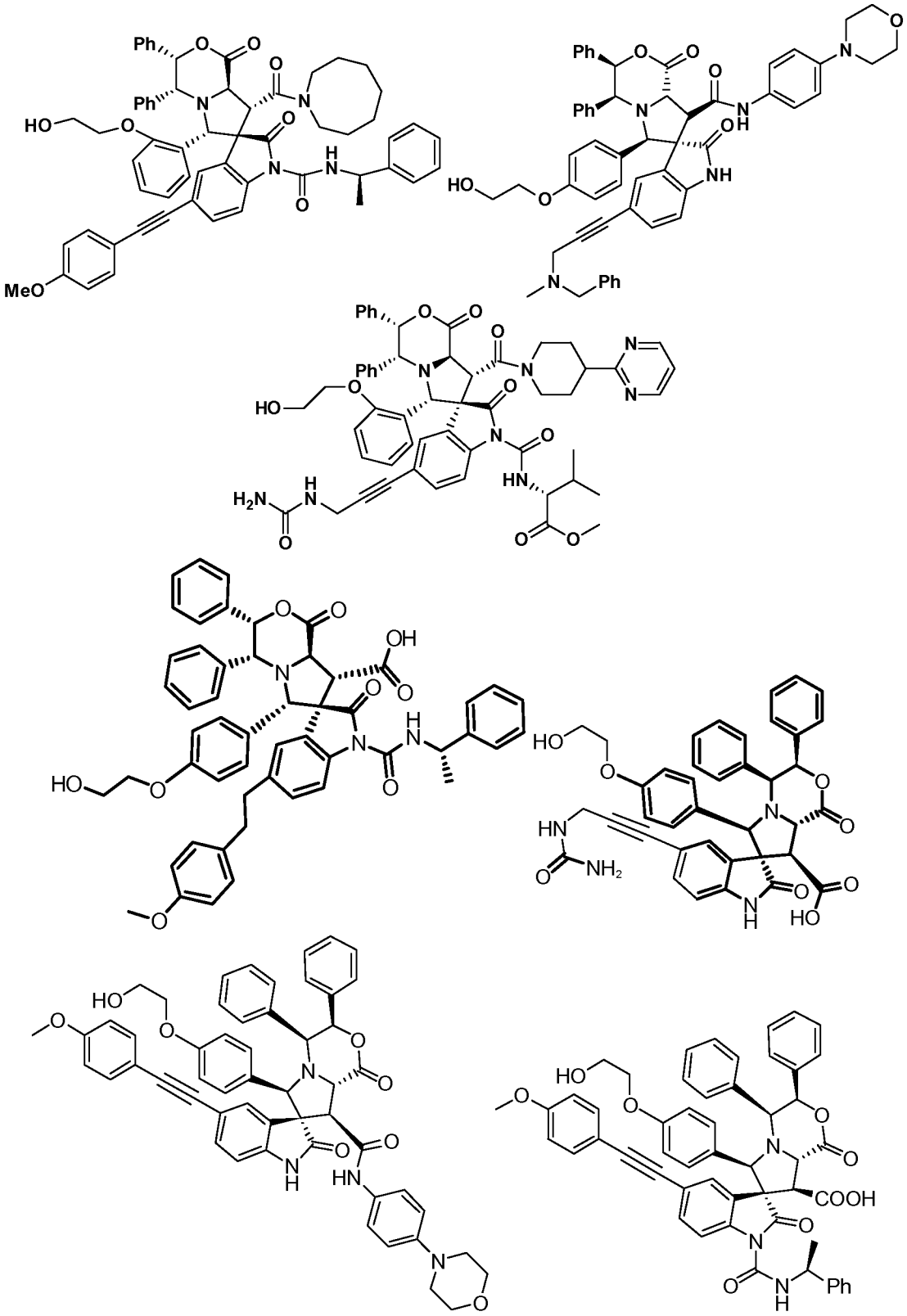


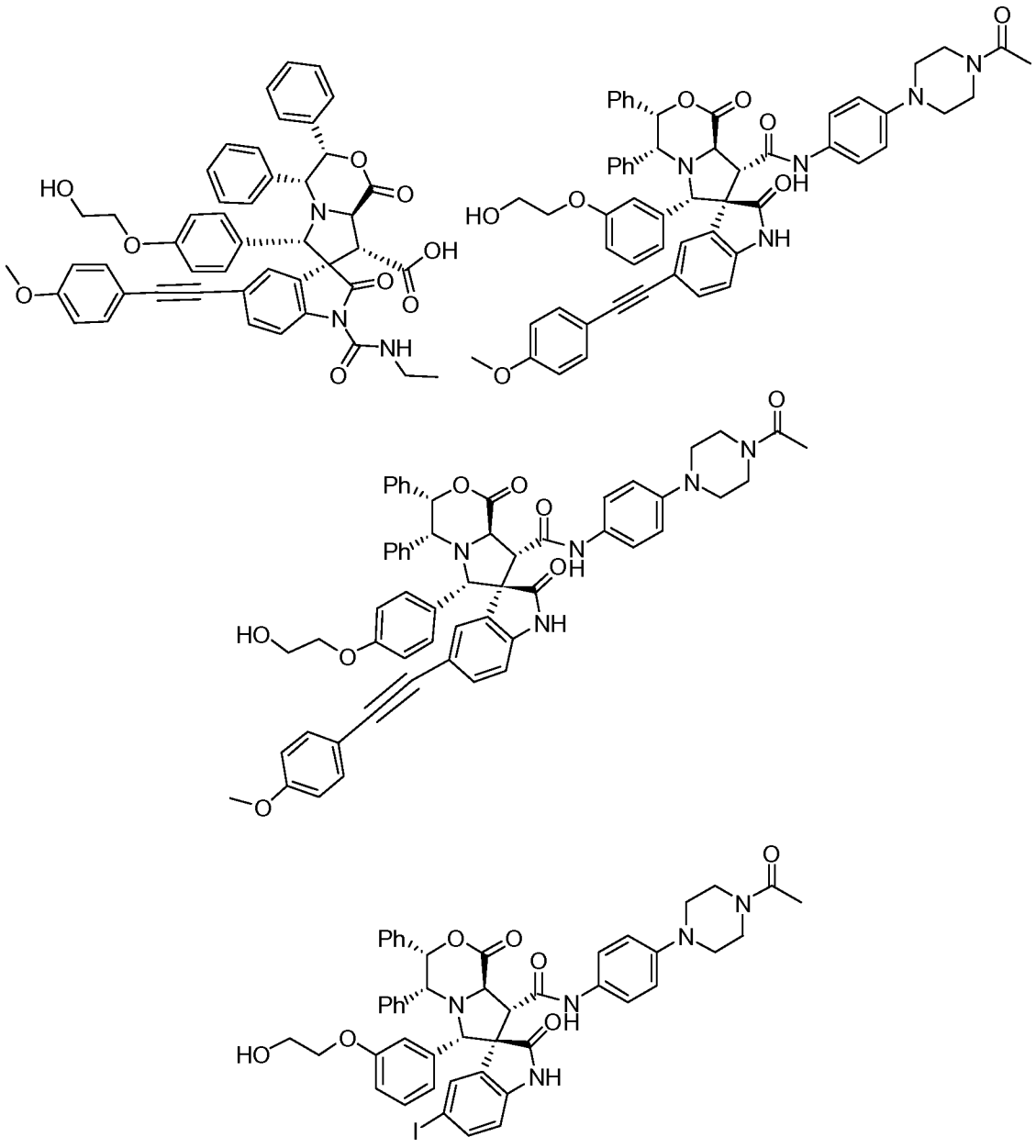


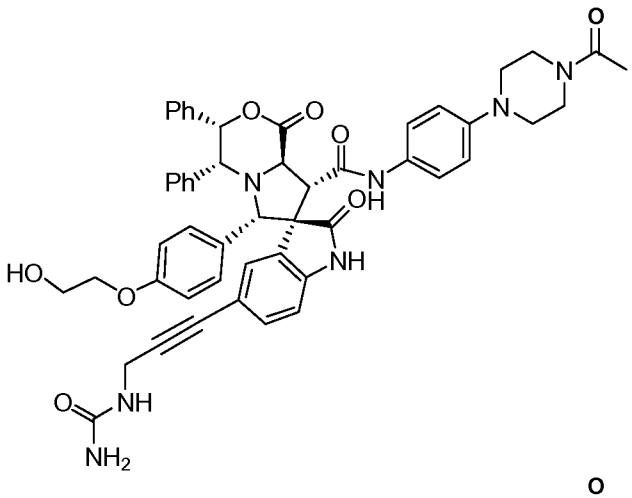


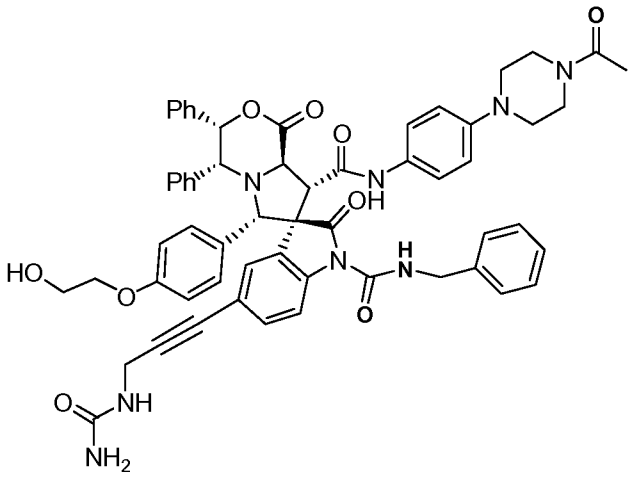


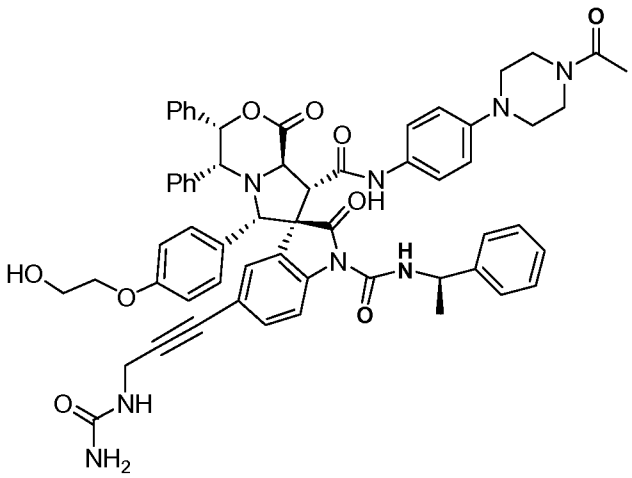


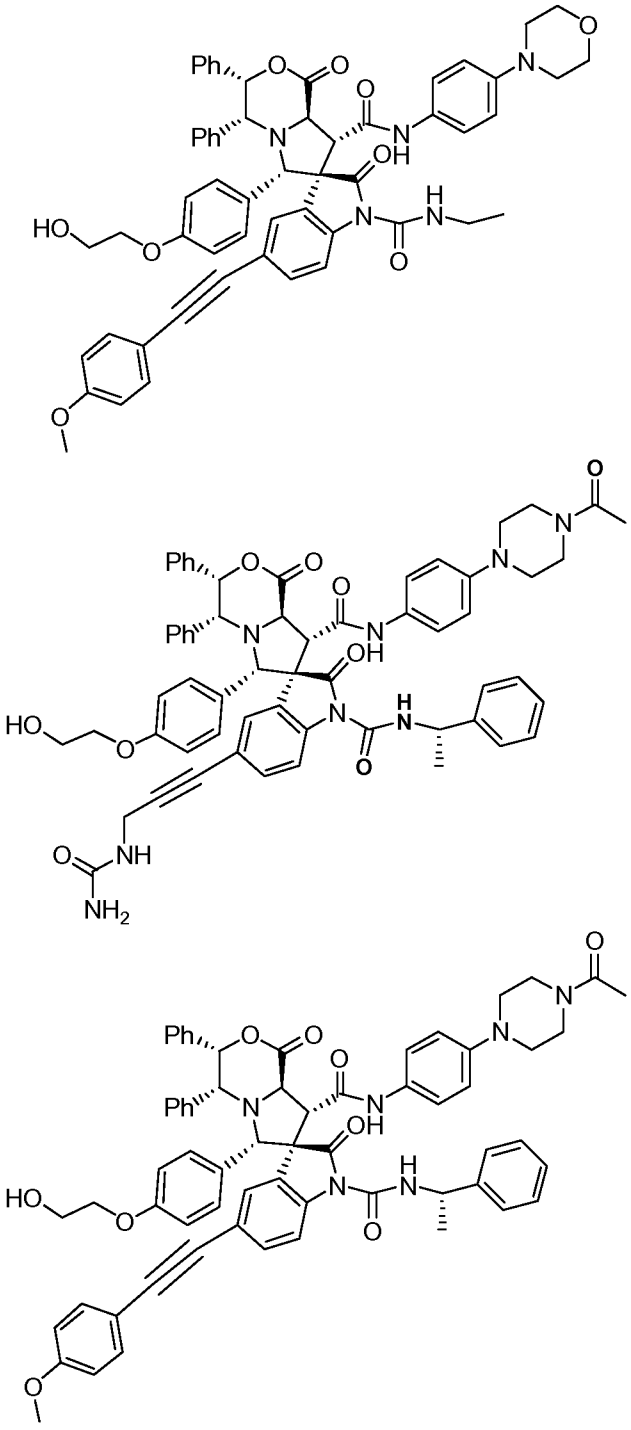


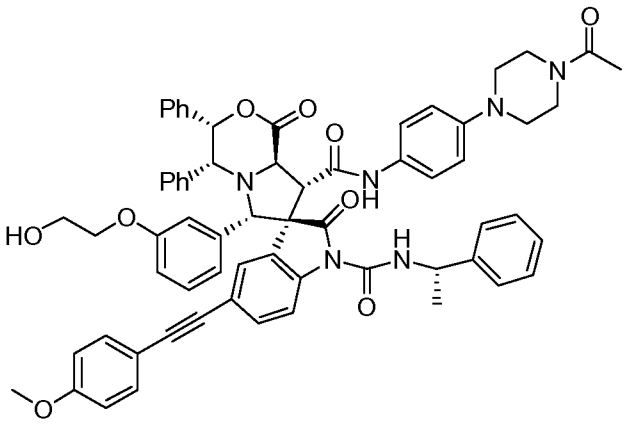


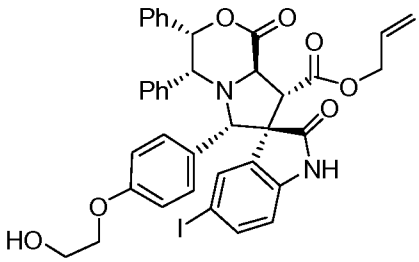


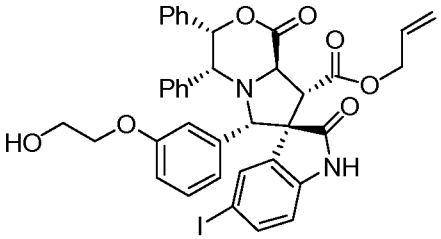


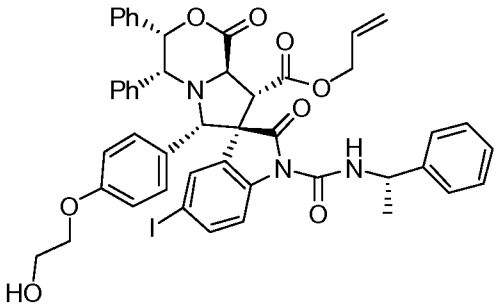


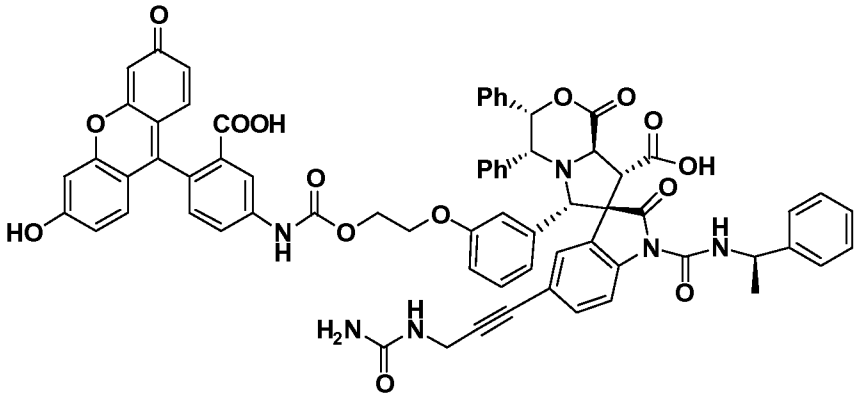


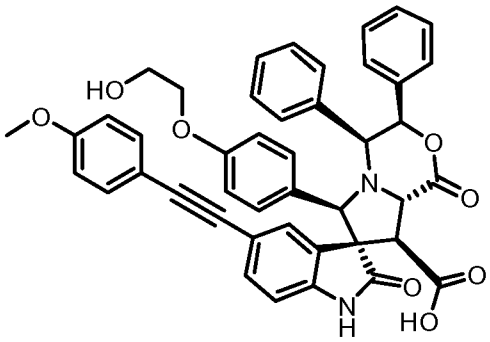


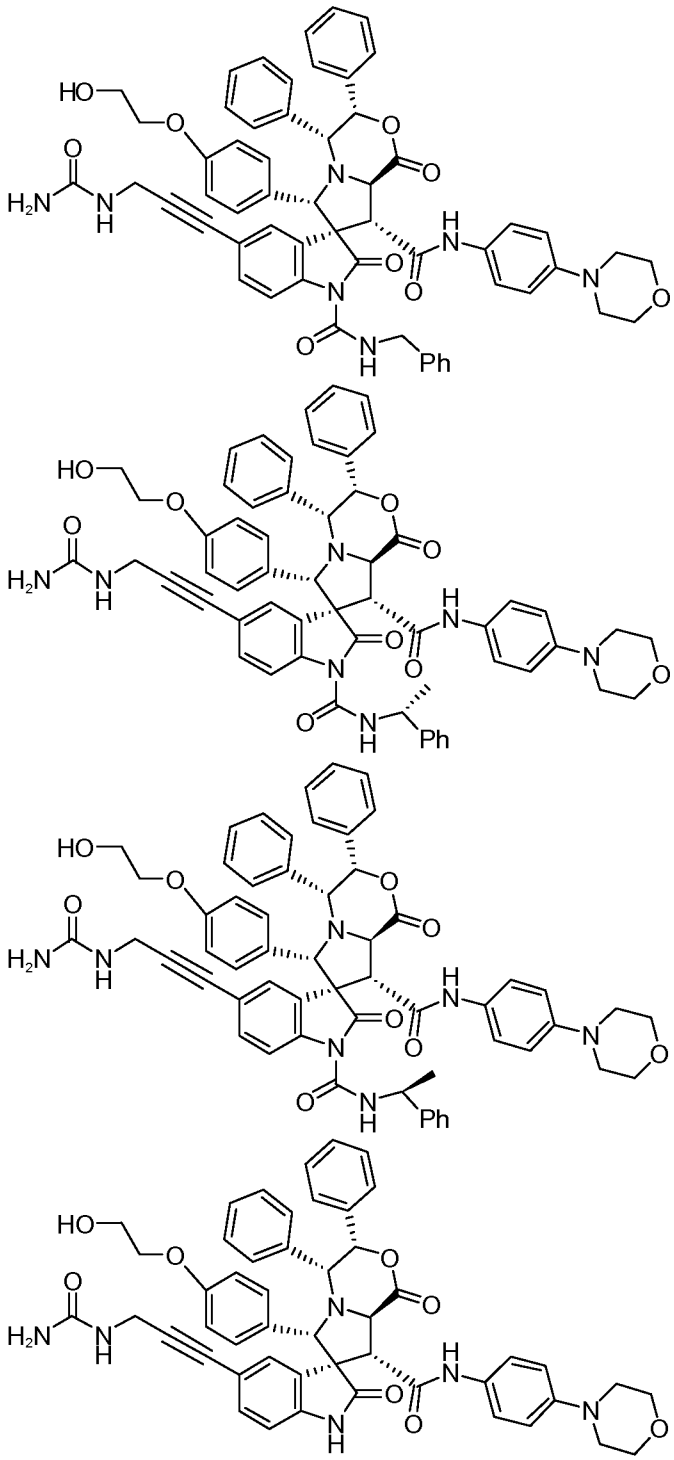


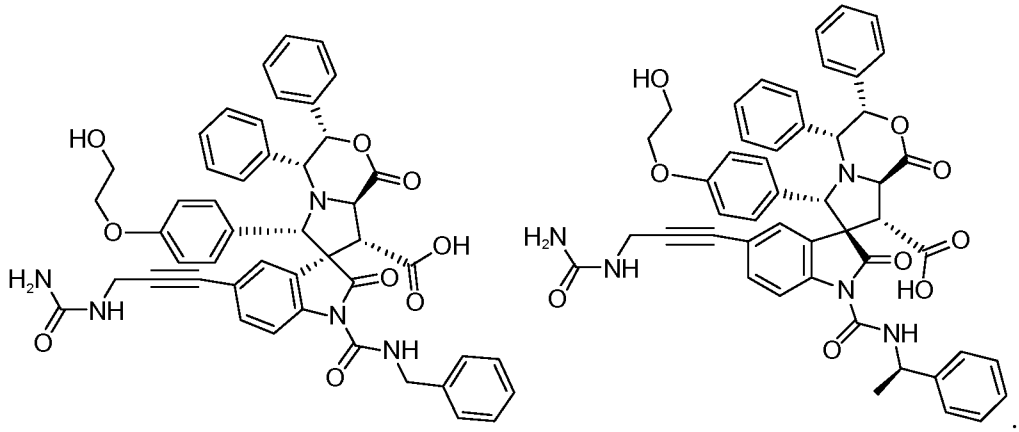




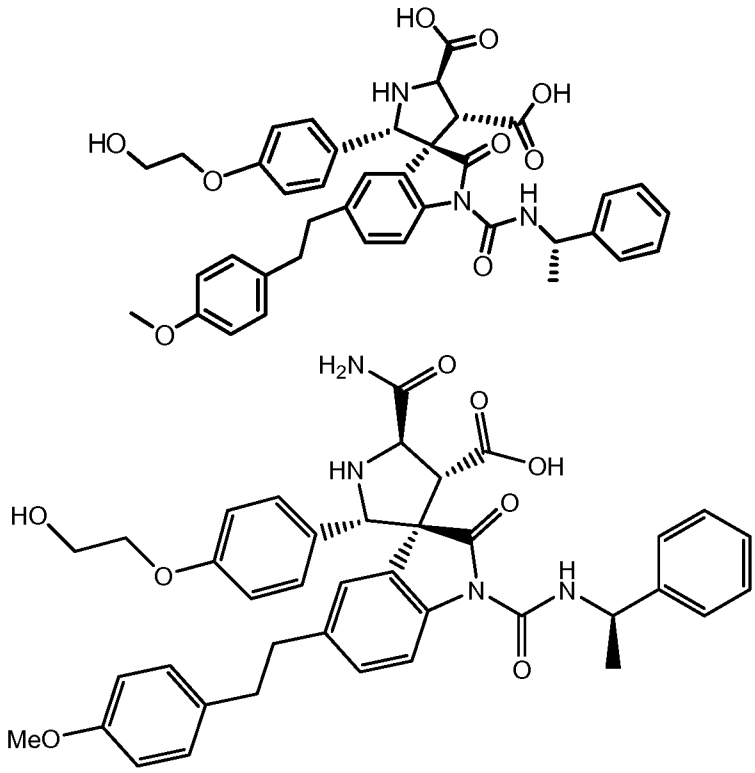


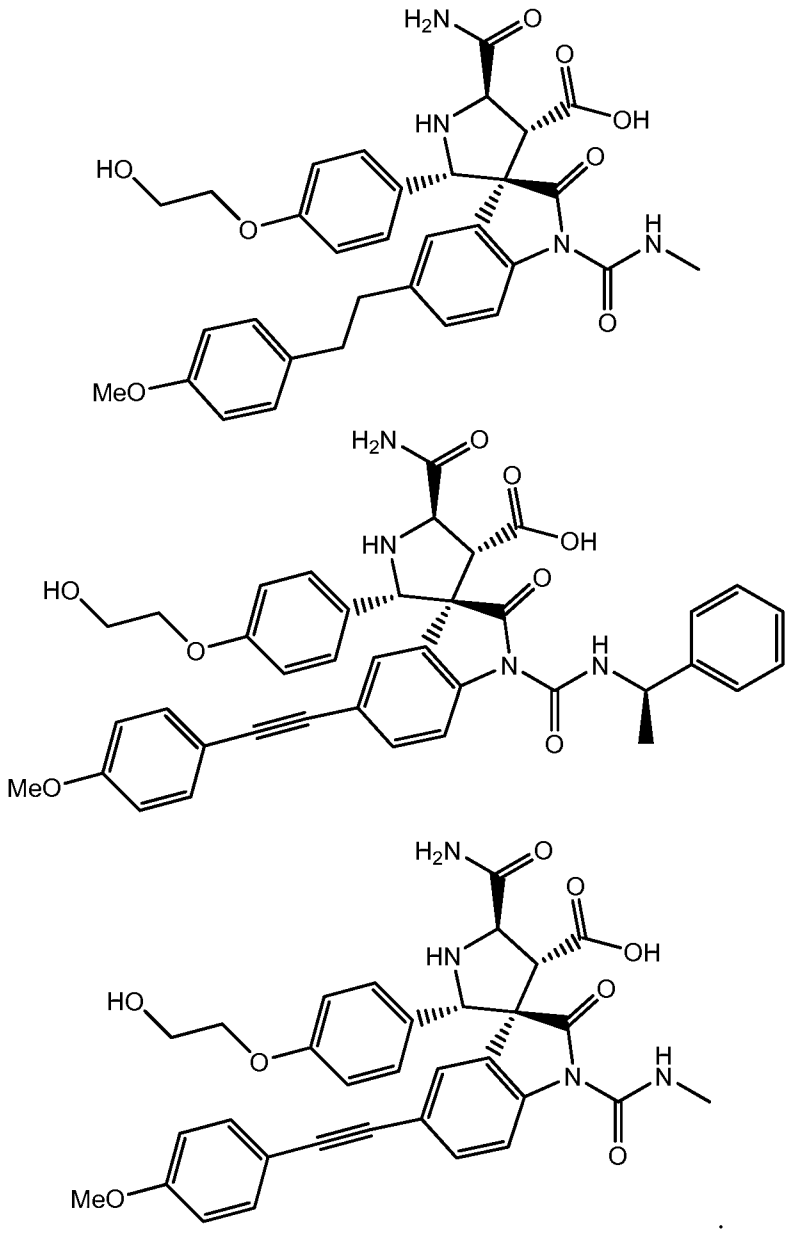






89. The compound of claim 1 of one of the formula:





90. A method of treating a proliferative disease, the method comprising steps of: administering a therapeutically effective amount of a compound of any one of claims 1-89 to a subject.

91. The method of claim 90, wherein the proliferative disease is cancer.

92. The method of claim 91, wherein the cancer is selected from the group consisting of

breast cancer, colon cancer, cervical cancer, and pancreatic cancer.

93. A pharmaceutical composition comprising a compound of any one of claims 1-89; and a pharmaceutically acceptable excipient.

94. The pharmaceutical composition of claim 93, wherein the compositions comprises a therapeutically effective amount of a compound of any one of claims 1-89.

95. A method of inhibiting Aurora A kinase, the method comprising steps of:
contacting an effective amount of a compound of any one of claims 1-89 with Aurora A kinase.

96. A method of imaging Aurora A kinase in a cell, the method comprising steps of:
contacting a compound of any one of claims 83-87 to at least one cell; and
imaging the cell.

97. The method of claim 96, wherein the cell is derived from a biopsy.

98. The method of claim 96, wherein the cell is derived from a Pap smear.

99. The method of claim 96, wherein the cell is part of a biological sample.

100. The method of claim 96, whereby the method is useful for the detection of malignant cells.

101. The method of claim 96, wherein the compound is a compound of any one of claims 83-87.

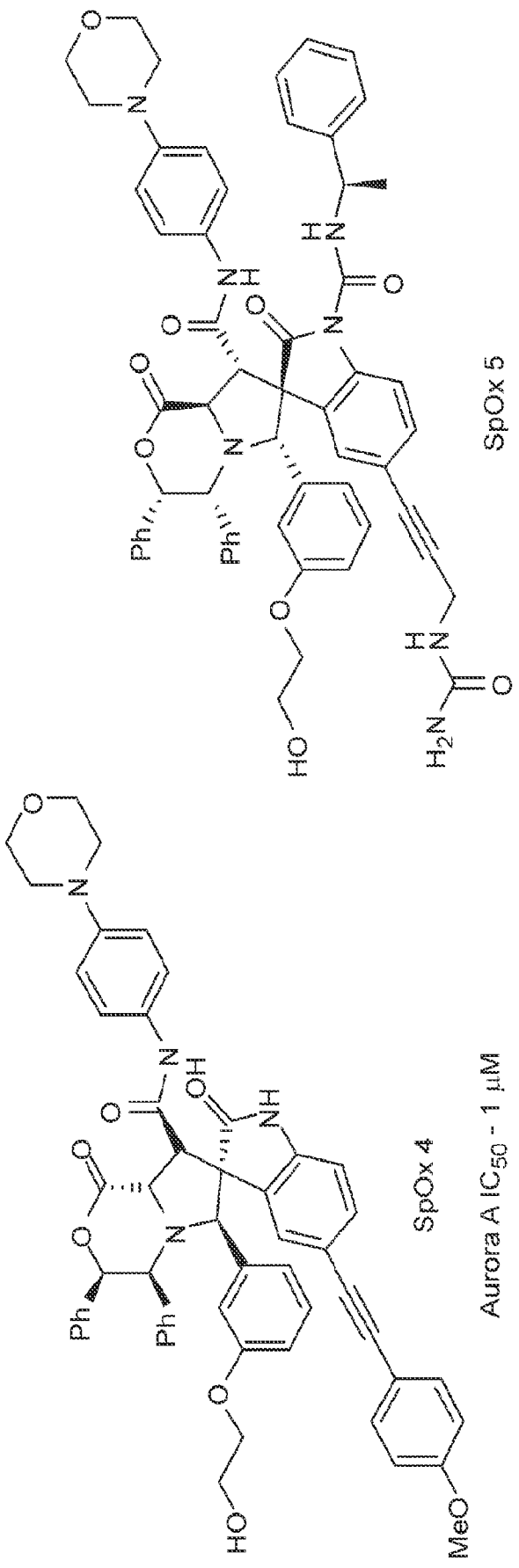

SpOx 5
Aurora A IC50 - 1 μM
Aurora B IC50 - 10 μM
Aurora C IC50 - 9 μM
SpOx 4
Aurora A IC50 - 1 μM
Aurora B IC50 - 10 μM
Aurora C IC50 - 9 μM

FIG. 1

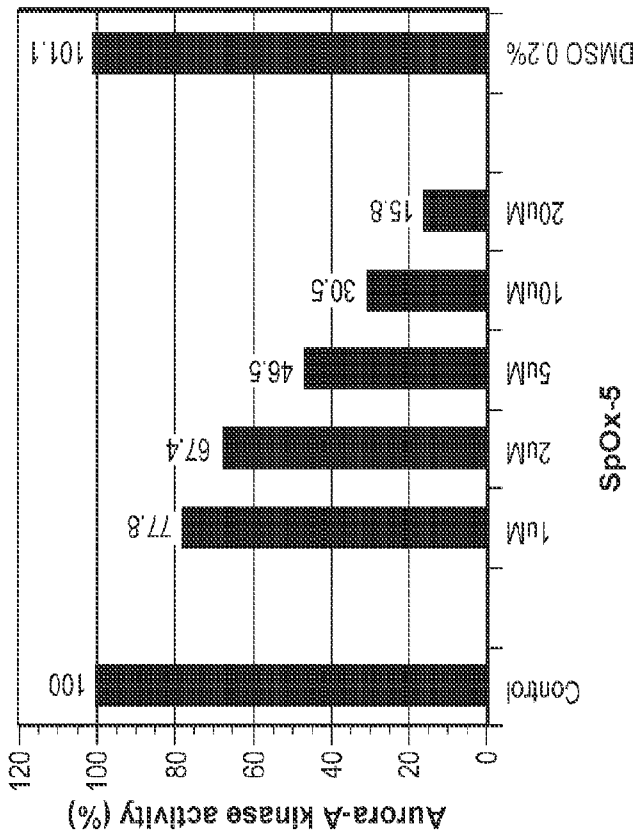

Aurora-A kinase activity (%)
0
20
40
60
80
100
120
Control
100
1uM
77.8
2uM
67.4
5uM
46.5
10uM
30.5
20uM
15.8
DMSO 0.2%
101.1
SpOx-5

FIG. 2B

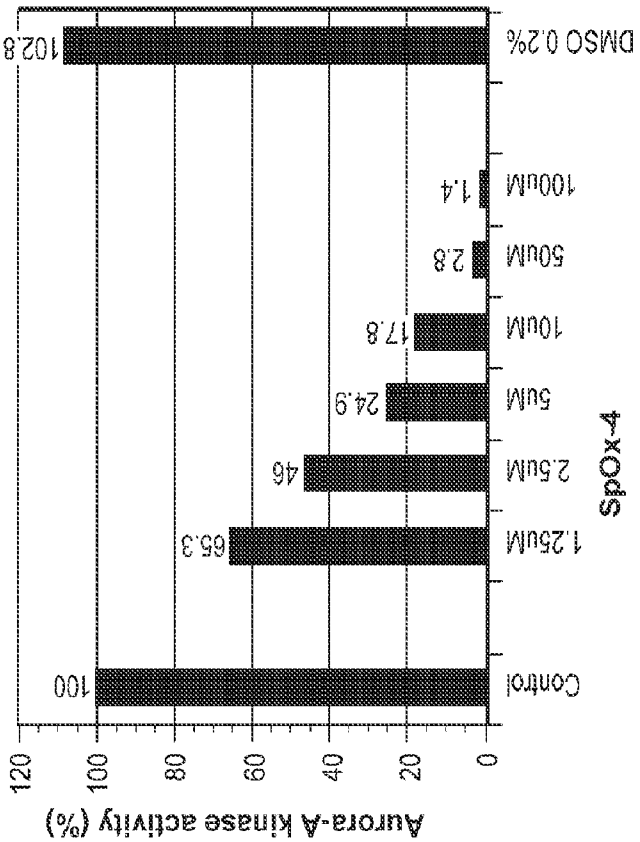

Aurora-A kinase activity (%)
0
20
40
60
80
100
120
Control
100
1.25uM
65.3
2.5uM
46
5uM
24.9
10uM
17.8
50uM
2.8
100uM
1.4
DMSO 0.2%
102.8
SpOx-4

FIG. 2A

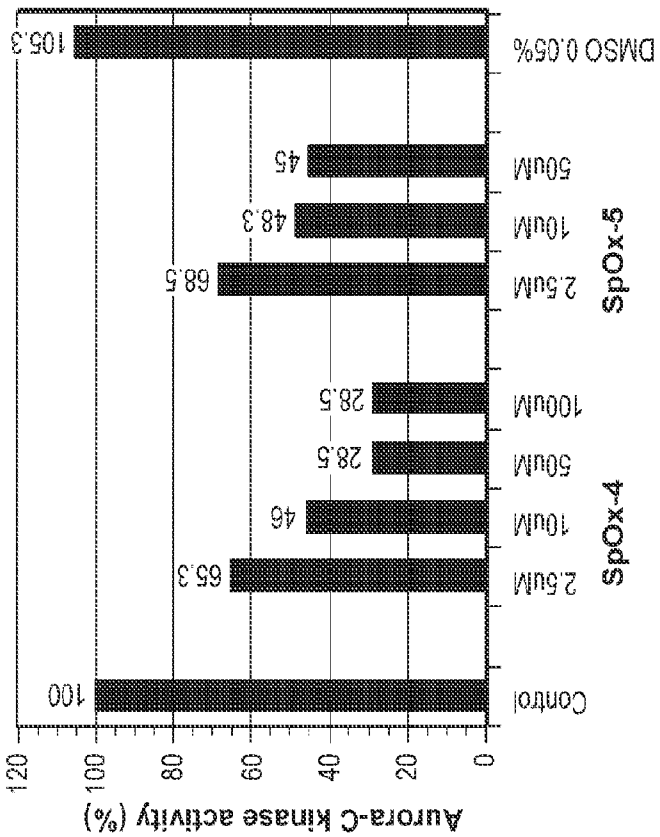

Aurora-C kinase activity (%)
0
20
40
60
80
100
120
Control
100
SpOx-4
2.5uM
65.3
10uM
46
50uM
28.5
100uM
28.5
SpOx-5
2.5uM
68.5
10uM
48.3
50uM
45
DMSO 0.05%
105.3

FIG. 2D

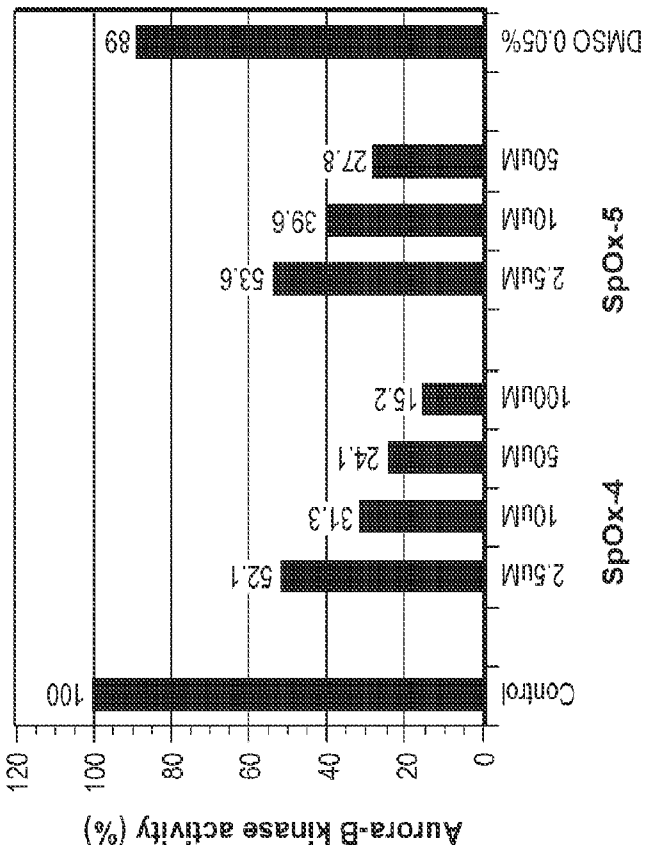

Aurora-B kinase activity (%)
0
20
40
60
80
100
120
Control
100
SpOx-4
2.5uM
52.1
10uM
31.3
50uM
24.1
100uM
15.2
SpOx-5
2.5uM
53.6
10uM
39.6
50uM
27.8
DMSO 0.05%
89

FIG. 2C

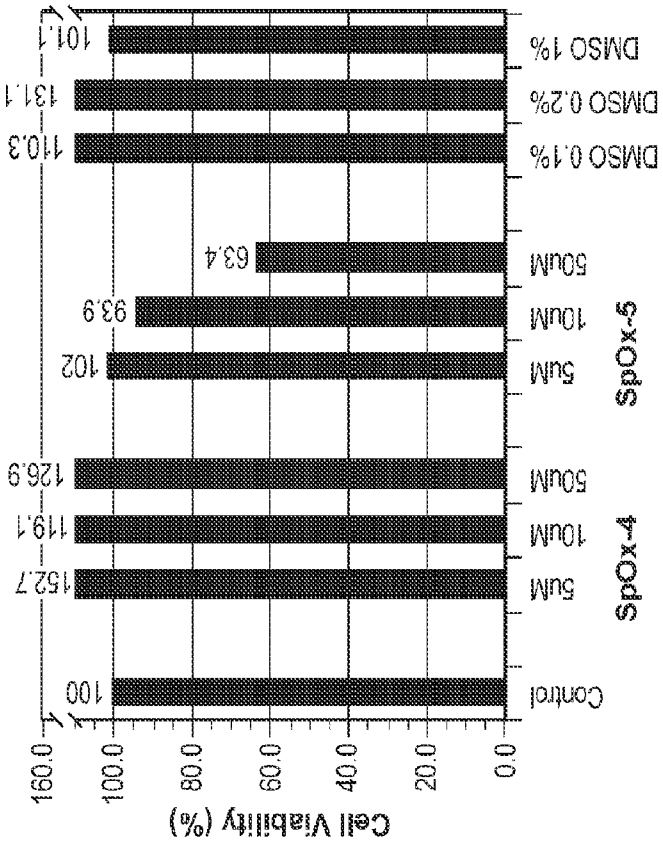

Cell Viability (%)
160.0
100.0
80.0
60.0
40.0
20.0
0.0
Control
100
SpOx-4
5uM
152.7
10uM
119.1
50uM
126.9
SpOx-5
5uM
102
10uM
93.9
50uM
63.4
DMSO 0.1%
110.3
DMSO 0.2%
131.1
DMSO 1%
101.1
COLO-205, 48 hs

FIG. 3A

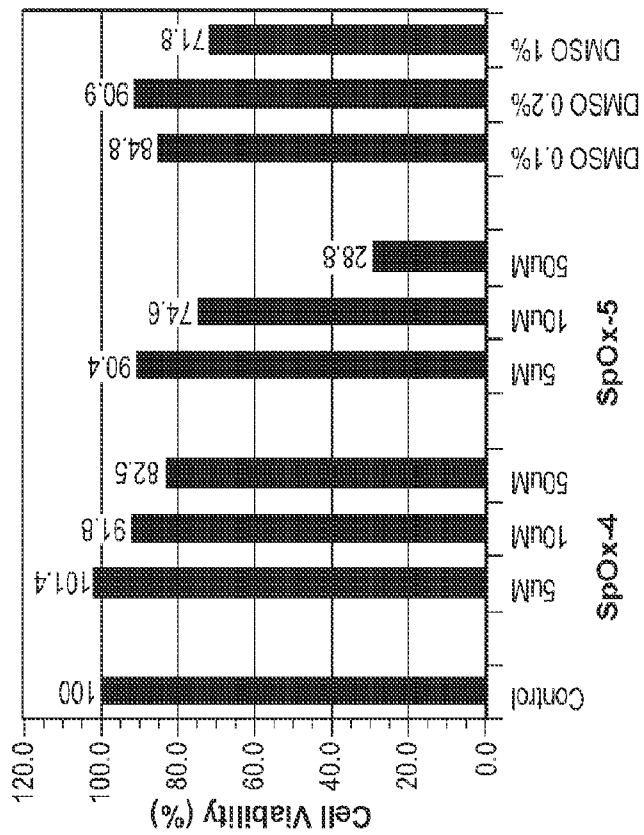

Cell Viability (%)
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Control
100
SpOx-4
5uM
101.4
10uM
91.8
50uM
82.5
SpOx-5
5uM
90.4
10uM
74.6
50uM
28.8
DMSO 0.1%
84.8
DMSO 0.2%
90.9
DMSO 1%
71.8
COLO-205, 72 hs

FIG. 3B

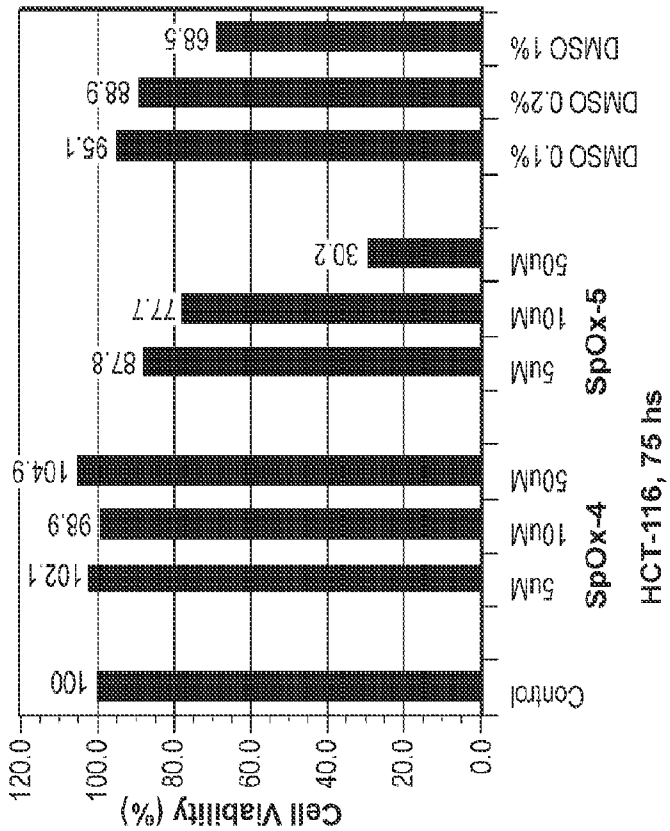

Cell Viability (%)
120.0
100.0
80.0
60.0
40.0
20.0
0.0
100
102.1
98.9
104.9
87.8
77.7
30.2
95.1
88.9
68.5
Control
5uM
10uM
50uM
SpOx-4
5uM
10uM
50uM
SpOx-5
DMSO 0.1%
DMSO 0.2%
DMSO 1%
HCT-116, 75 hs

FIG. 3D

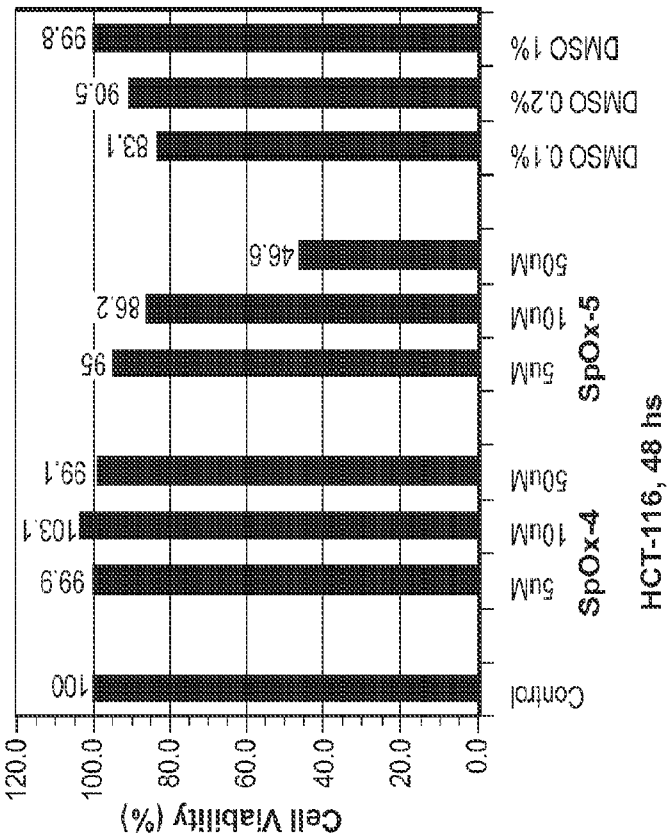

Cell Viability (%)
120.0
100.0
80.0
60.0
40.0
20.0
0.0
100
99.9
103.1
99.1
95
86.2
46.6
83.1
90.5
99.8
Control
5uM
10uM
50uM
SpOx-4
5uM
10uM
50uM
SpOx-5
DMSO 0.1%
DMSO 0.2%
DMSO 1%
HCT-116, 48 hs

FIG. 3C

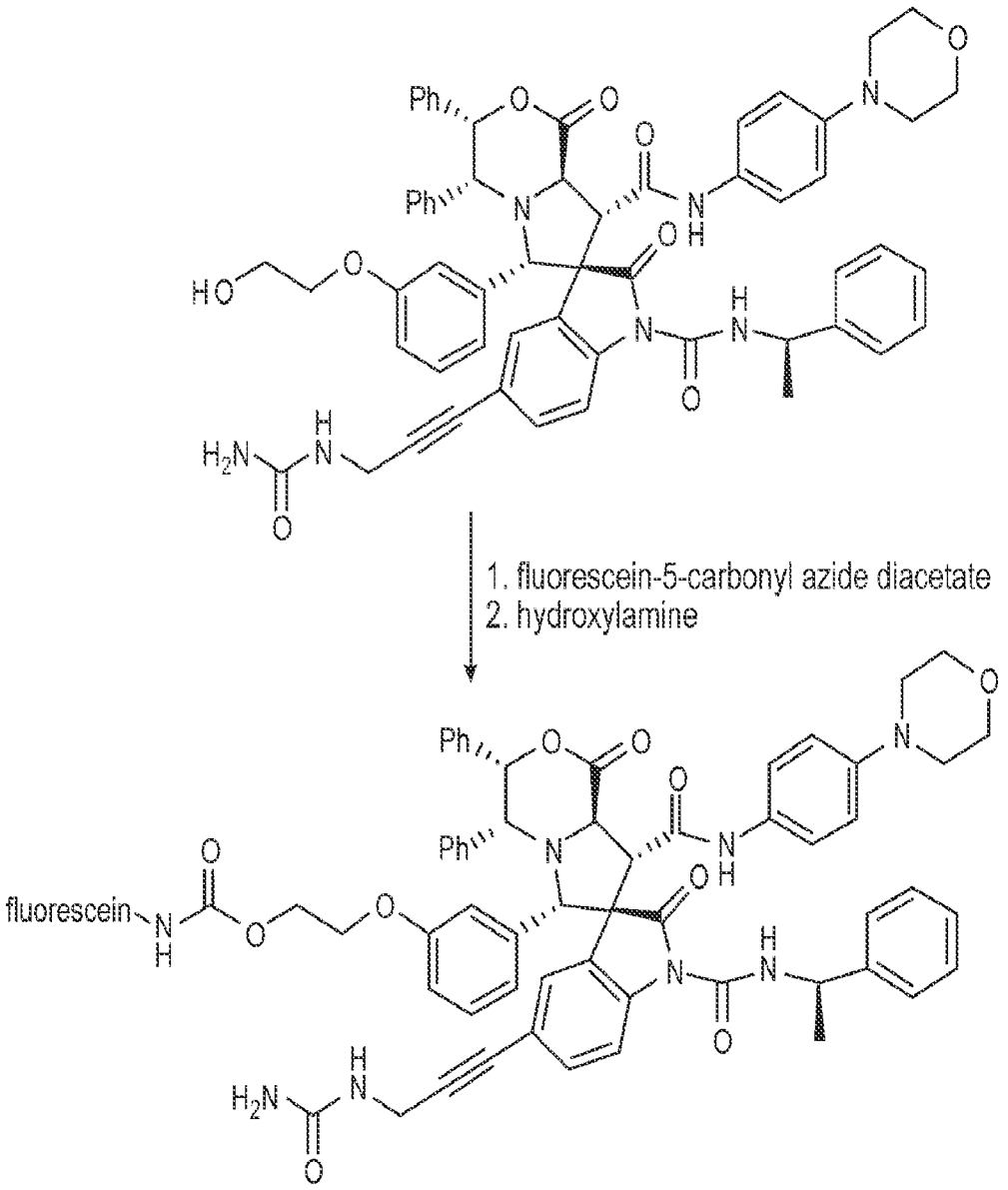

1. fluorescein-5-carbonyl azide diacetate
2. hydroxylamine
fluorescein

FIG. 4

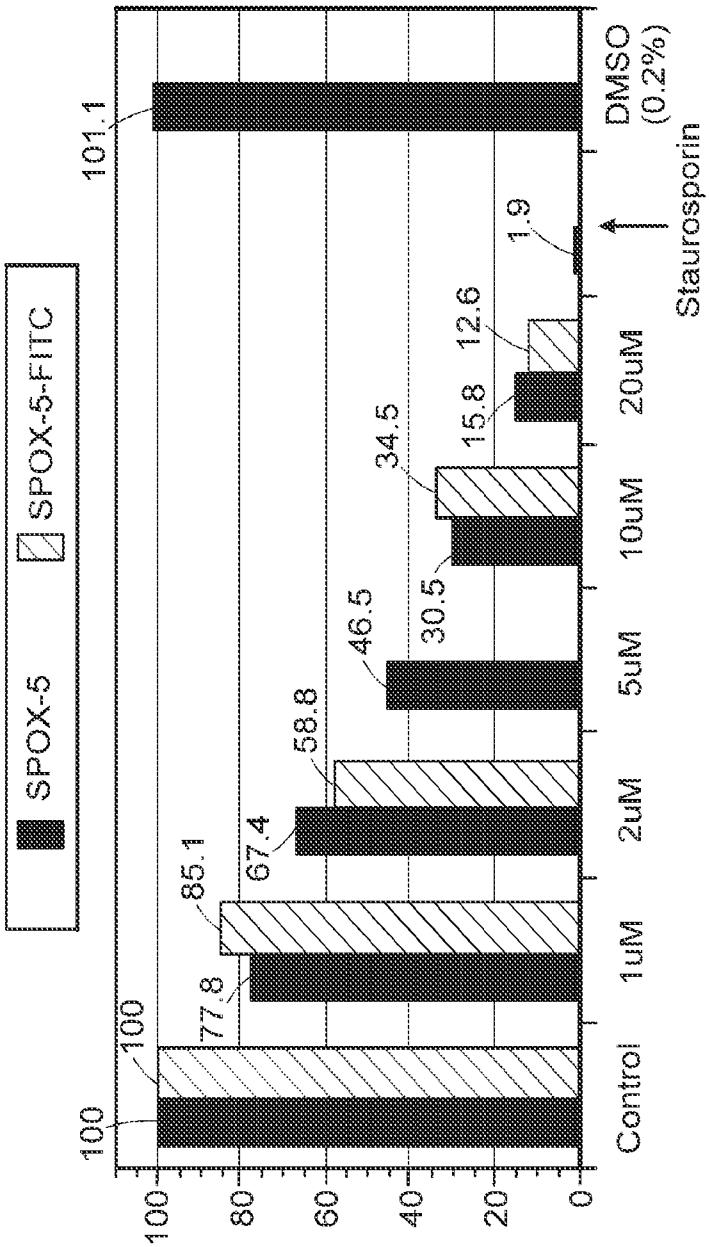

SPOX-5
SPOX-5-FITC
100
80
60
40
20
0
100
100
77.8
85.1
67.4
58.8
46.5
30.5
34.5
15.8
12.6
1.9
101.1
Control
1uM
2uM
5uM
10uM
20uM
Staurosporin
DMSO (0.2%)

FIG. 5

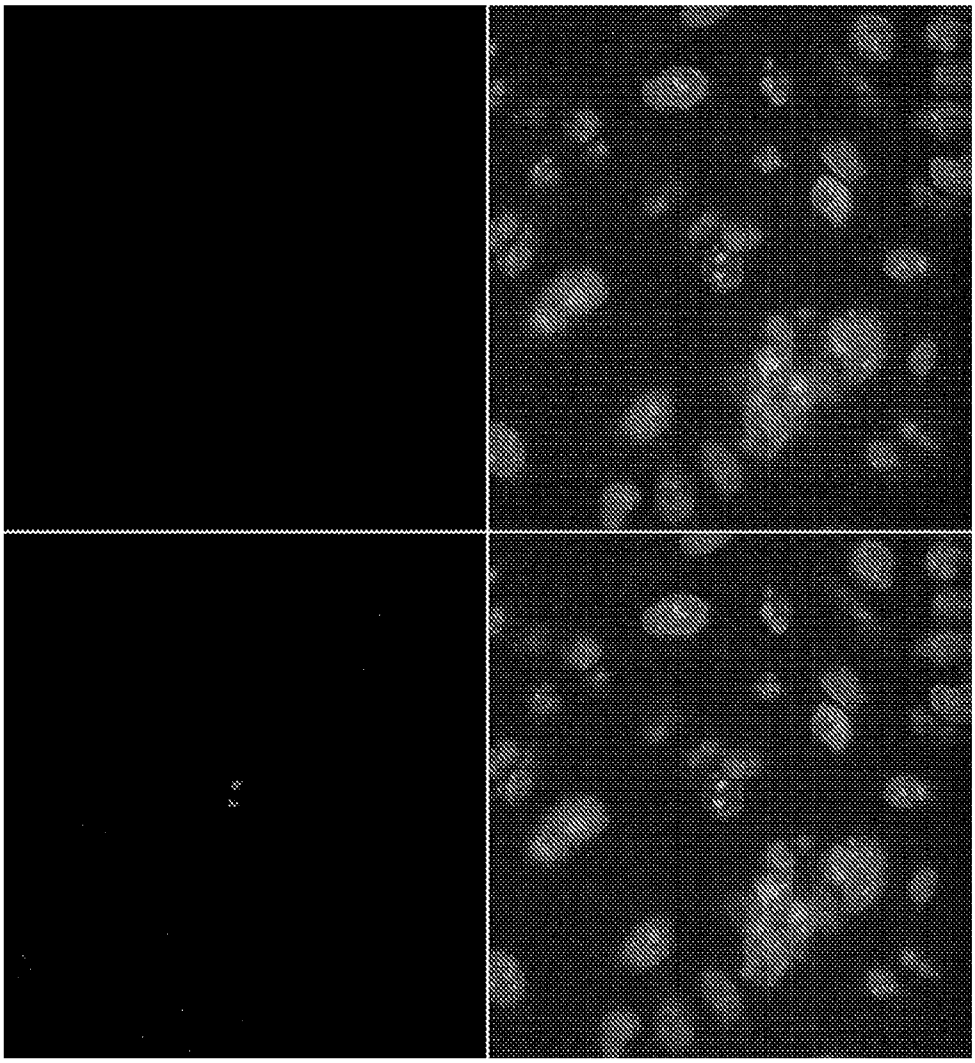


FIG. 6

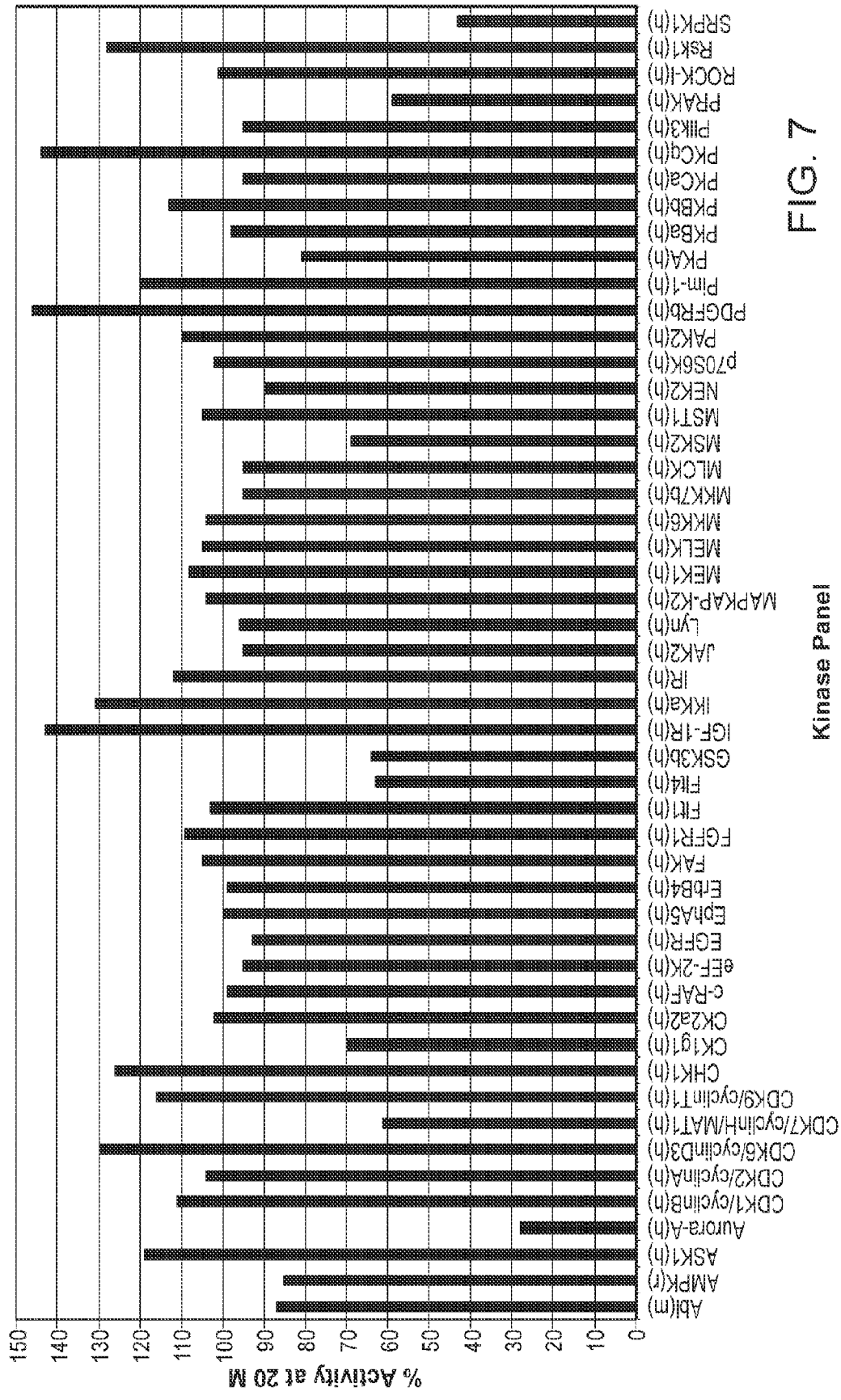

% Activity at 20 M
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Abl(m)
AMPK(r)
ASK1(h)
Aurora-A(h)
CDK1/cyclinB(h)
CDK2/cyclinA(h)
CDK6/cyclinD3(h)
CDK7/cyclinH/MAT1(h)
CDK9/cyclinT1(h)
CHK1(h)
CK1g1(h)
CK2a2(h)
c-RAF(h)
eEF-2K(h)
EGFR(h)
EphA5(h)
ErbB4(h)
FAK(h)
FGFR1(h)
Flt1(h)
Flt4(h)
GSK3b(h)
IGF-1R(h)
IKKa(h)
IR(h)
JAK2(h)
Lyn(h)
MAPKAP-K2(h)
MEK1(h)
MELK(h)
MKK6(h)
MKK7b(h)
MLCK(h)
MSK2(h)
MST1(h)
NEK2(h)
p70S6K(h)
PAK2(h)
PDGFRb(h)
Plm-1(h)
PKA(h)
PKBa(h)
PKBb(h)
PKCa(h)
PKCq(h)
Plik3(h)
PRAK(h)
ROCK-I(h)
Rsk1(h)
SRPK1(h)
Kinase Panel

FIG. 7

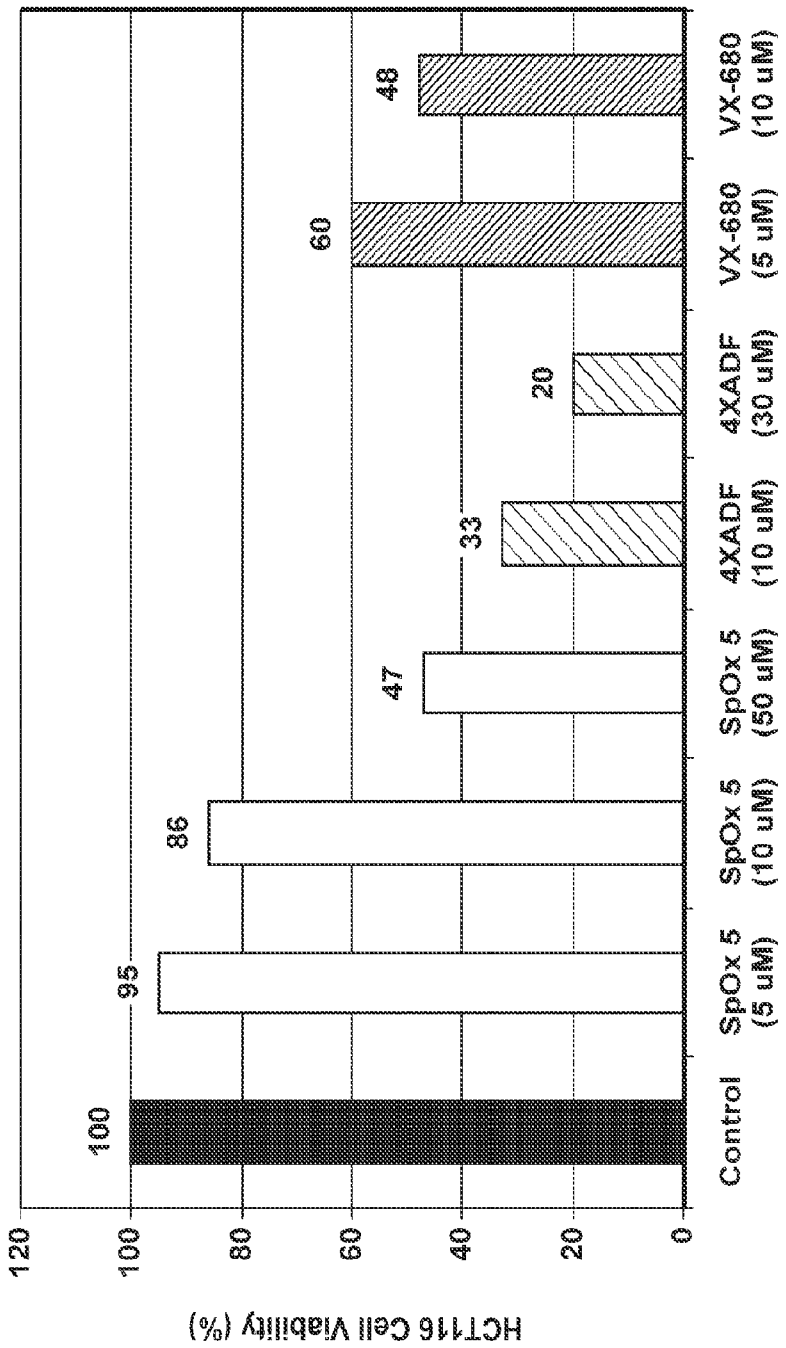
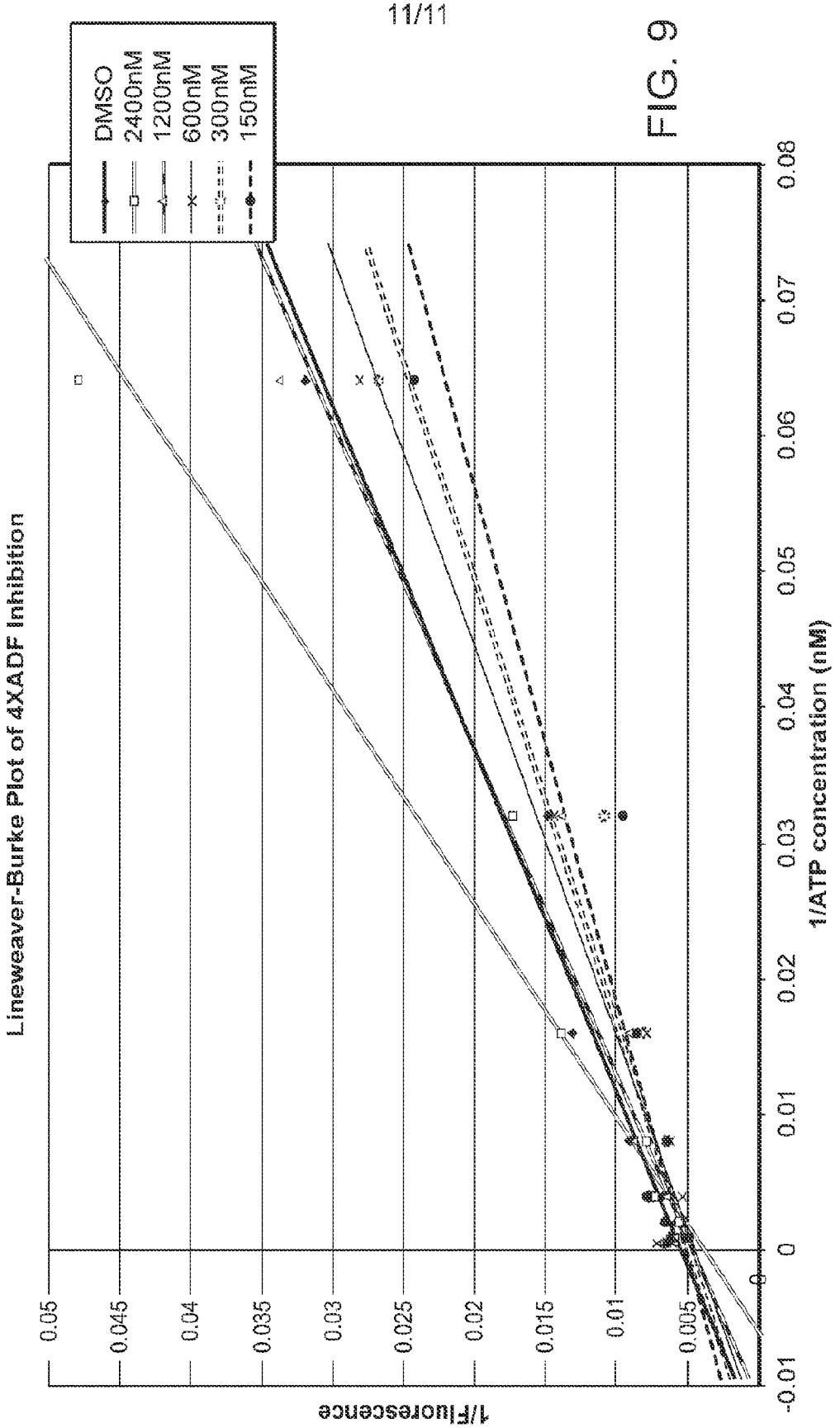

HCT116 Cell Viability (%)
120
100
80
60
40
20
0
100
95
86
47
33
60
20
48
Control
SpOx 5 (5 uM)
SpOx 5 (10 uM)
SpOx 5 (50 uM)
4XADF (10 uM)
4XADF (30 uM)
VX-680 (5 uM)
VX-680 (10 uM)

FIG. 8

FIG. 9


Lineweaver-Burke Plot of 4XADF Inhibition
DMSO
2400nM
1200nM
600nM
300nM
150nM
1/Fluorescence
1/ATP concentration (nM)
0.05
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
-0.01
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08