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(54) Title: TETRACYCLINE COMPOUNDS AND METHODS OF TREATMENT

(57) Abstract: The present invention is directed to methods of treating hematological cancers, such as acute myleiod leukemia, with tetracyclines, or a pharmaceutically acceptable salt thereof.

TETRACYCLINE COMPOUNDS AND METHODS OF TREATMENT

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/381,383, filed on August 30, 2016 and 62/437,533, filed on December 21, 2016. The entire teachings of the above application(s) are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Hematological malignancies are cancers that affect the blood and lymph system. Some types of hematologic malignancies include: Multiple myeloma, Hodgkin lymphoma, Non-Hodgkin lymphoma and Leukemia. The cancer may begin in blood-forming tissue (e.g., bone marrow), or in the cells of the immune system. For example, leukemia originates in blood-forming tissue. Leukemia is characterized by the uncontrolled growth of blood cells, usually white blood cells (leukocytes), in the bone marrow. White blood cells are a fundamental component of the body's immune response. The leukemia cells crowd out and replace normal blood and marrow cells.

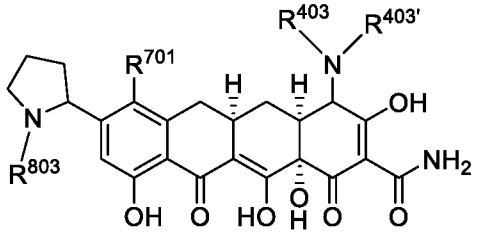
There are four main types of leukemia: Acute myeloid leukemia (AML); Chronic myeloid leukemia (CML); Acute lymphocytic leukemia (ALL); and Chronic lymphocytic leukemia (CLL). The primary differences between the four main types of leukemia have to do with their rates of progression and where the cancer develops. Acute myeloid leukemia (AML), also known as acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia or acute nonlymphocytic leukemia, is a fast-growing form of cancer of the blood and bone marrow. AML is the most common type of acute leukemia. It occurs when the bone marrow begins to make blasts, cells that have not yet completely matured. These blasts normally develop into white blood cells. However, in AML, these cells do not develop and are unable to ward off infections. In AML, the bone marrow may also make abnormal red blood cells and platelets. The number of these abnormal cells increases rapidly, and the abnormal (leukemia) cells begin to crowd out the normal white blood cells, red blood cells and platelets that the body needs.

The standard treatment for AML includes remission-induction treatment consisting of administration of the chemotherapeutic agents cytarabine and daunorubicin (7+3). This treatment has been the standard of care for decades. Few other therapeutic approaches for

malignant disease have remained so unchanged for such a long period. In addition, the co-morbidities and high susceptibility to treatment-related toxicity still limit treatment success. Despite advances in treatment strategies for hematological cancer there remains a need to identify novel, potent and/or well-tolerated tetracyclines, particularly for the treatment of leukemias, such as AML, to be used either as a single agent or in combination with other anti-neoplastic agents.

SUMMARY OF THE INVENTION

In a first aspect of the invention, there is provided a method of treating an Acute Myeloid Leukemia (AML), said method comprising administering to a subject in need of treatment an effective amount of a compound having Structural Formula (XX):



(XX)

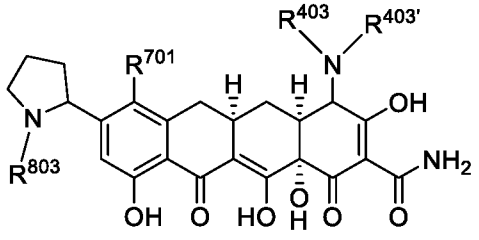
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof, wherein:

R^{803} is H, a C_{1-6} alkyl, a C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, a C_{3-12} carbocyclyl-(C_{0-3})alkylenyl, an amino-(C_1-C_4) alkyl, a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl, or a (4-13 member)heterocyclyl-(C_0-C_3)alkylenyl, wherein the heterocyclyl portion is optionally substituted with a C_{1-3} alkyl;

R^{701} is H, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl, C_{1-4} haloalkoxy; and

R^{403} and $R^{403'}$, each independently, is H; a C_{1-4} alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl-, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; or a $H_2NC(O)$-(C_1-C_3)alkylenyl-.

In a second aspect of the invention, there is provided use of a compound having Structural Formula (XX):



(XX)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof, wherein:

R^{803} is H, a C_{1-6} alkyl, a C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, a C_{3-12} carbocyclyl-(C_{0-3})alkylenyl, an amino-(C_1-C_4) alkyl, a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl, or a (4-13 member)heterocyclyl-(C_0-C_3)alkylenyl, wherein the heterocyclyl portion is optionally substituted with a C_{1-3} alkyl;

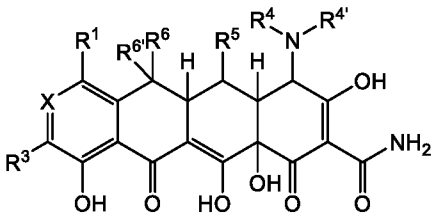
R^{701} is H, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl, C_{1-4} haloalkoxy; and

R^{403} and $R^{403'}$, each independently, is H; a C_{1-4} alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl-, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; or a $H_2NC(O)$-(C_1-C_3)alkylenyl-,

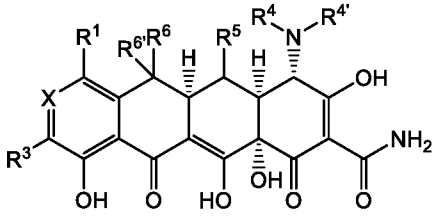
in the manufacture of a medicament for treating an Acute Myeloid Leukemia (AML).

A first embodiment of the present invention is directed to a method of treating a hematological cancer in a subject in need thereof comprising administering to the subject an effective amount of a compound represented by:

Structural Formula (I) or (I'):

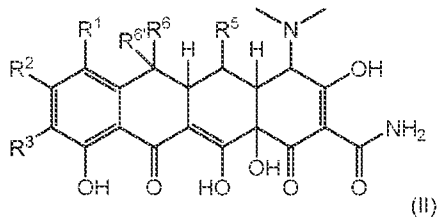


(I)

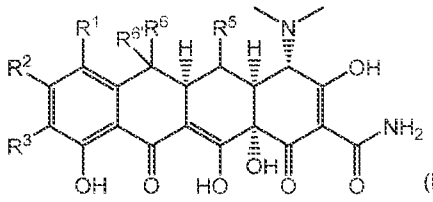


(I'),

Structural Formula (II) or (II'):

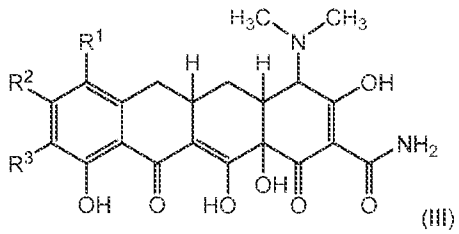


(II)

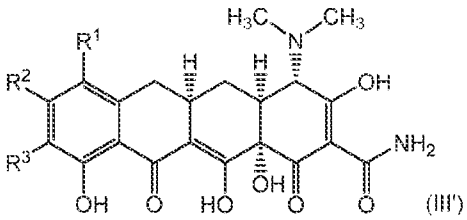


(II') or

Structural Formula (III) or (III'):



(III)



(III')

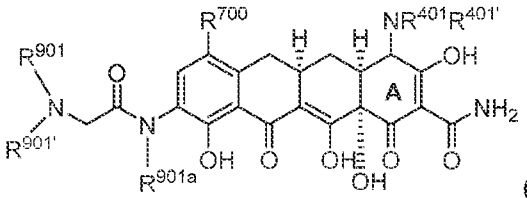
or a pharmaceutically acceptable salt thereof, wherein the variables are as defined and described herein.

Another embodiment of the present invention is the use of a compound represented by Structural Formula (I), (I'), (II), (II'), (III) or (III') or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a hematological cancer. In one aspect the hematogical malignancy is leukemia. In a specific aspect, the leukemia is AML.

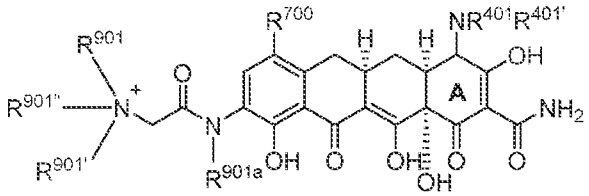
Another embodiment of the present invention is a compound represented by Structural Formula (I), (I'), (II), (II'), (III) or (III'), or a pharmaceutically acceptable salt

thereof, four use in treating hematological cancers. In one aspect the hematogical malignancy is leukemia. In a specific aspect, the leukemia is AML.

Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by any one of structural formulas (X) or (X-1)



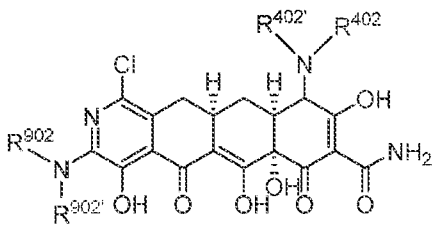
(X),



(X-1),

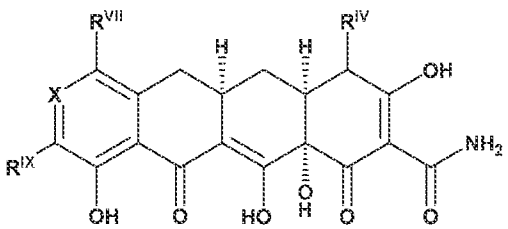
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by any one of structural formulas (XI), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof,



(XI).

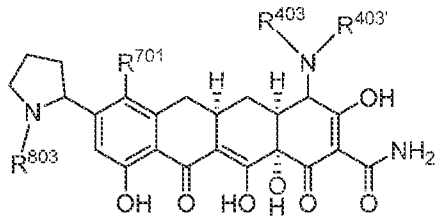
Another embodiment of the present invention is a compound represented by structural formula (XII), or a pharmaceutically acceptable salt thereof:



(XII).

Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by structural formula (XII), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

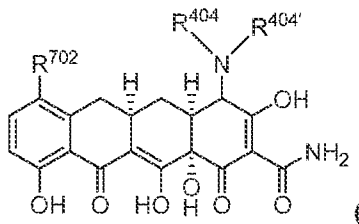
Another embodiment of the present invention is a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula



(XX)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

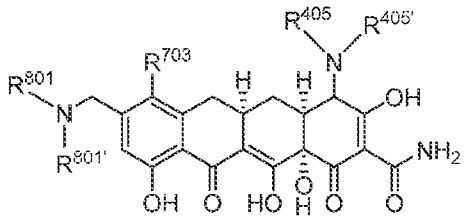
Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula:



(XXI)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

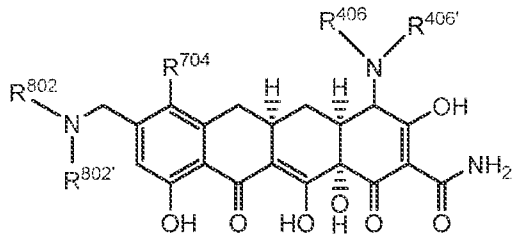
Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by any one of structural formulas



(XXII)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

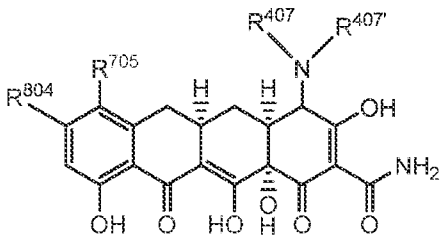
Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula



(XXIII)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

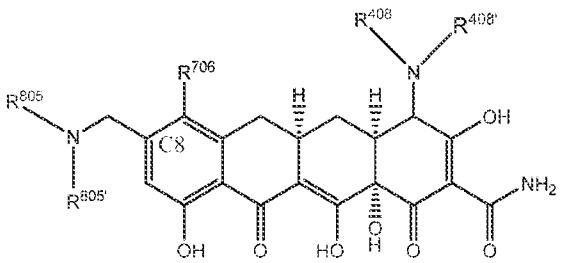
Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula



(XXIV)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

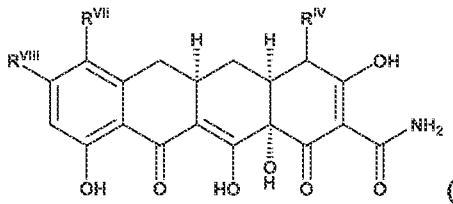
Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula



(XXV),

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

Another embodiment of the present invention is any compound represented by structural formula (XIII):

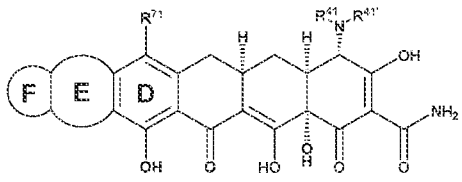


(XIII),

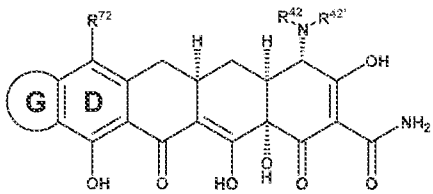
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

Another embodiment of the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by structuiral formula (XIII), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

Another embodiment of the present invention is a compound represented by any one of structural formulas (XIV) or (XV):



(XIV),



(XV),

or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of any of the foregoing embodiments.

Another embodiment of the present invention is a method of treating a subject suffering from a hematological tumor, comprising administering to the subject a

therapeutically effective amount of any compound of a pharmaceutical composition of the foregoing embodiments.

Another embodiment of the present invention is a method for treating a bacterial infection in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound represented by any one of structural formulas XIV or XV or a compound of Formuls XIII or XII.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a Western Blot that shows levels of COX1, COX4 and actin in MV4-11 cells treated with Compound 1 as described in Example 2.

FIG. 2 depicts a Western Blot that shows levels of COX1, COX4 and actin in MV4-11 cells treated with Compound 2 as described in Example 2.

FIG. 3 depicts a Western Blot that shows levels of COX1, COX4 and actin in MV4-11 cells treated with Compound 3a as described in Example 2.

FIG. 4 depicts a Western Blot that shows levels of COX1, COX4 and actin in MV4-11 cells treated with Compound 4a as described in Example 2.

FIG. 5 depicts a Western Blot that shows levels of COX1, COX4 and actin in MV4-11 cells treated with Compound 5 as described in Example 2.

FIG. 6 is a graph showing the dose-response fitting functions for cytarabine (top panel) and Compound 3a (bottom panel). The X-axis is the concentration of compound tested and the Y-axis is the Normalized effect-Survival % (count/E0). Normalization was done after modeling regarding the estimated basal (E0) parameter.

FIG. 7A is a graph of Tumor Volume vs. Days After Start of Treatment (Compound 3a at dose 1 and dose 2 of Table 1C) of CB17 SCID mice testing in the xenograft model using MV4-11 leukemia model.

FIG. 7B is a graph of Body Weight Change (%) vs. Days After Start of Treatment (Compound 3a at does 1 and dose 2 of Table 1C) of CB17 SCID mice testing in the xenograft model using MV4-11 leukemia model.

FIG. 7C is a graph of Tumor Volume vs. Days After Start of Treatment (Compound 4a at dose 1 and dose 2 of Table 1C) of CB17 SCID mice testing in the xenograft model using MV4-11 leukemia model.

FIG. 7D is a graph of Body Weight Change (%) vs. Days After Start of Treatment (Compound 4a at does 1 and dose 2 of Table 1C) of CB17 SCID mice testing in the xenograft model using MV4-11 leukemia model.

FIG. 7E is a graph of Tumor Volume vs. Days After Start of Treatment (Compound 5 at dose 1 and dose 2 of Table 1C) of CB17 SCID mice testing in the xenograft model using MV4-11 leukemia model.

FIG. 7F is a graph of Body Weight Change (%) vs. Days After Start of Treatment (Compound 5 at does 1 and dose 2 of Table 1C) of CB17 SCID mice testing in the xenograft model using MV4-11 leukemia model.

FIG. 8 shows the dose-response results for Compound 3a in the Rat Heart Mitochondrial Translation Assay.

FIG. 9 shows the results for MV411 MT-COX1 (Cytochrome oxidase subunit 1, expressed in mitochrondria) expression. The X-axis (drug concentration) shows results from left to right on the page as follows: Compound 3a, Tigecycline and Cytarabine.

FIG. 10 shows the results for MV411 COX-IV expression (Cytochrome oxidase subunit 4, expressed in nucleus). The X-axis (drug concentration) shows results from left to right on the page as follows: Compound 3a, Tigecycline and Cytarabine.

FIG. 11 shows the results for MV411 PIG3 expression ($TP_{53}I_3$-a p53 responsive protein, expression induced in response to p53 activation, role associated with response to oxidative stress). The X-axis (drug concentration) shows results from left to right on the page as follows: Compound 3a, Tigecycline and Cytarabine.

FIG. 12 shows the results for MV411 BAX expression (pro-apoptotic protein expression induce by p53 activation, forms a heterodimer with BCL2 to induce apoptosis). The X-axis (drug concentration) shows results from left to right on the page as follows: Compound 3a, Tigecycline and Cytarabine.

FIG. 13 shows the results of CDKN2A expression (also known as $p14^{ARF}$ or ARF –nuclear gene, translation regulated by cMyc, functions to stabilize/activate p53 by binding and sequestering Mdm2). The X-axis (drug concentration) shows

results from left to right on the page as follows: Compound 3a, Tigecycline and Cytarabine.

FIG. 14A through **FIG. 14E**, collectively, represent a table of Minimal Inhibitory Concentrations (MIC) values, in μg/mL, of the example compounds disclosed in the preset application.

FIG. 15A through **FIG. 15M**, collectively, represent a table of "Inhibitory Concentrations 50%" (IC_{50}) values of example compounds disclosed in the present application measured against the indicated hematological cancer cell lines.

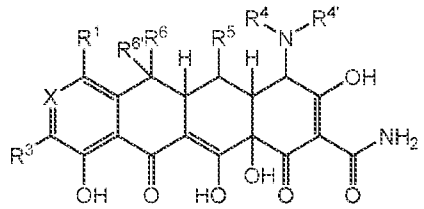
FIG. 16A through **FIG. 16F**, collectively, represent a table of "Inhibitory Concentrations 50%" (IC_{50}) values of example compounds disclosed in the present application measured against the indicated hematological cancer cell lines.

FIG. 17A through **FIG. 17D**, collectively, represent a table of "Inhibitory Concentrations 50%" (IC_{50}) values of example compounds disclosed in the present application measured against the indicated hematological cancer cell lines.

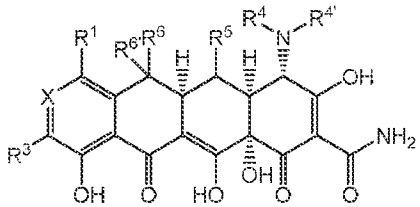
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of treating a hematological cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of a compound represented by any one of Structural Formulas (I), (I'), (II), (II'), (III) or (III') or a pharmaceutically acceptable salt thereof. The variables in Structural Formulas (I), (I'), (II), (II'), (III) or (III') are described herein in the following paragraphs. It is understood that the invention encompasses all combinations of the substituent variables (i.e., R^1, R^2, R^3, etc.) defined herein.

In a first embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound having Structural Formula (I) or (I'):



(I)



(I'),

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from N and C(R^2);

each of R^1, R^2, R^3, R^5 and R^6 is independently selected from hydrogen, halo, -(C_1-C_6 alkyl), -OR^A, -C(O)$NR^BR^{B'}$, -$NR^BR^{B'}$, -$S(O)_{0-2}R^C$, -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl; or

R^1 and R^2 are optionally taken together with atoms to which they are bound to form a carbocyclyl or heterocyclyl ring; or

R^2 and R^3 are optionally taken together with atoms to which they are bound to form a carbocyclyl or heterocyclyl ring;

R^4 is selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl;

$R^{4'}$ is selected from hydrogen, -(C_1-C_6 alkyl), $S(O)_{1-2}R^C$, -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), and -C(O)-(C_1-C_6 alkyl)-NR^DR^E; or

R^4 and $R^{4'}$ are optionally taken together with the nitrogen atom to which they are commonly bound to form a 4-8 membered ring optionally comprising 1-2 additional heteroatoms independently selected from N, O and S;

$R^{6'}$ is selected from hydrogen, -(C_1-C_6 alkyl) and -(C_3-C_6 cycloalkyl);

each R^A is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6

alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, and -C(O)N(R^D)(R^E);

each R^B and each $R^{B'}$ is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -S(O)$_{1-2}$-(C_1-C_6 alkyl), -S(O)$_{1-2}$-(C_0-C_6 alkylene)-carbocyclyl, -S(O)$_{1-2}$-(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, and -C(O)-(C_0-C_6 alkylene)-N(R^D)(R^E);

each R^C is independently selected from -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl and -(C_0-C_6 alkylene)-heterocyclyl; and

each R^D and each R^E is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl,

wherein any alkyl, alkylene, carbocyclyl or heterocyclyl portion of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6, $R^{6'}$, R^A, R^B, $R^{B'}$, R^C, R^D, or R^E or formed by taking R^1 and R^2, R^2 and R^3, or R^4 and $R^{4'}$ together is optionally and independently substituted.

In a first aspect of the first embodiment:

any alkyl, or alkylene portion of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6 is optionally and independently substituted with one or more substituents independently selected from halo, =O, OR^A, $NR^BR^{B'}$, and S(O)$_{0-2}R^C$;

any alkyl or alkylene portion of $R^{6'}$, R^A, or R^C is optionally and independently substituted with one or more fluoro;

any carbocyclyl or heterocyclyl portion of any of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6, or any ring formed by taking together R^1 and R^2, R^2 and R^3 or R^4 and $R^{4'}$ is optionally and independently substituted on a carbon atom with one or more substituents independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and S(O)$_{0-2}R^C$;

any heterocyclyl portion of any of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6, or any ring formed by taking together R^1 and R^2, R^2 and R^3 or R^4 and $R^{4'}$ is optionally and independently substituted on a substitutable nitrogen atom with R^F;

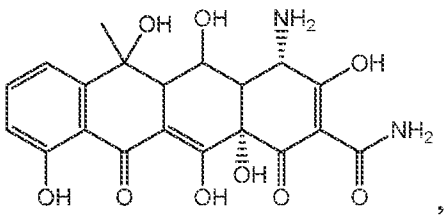
each R^F is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 hydroxyalkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6

alkylene)-heterocyclyl, -S(O)$_{1-2}$-(C$_1$-C$_6$ alkyl), -S(O)$_{1-2}$-(C$_0$-C$_6$ alkylene)-carbocyclyl, -S(O)$_{1-2}$-(C$_0$-C$_6$ alkylene)-heterocyclyl, -C(O)-(C$_1$-C$_6$ alkyl), -C(O)-(C$_0$-C$_6$ alkylene)-carbocyclyl, -C(O)H, -C(O)-(C$_0$-C$_6$ alkylene)-heterocyclyl, -(C$_0$-C$_6$ alkylene)-C(O)$_2$-(C$_1$-C$_6$ alkyl), -(C$_1$-C$_6$ alkylene)-NR^{B}R$^{B'}$ and -C(O)N(R^D)(R^E);

any carbocyclyl or heterocyclyl portion of R^A, R^B, R$^{B'}$, R^C, R^D, R^E, R^F, any cycloalkyl portion of R$^{6'}$, or any substituent of R^1, R^2, R^3, R^4, R$^{4'}$, R^5, R^6 is optionally and independently substituted on a carbon atom with a one or more substituents independently selected from fluoro, chloro, C$_1$-C$_4$ alkyl, C$_1$-C$_4$ fluoroalkyl, -O-C$_1$-C$_4$ alkyl, -O-C$_1$-C$_4$ fluoroalkyl, =O, -OH, -NH$_2$, -NH(C$_1$-C$_4$ alkyl), and -N(C$_1$-C$_4$ alkyl)$_2$;

any heterocyclyl portion of R^A, R^B, R$^{B'}$, R^C, R^D, R^E, R^F, or any heterocyclyl substituent of R^1, R^2, R^3, R^4, R$^{4'}$, R^5, or R^6 is optionally substituted on a substitutable nitrogen atom with -C$_1$-C$_4$ alkyl, or -S(O)$_{1-2}$-(C$_1$-C$_4$ alkyl). The remaining variables are as described and defined in the first embodiment.

In a second aspect of the first embodiment, the compound is other than: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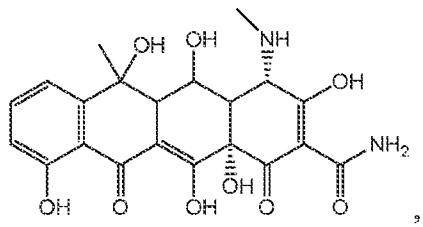
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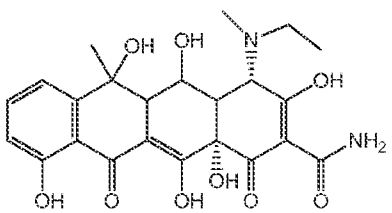
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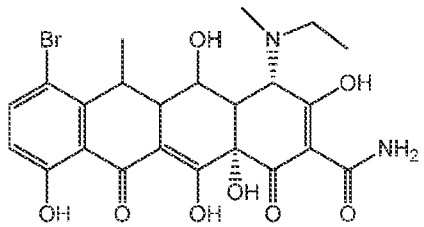
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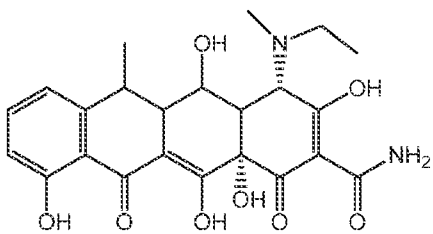
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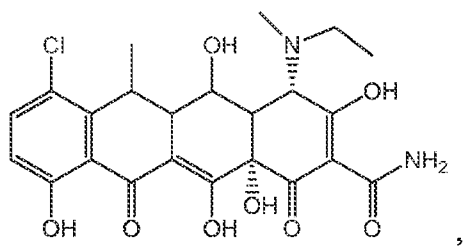
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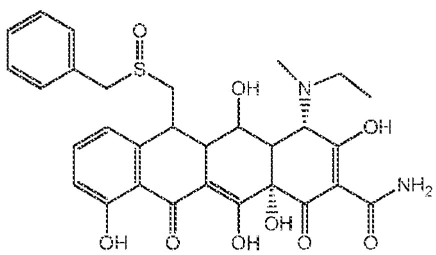

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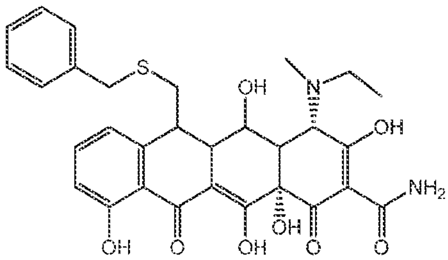

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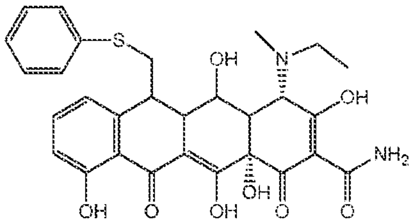

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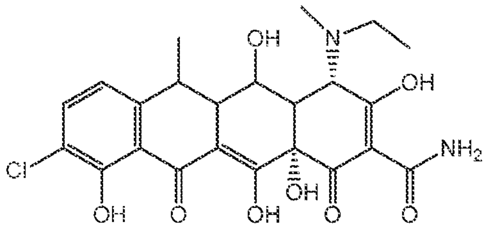


, or a salt of any of the foregoing. The remaining variables are as described and defined in the first embodiment, or first aspect thereof.

In a third aspect of the first embodiment, each of R^5, R^6 and $R^{6'}$ is hydrogen. The remaining variables are as described and defined in the first embodiment, or the first or second aspect thereof.

In a fourth aspect of the first embodiment, X is $C(R^2)$. The remaining variables are as described and defined in the first embodiment, or the first, second or third aspect thereof.

In a fifth aspect of the first embodiment:

X is selected from N and $C(R^2)$;

each of R^1, R^2, R^3, R^5 and R^6 is independently selected from hydrogen, halo, -(C_1-C_6 alkyl), -OR^A, $NR^BR^{B'}$, -C(O)$NR^BR^{B'}$, $S(O)_{0\text{-}2}R^C$, -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl; or

R^1 and R^2 are optionally taken together with atoms to which they are bound to form a carbocyclyl or heterocyclyl ring; or

R^2 and R^3 are optionally taken together with atoms to which they are bound to form a carbocyclyl or heterocyclyl ring;

R^4 is selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl;

$R^{4'}$ is selected from hydrogen, -(C_2-C_6 alkyl), $S(O)_{1\text{-}2}R^C$, -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), and -C(O)-(C_1-C_6 alkyl)-NR^DR^E; or

R^4 and $R^{4'}$ are optionally taken together with the nitrogen atom to which they are commonly bound to form a 4-8 membered ring optionally comprising 1-2 additional heteroatoms independently selected from N, O and S;

$R^{6'}$ is selected from hydrogen, -(C_1-C_6 alkyl) and -(C_3-C_6 cycloalkyl);

each R^A is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, and -C(O)N(R^D)(R^E);

each R^B and each $R^{B'}$ is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -S(O)$_{1-2}$-(C_1-C_6 alkyl), -S(O)$_{1-2}$-(C_0-C_6 alkylene)-carbocyclyl, -S(O)$_{1-2}$-(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, and -C(O)N(R^D)(R^E);

each R^C is independently selected from -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl and -(C_0-C_6 alkylene)-heterocyclyl; and

each R^D and each R^E is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl;

wherein any alkyl, alkylene, carbocyclyl or heterocyclyl portion of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6, $R^{6'}$, R^A, R^B, $R^{B'}$, R^C, R^D, or R^E or formed by taking R^1 and R^2, R^2 and R^3, or R^4 and $R^{4'}$ together is optionally and independently substituted. The remaining variables are as described and defined in the first embodiment, or the first, second, third or fourth aspect thereof.

In a sixth aspect of the first embodiment:

any alkyl or alkylene portion of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, or R^6 is optionally and independently substituted with one or more substituents independently selected from halo, =O, OR^A, $NR^BR^{B'}$, and S(O)$_{0-2}R^C$;

any alkyl or alkylene portion of $R^{6'}$, R^A, or R^C, is optionally and independently substituted with one or more fluoro;

any carbocyclyl or heterocyclyl portion of any of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, or R^6, or any ring formed by taking together R^1 and R^2, R^2 and R^3, or R^4 and $R^{4'}$ is optionally and independently substituted on a carbon atom with one or more substituents independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, C_3-C_{10} carbocyclyl, a 4-13 membered heterocyclyl, OR^A, $NR^BR^{B'}$, and S(O)$_{0-2}R^C$;

any heterocyclyl portion of any of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, or R^6, or any ring formed by taking together R^1 and R^2, R^2 and R^3, or R^4 and $R^{4'}$ is optionally and independently substituted on a substitutable nitrogen atom with R^F;

each R^F is independently selected from -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -S(O)$_{1-2}$-(C_1-C_6 alkyl), -S(O)$_{1-2}$-(C_0-C_6 alkylene)-carbocyclyl, -S(O)$_{1-2}$-(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, and -C(O)N(R^D)(R^E);

any carbocyclyl or heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, any cycloalkyl portion of R^6, or any substituent of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, or $R^{6'}$ is optionally and independently substituted on a carbon atom with a one or more substituents independently selected from halo, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, =O, -OH, -NH_2, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$; and

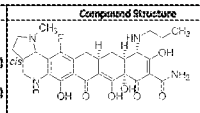
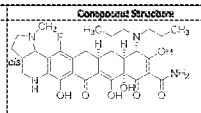
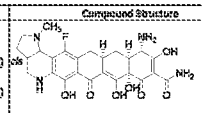
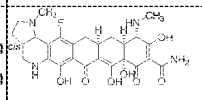
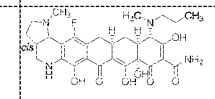
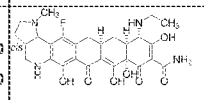
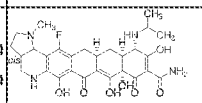
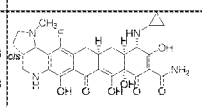
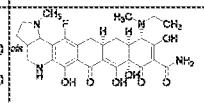
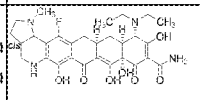
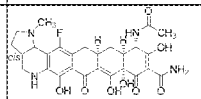
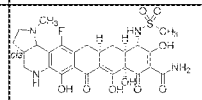
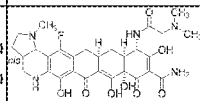
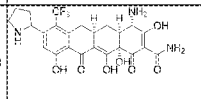
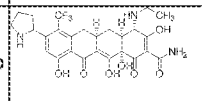
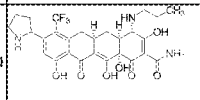
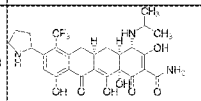
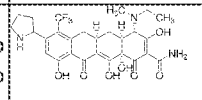
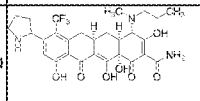
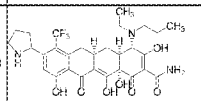
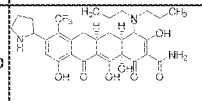
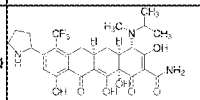
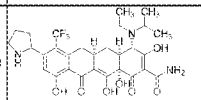
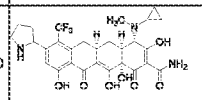
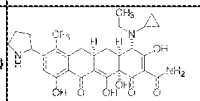
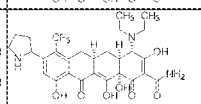
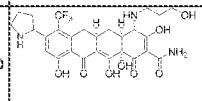
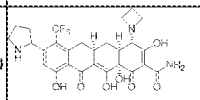
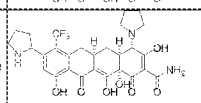
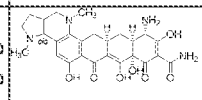
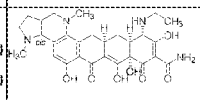
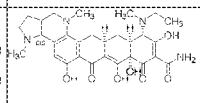
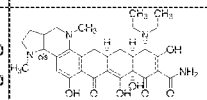
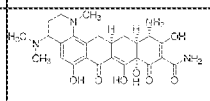
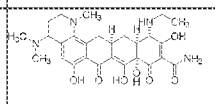
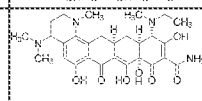
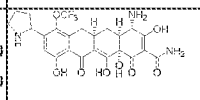
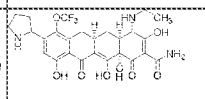
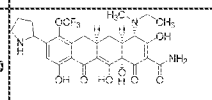
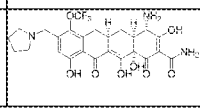
any heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, or any heterocyclyl substituent of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, or R^6 is optionally substituted on a substitutable nitrogen atom with -C_1-C_4 alkyl, or -S(O)$_{1-2}$-(C_1-C_4 alkyl). The remaining variables are as described and defined in the first embodiment, or the first, second, third, fourth or fifth aspect thereof.

In a seventh aspect of the first embodiment, X is N. The remaining variables are as described and defined in the first embodiment, or the first, second, third, fourth, fifth or sixth aspect thereof.

In an eighth aspect of the first embodiment, R^1 is selected from hydrogen, halo, -(C_1-C_6 alkyl) optionally substituted with one or more halo, -$NR^BR^{B'}$, -C(O)$NR^BR^{B'}$, -OR^A, -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl, wherein R^A is C_1-C_6 alkyl optionally substituted with one or more fluoro. The remaining variables are as described and defined in the first embodiment, or the first, second, third, fourth, fifth, sixth or seventh aspect thereof.

In a ninth aspect of the first embodiment, R^3 is selected from hydrogen and -N(R^B)($R^{B'}$), wherein R^B is hydrogen. The remaining variables are as described and defined in the first embodiment, or the first, second, third, fourth, fifth, sixth, seventh or eighth aspect thereof.

In a tenth aspect of the first embodiment, the compound for use in treating a hematological cancer is selected from any of the compounds in the following tables or a pharmaceutically acceptable salt thereof:

Compound No.	Compound Structure	Compound No.	Compound Structure	Compound No.	Compound Structure
S3-7-1-A (diastereomer A) S3-7-1-B (diastereomer B)		S3-7-2		S3-7-5-A (diastereomer A) S3-7-5-B (diastereomer B)	
S3-7-4-A (diastereomer A) S3-7-4-B (diastereomer B)		S3-7-3		S3-7-6-A (diastereomer A) S3-7-6-B (diastereomer B)	
S3-7-7-A (diastereomer A) S3-7-7-B (diastereomer B)		S3-7-8-A (diastereomer A) S3-7-8-B (diastereomer B)		S3-7-9-A (diastereomer A) S3-7-9-B (diastereomer B)	
S3-7-10-A (diastereomer A) S3-7-10-B (diastereomer B)		S3-7-11		S3-7-12	
S3-7-13-A (diastereomer A) S3-7-13-B (diastereomer B)		S4-14-1 (diastereomer A)		S4-14-2 (diastereomer A)	
S4-14-3 (diastereomer A)		S4-14-4 (diastereomer A)		S4-14-5-A (diastereomer A) S4-14-5-B (diastereomer B)	
S4-14-7 (diastereomer A)		S4-14-8 (diastereomer A)		S4-14-9 (diastereomer A)	
S4-14-10 (diastereomer A)		S4-14-11 (diastereomer A)		S4-14-12 (diastereomer A)	
S4-14-15 (diastereomer A)		S4-14-16-A (diastereomer A) S4-14-16-B (diastereomer B)		S4-14-16 (diastereomer A)	
S4-14-17 (diastereomer A)		S4-14-18 (diastereomer A)		S5-10-1-A (diastereomer A) S5-10-1-B (diastereomer B)	
S5-10-1-2-A (diastereomer A) S5-10-1-2-B (diastereomer B)		S5-10-3-A (diastereomer A) S5-10-3-B (diastereomer B)		S5-10-4-A (diastereomer A) S5-10-4-B (diastereomer B)	
S5-6-1 (single diastereomer)		S5-6-2 (single diastereomer)		S5-6-3 (single diastereomer)	
S7-14-1-A (diastereomer A) S7-14-1-B (diastereomer B)		S7-14-2-A (diastereomer A)		S7-14-3-A (diastereomer A)	
S8-4-1		S8-4-2		S8-4-3	

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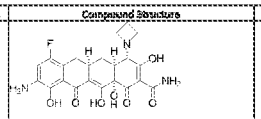
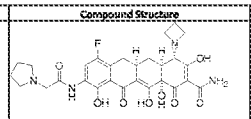
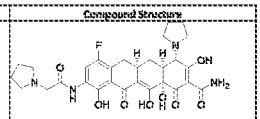
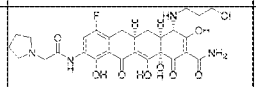
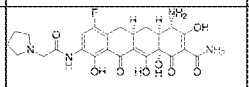
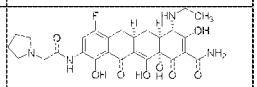
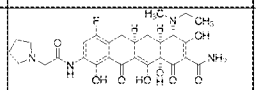
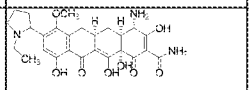
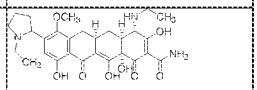
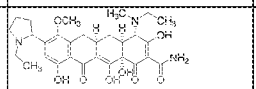
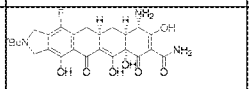
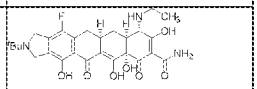
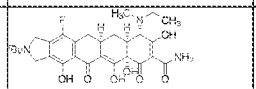
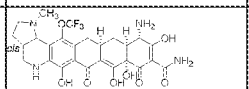
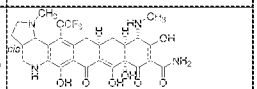
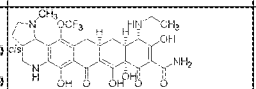
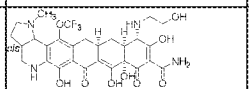
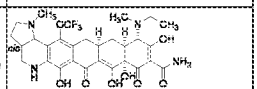
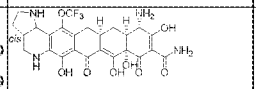
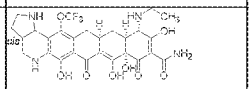
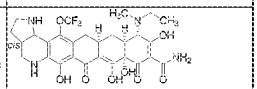
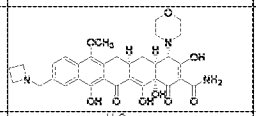
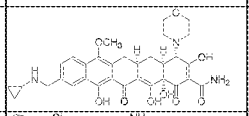
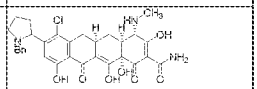
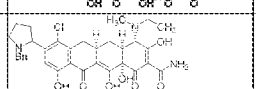
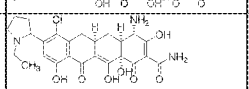
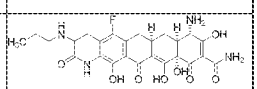
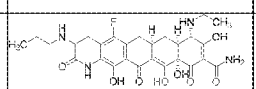
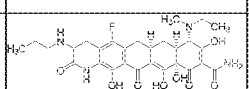
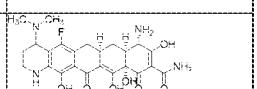
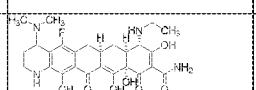
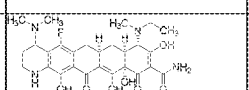
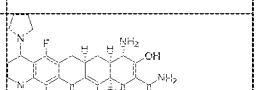
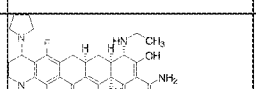
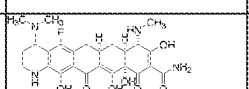
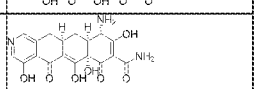
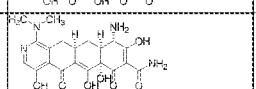
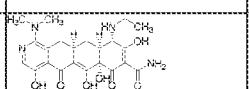
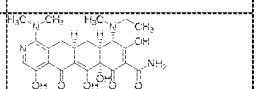
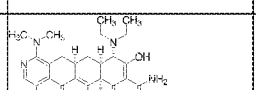
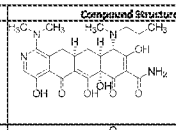
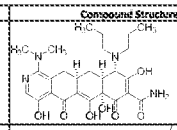
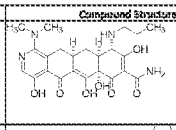
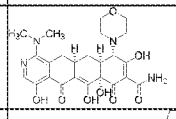
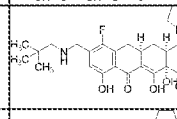
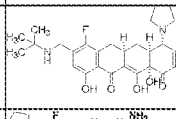
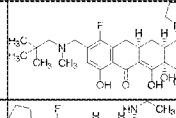
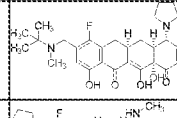
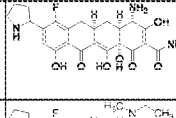
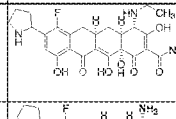
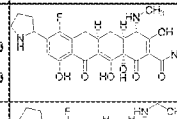
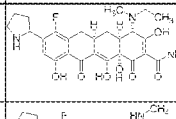
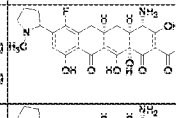
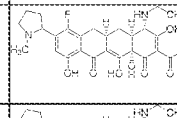
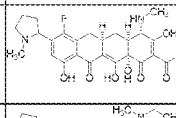
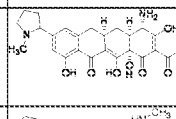
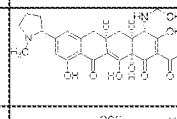
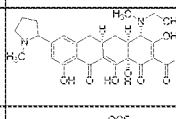
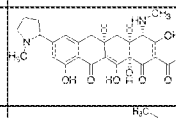
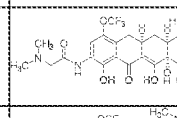
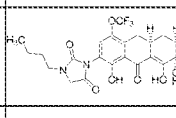
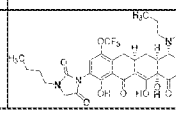
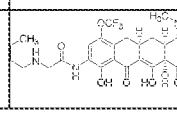
Compound No.	Compound Structure	Compound No.	Compound Structure	Compound No.	Compound Structure
S5-6-1		S5-5-1		S5-5-2	
S5-5-3		S5-5-4		S5-5-5	
S5-5-6		S10-6-1 (single diastereomer)		S10-6-2 (single diastereomer)	
S10-6-3 (single diastereomer)		S11-3-1		S11-3-2	
S11-3-3		S12-8-1-A (diastereomer A) S12-8-1-B (diastereomer B)		S12-8-2-A (diastereomer A)	
S12-8-3-A (diastereomer A) S12-8-3-B (diastereomer B)		S12-8-4-A (diastereomer A)		S12-8-5-A (diastereomer A)	
S12-8-6-A (diastereomer A) S12-8-6-B (diastereomer B)		S12-8-7-A (diastereomer A)		S12-8-8-A (diastereomer A)	
S13-5-1		S13-5-2		S14-8-1	
S14-8-2		S14-8-3-A (diastereomer A) S14-8-3-B (diastereomer B)		S15-10-1	
S15-10-2		S15-10-3-A (diastereomer A) S15-10-3-B (diastereomer B)		S16-7-1 (single diastereomer)	
S16-7-2 (single diastereomer)		S16-7-3 (single diastereomer)		S16-7-4 (single diastereomer)	
S16-7-5 (single diastereomer)		S16-7-6 (single diastereomer)		S17-3-1	
S17-3-2		S17-3-3		S17-3-4	
S17-3-5		S17-3-6		S17-3-7	

Compound No.	Compound Structure	Compound No.	Compound Structure	Compound No.	Compound Structure
S17-3-8		S17-3-9		S17-3-10	
S17-3-11		S18-3-1-1		S18-3-1-2	
S18-3-2-1		S18-3-2-2		S18-7-1-B (diastereomer B)	
S19-7-2		S19-7-3-A (diastereomer A) S19-7-3-B (diastereomer B)		S19-7-4-A (diastereomer A) S19-7-4-B (diastereomer B)	
S19-7-5-A (diastereomer A) S19-7-5-B (diastereomer B)		S19-7-6		S19-7-7-A (diastereomer A) S19-7-7-B (diastereomer B)	
S20-6-1 (single diastereomer)		S20-6-2 (single diastereomer)		S20-6-3 (single diastereomer)	
S20-6-4 (single diastereomer)		S21-5-1		S21-5-2	
S25-5-3		S21-5-4			

The compounds set forth in the above tables were prepared according to the synthetic procedures described in WO2014/036502, incorporated herein by reference in its entirety. The compound numbers in the tables set forth above reference synthetic schemes in WO2014/03650 all of which are found in U.S. Patent No. 9,573,895 the entire content of which is hereby incorporated by reference.

In a second embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Structural Formula (I) or (I'), wherein R^4 is selected from hydrogen and -(C_1-C_6 alkyl); $R^{4'}$ is selected from hydrogen, -(C_2-C_6 alkyl) optionally substituted with one or more substituents independently selected from hydroxy and halo, -(C_3-C_6 cycloalkyl), -C(O)-(C_1-C_6 alkyl), -C(O)-(C_1-C_6 alkylene)-N(R^D)(R^E), and S(O)$_{1-2}R^C$; or R^4 and $R^{4'}$ are taken together with the nitrogen atom to which they are commonly bound to form a 4-6 membered ring optionally comprising 1-2 additional heteroatoms independently selected from N, O and S; R^C is -(C_1-C_6 alkyl); and each of R^D and R^E is independently selected from hydrogen and -(C_1-C_6 alkyl). The remaining variables are as described and defined in the first embodiment, or any aspect thereof.

In a first aspect of the second embodiment, R^4 is selected from hydrogen, methyl, ethyl and propyl; and $R^{4'}$ is selected from hydrogen, ethyl, propyl, cyclopropyl, -$C(O)CH_3$, -$C(O)CH_2N(CH_3)_2$, and -$S(O)_2CH_3$. The remaining variables are as described and defined in the first embodiment, or any aspect thereof, or in the second embodiment.

In a second aspect of the second embodiment, R^4 is selected from hydrogen and -(C_1-C_6 alkyl); $R^{4'}$ is selected from hydrogen, -(C_2-C_6 alkyl), -(C_3-C_6 cycloalkyl), -C(O)-(C_1-C_6 alkyl), -C(O)-(C_1-C_6 alkylene)-$N(R^D)(R^E)$, and $S(O)_{1-2}R^C$; R^C is -(C_1-C_6 alkyl); and each of R^D and R^E is independently selected from hydrogen and -(C_1-C_6 alkyl). The remaining variables are as described and defined in the first embodiment, or any aspect thereof, or the second embodiment, or first aspect thereof.

In a third aspect of the second embodiment, R^4 and $R^{4'}$ are both hydrogen.

In a fourth aspect of the second embodiment, R^4 is -(C_1-C_6 alkyl) and $R^{4'}$ is -(C_2-C_6 alkyl).

In a fifth aspect of the second embodiment, R^4 is hydrogen and $R^{4'}$ is -(C_2-C_6 alkyl).

In a third embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Structural Formula (I) or (I'), wherein R^1 is selected from hydrogen, halo, and -(C_1-C_6 alkyl) optionally substituted with one or more substituents independently selected from halo, -$NR^BR^{B'}$, -$C(O)NR^BR^{B'}$, -OR^A, -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl, wherein R^A is C_1-C_6 alkyl optionally substituted with one or more fluoro. The remaining variables are as described and defined in the first or second embodiment, or any aspect thereof.

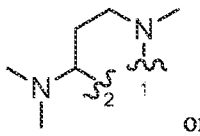
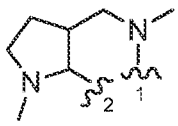
In a first aspect of the third embodiment, X is $C(R^2)$. The remaining variables are as described and defined in the first or second embodiment, or any aspect thereof, or the third embodiment.

In a second aspect of the third embodiment, R^1 is selected from hydrogen, fluoro, chloro, CF_3 and OCF_3. The remaining variables are as described and defined in the first or second embodiment, or any aspect thereof, or the third embodiment, or first aspect thereof.

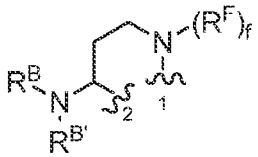
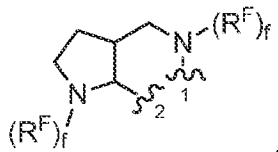
In a third aspect of the third embodiment, R^1 is selected from hydrogen, halo, and -(C_1-C_6 alkyl) optionally substituted with one or more substituents independently selected from halo, and -OR^A, wherein R^A is C_1-C_6 alkyl optionally substituted with one or more fluoro. The remaining variables are as described and defined in the first or second embodiment, or any aspect thereof, or the third embodiment, or first or second aspect thereof.

In a fourth aspect of the third embodiment, R^1 is selected from hydrogen, fluoro, chloro, $-CF_3$, $-OCH_3$, $-OCF_3$, $-N(CH_3)_2$ and $-NHCH_3$. The remaining variables are as described and defined in the first or second embodiment, or any aspect thereof, or the third embodiment, or first, second or third aspect thereof.

In a fourth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Structural Formula (I) or (I'), wherein R^1 and R^2 are taken together with the atoms to which they are bound to form a nitrogen-containing heterocyclyl ring, wherein the ring comprising R^1 and R^2 is optionally substituted on any substitutable nitrogen atom with C_1-C_4 alkyl; and optionally substituted on a carbon atom with $NR^BR^{B'}$, wherein each of R^B and $R^{B'}$ is independently selected from hydrogen and C_1-C_6 alkyl. The remaining variables are as described and defined in the first, second or third embodiment, or any aspect thereof.

In a first aspect of the fourth embodiment, R^1 and R^2 are taken together with the carbon atoms to which they are bound to form:  or  , wherein "$\sim$ 1" represents a point of attachment to the carbon atom bound to R^1 and "$\sim$ 2" represents a point of attachment to the carbon atom bound to R^2. The remaining variables are as described and defined in the first, second or third embodiment, or any aspect thereof, or the fourth embodiment.

In a second aspect of the fourth embodiment, X is $C(R^2)$. The remaining variables are as described and defined in the first, second or third embodiment, or any aspect thereof, or the fourth embodiment, or the first aspect thereof.

In a third aspect of the fourth embodiment, X is $C(R^2)$; and R^1 and R^2 are taken together with the carbon atoms to which they are bound to form:  or  , wherein "$\sim$ 1" represents a point of attachment to the carbon atom bound to R^1; "$\sim$ 2" represents a point of attachment to the carbon atom bound to R^2; and f is

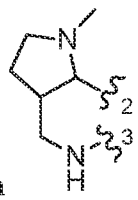
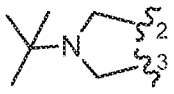
0 or 1. The remaining variables are as described and defined in the first, second or third embodiment, or any aspect thereof, or the fourth embodiment, or the first or second aspect thereof.

In a fifth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Structural Formula (I) or (I'), wherein R^2 is -(C_0-C_6 alkylene)-heterocyclyl optionally substituted on a nitrogen atom, if present, with -(C_1-C_6 alkyl); -(C_0-C_6 alkylene)-carbocyclyl; or -(C_1-C_6)alkyl substituted with $NR^BR^{B'}$. The remaining variables are as described and defined in the first, second, third or fourth embodiment, or any aspect thereof.

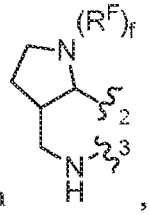
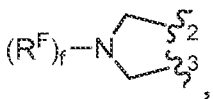
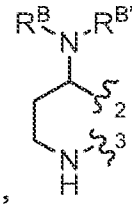
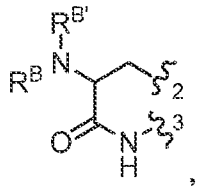
In a first aspect of the fifth embodiment, R^2 is pyrrolidinyl optionally substituted on a nitrogen atom with C_1-C_4 alkyl or benzyl. The remaining variables are as described and defined in the first, second, third or fourth embodiment, or any aspect thereof, or the fifth embodiment.

In a third aspect of the fifth embodiment, R^2 is -(C_0-C_6 alkylene)-heterocyclyl optionally substituted on a nitrogen atom, if present, with -(C_1-C_6 alkyl) or -(C_0-C_6 alkylene)-carbocyclyl. The remaining variables are as described and defined in the first, second, third or fourth embodiment, or any aspect thereof, or the fifth embodiment, or first or second aspect thereof.

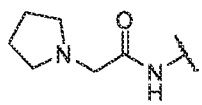
In a sixth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Structural Formula (I) or (I'), wherein R^2 and R^3 are taken together with the atoms to which they are bound to form a heterocyclyl, e.g., a nitrogen-containing heterocyclyl ring, wherein the ring comprising R^2 and R^3 is optionally and independently substituted on any substitutable nitrogen atom with C_1-C_4 alkyl. The remaining variables are as described and defined in the first, second, third, fourth or fifth embodiment, or any aspect thereof.

In a first aspect of the sixth embodiment, R^2 and R^3 are taken together with the atoms to which they are bound to form  or  wherein "$\sim$2" represents a point of attachment to the carbon atom bound to R^2, and "$\sim$3" represents a point of attachment to the carbon atom bound to R^3. The remaining variables are as described and

defined in the first, second, third, fourth or fifth embodiment, or any aspect thereof, or the sixth embodiment.

In a second aspect of the sixth embodiment, R^2 and R^3 are taken together with the atoms to which they are bound to form  ,  ,  or  , wherein "~2" represents a point of attachment to the carbon atom bound to R^2; "~3" represents a point of attachment to the carbon atom bound to R^3; and f is 0 or 1. The remaining variables are as described and defined in the first, second, third, fourth or fifth embodiment, or any aspect thereof, or the sixth embodiment, or first aspect thereof.

In a seventh embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Structural Formula (I) or (I'), wherein R^3 is selected from hydrogen and $-N(R^B)(R^{B'})$, wherein R^B is hydrogen and $R^{B'}$ is $-C(O)-(C_0-C_6$ alkylene)-heterocyclyl or $-C(O)-(C_0-C_6$ alkylene)$-N(R^D)(R^E)$. The remaining variables are as described and defined in the first, second, third, fourth, fifth or sixth embodiment, or any aspect thereof.

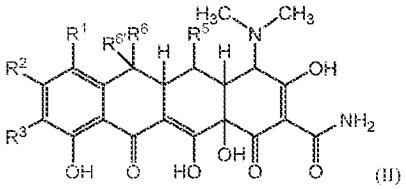
In a first aspect of the seventh embodiment, R^3 is selected from hydrogen and  . The remaining variables are as described and defined in the first, second, third, fourth, fifth or sixth embodiment, or any aspect thereof, or the seventh embodiment.

In a second aspect of the seventh embodiment, X is $C(R^2)$. The remaining variables are as described and defined in the first, second, third, fourth, fifth or sixth embodiment, or any aspect thereof, or the seventh embodiment, or first aspect thereof.

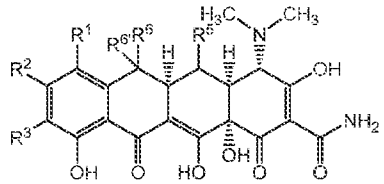
In a third aspect of the seventh embodiment, R^3 is selected from hydrogen and $-N(R^B)(R^{B'})$, wherein R^B is hydrogen and $R^{B'}$ is $-C(O)-(C_0-C_6$ alkylene)-heterocyclyl. The remaining variables are as described and defined in the first, second, third, fourth, fifth or

sixth embodiment, or any aspect thereof, or the seventh embodiment, or first or second aspect thereof.

In an eighth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Formula II:



(II)



(II'),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are taken together with atoms to which they are bound to form a carbocyclyl or heterocyclyl ring and R^3 is selected from hydrogen, halo, -(C_1-C_6 alkyl), -OR^A, -$C(O)NR^BR^{B'}$, $NR^BR^{B'}$, $S(O)_{0-2}R^C$, -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl; or

R^2 and R^3 are taken together with atoms to which they are bound to form a carbocyclyl or heterocyclyl ring and R^1 is selected from hydrogen, halo, -(C_1-C_6 alkyl), -OR^A, -$C(O)NR^BR^{B'}$, $NR^BR^{B'}$, $S(O)_{0-2}R^C$, -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl;

each of R^5 and R^6 is independently selected from hydrogen, halo, -(C_1-C_6 alkyl), -OR^A, -$C(O)NR^BR^{B'}$, $NR^BR^{B'}$, $S(O)_{0-2}R^C$, -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl;

$R^{6'}$ is selected from hydrogen, -(C_1-C_6 alkyl) and -(C_3-C_6 cycloalkyl);

each R^A is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, and -$C(O)N(R^D)(R^E)$;

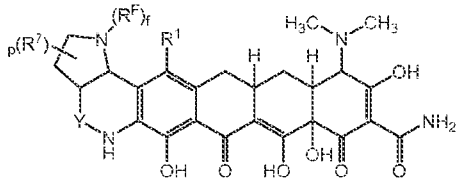
each R^B and each $R^{B'}$ is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -$S(O)_{1-2}$-(C_1-C_6 alkyl), -$S(O)_{1-2}$-(C_0-C_6 alkylene)-carbocyclyl, -$S(O)_{1-2}$-(C_0-C_6

alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, and -C(O)-(C_0-C_6 alkylene)-$N(R^D)(R^E)$;

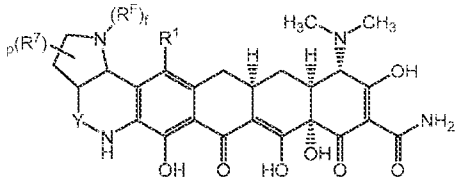
each R^C is independently selected from -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl and -(C_0-C_6 alkylene)-heterocyclyl; and

each R^D and each R^E is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, and -(C_0-C_6 alkylene)-heterocyclyl, wherein any alkyl, alkylene, carbocyclyl or heterocyclyl portion of R^1, R^2, R^3, R^5, R^6, $R^{6'}$, R^A, R^B, $R^{B'}$, R^C, R^D, or R^E or formed by taking R^1 and R^2 or R^2 and R^3 together is optionally and independently substituted. Alternative values for the variables in Formula II are as described and defined in the first through seventh embodiments, or any aspect thereof.

In a first aspect of the eighth embodiment, the compound is represented by Formula IIa:



(IIa)



(IIa'),

or a pharmaceutically acceptable salt thereof, wherein:

each R^7, if present, is independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

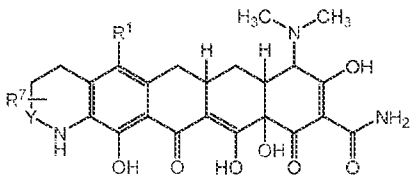
p is 0, 1, 2, 3 or 4;

Y is C(O) or $C(R^8)_2$ wherein each R^8 is independently selected from hydrogen, -(C_1-C_6)alkyl and -(C_3-C_6 cycloalkyl); and

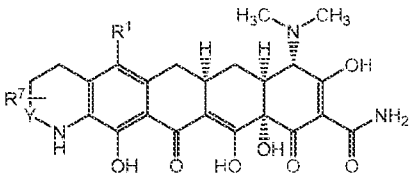
f is 0 or 1. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment.

In a further aspect of the first aspect of the eighth embodiment, p is 0. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first aspect thereof.

In a second aspect of the eighth embodiment, the compound is represented by Formula IIb:



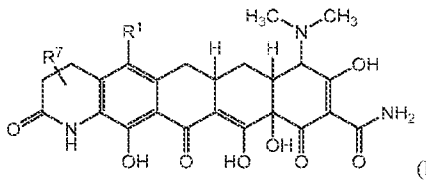
(IIb)



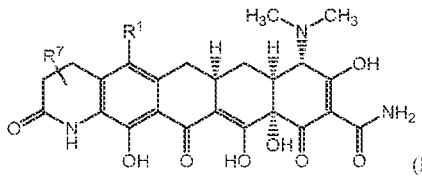
(IIb') (IIb),

or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$; and Y is C(O) or $C(R^8)_2$ wherein each R^8 is independently selected from hydrogen, -(C_1-C_6)alkyl and -(C_3-C_6 cycloalkyl). The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first aspect thereof.

In a third aspect of the eighth embodiment, the compound is represented by Formula IIb-1:



(IIb-1)

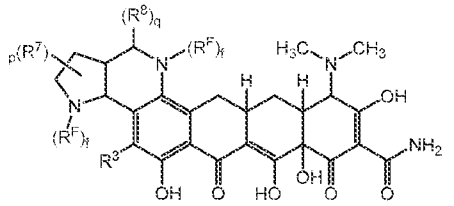


(IIb'-1)

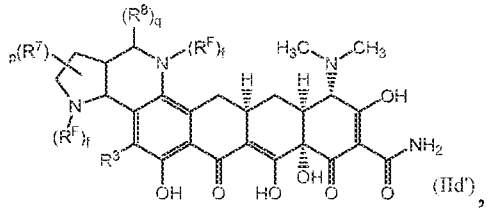
or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13

membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first or second aspect thereof.

In a fourth aspect of the eighth embodiment, the compound is represented by Formula IId:



(IId)



(IId'),

or a pharmaceutically acceptable salt thereof, wherein:

each R^7 and R^8, if present, is independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, C_3-C_{10} carbocyclyl, a 4-13 membered heterocyclyl, OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

p is 0, 1, 2, 3 or 4;

q is 0, 1 or 2; and

each f is independently 0 or 1. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through third aspects thereof.

In a further aspect of the fourth aspect of the eighth embodiment, p and q are each 0. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through fourth aspects thereof.

In a fifth aspect of the eighth embodiment, each R^F is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 hydroxyalkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -(C_0-C_6 alkylene)-$C(O)_2$-(C_1-C_6 alkyl) and -(C_1-C_6 alkylene)-$NR^BR^{B'}$. The remaining variables are as described and defined in the

first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through fourth aspects thereof.

In a sixth aspect of the eighth embodiment, each f is 0. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through fifth aspects thereof.

In a seventh aspect of the eighth embodiment, each f is 1. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through sixth aspects thereof.

In an eighth aspect of the eighth embodiment, the ring formed by R^1 and R^2 or R^2 and R^3 together with atoms to which they are bound is a 4-7 membered non-aromatic heterocyclic ring optionally containing 1-2 heteroatoms independently selected from N, S and O. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through seventh aspects thereof.

In a ninth aspect of the eighth embodiment:

any alkyl, or alkylene portion of R^1, R^2, R^3, R^5, R^6 is optionally and independently substituted with one or more substituents independently selected from halo, =O, OR^A, $NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

any alkyl or alkylene portion of $R^{6'}$, R^A, or R^C, is optionally and independently substituted with one or more fluoro;

any carbocyclyl or heterocyclyl portion of any of R^1, R^2, R^3, R^5, R^6, or any ring formed by taking together R^1 and R^2 or R^2 and R^3 is optionally and independently substituted on a carbon atom with one or more substituents independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

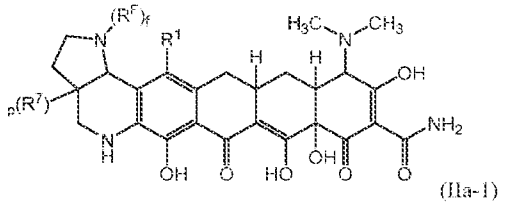
any heterocyclyl portion of any of R^1, R^2, R^3, R^5, R^6, or any ring formed by taking together R^1 and R^2 or R^2 and R^3 is optionally and independently substituted on a substitutable nitrogen atom with R^F;

each R^F is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 hydroxyalkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -$S(O)_{1-2}$-(C_1-C_6 alkyl), -$S(O)_{1-2}$-(C_0-C_6 alkylene)-carbocyclyl, -$S(O)_{1-2}$-(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6

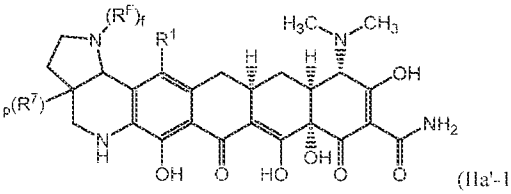
alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, -(C_0-C_6 alkylene)-$C(O)_2$-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-$NR^BR^{B'}$ and -$C(O)N(R^D)(R^E)$;

any carbocyclyl or heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, any cycloalkyl portion of $R^{6'}$, or any substituent of R^1, R^2, R^3, R^5, R^6 is optionally and independently substituted on a carbon atom with a one or more substituents independently selected from fluoro, chloro, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, =O, -OH, $-NH_2$, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$; and any heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, or any heterocyclyl substituent of R^1, R^2, R^3, R^5, or R^6 is optionally substituted on a substitutable nitrogen atom with -C_1-C_4 alkyl, or -$S(O)_{1-2}$-(C_1-C_4 alkyl). The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through eighth aspects thereof.

In a tenth aspect of the eighth embodiment, the compound is represented by Formula IIa-1:



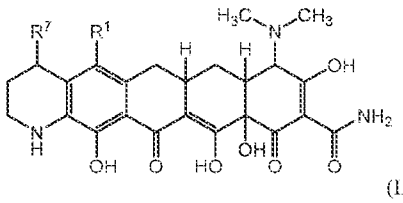
(IIa-1)



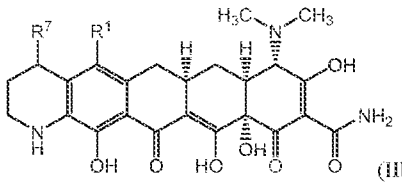
(IIa'-1),

or a pharmaceutically acceptable salt thereof, wherein p is 0 or 1 and R^7, if present, is -C_1-C_6 alkyl. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through ninth aspects thereof.

In an eleventh aspect of the eighth embodiment, the compound is represented by Formula IIb-2:



(IIb-2)

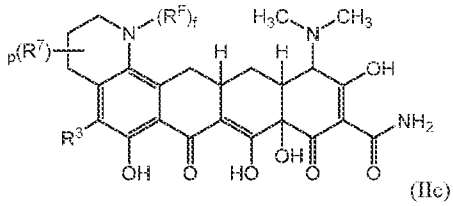


(IIb'-2)

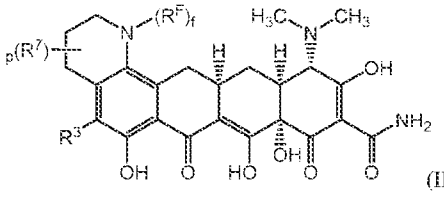
or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through tenth aspects thereof.

In a twelfth aspect of the eighth embodiment, any carbocyclyl or heterocyclyl portion of any ring formed by taking together R^1 and R^2 or R^2 and R^3 is optionally and independently substituted on a carbon atom with one or more substituents independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl) and -(C_0-C_6 alkylene)-$NR^BR^{B'}$. The remaining variables are as described and defined in the first through seventh embodiments, or any aspect thereof, or the eighth embodiment, or first through eleventh aspects thereof.

In a ninth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound represented by Formula IIc:



(IIc)

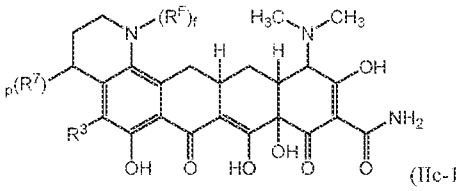


(IIc'),

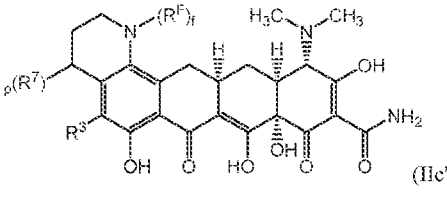
or a pharmaceutically acceptable salt thereof, wherein R^7, if present, is selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$; p is 0 or 1; and f is 0 or 1. Values and alternative values for the remaining variables are as described and defined in the first through eighth embodiments, or any aspect thereof.

In a first aspect of the ninth embodiment, p is 1. The remaining variables are as described and defined in the first through eighth embodiments, or any aspect thereof, or the ninth embodiment.

In a second aspect of the ninth embodiment, the compound is represented by Formula IIc-1:



(IIc-1)



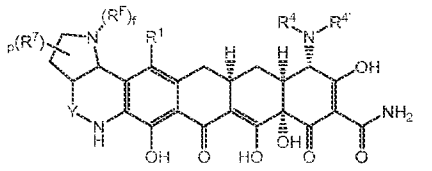
(IIc'-1),

or a pharmaceutically acceptable salt thereof. The variables are as described and defined in the first through eighth embodiments, or any aspect thereof, or the ninth embodiment, or first aspect thereof.

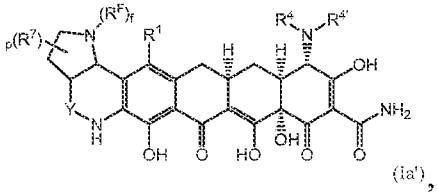
In a third aspect of the ninth embodiment, R^7, if present, is selected from -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl) and -(C_0-C_6 alkylene)-$NR^BR^{B'}$. The remaining variables are as described and defined in the first through eighth embodiments, or any aspect thereof, or the ninth embodiment, or first or second aspect thereof.

In a fourth aspect of the ninth embodiment, R^7, if present, is -$NR^BR^{B'}$. The remaining variables are as described and defined in the first through eighth embodiments, or any aspect thereof, or the ninth embodiment, or first through third aspects thereof.

In a tenth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Formula Ia:



(Ia)



(Ia'),

or a pharmaceutically acceptable salt thereof, wherein:

each R^7, if present, is independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

p is 0, 1, 2, 3 or 4;

Y is C(O) or $C(R^8)_2$ wherein each R^8 is independently selected from hydrogen, -(C_1-C_6)alkyl and -(C_3-C_6 cycloalkyl); and

f is 0 or 1. Values and alternative values for the variables are as described and defined in the first through ninth embodiments, or any aspect thereof.

In a first aspect of the tenth embodiment, p is 0. The remaining variables are as described and defined in the first through ninth embodiments, or any aspect thereof, or the tenth embodiment.

In a second aspect of the tenth embodiment, each R^8 is hydrogen. The remaining variables are as described and defined in the first through ninth embodiments, or any aspect thereof, or the tenth embodiment, or first aspect thereof.

In an eleventh embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein X is $C(R^2)$; and R^2 is optionally substituted -(C_0-C_1 alkylene)-(4-6-membered heterocyclyl). Values and alternative values for the variables are as described and defined in the first through tenth embodiments, or any aspect thereof.

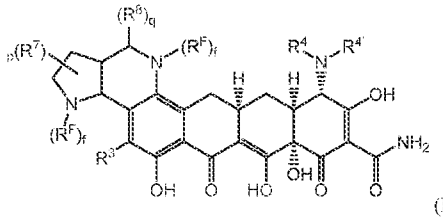
In a first aspect of the eleventh embodiment, R^3 is hydrogen. The remaining variables are as described and defined in the first through tenth embodiments, or any aspect thereof, or the eleventh embodiment.

In a second aspect of the eleventh embodiment, R^2 is optionally substituted -(C_0-C_1 alkylene)-pyrrolidinyl. The remaining variables are as described and defined in the first through tenth embodiments, or any aspect thereof, or the eleventh embodiment, or first aspect thereof.

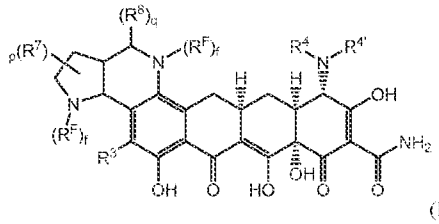
In a third aspect of the eleventh embodiment, R^2 is optionally substituted pyrrolidin-2-yl. The remaining variables are as described and defined in the first through tenth embodiments, or any aspect thereof, or the eleventh embodiment, or first or second aspect thereof.

In a fourth aspect of the eleventh embodiment, R^2 is optionally substituted -(C_1 alkylene)-(pyrrolidin-1-yl). The remaining variables are as described and defined in the first through tenth embodiments, or any aspect thereof, or the eleventh embodiment, or first through third aspects thereof.

In a twelfth embodiment of the invention, the compound administered in the method of treating a hematological is a compound of Formula Ib:



(Ib)



(Ib'),

or a pharmaceutically acceptable salt thereof, wherein:

each R^7 and R^8, if present, is independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, C_3-C_{10} carbocyclyl, a 4-13 membered heterocyclyl, OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

p is 0, 1, 2, 3 or 4;

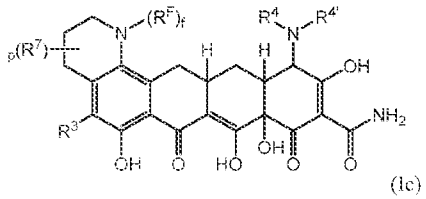
q is 0, 1 or 2; and

each f is independently 0 or 1. Values and alternative values for the variables are as described and defined in the first through eleventh embodiments, or any aspect thereof.

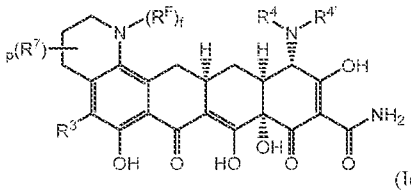
In a first aspect of the twelfth embodiment, p and q are each 0. The remaining variables are as described and defined in the first through eleventh embodiments, or any aspect thereof, or the twelfth embodiment.

In a second aspect of the twelfth embodiment, R^3 is hydrogen. The remaining variables are as described and defined in the first through eleventh embodiments, or any aspect thereof, or the twelfth embodiment, or first aspect thereof.

In a thirteenth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound represented by Formula Ic:



(Ic)

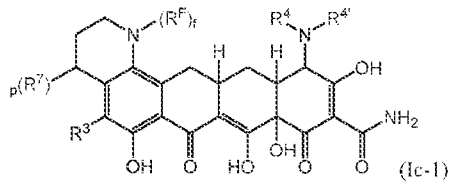


(Ic'),

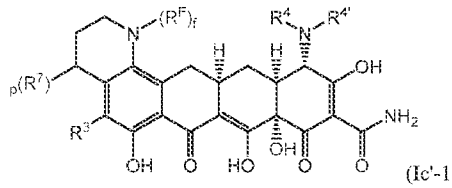
or a pharmaceutically acceptable salt thereof, wherein R^7, if present, is selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$; p is 0 or 1; and f is 0 or 1. Values and alternative values for the remaining variables are as described and defined in the first through twelfth embodiments, or any aspect thereof.

In a first aspect of the thirteenth embodiment, p is 1. The remaining variables are as described and defined in the first through twelfth embodiments, or any aspect thereof, or the thirteenth embodiment.

In a second aspect of the thirteenth embodiment, the compound is represented by Formula Ic-1:



(Ic-1)



(Ic'-1),

or a pharmaceutically acceptable salt thereof. The variables are as described and defined in the first through twelfth embodiments, or any aspect thereof, or the thirteenth embodiment, or first aspect thereof.

In a third aspect of the thirteenth embodiment, R^7, if present, is selected from -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl) and -(C_0-C_6 alkylene)-$NR^BR^{B'}$. The remaining variables are as described and defined in the first through twelfth embodiments, or any aspect thereof, or the thirteenth embodiment, or first or second aspect thereof.

In a fourth aspect of the thirteenth embodiment, R^7, if present, is -$NR^BR^{B'}$. The remaining variables are as described and defined in the first through twelfth embodiments, or any aspect thereof, or the thirteenth embodiment, or first through third aspects thereof.

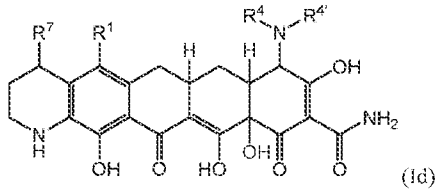
In a fourteenth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X is N and R^3 is hydrogen. Values and alternative values for the remaining variables are as described and defined in the first through thirteenth embodiments, or any aspect thereof.

In a first aspect of the fourteenth embodiment, R^1 is selected from hydrogen and $NR^BR^{B'}$. The remaining variables are as described and defined in the first through thirteenth embodiments, or any aspect thereof, or the fourteenth embodiment.

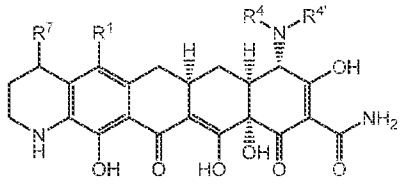
In a fifteenth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein X is $C(R^2)$ and R^2 is (C_1 alkylene)-$NR^BR^{B'}$. Values and alternative values for the remaining variables are as described and defined in the first through fourteenth embodiments, or any aspect thereof.

In a first aspect of the fifteenth embodiment, R^B and $R^{B'}$ are each independently selected from hydrogen and –(C_1-C_6 alkyl). The remaining variables are as described and defined in the first through fourteenth embodiments, or any aspect thereof, or the fifteenth embodiment.

In a sixteenth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound represented by Formula Id:



(Id)

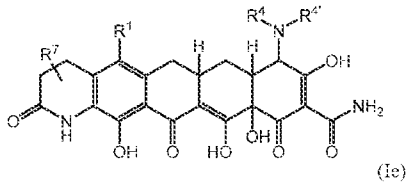


(Id'),

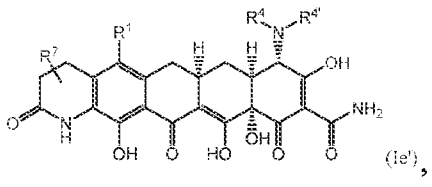
or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$. Values and alternative values for the variables are as defined in the first through fifteenth embodiments, or any aspect thereof.

In a first aspect of the sixteenth embodiment, R^7 is 4-6 membered heterocyclyl or -$NR^BR^{B'}$. The remaining variables are as described and defined in the first through fifteenth embodiments, or any aspect thereof, or the sixteenth embodiment.

In a seventeenth embodiment of the invention, the compound administered in the method of treating a hematological cancer is a compound represented by Formula Ie:



(Ie)



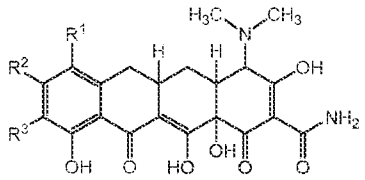
(Ie'),

or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylene)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylene)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylene)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$. Values and alternative values for the variables are as defined in the first through sixteenth embodiments, or any aspect thereof.

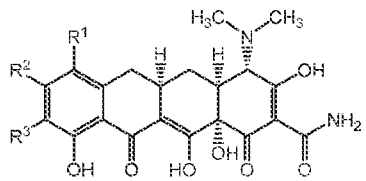
In a first aspect of the seventeenth embodiment, R^7 is 4-6 membered heterocyclyl or $-NR^BR^{B'}$. The remaining variables are as described and defined in the first through sixteenth embodiments, or any aspect thereof, or the seventeenth embodiment.

In an additional aspect of any of the preceding embodiments, or any aspect thereof, each R^A is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylene)-carbocyclyl, -(C_0-C_6 alkylene)-heterocyclyl, -S-(C_1-C_6 alkyl), -S-(C_0-C_6 alkylene)-carbocyclyl, -S-(C_0-C_6 alkylene)-heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylene)-carbocyclyl, -C(O)-(C_0-C_6 alkylene)-heterocyclyl, and $-C(O)N(R^D)(R^E)$. The chemical moiety indicated when f in $-N(R^F)_f-$ is 0 in the structural formulae described herein is -N(H)-. Similarly, when q in $-(R^8)_q$ is 0, it means that the carbon atom attached to $-(R^8)_q$ is attached to two hydrogen atoms.

An eighteenth embodiment of the invention is a compound of Formula (III):



(III)



(III')

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from hydrogen, bromo, fluoro, chloro, C_1-C_6 alkyl, -O-C_1-C_6 alkyl, $-S(O)_m$-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, -O-C_3-C_7 cycloalkyl, $-S(O)_m$-C_3-C_7 cycloalkyl, -CN, $-NR^GR^{G'}$, and $-NH-C(O)-(C_1$-C_6 alkylene)$-NR^GR^{G'}$, wherein each alkyl, alkylene or cycloalkyl in the group represented by R^1 is optionally substituted with fluoro;

R^2 is selected from fluoro, -C_1-C_6 alkyl, and $-[C(R^H)(R^H)]_m-NR^IR^{I'}$;

R^3 is selected from hydrogen, fluoro, bromo, -CN, $-[C(R^H)(R^H)]_n-NR^IR^{I'}$, $-NR^GR^{G'}$, NO_2, $-NH-C(O)-C_1$-C_4 alkylene$-NR^GR^{G'}$, C_1-C_6 alkyl, -NH-C(O)-C_1-C_6alkyl, $-NH-S(O)_m-C_1$-C_6 alkyl, $-NH-S(O)_m-C_3$-C_{10} carbocyclyl, $-NH-S(O)_m$-(4-13 membered) heterocyclyl;

each R^G and $R^{G'}$ is independently selected from hydrogen and C_1-C_4 alkyl; or

R^G and $R^{G'}$ taken together with the nitrogen atom to which they are bound form a (4-7 membered) heterocylic ring optionally comprising one additional heteroatom selected from N, S and O, wherein the (4-7 membered) heterocylic ring is optionally substituted with fluoro, chloro, -OH, fluoro-substituted C_1-C_4 alkyl, -C_1-C_4 alkyl, or -C_1-C_4 alkylene-O-C_1-C_4 alkyl, and is optionally benzofused;

each R^H and $R^{H'}$ is independently selected from hydrogen, C_1-C_4 alkyl, and C_3-C_{10} carbocyclyl;

each R^I is selected from hydrogen, C_1-C_{12} alkyl, -C_0-C_6 alkylene-C_3-C_{10} carbocyclyl, and -C_0-C_6 alkylene-(4-13 membered) heterocyclyl;

each $R^{I'}$ is selected from hydrogen, C_1-C_8 alkyl, -C_0-C_6 alkylene-C_3-C_{10} carbocyclyl, -C_0-C_6 alkylene-(4-13 membered) heterocyclyl, -C(O)-C_1-C_6 alkyl, -C_0-C_6 alkylene-C(O)-$NR^GR^{G'}$, -C(O)-C_1-C_6 alkylene-$NR^GR^{G'}$, -C_2-C_6 alkylene-$NR^GR^{G'}$, -$S(O)_m$-C_1-C_6 alkyl, -$S(O)_m$-C_3-C_{10} carbocyclyl, and -$S(O)_m$-(4-13 membered) heterocyclyl, wherein each alkyl, carbocyclyl, alkylene or heterocyclyl in the group represented by R^I or $R^{I'}$ is optionally and independently substituted with one or more substituents independently selected from fluoro, chloro, -OH, -O-C_1-C_4 alkyl, C_1-C_4 alkyl, fluoro-substituted-C_1-C_4 alkyl, -$NR^GR^{G'}$, C_3-C_{10} carbocyclyl and a (4-13 membered) heterocyclyl; or

R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a (4-7 membered) monocyclic heterocylic ring, or a (6-13 membered) bicyclic, spirocyclic or bridged heterocylic ring, wherein the (4-7 membered) monocyclic heterocylic ring, or the (6-13 membered) bicyclic, spirocyclic or bridged heterocyclic ring optionally comprises 1 to 4 additional heteroatoms independently selected from N, S and O; and wherein the (4-7 membered) monocyclic heterocylic ring, or the (6-13 membered) bicyclic, spirocyclic or bridged heterocyclic ring is optionally substituted with one or more substituents independently selected from C_3-C_{10} carbocyclyl, (4-13 membered) heterocyclyl, fluoro, chloro, -OH, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -O-C_3-C_{10} carbocyclyl, -O-(4-13 membered) heterocyclyl, -C_0-C_4 alkyl-O-C_1-C_4 alkyl, -C_0-C_4 alkyl-O-C_1-C_4 fluoroalkyl, =O, -C(O)-C_1-C_4 alkyl, -C(O) $NR^GR^{G'}$, -$N(R^G)$-C(O)-C_1-C_4 alkyl, and -C_0-C_4 alkylene-$NR^GR^{G'}$, and wherein each carbocyclyl or heterocyclyl substituent is optionally substituted with fluoro, chloro, -OH, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, -NH_2, -NH(C_1-C_4 alkyl), or -$N(C_1$-C_4 alkyl)$_2$;

m is 0, 1 or 2; and

n is 1 or 2,

In a first aspect of the eighteenth embodiment, R^1 is hydrogen, bromo, fluoro, chloro, C_1-C_6 alkyl, -O-C_1-C_6 alkyl, -S(O)$_m$-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, -O-C_3-C_7 cycloalkyl, -S(O)$_m$-C_3-C_7 cycloalkyl, -CN, - $NR^GR^{G'}$ or -NH-C(O)-(C_1-C_6 alkylene)- $NR^GR^{G'}$. In some embodiments, each alkyl, alkylene or cycloalkyl in the group represented by R^1 is optionally substituted with fluoro. In other embodiments, R^1 is fluoro, chloro, -CN or -N(CH_3)$_2$. In other embodiments, R^1 is fluoro, chloro or -N(CH_3)$_2$. In other embodiments, R^1 is fluoro. In other embodiments, R^1 is chloro. In other embodiments, R^1 is -N(CH_3)$_2$. In other embodiments, R^1 is hydrogen. The remaining variables are as described and defined in the eighteenth embodiment.

In a second aspect of the eighteenth embodiment, R^2 is fluoro, -C_1-C_6 alkyl, or -[$C(R^H)(R^{H'})$]$_m$-$N(R^I)(R^{I'})$. In other embodiments, R^2 is fluoro, methyl, -$CH(R^H)$-$N(R^I)(R^{I'})$, -(CH_2)$_2$-$N(R^I)(R^{I'})$, -NH(pyridyl), -NH(C_1-C_8 alkyl), -NHC(O)-C_1-C_3 alkylene-piperidine, -NHC(O)-C_1-C_3 alkylene-pyrrolidine or -NHS(O)$_2$-phenyl, wherein each piperidine and each pyrrolidine in the group represented by R^2 is optionally substituted with one or more -C_1-C_6 alkyl. In other embodiments, R^2 is fluoro, methyl or -$CH(R^H)$-$N(R^I)(R^{I'})$. In other embodiments, R^2 is -$CH(R^H)$-$N(R^I)(R^{I'})$. In other embodiments, R^2 is fluoro. In other embodiments, R^2 is -$NHR^{I'}$. The remaining variables are as described and defined in the eighteenth embodiment, or the first aspect thereof.

In a third aspect of the eighteenth embodiment, R^3 is hydrogen, fluoro, bromo, -CN, -[$C(R^H)(R^H)$]$_n$-$N(R^I)(R^{I'})$, -$NR^GR^{G'}$, NO_2, -NH-C(O)-C_1-C_4 alkylene-$N(R^I)(R^{I'})$, C_1-C_6 alkyl, -NH-C(O)-C_1-C_6 alkyl, -NH-S(O)$_m$-C_1-C_6 alkyl, -NH-S(O)$_m$-C_3-C_{10} carbocyclyl or -NH-S(O)$_m$-(4-13 membered) heterocyclyl. In other embodiments, R^3 is hydrogen, NH_2 or -CH_2-NH-CH_2-$C(CH_3)_3$. In other embodiments, R^3 is hydrogen. In other embodiments, R^3 is -[$C(R^H)(R^H)$]$_n$-$N(R^I)(R^{I'})$ or -$NR^GR^{G'}$. The remaining variables are as described and defined in the eighteenth embodiment, or the first or second aspect thereof.

In a fourth aspect of the eighteenth embodiment, each R^H and $R^{H'}$ is independently selected from hydrogen, C_1-C_4 alkyl, and C_3-C_{10} carbocyclyl. In other embodiments, R^H is hydrogen or methyl. The remaining variables are as described and defined in the eighteenth embodiment, or the first, second, or third aspect thereof.

In a fifth aspect of the eighteenth embodiment, R^I is hydrogen, C_1-C_{12} alkyl, -C_0-C_6 alkylene-C_3-C_{10} carbocyclyl, or -C_0-C_6 alkylene-(4-13 membered) heterocyclyl. In some embodiments, each alkyl, carbocyclyl, alkylene or heterocyclyl in the group represented by R^I is optionally and independently substituted with one or more substituents independently selected from fluoro, chloro, -OH, -O-C_1-C_4 alkyl, C_1-C_4 alkyl, fluoro-substituted-C_1-C_4 alkyl, -$NR^GR^{G'}$, C_3-C_{10} carbocyclyl and a (4-13 membered) heterocyclyl. In other embodiments, R^I is hydrogen, C_1-C_3 straight chained alkyl, C_1-C_3 straight chained fluoroalkyl, cyclopropyl or -CH_2-cyclopropyl. In other embodiments, R^I is hydrogen, C_1-C_3 straight chained alkyl or -CH_2-cyclopropyl. The remaining variables are as described and defined in the eighteenth embodiment, or the first through fourth aspect thereof.

In a sixth aspect of the eighteenth embodiment, $R^{I'}$ is hydrogen, C_1-C_8 alkyl, -C_0-C_6 alkylene-C_3-C_{10} carbocyclyl, -C_0-C_6 alkylene-(4-13 membered) heterocyclyl, -C(O)-C_1-C_6 alkyl, -C_0-C_6 alkylene-C(O)$NR^GR^{G'}$, -C(O)-C_1-C_6 alkylene-$NR^GR^{G'}$, -C_2-C_6 alkylene-$NR^GR^{G'}$, -$S(O)_m$-C_1-C_6 alkyl, -$S(O)_m$-C_3-C_{10} carbocyclyl or -$S(O)_m$-(4-13 membered) heterocyclyl. In some embodiments, when R^2 is hydrogen or C_1-C_2 alkyl, R^3 is additionally benzyl. In other embodiments, each alkyl, carbocyclyl, alkylene or heterocyclyl in the group represented by $R^{I'}$ is optionally and independently substituted with one or more substituents independently selected from fluoro, chloro, -OH, -O-C_1-C_4 alkyl, C_1-C_4 alkyl, fluoro-substituted-C_1-C_4 alkyl, -$NR^GR^{G'}$, C_3-C_{10} carbocyclyl and a (4-13 membered) heterocyclyl. In other embodiments, $R^{I'}$ is hydrogen, C_1-C_8 alkyl, -CH_2-CHF_2, -C_2-C_6 alkylene-O-C_1-C_3 alkyl, -C_3-C_{10} cycloalkyl, -C_3-C_{10}cycloalkyl-substituted C_1-C_3 alkyl, cyclopropyl-substituted cyclopropyl, -$(CH_2)_2$-phenyl or -$S(O)_2$-phenyl. In other embodiments, $R^{I'}$ is hydrogen, C_1-C_8 alkyl, -CH_2-CHF_2, -C_1-C_6 alkylene-O-C_1-C_3 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkyl-substituted C_1-C_3 alkyl, or -$(CH_2)_2$-phenyl, and when R^I is hydrogen or -C_1-C_2 alkyl, $R^{I'}$ is additionally benzyl. In other embodiments, $R^{I'}$ is selected from hydrogen, C_1-C_8 alkyl, -CH_2-CHF_2, -C_1-C_6 alkylene-O-C_1-C_3 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_2$-phenyl and C_3-C_{10} cycloalkyl-substituted C_1-C_3 alkyl, wherein each cycloalkyl in the group represented by $R^{I'}$ is optionally substituted with-C_1-C_3 alkyl or optionally benzofused The remaining variables are as described and defined in the eighteenth embodiment, or the first through fifth aspect thereof.

In a seventh aspect of the eighteenth embodiment, R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a (4-7 membered) monocyclic heterocylic ring,

or a (6-13 membered) bicyclic, spirocyclic or bridged heterocylic ring, wherein the (4-7 membered) monocyclic heterocylic ring, or the (6-13 membered) bicyclic, spirocyclic or bridged heterocyclic ring optionally comprises 1 to 4 additional heteroatoms independently selected from N, S and O. In some embodiments, the (4-7 membered) monocyclic heterocylic ring, or the (6-13 membered) bicyclic, spirocyclic or bridged heterocyclic ring is optionally substituted with one or more substituents independently selected from C_3-C_{10} carbocyclyl, (4-13 membered) heterocyclyl, fluoro, chloro, -OH, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -O-C_3-C_{10} carbocyclyl, -O-(4-13 membered) heterocyclyl, -C_0-C_4 alkyl-O-C_1-C_4 alkyl, -C_0-C_4 alkyl-O-C_1-C_4 fluoroalkyl, =O, -C(O)-C_1-C_4 alkyl, -C(O)N $R^GR^{G'}$, -N(R^G)-C(O)-C_1-C_4 alkyl, and -C_0-C_4 alkylene-N $R^GR^{G'}$, and wherein each carbocyclyl or heterocyclyl substituent is optionally substituted with fluoro, chloro, -OH, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, -NH_2, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$. In other embodiments, R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a ring selected from pyrrolidine, piperidine, piperazine and morpholine, wherein the ring is optionally substituted with one or more substituents independently selected from -OH, -C_1-C_3 alkyl and -C_1-C_3 alkylene-O-C_1-C_3 alkyl, and wherein the ring is optionally benzofused or spirofused to cyclopropyl. In other embodiments, R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a ring selected from pyrrolidine and piperidine, wherein the ring is optionally substituted with one or more substituents independently selected from fluoro, C_1-C_3 alkyl and -C_1-C_3 alkylene-O-C_1-C_3 alkyl, and wherein the ring is optionally benzofused or spirofused to cyclopropyl. The remaining variables are as described and defined in the eighteenth embodiment, or the first through sixth aspect thereof.

In an eighth aspect of the eighteenth embodiment, R^G and $R^{G'}$ are independently hydrogen or C_1-C_4 alkyl. In other embodiments, R^G and $R^{G'}$ taken together with the nitrogen atom to which they are bound form a (4-7 membered) heterocylic ring optionally comprising one additional heteroatom selected from N, S and O, wherein the (4-7 membered) heterocylic ring is optionally substituted with fluoro, chloro, -OH, fluoro-substituted C_1-C_4 alkyl, -C_1-C_4 alkyl, or -C_1-C_4 alkylene-O- C_1-C_4 alkyl, and is optionally benzofused. The remaining variables are as described and defined in the eighteenth embodiment, or the first through seventh aspect thereof.

A nineteenth embodiment of the invention is a compound of Structural Formula (III) or (III'), wherein R^2 is fluoro, methyl, -$CH(R^H)$-$N(R^I)(R^{I'})$, -$(CH_2)_2$-$N(R^I)(R^{I'})$, -NH(pyridyl), -NH(C_1-C_8 alkyl), -NHC(O)-C_1-C_3alkylene-piperidine, -NHC(O)-C_1-C_3 alkylene-pyrrolidine or -$NHS(O)_2$-phenyl, and each piperidine and each pyrrolidine in the group represented by R^2 is optionally substituted with one or more -C_1-C_6 alkyl; R^H is hydrogen or methyl; R^I is hydrogen, C_1-C_3 straight chained alkyl, C_1-C_3 straight chained fluoroalkyl, cyclopropyl or -CH_2-cyclopropyl; $R^{I'}$ is hydrogen, C_1-C_8 alkyl, -CH_2-CHF_2, -C_2-C_6 alkylene-O-C_1-C_3 alkyl, -C_3-C_{10} cycloalkyl, -C_3-C_{10}cycloalkyl-substituted C_1-C_3 alkyl, cyclopropyl-substituted cyclopropyl, -$(CH_2)_2$-phenyl or -$S(O)_2$-phenyl, and when R^I is hydrogen or C_1-C_2 alkyl, $R^{I'}$ is additionally benzyl; or R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a ring selected from pyrrolidine, piperidine, piperazine or morpholine, wherein the ring is optionally substituted with one or more substituents independently selected from -OH, -C_1-C_3 alkyl and -C_1-C_3 alkylene-O-C_1-C_3 alkyl, and wherein the ring is optionally benzofused or spirofused to cyclopropyl. The remaining variables are as described and defined in the eighteenth embodiment, or any aspect thereof.

A twentieth embodiment of the invention is a compound of Structural Formula (III) or (III'), wherein R^2 is fluoro, methyl or -$CH(R^H)$-$N(R^I)(R^{I'})$; R^H is hydrogen or methyl; R^I is hydrogen, C_1-C_3 straight chained alkyl or -CH_2-cyclopropyl; $R^{I'}$ is hydrogen, C_1-C_8 alkyl, -CH_2-CHF_2, -C_1-C_6 alkylene-O-C_1-C_3 alkyl, C_3-C_{10} cycloalkyl, or C_3-C_{10} cycloalkyl-substituted C_1-C_3 alkyl, wherein each cycloalkyl in the group represented by $R^{I'}$ is optionally substituted with -C_1-C_3 alkyl or optionally benzofused, or -$(CH_2)_2$-phenyl; and when R^I is hydrogen or -C_1-C_2 alkyl, $R^{I'}$ is additionally benzyl; or R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a ring selected from pyrrolidine and piperidine, wherein the ring is optionally substituted with one or more substituents independently selected from fluoro, -C_1-C_3 alkyl and -C_1-C_3 alkylene-O-C_1-C_3 alkyl, and wherein the ring is optionally benzofused or spirofused to cyclopropyl. The remaining variables are as described and defined in the eighteenth or nineteeth embodiment, or any aspect thereof.

A twenty-first embodiment of the invention is a compound of Structural Formula (III) or (III'), wherein X is fluoro, chloro, -CN or -$N(CH_3)_2$; and Z is hydrogen, NH_2 or -CH_2-NH-CH_2-$C(CH_3)_3$. The remaining variables are as described and defined in the eighteenth through twentieth embodiments, or any aspect thereof.

A twenty-second embodiment of the invention is a compound of Structural Formula (III) or III'), wherein

R^1 is selected from -OCH_3, -CF_3, Cl, F, and -$N(CH3)_2$;

Z is hydrogen and when R^1 is F, Z is additionally selected from hydrogen, -NH_2, -$NH(C_1$-C_2 alkyl), and -$N(C_1$-C_2 alkyl)$_2$; and

R^2 is -CH_2-$NR^IR^{I'}$;

wherein

R^I is selected from hydrogen and C_1-C_3 alkyl; and

$R^{I'}$ is selected from hydrogen, C_1-C_8 alkyl, C_0-C_6 alkylene C_3-C_{10} carbocyclyl, C_0-C_6 alkylene-(4-13 membered) heterocyclyl, and C_2-C_6 alkylene -$N(R^G)(R^{G'})$, wherein each carbocyclyl or heterocyclyl in the group represented by $R^{I'}$ is optionally and independently substituted with one or more substituents independently selected from fluoro, -OH, -O-C_1-C_3 alkyl, C_1-C_3 alkyl, fluoro-substituted C_1-C_3 alkyl, -$N(R^G)(R^{G'})$, C_3-C_{10} carbocyclyl or a (4-13 membered) heterocyclyl; or

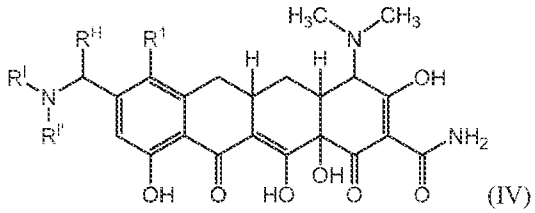
R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a (4-7 membered) saturated monocyclic heterocylic ring, or a (6-13 membered) saturated bicyclic, spirocyclic or bridged heterocylic ring, wherein the (4-7 membered) monocyclic heterocylic ring, or the (6-13 membered) bicyclic, spirocyclic or bridged heterocyclic ring, is optionally substituted with one or more substituents independently selected from C_3-C_{10} carbocyclyl, (4-13 membered) heterocyclyl, fluoro, -OH, -C_1-C_3 fluoroalkyl, -C_1-C_3 alkyl, -O-C_3-C_{10} carbocyclyl, -O-(4-13 membered) heterocyclyl, C_0-C_2 alkylene-O-C_1-C_3 alkyl, C_0-C_2 alkylene-O-C_1-C_3 fluoroalkyl, =O, and C_0-C_4 alkylene-$N(R^G)(R^{G'})$), and wherein each carbocyclyl or heterocyclyl substituent is optionally substituted with fluoro, -OH, C_1-C_3 fluoroalkyl, C_1-C_3 alkyl, -O-C_1-C_3 alkyl, -O-C_1-C_3 fluoroalkyl, -NH_2 -$NH(C_1$-C_4 alkyl), or -$N(C_1$-C_4 alkyl)$_2$; and

each R^G and $R^{G'}$ is independently selected from hydrogen and C_1-C_4 alkyl. The remaining variables are as described and defined in the eighteenth through twenty-first embodiments, or any aspect thereof.

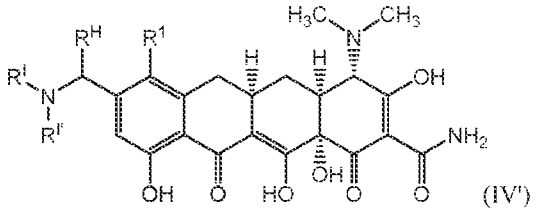
A twenty-third embodiment of the invention is a compound of Structural Formula (III) or (III'), wherein R^1 is -OCH_3. In other embodiments, R^1 is -CF_3. In other embodiments, R^1 is -Cl. In other embodiments, R^1 is -F and R^3 is hydrogen. In other embodiments, R^1 is - F and R^3 is selected from -NH_2, -$NH(C_1$-C_2 alkyl), and -$N(C_1$-C_2

alkyl)$_2$. In other embodiments, R^1 is -N(CH$_3$)$_2$. In other embodiments, R^2 is -NH$^{R'}$; and $R^{R'}$ is pyridyl, C$_1$-C$_8$ alkyl, -C(O)-C$_1$-C$_3$ alkylene-piperidine or -C(O)-C$_1$-C$_3$ alkylene-pyrrolidine. Each piperidine or pyrrolidine in the group represented by $R^{R'}$ is optionally substituted with one or more C$_1$-C$_3$ alkyl. The remaining variables are as described and defined in the eighteenth through twenty-second embodiments, or any aspect thereof.

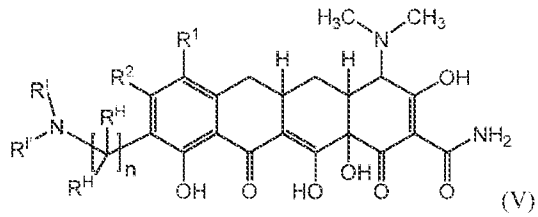
A twenty-fourth embodiment of the invention is a compound of Structural Formulae (IV), (IV'), (V), (V'), (Va), (Va'), (VI), (VI'), (VII) or (VII'):



(IV)



(IV')



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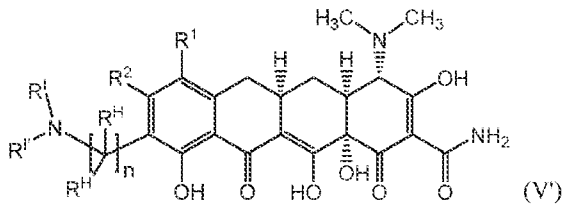
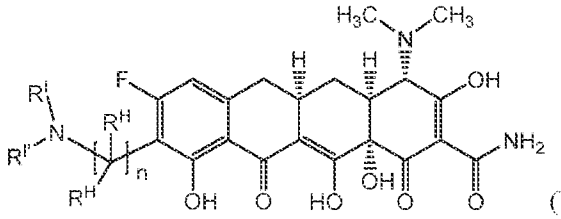
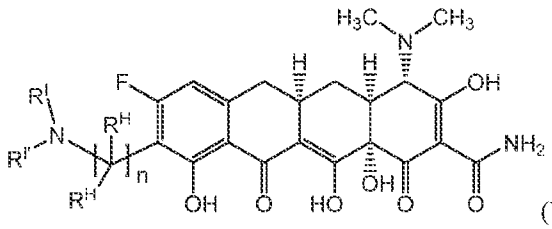


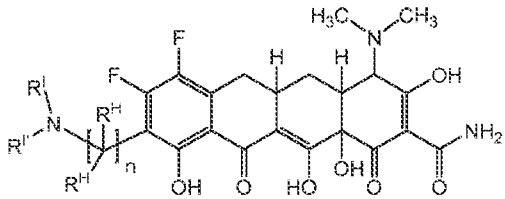
(V')



(Va)



(Va'),



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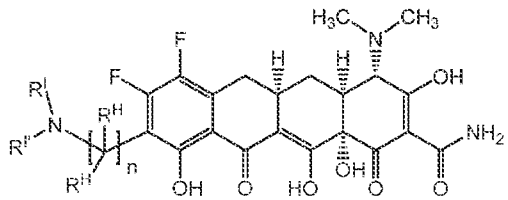
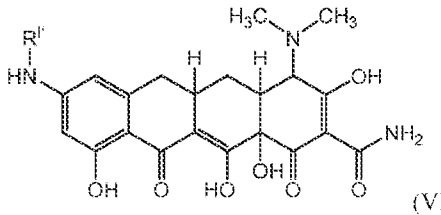
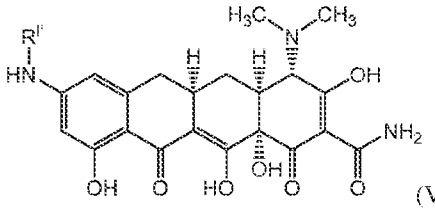


(VI'), or



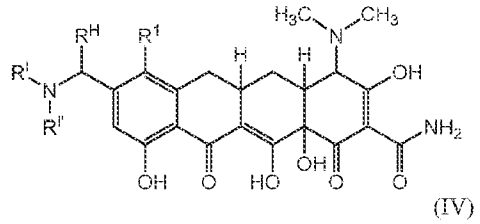
(VII)



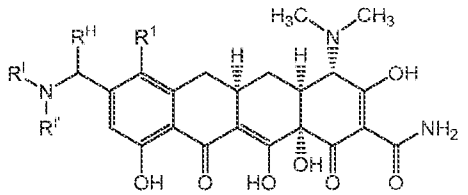
(VII')

or a pharmaceutically acceptable salt thereof, wherein values and alternative values for the variables are found in the eighteenth to twenty-third embodiments of the invention.

A twenty-fifth embodiment of the invention is a compound of Structural Formulae (IV) or (IV')



(IV)



(IV'),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from, bromo, fluoro, chloro, C_1-C_6 fluoroalkyl, -O-C_1-C_6 alkyl, -S(O)$_m$-C_1-C_6 alkyl, C_3-C_7 cycloalkyl, -O-C_3-C_7 cycloalkyl, -S(O)$_m$-C_3-C_7 cycloalkyl, -CN, and -NH-C(O)-(C_1-C_6 alkylene)-$NR^GR^{G'}$, wherein each alkyl, alkylene or cycloalkyl in the group represented by R^1 is optionally substituted with fluoro;

each R^G and $R^{G'}$ is independently selected from hydrogen and C_1-C_4 alkyl; or

R^G and $R^{G'}$ taken together with the nitrogen atom to which they are bound form a (4-7 membered) heterocylic ring optionally comprising one additional heteroatom selected from N, S and O, wherein the (4-7 membered) heterocylic ring is optionally substituted with fluoro, chloro, -OH, fluoro-substituted C_1-C_4 alkyl, -C_1-C_4 alkyl, or -C_1-C_4 alkylene-O-C_1-C_4 alkyl, and is optionally benzofused;

each R^H and $R^{H'}$ is independently selected from hydrogen, C_1-C_4 alkyl, and C_3-C_{10} carbocyclyl;

each R^I is selected from hydrogen, C_1-C_{12} alkyl, -C_0-C_6 alkylene-C_3-C_{10} carbocyclyl, and -C_0-C_6 alkylene-(4-13 membered) heterocyclyl;

each $R^{I'}$ is selected from hydrogen, C_1-C_8 alkyl, -C_0-C_6 alkylene-C_3-C_{10} carbocyclyl, -C_0-C_6 alkylene-(4-13 membered) heterocyclyl, -C(O)-C_1-C_6 alkyl, -C_0-C_6 alkylene-C(O)-$NR^GR^{G'}$, -C(O)-C_1-C_6 alkylene-$NR^GR^{G'}$, -C_2-C_6 alkylene-$NR^GR^{G'}$, -S(O)$_m$-C_1-C_6 alkyl, -S(O)$_m$-C_3-C_{10} carbocyclyl, and -S(O)$_m$-(4-13 membered) heterocyclyl, wherein

each alkyl, carbocyclyl, alkylene or heterocyclyl in the group represented by R^I or $R^{I'}$ is optionally and independently substituted with one or more substituents independently selected from fluoro, chloro, -OH, -O-C_1-C_4 alkyl, C_1-C_4 alkyl, fluoro-substituted-C_1-C_4 alkyl, -$NR^GR^{G'}$, C_3-C_{10} carbocyclyl and a (4-13 membered) heterocyclyl; or

R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a (4-7 membered) monocyclic heterocylic ring, or a (6-13 membered) bicyclic, spirocyclic or bridged heterocylic ring, wherein the (4-7 membered) monocyclic heterocylic ring, or the (6-13 membered) bicyclic, spirocyclic or bridged heterocyclic ring optionally comprises 1 to 4 additional heteroatoms independently selected from N, S and O; and wherein the (4-7 membered) monocyclic heterocylic ring, or the (6-13 membered) bicyclic, spirocyclic or bridged heterocyclic ring is optionally substituted with one or more substituents independently selected from C_3-C_{10} carbocyclyl, (4-13 membered) heterocyclyl, fluoro, chloro, -OH, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -O-C_3-C_{10} carbocyclyl, -O-(4-13 membered) heterocyclyl, -C_0-C_4 alkyl-O-C_1-C_4 alkyl, -C_0-C_4 alkyl-O-C_1-C_4 fluoroalkyl, =O, -C(O)-C_1-C_4 alkyl, -C(O) $NR^GR^{G'}$, -$N(R^G)$-C(O)-C_1-C_4 alkyl, and -C_0-C_4 alkylene-$NR^GR^{G'}$, and wherein each carbocyclyl or heterocyclyl substituent is optionally substituted with fluoro, chloro, -OH, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, -NH_2, -NH(C_1-C_4 alkyl), or -N(C_1-C_4 alkyl)$_2$; and

m is 0, 1 or 2.

In a first aspect of the twenty-fifth embodiment,

R^H is selected from hydrogen and methyl;

R^I is selected from hydrogen, C_1-C_3 straight chained alkyl, C_1-C_3 straight chained fluoroalkyl, cyclopropyl, and -CH_2-cyclopropyl;

$R^{I'}$ is selected from hydrogen, C_1-C_8 alkyl, -CH_2-CHF_2, -C_2-C_6 alkylene-O-C_1-C_3 alkyl, -C_3-C_{10} cycloalkyl, -C_3-C_{10} cycloalkyl-substituted C_1-C_3 alkyl, cyclopropyl-substituted cyclopropyl, -$(CH_2)_2$-phenyl, and -$S(O)_2$-phenyl, when R^2 is hydrogen or C_1-C_2 alkyl, R^3 is additionally selected from benzyl; or

R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a ring selected from pyrrolidine, piperidine, piperazine or morpholine, wherein the ring is optionally substituted with one or more substituents independently selected from -OH, -C_1-C_3 alkyl and -C_1-C_3 alkylene-O-C_1-C_3 alkyl, and wherein the ring is optionally fused to phenyl or spirofused to cyclopropyl.

In a second aspect of the twenty-fifth embodiment,

R^H is selected from hydrogen and methyl;

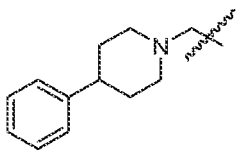
R^I is selected from hydrogen, C_1-C_3 straight chained alkyl and -CH_2-cyclopropyl;

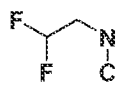
$R^{I'}$ is selected from hydrogen, C_1-C_8 alkyl, -CH_2-CHF_2, -C_1-C_6 alkylene-O-C_1-C_3 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_2$-phenyl and C_3-C_{10} cycloalkyl-substituted C_1-C_3 alkyl, wherein each cycloalkyl in the group represented by R^3 is optionally substituted with-C_1-C_3 alkyl or optionally benzofused and when R^2 is hydrogen or -C_1-C_2 alkyl, R^3 is additionally selected from benzyl; or

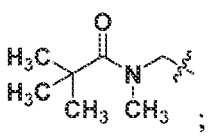
R^I and $R^{I'}$ taken together with the nitrogen atom to which they are bound form a ring selected from pyrrolidine and piperidine, wherein the ring is optionally substituted with one or more substituents independently selected from fluoro -C_1-C_3 alkyl and -C_1-C_3 alkylene-O-C_1-C_3 alkyl, and wherein the ring is optionally fused to phenyl or spirofused to cyclopropyl.

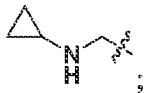
In a third aspect of the twenty-fifth embodiment, R^1 is fluoro or chloro.

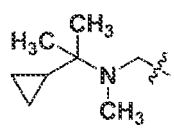
In a fourth aspect of the twenty-fifth embodiment, the compound used in the method of treating hematological malignancies is seleted from any one of the following:

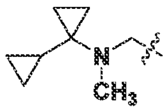
R^1 is fluoro and -$CH(R^H)$-$NR^IR^{I'}$ is  ;

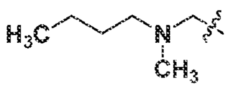
R^1 is fluoro and -$CH(R^H)$-$NR^IR^{I'}$ is  ;

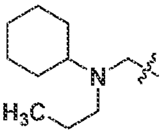
R^1 is fluoro and -$CH(R^H)$-$NR^IR^{I'}$ is  ;

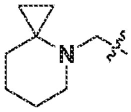
R^1 is fluoro and -$CH(R^H)$-$NR^IR^{I'}$ is  ;

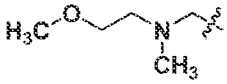
R^1 is fluoro and -$CH(R^H)$-$NR^IR^{I'}$ is  ;

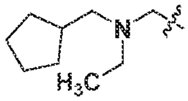
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

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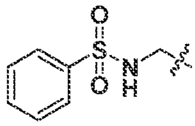
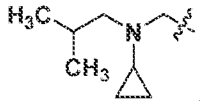
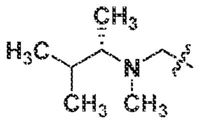
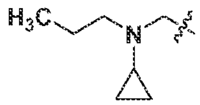
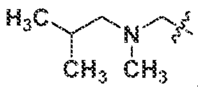
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and --CH(R^H)-NR^{I}R$^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

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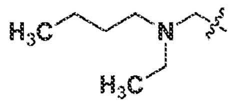
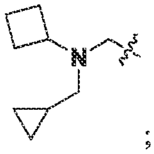
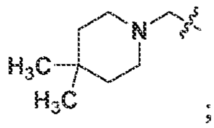
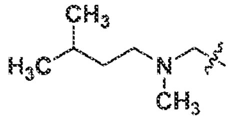
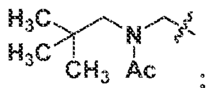
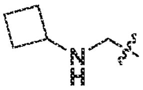
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

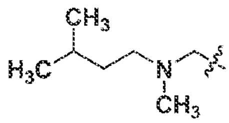
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

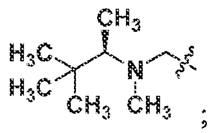
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

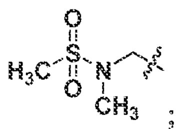
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

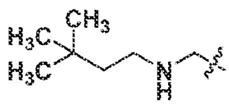
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

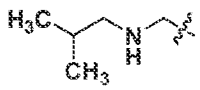
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

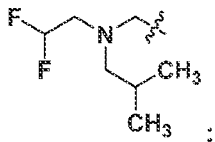
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

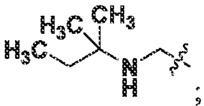
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

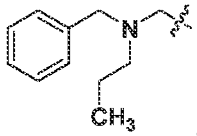
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

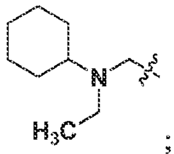
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

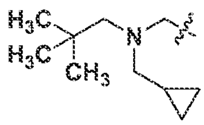
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

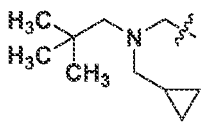
R^1 is fluoro and $-CH(R^H)-NR^IR^{I'}$ is  ;

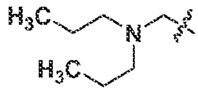
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

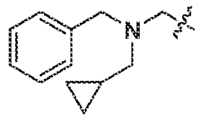
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

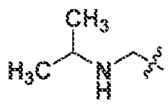
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

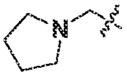
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

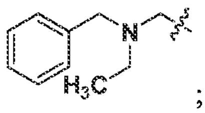
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

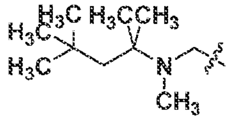
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

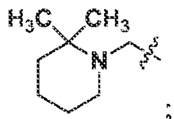
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

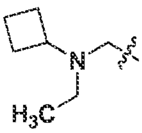
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

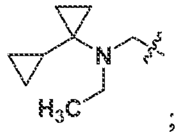
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

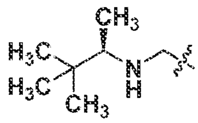
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

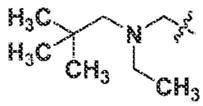
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

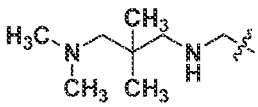
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

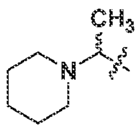
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

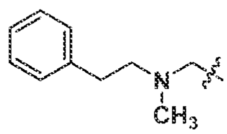
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

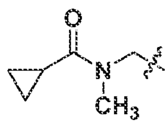
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

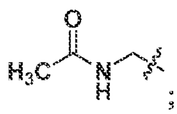
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

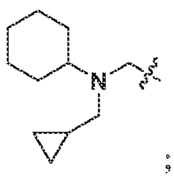
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

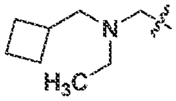
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

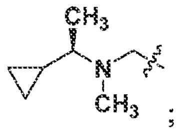
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

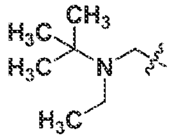
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

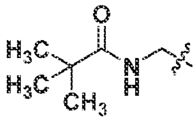
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

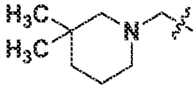
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

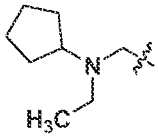
R^1 is fluoro and -CH(R^H)-$NR^IR^{I'}$ is  ;

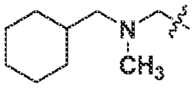
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

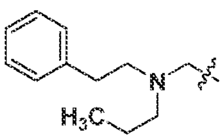
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

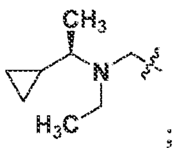
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

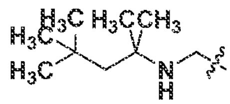
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

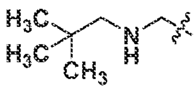
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

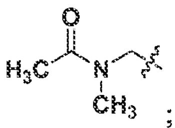
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

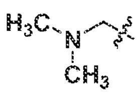
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

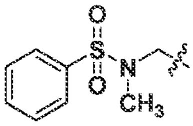
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

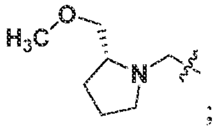
R^1 is fluoro and --CH(R^H)-N$R^I$$R^{I'}$ is  ;

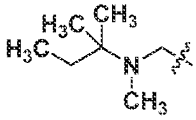
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

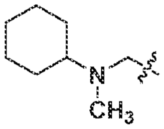
R^1 is fluoro and -CH(R^H)-N$R^I$$R^{I'}$ is  ;

R^1 is fluoro and --CH(R^H)-N$R^I$$R^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

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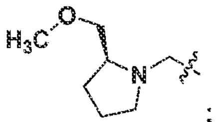
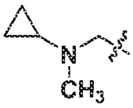
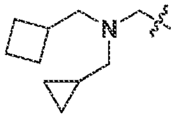
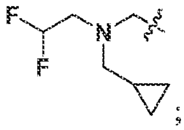
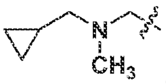
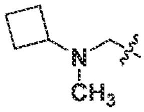
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

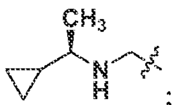
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

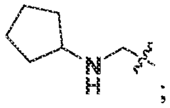
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

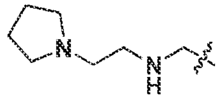
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

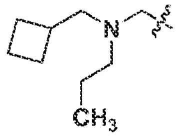
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

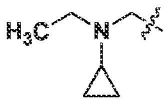
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

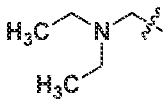
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

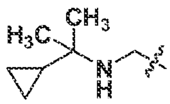
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

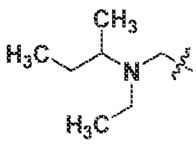
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

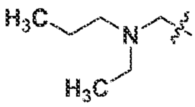
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

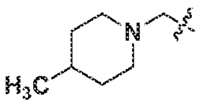
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

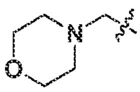
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

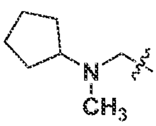
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

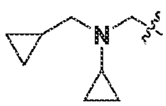
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

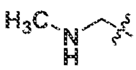
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

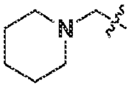
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

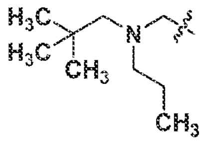
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

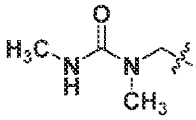
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

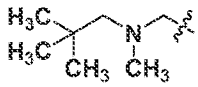
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

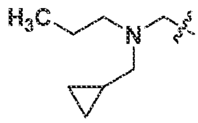
R^1 is fluoro and -CH(R^H)-N$R^IR^{I'}$ is  ;

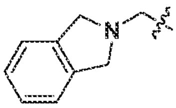
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

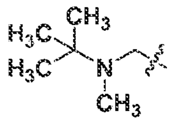
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

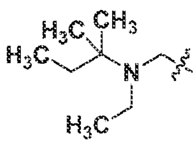
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

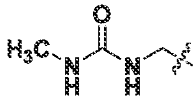
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

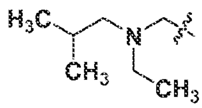
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

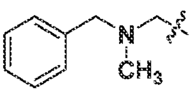
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

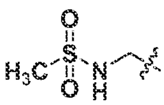
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

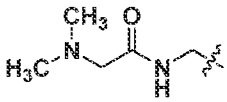
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

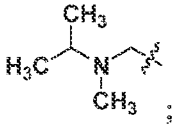
R^1 is fluoro and --CH(R^H)-N$R^I R^{I'}$ is  ;

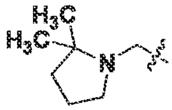
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

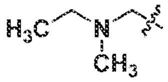
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

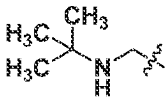
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

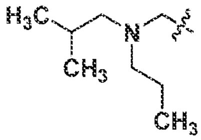
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

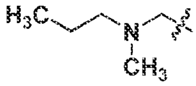
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

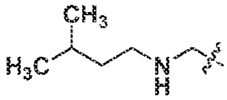
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

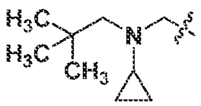
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

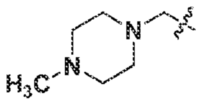
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

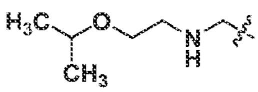
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

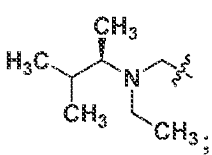
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

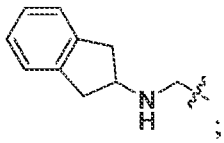
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

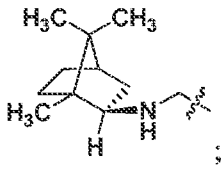
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

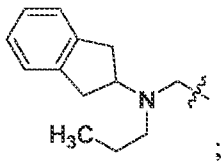
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

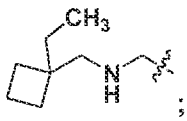
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

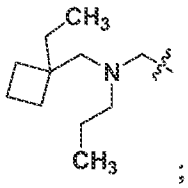
R^1 is fluoro and -CH(R^H)-NR^{I}R$^{I'}$ is  ;

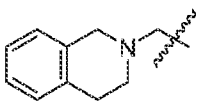
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

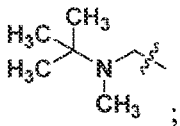
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

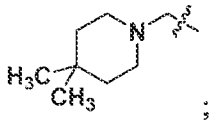
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

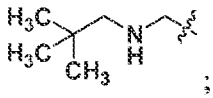
R^1 is fluoro and -CH(R^H)-N$R^I R^{I'}$ is  ;

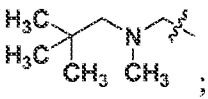
R^1 is chloro and -CH(R^H)-N$R^I R^{I'}$ is 

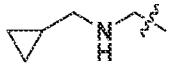
R^1 is chloro and -CH(R^H)-N$R^I R^{I'}$ is  ;

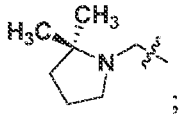
R^1 is chloro and -CH(R^H)-N$R^I R^{I'}$ is  ;

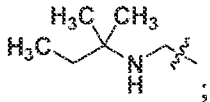
R^1 is chloro and -CH(R^H)-N$R^I R^{I'}$ is  ;

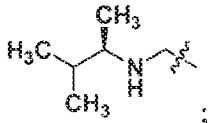
R^1 is chloro and --CH(R^H)-N$R^I R^{I'}$ is  ;

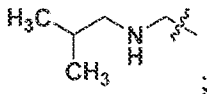
R^1 is chloro and $-CH(R^H)-NR^IR^{I'}$ is  ;

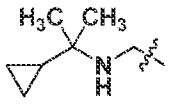
R^1 is chloro and $-CH(R^H)-NR^IR^{I'}$ is  ;

R^1 is chloro and $-CH(R^H)-NR^IR^{I'}$ is  ;

R^1 is chloro and $-CH(R^H)-NR^IR^{I'}$ is  ;

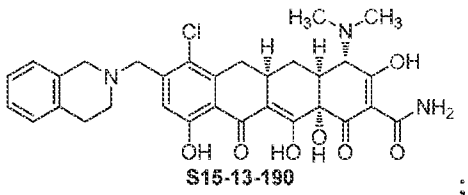
R^1 is chloro and $-CH(R^H)-NR^IR^{I'}$ is  ;

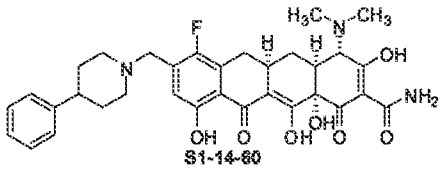
R^1 is chloro and $-CH(R^H)-NR^IR^{I'}$ is  ; and

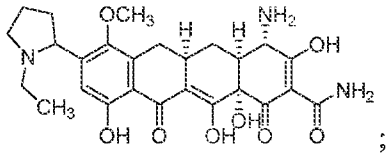
R^1 is chloro and $-CH(R^H)-NR^IR^{I'}$ is  or a pharmaceutically acceptable salt of any of the foregoing. The above listed compounds were prepared according to the synthetic procedures detailed in U.S. Patent No. 9,315,451 incorporated herein by reference in its entirety.

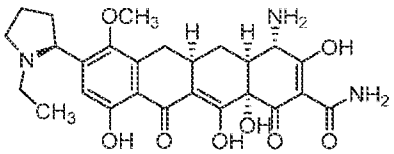
In a fifth aspect of the twenty-fifth embodiment, R^1 is $-OCH_3$, $-CF_3$, Cl or F.

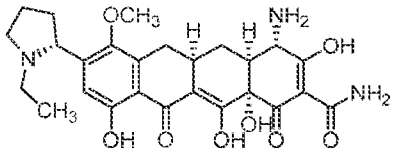
A twenty-sixth embodiment of the invention is a compound selected from

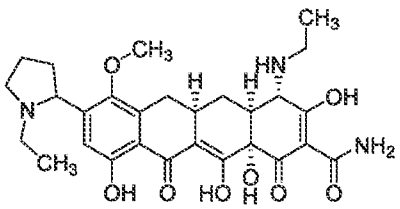
Compound 1: 
S15-13-190 ;

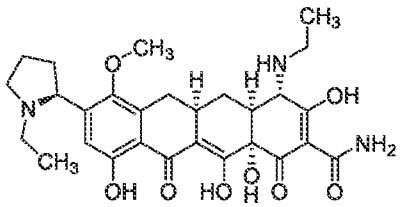
Compound 2: 
S1-14-60 ;

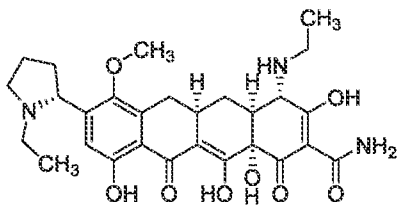
Compound 3  ;

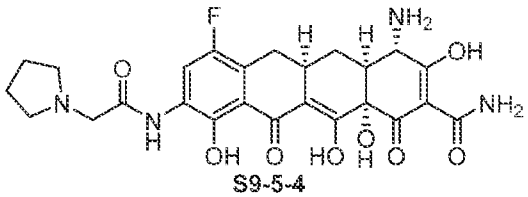
Compound 3a 

Compound 3b 

Compound 4 

Compound 4a 

Compound 4b  ; and



S9-5-4

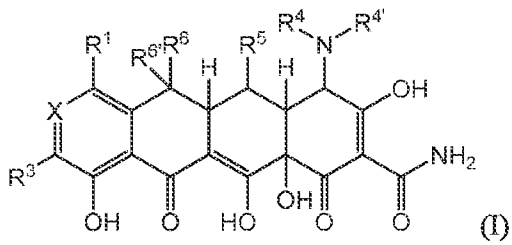
Compound 5

or a pharmaceutically acceptable salt thereof.

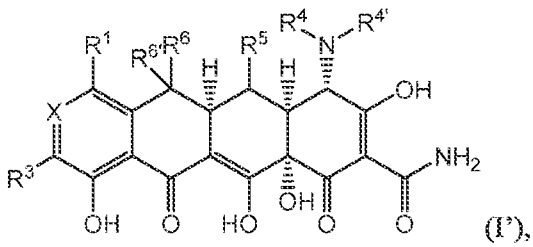
FURTHER EMBODIMENTS

In further embodiments, the present invention relates to a method of treating a hematological cancer in a subject in need thereof and compounds for use in treating such cancer. The method comprises administering to the subject an effective amount of a compound represented by any one of structural formulas described below or a pharmaceutically acceptable salt thereof.

A twenty-seventh embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound having Structural Formula (I) or (I'):



(I)



(I'),

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof. In a first aspect of the twenty-sixth embodiment:

X is selected from $C(R^2)$ and N;

R^1 is $-OR^A$, hydrogen, halo, -(C_1-C_6 alkyl), $-C(O)NR^BR^{B'}$, $-NR^BR^{B'}$, $-S(O)_{0-2}R^C$, (C_0-C_6 alkylenyl)-(C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)-(4- to 13-member) heterocyclyl;

R^2 is -(C_0-C_6 alkylenyl)-(4- to 13-member) heterocyclyl, hydrogen, halo, -(C_1-C_6 alkyl), $-OR^A$, $-C(O)NR^BR^{B'}$, $-NR^BR^{B'}$, $-S(O)_{0-2}R^C$, or (C_0-C_6 alkylenyl)-(C_{3-12}) carbocyclyl; or

R^1 and R^2 are optionally taken together with atoms to which they are bound to form a C_{3-12} carbocyclyl or a 4- to 13-member heterocyclyl ring;

each of R^3, R^5 and R^6 is independently selected from hydrogen, halo, -(C_1-C_6 alkyl), $-OR^A$, $-C(O)NR^BR^{B'}$, $NR^BR^{B'}$, $S(O)_{0-2}R^C$, -(C_0-C_6 alkylenyl)-(C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)-(4- to 13-member) heterocyclyl; or

R^2 and R^3 are optionally taken together with atoms to which they are bound to form a C_{3-12} carbocyclyl or a 4- to 13-member heterocyclyl ring;

R^4 is selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl;

$R^{4'}$ is selected from hydrogen, -(C_1-C_6 alkyl), $S(O)_{1-2}R^C$, -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, -C(O)-(C_1-C_6 alkyl), and -C(O)-(C_1-C_6 alkyl)-NR^DR^E, $-C(NR^*)NR^{**}R^{***}$, wherein R*, R**, and R***, each independently, is H or a C_{1-4} alkyl, -C(O)-(C_{3-12})carbocyclyl; or

R^4 and $R^{4'}$ are optionally taken together with the nitrogen atom to which they are commonly bound to form a 4-8 membered ring optionally comprising 1-2 additional heteroatoms independently selected from N, O and S;

$R^{6'}$ is selected from hydrogen, -(C_1-C_6 alkyl) and -(C_3-C_6 cycloalkyl);

each R^A is independently selected from -(C_1-C_6 alkyl), hydrogen, -(C_0-C_6 alkylenyl)-(C_{3-12}) carbocyclyl, -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -C(O)-(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, and $-C(O)N(R^D)(R^E)$;

each R^B and each $R^{B'}$ is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, -$S(O)_{1-2}$-(C_1-C_6 alkyl), -$S(O)_{1-2}$-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -$S(O)_{1-2}$-(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, -C(O)-(C_0-C_6 alkylenyl)-$N(R^D)(R^E)$, and $-N^+(R^F)_3$, wherein R^F, for each occurrence independently, is H, a C_{1-6} alkyl, a C_{1-6} haloalkyl, a (C_{1-4} alkoxy)-(C_{1-6})alkyl, an amino(C_{1-6})alkyl or a mono- or di(C_{1-4} alkyl)amino-(C_{1-6})alkyl, a (C_{3-12})carbocyclyl-(C_0-

3)alkylenyl, a or any two R^F, taken together with the nitrogen atom to which they are attached, for a 4- to 13-member heterocyclyl, optionally including one additional heteroatom selected from O, N or S;

each R^C is independently selected from -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl and -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl; and

each R^D and each R^E is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl,

wherein:

any alkyl, or alkylenyl portion of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6 is optionally and independently substituted with one or more substituents independently selected from halo, =O, OR^A, $NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

any alkyl or alkylenyl portion of $R^{6'}$, R^A, or R^C, is optionally and independently substituted with one or more fluoro;

any carbocyclyl or heterocyclyl portion of any of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6, or any ring formed by taking together R^1 and R^2, R^2 and R^3 or R^4 and $R^{4'}$ is optionally and independently substituted on a carbon atom with one or more substituents independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylenyl)-(C_3-C_{10} carbocyclyl), -(C_0-C_6 alkylenyl)-(4-13 membered heterocyclyl), OR^A, -(C_0-C_6 alkylenyl)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

any heterocyclyl portion of any of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6, or any ring formed by taking together R^1 and R^2, R^2 and R^3 or R^4 and $R^{4'}$ is optionally and independently substituted on a substitutable nitrogen atom with R^F;

each R^F is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 hydroxyalkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, -$S(O)_{1-2}$-(C_1-C_6 alkyl), -$S(O)_{1-2}$-(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -$S(O)_{1-2}$-(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, -(C_0-C_6 alkylenyl)-$C(O)_2$-(C_1-C_6 alkyl), -(C_1-C_6 alkylenyl)-$NR^BR^{B'}$ and -$C(O)N(R^D)(R^E)$;

any carbocyclyl or heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, any cycloalkyl portion of $R^{6'}$, or any substituent of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6 is optionally and independently substituted on a carbon atom with a one or more substituents independently selected from

fluoro, chloro, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, =O, -OH, -NH_2, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$;

any heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, or any heterocyclyl substituent of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, or R^6 is optionally substituted on a substitutable nitrogen atom with -C_1-C_4 alkyl, or -S(O)$_{1-2}$-(C_1-C_4 alkyl).

In a second aspect of the twenty-sixth embodiment:

X is selected from N and C(R^2);

each of R^1, R^2, R^3, R^5 and R^6 is independently selected from hydrogen, halo, -(C_1-C_6 alkyl), -OR^A, -C(O)$NR^BR^{B'}$, $NR^BR^{B'}$, S(O)$_{0-2}R^C$, -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl; or

R^1 and R^2 are optionally taken together with atoms to which they are bound to form a C_{3-12} carbocyclyl or 4- to 13-member heterocyclyl ring; or

R^2 and R^3 are optionally taken together with atoms to which they are bound to form a C_{3-12} carbocyclyl or 4- to 13-member heterocyclyl ring;

R^4 is selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl;

$R^{4'}$ is selected from hydrogen, -(C_2-C_6 alkyl), S(O)$_{1-2}R^C$, -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, -C(O)-(C_1-C_6 alkyl), and -C(O)-(C_1-C_6 alkyl)-NR^DR^E; or

R^4 and $R^{4'}$ are optionally taken together with the nitrogen atom to which they are commonly bound to form a 4-8 membered ring optionally comprising 1-2 additional heteroatoms independently selected from N, O and S;

$R^{6'}$ is selected from hydrogen, -(C_1-C_6 alkyl) and -(C_3-C_6 cycloalkyl);

each R^A is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -C(O)-(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, and -C(O)N(R^D)(R^E);

each R^B and each $R^{B'}$ is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, -S(O)$_{1-2}$-(C_1-C_6 alkyl), -S(O)$_{1-2}$-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -S(O)$_{1-2}$-(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, -C(O)-(C_1-C_6

alkyl), -C(O)-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, and -C(O)N(R^D)(R^E);

each R^C is independently selected from -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl and -(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl; and

each R^D and each R^E is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl,

wherein:

any alkyl, or alkylenyl portion of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6 is optionally and independently substituted with one or more substituents independently selected from halo, =O, OR^A, $NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

any alkyl or alkylenyl portion of $R^{6'}$, R^A, or R^C, is optionally and independently substituted with one or more fluoro;

any carbocyclyl or heterocyclyl portion of any of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6, or any ring formed by taking together R^1 and R^2, R^2 and R^3, or R^4 and $R^{4'}$ is optionally and independently substituted on a carbon atom with one or more substituents independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, C_3-C_{10} carbocyclyl, a 4-13 membered heterocyclyl, OR^A, $NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

any heterocyclyl portion of any of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6, or any ring formed by taking together R^1 and R^2, R^2 and R^3, or R^4 and $R^{4'}$ is optionally and independently substituted on a substitutable nitrogen atom with R^F;

each R^F is independently selected from -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, -$S(O)_{1-2}$-(C_1-C_6 alkyl), -$S(O)_{1-2}$-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -$S(O)_{1-2}$-(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylenyl)- (4- to 13-member)heterocyclyl, and -C(O)N(R^D)(R^E);

any carbocyclyl or heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, any cycloalkyl portion of $R^{6'}$, or any substituent of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, R^6 is optionally and independently substituted on a carbon atom with a one or more substituents independently selected from fluoro, chloro, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, =O, -OH, -NH_2, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$; and

any heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, or any heterocyclyl substituent of R^1, R^2, R^3, R^4, $R^{4'}$, R^5, or R^6 is optionally substituted on a substitutable nitrogen atom with -C_1-C_4 alkyl, or -$S(O)_{1-2}$-(C_1-C_4 alkyl). The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the first aspect of the 26th embodiment.

In a third aspect of the 26th embodiment, each of R^5, R^6 and $R^{6'}$ is hydrogen. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the first and second aspects of the 26th embodiment.

In a fourth aspect of the 26th embodiment, R^4 is selected from hydrogen and -(C_1-C_6 alkyl); $R^{4'}$ is selected from hydrogen, -(C_2-C_6 alkyl) optionally substituted with one or more substituents independently selected from hydroxy and halo, -(C_3-C_6 cycloalkyl), -C(O)-(C_1-C_6 alkyl), -C(O)-(C_1-C_6 alkylenyl)-N(R^D)(R^E), and $S(O)_{1-2}R^C$; or R^4 and $R^{4'}$ are taken together with the nitrogen atom to which they are commonly bound to form a 4-6 membered ring optionally comprising 1-2 additional heteroatoms independently selected from N, O and S; R^C is -(C_1-C_6 alkyl); and each of R^D and R^E is independently selected from hydrogen and -(C_1-C_6 alkyl). The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through three of the 26th embodiment.

In the fifth aspect of the 26th embdoiemnt, R^4 is selected from hydrogen and -(C_1-C_6 alkyl); $R^{4'}$ is selected from hydrogen, -(C_2-C_6 alkyl), -(C_3-C_6 cycloalkyl), -C(O)-(C_1-C_6 alkyl), -C(O)-(C_1-C_6 alkylenyl)-N(R^D)(R^E), and $S(O)_{1-2}R^C$; R^C is -(C_1-C_6 alkyl); and each of R^D and R^E is independently selected from hydrogen and -(C_1-C_6 alkyl). The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through four of the 26th embodiment.

In the sixth aspect of the 26th embodiment, R^4 is selected from hydrogen, methyl, ethyl and propyl; and $R^{4'}$ is selected from hydrogen, ethyl, propyl, cyclopropyl, -$C(O)CH_3$, -$C(O)CH_2N(CH_3)_2$, and -$S(O)_2CH_3$. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through five of the 26th embodiment.

In the seventh aspect of the 26th embodiment, R^1 is selected from hydrogen, halo, -(C_1-C_6 alkyl) optionally substituted with one or more substituents independently selected from halo, -$NR^BR^{B'}$, -$C(O)NR^BR^{B'}$, -OR^A, -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, wherein R^A is C_1-C_6 alkyl optionally substituted with one or more fluoro. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through six of the 26th embodiment.

In the eight aspect of the 26th embodiment, R^3 is selected from hydrogen and -$N(R^B)(R^{B'})$, wherein R^B is hydrogen. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through seven of the 26th embodiment.

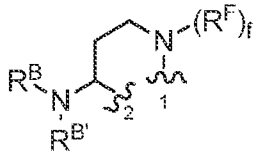
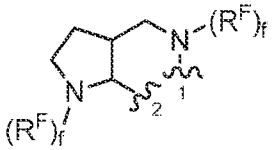
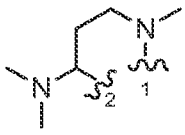
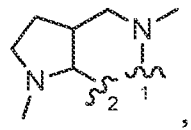
In the ninth aspect of the 26th embodiment, X is $C(R^2)$. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through eight of the 26th embodiment.

In the tenth aspect of the 26th embodiment, X is $C(R^2)$; and R^1 is selected from hydrogen, halo, -(C_1-C_6 alkyl) optionally substituted with one or more substituents independently selected from halo, -$NR^BR^{B'}$, -$C(O)NR^BR^{B'}$, -OR^A, -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl, and -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl, wherein R^A is C_1-C_6 alkyl optionally substituted with one or more fluoro. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through eight of the 26th embodiment.

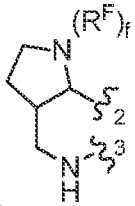
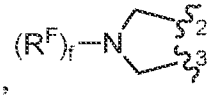
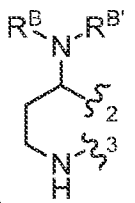
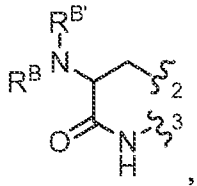
In the tenth aspect of the 26th embodiment, R^1 is selected from hydrogen, halo, -(C_1-C_6 alkyl) optionally substituted with one or more substituents independently selected from halo, and -OR^A, wherein R^A is C_1-C_6 alkyl optionally substituted with one or more fluoro. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through nine of the 26th embodiment.

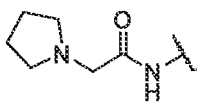
In the eleventh aspect of the 26th embodiment, R^1 is selected from hydrogen, fluoro, chloro, CF_3, OCH_3, OCF_3, $N(CH_3)_2$ and $NHCH_3$, for example, R^1 is selected from hydrogen, fluoro, chloro, CF_3 and OCF_3. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through ten of the 26th embodiment.

In the twelfth aspect of the 26th embodiment, X is $C(R^2)$; and R^1 and R^2 are taken together with the atoms to which they are bound to form a 4- to 13-member nitrogen-containing heterocyclyl ring, wherein the ring comprising R^1 and R^2 is optionally substituted on any substitutable nitrogen atom with C_1-C_4 alkyl; and optionally substituted on a carbon atom with $NR^BR^{B'}$, wherein each of R^B and $R^{B'}$ is independently selected from hydrogen and C_1-C_6 alkyl. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through elleven of the 26th embodiment.

In the thirteenth aspect of the 26th embodiment, X is $C(R^2)$; and R^1 and R^2 are taken together with the carbon atoms to which they are bound to form:  or  , wherein "∿ 1" represents a point of attachment to the carbon atom bound to R^1; and "∿ 2" represents a point of attachment to the carbon atom bound to R^2; and f is 0 or 1. For example, R^1 and R^2 are taken together with the carbon atoms to which they are bound to form:  or  , wherein "∿ 1" represents a point of attachment to the carbon atom bound to R^1 and "∿ 2" represents a point of attachment to the carbon atom bound to R^2. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through twelve of the 26th embodiment.

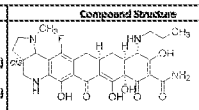
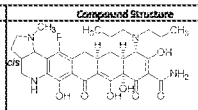
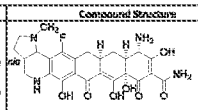
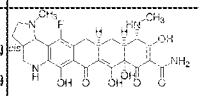
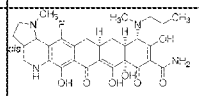
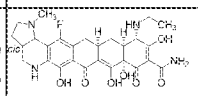
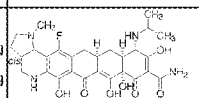
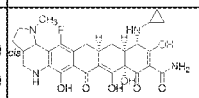
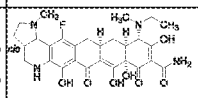
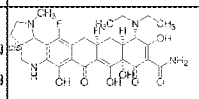
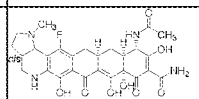
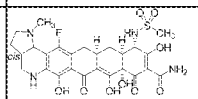
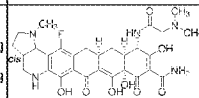
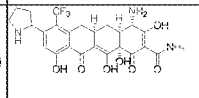
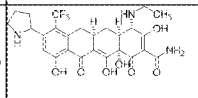
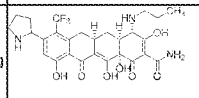
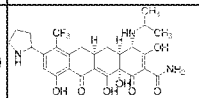
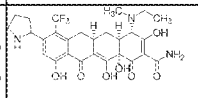
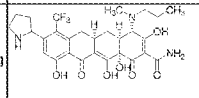
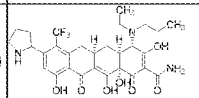
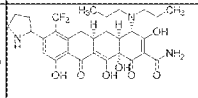
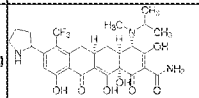
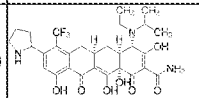
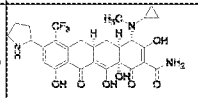
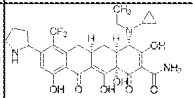
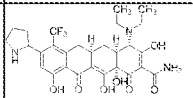
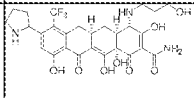
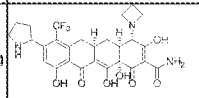
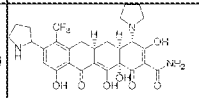
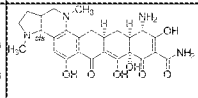
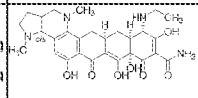
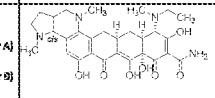
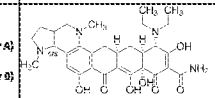
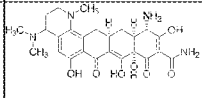
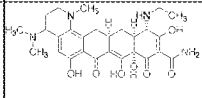
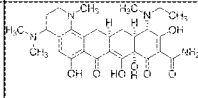
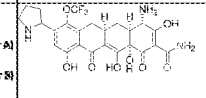
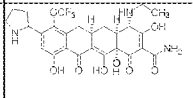
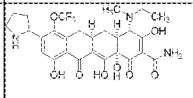
In the fourteenth aspect of the 26th embodiment, X is $C(R^2)$; and R^2 is -(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl optionally substituted on a nitrogen atom with -(C_1-C_6 alkyl); -(C_0-C_6 alkylenyl)- (C_{3-12}) carbocyclyl; or -(C_1-C_6)alkyl substituted with $NR^BR^{B'}$. For example, R^2 is pyrrolidinyl optionally substituted on a nitrogen atom with C_1-C_4 alkyl or benzyl. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through elleven of the 26th embodiment.

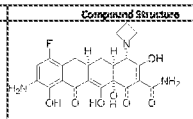
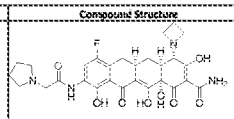
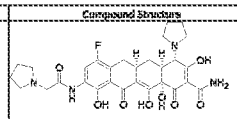
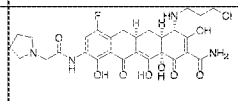
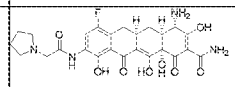
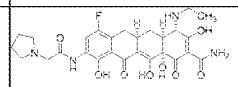
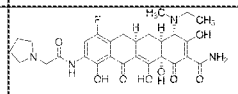
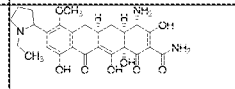
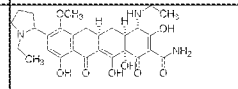
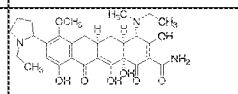
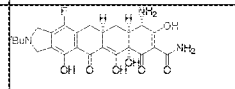
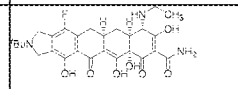
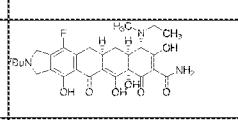
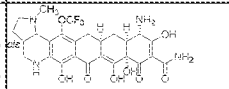
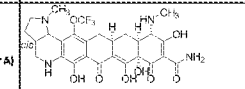
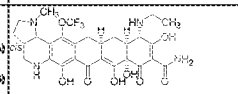
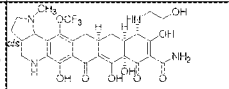
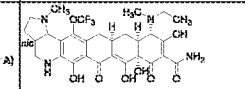
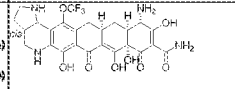
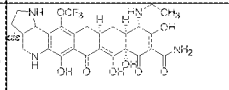
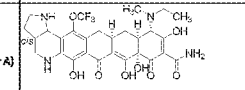
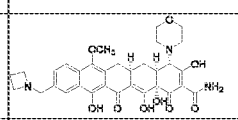
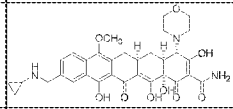
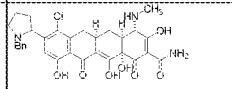
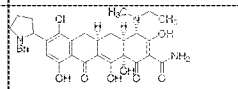
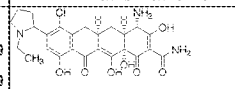
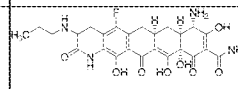
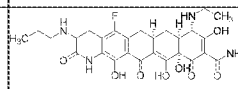
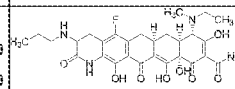
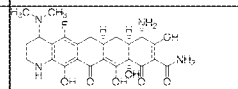
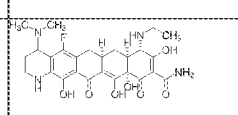
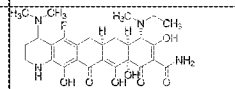
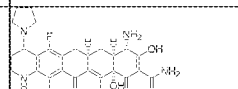
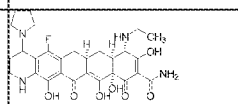
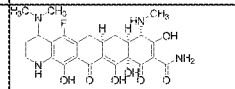
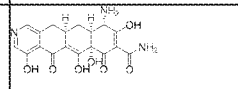
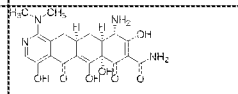
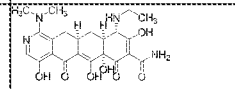
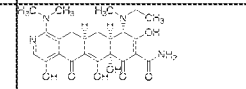
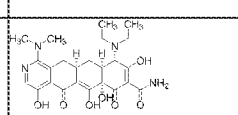
In the fifteenth aspect of the 26th embodiment, X is C(R^2); and R^2 and R^3 are taken together with the atoms to which they are bound to form a nitrogen-containing 4- to 13-memberheterocyclyl. For example, R^2 and R^3 are taken together with the atoms to which they are bound to form  ,  ,  or  , wherein "$\sim$ 2" represents a point of attachment to the carbon atom bound to R^2; "$\sim$ 3" represents a point of attachment to the carbon atom bound to R^3; and f is 0 or 1. The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through eleven of the 26th embodiment.

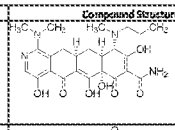
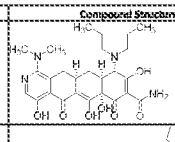
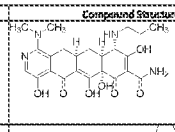
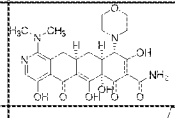
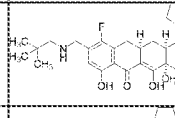
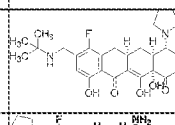
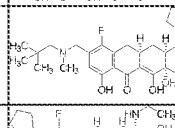
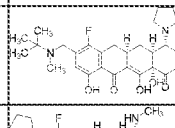
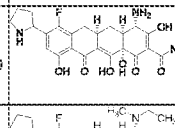
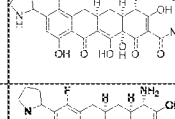
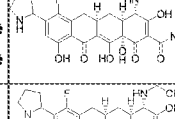
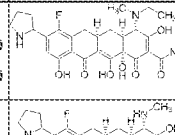
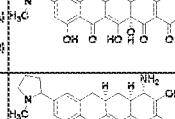
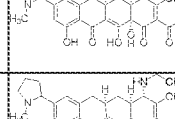
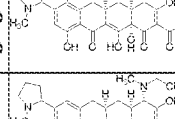
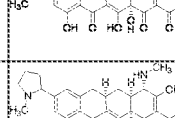
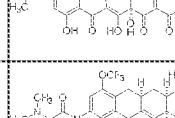
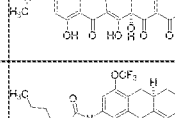
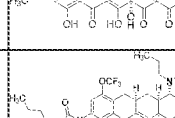
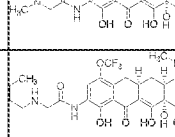
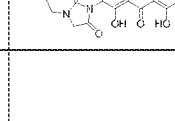
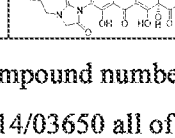
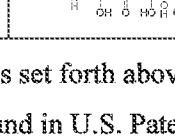
In the sixteenth aspect of the 26th embodiment, X is C(R^2); and R^3 is selected from hydrogen and -N(R^B)($R^{B'}$), wherein R^B is hydrogen and $R^{B'}$ is -C(O)-(C_0-C_6 alkylenyl)- (4- to 13-member) heterocyclyl or -C(O)-(C_0-C_6 alkylenyl)-N(R^D)(R^E). For example, R^3 is selected from hydrogen and  . The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through fourteen of the 26th embodiment.

In the seventeenth aspect of the 26th embodiment, X is C(R^2). The remainder of the values and example values of the variables in structural formulas (I) and (I') of the 26th embodiment are as defined above with respect to the aspects one through nine of the 26th embodiment.

In the eighteenth aspect of the 26th embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

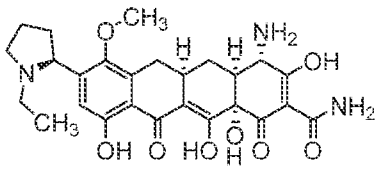
Compound No.	Compound Structure	Compound No.	Compound Structure	Compound No.	Compound Structure
S3-7-3-A (diastereomer A) S3-7-3-B (diastereomer B)		S3-7-4		S3-7-5-A (diastereomer A) S3-7-5-B (diastereomer B)	
S3-7-6-A (diastereomer A) S3-7-6-B (diastereomer B)		S3-7-7		S3-7-8-A (diastereomer A) S3-7-8-B (diastereomer B)	
S3-7-9-A (diastereomer A) S3-7-9-B (diastereomer B)		S3-7-10-A (diastereomer A) S3-7-10-B (diastereomer B)		S3-7-11-A (diastereomer A) S3-7-11-B (diastereomer B)	
S3-7-12		S3-7-13-A (diastereomer A) S3-7-13-B (diastereomer B)		S4-14-1 (diastereomer A)	
S4-14-2 (diastereomer A)		S4-14-3 (diastereomer A)		S4-14-4 (diastereomer A)	
S4-14-5-A (diastereomer A) S4-14-5-B (diastereomer B)		S4-14-7 (diastereomer A)		S4-14-8 (diastereomer A)	
S4-14-9 (diastereomer A)		S4-14-10 (diastereomer A)		S4-14-11 (diastereomer A)	
S4-14-12 (diastereomer A)		S4-14-13 (diastereomer A)		S4-14-14-A (diastereomer A) S4-14-14-B (diastereomer B)	
S4-14-15 (diastereomer A)		S4-14-17 (diastereomer A)		S5-10-1-A (diastereomer A) S5-10-1-B (diastereomer B)	
S5-10-1-2-A (diastereomer A) S5-10-1-2-B (diastereomer B)		S5-10-3-A (diastereomer A) S5-10-3-B (diastereomer B)		S5-10-4-A (diastereomer A) S5-10-4-B (diastereomer B)	
S6-6-1 (single diastereomer)		S6-6-2 (single diastereomer)		S6-6-3 (single diastereomer)	
S7-14-1-A (diastereomer A) S7-14-1-B (diastereomer B)		S7-14-2-A (diastereomer A)		S7-14-3-A (diastereomer A)	
S8-4-1		S8-4-2		S8-4-3	

Compound No.	Compound Structure	Compound No.	Compound Structure	Compound No.	Compound Structure
S5-5-1		S9-5-1		S9-5-2	
S9-5-3		S9-5-4		S9-5-5	
S9-5-6		S10-4-1 (single diastereomer)		S10-4-2 (single diastereomer)	
S10-4-3 (single diastereomer)		S11-3-1		S11-3-2	
S11-3-3		S12-8-1-A (diastereomer A) S12-8-1-B (diastereomer B)		S12-8-2-A (diastereomer A)	
S12-8-3-A (diastereomer A) S12-8-3-B (diastereomer B)		S12-8-4-A (diastereomer A)		S12-8-5-A (diastereomer A)	
S12-8-6-A (diastereomer A) S12-8-6-B (diastereomer B)		S12-8-7-A (diastereomer A)		S12-8-8-A (diastereomer A)	
S13-5-1		S13-5-2		S14-8-1	
S14-8-2		S14-8-3-A (diastereomer A) S14-8-3-B (diastereomer B)		S15-10-1	
S15-10-2		S15-10-3-A (diastereomer A) S15-10-3-B (diastereomer B)		S16-7-1 (single diastereomer)	
S16-7-2 (single diastereomer)		S16-7-3 (single diastereomer)		S16-7-4 (single diastereomer)	
S16-7-5 (single diastereomer)		S16-7-6 (single diastereomer)		S17-3-1	
S17-3-2		S17-3-3		S17-3-4	
S17-3-5		S17-3-6		S17-3-7	

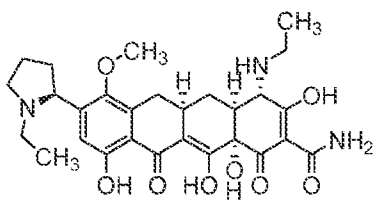
Compound No.	Compound Structure	Compound No.	Compound Structure	Compound No.	Compound Structure
S17-3-8		S17-3-9		S17-3-10	
S17-3-11		S18-5-1-1		S18-5-1-2	
S18-5-2-1		S18-5-2-2		S19-7-3-B (diastereomer B)	
S19-7-2		S19-7-3-A (diastereomer A) S19-7-3-B (diastereomer B)		S19-7-4-A (diastereomer A) S19-7-4-B (diastereomer B)	
S19-7-5-A (diastereomer A) S19-7-5-B (diastereomer B)		S19-7-6		S19-7-7-A (diastereomer A) S19-7-7-B (diastereomer B)	
S20-4-1 (single diastereomer)		S20-4-2 (single diastereomer)		S20-4-3 (single diastereomer)	
S20-4-4 (single diastereomer)		S21-5-1		S21-5-2	
S21-5-3		S21-5-4			

The compound numbers in the tables set forth above reference synthetic schemes in WO2014/03650 all of which are found in U.S. Patent No. 9,573,895 the entire content of which is hereby incorporated by reference.

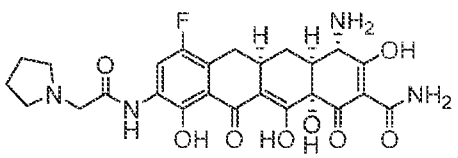
In the nineteenth aspect of the 26th embodiment, the compound is represented by any one of the following structural formulas:



compound 3A/K4 ,



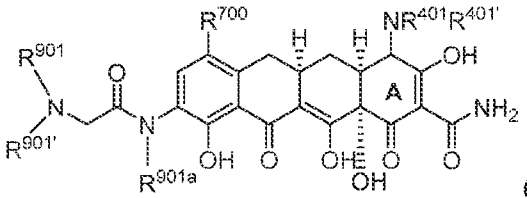
, and



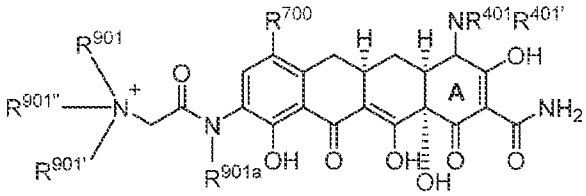
.

or a pharmaceutically acceptable salt thereof.

In a 27th embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by any one of structural formulas (X) or (X-1)



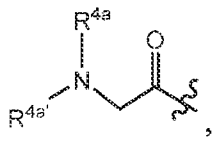
(X),



(X-1),

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

In the first aspect of the 27th embodiment, R^{700}, for each occurrence independently, is a halogen; R^{901a}, for each occurrence independently, is H or a C_1-C_4 alkyl; R^{401} and $R^{401'}$, for each occurrence independently, is H or a C_1-C_4 alkyl, a C_1-C_4 hydroxyalkyl, a (C_{1-4} alkyl)C(O)-, a C_{3-12} carbocyclyl-C(O)-, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group, a (C_{1-4} alkyl)S(O)$_{1-2}$- , a (C_{1-4} alkyl)C(O)NH(C_{1-4} alkylenyl)-, a (C_{1-4} alkyl)S(O)$_{1-2}$NH(C_{1-4} alkylenyl)- , or a moiety represented by the following structural formula:



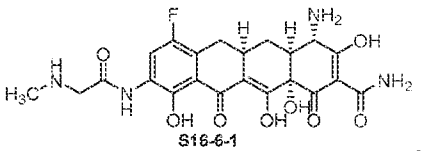
,

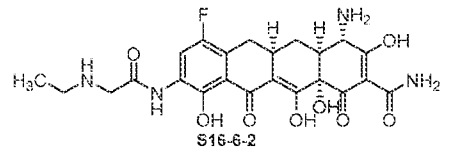
wherein "≈" represents the point of attachment to the nitrogen atom, and R^{4a} and $R^{4a'}$, for each occurrence independently, is H or a C_1-C_4 alkyl, or, taken together with the nitrogen atom to which they are attached, form a 4-13 member heterocyclyl; and R^{901}, $R^{901'}$, and $R^{901''}$, for each occurrence independently, is H, a C_1-C_6 alkyl, a C_1-C_6 haloalkyl, a C_1-C_6 hydroxyalkyl, a (C_1-C_4 alkoxy)-(C_{1-6})alkyl, an amino-(C_1-C_6) alkyl, a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-6})alkyl, a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl, a (4-13 member)heterocyclyl-(C_0-C_3)alkylenyl, or any two of R^{901}, $R^{901'}$, and $R^{901''}$, taken together with the nitrogen atom to which they are attached, form a 4-13 member heterocyclyl.

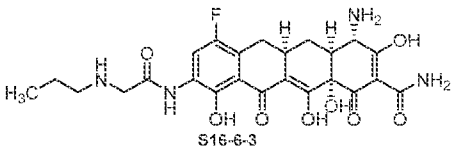
In the second aspect of the 27th embodiment, R^{700} is F; and R^{901}, $R^{901'}$, and $R^{901''}$, for each occurrence independently, is H, a C_1-C_6 alkyl, a C_1-C_6 haloalkyl, a C_1-C_6 hydroxyalkyl, a (C_1-C_4 alkoxy)-(C_{1-6})alkyl, an amino-(C_1-C_6) alkyl, a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-6})alkyl, a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl, a (4-13 member)heterocyclyl-(C_0-C_3)alkylenyl. The remainder of the values and example values of the variables in structural formulas (X) and (X-1) of the 27th embodiment are as defined above with respect to the first aspect of the 27th embodiment.

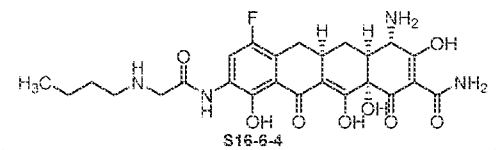
In the third aspect of the 27th embodiment, the compound is represented by the structural formula (X); R^{700} is F; and R^{901} and $R^{901'}$, taken together with the nitrogen atom to which they are attached, form a 4-13 member heterocyclyl. The remainder of the values and example values of the variables in structural formulas (X) and (X-1) of the 27th embodiment are as defined above with respect to aspects one through two of the 27th embodiment.

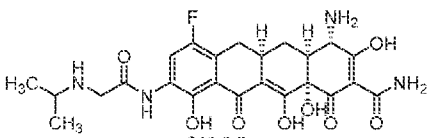
In the fourth aspect of the 27th embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:


S16-6-1,


S16-6-2,


S16-6-3,


S16-6-4,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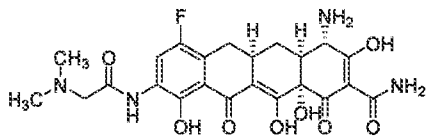
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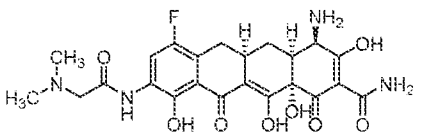
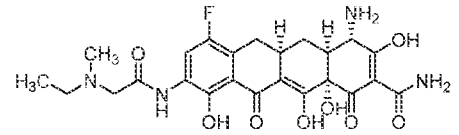

S16-6-7,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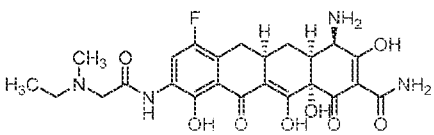
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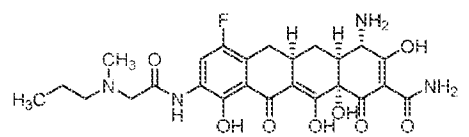
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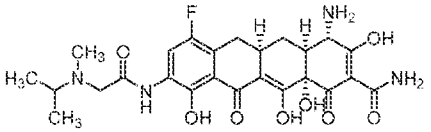
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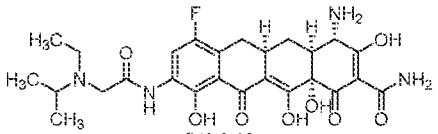
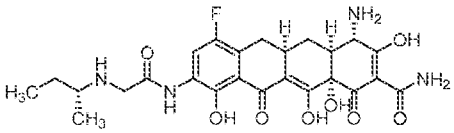
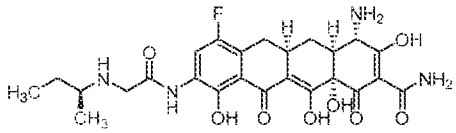

S16-6-12 ,


S16-6-13 ,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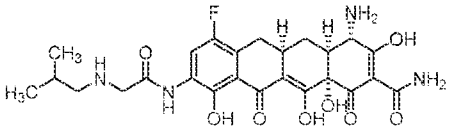
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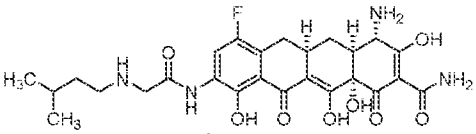
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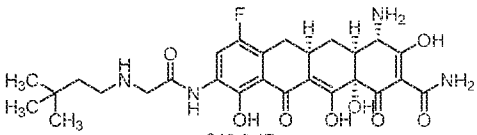
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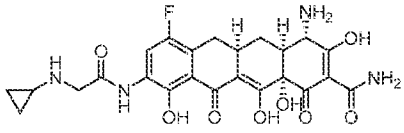
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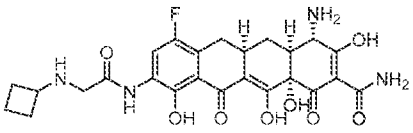
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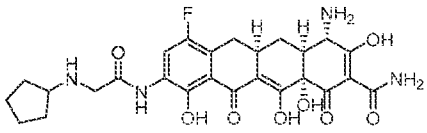
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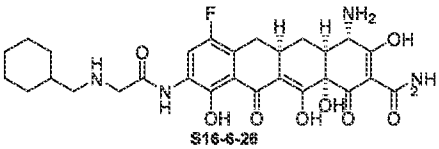
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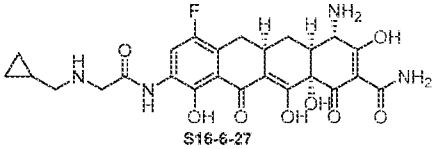
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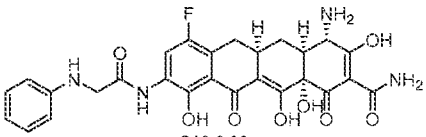
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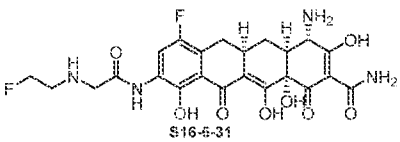
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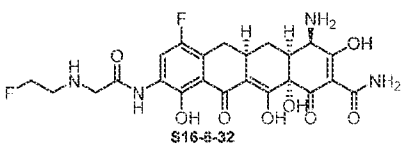
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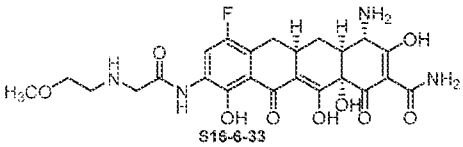
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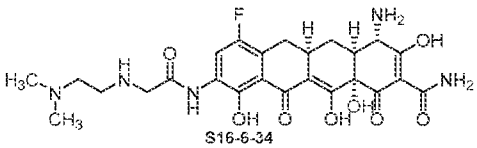
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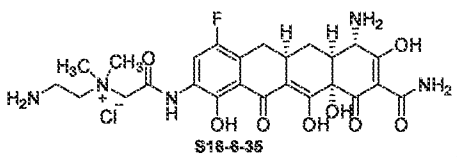
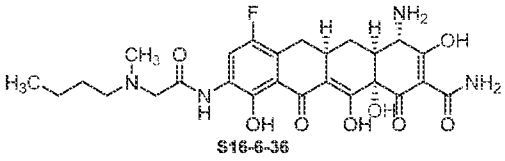
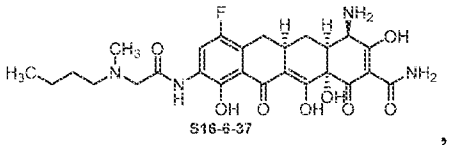

S18-6-35 ,

5


S16-6-36 ,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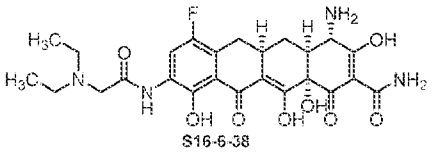
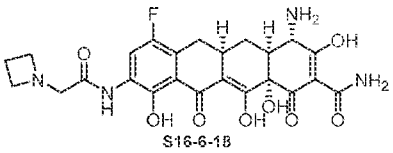

S16-6-38 .

In the fifth aspect of the 27th embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof: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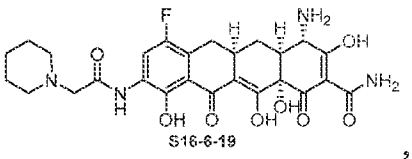
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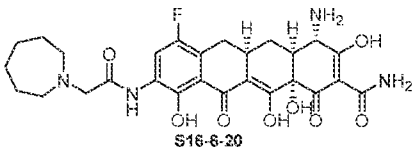
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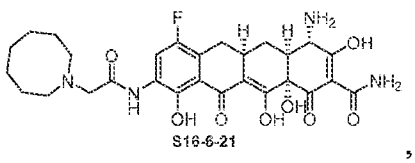
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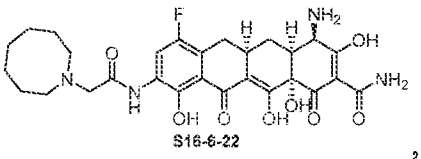
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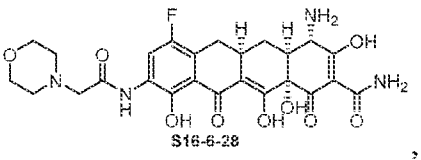
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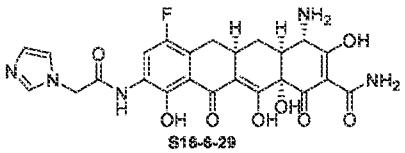
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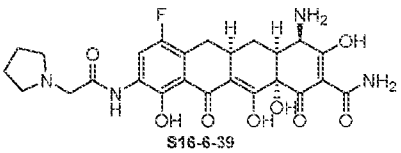
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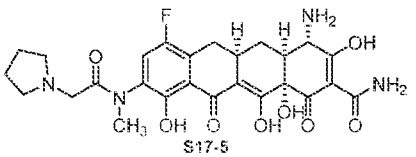
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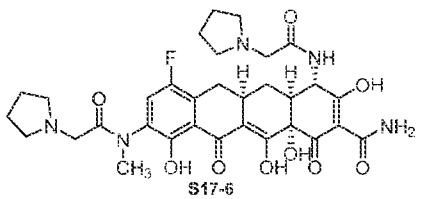
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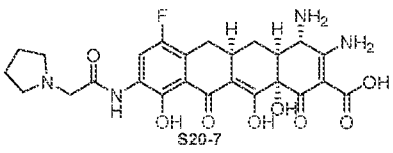
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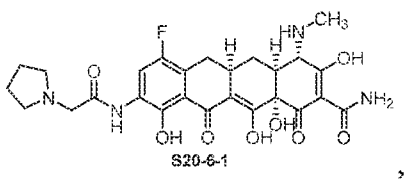
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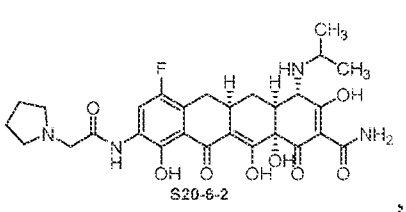
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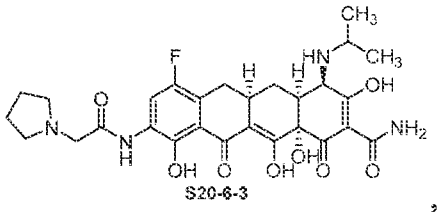
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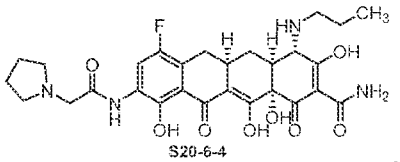
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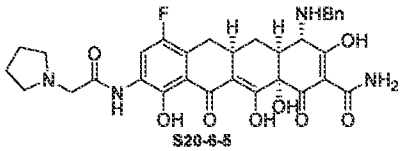
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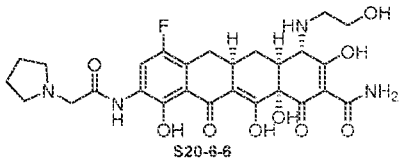
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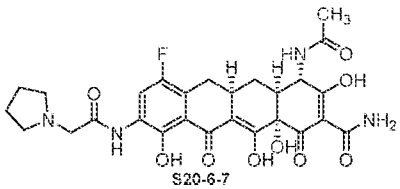
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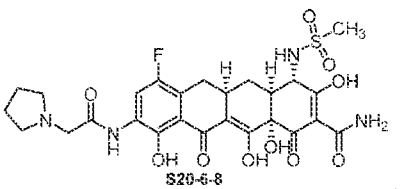
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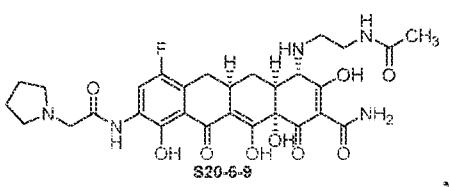
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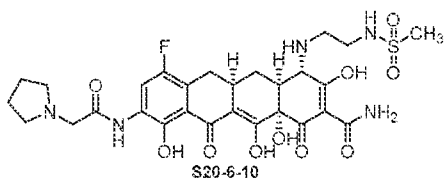
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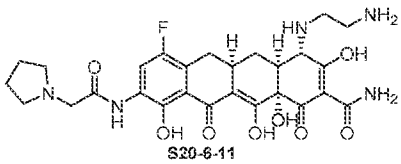
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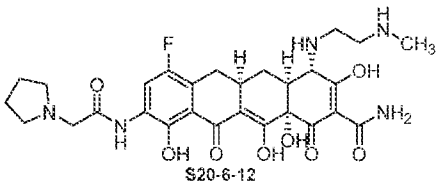
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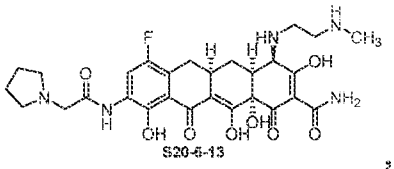
S20-6-13

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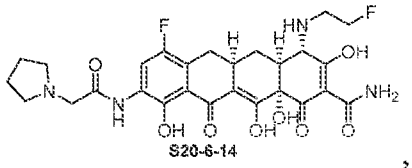
S20-6-14

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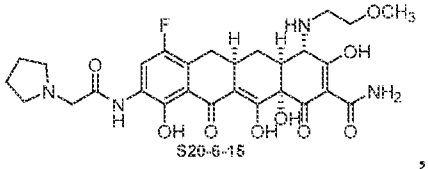
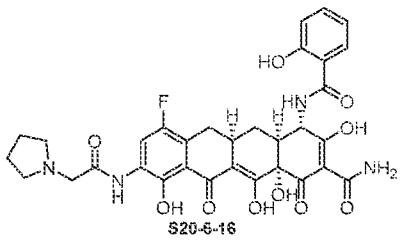
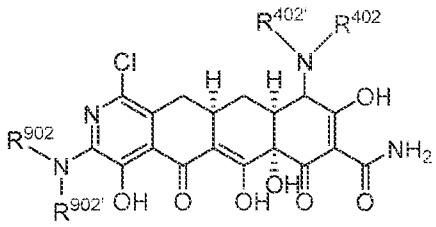

S20-6-15

, and

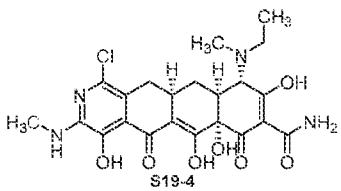

S20-6-16

.

In the 28th embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by any one of structural formulas (XI), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof,

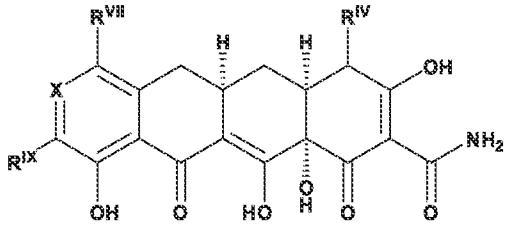

(XI),

wherein R^{902}, $R^{902'}$, R^{402}, and $R^{402'}$, for each occurrence independently, is H or a C_1-C_6 alkyl. For example, the compound of structural formula (XI) is represented by the following structural formula, or a pharmaceutically acceptable salt thereof:


S19-4

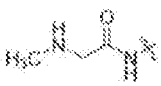
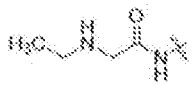
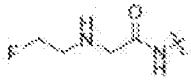
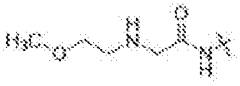
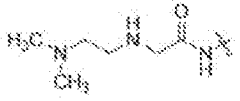
.

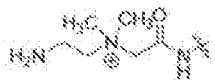
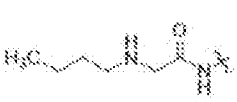
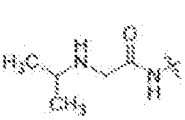
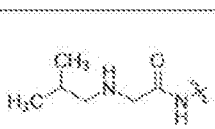
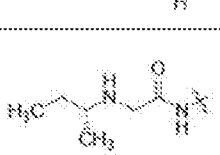
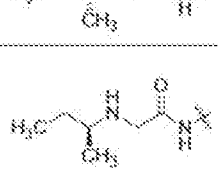
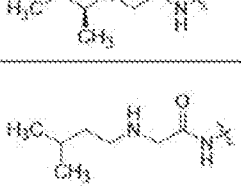
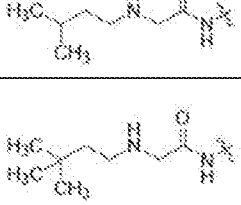
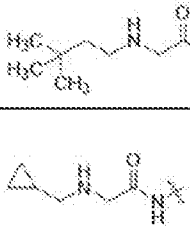
In the 29th embodiment, the present invention is a compound represented by structural formula (XII), or a pharmaceutically acceptable salt thereof:

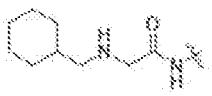
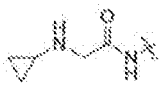
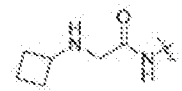
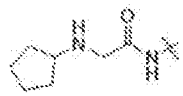
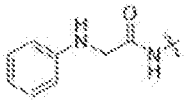
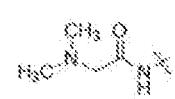
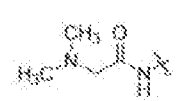
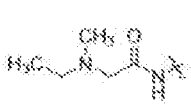
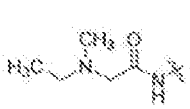
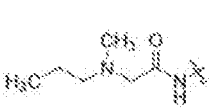


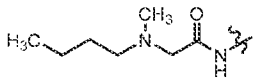
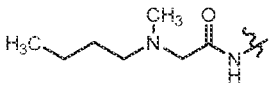
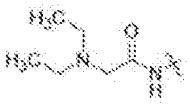
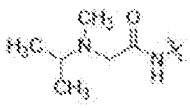
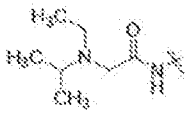
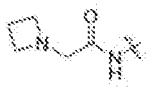
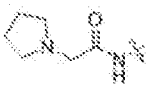
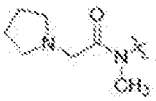
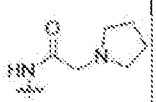
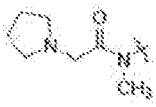
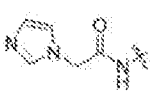
(XII),

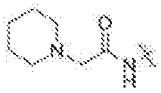
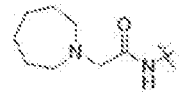
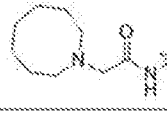
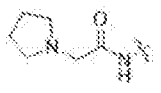
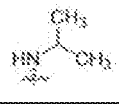
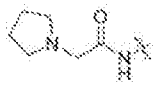
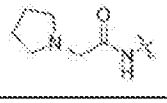
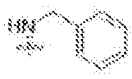
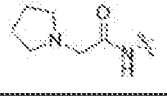
wherein:

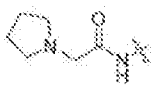
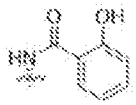
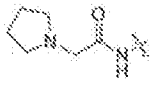
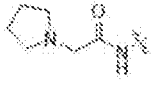
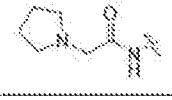
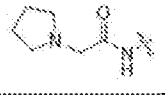
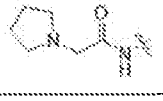
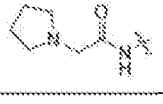
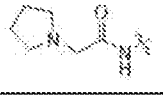
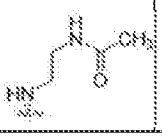
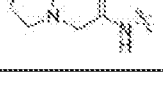
Compound number	R^{IV}	R^{VII}	R^{IX}	X
S16-5				CH
S17-3				CH
S16-6-4				CH
S16-6-2				CH
S16-6-31				CH
S16-6-32				CH
S16-6-33				CH
S16-6-34				CH

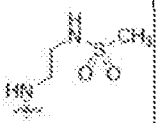
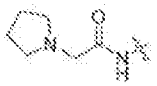
Compound number	R^{IV}	R^{VII}	R^{IX}	X
S16-6-35				CH
S16-6-3				CH
S16-6-4				CH
S16-6-5				CH
S16-6-15				CH
S16-6-13				CH
S16-6-14				CH
S16-6-16				CH
S16-6-17				CH
S16-6-27				CH

Compound number	R^{IV}	R^{VII}	R^{IX}	X
S16-6-29				CH
S16-6-23				CH
S16-6-24				CH
S16-6-25				CH
S16-6-30				CH
S16-6-6				CH
S16-6-7				CH
S16-6-8				CH
S16-6-9				CH
S16-6-10				CH

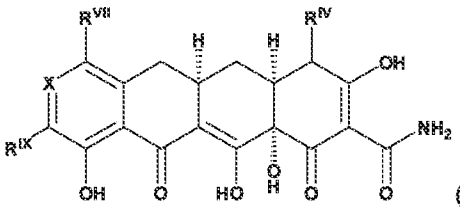
Compound number	R^{IV}	R^{VII}	R^{IX}	X
S16-6-36				CH
S16-6-37				CH
S16-6-38				CH
S16-6-11				CH
S16-6-12				CH
S16-6-18				CH
S16-6-39				CH
S17-5				CH
S17-6				CH
S16-6-29				CH

Compound number	R^{IV}	R^{VII}	R^{IX}	X
S16-6-19				CH
S16-6-28				CH
S16-6-20				CH
S16-6-21				CH
S16-6-22				CH
S20-6-1				CH
S20-6-4				CH
S20-6-2				CH
S20-6-3				CH
S20-6-5				CH

Compound number	R^{IV}	R^{VII}	R^{IX}	X
S20-6-7				CH
S20-6-16				CH
S20-6-8				CH
S20-6-14				CH
S20-6-6				CH
S20-6-15				CH
S20-6-11				CH
S20-6-12				CH
S20-6-13				CH
S20-6-9				CH

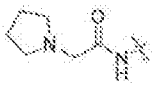
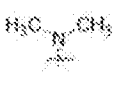
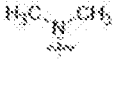
Compound number	R^{IV}	R^{VII}	R^{IX}	X
S20-6-10				CH
S19-4				N

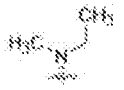
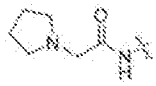
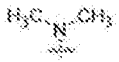
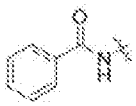
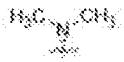
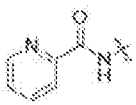
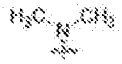
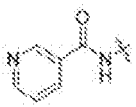
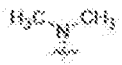
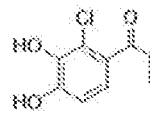
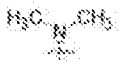
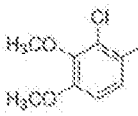
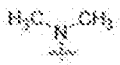
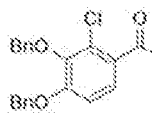
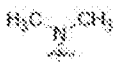
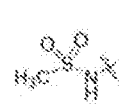
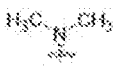
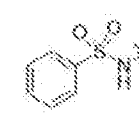
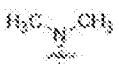
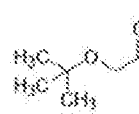
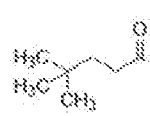
In the 30th embodiement, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof:

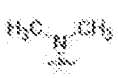
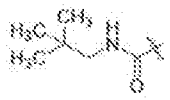
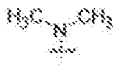
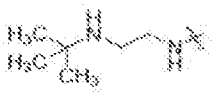
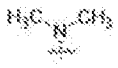
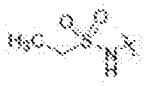


(XII),

wherein:

Compound number	R^{IV}	R^{VII}	R^{IX}	X
K43				CH
K44				CH
K45				N
K46				N

Compound number	R^{IV}	R^{VII}	R^{IX}	X
K47				CH
K48				CH
K49				CH
K50				CH
K51				CH
K52				CH
K53				CH
K54				CH
K55				CH
K56				CH
K57				CH

Compound number	R^{IV}	R^{VII}	R^{IX}	X
K58				CH
K59				CH
K60				CH
K61				CH
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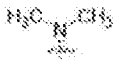
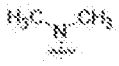
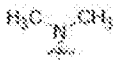
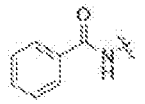
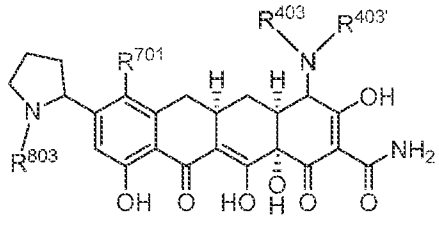
K63				CH
K64				CH
K65				CH

In the 31st embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula



(XX)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

In the first aspect of the 31st embodiment, R^{803} is H, a C_{1-6} alkyl, a C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, a C_{3-12} carbocyclyl-(C_{0-3})alkylenyl, an amino-(C_1-C_4) alkyl, a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl, a (4-13 member)heterocyclyl-(C_0-C_3)alkylenyl, wherein the heterocyclyl portion is optionally substituted with a C_{1-3} alkyl; R^{701} is H, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkoxy; and R^{403} and $R^{403'}$, each independently, is H; a C_{1-4} alkyl; a C_1-C_4 haloalkyl; a C_1-C_4 hydroxyalkyl; a (C_1-C_4 alkoxy)-(C_{1-4})alkyl; an amino-(C_1-C_4) alkyl; a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; a (C_{1-4} alkyl)C(O)-, a (C_{1-4} alkyl)S(O)$_{1-2}$-; a (C_{1-4} alkyl)C(O)NH(C_{1-4} alkylenyl)-; a (C_{1-4} alkyl)S(O)$_{1-2}$NH(C_{1-4} alkylenyl)-; a HOC(O)-(C_1-C_3)alkylenyl; a $H_2NC(O)$-(C_1-C_3)alkylenyl; a (C_{1-4} alkyloxy)C(O)-(C_1-C_3)alkylenyl.

In the second aspect of the 31st embodiment, R^{701} is –OCH_3, and R^{803} is ethyl. The remainder of the values and example values of the variables in structural formula (XX) of the 31st embodiment are as defined above with respect to the first aspect of the 31st embodiment.

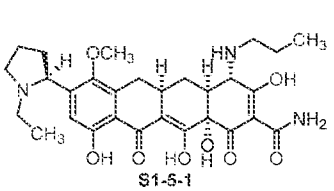
In the third aspect of the 31st embodiment, R^{701} is –OCH_3, and R^{403} and $R^{403'}$ each is hydrogen. The remainder of the values and example values of the variables in structural formula (XX) of the 31st embodiment are as defined above with respect to the first or second aspects of the 31st embodiment.

In the fourth aspect of the 31st embodiment, R^{803} is ethyl and R^{403} and $R^{403'}$ each is hydrogen. The remainder of the values and example values of the variables in structural formula (XX) of the 31st embodiment are aas defined above with respect to aspects one through three of the 31st embodiment.

In the fifth aspect of the 31st embodiment, R^{701} is a –OCF_3, and R^{803} is methyl. The remainder of the values and example values of the variables in structural formula (XX) of the

31st embodiment are as defined above with respect to aspects one through four of the 31st embodiment.

In the sixth aspect of the 31st embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof: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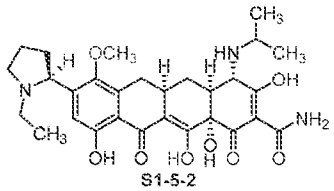
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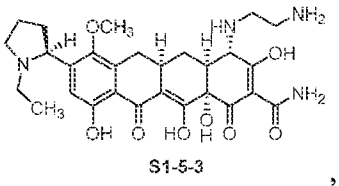
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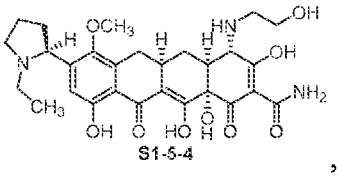
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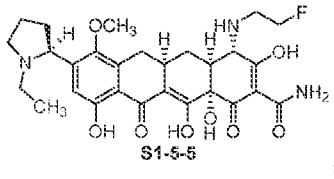
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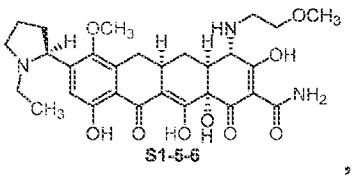
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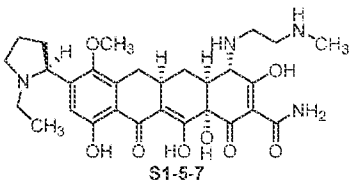
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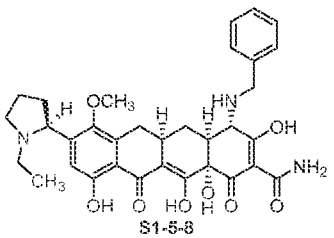
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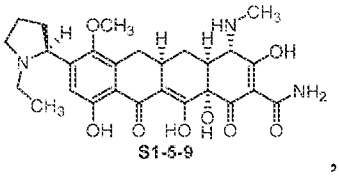
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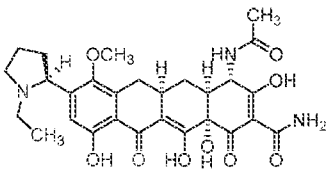
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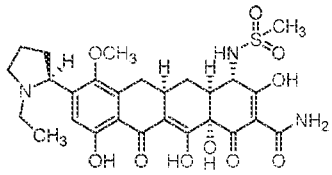
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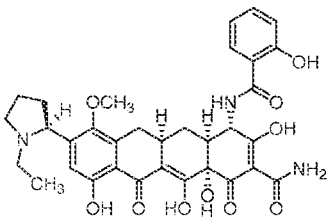
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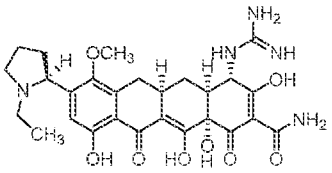
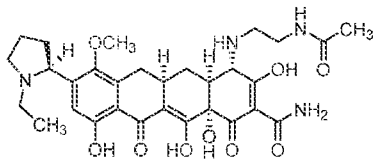

S1-5-13 ,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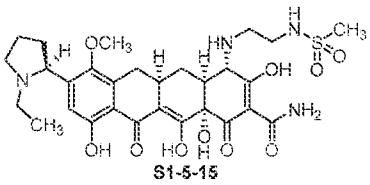
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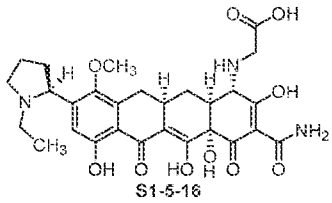
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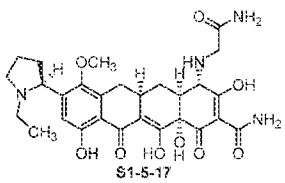
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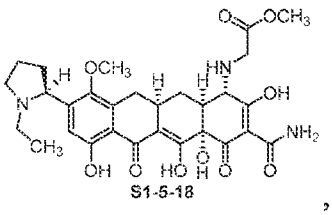
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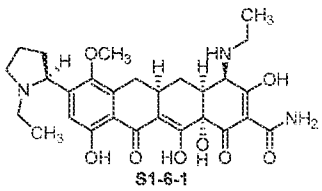
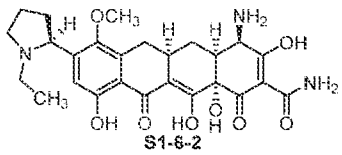

S1-6-1 ,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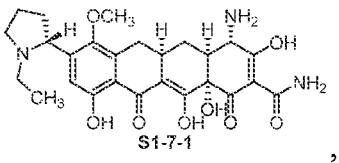
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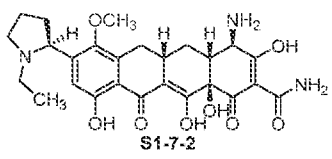
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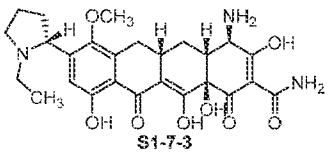
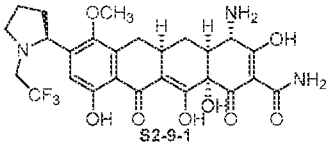

S1-7-3 .

In the seventh aspect of the 31st embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:


S2-9-1

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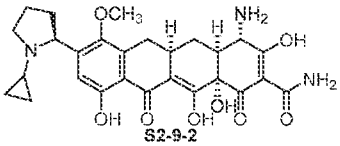
S2-9-2

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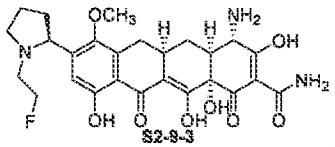
S2-9-3

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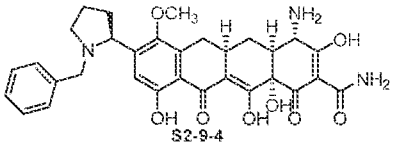
S2-9-4

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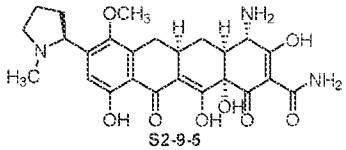
S2-9-5

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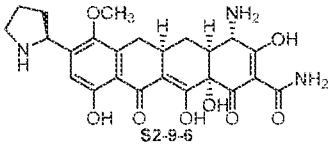
S2-9-6

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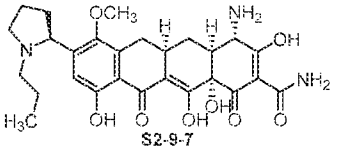
S2-9-7

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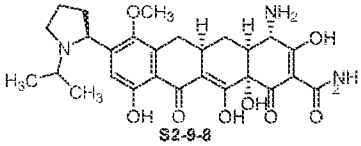
S2-9-8

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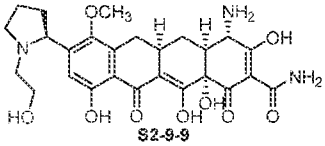
S2-9-9

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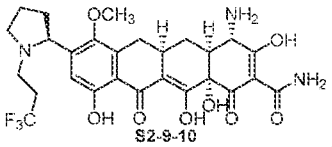
S2-9-10

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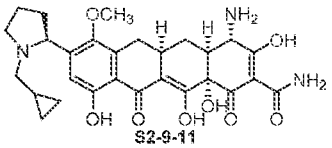
S2-9-11

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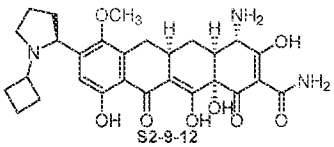
S2-9-12

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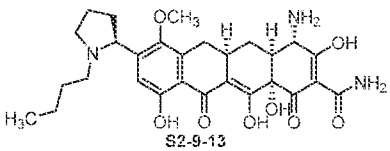
S2-9-13

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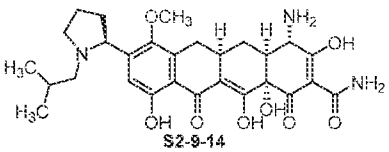
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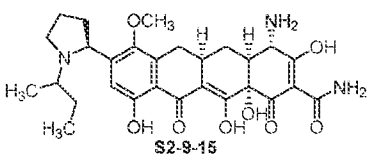
S2-9-15

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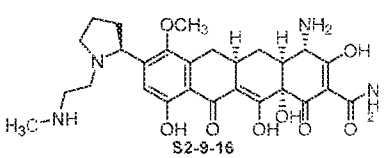
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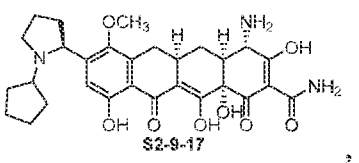
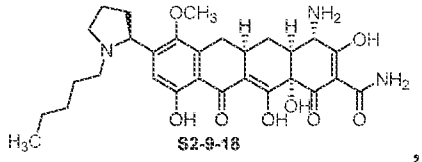

S2-9-17,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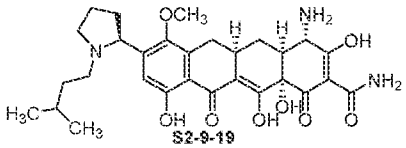
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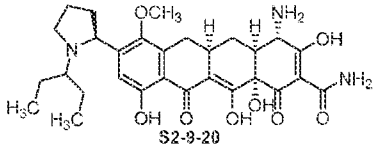
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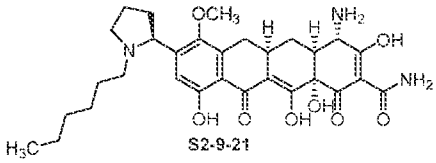
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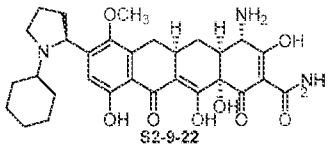
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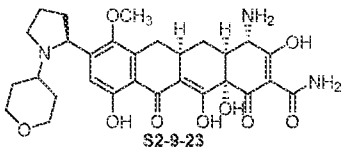
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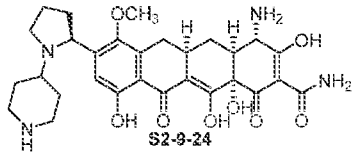
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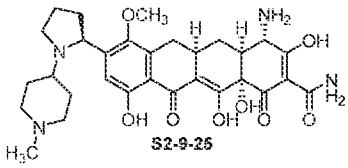
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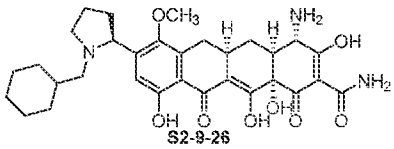
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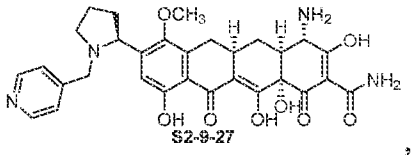
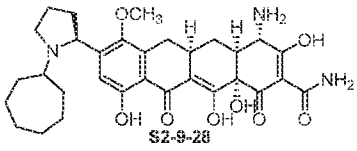

S2-9-27,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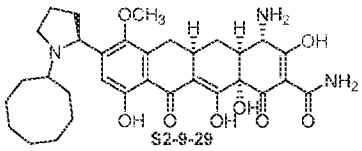
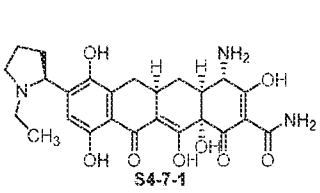
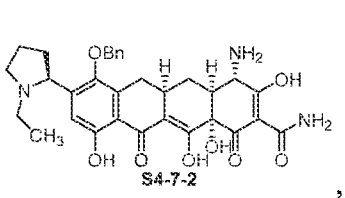
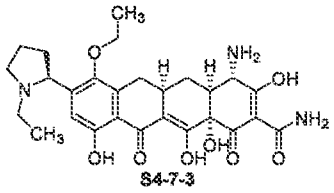
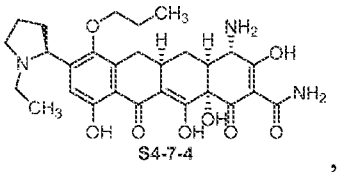

S2-9-29.

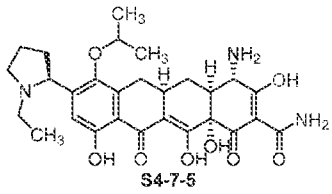
In the eighth aspect of the 31st embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:


S4-7-1 ,


S4-7-2 ,


S4-7-3 ,


S4-7-4 ,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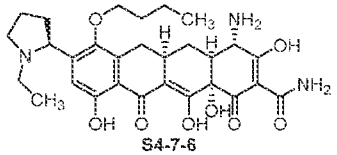
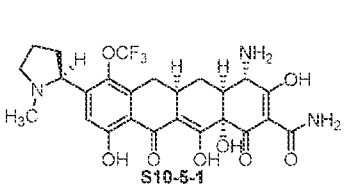
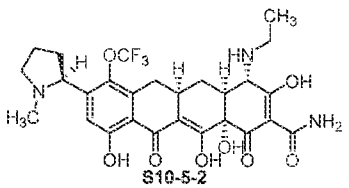
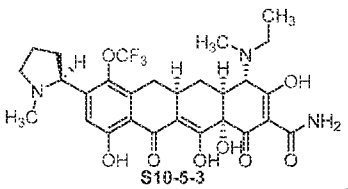
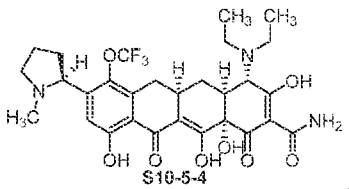

S4-7-6 .

In the ninth aspect of the 31st embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

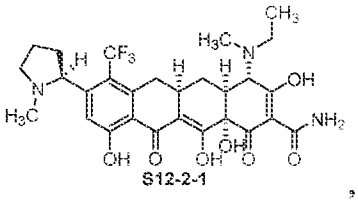

S10-5-1 ,


S10-5-2 ,

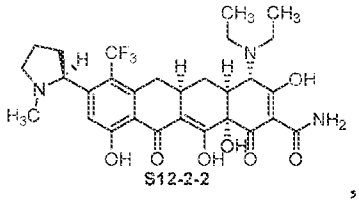

S10-5-3 ,


S10-5-4 .

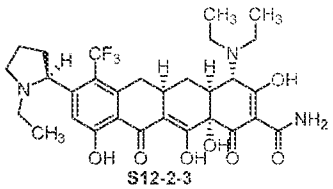
In the tenth aspect of the 31st embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:



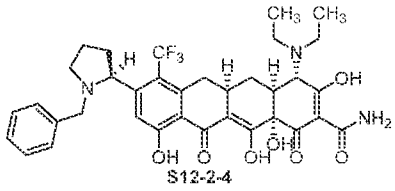
S12-2-1 ,



S12-2-2 ,

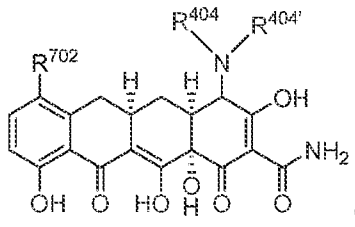


S12-2-3



S12-2-4 .

In the 32nd embodiment, the present invention is method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula:



(XXI)

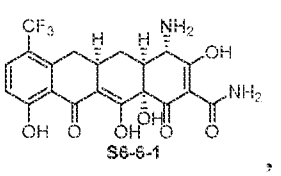
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof. In a first aspect of the 32nf embodiment, R^{702} is H, a halogen, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkoxy; and R^{404} and $R^{404'}$, each independently, is H; a C_{1-4} alkyl; a C_1-C_4 haloalkyl; a C_1-C_4 hydroxyalkyl; a (C_1-C_4 alkoxy)-(C_{1-4})alkyl; an amino-(C_1-C_4) alkyl; a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; a (C_{1-4} alkyl)C(O)-, a (C_{1-4} alkyl)S(O)$_{1-2}$-; a (C_{1-4} alkyl)C(O)NH-C_{1-4} alkylenyl; a (C_{1-4} alkyl)S(O)$_{1-2}$NH-C_{1-4} alkylenyl; a HOC(O)-(C_1-C_3)alkylenyl; a $H_2NC(O)$-(C_1-C_3)alkylenyl; a (C_{1-4} alkyloxy)C(O)-(C_1-C_3)alkylenyl.

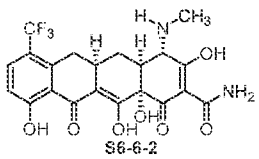
In the second aspect of the 32st embodiment, R^{702} is a C_{1-4} haloalkyl. The remainder of the values and example values of the variables in structural formula (XXI) of the 32st embodiment are as defined above with respect to aspect one of the 32st embodiment.

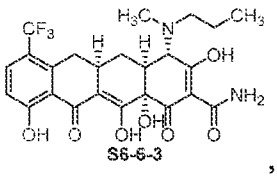
In the third aspect of the 32st embodiment, R^{702} is H or a halogen. The remainder of the values and example values of the variables in structural formula (XXI) of the 32st embodiment are as defined above with respect to aspects one or two of the 32st embodiment.

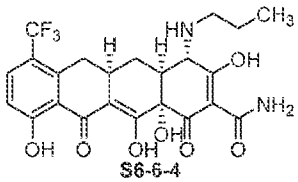
In the fourth aspect of the 32st embodiment, R^{702} is --OCH_3. The remainder of the values and example values of the variables in structural formula (XXI) of the 32st embodiment are as defined above with respect to aspect o to three of the 32st embodiment.

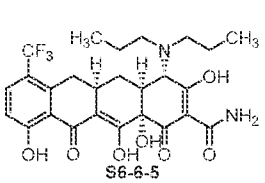
In the fifth aspect of the 32st embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

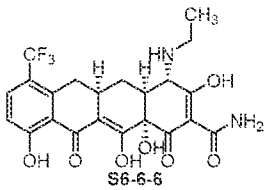

S6-6-1 ,

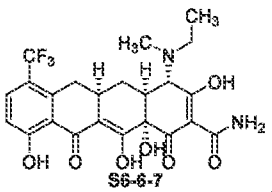

S6-6-2 ,

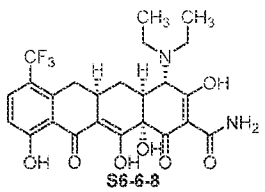

S6-6-3 ,

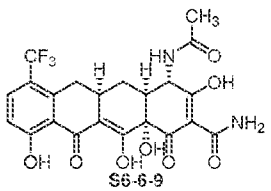

S6-6-4 ,

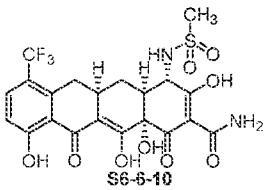

S6-6-5 ,


S6-6-6 ,

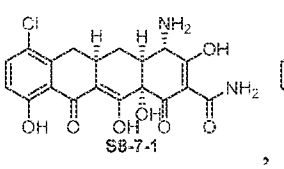

S6-6-7 ,


S6-6-8 ,


S6-6-9 ,


S6-6-10 .

In the sixth aspect of the 32st embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof: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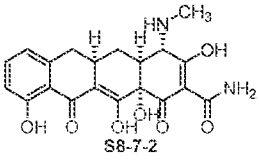
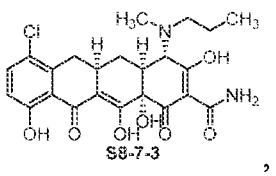
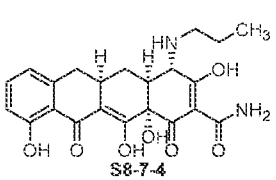
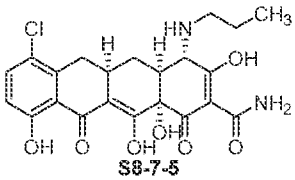

S8-7-2 ,


S8-7-3 ,


S8-7-4 ,

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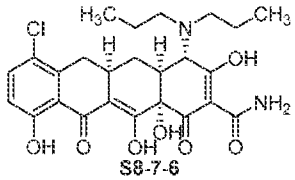
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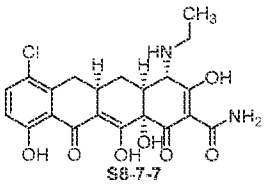
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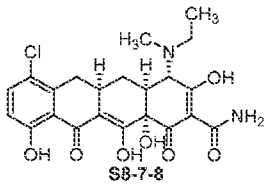
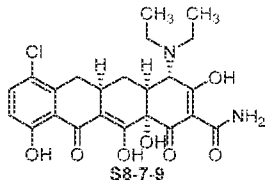

S8-7-8 ,

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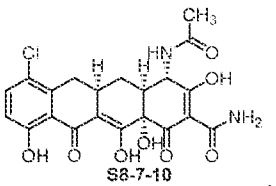
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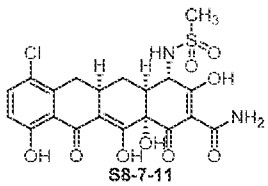
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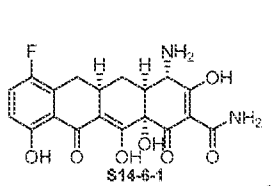
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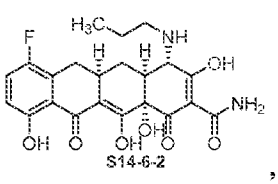
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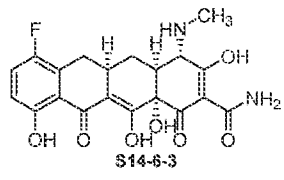
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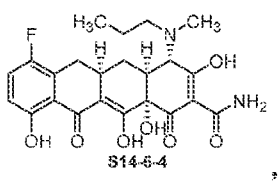
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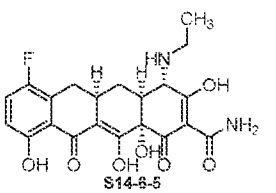
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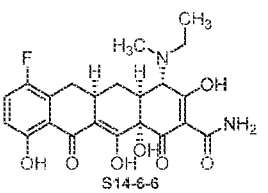
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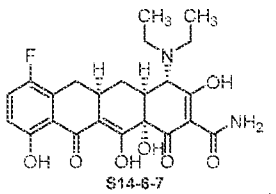
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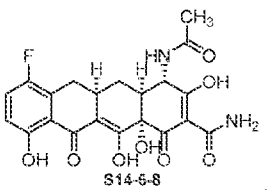
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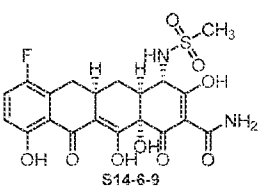
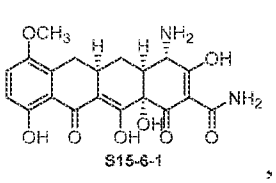

S14-6-9 .

In the seventh aspect of the 32st embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof: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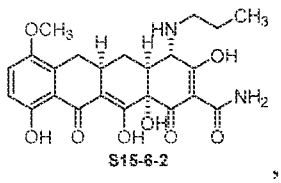
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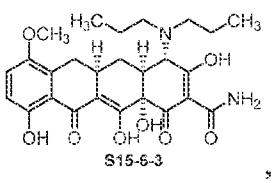
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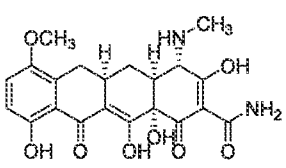
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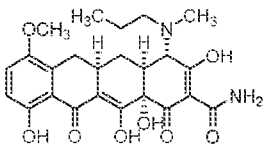
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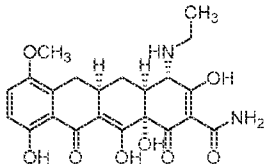
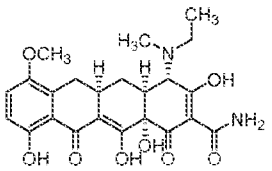
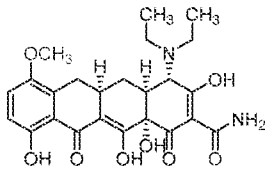
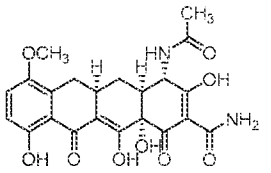
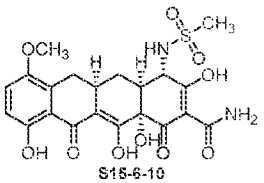

S15-6-6 ,

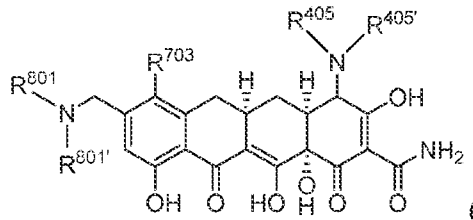

S15-6-7 ,


S15-6-8 ,


S15-6-9 ,

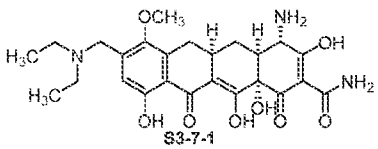

S15-6-10 .

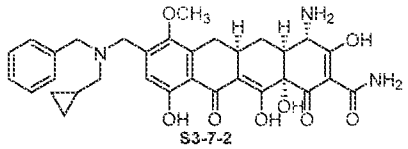
In the 33rd embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by any one of structural formulas

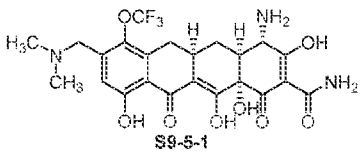

(XXII)

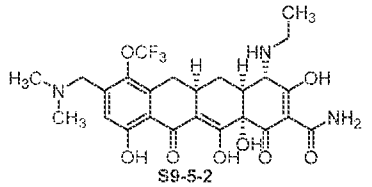
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof. In a first aspect of the 33rd embodiment, R^{703} is H, a halogen, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkoxy, and R^{801} and $R^{801'}$ each independently is H, a C_{1-6} alkyl, a C_{3-12} carbocyclyl-(C_{0-3})alkylenyl; and R^{405} and $R^{405'}$, each independently, is H; a C_{1-4} alkyl; a C_1-C_4 haloalkyl; a C_1-C_4 hydroxyalkyl; a (C_1-C_4 alkoxy)-(C_{1-4})alkyl; an amino-(C_1-C_4) alkyl; a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; a (C_{1-4} alkyl)C(O)-, a (C_{1-4} alkyl)S(O)$_{1-2}$-; a (C_{1-4} alkyl)C(O)NH(C_{1-4} alkylenyl)-; a (C_{1-4} alkyl)S(O)$_{1-2}$NH(C_{1-4} alkylenyl)-; a HOC(O)-(C_1-C_3)alkylenyl; a $H_2NC(O)$-(C_1-C_3)alkylenyl; a (C_{1-4} alkyloxy)C(O)-(C_1-C_3)alkylenyl.

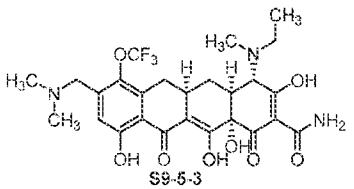
In the second aspect of the 33rd embodiment, R^{703} is a C_{1-4} alkyloxy and R^{405} and $R^{405'}$, each independently, is H or a C_{1-4} alkyl. The remainder of the values and example values of the variables in structural formula (XXII) of the 33rd embodiment are as defined above with respect to aspect one of the 33rd embodiment. Examples of the compounds of the 33rd embodimnent include compounds represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

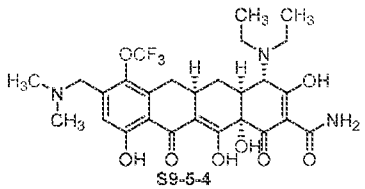

S3-7-1


S3-7-2

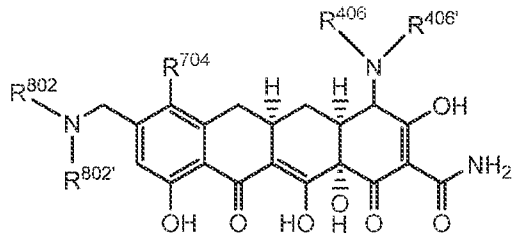

S9-5-1


S9-5-2


S9-5-3


S9-5-4

In a 34th embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula

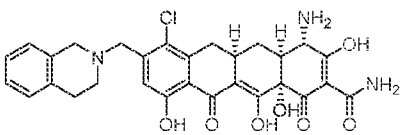

(XXIII)

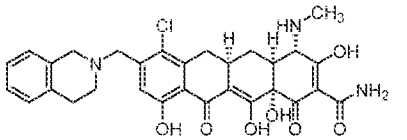
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof. In a first aspect of the 34th embodiment, R^{704} is H, a halogen, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkoxy; R^{802} and $R^{802'}$, taken together with the nitrogen atom to which they are attached, form a 4-13 monocyclyc or a 7-13 bycyclic heterocyclyl; and R^{406} and $R^{406'}$, each independently, is H; a C_{1-4} alkyl; a C_1-C_4 haloalkyl; a C_1-C_4 hydroxyalkyl; a (C_1-C_4 alkoxy)-(C_{1-4})alkyl; an amino-(C_1-C_4) alkyl; a

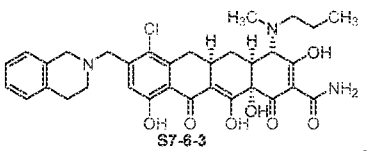
mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; a (C_{1-4} alkyl)C(O)-, a (C_{1-4} alkyl)S(O)$_{1-2}$-; a (C_{1-4} alkyl)C(O)NH(C_{1-4} alkylenyl)-; a (C_{1-4} alkyl)S(O)$_{1-2}$NH(C_{1-4} alkylenyl)-; a HOC(O)-(C_1-C_3)alkylenyl; a $H_2NC(O)$-(C_1-C_3)alkylenyl; a (C_{1-4} alkyloxy)C(O)-(C_1-C_3)alkylenyl.

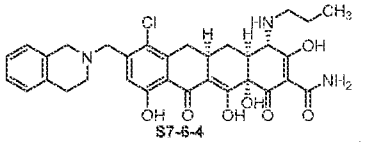
In the second aspect of the 34th embodiment, R^{704} is a halogen; and R^{802} and $R^{802'}$, taken together with the nitrogen atom to which they are attached, form 1,2,3,4-tetrahydroisoquinoline. The remainder of the values and example values of the variables in structural formula (XXIII) of the 34th embodiment are as defined above with respect to aspect one of the 34th embodiment.

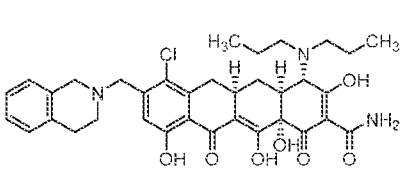
Examples of the compounds of the 34th embodiment include compounds represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

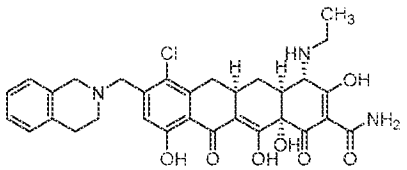

S7-6-1 ,

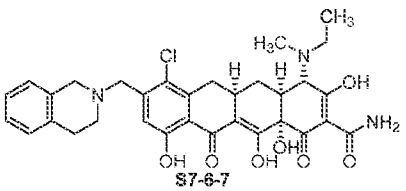

S7-6-2 ,

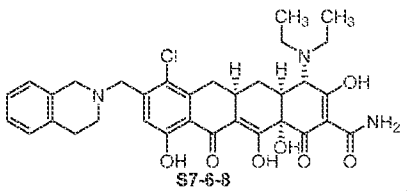

S7-6-3 ,

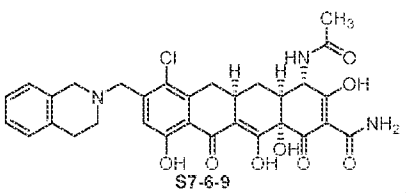

S7-6-4 ,

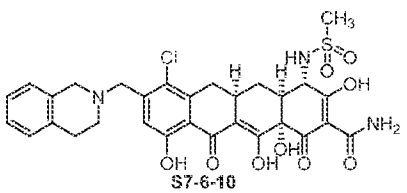

S7-6-5 ,


S7-6-6 ,

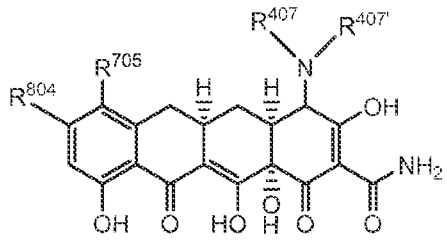

S7-6-7 ,


S7-6-8 ,


S7-6-9 ,


S7-6-10 .

In the 35th embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula



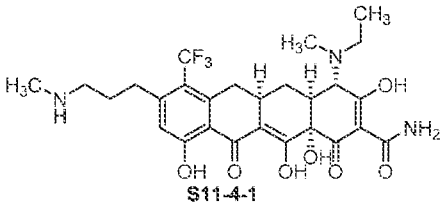
(XXIV)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof. In a first aspect of the 35th embodiment, R^{705} is H, a halogen, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, or C_{1-4} haloalkoxy; R^{804} is an amino-C_{1-6} alkyl, a mono- or di- (C_1-C_4 alkyl)amino(C_{1-6})alkyl, or, a C-attached 4-13 monocyclyc heterocyclyl, wherein the hetrocyclyl is optionally N-substituted with a C_{1-4} alkyl; and R^{407} and $R^{407'}$, each independently, is H; a C_{1-4} alkyl; a C_1-C_4 haloalkyl; a C_1-C_4 hydroxyalkyl; a (C_1-C_4 alkoxy)-(C_{1-4})alkyl; an amino-(C_1-C_4) alkyl; a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; a (C_{1-4} alkyl)C(O)-, a (C_{1-4} alkyl)S(O)$_{1-2}$-; a (C_{1-4} alkyl)C(O)NH(C_{1-4} alkylenyl)-; a (C_{1-4} alkyl)S(O)$_{1-2}$NH(C_{1-4} alkylenyl)-; a HOC(O)-(C_1-C_3)alkylenyl; a H_2NC(O)-(C_1-C_3)alkylenyl; a (C_{1-4} alkyloxy)C(O)-(C_1-C_3)alkylenyl.

In the second aspect of the 35th embodiment, R^{705} is a C_{1-4} haloalkyl; and R^{804} is a mono- or di- (C_1-C_2 alkyl)amino(C_{1-6})alkyl. The remainder of the values and example values of the variables in structural formula (XXIV) of the 35th embodiment are as defined above with respect to aspect one of the 35th embodiment.

In the third aspect of the 35th embodiment, R^{705} is a C_{1-4} haloalkyl; and R^{804} is a 4-5 monocyclyc heterocyclyl, N-substituted with methyl or ethyl. The remainder of the values and example values of the variables in structural formula (XXIV) of the 35th embodiment are as defined above with respect to aspect one of the 35th embodiment.

In the fourth aspect of the 35th embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:


S11-4-1

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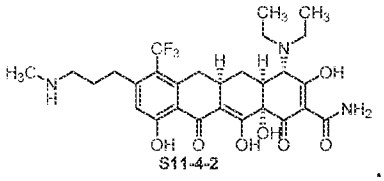
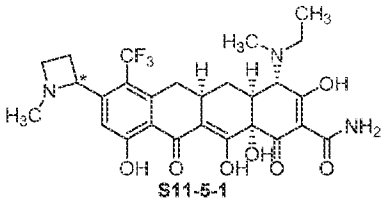

S11-4-2

.

In the fifth aspect of the 35th embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:


S11-5-1

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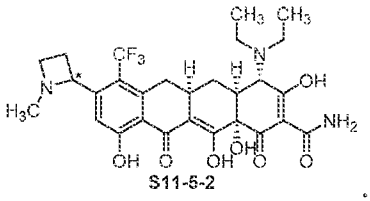
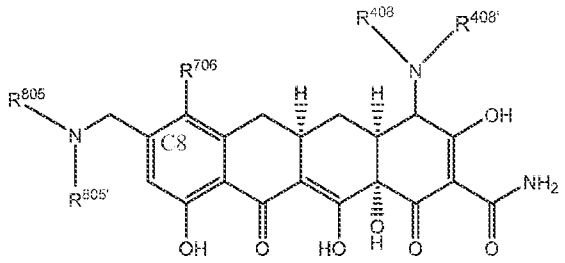

S11-5-2

.

In the 36th embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by the following structural formula



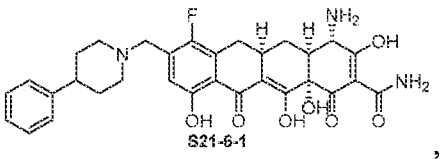
(XXV),

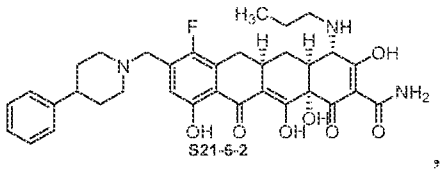
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof. In a first aspect of the 36th embodiment, R^{706} is H, a halogen, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, or C_{1-4} haloalkoxy; R^{805} and $R^{805'}$, taken together with the nitrogen atom to which they are attached, form a 4-13 monocyclyc heterocyclyl optionally substituted with a C_{3-12} carbocyclyl; and R^{408} and $R^{408'}$, each independently, is H; a C_{1-4} alkyl; a C_1-C_4 haloalkyl; a C_1-C_4 hydroxyalkyl; a (C_1-C_4 alkoxy)-(C_{1-4})alkyl; an amino-(C_1-C_4) alkyl; a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; a (C_{1-4} alkyl)C(O)-, a (C_{1-4} alkyl)S(O)$_{1-2}$-; a (C_{1-4} alkyl)C(O)NH(C_{1-4} alkylenyl)-; a (C_{1-4} alkyl)S(O)$_{1-2}$NH(C_{1-4} alkylenyl)-; a HOC(O)-(C_1-C_3)alkylenyl; a $H_2NC(O)$-(C_1-C_3)alkylenyl; a (C_{1-4} alkyloxy)C(O)-(C_1-C_3)alkylenyl.

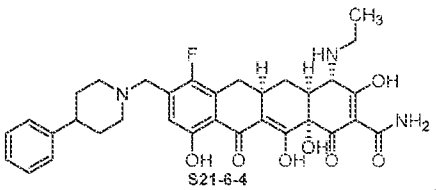
In the second aspect of the 36th embodiment, R^{706} is a halogen, and R^{805} and $R^{805'}$, taken together with the nitrogen atom to which they are attached, form a 5-6 monocyclyc

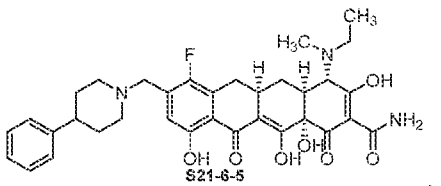
heterocyclyl optionally substituted with a phenyl. The remainder of the values and example values of the variables in structural formula (XXV) of the 36th embodiment are as defined above with respect to aspect one of the 36th embodiment.

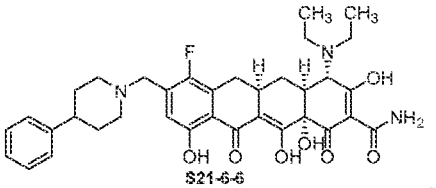
Example embodiments of the 36th embodiment include the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

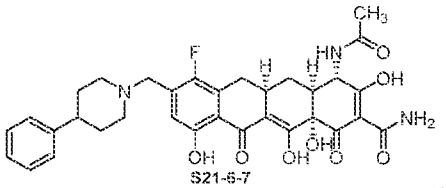

S21-6-1,

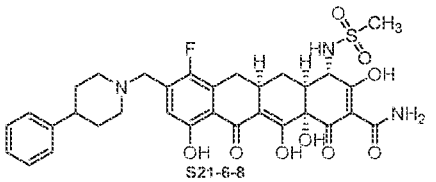

S21-6-2,


S21-6-4,

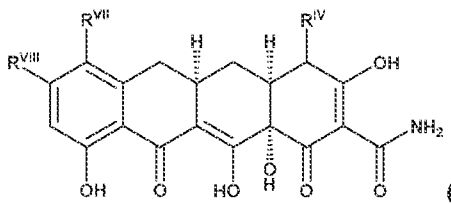

S21-6-5,


S21-6-6,

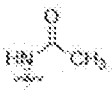

S21-6-7,

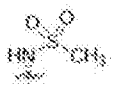
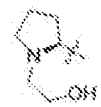

S21-6-8.

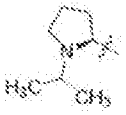
In the 37th embodiment, the present invention is any compound represented by structural formula (XIII):

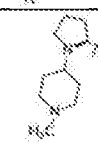

(XIII),

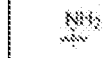
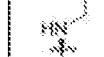
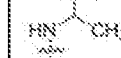
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof. In the first aspect of the 37th embodiment,

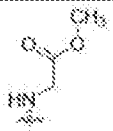
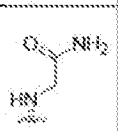
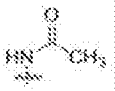
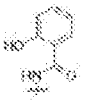
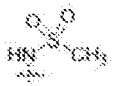
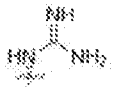
Compound number	R^{IV}	R^{VII}	R^{VIII}
S8-7-2			
S8-7-4			
S15-6-1			
S15-6-4			
S15-6-6			
S15-6-2			
S15-6-7			
S15-6-8			
S15-6-5			
S15-6-3			
S15-6-9			

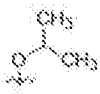
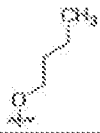
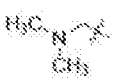
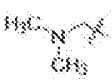
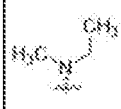
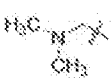
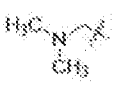
Compound number	R^{IV}	R^{VII}	R^{VIII}
S15-6-10			
S2-9-6			
S2-9-5			
S1-7-3			
S1-7-1			
S1-7-2			
S1-6-2			
S2-9-3			
S2-9-1			
S2-9-9			
S2-9-16			

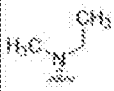
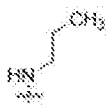
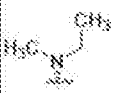
Compound number	R^{IV}	R^{VII}	R^{VIII}
S2-9-7			
S2-9-10			
S2-9-8			
S2-9-13			
S2-9-14			
S2-9-11			
S2-9-15			
S2-9-18			
S2-9-19			
S2-9-20			

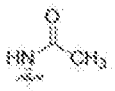
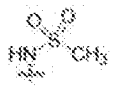
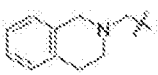
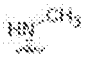
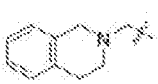
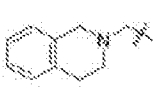
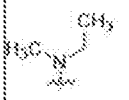
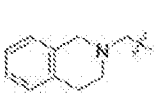
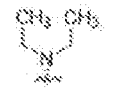
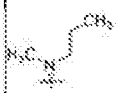
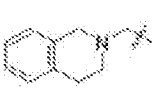
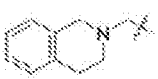
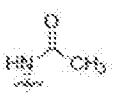
Compound number	R^{IV}	R^{VII}	R^{VIII}
S2-9-21			
S2-9-2			
S2-9-12			
S2-9-17			
S2-9-22			
S2-9-28			
S2-9-29			
S2-9-23			
S2-9-24			
S2-9-25			
S2-9-26			

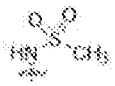
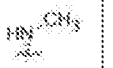
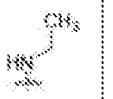
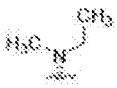
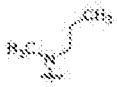
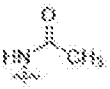
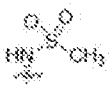
Compound number	R^{IV}	R^{VII}	R^{VIII}
S2-9-4			
S2-9-27			
S1-5-9			
S1-6-1			
S1-5-1			
S1-5-2			
S1-5-8			
S1-5-4			
S1-5-6			
S1-5-5			
S1-5-3			

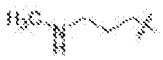
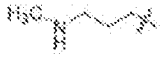
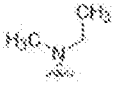
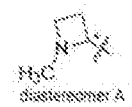
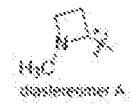
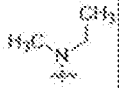
Compound number	R^{IV}	R^{VII}	R^{VIII}
S1-5-7			
S1-5-14			
S1-5-15			
S1-5-18			
S1-5-17			
S1-5-16			
S1-5-10			
S1-5-12			
S1-5-11			
S1-5-13			
S4-7-1			

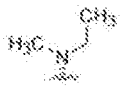
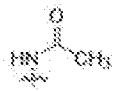
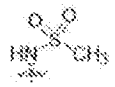
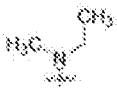
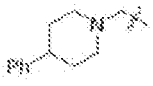
Compound number	R^{IV}	R^{VII}	R^{VIII}
S4-7-3			
S4-7-4			
S4-7-5			
S4-7-6			
S4-7-2			
S3-7-1			
S3-7-2			
S9-5-1			
S9-5-2			
S9-5-3			
S9-5-4			

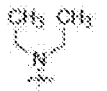
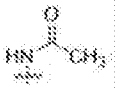
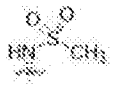
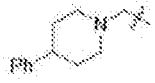
Compound number	R^{IV}	R^{VII}	R^{VIII}
S10-5-1			
S10-5-2			
S10-5-3			
S10-5-4			
S8-7-1			
S8-7-7			
S8-7-5			
S8-7-8			
S8-7-9			
S8-7-3			
S8-7-6			

Compound number	R^{IV}	R^{VII}	R^{VIII}
S8-7-10			
S8-7-11			
S7-6-1			
S7-6-2			
S7-6-6			
S7-6-4			
S7-6-7			
S7-6-8			
S7-6-3			
S7-6-5			
S7-6-9			

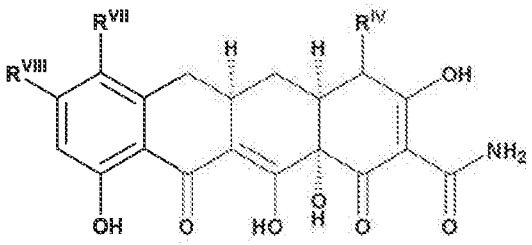
Compound number	R^{IV}	R^{VII}	R^{VIII}
S7-6-10			
S6-6-1			
S6-6-2			
S6-6-6			
S6-6-7			
S6-6-3			
S6-6-8			
S6-6-5			
S6-6-4			
S6-6-9			
S6-6-10			

Compound number	R^{IV}	R^{VII}	R^{VIII}
S11-4-1			
S11-4-2			
S11-5-1			
S11-5-2			
S12-2-1			
S12-2-2			
S12-2-3			
S12-2-4			
S14-6-1			
S14-6-3			
S14-6-5			

Compound number	R^{IV}	R^{VII}	R^{VIII}
S14-6-2			
S14-6-6			
S14-6-4			
S14-6-7			
S14-6-8			
S14-6-9			
S21-6-1			
S21-6-3			
S21-6-4			
S21-6-2			
S21-6-5			

Compound number	R^{IV}	R^{VII}	R^{VIII}
S21-6-6			
S21-6-7			
S21-6-8			

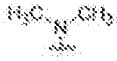
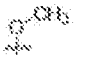
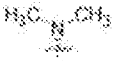
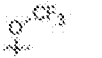
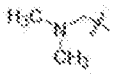
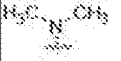
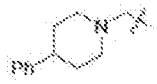
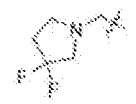
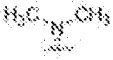
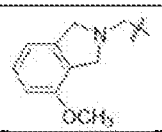
In the 38th embodiment, the present invention is a method of treating a hematological cancer comprising administering to a subject in need of treatment an effective amount of a compound represented by any one of structural formulas:

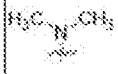
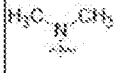
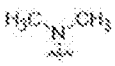
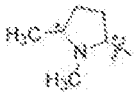
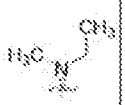
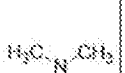
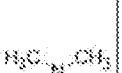
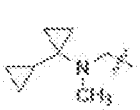
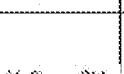
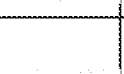


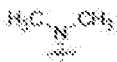
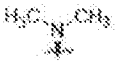
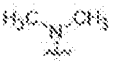
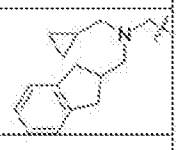
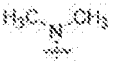
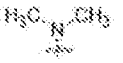
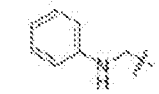
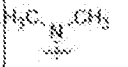
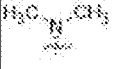
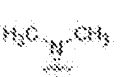
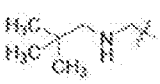
(XIII),

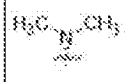
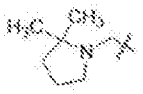
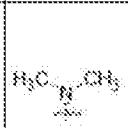
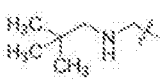
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof, wherein:

Compound number	R^{IV}	R^{VII}	R^{VIII}
K1			
K2			
K3			
K4 (compound 3A)			

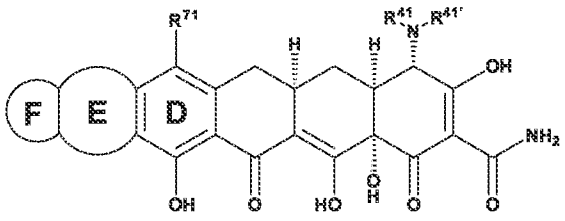
Compound number	R^{IV}	R^{VII}	R^{VIII}
K5			
K6			
K7			
K8			
K9			
K10			
K11			
K12			
K13			
K14			
K15			
K16			

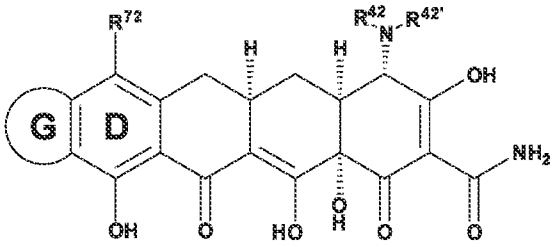
Compound number	R^{IV}	R^{VII}	R^{VIII}
K17			
K18			
K19			
K20			
K21			
K22			
K23			
K24			
K25			
K26			
K27			
K28			

Compound number	R^{IV}	R^{VII}	R^{VIII}
K29			
K30			
K31			
K32			
K33			
K34			
K35			
K36			
K37			
K38			
K39			
K40			

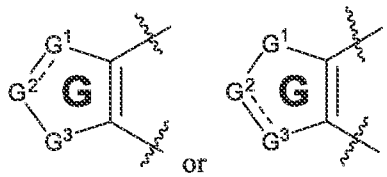
Compound number	R^{IV}	R^{VII}	R^{VIII}
K41			
K42			

In a 40th embodiment, the present invention is a compound represented by any one of structural formulas (XIV) or (XV):


(XIV),


(XV),

or a pharmaceutically acceptable salt thereof. In a first aspect of the 40th embodiment, ring E is a 4- or 5-member carbocyclyl; ring F is a 5- or 6-member heterocyclyl that includes at least one nitrogen atom; ring G is represented by any one of the following structural formulas


or

wherein "〰" represents the point of attachment of ring G to ring D, "⁼⁼⁼⁼⁼⁼⁼" is a single or a double bond, G^1, G^2, and G^3, each independently, is –CH=, -CH_2-, -N=, or –NH-,

as valence permits, provided that when "⋯⋯" is a single bond, then at least two of G^1, G^2, and G^3 are -NH-;

R^{71} and R^{72}, each independently, is selected from hydrogen, halo, -(C_1-C_6 alkyl), $-OR^A$, $-C(O)NR^BR^{B'}$, $NR^BR^{B'}$, $S(O)_{0-2}R^C$, -(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, and -(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl;

R^{41}, $R^{41'}$, R^{42}, and $R^{42'}$, each independently, is selected from hydrogen, -(C_1-C_6 alkyl), $S(O)_{1-2}R^C$, -(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, -C(O)-(C_1-C_6 alkyl), and -C(O)-(C_1-C_6 alkyl)-NR^DR^E; or

R^{41} and $R^{41'}$, and, separately, R^{42} and $R^{42'}$, are taken together with the nitrogen atom to which they are commonly bound to form a 4-8 membered ring optionally comprising 1-2 additional heteroatoms independently selected from N, O and S;

each R^A is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -C(O)-(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, and $-C(O)N(R^D)(R^E)$;

each R^B and each $R^{B'}$ is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, $-S(O)_{1-2}$-(C_1-C_6 alkyl), $-S(O)_{1-2}$-(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, $-S(O)_{1-2}$-(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, and $-C(O)$-(C_0-C_6 alkylenyl)-$N(R^D)(R^E)$;

each R^C is independently selected from -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl and -(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl; and

each R^D and each R^E is independently selected from hydrogen, -(C_1-C_6 alkyl), -(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, and -(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl;

wherein:

any alkyl, or alkylenyl portion of R^{71}, R^{72}, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$ is optionally and independently substituted with one or more substituents independently selected from halo, =O, OR^A, $NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

any alkyl or alkylenyl portion of R^A or R^C, is optionally and independently substituted with one or more fluoro;

rings E, F, and G, or any carbocyclyl or heterocyclyl portion of any of R^{71}, R^{72}, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, or any ring formed by taking together R^{41} and $R^{41'}$ or R^{42} and $R^{42'}$ is optionally and independently substituted on a carbon atom with one or more substituents independently selected from halo, =O, C_1-C_4 fluoroalkyl, C_1-C_4 alkyl, -(C_0-C_6 alkylenyl)-(C_{3-12} carbocyclyl), -(C_0-C_6 alkylenyl)-(4- to 13-membered heterocyclyl), OR^A, -(C_0-C_6 alkylenyl)-$NR^BR^{B'}$, and $S(O)_{0-2}R^C$;

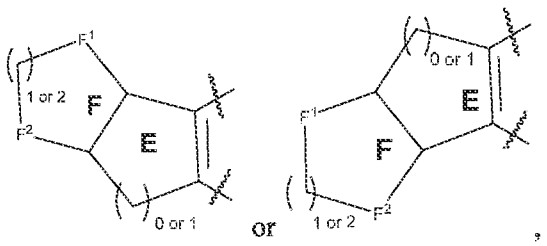
rings F and G, or any heterocyclyl portion of any of R^{71}, R^{72}, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, or any ring formed by taking together R^{41} and $R^{41'}$ or R^{42} and $R^{42'}$ is optionally and independently substituted on a substitutable nitrogen atom with R^F;

each R^F is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 hydroxyalkyl), -(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, -$S(O)_{1-2}$-(C_1-C_6 alkyl), -$S(O)_{1-2}$-(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -$S(O)_{1-2}$-(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, -C(O)-(C_1-C_6 alkyl), -C(O)-(C_0-C_6 alkylenyl)-(C_{3-12})carbocyclyl, -C(O)H, -C(O)-(C_0-C_6 alkylenyl)-(4- to 13-member)heterocyclyl, -(C_0-C_6 alkylenyl)-$C(O)_2$-(C_1-C_6 alkyl), -(C_1-C_6 alkylenyl)-$NR^BR^{B'}$ and -$C(O)N(R^D)(R^E)$;

any carbocyclyl or heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, or any substituent of R^{71}, R^{72}, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$ is optionally and independently substituted on a carbon atom with one or more substituents independently selected from fluoro, chloro, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, -O-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, =O, -OH, $-NH_2$, -NH(C_1-C_4 alkyl), and -$N(C_1$-C_4 alkyl)$_2$; and

any heterocyclyl portion of R^A, R^B, $R^{B'}$, R^C, R^D, R^E, R^F, or any heterocyclyl substituent of R^{71}, R^{72}, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$ is optionally substituted on a substitutable nitrogen atom with -C_1-C_4 alkyl, or -$S(O)_{1-2}$-(C_1-C_4 alkyl).

In the second aspect of the 40th embodiment, ring E and ring F, together, are represented by any one of the following structural formulas:



wherein F^1 and F^2, for each occurrence independently, is selected from -CH_2- or -NR^0-, wherein R^0, for each occurrence independently, is H or a C1-C4 alkyl, and "〰" represents the point of attachment of ring E to ring D. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspect one of the 40th embodiment.

In the third aspect of the 40th embodiment, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, each independently, is selected from hydrogen; -(C_1-C_6 alkyl), optionally substituted with one or more substituents independently selected from hydroxy and halo; -(C_3-C_6 cycloalkyl); -C(O)-(C_1-C_6 alkyl); -C(O)-(C_1-C_6 alkylenyl)-N(R^D)(R^E); and S(O)$_{1-2}R^C$; or R^{41} and $R^{41'}$ or R^{42} and $R^{42'}$ are taken together with the nitrogen atom to which they are commonly bound to form a 4-6 membered ring optionally comprising 1-2 additional heteroatoms independently selected from N, O and S; R^C is -(C_1-C_6 alkyl); and each of R^D and R^E is independently selected from hydrogen and -(C_1-C_6 alkyl). The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one and two of the 40th embodiment.

In the fourth aspect of the 40th embodiment, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, each independently, is selected from hydrogen, -(C_1-C_6 alkyl), -(C_3-C_6 cycloalkyl), -C(O)-(C_1-C_6 alkyl), -C(O)-(C_1-C_6 alkylenyl)-N(R^D)(R^E), and S(O)$_{1-2}R^C$; R^C is -(C_1-C_6 alkyl); and each of R^D and R^E is independently selected from hydrogen and -(C_1-C_6 alkyl). The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through three of the 40th embodiment.

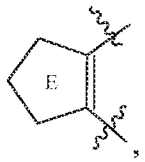
In the fifth aspect of the 40th embodiment, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, each independently, is selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, -C(O)CH_3, -C(O)$CH_2N(CH_3)_2$, and -S(O)$_2CH_3$. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through four of the 40th embodiment.

In the sixth aspect of the 40th embodiment, R^{71} and R^{72}, each independently, is selected from hydrogen; halo; -(C_1-C_6 alkyl), optionally substituted with one or more substituents independently selected from hydroxyl, halo, and -$NR^BR^{B'}$; -$NR^BR^{B'}$; -C(O)$NR^BR^{B'}$, -OR^A, -(C_0-C_6 alkylenyl)-(C_3-C_8)carbocyclyl, and -(C_0-C_6 alkylenyl)-(4- to 8-member)heterocyclyl, wherein R^A is C_1-C_6 alkyl optionally

substituted with one or more fluoro. For example, R^{71} and R^{72}, each independently, is selected from hydrogen; halo; -(C_1-C_6 alkyl), optionally substituted with one or more halo; and -OR^A, wherein R^A is C_1-C_6 alkyl optionally substituted with one or more fluoro. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through five of the 40th embodiment.

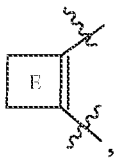
In the seventh aspect of the 40th embodiment, R^{71} and R^{72}, each independently, is selected from hydrogen, fluoro, chloro, -CF_3, -OCH_3, -OCF_3, -$N(CH_3)_2$ and -$NHCH_3$. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through seven of the 40th embodiment.

In the eight aspect of the 40th embodiment, ring E is represented by the following structural formula



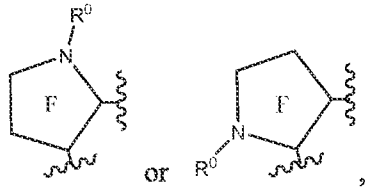
wherein each "〰" represents a point of attachment of the ring E to the ring D. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through seven of the 40th embodiment.

In the ninth aspect of the 40th embodiment, wherein ring E is represented by the following structural formula



wherein each "〰" represents a point of attachment of the ring E to the ring D. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through eight of the 40th embodiment.

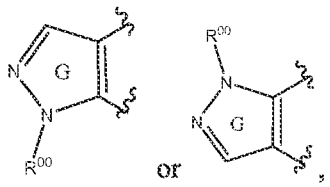
In the tenth aspect of the 40th embodiment, ring F is represented by any one of the following structural formulas



wherein each "〰" represents a point of attachment of the ring F to the ring E, and wherein R^0,

for each occurrence independently, is H or a C1-C4 alkyl. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through nine of the 40th embodiment.

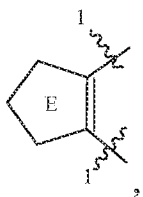
In the eleventh aspect of the 40th embodiment, ring G is represented by any one of the following structural formulas:



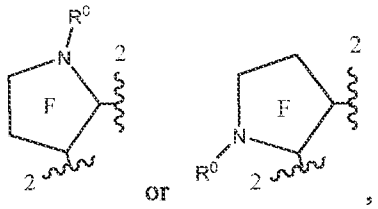
wherein each "〰" represents a point of attachment of the ring G to the ring D, and wherein R^{00}, for each occurrence independently, is H or a C1-C4 alkyl. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through ten of the 40th embodiment.

In the twelfth aspect of the 40th embodiment, R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, each independently, is H or a C1-C4 alkyl; R^{71} and R^{72}, each independently, is F or $-CF_3$. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through eleven of the 40th embodiment.

In the thirteenth aspect of the 40th embodiment, ring E is represented by the following structural formula

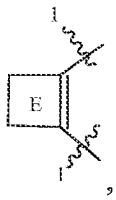


wherein each "1 ∿∿ " represents a point of attachment or the ring E to the ring D, ring F is represented by any one of the following structural formulas

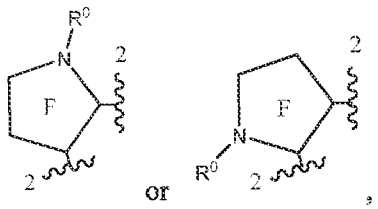


wherein each "2 ∿∿ " represents a point of attachment or the ring F to the ring E, R^0, for each occurrence independently, is H or a C1-C4 alkyl; R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, each independently, is H or a C1-C4 alkyl; and R^{71} and R^{72}, each independently, is F or $-CF_3$. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through twelve of the 40th embodiment.

In the fourteenth aspect of the 40th embodiment, ring E is represented by the following structural formula

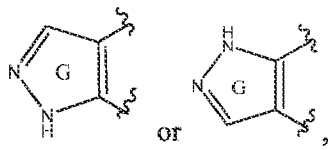


wherein each "1 ∿∿ " represents a point of attachment of the ring E to the ring D, ring F is represented by any one of the following structural formulas



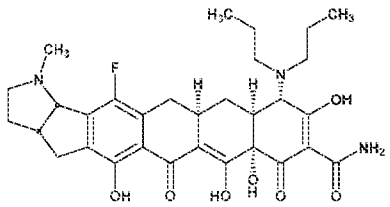
wherein each "2 ∿∿ " represents a point of attachment of the ring F to the ring E, R^0, for each occurrence independently, is H or a C_1-C_4 alkyl; R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, each independently, is H or a C_1-C_4 alkyl; and R^{71} and R^{72}, each independently, is F or $-CF_3$. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through thirteen of the 40th embodiment.

In the fifteenth aspect of the 40th embodiment, ring G is represented by any one of the following structural formulas:

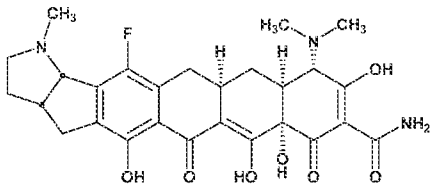


wherein each "〰" represents a point of attachment of the ring G to the ring D; R^{41}, $R^{41'}$, R^{42}, or $R^{42'}$, each independently, is H or a C_1-C_4 alkyl; and R^{71} and R^{72}, each independently, is F or -CF_3. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through fourteen of the 40th embodiment.

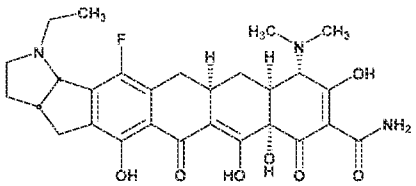
In the sixteenth aspect of the 40th embodiment, the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:



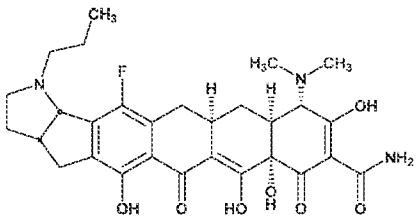
S5-9-7



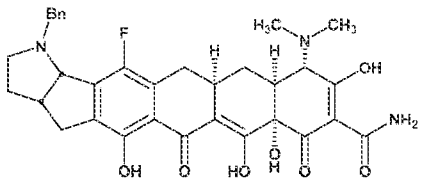
S5-9-2, diastereomers A and B



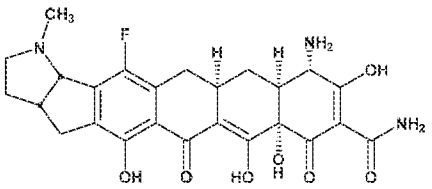
S5-9-3, diastereomers A and B



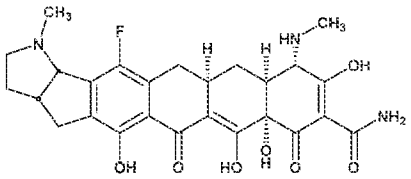
S5-9-4, diastereomers A and B



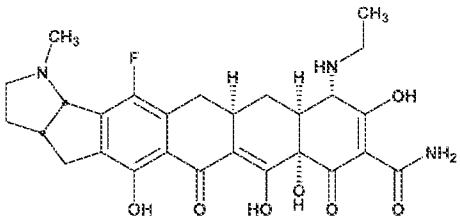
S5-9-5, diastereomers A and B



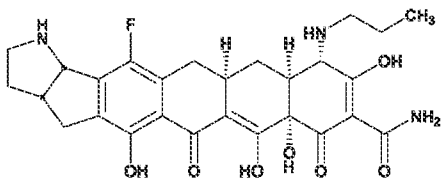
S5-9-10, diastereomers A and B



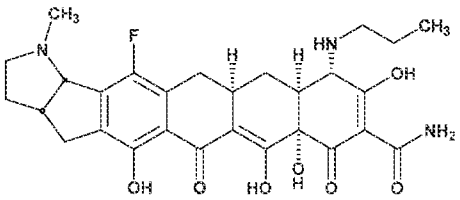
S5-9-9, diastereomers A and B



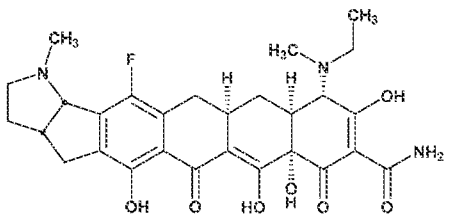
S5-9-11, diastereomers A and B



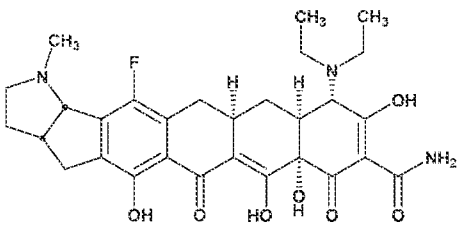
S5-9-8, diastereomer B



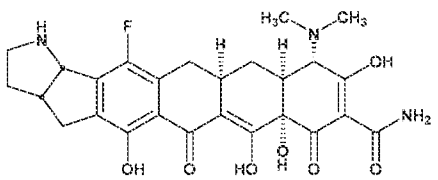
S5-9-6, diastereomers A and B



S5-9-12, diastereomers A and B

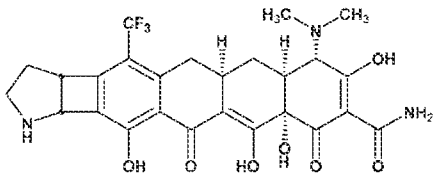


S5-9-13, diastereomers A and B

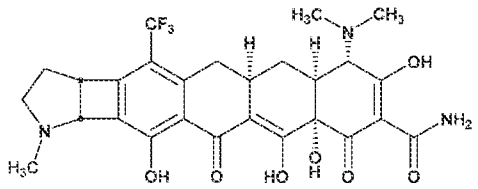


S5-9-1, diastereomers A and B

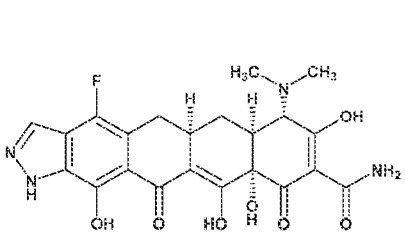
5



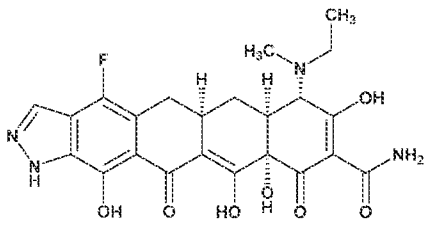
S13-9-1, diastereomers A and B



S13-9-2, diastereomers A and B



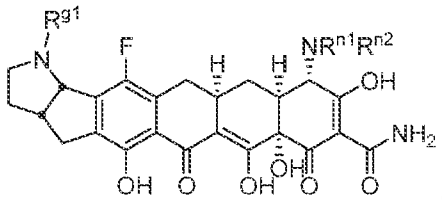
S18-3-1



S18-3-2 ,

or a pharmaceutically acceptable salt of any of the foregoing.

In the seventeenth aspect of the 40th embodiment, the compound is represented by the following structural formula

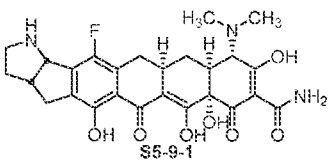


,

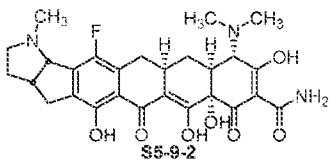
or a pharmaceutically acceptable salt thereof, wherein R^{g1}, R^{n1}, and R^{n2}, each independently, is H

or a C_1-C_4 alkyl, optionally substituted with a phenyl. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through fifteen of the 40th embodiment.

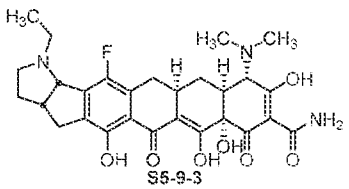
In the eighteenth aspect of the 40th embodiment, the compound is represented by any one of the following structural formulas:



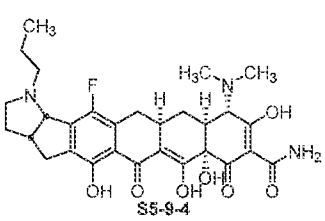
S5-9-1 ,

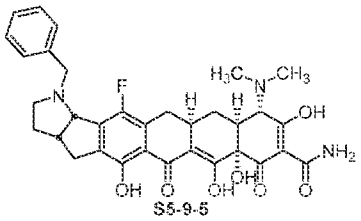


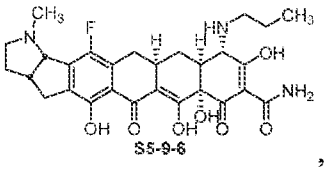
S5-9-2 ,

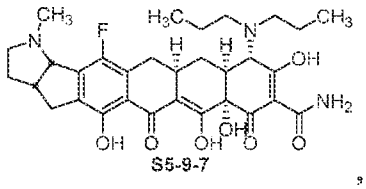


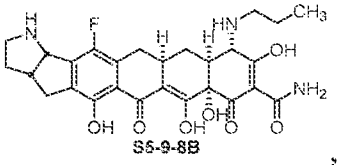
S5-9-3 ,

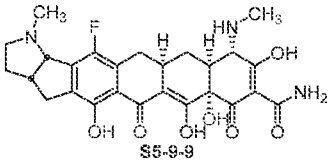

S5-9-4 ,

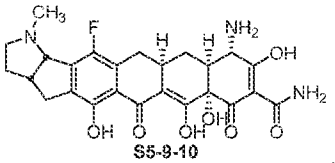

S5-9-5 ,

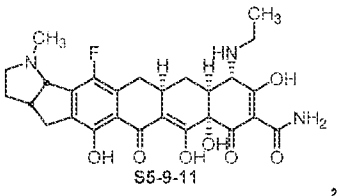

S5-9-6 ,

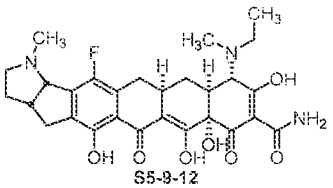

S5-9-7 ,

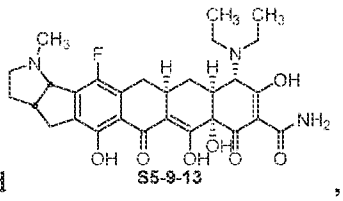

S5-9-8B ,


S5-9-9 ,


S5-9-10 ,

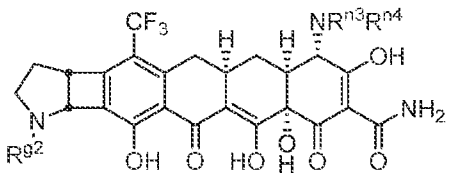

S5-9-11 ,


S5-9-12 , and


S5-9-13 ,

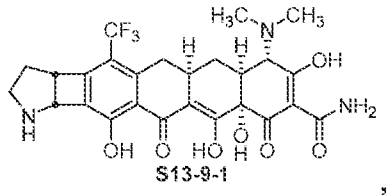
or a pharmaceutically acceptable salt of any of the foregoing.

In the nineteenth aspect of the 40th embodiment, the compound is represented by the following structural formula

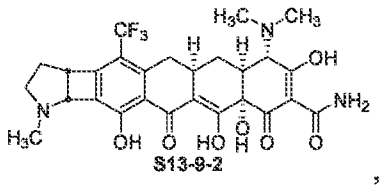


or a pharmaceutically acceptable salt thereof, wherein R^{g2}, R^{n3}, and R^{n4}, each independently, is H or a C_1-C_4 alkyl. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through fifteen of the 40th embodiment.

In the twentieth aspect of the 40th embodiment, the compound is represented by any one of the following structural formulas:


S13-9-1

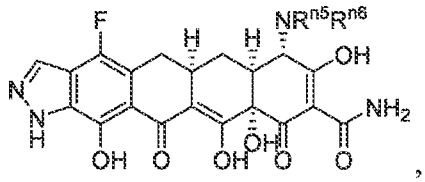
,


S13-9-2

,

or a pharmaceutically acceptable salt thereof.

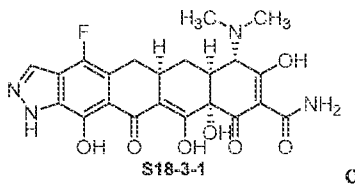
In the twenty-first aspect of the 40th embodiment, the compound is represented by the following structural formula



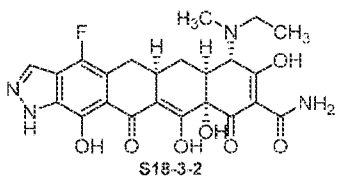
,

or a pharmaceutically acceptable salt thereof, wherein R^{n5} and R^{n6}, each independently, is H or a C_1-C_4 alkyl. The remainder of the values and example values of the variables in structural formulas (XIV) and (XV) of the 40th embodiment are as defined above with respect to aspects one through fifteen of the 40th embodiment.

In the twenty-second aspect of the 40th embodiment, the compound is represented by any one of the following structural formulas:


S18-3-1

or


S18-3-2

or a pharmaceutically acceptable salt of any of the foregoing.

In the 41st embodiment, the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of any

compound described herein with respect to embodiments 1 through 40, in particular embodiments 37-40, and various aspects thereof.

In the 42nd embodiment, the present invention is a method of treating a subject suffering from a hematological tumor, comprising administering to the subject a therapeutically effective amount of any compound described herein with respect to embodiments 1 through 40 and various aspects thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 41.

In the first aspect of the 42nd embodiment, the hematological cancer is a leukemia. Examples of leukemia include acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, acute monocytic leukemia.

In the second aspect of the 42nd embodiment, the leukemia is acute myeloid leukemia.

In the third aspect of the 42nd embodiment, the hematological cancer is a lymphoma. Examples of lymphomas include Hodgkin's lymphoma, non-Hodgkin's lymphomas, multiple myeloma, myelodysplastic or myeloproliferative syndrome, mantle cell lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma/leukemia and B-cell lymphoma.

In the fourth aspect of the 42nd embodiment, the methof includes administration of one or more additional therapeutic agents. Examples of the additional therapeutic agents include cytarabine and an anthracycline drugs. Examples of the anthracycline drug include daunorubicin or idarubicin.

In the fifth aspect of the 42nd embodiment, the method further includes administration of cladribine.

In various aspects of the 42nd embodiment, the subject is a human.

In the 43rd embodiment, the present invention is a method for treating a bacterial infection in a subject (including preventing an infection or colonization in a subject) in need thereof, comprising administering to the subject a therapeutically effective amount of any compound described herein with respect to embodiments 1 through 40, particularly embodiments 37-40, and various aspects thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 41.

In the first aspect of the 43rd embodiment, the infection is caused by a Gram-positive organism. Examples of the Gram-positive organisms include an organism selected from the class Bacilli; phylum Actinobacteria; and class Clostridia.

In the second aspect of the 43rd embodiment, the infection is caused by a Gram-negative organism. Examples of Gram-negative organisms include an organism selected from the group consisting of *Enterobactericeae, Bacteroidetes, Vibrionaceae, Pasteurellaceae, Pseudomonadaceae, Neisseriaceae, Rickettsiae, Moraxellaceae* any species of *Proteeae, Acinetobacter* spp., *Helicobacter* spp., and *Campylobacter* spp.

In the third aspect of the 43rd embodiment, the infection is caused by an organism selected from order Rickettsiales and order Chlamydiales.

In the fourth aspect of the 43rd embodiment, the infection is caused by an organism selected from the phylum Chlamydiae and phylum Spriochaetales.

In the fifth aspect of the 43rd embodiment, the infection is caused by an organism selected from the class Mollicutes.

In the sixth aspect of the 43rd embodiment, the infection is caused by more than one organism.

In the seventh aspect of the 43rd embodiment, the infection is caused by an organism resistant to one or more antibiotics.

In the eighth aspect of the 43rd embodiment, the infection is caused by a Gram-positive organism, and the Gram-positive organism is selected from *S. aureus, CoNS, S. pneumoniae, S. pyogenes, S. agalactiae, E. faecalis and E. faecium.*

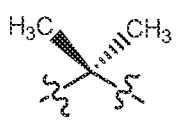
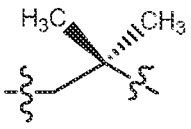
In the ninth aspect of the 43rd embodiment, the infection is caused by a Gram-negative organism, and the Gram-negative organism is selected from *H. influenza, M. catarrhalis* and *Legionella pneumophila.*

Definitions

"Alkyl" means an optionally substituted saturated aliphatic branched or straight-chain monovalent hydrocarbon radical having the specified number of carbon atoms. Thus, "(C_1-C_6) alkyl" means a radical having from 1- 6 carbon atoms in a linear or branched arrangement. "(C_1-C_6)alkyl" includes methyl, ethyl, propyl, butyl, pentyl and hexyl. "(C_1-C_{12}) alkyl" means a radical having from 1- 12 carbon atoms in a linear or branched arrangement. "(C_1-C_{12})alkyl" includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl. Unless otherwise specified, suitable substitutions for a "substituted alkyl" include halogen, -OH, -O-C_1-C_4 alkyl, C_1-C_4 alkyl, fluoro-substituted-C_1-C_4 alkyl, -O-C_1-C_4 fluoroalkyl, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, C_3-

C_{12} carbocyclyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl or naphthalenyl), a (4-13 membered) heterocyclyl (e.g., pyrrolidine, piperidine, piperazine, tetrahydrofuran, tetrahydropyran or morpholine) or -$N(R^X)(R^{X'})$, wherein R^X and $R^{X'}$ are independently hydrogen or C_1-C_4 alkyl, or taken together with the nitrogen atom to which they are bound form a (4-7 membered) heterocylic ring optionally comprising one additional heteroatom selected from N, S and O, wherein the (4-7 membered) heterocylic ring is optionally substituted with fluoro, chloro, -OH, fluoro-substituted C_1-C_4 alkyl, -C_1-C_4 alkyl, or -C_0-C_4 alkylene-O-C_1-C_4 alkyl, and is optionally benzofused.

"Benzofused," when referring to a ring system, means fused to a phenyl ring, forming a fused bicyclyl ring.

"Alkylene" or "alkylenyl" (used interchangeably) mean an optionally substituted saturated aliphatic branched or straight-chain divalent hydrocarbon radical having the specified number of carbon atoms. An alkyl moiety of an alkylene group can be a part of a larger moiety such as alkoxy, alkylammonium, and the like. Thus, "(C_1-C_6)alkylene" means a divalent saturated aliphatic radical having from 1- 6 carbon atoms in a linear arrangement, e.g., -[$(CH_2)_n$]-, where n is an integer from 1 to 6, "(C_1-C_6)alkylene" includes methylene, ethylene, propylene, butylene, pentylene and hexylene. Alternatively, "(C_1-C_6)alkylene" means a divalent saturated radical having from 1-6 carbon atoms in a branched arrangement, for example: -[$CH_2CH_2CH_2CH_2CH(CH_3)$]-, -[$CH_2CH_2CH_2CH_2C(CH_3)_2$]-, -[$CH_2C(CH_3)_2CH(CH_3)$)]-, and the like. A "($C_1$-$C_{12}$)alkylene" includes methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, heptyl or octyl. A specific branched C_3-alkylene is  and a specific C_4-alkylene is  . Other examples of a divalent C_{1-6} alkyl group include, for example, a methylene group, an ethylene group, an ethylidene group, an n-propylene group, an isopropylene group, an isobutylene group, an s-butylene group, an n-butylene group, and a t-butylene group.

A "C_0 alkylenyl" is a covalent bond.

"Alkoxy" means an alkyl radical attached through an oxygen linking atom. "(C_1-C_4)-alkoxy" includes methoxy, ethoxy, propoxy, and butoxy.

"Alkylthio" means an alkyl radical attached through a sulfur linking atom. "(C_1-C_4)alkylthio" include methylthio, ethylthio, propylthio and butylthio.

"Alkylsulfinyl" means an alkyl radical attached through a -S(O)- linking group. "(C_1-C_4)alkylsulfinyl" include methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl.

"Alkylsulfonyl" means an alkyl radical attached through a -$S(O)_2$- linking group. "(C_1-C_4)alkylsulfonyl" include methylsulfonyl, ethylsulfonyl, propylsulfonyl and butylsulfonyl.

"Aryl" or "aromatic" means an aromatic 6-18 membered monocyclic or polycyclic (e.g. bicyclic or tricyclic) carbocyclic ring system. In one embodiment, "aryl" is a 6-18 membered monocylic or bicyclic system. Aryl systems include, but not limited to, phenyl, naphthalenyl, fluorenyl, indenyl, azulenyl, and anthracenyl.

"Aryloxy" means an aryl moiety attached through an oxygen linking atom. Aryloxy includes, but not limited to, phenoxy.

"Arylthio" means an aryl moiety attached through a sulfur linking atom. Arylthio includes, but not limited to, phenylthio.

"Arylsulfinyl" means an aryl moiety attached through a -S(O)- linking group. Arylsulfinyl includes, but not limited to, phenylsulfinyl.

"Arylsulfonyl" means an aryl moiety attached through a -$S(O)_2$- linking group. Arylsulfonyl includes, but not limited to, phenylsulfonyl.

"Amine" means H_2N- and can also be used to refer to aminium group H_3N^+-.

The term "alkylamine" includes a mono-, a dialkylamine and can also be used to refer to aminium (bearing a positive charge). A "monoalkyl amine" means an H(alkyl)N-, a "dialkylamine" means (alkyl)(alkyl)N-, and an "aminium" means (alkyl)(alkyl)(alkyl)N^+-, H(alkyl)(alkyl)N^+-, or H_2(alkyl)N^+-, where each instance of "alkyl" independently refers to an alkyl having a specified number of atoms.

"Carbocyclyl" means a cyclic group having a specified number of atoms, wherein all ring atoms in the ring bound to the rest of the compound (also known as the "first ring") are carbon atoms. Exples of "carbocyclyl" includes 3-18 (for example 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 12, 1, 14, 15, 16, 17, or 17 or any range therein, such as 3-12 or 3-10) membered saturated or unsaturated aliphatic cyclic hydrocarbon rings, or 6-18 membered aryl rings. A carbocyclyl moiety can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic, or polycyclic.

A "cycloalkyl" is an example of a fully saturated carbocyclyl.

Monocyclic carbocyclyls are saturated or unsaturated aliphatic cyclic hydrocarbon rings or aromatic hydrocarbon rings having the specified number of carbon atoms, such as 3-7 carbon atoms. Monocyclic carbocyclyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, cycloalkenyl, cycloalkynyl and phenyl.

A fused bicyclic carbocyclyl has two rings which have two adjacent ring atoms in common and can be, e.g., a (6-13 membered) fused bicyclic. The first ring attached to the parent molecular group is a monocyclic carbocyclyl and the ring fused to the first ring (also known as the "second ring") is also a monocyclic carbocyclyl.

A bridged bicyclic carbocyclyl has two rings which have three or more adjacent ring atoms in common and can be, e.g., a (4-13 membered) bridged bicyclic or (6-13 membered) bridged tricyclic such as adamantyl. The first ring attached to the parent molecular group is a monocyclic carbocyclyl and the second ring is also a monocyclic carbocyclyl.

A spiro bicyclic carbocyclyl has two rings which have only one ring atom in common and can be, e.g., a (6-13 membered) spiro bicyclic. The first ring attached to the parent molecular group is a monocyclic carbocyclyl and the second ring is also a monocyclic carbocyclyl.

Polycyclic carbocyclyls have more than two rings (e.g., three rings resulting in a tricyclic ring system) and adjacent rings have at least one ring atom in common. The first ring is a monocyclic carbocyclyl and the remainder of the ring structures are monocyclic carbocyclyls . Polycyclic ring systems include fused, bridged and spiro ring systems. A fused polycyclic ring system has at least two rings that have two adjacent ring atoms in common. A spiro polycyclic ring system has at least two rings that have only one ring atom in common. A bridged polycyclic ring system has at least two rings that have three or more adjacent ring atoms in common.

Suitable substituents for a "substituted carbocyclyls" include, but are not limited to halogen, -OH, -O-C_1-C_4 alkyl, C_1-C_4 alkyl, fluoro-substituted-C_1-C_4 alkyl, C_3-C_{18} carbocyclyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) phenyl, naphthalenyl, a (4-13 membered) heterocyclyl (e.g., pyrrolidine, piperidine, piperazine, tetrahydrofuran, tetrahydropyran or morpholine), or -$N(R^X)(R^{X'})$, wherein R^X and $R^{X'}$ are as described above.

"Cycloalkoxy" means a cycloalkyl radical attached through an oxygen linking atom. "(C_3-C_6)cycloalkoxy" includes cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

"Cycloalkene" means an aliphatic cyclic hydrocarbon ring having one or more double bonds in the ring.

"Cycloalkyne" means an aliphatic cyclic hydrocarbon ring having one or more triple bonds in the ring.

"Hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom selected from N, S, and O. "Hetero" also refers to the replacement of at least one carbon atom member in an acyclic system. When one heteroatom is S, it can be optionally mono- or di-oxygenated (i.e. -S(O)- or -$S(O)_2$-). A hetero ring system or a hetero acyclic system may have 1, 2, 3 or 4 carbon atom members replaced by a heteroatom.

"Heterocyclyl" means a cyclic 3-18 membered, for example 3-13-membered, 3-15, 5-18, 5-12, 3-12, 5-6 or 5-7-membered saturated or unsaturated aliphatic or aromatic ring system containing 1, 2, 3, 4 or 5 heteroatoms independently selected from N, O and S. When one heteroatom is S, it can be optionally mono- or di-oxygenated (i.e. -S(O)- or -$S(O)_2$-). The heterocyclyl can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic or polycyclic. Non-limiting examples include (4-7 membered) monocyclic, (6-13 membered) fused bicyclic, (6-13 membered) bridged bicyclic, or (6-13 membered) spiro bicyclic.

"Saturated heterocyclyl" means an aliphatic heterocyclyl group without any degree of unsaturation (i.e., no double bond or triple bond). It can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic or polycyclic.

Examples of monocyclic saturated heterocyclyls include, but are not limited to, azetidine, pyrrolidine, piperidine, piperazine, azepane, hexahydropyrimidine, tetrahydrofuran, tetrahydropyran, morpholine, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-2H-1,2-thiazine, tetrahydro-2H-1,2-thiazine 1,1-dioxide, isothiazolidine, isothiazolidine 1,1-dioxide.

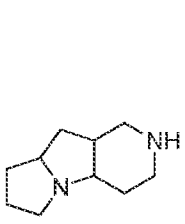
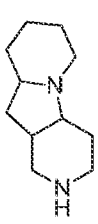
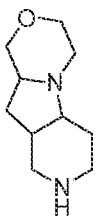
One type of "heterocyclyl" is a "heteroaryl" or "heteroaromatic ring", which refers to a 5-18 membered monovalent heteroaromatic monocyclic or bicylic ring radical. A heteroaryl contains 1, 2, 3 or 4 heteroatoms independently selected from N, O, and S.

A fused bicyclic heterocyclyl has two rings which have two adjacent ring atoms in common. The first ring is a monocyclic heterocyclyl and the second ring is a monocyclic carbocycle or a monocyclic heterocyclyl. For example, the second ring is a (C_3-C_6)cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of fused bicyclic heterocyclyls include, but are not limited to, octahydrocyclopenta [c]pyrrolyl, indoline, isoindoline, 2,3-dihydro-1H-benzo[d]imidazole, 2,3-dihydrobenzo[d]oxazole, 2,3-dihydrobenzo[d]thiazole, octahydrobenzo[d]oxazole, octahydro-1H-benzo[d]imidazole, octahydrobenzo[d]thiazole, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[3.1.0]hexane, and 3-azabicyclo[3.2.0]heptane.

A spiro bicyclic heterocyclyl has two rings which have only one ring atom in common. The first ring is a monocyclic heterocyclyl and the second ring is a monocyclic carbocycle or a monocyclic heterocyclyl. For example, the second ring is a (C_3-C_6)cycloalkyl. Examples of spiro bicyclic heterocyclyl includes, but are not limited to, azaspiro[4.4]nonane, 7-azaspiro[4.4]nonane, azasprio[4.5]decane, 8-azaspiro[4.5]decane, azaspiro[5.5]undecane, 3-azaspiro[5.5]undecane and 3,9-diazaspiro[5.5]undecane.

A bridged bicyclic heterocyclyl has two rings which have three or more adjacent ring atoms in common. The first ring is a monocyclic heterocyclyl and the other ring is a monocyclic carbocycle or a monocyclic heterocyclyl. Examples of bridged bicyclic heterocyclyls include, but are not limited to, azabicyclo[3.3.1]nonane, 3-azabicyclo[3.3.1]nonane, azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.1]octane, 6-azabicyclo[3.2.1]octane and azabicyclo[2.2.2]octane, 2-azabicyclo[2.2.2]octane.

Polycyclic heterocyclyls have more than two rings, wherein the first ring can be a heterocyclyl (e.g., three rings resulting in a tricyclic ring system) and adjacent rings having at least one ring atom in common and are heterocyclyl or carbocyclyl. Polycyclic ring systems include fused, bridged and spiro ring systems. A fused polycyclic ring system has at least two rings that have two adjacent ring atoms in common. A spiro polycyclic ring system has at least two rings that have only one ring atom in common. A bridged polycyclic ring system has at least two rings that have three or more adjacent ring atoms in common.

Examples of polycyclic heterocyclyls include  ,  , and  .

"Heteroaryl" or "heteroaromatic ring" means a 5-18 membered monovalent heteroaromatic monocyclic or bicylic ring radical. A heteroaryl contains 1, 2, 3 or 4 heteroatoms independently selected from N, O, and S. Heteroaryls include, but are not limited to furan, oxazole, thiophene, 1,2,3-triazole, 1,2,4-triazine, 1,2,4-triazole, 1,2,5-thiadiazole 1,1-dioxide, 1,2,5-thiadiazole 1-oxide, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,5-triazine, imidazole, isothiazole, isoxazole, pyrazole, pyridazine, pyridine, pyridine-N-oxide, pyrazine, pyrimidine, pyrrole, tetrazole, and thiazole. Bicyclic heteroaryl rings include, but are not limited to, bicyclo[4.4.0] and bicyclo[4.3.0] fused ring systems such as indolizine, indole, isoindole, indazole, benzimidazole, benzthiazole, purine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine.

"Halogen" and "halo" are used interchangably herein and refer to fluorine, chlorine, bromine, or iodine.

"Haloalkyl" and "halocycloalkyl" include mono, poly, and perhaloalkyl groups where each halogen is independently selected from fluorine, chlorine, and bromine.

"Fluoro" means -F.

"Chloro" means -Cl.

As used herein, "fluoro-substituted-alkyl" or "fluoroalkyl" means an alkyl having a specified number of atoms and substituted with one or more -F groups. Examples of fluoro-substituted-alkyls include, but are not limited to, $-CF_3$, $-CH_2CF_3$, $-CH_2CF_2H$, $-CH_2CH_2F$ and $-CH_2CH_2CF_3$.

"Hydroxyalkyl," as used herein, refers to an alkyl group substituted with one or more hydroxyls. Hydroxyalkyl includes mono, poly, and perhydroxyalkyl groups. Examples of hydroxyalkyls include $-CH_2CH_2OH$ and $-CH_2CH(OH)CH_2OH$.

"Oxo" means substituted with =O.

As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position.

Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

In the paragraphs below, where "Ph" is phenyl.

Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; -CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; -CN; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR$-, $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$;$-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene)O-$N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene)C(O)O-$N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, -(halo$R^\bullet$), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$,$-(CH_2)_{0-2}CH(OR^\bullet)_2$; -O(halo$R^\bullet$),

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

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

Suitable substituents on the aliphatic group of R^* include halogen, -$R^{\bullet}$, -(halo$R^{\bullet}$), -OH, -$OR^{\bullet}$, -O(halo$R^{\bullet}$), -CN, -C(O)OH, -$C(O)OR^{\bullet}$, -NH_2, -$NHR^{\bullet}$, -$NR^{\bullet}_2$, or -NO_2, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, -CH_2Ph, -$O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include -$R^{\dagger}$, -$NR^{\dagger}_2$, -$C(O)R^{\dagger}$, -$C(O)OR^{\dagger}$, -$C(O)C(O)R^{\dagger}$, -$C(O)CH_2C(O)R^{\dagger}$, -$S(O)_2R^{\dagger}$, -$S(O)_2N$$R^{\dagger}_2$, -$C(S)NR^{\dagger}_2$, -$C(NH)NR^{\dagger}_2$, or -$N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted -OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the

definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, -$R^{\bullet}$, -(halo$R^{\bullet}$), -OH, -$OR^{\bullet}$, -O(halo$R^{\bullet}$), -CN, -C(O)OH, -C(O)$OR^{\bullet}$, -NH_2, -$NHR^{\bullet}$, -$NR^{\bullet}_2$, or -NO_2, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, -CH_2Ph, -$O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Another embodiment of the present invention is a pharmaceutical composition comprising one or more pharmaceutically acceptable carrier and/or diluent and a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

"Pharmaceutically acceptable carrier" and "pharmaceutically acceptable diluent" means non-therapeutic components that are of sufficient purity and quality for use in the formulation of a composition of the invention that, when appropriately administered to an animal or human, typically do not produce an adverse reaction, and that are used as a vehicle for a drug substance (i.e., a compound of the present invention).

Pharmaceutically acceptable salts of the compounds of the present invention are also included. For example, an acid salt of a compound of the present invention containing an amine or other basic group can be obtained by reacting the compound with a suitable organic or inorganic acid, resulting in pharmaceutically acceptable anionic salt forms. Examples of anionic salts include the acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts.

Salts of the compounds of the present invention containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically

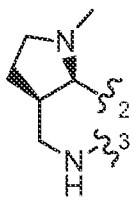
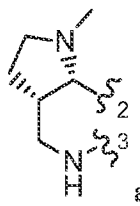
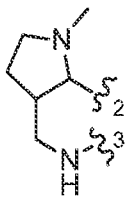
acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine, collidine, quinine, quinoline, and basic amino acids such as lysine and arginine.

The invention also includes various isomers and mixtures thereof. Certain of the compounds of the present invention may exist in various stereoisomeric forms. Stereoisomers are compounds which differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms. "*R*" and "*S*" represent the configuration of substituents around one or more chiral carbon atoms. When a chiral center is not defined as R or S, either a pure enantiomer or a mixture of both configurations is present.

"Racemate" or "racemic mixture" means a compound of equimolar quantities of two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light.

The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by weight optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer that is present divided by the combined weight of the enantiomer that is present and the weight of its optical isomer.

"Cis" means on the same side. "Trans" means on opposite sides. The designation "cis" is used when two substituents have an ""up-up" or a "down-down" relationship. The designation "trans" is used when two substituents have an "up-down" or "down-up" relationship. Typically, two substituents that are "cis" to one another are arranged on the same side of a molecule. When the term "cis" is used with reference to a fused, saturated or partially saturated ring system, the term is intended to indicate that the two atoms attached to the common ring atoms are cis substituents. For example,  and  are cis diastereomers of a moiety having the following structural formula:  .

As used herein, the term "subject" means a mammal in need of treatment or prevention, e.g., a human, companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, pigs, horses, sheep, goats and the like) and laboratory animals (e.g., rats, mice, guinea pigs and the like). Typically, the subject is a human in need of the specified treatment.

As used herein, the term "treating" or 'treatment" refers to obtaining desired pharmacological and/or physiological effect. The effect can include achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome; ameliorating or improving a clinical symptom or indicator

associated with the disorder; delaying, inhibiting or decreasing the likelihood of the progression of the disease, disorder or syndrome.

As used herein, "preventing" or "prevention" refers to reducing the likelihood of the onset or development of disease, disorder or syndrome.

"Effective amount" means that amount of active compound agent that elicits the desired biological response in a subject. In one embodiment, the effective amount of a compound of the invention is from about 0.01 mg/kg/day to about 1000 mg/kg/day, from about 0.1 mg/kg/day to about 100 mg/kg/day, or from about 0.5 mg/kg/day to about 50 mg/kg/day.

As used herein the terms hematological malignancy and hematological cancer are used interchangeably and refer to cancers of the blood (leukemia) or cancers of the lymph system (lymphomas). Leukemias can include acute myeloid leukemia (AML), also known as acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia or acute nonlymphocytic leukemia, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), acute monocytic leukemia (AMoL). Lymphomas can include, Hodgkin's lymphoma, non-Hodgkin's lymphomas, multiple myeloma, myelodysplastic or myeloproliferative syndrome, mantle cell lymphoma, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma/leukemia and B-cell lymphoma.

Indications

Hematological malignancies are cancers that affect the blood and lymph system. Some types of hematologic malignancies include: Multiple myeloma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma and Leukemia. The cancer may begin in blood-forming tissue (e.g., bone marrow), or in the cells of the immune system. For example, leukemia originates in blood-forming tissue. Leukemia is characterized by the uncontrolled growth of blood cells, usually white blood cells (leukocytes), in the bone marrow. White blood cells are a fundamental component of the body's immune response. The leukemia cells crowd out and replace normal blood and marrow cells.

There are four main types of leukemia: Acute myeloid leukemia (AML); Chronic myeloid leukemia (CML); Acute lymphocytic leukemia (ALL); and Chronic lymphocytic leukemia (CLL). The primary differences between the four main types of leukemia have to

do with their rates of progression and where the cancer develops. Acute myeloid leukemia (AML), also known as acute myelogenous leukemia, acute myeloblastic leukemia, acute granulocytic leukemia or acute nonlymphocytic leukemia, is a fast-growing form of cancer of the blood and bone marrow. AML is the most common type of acute leukemia. It occurs when the bone marrow begins to make blasts, cells that have not yet completely matured. These blasts normally develop into white blood cells. However, in AML, these cells do not develop and are unable to ward off infections. In AML, the bone marrow may also make abnormal red blood cells and platelets. The number of these abnormal cells increases rapidly, and the abnormal (leukemia) cells begin to crowd out the normal white blood cells, red blood cells and platelets that the body needs.

In certain embodiments, provided herein is a method of treating a hematological cancer in a subject in need of treatment comprising administering to the subject in need of treatment an effective amoung of any of the compounds disclosed herein, including a compound of Formula (I), Formula (I'), Formula (II), Formula (II'), Formula (III), Formula (III'), Formula (IV), Formula (IV'), Formula (V), Formula (V'), Formula (VI), Formula (VI'), Formula (VII) or Formula (VII'), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof. In further embodiments, provided herein is a method of treating a hematological cancer in a subject in need of treatment comprising administering to the subject in need of treatment an effective amoung of any of the compounds disclosed herein, including a compound of Formula (X), (X-1), (XI), (XII), (XX), (XXI), (XXII), (XXIII), (XXIV), (XXV), (XIII), (XIV), or (XV).

In one aspect, the hematological cancer is selected from Acute Myeloid Leukemia, Multiple myeloma, Hodgkin lymphoma, Non-Hodgkin lymphoma and Leukemia

In particular embodiments, provided herein is a method of treating a leukemia in a subject in need of treatment comprising administering to the subject in need of treatment an effective amoung of any of the compounds disclosed herein, including a compound of Formula (I), Formula (I'), Formula (II), Formula (II'), Formula (III), Formula (III'), Formula (IV), Formula (IV'), Formula (V), Formula (V'), Formula (VI), Formula (VI'), Formula (VII) or Formula (VII'), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof. In further embodiments, provided herein is a method of treating a leukemia in a subject in need of treatment comprising administering to the subject in need of treatment an effective amoung of any of the compounds disclosed herein,

including a compound of Formula (X), (X-1), (XI), (XII), (XX), (XXI), (XXII), (XXIII), (XXIV), (XXV), (XIII), (XIV), or (XV).

In some embodiments, provided herein is a method of treating acute myeloid leukemia in a subject in need of treatment comprising administering to the subject an effective amount of any of the compounds disclosed herein, including a compound of Formula (I), Formula (I'), Formula (II), Formula (II'), Formula (III), Formula (III'), Formula (IV), Formula (IV'), Formula (V), Formula (V'), Formula (VI), Formula (VI'), Formula (VII) or Formula (VII'), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof. In some embodiments, provided herein is a method of treating acute myeloid leukemia in a subject in need of treatment comprising administering to the subject an effective amount of any of the compounds disclosed herein, including a compound of Formula (X), (X-1), (XI), (XII), (XX), (XXI), (XXII), (XXIII), (XXIV), (XXV), (XIII), (XIV), or (XV).

In certain embodiments, provided herein is a method of treating acute myeloid leukemia comprising administering to a subject an effective amount of a compound of Formula (I), Formula (I'), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof. In one aspect of this embodiment, the compound is selected from Compounds 3, 3a, 3b, 4, 4a, 4b and 5 as defined herein or a pharmaceutically acceptable salt thereof. In a specific aspect, the compound is Compound 3a.

In certain embodiments, provided herein is a method of treating acute myeloid leukemia in a subject in need of treatment comprising administering to the subject an effective amount of a compound of Formula (II), Formula (II'), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof.

In certain embodiments, provided herein is a method of treating acute myeloid leukemia in a subject in need of treatment comprising administering to the subject an effective amount of a compound of Formula (III), Formula (III') or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof. In one aspect of this embodiment, the compound is selected from Compounds 1 and 2 as described herein or a pharmaceutically acceptable salt thereof.

In certain embodiments, provided herein is a method of treating acute myeloid leukemia in a subject in need of treatment comprising administering to the subject an

effective amount of a compound of Formula (IV), Formula (IV') or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof.

In other embodiments, provided herein is a method of treating acute myeloid leukemia in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (V), Formula (V') or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof.

In certain embodiments, provided herein is a method of treating acute myeloid leukemia in a subject in need of treatment comprising administering to the subject an effective amount of a compound of Formula (VI), Formula (VI') or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof.

In certain embodiments, provided herein is a method of treating acute myeloid leukemia in a subject in need of treatment comprising administering to the subject an effective amount of a compound of Formula (VII), Formula (VII') or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof.

In some embodiments, the compound of Formula (I) is a compound selected from formulae (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Ic-1), (Ic'-1), (Id), (Id'), (Ie) and (Ie'). In some embodiments, the compound of Formula (II) is a compound selected from formulae (IIa), (IIa'), (IIa-1), (IIa'-1), (IIb), (IIb'), (IIb-1), (IIb'-1), (IIb-2), (IIb'-2), (IIc), (IIc'), (IIc-1), (IIc'-1), (IId) and (IId'). In some embodiments, the compound is selected from Formula (III), Formula (III'), Formula (IV), Formula (IV'), Formula (V), Formula (V'), Formula (VI), Formula (VI'), Formula (VII) and Formula (VII').

In some embodiments, the methods described herein comprise administering to a subject in need of treatment an effective amount of a compound selected from Compound 1, Compound 2, Compound 3, Compound 3a, Compound 3b, Compound 4, Compound 4a, Compound 4b and Compound 5.

In certain embodiments, the compound is Compound 1. In certain embodiments, the compound is Compound 2. In certain embodiments, the compound is Compound 3a. In certain embodiments, the compound is Compound 4a. In certain embodiments, the compound is Compound 5.

In other embodiments, provided herein is the use of an effective amount of a compound of Formula (I), Formula (I'), Formula (II), Formula (II'), Formula (III), Formula

(III'), Formula (IV), Formula (IV'), Formula (V), Formula (V'), Formula (VI), Formula (VI'), Formula (VII) or Formula (VII'), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof, in the manufacture of a medicament for the treatment of a hematological cancer. In one aspect, the hematological cancer is Multiple myeloma, Hodgkin lymphoma, Non-Hodgkin lymphoma and Leukemia. In a particular aspect the hematological cancer is leukemia. In a more particular aspect, the leukemia is acute myeloid leukemia. All compound and Formula embodiments described above are contemplated for these uses.

In other embodiments, provided herein is the use of an effective amount of a compound of Formula (I), Formula (I'), Formula (II), Formula (II'), Formula (III), Formula (III'), Formula (IV), Formula (IV'), Formula (V), Formula (V'), Formula (VI), Formula (VI'), Formula (VII), Formula (VII'), Formula (X), Formula (X-1), Formula (XI), Formula (XII), Formula (XX), Formula (XXI), Formula (XXII), Formula (XXIII), Formula (XXIV), Formula (XXV), Formula (XIII), Formula (XIV), or Formula (XV).

or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable composition thereof, for the treatment of a hematological cancer. In one aspect, the hematological cancer is Multiple myeloma, Hodgkin lymphoma, Non-Hodgkin lymphoma and Leukemia. In a particular aspect the hematological cancer is leukemia. In a more particular aspect, the leukemia is acute myeloid leukemia.

All compound and Formulas described above are contemplated for these uses.

Bacterial Infections

Compounds of the invention, in particular, a compound represnetd by any one of structural formulas XV or XIV or a compound of Formulas XIII or XII, can be used to prevent or treat important mammalian and veterinary diseases such as diarrhea, urinary tract infections, infections of skin and skin structure including wounds, cellulitis, and abscesses, ear, nose and throat infections, mastitis and the like. In addition, methods for treating neoplasms using tetracycline compounds of the invention are also included (van der Bozert et al., Cancer Res., 48: 6686-6690 (1988)).

Infections that can be treated using compounds of the invention or a pharmaceutically acceptable salt thereof include, but are not limited to, skin infections, GI infections, urinary tract infections, genito-urinary infections, respiratory tract infections, sinuses infections,

middle ear infections, systemic infections, intra-abdominal infections, pyelonephritis, pneumonia, bacterial vaginosis, streptococcal sore throat, chronic bacterial prostatitis, gynecological and pelvic infections, sexually transmitted bacterial diseases, ocular and otic infections, cholera, influenza, bronchitis, acne, psoriasis, rosacea, impetigo, malaria, sexually transmitted disease including syphilis and gonorrhea, Legionnaires' disease, Lyme disease, Rocky Mountain spotted fever, Q fever, typhus, bubonic plague, gas gangrene, hospital acquired infections, leptospirosis, whooping cough, anthrax and infections caused by the agents responsible for lymphogranuloma venereum, inclusion conjunctivitis, or psittacosis. Infections can be bacterial, fungal, parasitic and viral infections (including those which are resistant to other tetracycline compounds).

In one embodiment, the infection is a respiratory infection. In a particular aspect, the respiratory infection is Community-Acquired Bacterial Pneumonia (CABP). In a more particular embodiment, the respiratory infection, for example, CABP is caused by a bacterium selected from *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H. influenza*, *M. catarrhalis* and *Legionella pneumophila.*

In another embodiment, the infection is a skin infection. In a particular aspect the skin infection is an acute bacterial skin and skin structure infection (ABSSSI). In a more particular embodiment, the skin infection, for example ABSSSI is caused by a bacterium selected from *S. aureus*, CoNS, *S. pyogenes*, *S. agalactiae*, *E. faecalis* and *E. faecium.*

In one embodiment, the infection can be caused by a bacterium (e.g. an anaerobic or aerobic bacterium).

In another embodiment, the infection is caused by a Gram-positive bacterium. In a specific aspect of this embodiment, the infection is caused by a Gram-positive bacterium selected from class Bacilli, including, but not limited to, *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp., *Bacillus* spp., *Listeria* spp.; phylum Actinobacteria, including, but not limited to, *Propionibacterium* spp., *Corynebacterium* spp., *Nocardia* spp., *Actinobacteria spp., and* class Clostridia, including, but not limited to, *Clostridium* spp.

In another embodiment, the infection is caused by a Gram-positive bacterium selected from *S. aureus*, CoNS, *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *E. faecalis* and *E. faecium.*

In another embodiment, the infection is caused by a Gram-negative bacterium. In one aspect of this embodiment, the infection is caused by a phylum Proteobacteria (*e.g.*, Betaproteobacteria and Gammaproteobacteria), including *Escherichia coli*, *Salmonella*,

Shigella, other *Enterobacteriaceae*, *Pseudomonas*, *Moraxella*, *Helicobacter*, *Stenotrophomonas*, *Bdellovibrio*, acetic acid bacteria, *Legionella* or alpha-proteobacteria such as *Wolbachia*. In another aspect, the infection is caused by a Gram-negative bacterium selected from cyanobacteria, spirochaetes, green sulfur or green non-sulfur bacteria. In a specific aspect of this embodiment, the infection is caused by a Gram-negative bacteria selected from *Enterobactericeae* (e.g., *E. coli, Klebsiella pneumoniae* including those containing extended-spectrum β-lactamases and/or carbapenemases), *Bacteroidetes* (e.g., *Bacteroides fragilis).*, *Vibrionaceae* (*Vibrio cholerae*), *Pasteurellaceae* (e.g., *Haemophilus influenzae*), *Pseudomonadaceae* (e.g., *Pseudomonas aeruginosa*), *Neisseriaceae* (e.g. *Neisseria meningitidis*), *Rickettsiae*, *Moraxellaceae* (e.g., *Moraxella catarrhalis*), any species of *Proteeae, Acinetobacter* spp., *Helicobacter* spp., and *Campylobacter* spp. In a particular embodiment, the infection is caused by Gram-negative bacterium selected from the group consisting of *Enterobactericeae* (e.g., *E. coli, Klebsiella pneumoniae*), *Pseudomonas*, and *Acinetobacter spp.* In another embodiment, the infection is caused by an organism selected from the group consisting of *K. pneumoniae, Salmonella, E. hirae, A. baumanii, M. catarrhalis, H. influenzae, P. aeruginosa, E. faecium, E. coli, S. aureus,* and *E. faecalis.*

In another embodiment, the infection is cause by a gram negative bacterium selected from *H. influenza, M. catarrhalis* and *Legionella pneumophila.*

In one embodiment, the infection is caused by an organism that grows intracellularly as part of its infection process.

In another embodiment, the infection is caused by an organism selected from the group consisting of order Rickettsiales; phylum Chlamydiae; order Chlamydiales; *Legionella* spp.; class Mollicutes, including, but not limited to, *Mycoplasma* spp. (e.g. *Mycoplasma pneumoniae*); *Mycobacterium* spp. (e.g. *Mycobacterium tuberculosis*); and phylum Spriochaetales (e.g. *Borrelia* spp. and *Treponema* spp.).

In another embodiment, the infection is caused by a Category A Biodefense organism as described at http://www.bt.cdc.gov/agent/agentlist-category.asp, the entire teachings of which are incorporated herein by reference. Examples of Category A organisms include, but are not limited to, *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Clostridium botulinum* (botulism) or *Francisella tularensis* (tularemia). In another embodiment the infection is a *Bacillus anthracis* infection. "*Bacillus anthracis* infection" includes any state,

diseases, or disorders caused or which result from exposure or alleged exposure to *Bacillus anthracis* or another member of the *Bacillus cereus* group of bacteria.

Additional infections that can be treated using compounds of the invention or a pharmaceutically acceptable salt thereof include, but are not limited to, anthrax, botulism, bubonic plague, and tularemia.

In another embodiment, the infection is caused by a Category B Biodefense organism as described at http://www.bt.cdc.gov/agent/agentlist-category.asp, the entire teachings of which are incorporated herein by reference. Examples of Category B organisms include, but are not limited to, *Brucella* spp, *Clostridium perfringens, Salmonella* spp., *Escherichia coli* O157:H7, *Shigella* spp., *Burkholderia mallei, Burkholderia pseudomallei, Chlamydia psittaci, Coxiella burnetii, Staphylococcal enterotoxin B, Rickettsia prowazekii, Vibrio cholerae*, and *Cryptosporidium parvum*.

Additional infections that can be treated using compounds of the invention or a pharmaceutically acceptable salt thereof include, but are not limited to, Brucellosis, *Clostridium perfringens*, food-borne illnesses, Glanders, Melioidosis, Psittacosis, Q fever, and water-borne illnesses.

In yet another embodiment, the infection can be caused by one or more than one organism described above. Examples of such infections include, but are not limited to, intra-abdominal infections (often a mixture of a gram-negative species like *E. coli* and an anaerobe like *B. fragilis*), diabetic foot (various combinations of *Streptococcus, Serratia, Staphylococcus* and *Enterococcus* spp., anaerobes (S.E. Dowd, et al., PloS one 2008;3:e3326, the entire teachings of which are incorporated herein by reference) and respiratory disease (especially in patients that have chronic infections like cystic fibrosis – e.g., *S. aureus* plus *P. aeruginosa* or *H. influenzae*, atypical pathogens), wounds and abscesses (various gram-negative and gram-positive bacteria, notably MSSA/MRSA, coagulase-negative staphylococci, enterococci, *Acinetobacter*, *P. aeruginosa, E. coli, B. fragilis*), and bloodstream infections (13% were polymicrobial (H. Wisplinghoff, et al., Clin. Infect. Dis. 2004;39:311-317, the entire teachings of which are incorporated herein by reference)).

In one embodiment, the infection is caused by an organism resistant to one or more antibiotics.

In another embodiment, the infection is caused by an organism resistant to tetracycline or any member of first and second generation of tetracycline antibiotics (e.g., doxycycline or minocycline).

In another embodiment, the infection is caused by an organism resistant to methicillin.

In another embodiment, the infection is caused by an organism resistant to vancomycin.

In another embodiment, the infection is caused by an organism resistant to a quinolone or fluoroquinolone.

In another embodiment, the infection is caused by an organism resistant to tigecycline or any other tetracycline derivative. In a particular embodiment, the infection is caused by an organism resistant to tigecycline.

In another embodiment, the infection is caused by an organism resistant to a β-lactam or cephalosporin antibiotic or an organism resistant to penems or carbapenems.

In another embodiment, the infection is caused by an organism resistant to an antimicrobial peptide or a biosimilar therapeutic treatment. Antimicrobial peptides (also called host defense peptides) are an evolutionarily conserved component of the innate immune response and are found among all classes of life. In this case, antimicrobial peptide refers to any naturally occurring molecule or any semi/synthetic molecule that are analogs of anionic peptides, linear cationic α-helical peptides, cationic peptides enriched for specific amino acids (i.e, rich in proline, arginine, phenylalanine, glycine, tryptophan), and anionic and cationic peptides that contain cystein and form disulfide bonds.

In another embodiment, the infection is caused by an organism resistant to macrolides, lincosamides, streptogramin antibiotics, oxazolidinones, and pleuromutilins.

In another embodiment, the infection is caused by an organism resistant to PTK0796 (7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline).

In another embodiment, the infection is caused by a multidrug-resistant pathogen (having intermediate or full resistance to any two or more antibiotics).

Cancer Combination Therapies

In some embodiments, a compound described herein is administered together with an additional cancer treatment. Exemplary cancer treatments include, for example, chemotherapy, targeted therapies such as antibody therapies, kinase inhibitors,

immunotherapy, and hormonal therapy, and anti-angiogenic therapies. Examples of each of these treatments are provided below.

As used herein, the term "combination," "combined," and related terms refer to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention can be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

The amount of both a compound of the invention and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that can be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of a compound of the invention can be administered.

Chemotherapy

In some embodiments, a compound described herein is administered with a chemotherapy. Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. "Chemotherapy" usually refers to cytotoxic drugs which affect rapidly dividing cells in general, in contrast with targeted therapy. Chemotherapy drugs interfere with cell division in various possible ways, e.g., with the duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and are not specific for cancer cells, although some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can.

Examples of chemotherapeutic agents used in cancer therapy include, for example, antimetabolites (e.g., folic acid, purine, and pyrimidine derivatives) and alkylating agents (e.g., nitrogen mustards, nitrosoureas, platinum, alkyl sulfonates, hydrazines, triazenes, aziridines, spindle poison, cytotoxic agents, topoisomerase inhibitors and others). Exemplary agents include Aclarubicin, Actinomycin, Alitretinon, Altretamine, Aminopterin, Aminolevulinic acid, Amrubicin, Amsacrine, Anagrelide, Arsenic trioxide, Asparaginase, Atrasentan, Belotecan, Bexarotene, Bendamustine, Bleomycin, Bortezomib, Busulfan,

Camptothecin, Capecitabine, Carboplatin, Carboquone, Carmofur, Carmustine, Celecoxib, Chlorambucil, Chlormethine, Cisplatin, Cladribine, Clofarabine, Crisantaspase, Cyclophosphamide, Cytarabine, Dacarbazine, Dactinomycin, Daunorubicin, Decitabine, Demecolcine, Docetaxel, Doxorubicin, Efaproxiral, Elesclomol, Elsamitrucin, Enocitabine, Epirubicin, Estramustine, Etoglucid, Etoposide, Floxuridine, Fludarabine, Fluorouracil (5FU), Fotemustine, Gemcitabine, Gliadel implants, Hydroxycarbamide, Hydroxyurea, Idarubicin, Ifosfamide, Irinotecan, Irofulven, Ixabepilone, Larotaxel, Leucovorin, Liposomal doxorubicin, Liposomal daunorubicin, Lonidamine, Lomustine, Lucanthone, Mannosulfan, Masoprocol, Melphalan, Mercaptopurine, Mesna, Methotrexate, Methyl aminolevulinate, Mitobronitol, Mitoguazone, Mitotane, Mitomycin, Mitoxantrone, Nedaplatin, Nimustine, Oblimersen, Omacetaxine, Ortataxel, Oxaliplatin, Paclitaxel, Pegaspargase, Pemetrexed, Pentostatin, Pirarubicin, Pixantrone, Plicamycin, Porfimer sodium, Prednimustine, Procarbazine, Raltitrexed, Ranimustine, Rubitecan, Sapacitabine, Semustine, Sitimagene ceradenovec, Strataplatin, Streptozocin, Talaporfin, Tegafur-uracil, Temoporfin, Temozolomide, Teniposide, Tesetaxel, Testolactone, Tetranitrate, Thiotepa, Tiazofurine, Tioguanine, Tipifarnib, Topotecan, Trabectedin, Triaziquone, Triethylenemelamine, Triplatin, Tretinoin, Treosulfan, Trofosfamide, Uramustine, Valrubicin, Verteporfin, Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine, Vorinostat, Zorubicin, and other cytostatic or cytotoxic agents described herein.

Because some drugs work better together than alone, two or more drugs are often given at the same time. Often, two or more chemotherapy agents are used as combination chemotherapy. In some embodiments, the chemotherapy agents (including combination chemotherapy) can be used in combination with a compound described herein.

In a specific embodiment, the two additional therapeutic agents used in combination with the compounds of the invention and include, cytarabine (ara-C) and an anthracycline drug such as daunorubicin (daunomycin) or idarubicin. In certain instances, a third additional agent, cladribine, is used.

Targeted therapy

Targeted therapy constitutes the use of agents specific for the deregulated proteins of cancer cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within a cancer cell. Prominent examples are the tyrosine kinase inhibitors such as axitinib, bosutinib, cediranib,

desatinib, erolotinib, imatinib, gefitinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sorafenib, sunitinib, and vandetanib, and also cyclin-dependent kinase inhibitors such as alvocidib and seliciclib. Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. Examples include the anti-HER2/neu antibody trastuzumab (Herceptin®) typically used in breast cancer, and the anti-CD20 antibody rituximab and tositumomab typically used in a variety of B-cell malignancies. Other exemplary antibodies include cetuximab, panitumumab, trastuzumab, alemtuzumab, bevacizumab, edrecolomab, and gemtuzumab. Exemplary fusion proteins include aflibercept and denileukin diftitox. In some embodiments, targeted therapy can be used in combination with a compound described herein, *e.g.*, Gleevec (Vignari and Wang 2001).

Targeted therapy can also involve small peptides as "homing devices" which can bind to cell surface receptors or affected extracellular matrix surrounding a tumor. Radionuclides which are attached to these peptides (*e.g.*, RGDs) eventually kill the cancer cell if the nuclide decays in the vicinity of the cell. An example of such therapy includes BEXXAR®.

Phamaceutical Formulations

The compositions of the invention include ocular, oral, nasal, transdermal, topical with or without occlusion, intravenous (both bolus and infusion), inhalable, and injection (intraperitoneally, subcutaneously, intramuscularly, intratumorally, or parenterally) formulations. The composition may be in a dosage unit such as a tablet, pill, capsule, powder, granule, liposome, ion exchange resin, sterile ocular solution, or ocular delivery device (such as a contact lens and the like facilitating immediate release, timed release, or sustained release), parenteral solution or suspension, metered aerosol or liquid spray, drop, ampoule, auto-injector device, or suppository; for administration ocularly, orally, intranasally, sublingually, parenterally, or rectally, or by inhalation or insufflation.

Compositions of the invention suitable for oral administration include solid forms such as pills, tablets, caplets, capsules (each including immediate release, timed release, and sustained release formulations), granules and powders; and, liquid forms such as solutions, syrups, elixirs, emulsions, and suspensions. Forms useful for ocular administration include sterile solutions or ocular delivery devices. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

The compositions of the invention may be administered in a form suitable for once-weekly or once-monthly administration. For example, an insoluble salt of the active compound may be adapted to provide a depot preparation for intramuscular injection (e.g., a decanoate salt) or to provide a solution for ophthalmic administration.

The dosage form containing the composition of the invention contains an effective amount of the active ingredient necessary to provide a therapeutic effect. The composition may contain from about 5,000 mg to about 0.5 mg (preferably, from about 1,000 mg to about 0.5 mg) of a compound of the invention or salt form thereof and may be constituted into any form suitable for the selected mode of administration. The composition may be administered about 1 to about 5 times per day. Daily administration or post-periodic dosing may be employed.

For oral administration, the composition is preferably in the form of a tablet or capsule containing, e.g., about 500 to about 0.5 milligrams of the active compound. Dosages will vary depending on factors associated with the particular patient being treated (e.g., age, weight, diet, and time of administration), the severity of the condition being treated, the compound being employed, the mode of administration, and the strength of the preparation.

The oral composition is preferably formulated as a homogeneous composition, wherein the active ingredient is dispersed evenly throughout the mixture, which may be readily subdivided into dosage units containing equal amounts of a compound of the invention. Preferably, the compositions are prepared by mixing a compound of the invention (or pharmaceutically acceptable salt thereof) with one or more optionally present pharmaceutical carriers (such as a starch, sugar, diluent, granulating agent, lubricant, glidant, binding agent, and disintegrating agent), one or more optionally present inert pharmaceutical excipients (such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and syrup), one or more optionally present conventional tableting ingredients (such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, and any of a variety of gums), and an optional diluent (such as water).

Binder agents include starch, gelatin, natural sugars (e.g., glucose and beta-lactose), corn sweeteners and natural and synthetic gums (e.g., acacia and tragacanth). Disintegrating agents include starch, methyl cellulose, agar, and bentonite.

Tablets and capsules represent an advantageous oral dosage unit form. Tablets may be sugarcoated or filmcoated using standard techniques. Tablets may also be coated or

otherwise compounded to provide a prolonged, control-release therapeutic effect. The dosage form may comprise an inner dosage and an outer dosage component, wherein the outer component is in the form of an envelope over the inner component. The two components may further be separated by a layer which resists disintegration in the stomach (such as an enteric layer) and permits the inner component to pass intact into the duodenum or a layer which delays or sustains release. A variety of enteric and non-enteric layer or coating materials (such as polymeric acids, shellacs, acetyl alcohol, and cellulose acetate or combinations thereof) may be used.

Compounds of the invention may also be administered via a slow release composition; wherein the composition includes a compound of the invention and a biodegradable slow release carrier (e.g., a polymeric carrier) or a pharmaceutically acceptable non-biodegradable slow release carrier (e.g., an ion exchange carrier).

Biodegradable and non-biodegradable slow release carriers are well known in the art. Biodegradable carriers are used to form particles or matrices which retain an active agent(s) and which slowly degrade/dissolve in a suitable environment (e.g., aqueous, acidic, basic and the like) to release the agent. Such particles degrade/dissolve in body fluids to release the active compound(s) therein. The particles are preferably nanoparticles or nanoemulsions (e.g., in the range of about 1 to about 500 nm in diameter, preferably about 50 to about 200 nm in diameter, and most preferably about 100 nm in diameter). In a process for preparing a slow release composition, a slow release carrier and a compound of the invention are first dissolved or dispersed in an organic solvent. The resulting mixture is added into an aqueous solution containing an optional surface-active agent(s) to produce an emulsion. The organic solvent is then evaporated from the emulsion to provide a colloidal suspension of particles containing the slow release carrier and the compound of the invention.

The compound disclosed herein may be incorporated for administration orally or by injection in a liquid form such as aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil and the like, or in elixirs or similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone, and gelatin. The liquid forms in suitably flavored suspending or dispersing agents may also include synthetic and natural gums. For parenteral

administration, sterile suspensions and solutions are desired. Isotonic preparations, which generally contain suitable preservatives, are employed when intravenous administration is desired.

The compounds may be administered parenterally *via* injection. A parenteral formulation may consist of the active ingredient dissolved in or mixed with an appropriate inert liquid carrier. Acceptable liquid carriers usually comprise aqueous solvents and other optional ingredients for aiding solubility or preservation. Such aqueous solvents include sterile water, Ringer's solution, or an isotonic aqueous saline solution. Other optional ingredients include vegetable oils (such as peanut oil, cottonseed oil, and sesame oil), and organic solvents (such as solketal, glycerol, and formyl). A sterile, non-volatile oil may be employed as a solvent or suspending agent. The parenteral formulation is prepared by dissolving or suspending the active ingredient in the liquid carrier whereby the final dosage unit contains from about 0.005 to about 10% by weight of the active ingredient. Other additives include preservatives, isotonizers, solubilizers, stabilizers, and pain-soothing agents. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

Compounds of the invention may be administered intranasally using a suitable intranasal vehicle.

In another embodiment, the compounds of this invention may be administered directly to the lungs by inhalation.

Compounds of the invention may also be administered topically or enhanced by using a suitable topical transdermal vehicle or a transdermal patch.

For ocular administration, the composition is preferably in the form of an ophthalmic composition. The ophthalmic compositions are preferably formulated as eye-drop formulations and filled in appropriate containers to facilitate administration to the eye, for example a dropper fitted with a suitable pipette. Preferably, the compositions are sterile and aqueous based, using purified water. In addition to the compound of the invention, an ophthalmic composition may contain one or more of: a) a surfactant such as a polyoxyethylene fatty acid ester; b) a thickening agents such as cellulose, cellulose derivatives, carboxyvinyl polymers, polyvinyl polymers, and polyvinylpyrrolidones, typically at a concentration n the range of about 0.05 to about 5.0% (wt/vol); c) (as an alternative to or in addition to storing the composition in a container containing nitrogen and optionally

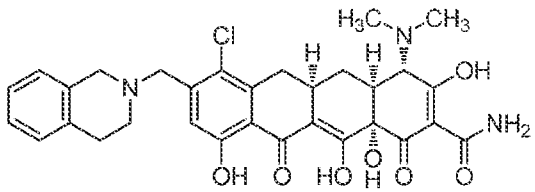
including a free oxygen absorber such as Fe), an anti-oxidant such as butylated hydroxyanisol, ascorbic acid, sodium thiosulfate, or butylated hydroxytoluene at a concentration of about 0.00005 to about 0.1% (wt/vol); d) ethanol at a concentration of about 0.01 to 0.5% (wt/vol); and e) other excipients such as an isotonic agent, buffer, preservative, and/or pH-controlling agent. The pH of the ophthalmic composition is desirably within the range of 4 to 8.

While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

EXEMPLIFICATION

Additional methods of synthesizing the compounds described herein and their synthetic precursors are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene, TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser, L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette, L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

Example 1: Synthesis of Compounds 1 through 5

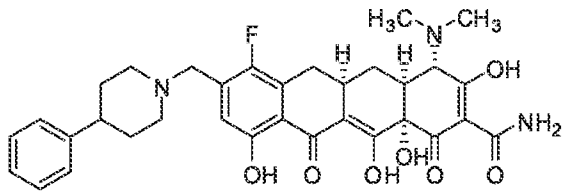


Compound 1:

Compound 1 was prepared according to the synthesis described in WO2010/129057 at pp. 69-70 (S15-13-190), incorporated herein by reference in its entirety.

^{1}H NMR (400 MHz, CD_3OD) δ 7.34-7.24 (comp, 4 H), 7.21-7.17 (m, 1 H), 4.69 (s, 2 H), 4.54 (s, 2 H), 4.11 (s, 1 H), 3.90-3.53 (m, 2 H), 3.47-3.39 (m, 2 H), 3.04 (s, 3 H), 2.96 (s,

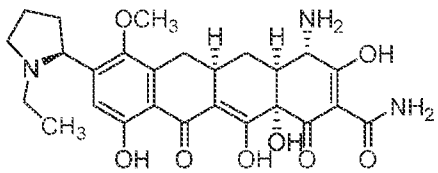
3 H), 3.28-2.94 (comp, 3 H), 2.50-2.40 (m, 1 H), 2.29-2.22 (m, 1 H), 1.72-1.61 (m, 1 H); MS (ESI) *m/z* 594.15 (M+H).



Compound 2:

Compound 2 was prepared according to the synthesis described in WO2010/129057 at pp. 248-249 (S1-14-60).

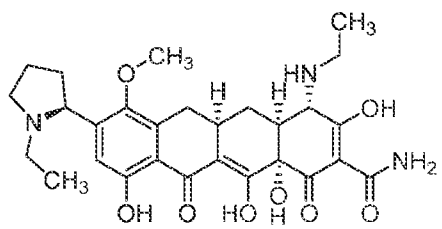
^{1}H NMR (400 MHz, CD_3OD) δ 7.24-7.11 (m, 5 H), 7.07 (d, J = 4.8 Hz, 1 H), 4.35 (s, 2 H), 4.04 (s, 1 H), 3.60-3.57 (m, 3 H), 3.16-2.80 (m, 11 H), 2.31-2.17 (m, 2 H), 2.06-1.96 (s, 4 H), 1.63-1.52 (m, 1 H); MS (ESI) *m/z* 606.2 (M+H).



Compound 3a

Compound 3a was prepared according to the synthesis described in WO2014/036502 at p. 142 (S10-4-1), incorporated herein by reference in its entirety.

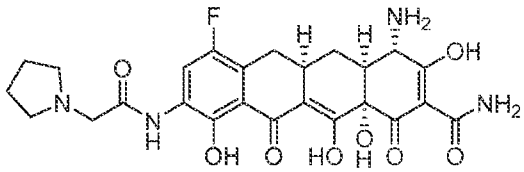
^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.09 (s, 1 H), 3.90 (s, 1 H), 3.86-3.80 (m, 1 H), 3.68 (s, 3 H), 3.37-3.30 (m, 1 H), 3.28-3.07 (m, 3 H), 3.00-2.91 (m, 1 H), 2.67-2.54 (m, 2 H), 2.41 (t, J = 14.2 Hz, 1 H), 2.34-2.21 (m, 5 H), 1.66-1.57 (m, 1 H), 1.25 (t, J = 7.3 Hz, 3 H); MS (ESI) *m/z* 514.28 (M+H).



Compound 4a

Compound 4a was prepared according to the synthesis described in WO2014/036502, at pp 142-143 (S10-4-2).

(single diastereomer): ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.10 (s, 1 H), 3.88 (s, 1 H), 3.85-3.80 (m, 1 H), 3.68 (s, 3 H), 3.46-3.31 (m, 3 H), 3.27-3.07 (m, 3 H), 3.01-2.92 (m, 1 H), 2.86-2.83 (m, 1 H), 2.62-2.55 (m, 1 H), 2.39 (t, J = 14.2 Hz, 1 H), 2.34-2.22 (m, 5 H), 1.64-1.55 (m, 1 H), 1.36 (t, J = 7.3 Hz, 3 H), 1.25 (t, J = 7.3 Hz, 3 H); MS (ESI) *m/z* 542.35 (M+H).



Compound 5

Compound 5 was prepared according to the synthesis described in WO2014/036502 at p. 140 (S9-5-4).

^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1 H), 4.33 (s, 2 H), 3.89 (s, 1 H), 3.82-3.76 (m, 2 H), 3.23-3.12 (m, 3 H), 3.02-2.94 (m, 1 H), 2.67-2.64 (m, 1 H), 2.32-2.14 (m, 4 H), 2.12-2.02 (m, 2 H), 1.63-1.54 (m, 1 H); MS (ESI) *m/z* 531.31 (M+H).

Compounds 1, 2, 3a, 4a and 5 are also referred to herein as Compounds K11, K31, K4, K5 and K43.

Example 2: Anti-cancer Activity of Compound 1-5

Compounds 1, 2, 3a, 4a and 5 and the Compounds of FIGs. 15A-15M, 16A-16F and 17A-17D were assayed for tumor cell proliferation using AML cancer cell lines THP-1 and MV4-11. The inhibition of cytrochrome-oxidase 1 (COX-1) expression in MV4-11 cells was also measured for Compounds 1, 2, 3a, 4a and 5.

A. THP-1 Anti-proliferation Assay

The inhibition of eukaryotic cell culture growth was established using THP-1 cells (ATCC Cat. # TIB-202), a human acute monocytic leukemia cell line. These are suspension cells. This cell-based assay for eukaryotic culture growth inhibition was performed in 384-well plate format to determine the *in vitro* cytotoxicity of the test compounds.

Compounds were solubilized in water. Compounds were diluted 1:2 in assay media and 1:2 serial dilutions were performed in 50:50 media:water mix. The high dose was 40 µM, 10% water final. 5 µL of compound at 5x the final concentration was dispensed to the 384 assay plate. 20 µL of THP-1 cells were added.

Compounds were plated in dose response format (10% water final concentration), followed by the addition of cells. Cells were grown and incubated with compounds in RPMI-1640 medium/pen/strep/L-glutamine/10% FBS/2-mercaptoethanol for 72 hr at 37 °C with 5% CO_2. At the end of the incubation time, cells were assayed for viability using Cell Titer GLO (Promega). Compounds that were considered cytotoxic resulted in a decreased luminescent signal.

B. MV4-11 Anti-proliferation Assay

MV4-11 cell line (MV-4-11, CRL-9591™) was obtained from American Type Culture Collection (ATCC). Cells were grown in a T-75 flask in RPMI Medium (GIBCO, Catalog No. 11875-093) containing 10% fetal bovine serum (ATCC, Catalog No. 30-2020) and penicillin-streptomycin (ATCC, Catalog No. 30-2300) at 37 °C in a humidified, 5% CO_2 incubator.

50 µL of cells (10,000 cells/well) were plated in a 96-well plate and incubated overnight at 37 °C in a humidified, 5% CO_2 incubator. The next day, 50 µL of medium containing 3-fold serially diluted compounds in duplicate was added to the wells such that the starting concentration of the compound in the first pair of the wells was 10 µM. After 72 hour incubation with the compound, cell viability was measured in a luminometer after the addition of 100 µL/well CellTiterGlo reagent (Promega) as recommended by the manufacturer. The IC_{50} values for the compounds were calculated using SoftMax software.

C. Anti-proliferative Activity

As the data in Table 1A shows, compounds 1, 2, 3a, 4a and 5 demonstrate potent anti-proliferative activity with IC_{50} values of 0.10 to 1.05 µM against two AML cancer cell lines, THP-1 and MV4-11.

Table 1A

Compound ID	IC50 (μM)	
	THP-1	MV4-11
1	0.57	0.22
2	1.05	0.41
3a	0.75	0.10
4a	0.90	0.13
5	0.64	0.17
Tigecycline	29.13	4.64

Further results of the testing of certain compounds described herein in the THP-1 and MV4-11 cell lines are reported in FIGs. 15A-15M, 16A-16F and 17A-17D.

D-1. Anti-proliferative Activity of Compounds in Additional Cell Lines

Compounds 1, 2, 3a, 4a and 5 as well as certain Compound included in FIGs. 15A-15M, 16A-16F and 17A-17D were tested in the following cell lines: MOLT4 and K562. Compounds 1, 2, 3a, 4a and 5 were also tested in the cell line HL60.

Cell Lines and Culture:

The MOLT4 cell line (CRL-1582™) aand K562 cell line (CCL-243™) were obtained from American Type Culture Collection (ATCC). They were grown in a T-75 flask in RPMI Medium (GIBCO, Catalog No. 11875-093) containing 10% fetal bovine serum (ATCC, Catalog No. 30-2020) and penicillin-streptomycin (ATCC, Catalog No. 30-2300) at 37°C in a humidified, 5% CO_2 incubator. The HL60 cell line (CCL-240™) was obtained from American Type Culture Collection (ATCC). They were grown in a T-75 flask in DMEM Medium (GIBCO, Catalog No. 11965-092) containing 20% fetal bovine serum (ATCC, Catalog No. 30-2020) and penicillin-streptomycin (ATCC, Catalog No. 30-2300) at 37°C in a humidified, 5% CO_2 incubator.

Proliferation Assay:

50 μL of cells (8,500 cells/well) were plated in a 96-well plate and incubated overnight at 37 °C in a humidified, 5% CO_2 incubator. The next day, 50 μL of medium containing 3-fold serially diluted compounds in duplicate was added to the

wells such that the starting concentration of the compound in the first pair of the wells was 10 μM. After 72 hour incubation with the compound, cell viability was measured in a luminometer after the addition of 100 μL/well CellTiterGlo reagent (Promega) as recommended by the manufacturer. The IC_{50} values for the compounds were calculated using SoftMax software.

TABLE 1B

Compound ID	IC50 (μM)		
	MOLT4	K562	HL60
1	0.19	0.43	0.36
2	0.31	0.48	Inactive
3a	0.12	0.11	0.37
4a	0.13	0.13	0.41
5	0.13	0.16	0.51
Tigecycline	5.1	7.2	15.4

Results of the testing of additional compounds described herein in the MOLT4 and K562 cell lines are reported in Tables 15A-15M, 16A-16F and 17A-17D.

D-2. Anti-proliferative Activity of Compounds in KG-1, KU812 and MEG-01 Cell Lines

Compounds were tested in the following cell lines: KG-1 acute myelogenous leukemis ATCC CCL-246, KU812 Human chronic myelogenous leukemia (CML) ATCC CRL-2099, and MEG-01 Human chronic myelogenous leukemis (CML) ATCC CRL-2021 according to the following conditions and procedures:

Growth medium: RPMI Medium 1640 Gibco #11875-093

Supplements: Fetal Bovine Serum (FBS) Gibco #10437-028

Complete cell culture medium was prepared by adding 50 mL FBS (final concentration 10%) to each 500 mL bottle of RPMI Medium 1640 (RPMI). Medium was allowed to equilibrate to 37C in a water bath before use.

One millimeter volumes of 2X the initial concentration (20 μM or 100 μM) in complete cell culture medium were prepared for each compound to be tested. 50 μl was added, in triplicate, to lane 2 wells of a 96-well plate and to lane 3 wells containing 50 μl complete cell

culture medium as diluent. Two-fold serial dilutions of compounds were continued in lanes 4-10 with 50 µl final volumes. 50 µl medium without compound was added to lane 11, and 100 µl medium was added to lanes 1, 12 and rows A,H in order to prevent or minimize a thermal gradient from forming in the experimental wells.

Cells grown to 1-4 x 10^5/mL were centrifuged, re-suspended in fresh medium at 2 x 10^5/mL and 50 µl (10,000 cells) was added to each well containing compound (lanes 2-10) and to 6 wells (lane 11) containing medium only. Addition of cells resulted in dilution of compound to the intended 1 X concentrations.

Plates were incubated at 37C in 5% CO_2 for 72 hours.

After 72 hours incubation, plates were allowed to equilibrate to room temperature for 30 minutes and assayed for cell proliferation using the Promega CellTiter-Glo Kit (Promega #G7572) which indirectly measures ATP. 100 µl of CellTiter-Glo substrate reconstituted with CellTiter-Glo buffer was added to each well containing cells as well as 6 wells containing medium only. Plates were incubated at room temperature, protected from light, for 10 minutes to allow luminescence signal to stabilize. Luminescence was read and recorded in a LUMIstar OPTIMA luminescence microplate reader using MARS Data Analysis Software (BMG LABTECH).

The luminescence values for compound-containing wells (in triplicate) were plotted as the mean % no-compound control vs concentration using Prism GraphPad. IC_{50}s, the concentration at which a compound reduced growth (as measured by ATP) by 50%, were obtained from the graphs.

% no-compound control= $\frac{\text{Fluorescence value (cells plus compound) X 100}}{\text{Fluorescence values (cells, no compound), averaged}}$

Plate format

media	media	media	media	media	media	media	media	media	media	media	media
media	TP-compound (10 µM)	5	2.5	1.25	0.63	0.31	0.16	0.08	0.04	cells	media
media	TP-compound (10 µM)	5	2.5	1.25	0.63	0.31	0.16	0.08	0.04	cells	media
media	TP-compound (10 µM)	5	2.5	1.25	0.63	0.31	0.16	0.08	0.04	cells	media
media	Tigecycline (50 µM)	25	12.5	6.25	3.12	1.56	0.78	0.39	0.20	cells	media
media	Tigecycline (50 µM)	25	12.5	6.25	3.12	1.56	0.78	0.39	0.20	cells	media
media	Tigecycline (50 µM)	25	12.5	6.25	3.12	1.56	0.78	0.39	0.20	cells	media
media	media	media	media	media	media	media	media	media	media	media	media

TP-Compound in the table above, refers to compounds described herein that were being tested.

The results of testing in the KG-1, KU812 and MEG-01 cell lines are reported in Tables 15A-15M, 16A-16F and 17A-17D.

E. Antiproliferative Activity Against 15 AML ex-vivo bone marrow sample

Antiproliferative activity of Compound 3a and cytarabine was measured against 15 AML ex-vivo bone marrow samples (including two cytarabine-resistant samples). The assay used was Vivia's Native Environment cell depletion assay. An outline of ths study is below:

-Five different concentrations of each drug was used as a monotherapy

-The incubation time point for measurement was 48 hours post drug exposure

The results are shown graphically in FIG. 6. Compound 3a provided potent *ex vivo* activity against the tumor cells from frozen bone marrow of the AML patients. The acitivty of Compound C3a was better that cytarabine with stronger potency and higher efficacy. According to the acitivty profile observed, Compound 3a had a mean EC50 value of 170 nM.

F. MV4-11 Xenografts

The in vivo anti-tumor efficacy of Compounds 3a, 4a and 5 in the subcutaneous MV4-11 leukemia model in CB17 SCID mice was tested.

Cell Culture:

The MV4-11cells (ATCC-CRL-9591) were maintained in vitro as a suspension culture at a density of 0.2-1.5 x 106 cells/ml in RPMI1640 medium supplemented with 10% heat inactivated fetal bovine serum, 100 U/ml penicillin and 100 µg/ml streptomycin at 37°C in an atmosphere of 5% CO2 in air. The tumor cells were routinely subcultured twice weekly. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

Animals:

CB17 SCID, female, 6-8 weeks, weighing approximately 18-22g.

Tumor Inoculation:

Each mouse was inoculated subcutaneously at the right flank with MV4-11 tumor cells (10×10^6) in 0.2 ml of PBS (with Matrigel 1:1) for tumor development. The animals were randomized and treatment was started when the average tumor volume reached approximately

150~200 mm^3 for the efficacy study. The test article administration and the animal numbers in each group are shown below.

TABLE 1 C: Groups and Treatments

Group	N[a]	Treatment	Dose (mg/kg)	Dosing Route	Schedule
1	10	Vehicle Control	--	I.P.	QD[b], 4 days on, 6 days off, day 0-14
2	10	Cytarabine	100	I.P.	QD, 5 days on, 2 days off, day 0-14
3	10	Tigecycline	50	I.P.	BID[c], day 0-14
4	10	Compound 3a – dose 1	12.5	I.P.	QD, 4 days on, 6 days off, day 0-14
5	10	Compound 3a -dose 2	12.5	I.P.	QD, 2 days on, 6 days off, day 0-14
6	10	Compound 4a - dose 1	12.5	I.P.	QD, 4 days on, 6 days off, day 0-14
7	10	Compound 4a – dose 2	12.5	I.P.	QD, 2 days on, 6 days off, day 0-14
8	10	Compound 5 - dose 1	12.5	I.P.	QD, 4 days on, 6 days off, day 0-14
9	10	Compound 5 - dose 2	12.5	I.P.	QD, 2 days on, 6 days off, day 0-14

Note:

a. N: number of animals per group;

b. QD: once per day;

c. BID: twice per day. BID dosing is 8 hours apart.

Endpoints:

The major endpoint monitored was tumor growth delay or cure. Tumor sizes were measured twice weekly in two dimensions using a caliper, and the volume expressed in mm^3 using the formula: $V = 0.5\ a \times b^2$ where a and b are the long and short diameters of the tumor, respectively. The tumor sizes were then used for the calculations of both T-C and T/C values. T-C is calculated with T as the median time (in days) required for the treatment group tumors to reach a predetermined size (e.g., 1,000 mm^3), and C is the median time (in days) for the control group tumors to reach the same size. The T/C value (in percent) is an indication of antitumor effectiveness, T and C are the mean volume of the treated and control groups, respectively, on a given day.

TGI was calculated for each group using the formula: TGI (%) = [1-(Ti-T0)/ (Vi-V0)] ×100; Ti is the average tumor volume of a treatment group on a given day, T0 is the average tumor volume of the treatment group on the first day of treatment, Vi is the average tumor

volume of the vehicle control group on the same day with Ti, and V0 is the average tumor volume of the vehicle group on the first day of treatment.

The results of Tumor Volume versus Time and Body Weight versus Days after Start of Treatment are shown in FIGs. 7A-7F. As can be see in FIG. 7, all animals treated with Compound 3a achieved ≥70% tumor shrinkage. Cytarabine (standard of care) and tigecycline dosed at maximum tolerated does (MTD) only demonstrated modest effect-no tumor response in either group.

G. Effect of Compound 3a on Rat Heart Mitochondrial Protein Synthesis

The effect of Compound 3a on mitochondrial protein synthesis was determined using an intact isolated rat heart mitochondrial protein synthesis assay previously described [See, 1, 2 below]. Intact, highly coupled mitochondria isolated from normal rat hearts were incubated in an incubation medium containing [S^{35}]-methionine. The compounds were diluted to generate a final dose-response curve from 0.15 to 40 μM. The rate of incorporation of [S^{35}]-methionine into protein was measured at 20, 40, and 60 minutes of incubation for each sample using a filter paper disc assay and expressed as pmol methionine incorporated per mg mitochondrial protein as described [1, 2, 3 below]. The time course data for control and all drug concentrations were nearly linear. The slope of each time-course data plot is calculated as the least squares best fit line through zero and the three time points for each sample. The rate of protein synthesis varies modestly with each mitochondrial preparation (mean and SEM = 20.3 +/- 2.4 pm / mg protein). To normalize for this variability, the rates were expressed as a percent of the rate of the control line for each preparation of mitochondria. Each experiment was repeated three times.

Dose-response curves were obtained by expressing the percent of control obtained for each concentration of Compound 3a against the concentration of Compound 3a. The dose-response curves for all three experiments were plotted together and fit using the equation y = ab/(b+x) (Sigma Plot 10.0) and the half-maximal inhibitory concentration (IC_{50}) is reported for each drug.

Summary of Results:

FIG. 8 shows the dose-response results for Compound 3a. The dose-response curve IC_{50} was 0.7 μM. As such the data represents both the ability of Compound 3a to cross the mitochondrial membranes and to inhibit mitochondrial translation.

1. McKee, E.E., Ferguson, M., Bentlye, At.T. and Marks, T.A. (2006) Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones. Antimicrob Agents Cehmother 50, 2042-2049.
2. McKee, E.E., Grier, B.L., Thompson, G.S. and McCourt, J.D. (1990) Isolaton and incubation conditions to study heart mitochrondrial protein synthesis. Am J Physiol 258, E492-502.
3. Flanagan, S., McKee, E.e., Das, D., Tulkens, P.M., Hosako, H., Fiedler-Kelly, J., Passarell, J., Rodovsky, A., and Prokocimer, P. Nonclinical and pharmacokinetic assessments to evaluate the potential of tedizolid and linezolid to affect mitochondrial function (2014) Antimicrobial Agents and Chemo 59: 178-185, doi 10.1128/AAC03684, PMID 25331703.

H. COX1 and COX4 Protein Levels in MV4-11 Cells

Materials:

1) MV4-11 cell line: MV411 cell line (MV-4-11, CRL-9591™) was obtained from American Type Culture Collection (ATCC).
2) Antibodies: The following antibodies were purchased as shown below in Table 2, and dilutions were used in the western blot analyses as recommended by the manufacturer.

Table 2

Antibody	Company	Catalogue Number
Anti- human COX1 in rabbit	BosterBio	PA1317
Anti- human COX4 in mouse	Santa Cruz Laboratories	SC376831
HRP-conjugated anti-mouse	Bio-Rad	170-5047
HRP-conjugated anti-rabbit	Bio-Rad	170-5046
HRP-anti human β-actin	Cell Signal Technologies	12262S

Methods:

1) Cell Lines and culture conditions: MV4-11 cells were grown in a T-75 flask in RPMI Medium (GIBCO, Catalog No. 11875-093) containing 10% fetal

bovine serum (ATCC, Catalog No. 30-2020) and penicillin-streptomycin (ATCC, Catalog No. 30-2300) at 37 °C in a humidified, 5% CO_2 incubator.

2) Compound treatment: Two mL of cells (500,000 cells) were plated in each well of a 6-well plate and incubated at 37 °C in a humidified, 5% CO_2 incubator. The next day, 2.5 µL, 6.25 µL, 12.5 µL, 25 µL and 50 µL of 400 µM compound was added to each well. These additions resulted in 0.5 µM, 1.25 µM, 2.5 µM, 5 µM, and 10 µM final concentrations of the compounds. One well did not receive any compound, which serves as untreated control. After 18 hours of incubation with the compounds, cells were collected by centrifugation at 2000 g for one minute and washed with one mL of PBS. The cell pellet was lysed in 50 µL of lysis buffer, and stored at -20 °C until further use.

3) Protein Estimation: Cell lysates were spun at 12,000 rpm for one minute, and 3 µL of the supernatant was used to check the protein concentration using the Coomassie blue reagent following the recommended protocol. For electrophoresis, equal amount of protein extract was used for each compound. The amount of protein extract loaded varied from 7.5 to 15 µg per sample for different compounds.

4) Western Blotting:

Sample Preparation

x µL of cell lysate (adjusted volumes for equal protein concentrations)

0.1 µL DTT (1M)

15-x µL of lysis buffer

5 µL of 4X Laemmle's sample buffer

The samples were heated at 95 °C for 5 minutes.

Gel Electrophoresis:

a) NuPAGE 4-12% Bis-Tris Gel (Novex, Catalog no. NP0322BOX) was assembled in a XCell II Blot module (Invitrogen, Catalog no. EI9051) and running buffer was added.

b) 20 µL of samples and 5 µL of pre-stained molecular weight markers were separately loaded in the wells.

c) Gels were run at 150V for about 1.5 hours untill the blue dye reached the bottom.

Protein Transfer from the gel to the nitro cellulose membrane:

a) After the run, the gel was removed and protein transfer was performed using iBlot (Invitrogen, Catalog No. IB301002) as per manufacturer's recommendations.

Primary Antibody incubation:

a) The nitrocellulose membrane was removed, and placed in 20 mL of blocking solution (5% TBST containing 5% milk) at room temperature for 1 hr.

b) The blot was washed 3 times for 5 min with TBST.

c) The blot was incubated overnight in 15 mL of TBST containing 0.5% BSA, 0.02% sodium azide and 15 µL of the anti-COX1 or 37.5 µL anti-COX4 antibody at room temperature.

d) The blot was washed 3 times for 5 min each with TBST.

Secondary Antibody incubation:

a) The blot was incubated in 15 mL of TBST containing 0.5% BSA and 1.5 µL of the HRP-conjugated secondary anti-rabbit antibody (for COX1 blots) or anti-mouse antibody (for COX4 blots) solution for 1 h at room temperature.

b) The blot was washed for 3 times for 5 min each with TBST.

Imaging

a) The blots were placed on plastic wrap.

b) A working solution of the substrate was prepared by mixing Substrate A and Substrate B in a 40:1 ratio (Thermo Scientific, Catalog No. 32132)

and one mL/blot was added such that the blot is evenly covered with the substrate solution. It was incubated at room temperature for 4 minutes.

c) The blot was covered with another layer of plastic wrap, placed in a cassette and exposed to an X-ray film in a safe lit dark-room.

d) After one minute, the film was removed from the cassette, and developed.

Probing for beta-actin:

a) To monitor beta-actin levels, the blots were washed three times for 5 minutes each in TBST, and incubated in 15 mL of TBST containing 0.5% BSA and 3 µL of the HRP-conjugated beta-actin antibody for one hour at room temperature.

b) The blot was washed three times for 5 minutes each with 15 mL of TBST, and imaged as described above.

Reagents and Buffers:

- 1X Cell lysis/Protein Extraction Reagent (Cell Signal Technology, Cat.no: 9803)
- 20 mM Tris-HCl (pH 7.5)
- 150 mM NaCl
- 1 mM Na_2EDTA
- 1 mM EGTA
- 1% Triton
- 2.5 mM sodium pyrophosphate
- 1 mM b-glycerophosphate
- 1 mM Na_3VO_4
- 1 µg/mL leupeptin
- Protease inhibitors (Roche, Catalog no. 11873580001)
- Protein Estimation: Coomassie protein assay reagent (ThermoScientific, Cat. No. 1856209)
- Sample Loading Buffer for Electrophoresis
- 4X Laemmli Sample buffer (Novex, Catalog No. NP0007)

- Electrophoresis Running Buffer
- NuPAGE MOPS/SDS running buffer (Novex, Catalog no. NP0001)
- Wash Buffer for Western blots
- Tris-buffered saline with Tween 20 (TBST buffer)
- 20 mM Tris-HCl (pH 7.5)
- 150 mM NaCl
- 0.1% Tween 20
- Blocking buffer for Western blots
- 5% Non-fat dry milk in TBST
- Signal detection kit: Pierce ECL Plus Substrate (Thermoscientific, Catalog no. 32132)
- Electrophoresis gel: NuPAGE 4-12% Bis-Tris Gel (Novex, Catalog no. NP0322BOX)

5) Effects on COX1 and COX4 Protein Levels in MV4-11 Cells

As shown in the western blots in FIGS. 1-5, all five compounds reduced the expression of mitochondrially translated COX1 protein with increasing compound concentrations, while COX4 and actin levels remained relatively unchanged.

Gene Expression Changes in MV4-11 When Treated with Compound 3a, Tigecycline and Cytarabine

MV411 cells were plated at about $1x10^5$/ml in 24 well plates, grown overnight at 37 °C/5% CO_2 in RPMI 1640/10% FBS. Wells were harvested for RNA preparation using Qiagen RNeasy kit. Samples prepped in triplicate, cDNA made using about 100ng total input RNA. qPCR assays run on Applicaed Biosystems Step One Plus instrument using commercially available primer/probe designs. The results for MV411 MT-COX1 (Cytochrome oxidase subunit 1, expressed in mitochrondria) expression are shown in FIG. 9. The results for MV411 COX-IV expression (Cytochrome oxidase subunit 4, expressed in nucleus) are shown in FIG. 10. The results for MV411 PIG3 expression ($TP_{53}I_3$-a p53 responsive protein, expression induced in response to p53 activation, role associated with response to oxidative stress) are shown in FIG. 11. The results for MV411 BAX expression (pro-apoptotic protein expression induce by p53 activation, forms

a heterodimer with BCL2 to induce apoptosis) are shown in FIG. 12. The results of CDKN2A expresson (also known as $p14^{ARF}$ or ARF –nuclear gene, translation regulated by cMyc, functions to stabilize/activate p53 by binding and sequestering Mdm2) are shown in FIG. 13.

Example 3: Synthesis of Example Compounds

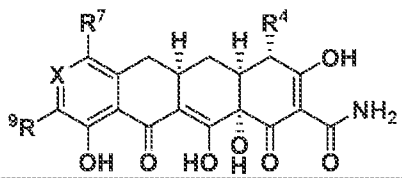
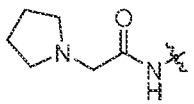
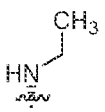
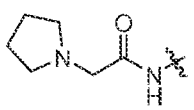
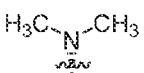
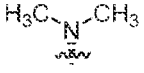
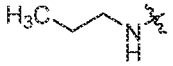
The following abbreviations are used in the paragraphs below:

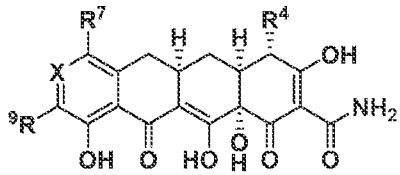
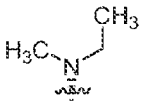
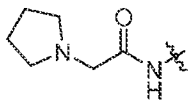
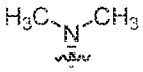
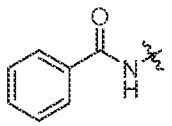
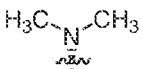
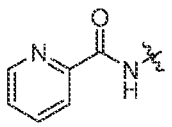
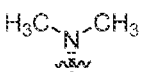
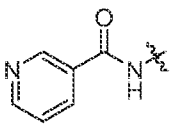
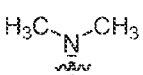
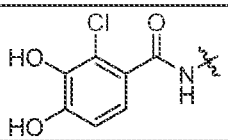
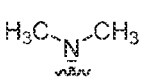
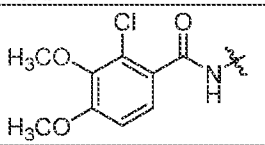
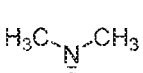
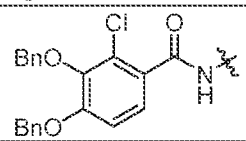
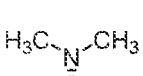
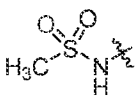
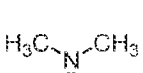
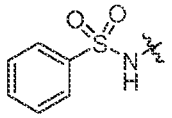
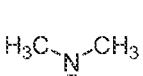
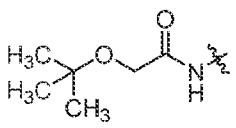
Ac	acetyl
aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
BHT	*t*-butyl hydroxyl toluene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DEM	diethoxymethane
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMSO	dimethylsulfoxide
DPPB	1,4-bis(diphenylphosphinebutane)
ESI	ESI ionization
Et	ethyl
eq	equivalent
h	hour
HPLC	high performance liquid chromatography
i	iso
IBX	2-iodoxybenzoic acid
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
M-D	Michael-Dieckmann annulation
MHz	mega hertz
Ms	methylsulfonyl
MS	mass spectrometry
MTBE	methyl *t*-butyl ether
m/z	mass/charge ratio
MW	molecular weight
NCS	*N*-chlorosuccinimide
NDMBA	1,3-dimethylbarbituric acid
NMO	*N*-methylmorpholine *N*-oxide

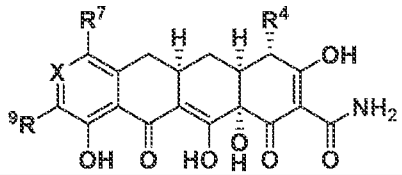
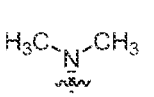
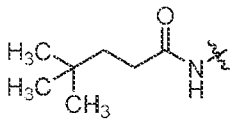
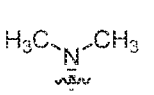
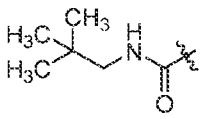
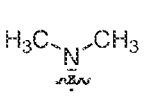
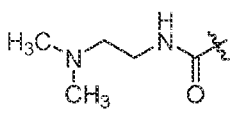
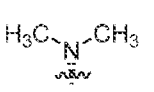
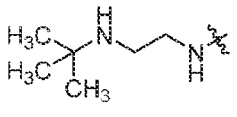
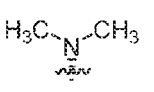
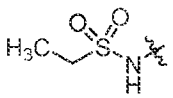
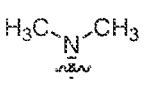
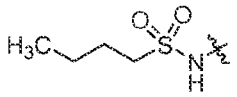
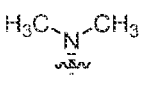
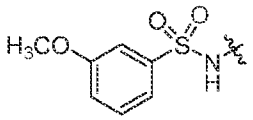
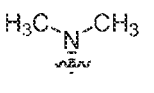
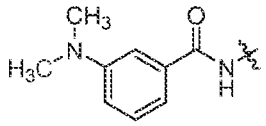
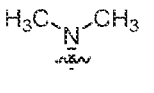
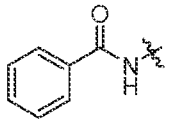
NMR	nuclear magnetic resonance spectrometry
Ph	phenyl
Pr	propyl
s	secondary
t	tertiary
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N'N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
STAB	sodium triacetoxyborohydride

Compounds referred herein as "K-number" (*e.g.*, K1, K2, K43, K44, etc.), have been prepared according to the procedures described in Tables 3A and 3B, below:

Table 3A

Compound Number					Synthetic Procedure
	R^4	R^7	R^9	X	
K43				CH	See Footnote 1
K44				CH	See Footnote 1
K45				N	See Footnote 3
K46				N	See Footnote 3

Compound Number					Synthetic Procedure
	R^4	R^7	R^9	X	
K47				CH	See Footnote 1
K48				CH	See Footnote 4
K49				CH	See Footnote 4
K50				CH	See Footnote 4
K51				CH	See Footnote 4
K52				CH	See Footnote 4
K53				CH	See Footnote 4
K54				CH	See Footnote 4
K55				CH	See Footnote 4
K56				CH	See Footnote 3

Compound Number					Synthetic Procedure
	R^4	R^7	R^9	X	
K57				CH	See Footnote 3
K58				CH	See Footnote 3
K59				CH	See Footnote 3
K60				CH	See Footnote 3
K61				CH	See Footnote 3
K62				CH	See Footnote 3
K63				CH	See Footnote 3
K64				CH	See Footnote 3
K65				CH	See Footnote 3

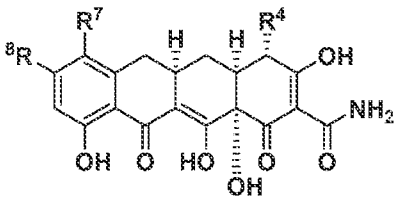
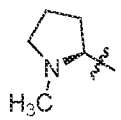
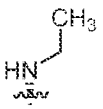
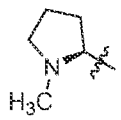
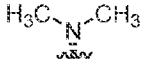
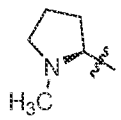
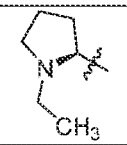
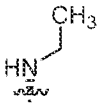
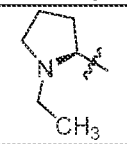
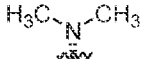
[1]Compound made in accordance with procedures described in US Patent No. 9,573,895B2 the entire content of which is hereby incorporated by reference.

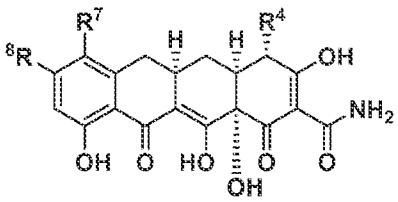
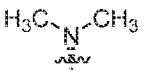
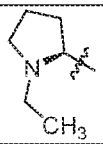
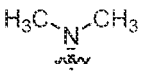
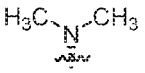
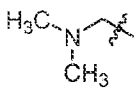
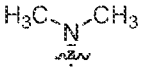
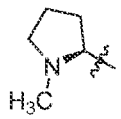
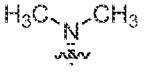
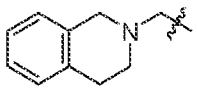
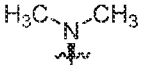
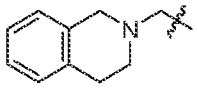
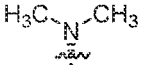
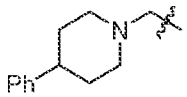
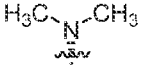
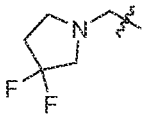
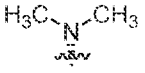
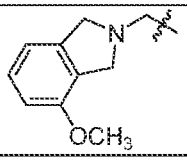
[2]Compouond made in accordance with procedures described in US Patent No. 9,315,451B2 the entire content of which is hereby incorporated by reference.

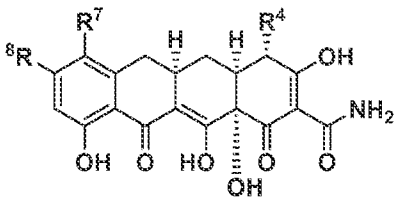
[3]Compound made in accordance with procedures described in US Patent No. 9,624,166B2 the entire content of which is hereby incorporated by reference.

[4]Compound made in accordance with procedures described in US Patent No. 8,906,887B2 the entire content of which is hereby incorporated by reference.

Table 3B

Compound No.				Synthetic Method
	R^4	R^7	R^8	
K1				See Footnote 5
K2				See Footnote 5
K3				See Footnote 6
K4				See Footnote 5
K5				See Footnote 5
K6				See Footnote 7

Compound No.				Synthetic Method
	R^4	R^7	R^8	
K7				See Footnote 6
K8				See Footnote 7
K9				See Footnote 6
K10				See Footnote 6
K11				See Footnote 6
K12				See Footnote 6
K13				See Footnote 6
K14				See Footnote 6
K15				See Footnote 6

Compound No.				Synthetic Method
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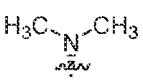
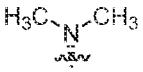
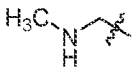
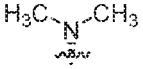
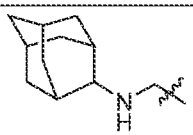
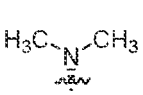
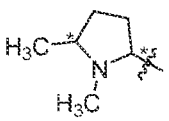
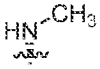
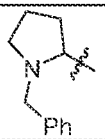
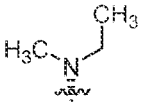
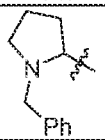
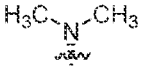
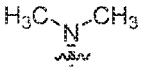
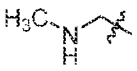
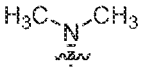
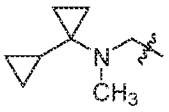
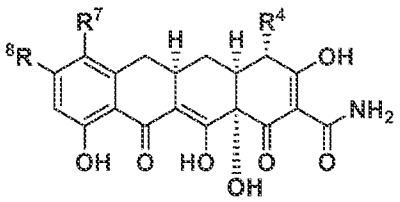
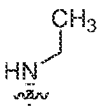
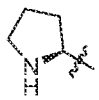
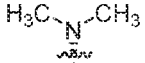
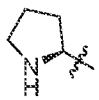
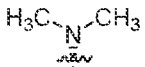
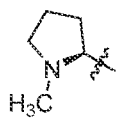
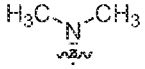
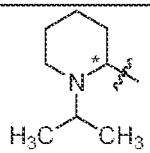
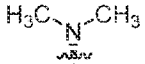
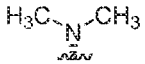
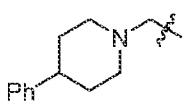
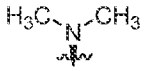
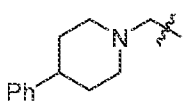
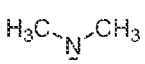
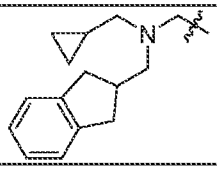
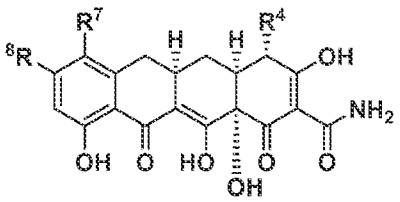
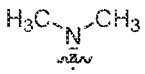
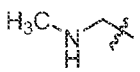
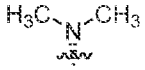
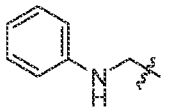
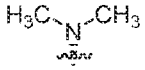
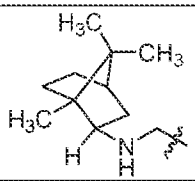
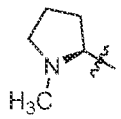
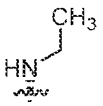
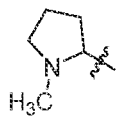
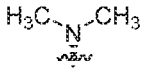
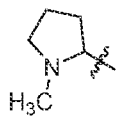
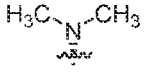
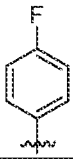
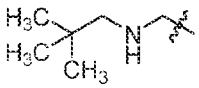
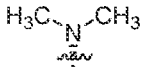
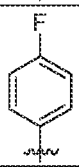
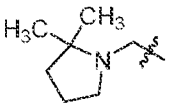
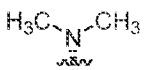
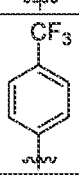
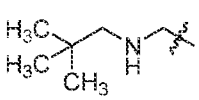
K16				See Footnote 6
K17				See Footnote 6
K18				See Footnote 6
K19				See Footnote 6
K20				See Footnote 5
K21				See Footnote 5
K22				See Footnote 7
K23				See Footnote 6
K24				See Footnote 6

Compound No.				Synthetic Method
	R^4	R^7	R^8	
K25				See Footnote 5
K26				See Footnote 5
K27				See Footnote 6
K28				See Footnote 6
K29				See Footnote 6
K30				See Footnote 8
K31				See Footnote 6
K32				See Footnote 6
K33				See Footnote 6

Compound No.				Synthetic Method
	R^4	R^7	R^8	
K34				See Footnote 6
K35				See Footnote 6
K36				See Footnote 6
K37				See Footnote 5
K38				See Footnote 5
K39				See Footnote 6
K40				See Footnote 6
K41				See Footnote 6
K42				See Footnote 6

[5]Compound made in accordance with procedures described in US Patent No. 9,573,895B2 the entire content of which is hereby incorporated by reference.

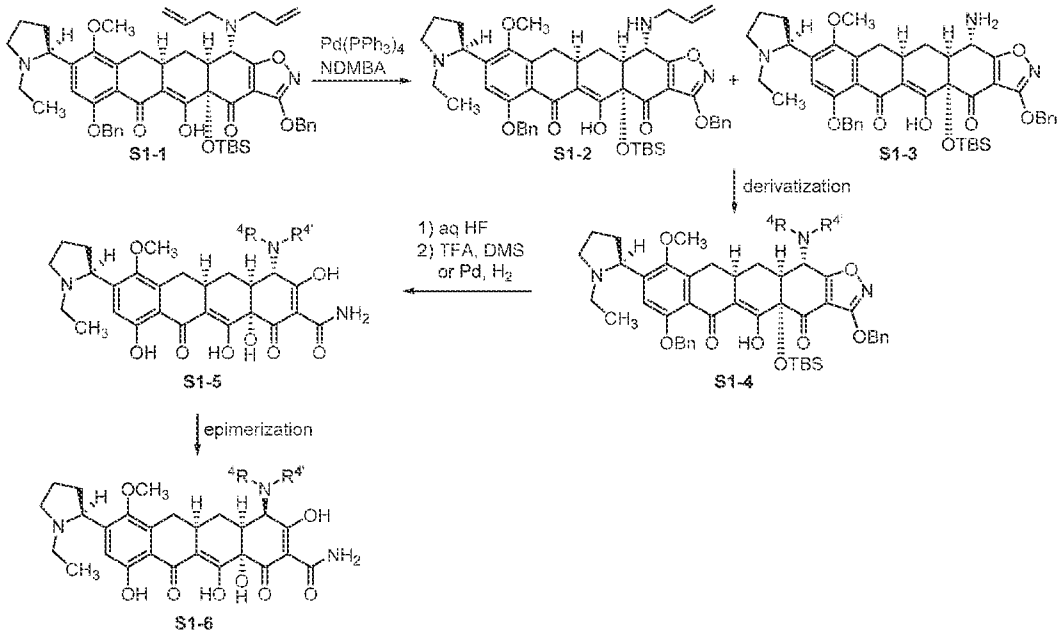
[6]Compouond made in accordance with procedures described in US Patent No. 9,315,451 the entire content of which is hereby incorporated by reference.

[7]Compound made in accordance with procedures described in US Patent No. 9,624,166 the entire content of which is hereby incorporated by reference.

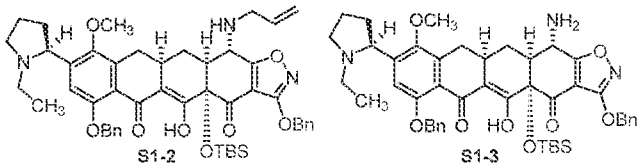
[8]Compound made in accordance with procedures described in US Patent No. 8,906,887 the entire content of which is hereby incorporated by reference.

Further example compounds disclosed herein have been prepared according to Schemes 1 through 21, described below.

Scheme 1

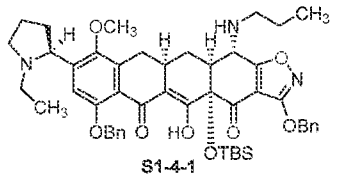


The following compounds were prepared per Scheme 1.

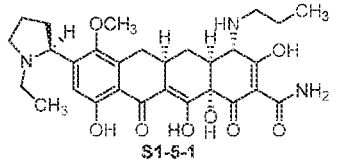


General Procedure **A** (de-allylation): To a mixture of compound **S1-1** (498 mg, 0.56 mmol, 1 eq, prepared according to literature procedures including WO 2014036502), 1,3-dimethylbarbituric acid (439 mg, 2.81 mmol, 5 eq) and $Pd(PPh_3)_4$ (32 mg, 0.028 mmol, 0.05 eq) was added DCM (5 mL) under nitrogen. The resulting reaction solution was stirred at rt for 5 h. The reaction mixture was quenched with aqueous saturated sodium bicarbonate (bubbling). The resulting reaction mixture was stirred at rt for 10 min, and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using 10%→100% EtOAc/hexanes to yield the desired product **S1-2** (82 mg, 17%, MS (ESI) *m/z* 846.47 (M+H)) and **S1-3** (307 mg, 68%).

S1-3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.54 (s, 1 H), 7.42-7.41 (m, 2 H), 7.37-7.34 (m, 2 H), 7.27-7.15 (m, 7 H), 5.29, 5.25 (ABq, J = 12.2 Hz, 2 H), 5.16, 5.07 (ABq, J = 12.2 Hz, 2 H), 3.82 (br s, 1 H), 3.61 (t, J = 8.5 Hz, 1 H), 3.48 (s, 3 H), 3.32-3.28 (m, 1 H), 2.95 (dd, J = 4.3, 15.3 Hz, 1 H), 2.69-2.59 (m, 1 H), 2.52-2.43 (m, 2 H), 2.18-1.98 (m, 5 H), 1.88-1.73 (m, 2 H), 1.56-1.38 (m, 2 H), 0.90 (t, J = 7.3 Hz, 3 H), 0.63 (s, 9 H), 0.11 (s, 3 H), 0.00 (s, 3 H); MS (ESI) *m/z* 806.51 (M+H).



General procedure B-1 (reductive alkylation): To a solution of amine **S1-3** (40 mg, 0.05 mmol, 1.0 eq) in DCM (1 mL) was added HOAc (5.7 μL, 0.1 mmol, 2 eq) and STAB (16 mg, 0.08 mmol, 1.5 eq) at 0 °C. Then propionaldehyde (3.6 μL, 0.05 mmol, 1.0 eq) was added. The resulting reaction mixture was stirred at 0 °C for 2 h. Saturated $NaHCO_3$ was added. The resulting mixture was extracted with DCM (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude product **S1-4-1** was used directly for the next reaction: MS (ESI) *m/z* 848.48 (M+H).

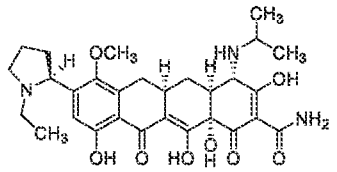


S1-5-1

General Procedure C (HF desilylation): Aqueous HF (48-50%, 0.1 mL) was added to a solution of compound **S1-4-1** (0.05 mmol, 1 eq) in CH_3CN (1 mL) in a polypropylene reaction vessel at rt. The mixture was stirred vigorously at rt overnight and poured slowly into saturated aqueous $NaHCO_3$ (3 mL) (vigorously bubbling). The resulting mixture was extracted with EtOAc (10 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was used directly in the next step without further purification (MS (ESI) *m/z* 734.40 (M+H)).

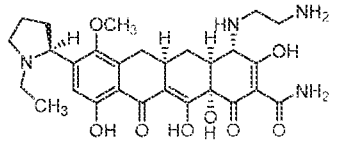
General Procedure D-1 (global deprotection): To a solution of the above intermediate in TFA (1 mL) was added dimethylsulfide (0.1 mL). The resulting reaction solution was stirred at rt overnight. The reaction was evaporated and the residue was dissolved in 0.05 *N* HCl in water. The resulting solution was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 μ RP-γ 100A column [10 μm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 2.0 mL (0.05 *N* HCl/water); gradient: 10→25% B in A over 20 min; mass-directed fraction collection]. Fractions containing the desired product were collected and freeze-dried to yield compound **S1-5-1** (14.3 mg, 46% over 3 steps): ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.14 (s, 1 H), 4.87-4.84 (m, 1 H), 3.90 (s, 1 H), 3.87-3.81 (m, 1 H), 3.68 (s, 3 H), 3.37-3.29 (m, 2 H), 3.28-3.07 (m, 4 H), 3.01-2.88 (m, 2 H), 2.62-2.55 (m, 1 H), 2.43-2.24 (m, 5 H), 1.83-1.73 (m, 2 H), 1.64-1.54 (m, 1 H), 1.26 (t, J = 7.3 Hz, 3 H), 1.03 (t, J = 7.3 Hz, 3 H); MS (ESI) *m/z* 556.30 (M+H).

The following compounds were prepared by using general procedures **B-1**, **C**, and **D-1**.



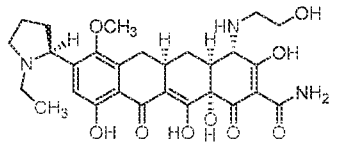
S1-5-2

Compound **S1-5-2** was prepared from compound **S1-3** and acetone: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.15 (s, 1 H), 4.90-4.85 (m, 1 H), 3.99 (s, 1 H), 3.88-3.82 (m, 2 H), 3.68 (s, 3 H), 3.38-3.33 (m, 1 H), 3.25 (dd, J = 16.0, 4.6 Hz, 1 H), 3.20-3.08 (m, 2 H), 3.02-2.94 (m, 1 H), 2.87 (d, J = 12.4 Hz, 1 H), 2.62-2.55 (m, 1 H), 2.42-2.37 (m, 5 H), 1.65-1.56 (m, 1 H), 1.44 (d, J = 6.4 Hz, 3 H), 1.40 (d, J = 6.4 Hz, 3 H), 1.26 (t, J = 7.3 Hz, 3 H); MS (ESI) *m/z* 556.31 (M+H).



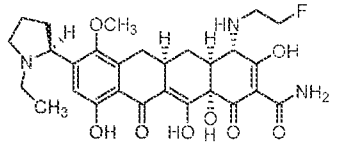
S1-5-3

Compound **S1-5-3** was prepared from compound **S1-3** and $BocNHCH_2CHO$: ^{1}H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 7.11 (s, 1 H), 4.09 (s, 1 H), 3.78-3.87 (m, 3 H), 3.68 (s, 3 H), 3.60-3.65 (m, 1 H), 3.39-3.43 (m, 2 H), 2.93-3.24 (m, 5 H), 2.55-2.62 (m, 1 H), 2.23-2.40 (m, 6 H), 1.52-1.62 (m, 1 H), 1.25 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 557.3 (M+H).



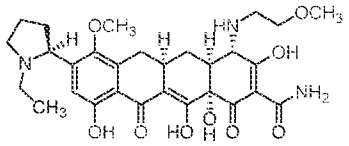
S1-5-4

Compound **S1-5-4** was prepared from compound **S1-3** and $TBSOCH_2CHO$: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.12 (s, 1 H), 4.01 (s, 1 H), 3.80-3.91 (m, 4 H), 3.67 (s, 3 H), 3.39-3.50 (m, 2 H), 3.05-3.24 (m, 4 H), 2.88-3.00 (m, 2 H), 2.55-2.61 (m, 1 H), 2.20-2.40 (m, 5 H), 1.55-1.62 (m, 1 H), 1.25 (t, J = 8.0 Hz, 3 H); MS (ESI) *m/z* 558.3 (M+H).



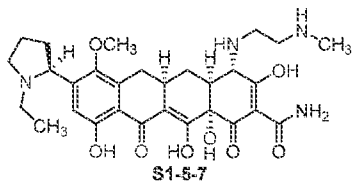
S1-5-5

Compound **S1-5-5** was prepared from compound **S1-3** and FCH_2CHO (prepared from the corresponding alcohol according to the literature procedure in WO 2011146089 Al): ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.13 (s, 1 H), 4.03 (s, 1 H), 3.69-3.88 (m, 4 H), 3.66 (s, 3 H), 3.25-3.38 (m, 3 H), 3.05-3.23 (m, 2 H), 2.89-3.00 (m, 2 H), 2.55-2.61 (m, 1 H), 2.21-2.42 (m, 6 H), 1.56-1.66 (m, 1 H), 1.23 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 560.3 (M+H).



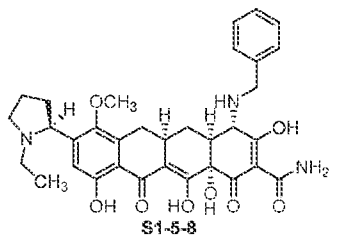
S1-5-6

Compound **S1-5-6** was prepared from compound **S1-3** and CH_3OCH_2CHO (prepared from the corresponding alcohol according to the literature procedure in WO 2011146089 A1): ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.03 (s, 1 H), 3.88 (s, 1 H), 3.69-3.75 (m, 1 H), 3.61-3.64 (m, 2 H), 3.67 (s, 3 H), 3.38-3.42 (m, 2 H), 3.30 (s, 3 H), 3.18-3.25 (m, 3 H), 2.95-3.15 (m, 2 H), 2.75-2.90 (m, 2 H), 2.45-2.51 (m, 1 H), 2.09-2.31 (m, 5 H), 1.44-1.54 (m, 1 H), 1.12 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 572.3 (M+H).



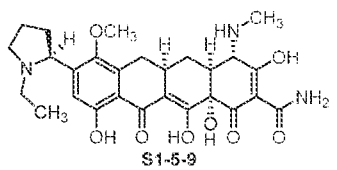
S1-5-7

Compound **S1-5-7** was prepared from compound **S1-3** and $BocN(CH_3)CH_2CHO$: ^1H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 7.11 (s, 1 H), 4.09 (s, 1 H), 3.79-3.89 (m, 2 H), 3.67 (s, 3 H), 3.55-3.60 (m, 2 H), 3.30 (s, 3 H), 2.95-3.18 (m, 4 H), 2.79 (s, 3 H), 2.55-2.61 (m, 1 H), 2.21-2.31 (m, 6 H), 1.56-1.63 (m, 1 H), 1.25 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 571.3 (M+H).



S1-5-8

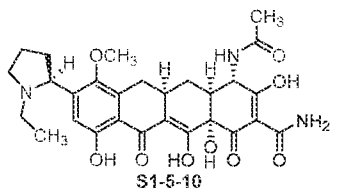
Compound **S1-5-8** was prepared from compound **S1-3** and PhCHO: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.55-7.62 (m, 2 H), 7.45-7.51 (m, 3 H), 7.09 (s, 1 H), 4.47-4.52 (m, 2 H), 3.80-3.75 (m, 2 H), 3.67 (s, 3 H), 3.09-3.23 (m, 4 H), 2.83-2.93 (m, 2 H), 2.55-2.61 (m, 1 H), 2.21-2.40 (m, 5 H), 2.00-2.08 (m, 1 H),1.51-1.63 (m, 1 H), 1.25 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 604.3 (M+H).



S1-5-9

Compound **S1-5-9** was prepared from compound **S1-2** (44 mg, 0.052 mmol, 1 eq) and HCHO by using general procedure **B-1** and **C**, followed by the following general procedure **D-2**.

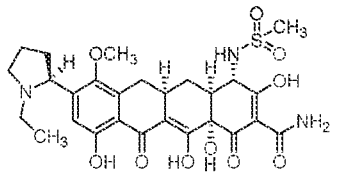
General procedure **D-2**: Pd-C (10wt%, 5 mg) was added in one portion into a solution of the above crude product in a mixture of CH_3OH (1 mL) and HCl/water (1 *N*, 130 μL, 0.13 mmol, 2.5 eq) at rt. The reaction vessel was sealed and purged with hydrogen by briefly evacuating the flask followed by flushing with hydrogen gas (1 atm). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 1 h 30 min. More Pd-C (10wt%, 5 mg) was added and the resulting reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 1 h. The reaction was filtered through a small Celite pad. The cake was washed with CH_3OH. The filtrate was concentrated. The residue was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 μ RP-γ 100A column [10 μm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 3.0 mL (0.05 *N* HCl/water); gradient: 5→25% B in A over 15 min; mass-directed fraction collection]. Fractions containing the desired product were collected and freeze-dried to yield compound **S1-5-9** (12.3 mg): ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.15 (s, 1 H), 4.96-4.89 (m, 1 H), 3.84-3.81 (m, 2 H), 3.68 (s, 3 H), 3.36-3.33 (m, 1 H), 3.27-2.99 (m, 5 H), 2.93 (s, 3 H), 2.88-2.83 (m, 1 H), 2.62-2.55 (m, 1 H), 2.42-2.24 (m, 4 H), 1.63-1.54 (m, 1 H), 1.26 (t, *J* = 7.3 Hz, 3 H); MS (ESI) *m/z* 528.23 (M+H).



S1-5-10

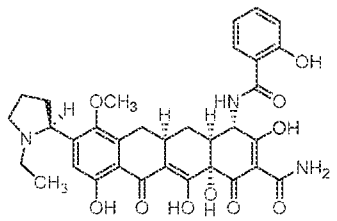
General procedure B-2 (acylation/sulfonylation): To a solution of compound **S1-3** (43 mg, 0.053 mmol, 1 eq) and TEA (30 μL, 0.21 mmol, 4 eq) in DCM (3 mL) was added acetic anhydride (16 μL, 0.16 mmol, 3 eq) at 0 °C. The resulting reaction mixture was stirred at 0 °C and allowed to warm up to rt overnight. The reaction was diluted with DCM, washed with saturated sodium bicarbonate and brine. The resulting organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was subjected to the general procedure **C** for HF desilylation at 50 °C and general procedure **D-1** to give **S1-5-10** (11.2 mg, 36% over 3 steps):

^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.04 (s, 1 H), 3.79-3.85 (m, 2 H), 3.69 (s, 3 H), 3.05-3.21 (m, 4 H), 2.90-3.00 (m, 1 H), 2.53-2.70 (m, 2 H), 2.21-2.45 (m, 6 H), 2.05 (s, 3 H),1.51-1.60 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H); MS (ESI) *m/z* 556.3 (M+H).



S1-5-11

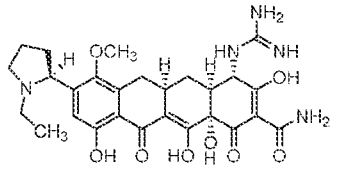
Compound **S1-5-11** was prepared from compound **S1-3** and Ms_2O following the same procedure as for compound **S1-5-10**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.01 (s, 1 H), 4.15 (m, 1 H), 3.75-3.83 (m, 2 H), 3.69 (s, 3 H), 3.16-3.40 (m, 4 H), 2.92-3.11 (m, 3 H), 2.41-2.61 (m, 3 H), 2.22-2.38 (m, 5 H), 1.75-1.83 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H); MS (ESI) *m/z* 592.3 (M+H).



S1-5-12

To a mixture of amine **S1-3** (48 mg, 0.06 mmol, 1.0 eq), HOBt (12 mg, 0.09 mmol, 1.5 eq) and EDC (17 mg, 0.09 mmol, 1.5 eq) in 10 mL RBF was added DCM (1 mL) under nitrogen. Then EtN^iPr_2 (21 μL, 0.12 mmol, 2 eq) and salicyclic acid (9 mg, 0.07 mmol, 1.1 eq) were added subsequently. The resulting reaction mixture was stirred at rt for 5 days. The resulting dark reaction mixture was extracted with DCM (10 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10 g silica gel column, 10-80% EtOAc/Hexane) to give the desired product (13 mg, 23%): MS (ESI) *m/z* 926.53 (M+H).

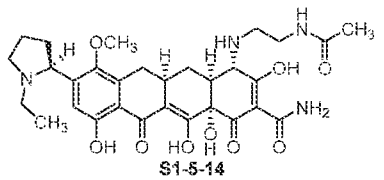
The above product was subjected to general procedure **C** and **D-1** to give compound **S1-5-12**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.83 (d, *J* = 7.3 Hz, 1 H), 7.40 (t, *J* = 7.3 Hz, 1 H), 7.03 (s, 1 H), 6.94-6.90 (m, 2 H), 5.07-5.06 (m, 1 H), 3.81-3.76 (m, 2 H), 3.65 (s, 3 H), 3.21-3.06 (m, 4 H), 2.98-2.94 (m, 1 H), 2.62-2.58 (m, 2 H), 2.45-2.22 (m, 5 H), 1.74-1.67 (m, 1 H), 1.23 (t, *J* = 7.3 Hz, 3 H); MS (ESI) *m/z* 634.39 (M+H).



S1-5-13

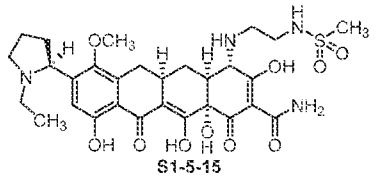
To a solution of amine **S1-3** (82 mg, 0.10 mmol, 1.0 eq) was subjected to general procedure **C** to give desilylated product 74 mg. To a solution of this intermediate (42 mg, 0.06 mmol, 1.0 eq) in DCM (1 mL) was added $HgCl_2$ (33 mg, 0.12 mmol, 2.2 eq) and TEA (30 μL, 0.21 mmol, 3.5 eq) at 0 °C. Then 1,3-bis(*tert*-butoxycarbonyl)-2-methylisothiourea (39 mg, 0.12 mmol, 2.2 eq) was added. The resulting reaction mixture was allowed to warm up to rt and stirred overnight. The resulting reaction mixture was filtered, washed with DCM (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (10 g silica gel column, 10% CH_3OH/DCM) to give the desired product (20 mg, 35%): MS (ESI) *m/z* 934.57 (M+H).

The above product was subjected to general procedure **D-1** to give compound **S1-5-13**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.06 (s, 1 H), 4.30 (s, 1 H), 3.78-3.84 (m, 1 H), 3.68 (s, 3 H), 3.32-3.40 (m, 2 H), 3.08-3.17 (m, 3 H), 2.90-3.00 (m, 1 H), 2.53-2.60 (m, 3 H), 2.21-2.39 (m, 5 H), 1.58-1.64 (m, 1 H), 1.22 (t, *J* = 6.8 Hz, 3 H); MS (ESI) *m/z* 556.3 (M+H).



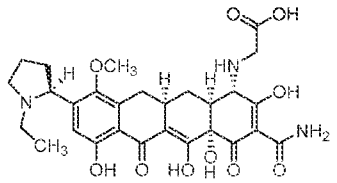
S1-5-14

Compound **S1-5-14** was prepared from compound **S1-3** and $BocNHCH_2CHO$ by using general procedure **B-1**. The resulting product was then treated with 4 *N* HCl in dioxane (1 mL) for 30 min and concentrated. The residue was subjected to general procedure **B-2**, **C** and **D-1**to give desired product **S1-5-14**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.10 (s, 1 H), 3.99 (s, 1 H), 3.79-3.83 (m, 1 H), 3.67 (s, 3 H), 3.55-3.60 (m, 1 H), 3.45-3.51 (m, 3 H), 3.31-3.35 (m, 1 H), 3.05-3.27 (m, 4 H), 2.92-3.00 (m, 1 H), 2.79-2.83 (m, 1 H), 2.55-2.60 (m, 1 H), 2.20-2.40 (m, 5 H), 1.98 (s, 3 H), 1.52-1.62 (m, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H); MS (ESI) *m/z* 599.3 (M+H).



S1-5-15

Compound **S1-5-15** was prepared similarly to compound **S1-5-14**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.08 (s, 1 H), 4.05 (s, 1 H), 3.78-3.85 (m, 2 H), 3.68 (m, 5 H), 3.45-3.52 (m, 6 H), 3.09-3.20 (m, 2 H), 2.89-3.00 (m, 2 H), 2.55-2.62 (m, 1 H), 2.21-2.51 (m, 6 H), 1.53-1.63 (m, 1 H), 1.23 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 635.3 (M+H).

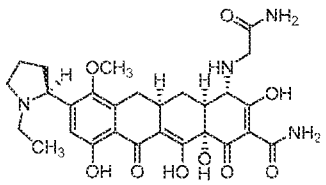


S1-5-16

General procedure B-3 (substitution): To a solution of amine **S1-3** (42 mg, 0.05 mmol, 1.0 eq) in DMF (0.7 mL) was added $BrCH_2CO_2{}^tBu$ (8 μL, 0.05 mmol, 1 eq) and $^iPr_2NEt$ (45 μL, 0.25 mmol, 5 eq). The resulting reaction mixture was stirred at rt overnight and heated to 50 °C for 6 h. The resulting reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was used directly for the next reaction.

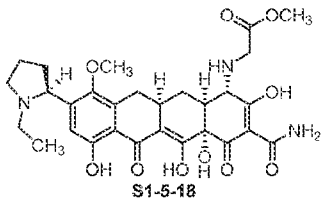
The crude product was then subjected to general procedure **C** and **D-1** to give desired product **S1-5-16**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.08 (s, 1 H), 4.19 (s, 2 H), 3.99 (s, 1 H), 3.78-3.83 (m, 1 H), 3.68 (s, 3 H), 3.05-3.22 (m, 3 H), 2.83-3.00 (m, 2 H), 2.52-2.61 (m, 1 H), 2.19-2.40 (m, 5 H), 1.56-1.67 (m, 1 H), 1.22 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 572.2 (M+H).

The following compounds were prepared by using general procedures **B-3**, **C**, and **D-1**.



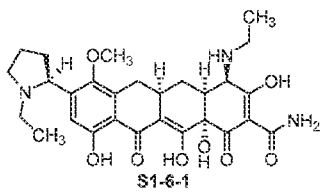
S1-5-17

Compound **S1-5-17** was prepared from compound **S1-3** and $BrCH_2CONH_2$: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 4.15 (s, 2 H), 3.98 (s, 1 H), 3.79-3.84 (m, 1 H), 3.68 (s, 3 H), 3.09-3.24 (m, 3 H), 2.83-3.00 (m, 2 H), 2.55-2.63 (m, 1 H), 2.20-2.40 (m, 5 H), 1.55-1.65 (m, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H); MS (ESI) *m/z* 571.3 (M+H).



S1-5-18

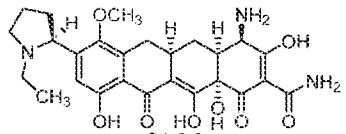
Compound **S1-5-18** was prepared from compound **S1-3** and $BrCH_2CO_2Me$: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 4.26 (s, 2 H), 4.03 (s, 1 H), 3.84 (s, 3 H), 3.79-3.82 (m, 1 H), 3.68 (s, 3 H), 3.09-3.24 (m, 3 H), 2.87-3.00 (m, 2 H), 2.55-2.62 (m, 1 H), 2.20-2.50 (m, 5 H), 1.55-1.63 (m, 1 H), 1.21 (t, *J* = 7.2 Hz, 3 H); MS (ESI) *m/z* 586.3 (M+H).



S1-6-1

To a solution of the corresponding C-4 epimer (71 mg, 0.12 mmol, 1 eq, prepared per literature procedures including WO 2014036502) in CH_3OH (1 mL) was added pyridine (38 μL, 0.47 mmol, 4 eq) at rt. The resulting reaction solution was stirred at rt for 3 days. The reaction was concentrated to give a yellow solid, which was dissolved in 0.05 *N* HCl in water. The resulting reaction solution was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 μ RP-γ 100A column [10 μm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 2.0 mL (0.05 *N* HCl/water); gradient: 10→25% B in A over 20 min; mass-directed fraction collection]. Fractions containing the desired product were collected and

freeze-dried to yield compound **S1-6-1** (27.2 mg, 38%): ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.18 (s, 1 H), 4.88-4.84 (m, 1 H), 4.72 (d, J = 4.0 Hz, 1 H), 3.88-3.82 (m, 1 H), 3.67 (s, 3 H), 3.41-3.30 (m, 3 H), 3.27-3.22 (m, 1 H), 3.20-3.06 (m, 2 H), 3.03-2.98 (m, 1 H), 2.96-2.88 (m, 2 H), 2.61-2.54 (m, 1 H), 2.41 (t, J = 14.8 Hz, 1 H), 2.36-2.23 (m, 3 H), 2.18-2.14 (m, 1 H), 1.56-1.46 (m, 1 H), 1.44 (t, J = 7.2 Hz, 3 H), 1.26 (t, J = 7.6 Hz, 3 H); MS (ESI) *m/z* 541.4 (M+H).

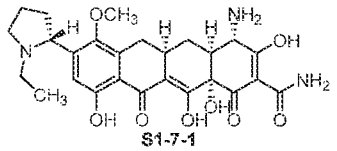


S1-6-2

To a suspension of 7-methoxy-8-[(2*S*)-1-ethyl-2-pyrrolidinyl]-6-demethyl-6-deoxytetracycline (550 mg, 0.89 mmol, 1 eq, prepared per literature procedures including *Org. Process Res. Dev.*, **2016**, *20* (2), 284–296.) in DMF (4.4 mL) was added a solution of NH_2OH (109 µL, 1.78 mmol, 2 eq) in water (109 µL) at rt. The resulting reaction mixture was stirred at 80 °C overnight with a needle in the septum to open to air. The resulting dark brown reaction solution was cooled to rt, and dropped into stirring MTBE (220 mL) to give a suspension.

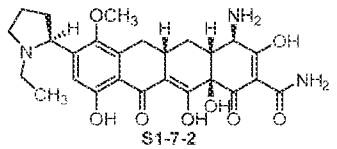
The solid was collected by filtration and washed with MTBE. The solid was then dried under vacuum. The solid was then dissolved in TFA (4 mL). Pd/C (10 wt%, 80 mg) was added. The reaction vessel was sealed and purged with hydrogen by briefly evacuating the flask followed by flushing with hydrogen gas (1 atm). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt overnight. More Pd-C (10wt%, 80 mg) was added and the resulting reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt overnight. The reaction was concentrated and diluted with CH_3OH. The mixture was filtered through a small Celite pad. The cake was washed with. The filtrate was concentrated. The residue was purified by preparative reverse phase HPLC CH_3OH on a Waters Autopurification system using a Phenomenex Polymerx 10 µ RP-γ 100A column [10 µm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 3.0 mL (0.05 *N* HCl/water); gradient: 10→20% B in A over 15 min; mass-directed fraction collection. Fractions containing the desired product were collected and freeze-dried to yield compound **S1-6-2** (91 mg): ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.12 (s, 1 H), 4.93-4.85 (m, 1 H), 4.76 (d, J = 4.8 Hz, 1 H), 3.86-3.81 (m, 1 H), 3.67 (s, 3 H), 3.37-3.31 (m, 1 H), 3.25

(dd, J = 15.2, 4.0 Hz, 1 H), 3.20-3.07 (m, 2 H), 2.90-2.82 (m, 2 H), 2.62-2.56 (m, 1 H), 2.43 (t, J = 14.8 Hz, 1 H), 2.36-2.23 (m, 3 H), 2.16-2.12 (m, 1 H), 1.53-1.43 (m, 1 H), 1.25 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 514.36 (M+H).



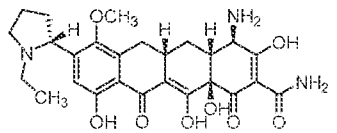
S1-7-1

Compound **S1-7-1** was prepared from the enantiomer of the left-hand side (LHS) and diallylenone **S2-3** according to literature procedures including WO 2014036502: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 4.77 (dd, J = 10.8, 8.0 Hz, 1 H), 3.92-3.86 (m, 2 H), 3.75 (s, 3 H), 3.37-3.29 (m, 1 H), 3.25-3.10 (m, 3 H), 3.01-2.93 (m, 1 H), 2.68 (dt, J = 12.4, 1.2 Hz, 1 H), 2.63-2.54 (m, 1 H), 2.38 (t, J = 14.8 Hz, 1 H), 2.32-2.24 (m, 3 H), 2.17-2.07 (m, 1 H), 1.64-1.55 (m, 1 H), 1.28 (t, J = 7.6 Hz, 3 H); MS (ESI) *m/z* 514.36 (M+H).



S1-7-2

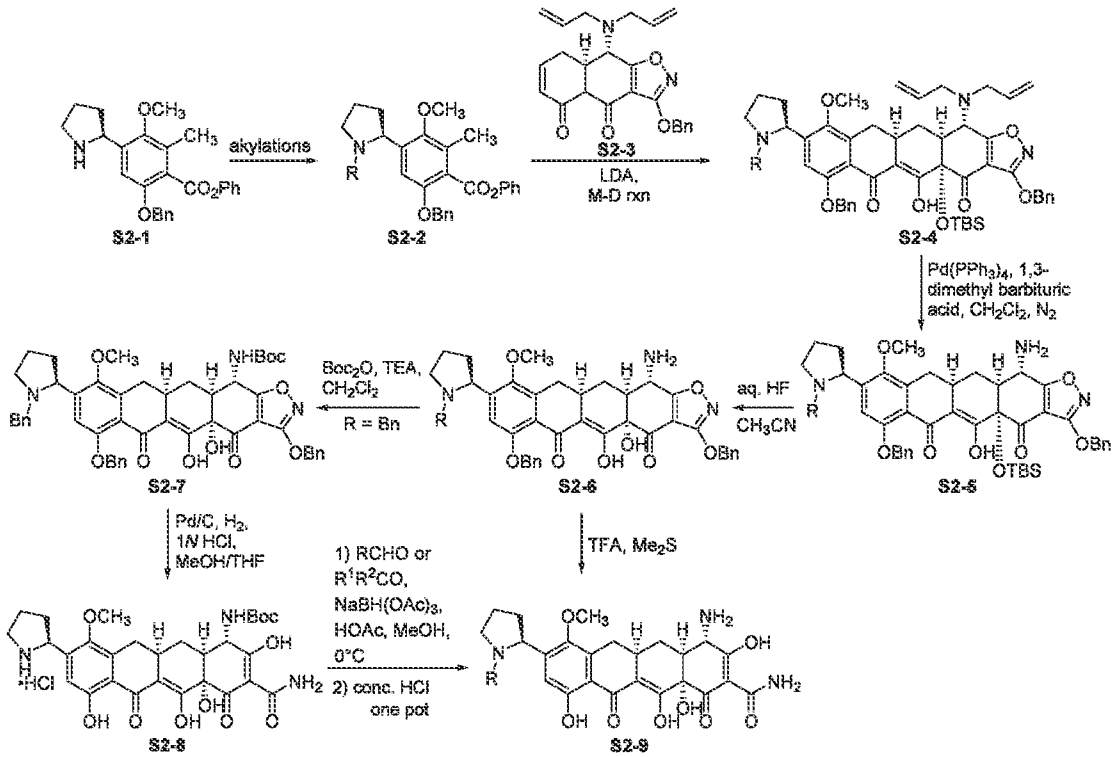
Compound **S1-7-2** was prepared from the normal LHS and the enantiomer of the diallylenone according to literature procedures including WO 2014036502: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.06 (s, 1 H), 4.76 (dd, J = 10.4, 7.6 Hz, 1 H), 3.91-3.85 (m, 2 H), 3.75 (s, 3 H), 3.37-3.30 (m, 1 H), 3.25-3.09 (m, 3 H), 3.00-2.92 (m, 1 H), 2.67-2.57 (m, 2 H), 2.39 (t, J = 14.8 Hz, 1 H), 2.34-2.24 (m, 3 H), 2.17-2.09 (m, 1 H), 1.65-1.56 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 514.36 (M+H).



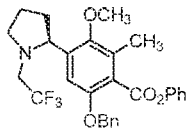
S1-7-3

Compound **S1-7-3** was prepared from the enantiomer of LHS and the enantiomer of the diallylenone according to literature procedures including WO 2014036502: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.15 (s, 1 H), 4.94-4.85 (m, 1 H), 3.91 (s, 1 H), 3.80-3.72 (m, 1 H), 3.68 (s, 3 H), 3.37-3.07 (m, 4 H), 3.00-2.91 (m, 1 H), 2.70-2.67 (m, 1 H), 2.62-2.56 (m, 1 H), 2.45-2.23 (m, 5 H), 1.65-1.56 (m, 1 H), 1.26 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 514.36 (M+H).

Scheme 2

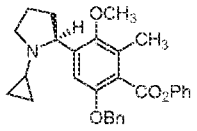


The following compounds were prepared per Scheme 2.


S2-2-1

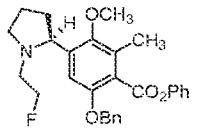
Compound **S2-1** (125 mg, 0.299 mmol, 1 eq, prepared per literature procedures: *Org. Process Res. Dev.*, 2016, 20 (2), 284–296) and $NaBH_3CN$ (76 mg, 1.209 mmol, 4 eq) were added to a mixture of CH_2Cl_2 and CH_3CN (0.8 + 0.8 mL). The flask cooled down to 0 °C, followed by the addition of trifluoroacetic acid (0.092 mL, 1.202 mmol, 4 eq) and trifluoroacetaldehyde monohydrate (75% in H_2O, 0.240 mL, 1.50 mmol, 5 eq). The cold bath was removed and the resulting mixture was stirred at room temperature for 2 h. EtOAc was added and the mixture washed with saturated $NaHCO_3$ solution. The organic phase was concentrated by rotovap. The residue was purified through flash column chromatography to afford the desired product **S2-2-1** as a colorless oil (59 mg, 40%, the unreacted SM can also be recovered): ^1H NMR (400 MHz, $CDCl_3$) δ 7.08-7.50 (m, 11 H), 5.09-5.17 (m, 2 H), 3.92-4.00 (m, 1 H), 3.70 (s, 3 H), 3.51-3.60 (m, 1 H), 3.08-3.20 (m, 1 H), 2.75-2.83 (m, 1 H), 2.49-2.57

(m, 1 H), 2.40 (s, 3 H), 2.20-2.28 (m, 1 H), 1.88-2.00 (m, 1 H), 1.55-1.65 (m, 1 H), 1.21-1.30 (m, 1 H); MS (ESI) *m/z* 500.3 (M+H).



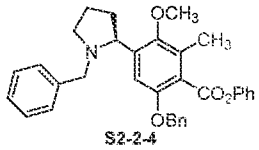
S2-2-2

To a flame-dried round-bottom flask, compound **S2-1** (125 mg, 0.299 mmol, 1 eq), $NaBH_3CN$ (57 mg, 0.907 mmol, 3 eq) and 4Å molecular sieves (100 mg) were added, the flask was vacuumed and refilled with N_2. Then anhydrous CH_3OH (2 mL), (1-ethoxycyclopropyl) trimethylsilane (0.240 mL, 1.193 mmol, 4 eq) and HOAc (0.086 mL, 1.500 mmol, 5 eq) were added and the resulted mixture was stirred at 55 °C for 16 h. EtOAc was added and the mixture was filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ solution. The organic phase was concentrated by rotovap. The residue was purified through flash column chromatography to afford the desired product **S2-2-2** as a colorless oil (89 mg, 65%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.58 (m, 10 H), 7.02 (s, 1 H), 5.11 (s, 2 H), 3.95-4.01 (m, 1 H), 3.71 (s, 3 H), 3.21-3.30 (m, 1 H), 2.55-2.63 (m, 1 H), 2.40 (s, 3 H), 2.20-2.30 (m, 1 H), 1.78-1.90 (m, 2 H), 1.55-1.70 (m, 2 H), 0.27-0.35 (m, 2 H), 0.00-0.16 (m, 2 H); MS (ESI) *m/z* 458.3 (M+H).



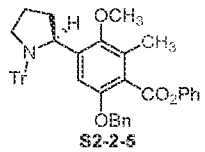
S2-2-3

Compound **S2-1** (125 mg, 0.299 mmol, 1 eq), *N,N*-diisopropylethylamine (DIPEA, 0.105 mL, 0.602 mmol, 2 eq) and NaI (5 mg, 0.033 mmol, 0.1 eq) were added into DMF (1 mL), then 2-fluoroethyl bromide (0.045 mL, 0.604 mmol, 2eq) was added and the resulted mixture was stirred at room temperature for 21 h. EtOAc was added and washed with brine solution. The organic phase was concentrated by rotovap. The residue was purified through flash column chromatography to afford the desired product **S2-2-3** as a colorless oil (79 mg, 57%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.09-7.50 (m, 11 H), 5.10-5.15 (m, 2 H), 4.30-4.51 (m, 2 H), 3.70 (s, 3 H), 3.40-3.50 (m, 1 H), 2.79-2.90 (m, 1 H), 2.37 (s, 3 H), 2.30-2.35 (m, 1 H), 2.18-2.26 (m, 1 H), 1.82-2.00 (m, 2 H), 1.53-1.61 (m, 1 H), 1.21-1.30 (m, 1 H), 0.82-0.91 (m, 1 H); MS (ESI) *m/z* 464.3 (M+H).



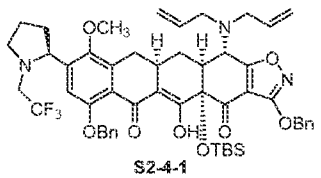
S2-2-4

To the pyrrolidine **S2-1** (8.74 mmol, 1 eq, crude material), NaI (10 mg), dimethylformamide (DMF, 10 mL) and triethylamine (TEA, 2.82 mL, 20.231 mmol) were added and cooled to 0 °C. A solution of benzyl bromide (1.650 mL, 13.867 mmol) in DMF (5 mL) was added. The reaction mixture was stirred at room temperature for 3 h. CH_2Cl_2 (100 mL) was added, and the resulting mixture was washed with brine solution. The organic phase was concentrated under reduced pressure. The residue was purified through flash column chromatography to afford the desired product **S2-2-4** as a white solid (3.83 g, 86% over 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09-7.59 (m, 16 H), 5.12-5.20 (m, 2 H), 3.80-3.90 (m, 2 H), 3.74 (s, 3 H), 3.03-3.12 (m, 1 H), 2.41 (s, 3 H), 2.20-2.30 (m, 2 H), 1.80-1.94 (m, 2 H), 1.60-1.70 (m, 2 H); MS (ESI) *m/z* 508.3 (M+H).



S2-2-5

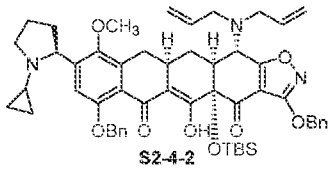
TrCl (87 mg, 0.31 mmol, 1.0 eq) and TEA (48 μL, 0.34 mmol, 1.1 eq) were added to **S2-1** (130 mg, 0.31 mmol, 1 eq) in CH_2Cl_2 (3 mL) at rt. The reaction mixture was stirred at rt for 3 days and diluted with DCM. The resulting solution washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the desired product **S2-2-5** as a yellow solid. This crude product was used in subsequent reaction without further purification.



S2-4-1

General Procedure E (Michael-Dieckmann annulation): *n*-BuLi (70 μL, 2.5 M in hexanes, 0.17 mmol, 1.4 eq) was added dropwise to a solution of diisopropylamine (23 μL, 0.17 mmol, 1.4 eq) and TEA·HCl (1 mg, 0.005 eq) in THF (1 mL) at –50 °C. The reaction mixture was warmed up to –20 °C and re-cooled to below –70 °C. A solution of **S2-2-1** (59 mg, 0.12 mmol, 1 eq) in THF (1 mL) was added dropwise *via* a cannula at below –73 °C over 10 min. The resulting red orange solution was stirred at –78 °C for 1 h, and cooled to –100 °C

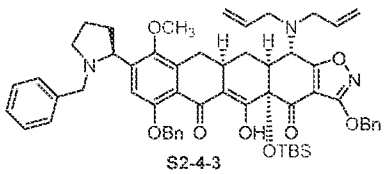
using a EtOH/liquid N_2 bath. A solution of enone **S2-3** (64 mg, 0.12 mmol, 1 eq, prepared according to literature procedures including WO 2014036502) in THF (1 mL) was added to the reaction mixture, followed by LHMDS (120 μL, 1.0 M in THF, 0.12 mmol, 1 eq). The reaction mixture was gradually warmed up to –15 °C and stirred at that temperature for 45 min. A saturated aqueous NH_4Cl (20 mL) solution was added to the reaction. The reaction mixture was extracted with EtOAc (40 mL). The organic phase was washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel using 0%→50% EtOAc/hexanes yielded the desired product **S2-4-1** as a yellow solid (59 mg, 53%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.2 (s, 1 H), 7.28-7.51 (m, 8 H), 6.83-6.95 (m, 3 H), 5.79-5.90 (m, 2 H), 5.10-5.27 (m, 7 H), 3.99-4.13 (m, 2 H), 3.68 (s, 3 H), 3.03-3.67 (m, 7 H), 2.57-2.80 (m, 6 H), 1.19-1.26 (m, 6 H), 0.85 (s, 9 H), 0.27 (s, 3 H), 0.15 (s, 3 H); MS (ESI) *m/z* 940.3 (M+H).



S2-4-2

Compound **S2-4-2** was prepared from **S2-2-2** and **S2-3** by using the General Procedure **A**:

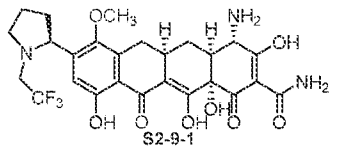
^{1}H NMR (400 MHz, $CDCl_3$) δ 16.1 (s, 1 H), 7.09-7.50 (m, 9 H), 6.70-7.00 (m, 2 H), 5.60-5.75 (m, 2 H), 4.95-5.13 (m, 7 H), 3.98-4.08 (m, 5 H), 3.59 (s, 3 H), 3.07-3.21 (m, 4 H), 2.15-2.50 (m, 4 H), 1.55-1.75 (m, 6 H), 1.13-1.21 (m, 5 H), 0.77 (s, 9 H), 0.17 (s, 3 H), 0.04 (s, 3 H); MS (ESI) *m/z* 898.3 (M+H).



S2-4-3

Compound **S2-4-3** was prepared from **S2-2-4** and **S2-3** by using the General Procedure **A**:

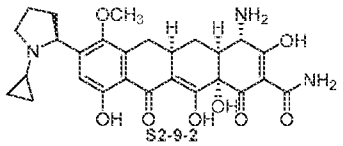
^{1}H NMR (400 MHz, $CDCl_3$) δ 16.1 (s, 1 H), 7.10-7.41 (m, 14 H), 6.71-6.89 (m, 2 H), 5.69-5.71 (m, 2 H), 4.98-5.18 (m, 9 H), 3.98-4.07 (m, 2 H), 3.65-3.79 (m, 1 H), 3.60 (s, 3 H), 3.00-3.28 (m, 4 H), 2.30-2.57 (m, 4 H), 2.10-2.21 (m, 2 H), 1.69-1.82 (m, 3 H), 1.10-1.20 (m, 3 H), 0.73 (s, 9 H), 0.17 (s, 3 H), 0.04 (s, 3 H); MS (ESI) *m/z* 948.3 (M+H).



S2-9-1

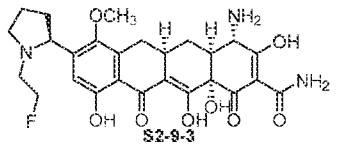
Compound **S2-9-1** was prepared from **S2-4-1** by using the General Procedure **A**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.08 (s, 1 H), 3.88 (s, 1 H), 3.70-3.74 (m, 1 H), 3.68 (s, 3 H), 3.55-3.62 (m, 2 H), 3.10-3.25 (m, 2 H), 2.90-3.00 (m, 1 H), 2.60-2.65 (m, 1 H), 2.35-2.50 (m, 3 H), 2.15-2.25 (m, 3 H), 2.00-2.10 (m, 1 H), 1.58-1.64 (m, 1 H); MS (ESI) *m/z* 568.3 (M+H).

The following compounds were prepared similarly to compound **S2-9-1**.



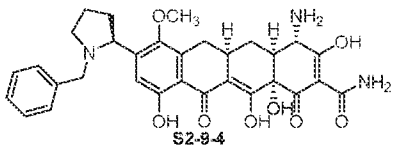
S2-9-2

S2-9-2: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 3.91 (s, 1 H), 3.77-3.83 (m, 1 H), 3.70 (s, 3 H), 3.50-3.57 (m, 1 H), 3.21-3.27 (m, 1 H), 2.87-3.00 (m, 2 H), 2.55-2.70 (m, 2 H), 2.21-2.44 (m, 6 H), 1.58-1.65 (m, 1 H), 0.85-0.91 (m, 2 H), 0.63-0.70 (m, 1 H), 0.30-0.40 (m, 1 H); MS (ESI) *m/z* 526.3 (M+H).



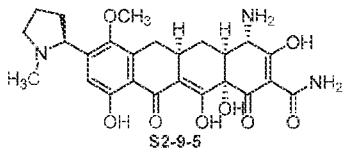
S2-9-3

S2-9-3: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.12 (s, 1 H), 3.92-3.96 (m, 1 H), 3.89 (s, 1 H), 3.60 (s, 3 H), 3.40-3.51 (m, 4 H), 3.21-3.26 (m, 1 H), 2.90-2.98 (m, 1 H), 2.55-2.78 (m, 2 H), 2.21-2.45 (m, 6 H), 1.55-1.82 (m, 2 H); MS (ESI) *m/z* 532.3 (M+H).



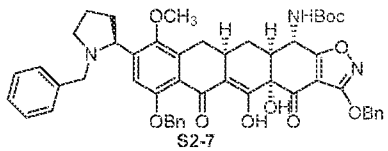
S2-9-4

S2-9-4: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.31-7.42 (m, 5 H), 7.02 (s, 1 H), 4.21-4.36 (m, 2 H), 3.89 (s, 1 H), 3.65 (s, 3 H), 3.56-3.62 (m, 1 H), 3.42-3.50 (m, 1 H), 3.18-3.22 (m, 1 H), 2.89-2.97 (m, 1 H), 2.55-2.65 (m, 2 H), 2.21-2.49 (m, 6 H), 1.55-1.65 (m, 1 H); MS (ESI) *m/z* 576.3 (M+H).



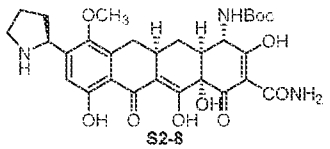
S2-9-5

Compound **S2-9-5** was prepared from **S2-2-5** and **S2-3** by using the General Procedure E. The resulting product was treated with 0.5 *N* HCl in THF (83 μL of 6 *N* aq HCl was added to 917 μL of THF) at rt for 45 min. Then saturated $NaHCO_3$ was added slowly and extracted with EtOAc. The organic solution was then washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was methylated with HCHO by using General procedure **B-1**, followed by General Procedure **A**, **C**, **D-1** to provide compound **S2-9-5**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.10 (s, 1 H), 3.90 (s, 1 H), 3.78-3.85 (m, 1 H), 3.68 (s, 3 H), 3.32-3.38 (m, 1 H), 3.21-3.28 (m, 1 H), 2.90-3.00 (m, 1 H), 2.79 (s, 3 H), 2.55-2.68 (m, 2 H), 2.21-2.41 (m, 6 H), 1.55-1.65 (m, 1 H); MS (ESI) *m/z* 500.2 (M+H).



S2-7

Compound **S2-7** was made from **S2-4-3** (3.47 g, 3.92 mmol) by using General Procedure **A** and **C**, followed by Boc protection of C-4 amino group. Thus **S2-6** (R=Bn) reacted with Boc_2O (655 mg, 3.0 mmol) and TEA (0.6 mL) in DCM (30 mL) at rt for 4 h. The reaction mixture was concentrated and purified by flash column chromatography (50 g silica gel, 0-60% EtOAc/Hexane) to give the desired product **S2-7** as a yellow oil (1.14 g, 33% over 4 steps).



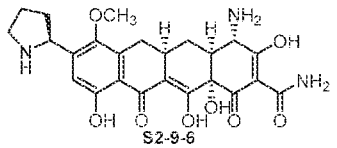
S2-8

Compound **2-7** (1.14 g, 1.34 mmol) was dissolved in a mixture of 1 *N* aq HCl (1.34 mL, 1 eq), THF (6 mL) and CH_3OH (6 mL). Pd-C (10wt%, 110 mg) was added in one portion. The reaction vessel was sealed and purged with hydrogen by briefly evacuating the flask followed by flushing with hydrogen gas (1 atm). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt for two overnights. The reaction was filtered through a small Celite pad. The cake was washed with CH_3OH. The filtrate was concentrated. The residue was re-slurried from MTBE to give product **S2-8** as a yellow solid, which was used for the following reductive alkylation reactions without further purification: MS (ESI) *m/z* 586.2 (M+H).

General Procedure **F** (reductive alkylation): To the solution of pyrrolidine **S2-8** (1 eq) in CH_3OH (1 mL) at 0 °C, aldehyde/ketone (4 eq), HOAc (4 eq) and $NaBH(OAc)_3$ (4 eq) were added. The resulting reaction mixture was stirred at 0 °C for 1 h or longer which monitored by LC-MS.

General Procedure **G** (deprotection of Boc): After the completeness of reductive amination, concentrated HCl (0.5 mL) was added. The resulted mixture was stirred at room temperature for 0.5 h. The organic solvents were removed under reduced pressure and preparative HPLC afforded the desired products as yellow solids.

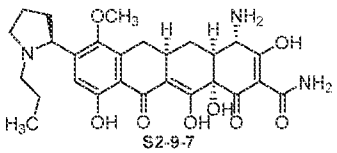
NOTE: The ketones and 4-pyridinecarboxaldehyde required much longer time for reductive amination.



S2-9-6

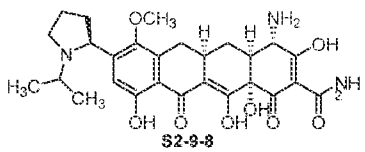
Compound **S2-9-6** was prepared from compound **S2-8** by using General Procedure **G**: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 6.96 (s, 1 H), 3.91 (s, 1 H), 3.71 (s, 3 H), 3.40-3.47 (m, 1 H), 3.30-3.35 (m, 1 H), 3.20-3.25 (m, 1 H), 2.88-2.95 (m, 1 H), 2.63-2.67 (m, 1 H), 2.39-2.50 (m, 2 H), 2.15-2.30 (m, 5 H), 1.58-1.65 (m, 1 H); MS (ESI) *m/z* 486.2 (M+H).

The following compounds were prepared from compound **S2-8** by using General Procedure **F** and **G**.



S2-9-7

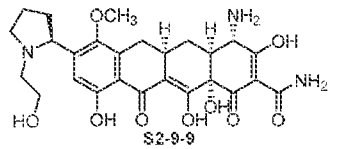
S2-9-7: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.09 (s, 1 H), 3.89 (s, 1 H), 3.78-3.88 (m, 1 H), 3.67 (s, 3 H), 3.34-3.38 (m, 1 H), 3.22-3.28 (m, 1 H), 2.94-3.05 (m, 4 H), 2.55-2.65 (m, 2 H), 2.21-2.49 (m, 5 H), 1.55-1.82 (m, 3 H), 0.88-0.94 (t, J = 8.0 Hz, 3 H); MS (ESI) *m/z* 528.2 (M+H).



S2-9-8

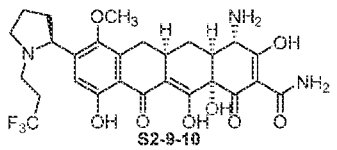
S2-9-8: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.19 (s, 1 H), 3.90 (s, 1 H), 3.68 (s, 3 H), 3.39-3.48 (m, 2 H), 3.27-3.11 (m, 4 H), 2.89-2.96 (m, 1 H), 2.55-2.71 (m, 2

H), 2.37-2.45 (m, 1 H), 2.21-2.31 (m, 3 H), 1.55-1.65 (m, 1 H), 1.28 (t, J = 6.0 Hz, 6 H); MS (ESI) *m/z* 528.3 (M+H).



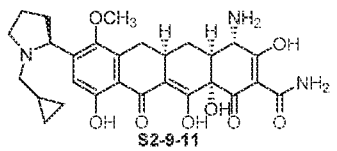
S2-9-9

S2-9-9: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.13 (s, 1 H), 3.92-3.97 (m, 1 H), 3.90 (s, 1 H), 3.72-3.80 (m, 3 H), 3.70 (s, 3 H), 3.37-3.41 (m, 1 H), 3.15-3.20 (m, 3 H), 2.90-3.00 (m, 1 H), 2.55-2.70 (m, 2 H), 2.20-2.41 (m, 5 H), 1.57-1.67 (m, 1 H); MS (ESI) *m/z* 530.2 (M+H).



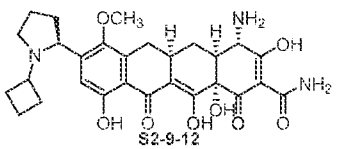
S2-9-10

S2-9-10: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 3.85-3.91 (m, 2 H), 3.68 (s, 3 H), 3.38-3.48 (m, 4 H), 2.90-3.00 (m, 1 H), 2.73-2.81 (m, 1 H), 2.68-2.78 (m, 3 H), 2.23-2.41 (m, 5 H), 1.58-1.65 (m, 1 H), 1.26-1.31 (m, 1 H); MS (ESI) *m/z* 582.3 (M+H).



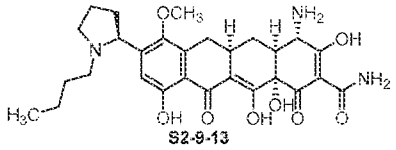
S2-9-11

S2-9-11: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.15 (s, 1 H), 3.91-4.00 (m, 1 H), 3.90 (s, 1 H), 3.69 (s, 3 H), 3.40-3.50 (m, 1 H), 3.20-3.41 (m, 4 H), 2.93-3.04 (m, 1 H), 2.56-2.71 (m, 2 H), 2.19-2.51 (m, 5 H), 1.54-1.65 (m, 1 H), 0.98-1.07 (m, 1 H), 0.58-0.77 (m, 2 H), 0.32-0.40 (m, 1 H), 0.20-0.27 (m, 1 H); MS (ESI) *m/z* 540.3 (M+H).



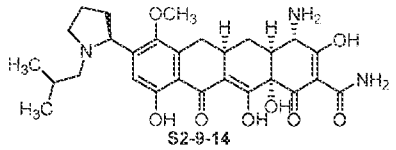
S2-9-12

S2-9-12: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.17 (s, 1 H), 3.83-3.91 (m, 2 H), 3.70-3.75 (m, 2 H), 3.68 (s, 3 H), 3.20-3.24 (m, 1 H), 2.88-2.95 (m, 1 H), 2.53-2.78 (m, 2 H), 2.21-2.42 (m, 8 H), 1.84-2.93 (m, 1 H), 1.58-1.80 (m, 4 H); MS (ESI) *m/z* 540.3 (M+H).



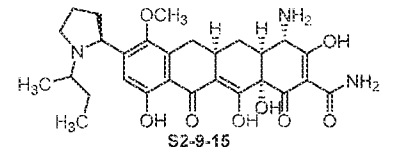
S2-9-13

S2-9-13: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.13 (s, 1 H), 3.92 (s, 1 H), 3.82-3.89 (m, 1 H), 3.70 (s, 3 H), 3.50-3.57 (m, 1 H), 3.03-3.12 (m, 2 H), 2.91-3.00 (m, 1 H), 2.55-2.71 (m, 3 H), 2.21-2.45 (m, 5 H), 1.55-1.71 (m, 3 H), 1.25-1.37 (m, 3 H), 0.88-0.93 (m, 3 H); MS (ESI) *m/z* 542.3 (M+H).



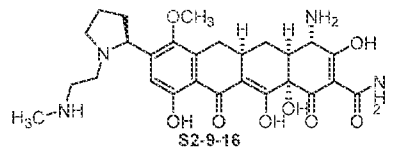
S2-9-14

S2-9-14: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.17 (s, 1 H), 3.88-3.95 (m, 2 H), 3.68 (s, 3 H), 3.45-3.51 (m, 1 H), 3.23-3.30 (m, 4 H), 2.82-3.05 (m, 3 H), 2.55-2.70 (m, 2 H), 2.23-2.45 (m, 3 H), 1.93-2.00 (m, 1 H), 1.57-1.63 (m, 1 H), 0.89-0.95 (m, 6 H); MS (ESI) *m/z* 542.3 (M+H).



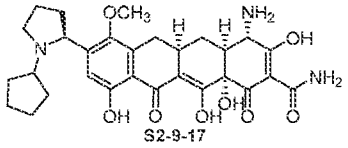
S2-9-15

S2-9-15: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt, two isomers) δ 7.11+7.13 (s, 1 H), 3.89 (s, 1 H), 3.68 (s, 3 H), 3.40-3.48 (m, 1 H), 3.10-3.18 (m, 1 H), 2.90-3.00 (m, 1 H), 2.52-2.63 (m, 2 H), 2.38-2.48 (m, 1 H), 2.20-2.31 (m, 5 H), 1.80-1.90 (m, 1 H), 1.56-1.62 (m, 2 H), 1.25-1.30 (m, 5 H), 0.88-0.93 (m, 3 H); MS (ESI) *m/z* 583.3 (M+H).



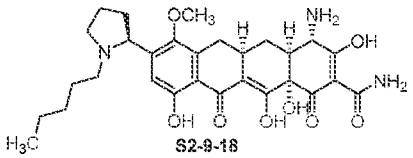
S2-9-16

S2-9-16: ^{1}H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 7.30 (s, 1 H), 3.95-4.03 (m, 1 H), 3.90 (s, 1 H), 3.70 (s, 3 H), 3.39-3.51 (m, 5 H), 3.21-3.25 (m, 1 H), 2.94-3.02 (m, 1 H), 2.58-2.69 (m, 5 H), 2.31-2.43 (m, 5 H), 2.20-2.27 (m, 1 H), 1.55-1.65 (m, 1 H); MS (ESI) *m/z* 543.3 (M+H).



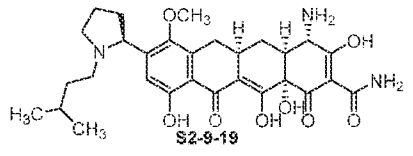
S2-9-17

S2-9-17: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.17 (s, 1 H), 3.92 (s, 1 H), 3.75-3.81 (m, 1 H), 3.68 (s, 3 H), 3.41-3.50 (m, 1 H), 2.90-3.00 (m, 1 H), 2.58-2.70 (m, 2 H), 2.20-2.42 (m, 6 H), 2.07-2.14 (m, 1 H), 1.50-1.90 (m, 8 H), 1.27-1.40 (m, 2 H); MS (ESI) *m/z* 554.3 (M+H).



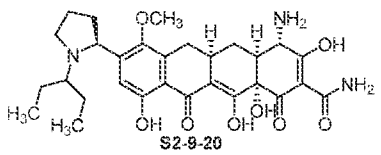
S2-9-18

S2-9-18: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.12 (s, 1 H), 3.85-3.91 (m, 2 H), 3.72-3.75 (m, 2 H), 3.69 (s, 3 H), 3.39-3.43 (m, 5 H), 2.75-3.00 (m, 3 H), 2.58-2.69 (m, 4 H), 2.21-2.45 (m, 6 H), 1.58-1.67 (m, 2 H), 1.27-1.31 (m, 1 H); MS (ESI) *m/z* 556.3 (M+H).



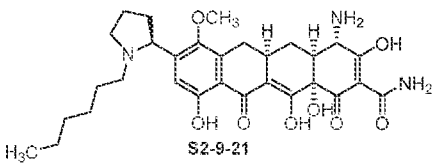
S2-9-19

S2-9-19: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.14 (s, 1 H), 3.91 (s, 1 H), 3.81-3.88 (m, 1 H), 3.69 (s, 3 H), 3.25-3.50 (m, 3 H), 3.05-3.15 (m, 2 H), 2.90-3.00 (m, 1 H), 2.55-2.70 (m, 2 H), 2.22-2.58 (m, 5 H), 1.47-1.70 (m, 4 H), 0.87 (t, J = 6.0 Hz, 6 H); MS (ESI) *m/z* 556.3 (M+H).



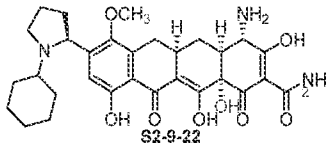
S2-9-20

S2-9-20: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.13 (s, 1 H), 3.78 (s, 1 H), 3.69 (s, 3 H), 3.41-3.50 (m, 2 H), 2.80-2.92 (m, 3 H), 2.50-2.61 (m, 3 H), 2.18-2.33 (m, 5 H), 1.61-1.88 (m, 4 H), 1.27-1.31 (m, 1 H), 0.85-0.97 (m, 6 H); MS (ESI) *m/z* 556.3 (M+H).



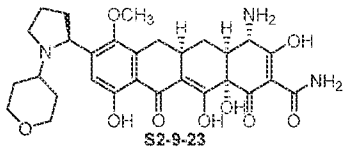
S2-9-21

S2-9-21: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 3.91 (s, 1 H), 3.82-3.90 (m, 1 H), 3.68 (s, 3 H), 3.02-3.10 (m, 2 H), 2.90-3.00 (m, 1 H), 2.55-2.70 (m, 2 H), 2.21-2.45 (m, 6 H), 1.55-1.70 (m, 4 H), 1.18-1.31 (m, 7 H), 0.83-0.91 (m, 3 H); MS (ESI) *m/z* 570.4 (M+H).



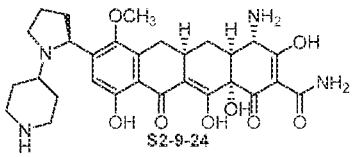
S2-9-22

S2-9-22: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 3.89 (s, 1 H), 3.68 (s, 3 H), 3.45-3.51 (m, 1 H), 3.07-3.12 (m, 1 H), 2.90-3.00 (m, 1 H), 2.55-2.67 (m, 2 H), 2.38-2.43 (m, 1 H), 2.20-2.31 (m, 5 H), 2.05-2.11 (m, 1 H), 1.88-2.00 (m, 3 H), 1.59-1.67 (m, 3 H), 1.11-1.42 (m, 6 H); MS (ESI) *m/z* 568.3 (M+H).



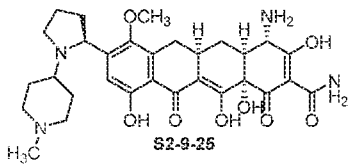
S2-9-23

S2-9-23: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.18 (s, 1 H), 3.88-4.01 (m, 2 H), 3.70-3.75 (m, 2 H), 3.68 (s, 3 H), 3.40-3.51 (m, 2 H), 3.30-3.38 (m, 2 H), 2.90-3.00 (m, 1 H), 2.59-2.70 (m, 2 H), 2.20-2.42 (m, 6 H), 1.96-2.02 (m, 1 H), 1.85-1.92 (m, 1 H), 1.58-1.78 (m, 4 H); MS (ESI) *m/z* 570.3 (M+H).



S2-9-24

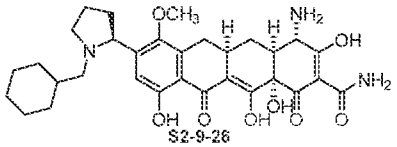
S2-9-24: ^{1}H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 7.25 (s, 1 H), 3.91 (s, 1 H), 3.73-3.81 (m, 1 H), 3.68 (s, 3 H), 3.45-3.61 (m, 5 H), 2.98-3.11 (m, 3 H), 2.69-2.70 (m, 2 H), 2.21-2.42 (m, 8 H), 1.83-2.05 (m, 2 H), 1.57-1.65 (m, 1 H); MS (ESI) *m/z* 569.3 (M+H).



S2-9-25

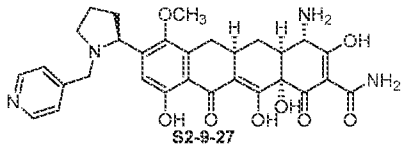
S2-9-25: ^{1}H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 7.20 (s, 1 H), 3.89 (s, 1 H), 3.72-3.80 (m, 1 H), 3.70 (s, 3 H), 3.53-3.61 (m, 5 H), 3.05-3.18 (m, 3 H), 2.83 (s, 3 H),

2.60-2.70 (m, 2 H), 2.23-2.41 (m, 8 H), 1.93-2.15 (m, 2 H), 1.58-1.63 (m, 1 H); MS (ESI) *m/z* 583.3 (M+H).



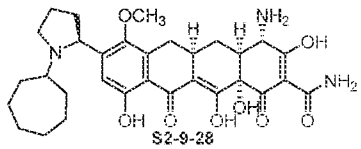
S2-9-26

S2-9-26: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.16 (s, 1 H), 3.91 (s, 1 H), 3.69 (s, 3 H), 3.21-3.51 (m, 5 H), 2.88-3.06 (m, 3 H), 2.52-2.72 (m, 2 H), 2.21-2.45 (m, 5 H), 1.77-1.85 (m, 1 H), 1.50-1.72 (m, 5 H), 1.05-1.30 (m, 3 H), 0.78-0.96 (m, 2 H); MS (ESI) *m/z* 582.4 (M+H).



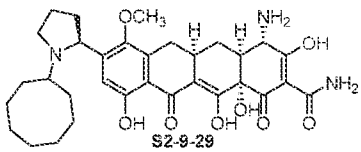
S2-9-27

S2-9-27: ^{1}H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 8.80-8.89 (m, 2 H), 8.12-8.20 (m, 2 H), 7.22 (s, 1 H), 4.58-4.63 (m, 2 H), 3.88-3.95 (m, 2 H), 3.65 (s, 3 H), 3.47-3.55 (m, 1 H), 3.21-3.30 (m, 1 H), 3.03-3.11 (m, 1 H), 2.85-2.95 (m, 1 H), 2.58-2.77 (m, 2 H), 2.25-2.41 (m, 5 H), 1.50-1.61 (m, 1 H); MS (ESI) *m/z* 577.3 (M+H).



S2-9-28

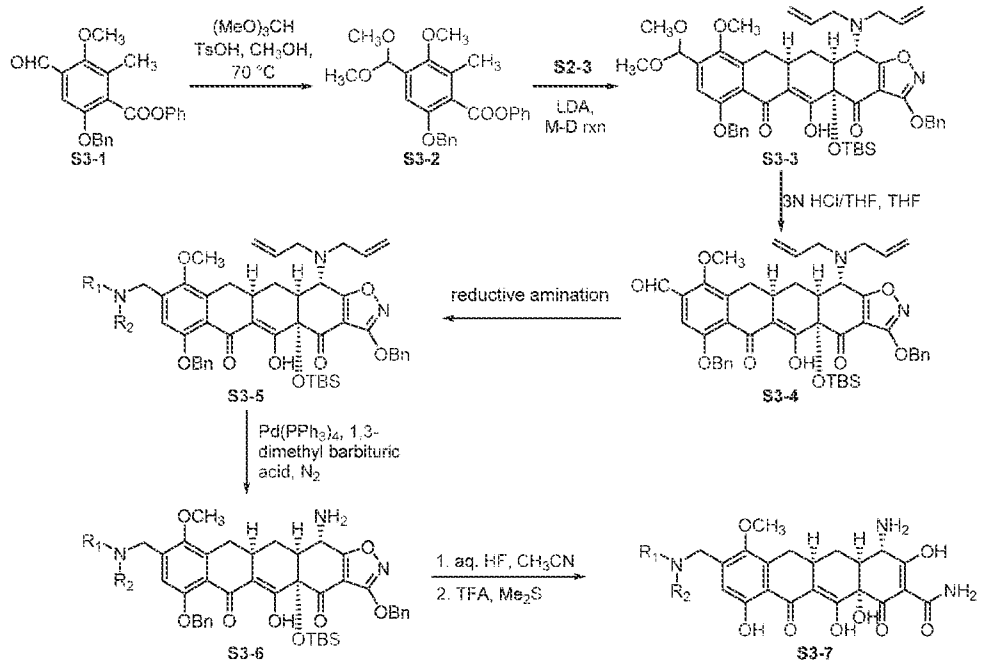
S2-9-28: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 3.90 (s, 1 H), 3.69 (s, 3 H), 3.39-3.45 (m, 2 H), 3.15-3.20 (m, 1 H), 2.93-3.00 (m, 1 H), 2.38-2.61 (m, 4 H), 2.20-2.31 (m, 5 H), 1.95-2.01 (m, 3 H), 1.60-1.80 (m, 5 H), 1.37-1.51 (m, 7 H); MS (ESI) *m/z* 582.3 (M+H).



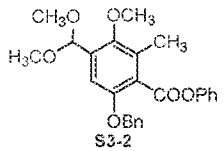
S2-9-29

S2-9-29: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.12 (s, 1 H), 3.73-3.78 (m, 1 H), 3.68 (s, 3 H), 2.78-2.83 (m, 2 H), 2.41-2.55 (m, 3 H), 2.25-2.31(m, 6 H), 2.11-2.18 (m, 1 H), 1.95-2.01 (m, 1 H), 1.70-1.80 (m, 4 H), 1.45-1.52 (m, 8 H), 1.25-1.30 (m, 3 H); MS (ESI) *m/z* 596.3 (M+H).

Scheme 3

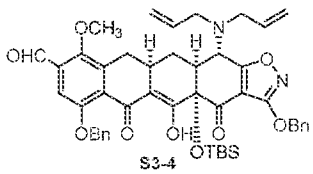


The following compounds were prepared per Scheme 3.

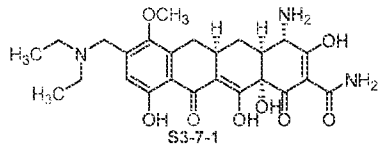


Compound **S3-1** (1.88 g, 5.0 mmol, 1 eq, prepared per literature procedures: *Org. Process Res. Dev.*, 2016, 20 (2), 284–296) was dissolved in CH_3OH (10 mL), trimethyl orthoformate (1.10 mL, 10.05 mmol, 2 eq) and *p*-toluenesulfonic acid monohydrate (29 mg, 0.152 mmol, 0.03 eq) were added. The reaction mixture was stirred at 70 °C for 24 h. Saturated $NaHCO_3$ and EtOAc were added. The organic phase was separated, concentrated by rotovap and purified by flash column chromatography to afford the desired product **S3-2** as a yellow oil (2.03 g, 96%):

^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.45 (m, 8 H), 7.05-7.11 (m, 3 H), 5.61 (s, 1 H), 5.15 (s, 2 H), 3.76 (s, 3 H), 3.36 (s, 6 H), 2.39 (s, 3H); MS (ESI) *m/z* 423.2 (M+H).

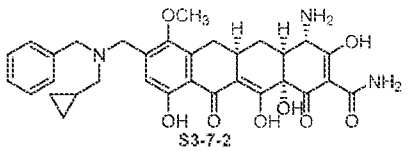


Compound **S3-4** was prepared from **S3-2** with enone **S2-3** by using General Procedure **E**, followed by acid treatment. The M-D product **S3-3** (1.30 g, 1.51 mmol, 1 eq) was dissolved in THF (20 mL). Then 3 *N* HCl/THF (4 mL) was added to make the final aqueous HCl concentration to 0.5 M. The reaction mixture was stirred at room temperature for 2 h. Saturated $NaHCO_3$ and EtOAc were added. The organic phase was concentrated by rotovap, and the residue was purified by flash column chromatography to afford the desired product **S3-4** as a yellow oil (1.15 g, 47% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.89 (s, 1 H), 10.35 (s, 1 H), 7.31-7.52 (m, 11 H), 5.78-5.85 (m, 2 H), 5.35 (s, 2 H), 5.08-5.25 (m, 5 H), 4.06-4.11 (m, 1 H), 3.86 (s, 3 H), 3.18-3.38 (m, 5 H), 2.41-2.63 (m, 4 H), 0.81 (s, 9 H), 0.25 (s, 3 H), 0.12 (s, 3 H); MS (ESI) *m/z* 817.3 (M+H).



S3-7-1

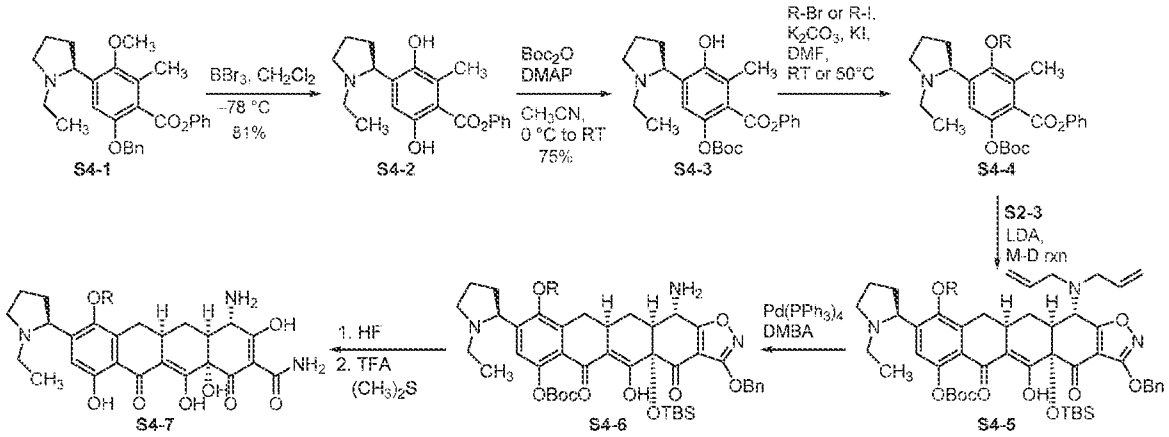
Compound **S3-7-1** was prepared from aldehyde **S3-4** and diethylamine by using General Procedure **B-1**, followed by General Procedures **A**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.01 (s, 1 H), 4.34 (d, *J* = 8.0, 1 H), 4.30 (d, *J* = 8.0, 1 H), 3.89 (s, 1H), 3.73 (s, 3 H), 3.13-3.27 (m, 5 H), 2.90-2.98 (m, 1 H), 2.62-2.67 (m, 1 H), 2.37-2.45 (m, 1 H), 2.20-2.28 (m, 1 H), 1.59-1.65 (m, 1 H), 1.30-1.42 (m, 6 H); MS (ESI) *m/z* 502.4 (M+H).



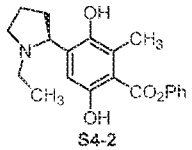
S3-7-2

Compound **S3-7-2** was prepared from aldehyde **S3-4** and benzylamine by using General Procedure **B-1**, followed by reacting with cyclopropanecarboxaldehyde using General Procedure **B-1** again and then **A**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, 2 hydrochloride salt, two rotamers) δ 7.40-7.60 (m, 5 H), 6.83+6.93 (s, 1 H), 4.48-4.68 (m, 2 H), 4.21-4.49 (m, 2 H), 3.88+3.53 (s, 3 H), 3.02-3.18 (m, 3 H), 2.88-2.97 (m, 1 H), 2.60-2.68 (m, 1 H), 2.19-2.38 (m, 2 H), 1.51-1.61 (m, 1 H), 1.18-1.27 (m, 1 H), 0.70-0.85 (m, 2 H), 0.38-0.45 (m, 2 H); MS (ESI) *m/z* 590.3 (M+H).

Scheme 4

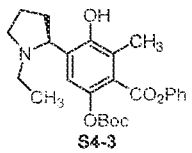


The following compounds were prepared per Scheme 4.



S4-2

Compound **S4-1** (504 mg, 1.13 mmol, 1eq, prepared per literature procedures: *Org. Process Res. Dev.*, 2016, 20 (2), 284–296) was dissolved in CH_2Cl_2 (3 mL) and cooled down to –78 °C under N_2, then BBr_3 solution (1.0 M in CH_2Cl_2, 3.4 mL, 3.4 mmol, 3 eq) was added dropwise during 5 min. The resulted yellow mixture was stirred at –78 °C for 4.5 h and carefully quenched by CH_3OH (2 mL). CH_2Cl_2 (40 mL) was added to the dark solution and washed with saturated $NaHCO_3$. The organic phase was concentrated by rotovap. The residue was purified by flash column chromatography (0→55% EtOAc/hexane) to afford the desired product **S4-2** as a yellow oil (312 mg, 81%): ^1H NMR (400 MHz, $CDCl_3$) δ 11.65 (br s, 1 H), 10.25 (br s, 1 H), 7.39-7.47 (m, 2 H), 7.15-7.30 (m, 3 H), 6.66 (s, 1 H), 3.39-3.55 (m, 2 H), 3.79-3.88 (m, 1 H), 2.58 (s, 3 H), 2.20-2.43 (m, 3 H), 1.90-2.11 (m, 3 H), 1.10-1.23 (m, 3 H); MS (ESI) *m/z* 342.2 (M+H).



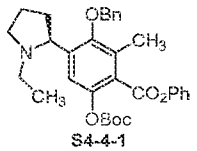
S4-3

Compound **S4-2** (141 mg, 0.413 mmol, 1 eq) and 4-dimethylaminopyridine (DMAP, 8 mg, 0.066 mmol, 0.16 eq) were dissolved in CH_3CN (1 mL) and the resulting solution was cooled down to 0 °C. A solution of di-*tert*-butyl dicarbonate (Boc_2O, 90 mg, 0.413 mmol, 1

eq) in CH_3CN (1.0 mL) was added slowly. The reaction mixture was warmed up to room temperature and the white precipitates appeared. After stirring overnight, CH_2Cl_2 (100 mL) was added and washed by saturated $NaHCO_3$. The organic phase was concentrated by rotovap and purified by flash column chromatography (0→50% EtOAc/hexane) to afford the desired product **S4-3** as a white solid (136 mg, 75%): ^1H NMR (400 MHz, $CDCl_3$) δ 11.62 (br s, 1 H), 7.38-7.45 (m, 2 H), 7.21-7.30 (m, 3 H), 6.75 (s, 1 H), 3.50-3.55 (m, 1 H), 3.37-3.42 (m, 1 H), 2.88-2.95 (m, 1 H), 2.35 (s, 3 H), 2.17-2.31 (m, 3 H), 1.86-2.00 (m, 3 H), 1.42 (s, 9 H), 1.08-1.14 (m, 3 H); MS (ESI) *m/z* 442.2 (M+H).

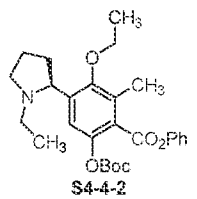
[NOTE: this product has low solubility in DCM, EtOAc and CH_3OH and should be able to be purified from simple recrystallization.]

General Procedure **H** (C7-OH alkylation): Phenol **S4-3** and K_2CO_3 were added into DMF, then R-Br/KI or R-I was added and the resulted mixture was stirred at room temperature or 50 °C for indicated hours. EtOAc was added and washed with brine solution. The organic phase was concentrated by rotovap. The residue was purified through flash column chromatography to afford the desired products **S4-4-1** to **S4-4-5** as colorless oils.



S4-4-1

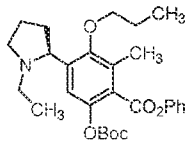
Phenol **S4-3** (125 mg, 0.283 mmol, 1 eq) was treated with K_2CO_3 (60 mg, 0.434 mmol, 1.5 eq), KI (5 mg, 0.030 mmol, 0.1 eq), and BnBr (0.031 mL, 0.286 mmol, 1 eq) in DMF (2 mL) at room temperature for 18 h to give product **S4-4-1** (111 mg, 74%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.51 (m, 11 H), 4.81 (s, 2 H), 3.65-3.71 (m, 1 H), 3.30-3.39 (m, 1 H), 2.59-2.65 (m, 1 H), 2.46 (s, 3 H), 2.05-2.21 (m, 2 H), 1.57-1.95 (m, 3 H), 1.42 (s, 9 H), 1.20-1.25 (m, 1 H), 1.00-1.09 (m, 3 H); MS (ESI) *m/z* 532.3 (M+H).



S4-4-2

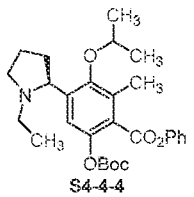
Phenol **S4-3** (88 mg, 0.199 mmol, 1 eq) was treated with K_2CO_3 (41 mg, 0.297 mmol, 1.5 eq), KI (3 mg, 0.018 mmol, 0.1 eq), and C_2H_5Br (0.030 mL, 0.402 mmol, 2 eq) in DMF

(2 mL) 50 °C for 23 h to give product **S4-4-2** (81 mg, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.43 (m, 2 H), 7.20-7.30 (m, 4 H), 4.06-4.12 (m, 1 H), 3.75-3.82 (m, 2 H), 3.57-3.65 (m, 1 H), 3.31-3.38 (m, 1 H), 2.55-2.62 (m, 1 H), 2.40 (s, 3 H), 2.15-2.25 (m, 2 H), 1.78-1.85 (m, 2 H), 1.53-1.62 (m, 2 H), 1.41 (s, 9 H), 1.20-1.25 (m, 2 H), 0.97-1.05 (m, 3 H); MS (ESI) *m/z* 470.3 (M+H).



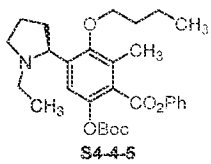
S4-4-3

Phenol **S4-3** (89 mg, 0.202 mmol, 1 eq) was treated with K_2CO_3 (41 mg, 0.297 mmol, 1.5 eq), and *n*-C_3H_7I (0.039 mL, 0.401 mmol) in DMF (2 mL) at 50 °C for 24 h to give product **S4-4-3** (98 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.45 (m, 2 H), 7.21-7.28 (m, 4 H), 4.05-4.11 (m, 1 H), 3.70-3.81 (m, 2 H), 3.30-3.37 (m, 1 H), 2.56-2.63 (m, 1 H), 2.40 (s, 3 H), 2.15-2.22 (m, 2 H), 1.78-1.85 (m, 2 H), 1.55-1.66 (m, 2 H), 1.41 (s, 9 H), 1.20-1.27 (m, 2 H), 1.00-1.15 (m, 6 H); MS (ESI) *m/z* 484.3 (M+H).



S4-4-4

Phenol **S4-3** (220mg, 0.499 mmol, 1 eq) was treated with K_2CO_3 (104 mg, 0.753 mmol, 1.5 eq), KI (9 mg, 0.054 mmol, 0.1 eq), and $(CH_3)_2CHBr$ (0.470 mL, 5.00 mmol, 10 eq) in DMF at 50 °C for 40 h to give product **S4-4-4** (133 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.45 (m, 2 H), 7.21-7.28 (m, 4 H), 4.07-4.16 (m, 2 H), 3.65-3.71 (m, 1 H), 3.30-3.40 (m, 1 H), 2.52-2.61 (m, 1 H), 2.40 (s, 3 H), 2.15-2.26 (m, 2 H), 1.78-1.95 (m, 2 H), 1.50-1.60 (m, 2 H), 1.42 (s, 9 H), 1.20-1.35 (m, 5 H), 0.98-1.05 (m, 3 H); MS (ESI) *m/z* 484.3 (M+H).

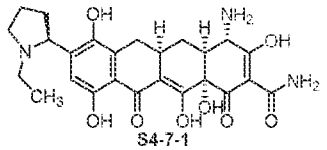


S4-4-5

Phenol **S4-3** (89 mg, 0.202 mmol, 1 eq) was treated with K_2CO_3 (41 mg, 0.297 mmol, 1.5 eq), KI (3 mg, 0.018 mmol, 0.1 eq), and *n*-C_4H_9Br (0.193 mL, 1.79 mmol, 9 eq) in DMF (2 mL) at 50 °C for 53 h to give product **S4-4-5** (75 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ

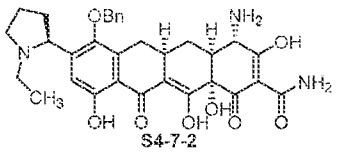
7.21-7.43 (m, 6 H), 4.08-4.13 (m, 2 H), 3.69-3.75 (m, 2 H), 3.30-3.36 (m, 1 H), 2.56-2.63 (m, 1 H), 2.40 (s, 3 H), 2.15-2.22 (m, 2 H), 1.75-1.82 (m, 2 H), 1.50-1.55 (m, 2 H), 1.43 (s, 9 H), 1.20-1.27 (m, 3 H), 0.97-1.05 (m, 6 H); MS (ESI) *m/z* 498.3 (M+H).

The following compounds were prepared from the corresponding left-hand sides **S4-4** and enone **S2-3** by using the General Procedures **E**, **A**, **C** and **D-1**.



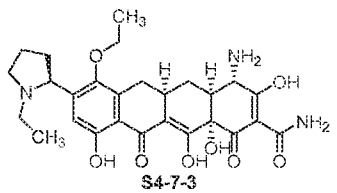
S4-7-1

Compound **S4-7-1** was isolated as a side product along with **S4-7-2** in the final step when using **S4-4-1** as the left-hand side: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.47-7.51 (m, 1 H), 6.91 (s, 1 H), 4.69-4.76 (m, 1 H), 3.82-3.90 (m, 2 H), 3.11-3.20 (m, 3 H), 2.90-2.98 (m, 1 H), 2.62-2.67 (m, 1 H), 2.45-2.52 (m, 1 H), 2.20-2.30 (m, 5 H), 1.55-1.62 (m, 1 H), 1.25 (t, J = 5.6 Hz, 3 H); MS (ESI) *m/z* 500.3 (M+H).



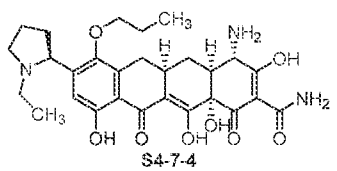
S4-7-2

S4-7-2: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.32-7.40 (m, 5 H), 6.98 (s, 1 H), 4.68-4.72 (m, 2 H), 4.47-4.51 (m, 1 H), 3.89 (s, 1 H), 3.67-3.72 (m, 1 H), 2.92-3.11 (m, 4 H), 2.61-2.67 (m, 1 H), 2.45-2.52 (m, 1 H), 2.00-2.25 (m, 5 H), 1.75-1.81 (m, 1 H), 1.55-1.62 (m, 1 H), 1.28 (t, J = 5.6 Hz, 3 H); MS (ESI) *m/z* 590.3 (M+H).



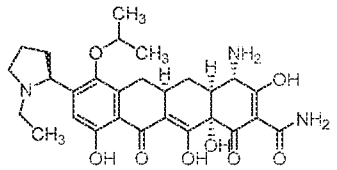
S4-7-3

S4-7-3: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.09 (s, 1 H), 3.89 (s, 1 H), 3.78-3.88 (m, 2 H), 3.68-3.75 (m, 1 H), 3.32-3.40 (m, 2 H), 3.05-3.22 (m, 3 H), 2.90-2.98 (m, 1 H), 2.53-2.62 (m, 2 H), 2.21-2.40 (m, 5 H), 1.55-1.64 (m, 1 H), 1.39 (t, J = 5.6 Hz, 3 H); 1.25 (t, J = 5.6 Hz, 3 H); MS (ESI) *m/z* 528.2 (M+H).



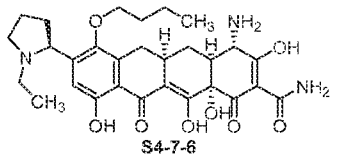
S4-7-4

S4-7-4: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.09 (s, 1 H), 3.89 (s, 1 H), 3.79-3.85 (m, 1 H), 3.69-3.75 (m, 1 H), 3.57-3.63 (m, 1 H), 3.32-3.40 (m, 2 H), 3.06-3.22 (m, 3 H), 2.89-2.96 (m, 1 H), 2.55-2.62 (m, 2 H), 2.21-2.40 (m, 6 H), 1.79-1.86 (m, 1 H), 1.55-1.64 (m, 1 H), 1.23 (t, J = 5.6 Hz, 3 H); 1.05 (t, J = 5.6 Hz, 3 H); MS (ESI) *m/z* 542.3 (M+H).



S4-7-5

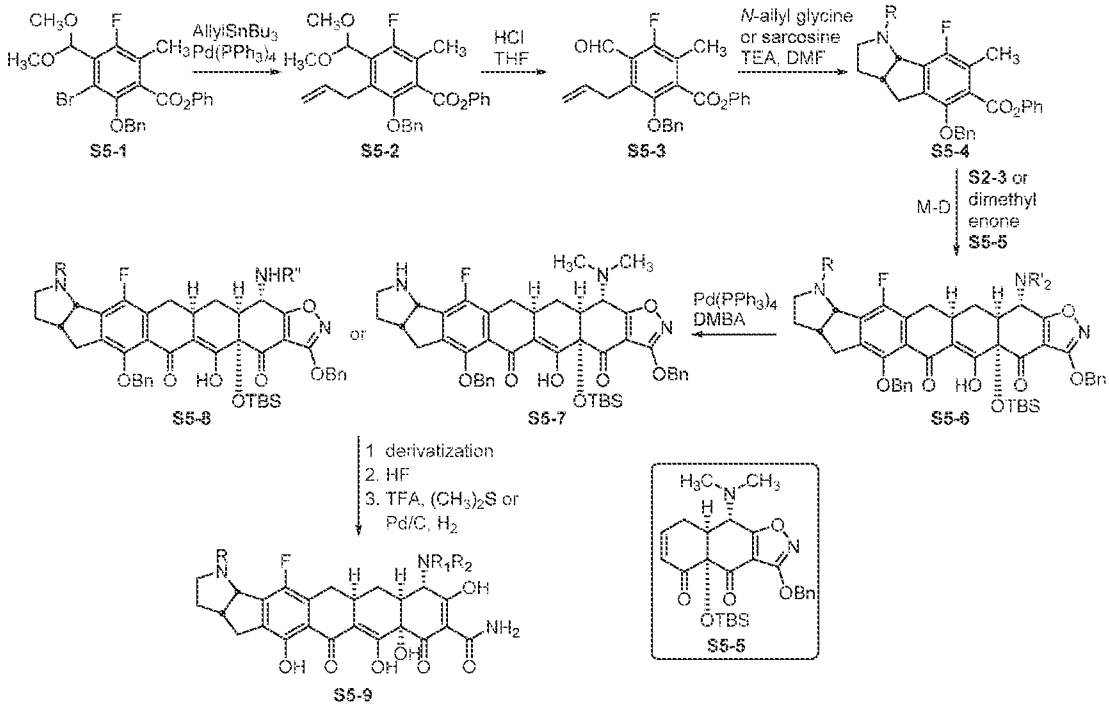
S4-7-5: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.11 (s, 1 H), 3.99-4.06 (m, 1 H), 3.89 (s, 1 H), 3.75-3.82 (m, 1 H), 3.32-3.40 (m, 2 H), 3.02-3.21 (m, 3 H), 2.88-2.94 (m, 1 H), 2.53-2.67 (m, 2 H), 2.20-2.38 (m, 6 H), 1.55-1.65 (m, 1 H), 1.36 (d, J = 7.6 Hz, 3 H), 1.21 (t, J = 6.0 Hz, 3 H); 1.12 (d, J = 7.6 Hz, 3 H); MS (ESI) *m/z* 542.3 (M+H).



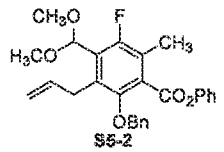
S4-7-6

S4-7-6: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.09 (s, 1 H), 3.89 (s, 1 H), 3.73-3.86 (m, 2 H), 3.59-3.65 (m, 1 H), 3.32-3.40 (m, 2 H), 3.06-3.25 (m, 3 H), 2.89-2.96 (m, 1 H), 2.55-2.67 (m, 2 H), 2.21-2.38 (m, 5 H), 1.75-1.83 (m, 2 H), 1.48-1.60 (m, 3 H), 1.24 (t, J = 5.6 Hz, 3 H); 0.98 (t, J = 5.6 Hz, 3 H); MS (ESI) *m/z* 556.3 (M+H).

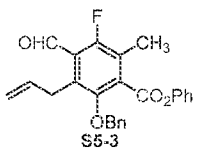
Scheme 5



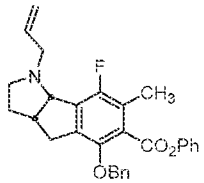
The following compounds were prepared per Scheme 5.



To a solution of compound **S5-1** (1.71 g, 3.50 mmol, 1 eq, prepared per literature procedures: *J. Med. Chem.*, 2013, *56*, 8112–8138) and $Pd(PPh_3)_4$ (404 mg, 0.35 mmol, 0.1 eq) in toluene (15 mL) was added allyltributyltin (1.29 mL, 4.2 mmol, 1.2 eq) under nitrogen. The resulting reaction mixture was refluxed in a preheated oil bath with a cold water condenser on the top. The reaction turned into a clear solution upon heating. The reaction was heated for 20 h and cooled down to rt. The reaction was concentrated by rotovap. The residue was purified by flash column chromatography (50 g silica gel, 1→10% EtOAc/hexane) to afford the desired product **S5-2** (1.55 g, 97%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 7 H), 7.26-7.24 (m, 1 H), 7.05-7.03 (m, 2 H), 6.06-6.00 (m, 1 H), 5.53 (d, J = 3.0 Hz, 1 H), 5.06-4.98 (m, 4 H), 3.71-3.67 (m, 2 H), 3.44 (d, J = 3.0 Hz, 6 H), 2.35 (s, 3 H); MS (ESI) *m/z* 499.29 (M–H).

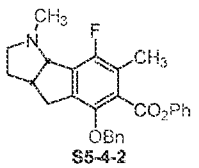


Compound **S5-2** (1.55 g, 3.4 mmol, 1 eq) was dissolved in a premixed solution of THF (9.17 mL) and 6 *N* aq HCl (0.83 mL). The resulting reaction solution was stirred at room temperature for 1 h. Saturated $NaHCO_3$ and EtOAc were added. The organic phase was separated and concentrated by rotovap. The residue was purified by flash column chromatography (50 g silica gel, 1→10% EtOAc/hexane) to afford the desired product **S5-3** as a white solid (1.24 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1 H), 7.41-7.34 (m, 7 H), 7.27-7.24 (m, 1 H), 7.05-7.03 (m, 2 H), 6.05-5.96 (m, 1 H), 5.06-5.03 (m, 1 H), 4.98 (s, 2 H), 4.98-4.91 (m, 1 H), 3.87-3.86 (m, 2 H), 2.40 (d, J = 2.4 Hz, 3 H); MS (ESI) *m/z* 403.27 (M−H).



S5-4-1

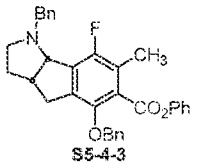
To a mixture of compound **S5-3** (702 mg, 1.74 mmol, 1 eq) and *N*-allylglycine·HCl (439 mg, 2.89 mmol, 1.7 eq) was added DMF (8 mL) under nitrogen, followed by TEA (408 μL, 2.89 mmol, 1.7 eq). The resulting reaction mixture was stirred at 80 °C for 1 h 45 min, and cooled to rt. The resulting reaction mixture was then partitioned between EtOAc and water. The organic phase was separated, washed with brine, and concentrated under reduced pressure. Flash chromatography on silica gel using 10%→40% EtOAc/hexanes yielded the desired product **S5-4-1** as a white solid (650 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 7 H), 7.26-7.22 (m, 1 H), 7.07-7.04 (m, 2 H), 6.01-5.97 (m, 1 H), 5.26-5.14 (m, 2 H), 5.01 (s, 2 H), 4.30 (br s, 1 H), 3.79 (br s, 1 H), 3.21-3.09 (m, 4 H), 2.87 (br d, J = 15.9 Hz, 1 H), 2.52 (br s, 1 H), 2.35 (s, 3 H), 2.13 (br s, 1 H), 1.66 (br s, 1 H); MS (ESI) *m/z* 458.30 (M+H).



S5-4-2

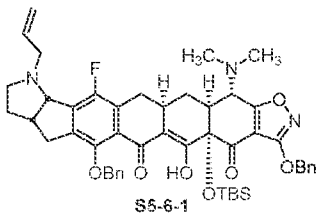
To a mixture of compound **S5-3** (290 mg, 0.72 mmol, 1 eq) and sarcosine (76 mg, 0.86 mmol, 1.2 eq) was added DMF (3 mL) under nitrogen. The resulting reaction mixture was stirred at 80 °C for 2 h 30 min, and cooled to rt. The resulting reaction mixture was then partitioned between EtOAc and water. The organic phase was separated, washed with brine, and concentrated under reduced pressure. Flash chromatography on silica gel using

10%→100% EtOAc/hexanes yielded the desired product **S5-4-2** as a white solid (250 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 7 H), 7.26-7.22 (m, 1 H), 7.06-7.04 (m, 2 H), 5.04, 5.00 (ABq, J = 11.0 Hz, 2 H), 4.09 (br s, 1 H), 3.24-3.12 (m, 3 H), 2.88 (br d, J = 12.8 Hz, 1 H), 2.64 (s, 3 H), 2.56 (br s, 1 H), 2.35 (d, J = 1.8 Hz, 3 H), 2.21-2.12 (m, 1 H), 1.76-1.69 (m, 1 H); MS (ESI) *m/z* 432.24 (M+H).



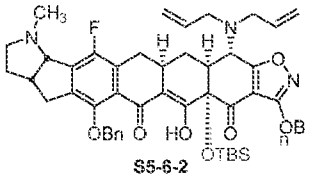
S5-4-3

To a mixture of compound **S5-3** (575 mg, 1.42 mmol, 1 eq) and *N*-benzylglycine·HCl (344 mg, 1.71 mmol, 1.2 eq) was added DMF (6 mL) under nitrogen, followed by TEA (302 µL, 2.13 mmol, 1.5 eq). The resulting reaction mixture was stirred at 80 °C for 2 h 30 min, and cooled to rt. The resulting reaction mixture was then partitioned between EtOAc and water. The organic phase was separated, washed with brine, and concentrated under reduced pressure. Flash chromatography on silica gel using 1%→20% EtOAc/hexanes yielded the desired product **S5-4-3** as a white solid (600 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.30 (m, 12 H), 7.26-7.22 (m, 1 H), 7.08-7.05 (m, 2 H), 5.03 (s, 2 H), 4.39 (br s, 2 H), 3.63-3.61 (m, 1 H), 3.16-3.12 (m, 2 H), 2.89-2.86 (m, 2 H), 2.44-2.42 (m, 1 H), 2.38 (d, J = 1.8 Hz, 3 H), 2.08 (br s, 1 H), 1.60-1.56 (m, 1 H); MS (ESI) *m/z* 508.27 (M+H).



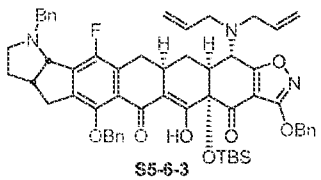
S5-6-1

Compound **S5-6-1** was prepared from **S5-4-1** (650 mg, 1.42 mmol, 1 eq) and C-4 dimethylamino enone **S5-5** (690 mg, 1.42 mmol, 1 eq) by using General Procedure E. Product **S5-6-1** (957 mg, a mixture of diastereomers, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.08 (s, 0.5 H), 16.05 (s, 0.5 H), 7.50-7.48 (m, 2 H), 7.41-7.30 (m, 8 H), 6.02-5.94 (m, 1 H), 5.36 (s, 2 H), 5.22 (br d, J = 16.5 Hz, 1 H), 5.14 (br d, J = 9.2 Hz, 1 H), 4.93-4.85 (m, 2 H), 4.33-4.26 (m, 1 H), 3.98-3.94 (m, 1 H), 3.84-3.76 (m, 1 H), 3.26-3.22 (m, 2 H), 3.06-2.92 (m 4 H), 2.80-2.65 (m, 1 H), 2.56-2.41 (m, 9 H), 2.14-2.10 (m, 2 H), 1.70-1.49 (m, 1 H), 0.82 (s, 4.5 H), 0.81 (s, 4.5 H), 0.27 (s, 3 H), 0.12 (s, 3 H); MS (ESI) *m/z* 846.62 (M+H).



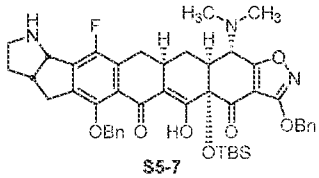
S5-6-2

Compound **S5-6-2** was prepared from **S5-4-2** (250 mg, 0.58 mmol, 1 eq) and C-4 diallylamino enone **S2-3** (310 mg, 0.58 mmol, 1 eq) by using General Procedure **E**. Product **S5-6-2** (421 mg, a mixture of diastereomers, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.84 (br s, 1 H), 7.41-7.39 (m, 2 H), 7.29-7.23 (m, 8 H), 5.75-5.65 (m, 1 H), 5.26 (s, 2 H), 5.13-5.09 (m, 2 H), 5.02-5.00 (m, 2 H), 4.82-4.68 (m, 2 H), 3.97-3.95 (m, 1 H), 3.24-2.88 (m, 10 H), 2.55-2.34 (m, 7 H), 2.09-2.01 (m, 2 H), 0.71 (s, 4.5 H), 0.69 (s, 4.5 H), 0.16 (s, 1.5 H), 0.15 (s, 1.5 H), 0.00 (s, 3 H); MS (ESI) *m/z* 872.56 (M+H).



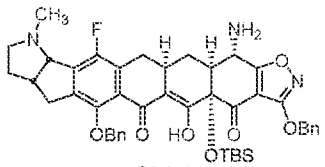
S5-6-3

Compound **S5-6-3** was prepared from **S5-4-3** (600 mg, 1.18 mmol, 1 eq) and C-4 diallylamino enone **S2-3** (631 mg, 1.18 mmol, 1 eq) by using General Procedure **E**. Diastereomer B (**S5-6-3B**, 405 mg, 36%) of product **S5-6-3** was isolated by flash column chromatography. But diastereomer A (**S5-6-3A**, 570 mg, 51%) was mixed with a small amount of diastereomer. **S5-6-3A**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.03 (s, 1 H), 7.53-7.51 (m, 2 H), 7.51-7.31 (m, 12 H), 7.28-7.24 (m, 1 H), 5.88-5.78 (m, 2 H), 5.39 (s, 2 H), 5.24 (d, J = 17.1 Hz, 2 H), 5.14 (d, J = 9.8 Hz, 2 H), 4.89-4.82 (m, 2 H), 4.46-4.40 (m, 2 H), 4.11 (d, J = 10.4 Hz, 1 H), 3.67 (d, J = 12.8 Hz, 1 H), 3.36-3.33 (m, 2 H), 3.27-3.21 (m, 3 H), 3.10-3.02 (m, 3 H), 2.85-2.83 (m, 1 H), 2.72-2.43 (m, 4 H), 2.16 (d, J = 14.0 Hz, 1 H), 2.05-2.02 (m, 1 H), 1.58-1.45 (m, 2 H), 0.85 (s, 9 H), 0.28 (s, 3 H), 0.14 (s, 3 H). **S5-6-3B**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.03 (s, 1 H), 7.53-7.51 (m, 2 H), 7.43-7.30 (m, 12 H), 7.26-7.24 (m, 1 H), 5.88-5.78 (m, 2 H), 5.39 (s, 2 H), 5.24 (d, J = 17.1 Hz, 2 H), 5.17 (d, J = 9.8 Hz, 2 H), 4.91, 4.87 (ABq, J = 11.0 Hz, 2 H), 4.13 (d, J = 9.8 Hz, 1 H), 3.68 (br d, J = 12.2 Hz, 1 H), 3.39-3.19 (m, 5 H), 3.02-2.78 (m, 4 H), 2.67-2.63 (m, 1 H), 2.58-2.54 (m, 1 H), 2.51-2.43 (m, 2 H), 2.17 (br d, J = 14.6 Hz, 1 H), 2.10-2.05 (m, 1 H), 1.58-1.55 (m, 2 H), 0.83 (s, 9 H), 0.28 (s, 3 H), 0.13 (s, 3 H); MS (ESI) *m/z* 948.56 (M+H).

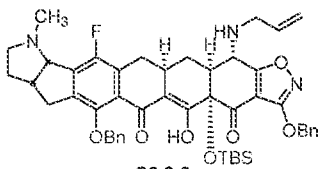


S5-7

Compound **S5-7** was prepared from **S5-6-1** (205 mg, 0.24 mmol, 1 eq) by using General Procedure **A** (168 mg, a mixture of diastereomers, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.61 (m, 1 H), 7.53-7.44 (m, 3 H), 7.38-7.32 (m, 6 H), 5.36 (s, 2 H), 4.98-4.82 (m, 3 H), 3.95 (d, J = 10.4 Hz, 1 H), 3.25-3.22 (m, 1 H), 3.14-3.00 (m, 4 H), 2.77-2.65 (m, 2 H), 2.56-2.37 (m, 9 H), 2.13 (br d, J = 14.6 Hz, 1 H), 1.98-1.95 (m, 1 H), 1.56-1.44 (m, 1 H), 0.82 (s, 4.5 H), 0.81 (s, 4.5 H), 0.27 (s, 3 H), 0.12 (s, 3 H); MS (ESI) *m/z* 806.55 (M+H).

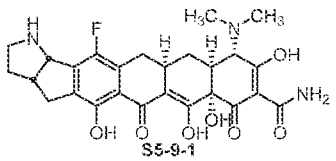


S5-8-1



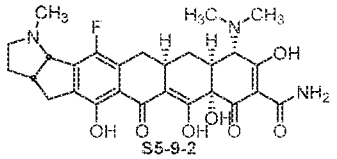
S5-8-2

Compounds **S5-8-1** and **S5-8-2** were prepared from **S5-6-2** (377 mg, 0.43 mmol, 1 eq) by using General Procedure **A**. **S5-8-1** (198 mg, a mixture of diastereomers, 58%): MS (ESI) *m/z* 792.46 (M+H). **S5-8-2** (58 mg, a mixture of diastereomers, 16%): MS (ESI) *m/z* 832.49 (M+H).



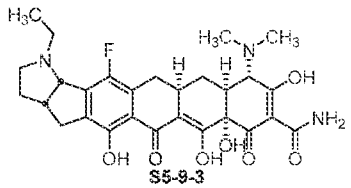
S5-9-1

Compound **S5-9-1** was prepared from **S5-7** (42 mg, 0.052 mmol, 1 eq) by using General Procedures **C** and **D-1**. The two diastereomers of **S5-9-1** were separated by preparative reverse phase HPLC. **S5-9-1A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.36 (d, J = 8.8 Hz, 1 H), 4.11 (s, 1 H), 3.50-3.45 (m, 1 H), 3.36-3.33 (m, 2 H), 3.27-3.18 (m, 2 H), 3.12-2.89 (m, 9 H), 2.50-2.42 (m, 1 H), 2.34-2.22 (m, 2 H), 1.86-1.77 (m, 1 H), 1.68-1.58 (m, 1 H). **S5-9-1B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.36 (d, J = 8.8 Hz, 1 H), 4.11 (s, 1 H), 3.51-3.43 (m, 1 H), 3.37-3.33 (m, 2 H), 3.27-3.17 (m, 2 H), 3.12-2.87 (m, 9 H), 2.50-2.42 (m, 1 H), 2.34-2.22 (m, 2 H), 1.86-1.77 (m, 1 H), 1.68-1.58 (m, 1 H); MS (ESI) *m/z* 514.32 (M+H).



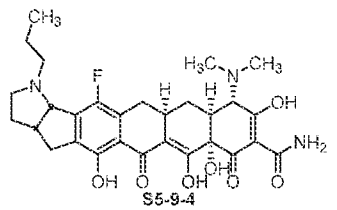
S5-9-2

Compound **S5-9-2** was prepared from **S5-7** (21 mg, 0.026 mmol, 1 eq) and HCHO by using General Procedures **B-1**, **C** and **D-1**. The two diastereomers of **S5-9-2** were separated by preparative reverse phase HPLC. **S5-9-2A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.22 (d, J = 8.8 Hz, 1 H), 4.11 (s, 1 H), 3.72-3.68 (m, 1 H), 3.61-3.57 (m, 1 H), 3.36-3.30 (m, 1 H), 3.24-3.18 (m, 5 H), 3.13-3.05 (m, 4 H), 3.00-2.92 (m, 5 H), 2.60-2.56 (m, 1 H), 2.37-2.24 (m, 2 H), 1.85-1.75 (m, 1 H), 1.69-1.60 (m, 1 H). **S5-9-2B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.21 (d, J = 8.4 Hz, 1 H), 4.11 (s, 1 H), 3.72-3.68 (m, 1 H), 3.61-3.57 (m, 1 H), 3.35-3.30 (m, 1 H), 3.26-3.20 (m, 5 H), 3.13-3.05 (m, 4 H), 3.01-2.89 (m, 5 H), 2.62-2.55 (m, 1 H), 2.36-2.23 (m, 2 H), 1.85-1.79 (m, 1 H), 1.69-1.59 (m, 1 H); MS (ESI) *m/z* 528.27 (M+H).



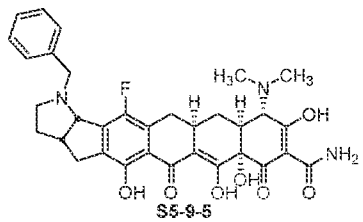
S5-9-3

Compound **S5-9-3** was prepared from **S5-7** (42 mg, 0.052 mmol, 1 eq) and CH_3CHO by using General Procedures **B-1**, **C** and **D-1**. The two diastereomers of **S5-9-3** were separated by preparative reverse phase HPLC. **S5-9-3A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.29 (d, J = 8.8 Hz, 1 H), 4.13 (s, 1 H), 3.86-3.77 (m, 1 H), 3.74-3.69 (m, 1 H), 3.58-3.53 (m, 1 H), 3.42-3.37 (m, 1 H), 3.28-2.92 (m, 12 H), 2.60-2.52 (m, 1 H), 2.36-2.25 (m, 2 H), 1.85-1.75 (m, 1 H), 1.69-1.59 (m, 1 H), 1.42 (t, J = 7.2 Hz, 3 H). **S5-9-3B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.27 (d, J = 8.8 Hz, 1 H), 4.12 (s, 1 H), 3.85-3.78 (m, 1 H), 3.75-3.70 (m, 1 H), 3.57-3.54 (m, 1 H), 3.42-3.37 (m, 1 H), 3.28-3.19 (m, 2 H), 3.14-2.90 (m, 10 H), 2.60-2.52 (m, 1 H), 2.34-2.25 (m, 2 H), 1.86-1.76 (m, 1 H), 1.68-1.59 (m, 1 H), 1.44 (t, J = 7.6 Hz, 3 H); MS (ESI) *m/z* 542.37 (M+H).



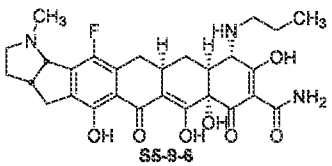
S5-9-4

Compound **S5-9-4** was prepared from **S5-6-1** (46 mg, 0.054 mmol, 1 eq) by using General Procedures **C** and **D-2**. The two diastereomers of **S5-9-4** were separated by preparative reverse phase HPLC. **S5-9-4A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.30 (d, J = 8.4 Hz, 1 H), 4.13 (s, 1 H), 3.74-3.62 (m, 2 H), 3.57-3.53 (m, 1 H), 3.39-3.29 (m, 1 H), 3.24-3.17 (m, 2 H), 3.12-2.92 (m, 10 H), 2.60-2.53 (m, 1 H), 2.36-2.25 (m, 2 H), 1.88-1.76 (m, 3 H), 1.69-1.59 (m, 1 H), 1.06 (t, J = 7.2 Hz, 3 H). **S5-9-4B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.28 (d, J = 8.4 Hz, 1 H), 4.11 (s, 1 H), 3.74-3.61 (m, 2 H), 3.56-3.53 (m, 1 H), 3.34-3.29 (m, 1 H), 3.27-3.18 (m, 2 H), 3.12-2.92 (m, 10 H), 2.59-2.53 (m, 1 H), 2.32-2.25 (m, 2 H), 1.88-1.76 (m, 3 H), 1.67-1.57 (m, 1 H), 1.06 (t, J = 7.6 Hz, 3 H); MS (ESI) m/z 556.33 (M+H).

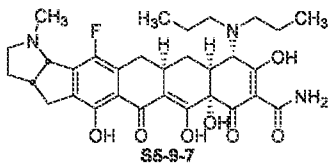


S5-9-5

Compound **S5-9-5** was prepared from **S5-7** (42 mg, 0.052 mmol, 1 eq) and PhCHO by using General Procedures **B-1**, **C** and **D-1**. The two diastereomers of **S5-9-5** were separated by preparative reverse phase HPLC. **S5-9-5A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.56-7.53 (m, 2 H), 7.50-7.49 (m, 3 H), 5.44 (d, J = 8.8 Hz, 1 H), 4.94 (d, J = 13.2 Hz, 1 H), 4.48 (d, J = 13.2 Hz, 1 H), 4.10 (s, 1 H), 3.61-3.57 (m, 1 H), 3.44-3.42 (m, 1 H), 3.34-3.30 (m, 2 H), 3.28-2.91 (m, 10 H), 2.58-2.52 (m, 1 H), 2.40-2.23 (m, 2 H), 1.76-1.64 (m, 2 H). **S5-9-5B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.58-7.56 (m, 2 H), 7.51-7.49 (m, 3 H), 5.43 (d, J = 8.8 Hz, 1 H), 4.94 (d, J = 13.2 Hz, 1 H), 4.51 (d, J = 13.2 Hz, 1 H), 4.13 (s, 1 H), 3.62-3.58 (m, 1 H), 3.47-3.41 (m, 1 H), 3.34-3.20 (m, 3 H), 3.15-2.91 (m, 9 H), 2.58-2.52 (m, 1 H), 2.37-2.26 (m, 2 H), 1.78-1.64 (m, 2 H); MS (ESI) m/z 604.41 (M+H).



S5-9-6

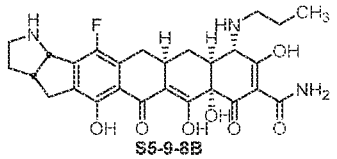


S5-9-7

Compounds **S5-9-6** and **S5-9-7** were prepared from **S5-6-2** (44 mg, 0.050 mmol, 1 eq) by using General Procedures **C** and **D-2**. The two diastereomers of **S5-9-6** were separated by preparative reverse phase HPLC, while **S5-9-7** was isolated as a mixture of diastereomers. **S5-9-6A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.21 (d, J = 9.2 Hz, 1 H), 3.88 (s,

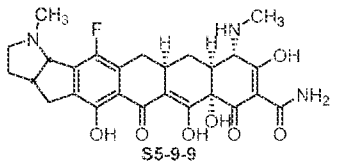
1 H), 3.70-3.66 (m, 1 H), 3.60-3.57 (m, 1 H), 3.34-3.29 (m, 2 H), 3.26-3.16 (m, 6 H), 3.04-2.98 (m, 1 H), 2.94-2.85 (m, 2 H), 2.61-2.54 (m, 1 H), 2.35-2.22 (m, 2 H), 1.83-1.72 (m, 3 H), 1.61-1.51 (m, 1 H), 1.02 (t, J = 7.1 Hz, 3 H). **S5-9-6B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.21 (d, J = 8.7 Hz, 1 H), 3.89 (s, 1 H), 3.72-3.68 (m, 1 H), 3.61-3.57 (m, 1 H), 3.55-3.29 (m, 2 H), 3.26-3.19 (m, 6 H), 3.06-2.98 (m, 1 H), 2.93-2.87 (m, 2 H), 2.61-2.55 (m, 1 H), 2.34-2.22 (m, 2 H), 1.85-1.73 (m, 3 H), 1.61-1.52 (m, 1 H), 1.03 (t, J = 7.3 Hz, 3 H); MS (ESI) m/z 542.30 (M+H).

S5-9-7: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt, a mixture of diastereomers) δ 5.23-5.20 (m, 1 H), 4.23 (s, 1 H), 3.73-3.68 (m, 1 H), 3.61-3.57 (m, 1 H), 3.51-3.47 (m, 1 H), 3.38-3.33 (m, 2 H), 3.26-3.20 (m, 7 H), 3.10-3.04 (m, 1 H), 2.99-2.89 (m, 3 H), 2.36-2.22 (m, 2 H), 1.86-1.76 (m, 5 H), 1.69-1.59 (m, 1 H), 1.05-0.98 (m, 6 H); MS (ESI) m/z 584.3 (M+H).



S5-9-8B

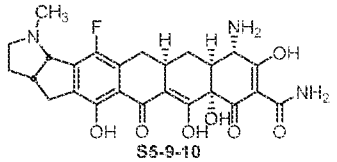
Compounds **S5-9-8B** was prepared from **S5-6-3B** (20 mg, 0.021 mmol, 1 eq) by using General Procedures **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.34 (d, J = 8.8 Hz, 1 H), 3.88 (s, 1 H), 3.48-3.43 (m, 1 H), 3.35-3.32 (m, 3 H), 3.26-3.16 (m, 3 H), 3.05-2.96 (m, 1 H), 2.93-2.85 (m, 2 H), 2.49-2.41 (m, 1 H), 2.32-2.21 (m, 2 H), 1.85-1.72 (m, 3 H), 1.60-1.51 (m, 1 H), 1.02 (t, J = 7.2 Hz, 3 H); MS (ESI) m/z 528.29 (M+H).



S5-9-9

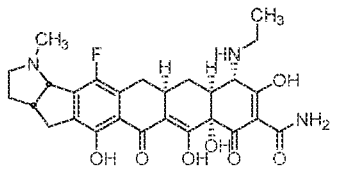
Compound **S5-9-9** was prepared from **S5-8-2** (58 mg, 0.07 mmol, 1 eq) and HCHO by using General Procedures **B-1** and **A**. Half of the material was processed per General Procedures **C** and **D-1** to give product **S5-9-9**. The two diastereomers of **S5-9-9** were separated by preparative reverse phase HPLC. **S5-9-9A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.21 (d, J = 8.8 Hz, 1 H), 3.82 (s, 1 H), 3.71-3.67 (m, 1 H), 3.63-3.56 (m, 1 H), 3.35-3.31 (m, 1 H), 3.23-3.16 (m, 5 H), 3.06-2.91 (m, 5 H), 2.83-2.80 (m, 1 H), 2.61-2.55 (m, 1 H), 2.35-2.28 (m, 1 H), 2.25-2.21 (m, 1 H), 1.84-1.74 (m, 1 H), 1.62-1.52 (m, 1 H). **S5-9-9B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.20 (d, J = 8.8 Hz, 1 H), 3.81 (s, 1 H), 3.72-

3.68 (m, 1 H), 3.61-3.56 (m, 1 H), 3.35-3.30 (m, 1 H), 3.26-3.18 (m, 5 H), 3.06-2.97 (m, 1 H), 2.95-2.89 (m, 4 H), 2.83-2.76 (m, 1 H), 2.62-2.55 (m, 1 H), 2.36-2.28 (m, 1 H), 2.25-2.20 (m, 1 H), 1.85-1.75 (m, 1 H), 1.63-1.53 (m, 1 H); MS (ESI) *m/z* 514.27 (M+H).



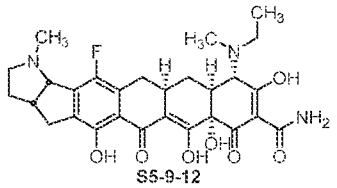
S5-9-10

Compound **S5-9-10** was prepared from **S5-8-1** (30 mg, 0.38 mmol, 1 eq) by using General Procedures **C** and **D-1** to give product **S5-9-10**. The two diastereomers of **S5-9-10** were separated by preparative reverse phase HPLC. **S5-9-10A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.22 (d, J = 8.8 Hz, 1 H), 3.89 (s, 1 H), 3.72-3.67 (m, 1 H), 3.62-3.57 (m, 1 H), 3.35-3.28 (m, 1 H), 3.23-3.17 (m, 5 H), 3.04-2.91 (m, 2 H), 2.72-2.65 (m, 1 H), 2.62-2.55 (m, 1 H), 2.37-2.30 (m, 1 H), 2.28-2.23 (m, 1 H), 1.84-1.77 (m, 1 H), 1.64-1.54 (m, 1 H). **S5-9-10B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.21 (d, J = 9.2 Hz, 1 H), 3.90 (s, 1 H), 3.72-3.68 (m, 1 H), 3.62-3.57 (m, 1 H), 3.35-3.29 (m, 1 H), 3.25-3.19 (m, 5 H), 3.04-2.96 (m, 1 H), 2.93-2.87 (m, 1 H), 2.69-2.65 (m, 1 H), 2.62-2.55 (m, 1 H), 2.36-2.23 (m, 2 H), 1.86-1.76 (m, 1 H), 1.64-1.54 (m, 1 H); MS (ESI) *m/z* 500.26 (M+H).



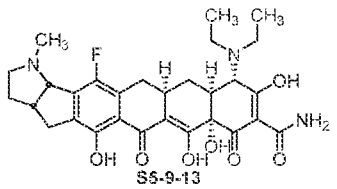
S5-9-11

Compound **S5-9-11** was prepared from **S5-8-1** and CH_3CHO by using General Procedures **B-1**, **C** and **D-1** to give product **S5-9-11**. The two diastereomers of **S5-9-11** were separated by preparative reverse phase HPLC. **S5-9-11A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.22 (d, J = 8.4 Hz, 1 H), 3.88 (s, 1 H), 3.71-3.68 (m, 1 H), 3.62-3.57 (m, 1 H), 3.46-3.39 (m, 1 H), 3.38-3.28 (m, 2 H), 3.23-3.17 (m, 5 H), 3.05-2.99 (m, 1 H), 2.96-2.91 (m, 1 H), 2.87-2.83 (m, 1 H), 2.62-2.55 (m, 1 H), 2.36-2.23 (m, 2 H), 1.84-1.74 (m, 1 H), 1.62-1.52 (m, 1 H), 1.36 (t, J = 7.2 Hz, 3 H). **S5-9-11B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.21 (d, J = 8.4 Hz, 1 H), 3.88 (s, 1 H), 3.72-3.68 (m, 1 H), 3.64-3.55 (m, 1 H), 3.48-3.41 (m, 1 H), 3.38-3.28 (m, 2 H), 3.26-3.18 (m, 5 H), 3.07-2.99 (m, 1 H), 2.96-2.84 (m, 2 H), 2.62-2.55 (m, 1 H), 2.36-2.22 (m, 2 H), 1.84-1.74 (m, 1 H), 1.66-1.52 (m, 1 H), 1.36 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 528.23 (M+H).



S5-9-12

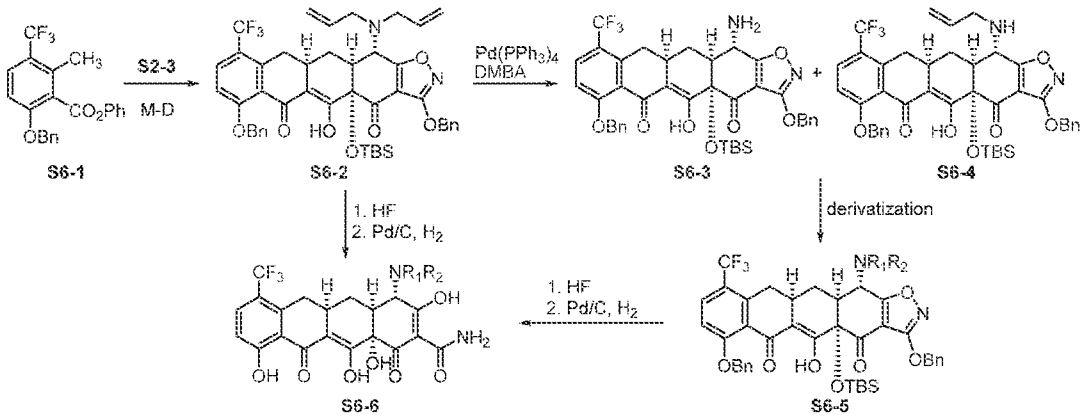
Compound **S5-9-12** was prepared from **S5-8-1** and CH_3CHO by using General Procedures **B-1**, and **B-1** again with HCHO followed by General Procedures **C** and **D-1** to give product **S5-9-12**. The two diastereomers of **S5-9-12** were separated by preparative reverse phase HPLC. **S5-9-12A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.22 (d, J = 8.8 Hz, 1 H), 4.23 (s, 0.5 H), 4.14 (s, 0.5 H), 3.71-3.67 (m, 1 H), 3.61-3.56 (m, 1 H), 3.50-3.46 (m, 1 H), 3.35-3.30 (m, 2 H), 3.24-3.17 (m, 5 H), 3.10-3.02 (m, 2.5 H), 2.95-2.91 (m, 3.5 H), 2.62-2.55 (m, 1 H), 2.36-2.22 (m, 2 H), 1.84-1.74 (m, 1 H), 1.67-1.58 (m, 1 H), 1.43-1.39 (m, 3 H). **S5-9-12B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.21 (d, J = 8.8 Hz, 1 H), 4.23 (s, 0.5 H), 4.14 (s, 0.5 H), 3.73-3.68 (m, 1 H), 3.62-3.57 (m, 1 H), 3.52-3.47 (m, 1 H), 3.38-3.30 (m, 2 H), 3.26-3.20 (m, 5 H), 3.09-2.88 (m, 6 H), 2.61-2.57 (m, 1 H), 2.36-2.22 (m, 2 H), 1.85-1.75 (m, 1 H), 1.67-1.58 (m, 1 H), 1.44-1.39 (m, 3 H); MS (ESI) *m/z* 542.30 (M+H).



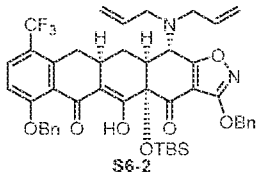
S5-9-13

Compound **S5-9-13** was prepared from **S5-8-1** and CH_3CHO by using General Procedures **B-1**, **C** and **D-1** to give product **S5-9-13**. The two diastereomers of **S5-9-13** were separated by preparative reverse phase HPLC. **S5-9-13A**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.22 (d, J = 9.2 Hz, 1 H), 4.25 (s, 1 H), 3.72-3.67 (m, 1 H), 3.62-3.54 (m, 2 H), 3.48-3.43 (m, 2 H), 3.35-3.28 (m, 2 H), 3.25-3.17 (m, 5 H), 3.09-3.02 (m, 1 H), 2.94-2.90 (m, 1 H), 2.62-2.54 (m, 1 H), 2.36-2.26 (m, 2 H), 1.84-1.75 (m, 1 H), 1.69-1.59 (m, 1 H), 1.41 (t, J = 7.2 Hz, 6 H). **S5-9-13B**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 5.21 (d, J = 9.2 Hz, 1 H), 4.25 (s, 1 H), 3.73-3.68 (m, 1 H), 3.63-3.55 (m, 2 H), 3.50-3.42 (m, 2 H), 3.36-3.28 (m, 2 H), 3.25-3.19 (m, 5 H), 3.12-3.02 (m, 1 H), 2.95-2.89 (m, 1 H), 2.62-2.54 (m, 1 H), 2.34-2.23 (m, 2 H), 1.85-1.75 (m, 1 H), 1.68-1.59 (m, 1 H), 1.41 (t, J = 7.2 Hz, 6 H); MS (ESI) *m/z* 556.29 (M+H).

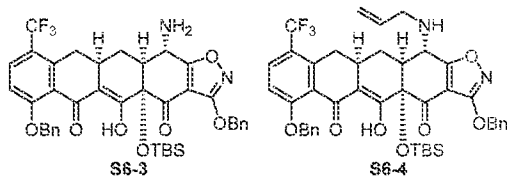
Scheme 6



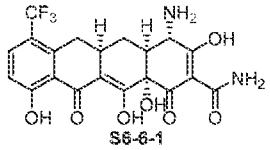
The following compounds were prepared per Scheme 6.



Compound **S6-2** was prepared from compound **S6-1** (prepared per literature procedures including *WO2011/025982 A2*) and diallylenone **S2-3** by using General Procedure **E**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.91 (s, 1 H), 7.65 (d, J = 9.2 Hz, 1 H), 7.51-7.44 (m, 4 H), 7.40-7.27 (m, 6 H), 6.93 (d, J = 9.2 Hz, 1 H), 5.85-5.75 (m, 2 H), 5.36 (s, 2 H), 5.30-5.19 (m, 4 H), 5.11 (d, J = 10.0 Hz, 2 H), 4.09 (d, J = 10.4 Hz, 1 H), 3.35-3.32 (m, 2 H), 3.22-3.12 (m, 3 H), 2.96-2.92 (m, 2 H), 2.52-2.45 (m, 2 H), 2.14-2.10 (m, 1 H), 0.82 (s, 9 H), 0.28 (s, 3 H), 0.14 (s, 3 H); MS (ESI) *m/z* 827.60 (M+H).

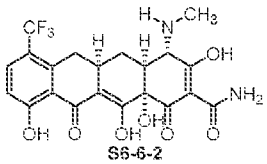


Compounds **S6-3** and **S6-4** were prepared from compound **S6-2** by using General Procedure **A**. **S6-3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.41 (s, 1 H), 7.64 (d, J = 9.2 Hz, 1 H), 7.52-7.46 (m, 4 H), 7.42-7.30 (m, 6 H), 6.95 (d, J = 9.2 Hz, 1 H), 5.45, 5.35 (ABq, J = 12.0 Hz, 2 H), 5.31, 5.24 (ABq, J = 12.8 Hz, 2 H), 4.00 (br s, 1 H), 3.07-3.03 (m, 1 H), 2.88-2.79 (m, 1 H), 2.69-2.66 (m, 1 H), 2.42 (t, J = 15.2 Hz, 1 H), 2.17-2.12 (m, 1 H), 1.47-1.38 (m, 1 H), 0.74 (s, 9 H), 0.23 (s, 3 H), 0.10 (s, 3 H); MS (ESI) *m/z* 747.50 (M+H). **S6-4**: MS (ESI) *m/z* 787.55 (M+H).

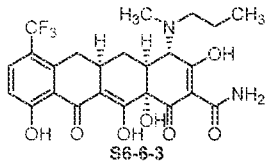


S6-6-1

Compound **S6-6-1** was prepared from compound **S6-3** by using General Procedures **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.75 (d, J = 9.2 Hz, 1 H), 6.95 (d, J = 9.2 Hz, 1 H), 3.90 (br s, 1 H), 3.22-3.17 (m, 1 H), 3.04-2.96 (m, 1 H), 2.63 (dt, J = 12.4, 2.0 Hz, 1 H), 2.54 (t, J = 14.8 Hz, 1 H), 2.22 (ddd, J = 13.2, 4.8, 2.0 Hz, 1 H), 1.63-1.54 (m, 1 H); MS (ESI) *m/z* 455.30 (M+H).

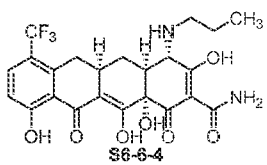


S6-6-2

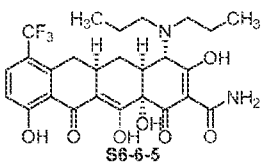


S6-6-3

Compounds **S6-6-2** and **S6-6-3** were prepared from compound **S6-4** with HCHO by using General Procedures **B-1**, **C** and **D-2**. **S6-6-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.75 (d, J = 9.2 Hz, 1 H), 6.94 (d, J = 9.2 Hz, 1 H), 3.83 (br s, 1 H), 3.19-3.15 (m, 1 H), 3.06-2.98 (m, 1 H), 2.91 (s, 3 H), 2.82-2.79 (m, 1 H), 2.51 (t, J = 14.8 Hz, 1 H), 2.20 (ddd, J = 13.2, 5.2, 2.4 Hz, 1 H), 1.60-1.51 (m, 1 H); MS (ESI) *m/z* 469.30 (M+H). **S6-6-3**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.77 (d, J = 9.2 Hz, 1 H), 6.95 (d, J = 9.2 Hz, 1 H), 4.22 (br s, 0.5 H), 4.14 (br s, 0.5 H), 3.40-3.29 (m, 1 H), 3.22-2.94 (m, 7 H), 2.53 (t, J = 14.8 Hz, 1 H), 2.26-2.19 (m, 1 H), 1.88-1.75 (m, 2 H), 1.70-1.59 (m, 1 H), 1.06-0.98 (m, 3 H); MS (ESI) *m/z* 511.36 (M+H).



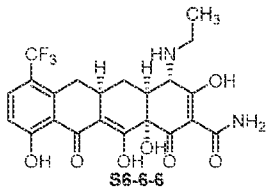
S6-6-4



S6-6-5

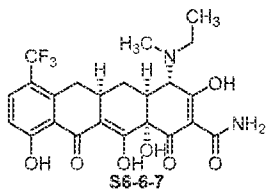
Compounds **S6-6-4** and **S6-6-5** were prepared from compound **S6-2** by using General Procedures **C** and **D-2**. **S6-6-4**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.75 (d, J = 9.2 Hz, 1 H), 6.93 (d, J = 9.2 Hz, 1 H), 3.90 (s, 1 H), 3.34-3.15 (m, 3 H), 3.06-2.97 (m, 1 H), 2.87 (d, J = 12.4 Hz, 1 H), 2.50 (t, J = 14.8 Hz, 1 H), 2.21 (ddd, J = 14.0, 5.2, 2.8 Hz, 1 H), 1.82-1.73 (m, 2 H), 1.60-1.50 (m, 1 H), 1.02 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 497.29 (M+H). **S6-6-5**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.77 (d, J = 9.2 Hz, 1 H), 6.96 (d, J = 9.2 Hz, 1 H), 4.24 (s, 1 H), 3.51-3.46 (m, 1 H), 3.41-3.26 (m, 2 H), 3.23-3.03 (m, 3 H),

2.95-2.92 (m, 1 H), 2.54 (t, *J* = 14.8 Hz, 1 H), 2.20 (ddd, *J* = 13.2, 4.4, 2.4 Hz, 1 H), 1.89-1.79 (m, 4 H), 1.68-1.59 (m, 1 H), 1.03 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H); MS (ESI) *m/z* 539.38 (M+H).



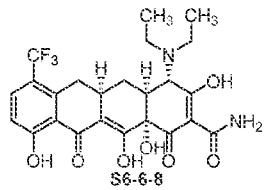
S6-6-6

Compound **S6-6-6** was prepared from compound **S6-3** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **C** and **D-2**: ^1H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.75 (d, *J* = 9.2 Hz, 1 H), 6.94 (d, *J* = 9.2 Hz, 1 H), 3.88 (s, 1 H), 3.47-3.39 (m, 1 H), 3.37-3.29 (m, 1 H), 3.19-3.15 (m, 1 H), 3.05-2.97 (m, 1 H), 2.84 (d, *J* = 12.4 Hz, 1 H), 2.51 (t, *J* = 14.8 Hz, 1 H), 2.21 (ddd, *J* = 13.6, 4.8, 2.4 Hz, 1 H), 1.60-1.51 (m, 1 H), 1.36 (t, *J* = 7.6 Hz, 3 H); MS (ESI) *m/z* 483.29 (M+H).



S6-6-7

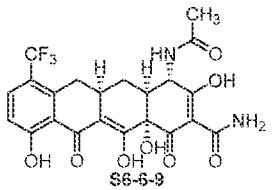
Compound **S6-6-7** was prepared from compound **S6-3** with CH_3CHO by using General Procedures **B-1** (at 0 °C), then **B-1** again with HCHO, **C** and **D-2**: ^1H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.76 (d, *J* = 9.2 Hz, 1 H), 6.95 (d, *J* = 9.2 Hz, 1 H), 4.25 (br s, 0.5 H), 4.16 (br s, 0.5 H), 3.52-3.43 (m, 1 H), 3.39-3.31 (m, 1 H), 3.22-3.18 (m, 5 H), 2.53 (t, *J* = 14.8 Hz, 1 H), 2.27-2.20 (m, 1 H), 1.70-1.58 (m, 1 H), 1.43-1.36 (m, 3 H); MS (ESI) *m/z* 497.32 (M+H).



S6-6-8

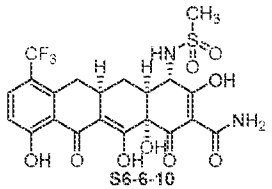
Compound **S6-6-8** was prepared from compound **S6-3** with CH_3CHO by using General Procedures **B-1**, **C** and **D-2**: ^1H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.76 (d, *J* = 9.2 Hz, 1 H), 6.95 (d, *J* = 9.2 Hz, 1 H), 4.27 (s, 1 H), 3.64-3.55 (m, 1 H), 3.46 (q, *J* = 7.6 Hz, 2 H), 3.36-3.29 (m, 1 H), 3.22-3.17 (m, 1 H), 3.11-3.03 (m, 1 H), 2.93-2.90 (m, 1 H), 2.53 (t, *J*

= 14.8 Hz, 1 H), 2.22 (ddd, *J* = 13.6, 5.2, 2.8 Hz, 1 H), 1.68-1.59 (m, 1 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H); MS (ESI) *m/z* 511.34 (M+H).



S6-6-9

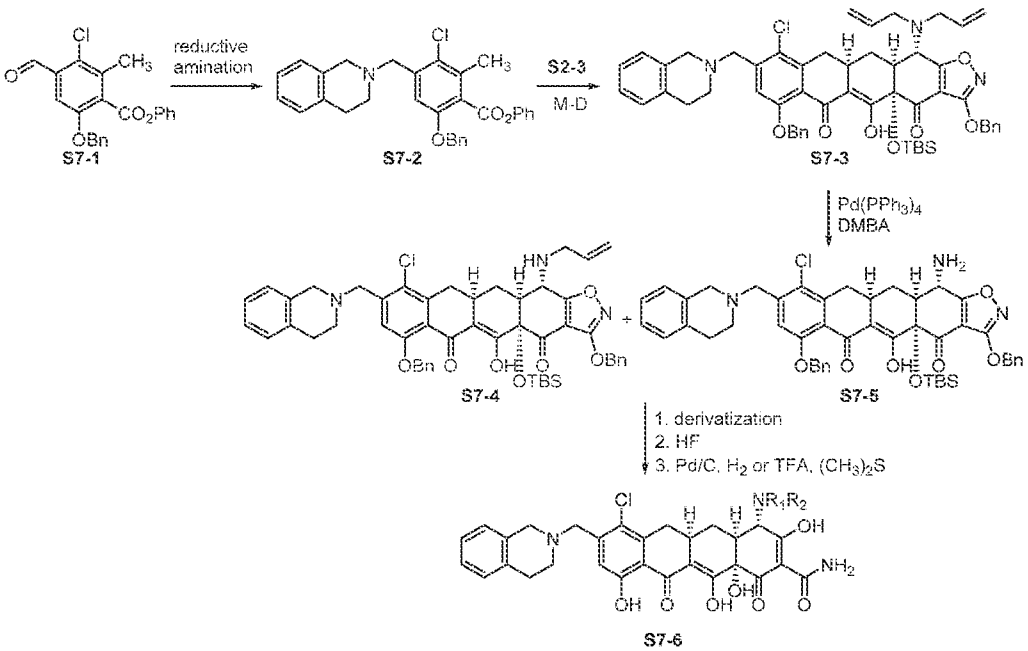
Compound **S6-6-9** was prepared from compound **S6-3** with Ac_2O by using General Procedures **B-2**, **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (d, *J* = 9.2 Hz, 1 H), 6.92 (d, *J* = 9.2 Hz, 1 H), 4.69 (d, *J* = 6.4 Hz, 1 H), 3.14-3.10 (m, 1 H), 3.04-2.96 (m, 1 H), 2.72 (t, *J* = 14.8 Hz, 1 H), 2.47-2.42 (m, 1 H), 2.39-2.33 (m, 1 H), 2.03 (s, 3 H), 1.62-1.55 (m, 1 H); MS (ESI) *m/z* 497.29 (M+H).



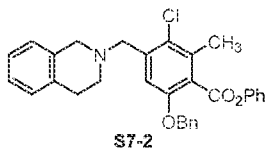
S6-6-10

Compound **S6-6-10** was prepared from compound **S6-3** with Ms_2O by using General Procedures **B-2**, **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (d, *J* = 9.2 Hz, 1 H), 6.91 (d, *J* = 9.2 Hz, 1 H), 4.10 (d, *J* = 4.4 Hz, 1 H), 3.19-3.14 (m, 1 H), 3.14 (s, 3 H), 3.04-2.96 (m, 1 H), 2.70 (t, *J* = 14.8 Hz, 1 H), 2.51 (dt, *J* = 14.0, 4.0 Hz, 1 H), 2.27 (ddd, *J* = 14.0, 6.4, 3.6 Hz, 1 H), 1.69-1.61 (m, 1 H); MS (ESI) *m/z* 533.32 (M+H).

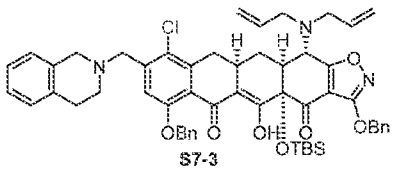
Scheme 7



The following compounds were prepared per Scheme 7.

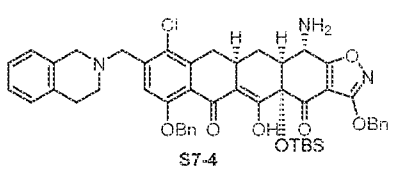


Compound **S7-2** was prepared from compound **S7-1** (prepared according to literature procedures including *J. Med. Chem.*, 2013, *56*, 8112–8138) and isoquinoline by using General Procedure **B-1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 9 H), 7.14-7.08 (m, 5 H), 7.00-6.99 (m, 1 H), 5.13 (br s, 2 H), 3.78 (br s, 2 H), 3.70 (br s, 2 H), 2.87 (br s, 2 H), 2.74 (br s, 2 H), 2.48 (s, 3 H); MS (ESI) *m/z* 498.5 (M+H).

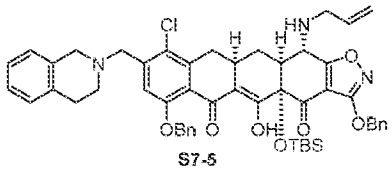


Compound **S7-3** was prepared from compound **S7-2** and diallyenone **S2-3** by using General Procedure **E**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.96 (br s, 1 H), 7.51-7.49 (m, 2 H), 7.40-7.31 (m, 5 H), 7.27-7.20 (m, 4 H), 7.16-7.12 (m, 3 H), 6.98-6.96 (m, 1 H), 5.86-5.76 (m, 2 H), 5.36 (s, 2 H), 5.23-5.16 (m, 4 H), 5.12-5.10 (m, 2 H), 4.09 (d, J = 9.6 Hz, 1 H), 3.74-3.65 (m, 4 H), 3.37-3.31 (m, 4 H), 3.23-3.17 (m, 2 H), 3.02-2.94 (m, 1 H), 2.84-2.70 (m, 4 H), 2.52-

2.42 (m, 2 H), 2.15-2.12 (m, 1 H), 0.83 (s, 9 H), 0.26 (s, 3 H), 0.14 (s, 3 H); MS (ESI) *m/z* 938.70 (M+H).

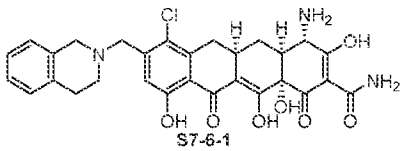


S7-4



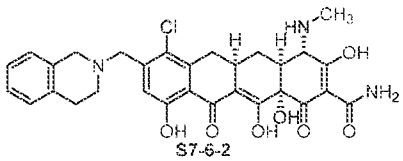
S7-5

Compounds **S7-4** and **S7-5** were prepared from compound **S7-3** by using General Procedure **A**. **S7-4**: MS (ESI) *m/z* 858.59 (M+H). **S7-5**: MS (ESI) *m/z* 898.71 (M+H).

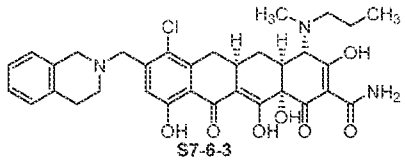


S7-6-1

Compound **S7-6-1** was prepared from compound **S7-4** by using General Procedures **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.33-7.25 (m, 4 H), 7.19 (d, J = 7.2 Hz, 1 H), 4.73, 4.68 (ABq, J = 13.6 Hz, 2 H), 4.55 (s, 2 H), 3.92 (s, 1 H), 3.84 (br s, 1 H), 3.62 (br s, 1 H), 3.42 (dd, J = 16.0, 4.4 Hz, 1 H), 3.30-3.18 (m, 2 H), 3.09-3.02 (m, 1 H), 2.72-2.69 (m, 1 H), 2.42 (t, J = 14.8 Hz, 1 H), 2.29 (ddd, J = 14.0, 5.2, 2.4 Hz, 1 H), 1.65-1.55 (m, 1 H); MS (ESI) *m/z* 566.35 (M+H).

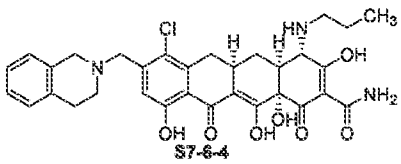


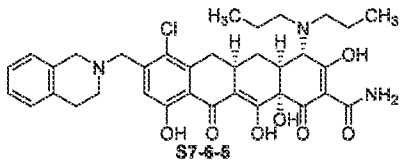
S7-6-2



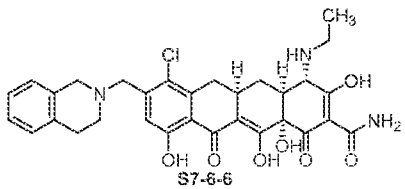
S7-6-3

Compounds **S7-6-2** and **S7-6-3** were prepared from compound **S7-5** with HCHO by using General Procedures **B-1**, **C** and **D-2**. **S7-6-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.33-7.26 (m, 4 H), 7.19 (d, J = 7.2 Hz, 1 H), 4.72, 4.67 (ABq, J = 13.2 Hz, 2 H), 4.55 (s, 2 H), 3.85 (br s, 2 H), 3.63 (br s, 1 H), 3.42 (dd, J = 16.0, 4.0 Hz, 1 H), 3.30-3.22 (m, 2 H), 3.10-3.04 (m, 1 H), 2.92 (s, 3 H), 2.85 (d, J = 12.6 Hz, 1 H), 2.43 (t, J = 14.8 Hz, 1 H), 2.29-2.23 (m, 1 H), 1.64-1.54 (m, 1 H); MS (ESI) *m/z* 580.4 (M+H). **S7-6-3**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.33-7.26 (m, 4 H), 7.21-7.19 (m, 1 H), 4.72, 4.68 (ABq, J = 15.6 Hz, 2 H), 4.55 (s, 2 H), 4.24 (s, 0.5 H), 4.17 (s, 0.5 H), 3.84 (br s, 1 H), 3.62 (br s, 1 H), 3.46-3.34 (m, 2 H), 3.32-2.96 (m, 8 H), 2.44 (br t, J = 15.2 Hz, 1 H), 2.99 (br t, J = 13.2 Hz, 1 H), 1.86-1.77 (m, 2 H), 1.68-1.65 (m, 1 H), 1.05-0.99 (m, 3 H); MS (ESI) *m/z* 622.4 (M+H).

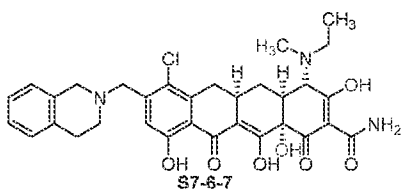

S7-6-4


S7-6-5

Compounds **S7-6-4** and **S7-6-5** were prepared from compound **S7-3** by using General Procedures **C** and **D-2**. **S7-6-4**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.31-7.18 (m, 5 H), 4.71 (q, J = 13.6 Hz, 2 H), 4.55 (s, 2 H), 3.93 (s, 1 H), 3.84 (br s, 1 H), 3.63 (br s, 1 H), 3.42-3.38 (m, 1 H), 3.38-3.17 (m, 4 H), 3.07 (br s, 1 H), 2.95 (d, J = 12.8 Hz, 1 H), 2.39 (t, J = 14.4 Hz, 1 H), 2.29 (d, J = 12.0 Hz, 1 H), 1.83-1.74 (m, 2 H), 1.61-1.52 (m, 1 H), 1.03 (t, J = 7.6 Hz, 3 H); MS (ESI) *m/z* 608.43 (M+H). **S7-6-5**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.34-7.19 (m, 5 H), 4.70 (s, 2 H), 4.55 (s, 2 H), 4.26 (s, 1 H), 3.87-3.85 (m, 1 H), 3.63 (br s, 1 H), 3.54-3.37 (m, 3 H), 3.29-3.13 (m, 5 H), 2.99 (d, J = 13.2 Hz, 1 H), 2.44 (t, J = 14.4 Hz, 1 H), 2.27 (d, J = 12.0 Hz, 1 H), 1.90-1.80 (m, 4 H), 1.71-1.61 (m, 1 H), 1.05-0.98 (m, 6 H); MS (ESI) *m/z* 650.45 (M+H).

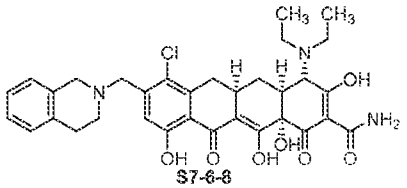

S7-6-6

Compound **S7-6-6** was prepared from compound **S7-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.33-7.18 (m, 5 H), 4.73, 4.67 (ABq, J = 13.6 Hz, 2 H), 4.55 (s, 2 H), 3.90 (s, 1 H), 3.84 (br s, 1 H), 3.62 (br s, 1 H), 3.48-3.32 (m, 3 H), 3.29-3.21 (m, 2 H), 3.10-3.03 (m, 1 H), 2.90 (d, J = 12.8 Hz, 1 H), 2.41 (t, J = 14.4 Hz, 1 H), 2.30-2.26 (m, 1 H), 1.63-1.53 (m, 1 H), 1.37 (t, J = 7.6 Hz, 3 H); MS (ESI) *m/z* 594.40 (M+H).


S7-6-7

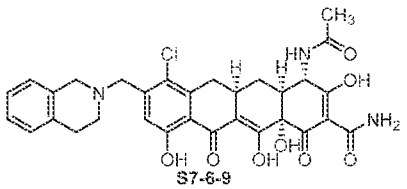
Compound **S7-6-7** was prepared from compound **S7-4** with CH_3CHO by using General Procedure **B-1** (at 0 °C), then **B-1** again with HCHO, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.33-7.26 (m, 4 H), 7.21-7.19 (m, 1 H), 4.73, 4.68 (ABq, J = 13.2 Hz, 2 H), 4.55 (s, 2 H), 4.26 (s, 0.5 H), 4.18 (s, 0.5 H), 3.85 (br s, 1 H), 3.62 (br s, 1 H), 3.56-3.34

(m, 3 H), 3.30-3.14 (m, 3 H), 3.04-2.95 (m, 4 H), 2.42 (br t, J = 15.2 Hz, 1 H), 2.30 (br t, J = 15.2 Hz, 1 H), 1.73-1.61 (m, 1 H), 1.44-1.37 (m, 3 H); MS (ESI) *m/z* 608.43 (M+H).



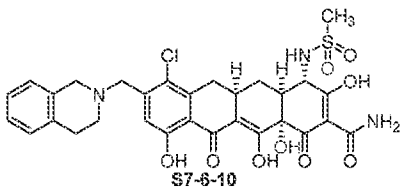
S7-6-8

Compound **S7-6-8** was prepared from compound **S7-4** with CH_3CHO by using General Procedures **B-1**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.34-7.25 (m, 4 H), 7.20-7.18 (m, 1 H), 4.74, 4.68 (ABq, J = 13.2 Hz, 2 H), 4.55 (s, 2 H), 4.28 (s, 1 H), 3.84 (br s, 1 H), 3.65-3.56 (m, 2 H), 3.53-3.34 (m, 4 H), 3.29-3.10 (m, 3 H), 2.98 (d, J = 13.2 Hz, 1 H), 2.41 (t, J = 14.8 Hz, 1 H), 2.30 (br d, J = 12.4 Hz, 1 H), 1.71-1.64 (m, 1 H), 1.43 (t, J = 7.2 Hz, 3 H), 1.42 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 622.42 (M+H).



S7-6-9

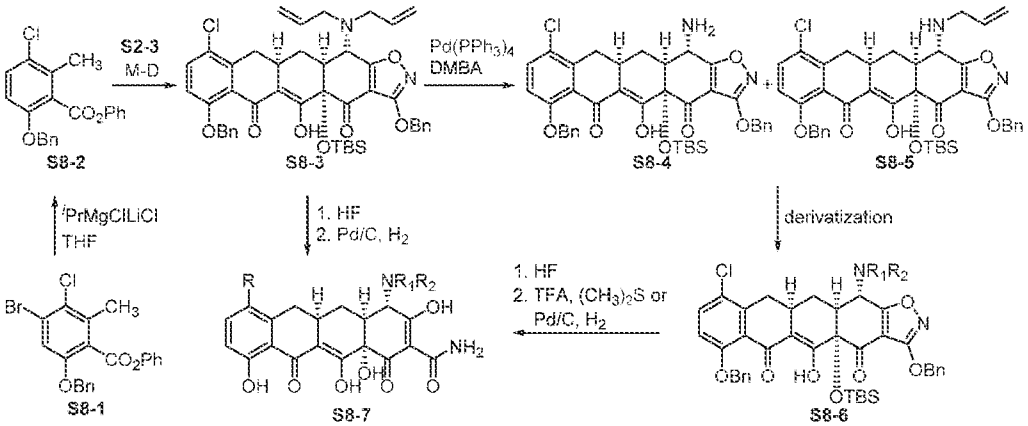
Compound **S7-6-9** was prepared from compound **S7-4** with Ac_2O by using General Procedures **B-2**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.33-7.24 (m, 4 H), 7.21-7.19 (m, 1 H), 4.72-4.65 (m, 3 H), 4.55 (s, 2 H), 3.84 (br s, 1 H), 3.61 (br s, 1 H), 3.37-3.33 (m, 1 H), 3.30-3.20 (m, 2 H), 3.05-2.99 (m, 1 H), 2.63 (t, J = 15.2 Hz, 1 H), 2.46-2.36 (m, 2 H), 2.05 (s, 3 H), 1.66-1.59 (m, 1 H); MS (ESI) *m/z* 608.42 (M+H).



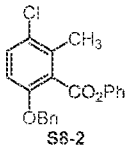
S7-6-10

Compound **S7-6-10** was prepared from compound **S7-4** with Ms_2O by using General Procedures **B-2**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.32-7.23 (m, 4 H), 7.20-7.18 (m, 1 H), 4.69 (s, 2 H), 4.54 (s, 2 H), 4.10 (d, J = 4.4 Hz, 1 H), 3.84 (br s, 1 H), 3.63 (br s, 1 H), 3.38 (dd, J = 16.8, 5.2 Hz, 1 H), 3.28-3.20 (m, 2 H), 3.16 (s, 3 H), 2.99-2.91 (m, 1 H), 2.60 (t, J = 16.0 Hz, 1 H), 2.48-2.44 (m, 1 H), 2.32-2.26 (m, 1 H), 1.72-1.64 (m, 1 H); MS (ESI) *m/z* 644.36 (M+H).

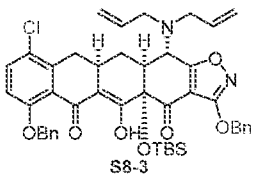
Scheme 8



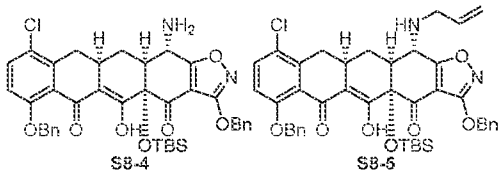
The following compounds were prepared per Scheme 8.


S8-2

Compound **S8-1** (1.62 g, 3.76 mmol, 1 eq, prepared per literature procedures including *J. Med. Chem.*, 2013, *56*, 8112–8138) was dissolved in THF (16 mL). The resulting reaction solution was cooled to –78 °C. A solution of ^{i}PrMgCl·LiCl (1.3 M, 4.89 mL, 4.89 mmol, 1.3 eq) was added. The resulting reaction solution was then stirred in an ice/water bath for 2 h and saturated NH_4Cl solution was added. The resulting reaction mixture was extracted with EtOAc. The organic phase was separated, washed with brine and concentrated. The residue was purified by flash column chromatography (100 g silica gel, 2→8% EtOAc/hexanes) to give compound **S8-2** as a white solid (1.1 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.34 (m, 8 H), 7.26-7.23 (m, 1 H), 7.10-7.08 (m, 2 H), 6.83-6.80 (m, 1 H), 5.13 (s, 2 H), 2.45 (s, 3 H).

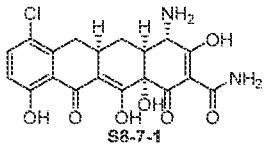

S8-3

Compound **S8-3** was prepared from compound **S8-2** and diallyenone **S2-3** by using General Procedure E: MS (ESI) *m/z* 793.60 (M+H).



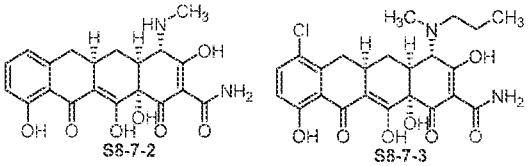
S8-4 S8-5

Compounds **S8-4** and **S8-5** were prepared from compound **S8-3** by using General Procedure **A**. **S8-4**: MS (ESI) *m/z* 713.45 (M+H). **S8-5**: MS (ESI) *m/z* 753.51 (M+H).



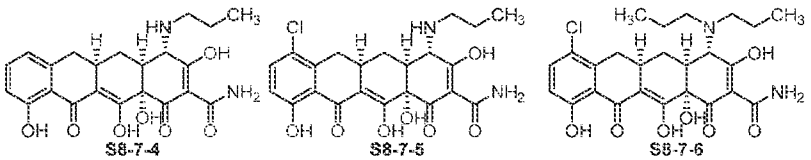
S8-7-1

Compound **S8-7-1** was prepared from compound **S8-4** by using General Procedures **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.49 (d, J = 8.8 Hz, 1 H), 6.83 (d, J = 8.8 Hz, 1 H), 3.90 (s, 1 H), 3.32-3.27 (s, 1 H), 3.10-2.94 (m, 1 H), 2.66-2.62 (m, 1 H), 2.34 (t, J = 15.6 Hz, 1 H), 2.23 (ddd, J = 13.6, 5.2, 2.8 Hz, 1 H), 1.63-1.54 (m, 1 H); MS (ESI) *m/z* 421.24 (M+H).



S8-7-2 S8-7-3

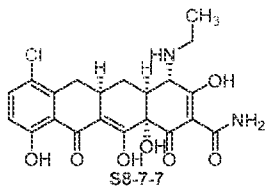
Compounds **S8-7-2** and **S8-7-3** were prepared from compound **S8-5** with HCHO by using General Procedures **B-1**, **C** and **D-2**. **S8-7-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.40 (dd, J = 8.4, 7.2 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 6.73 (d, J = 7.2 Hz, 1 H), 3.79 (s, 1 H), 3.04-2.95 (m, 1 H), 2.90 (s, 3 H), 2.87-2.82 (m, 1 H), 2.77-2.74 (m, 1 H), 2.54 (t, J = 14.8 Hz, 1 H), 2.15 (ddd, J = 13.2, 4.8, 2.8 Hz, 1 H), 1.56-1.47 (m, 1 H); MS (ESI) *m/z* 401.29 (M+H). **S8-7-3**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.50 (d, J = 9.2 Hz, 1 H), 6.84 (d, J = 9.2 Hz, 1 H), 4.22 (s, 0.5 H), 4.13 (s, 0.5 H), 3.41-3.32 (m, 2 H), 3.22-3.15 (m, 1 H), 3.09-2.91 (m, 5 H), 2.34 (t, J = 15.2 Hz, 1 H), 2.26-2.19 (m, 1 H), 1.88-1.74 (m, 2 H), 1.68-1.62 (m, 1 H), 1.06-0.99 (m, 3 H); MS (ESI) *m/z* 477.33 (M+H).



S8-7-4 S8-7-5 S8-7-6

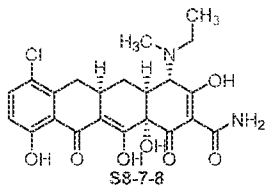
Compounds **S8-7-4**, **S8-7-5** and **S8-7-6** were prepared from compound **S8-3** by using General Procedures **C** and **D-2**. **S8-7-4**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ

7.40 (dd, *J* = 8.8, 7.2 Hz, 1 H), 6.79 (d, *J* = 8.8 Hz, 1 H), 6.73 (d, *J* = 7.2 Hz, 1 H), 3.86 (s, 1 H), 3.33-3.17 (m, 2 H), 3.03-2.94 (m, 1 H), 2.87-2.80 (m, 1 H), 2.53 (t, *J* = 14.4 Hz, 1 H), 2.17 (ddd, *J* = 13.2, 4.8, 2.4 Hz, 1 H), 1.82-1.72 (m, 2 H), 1.56-1.47 (m, 1 H), 1.03 (t, *J* = 7.6 Hz, 3 H); MS (ESI) *m/z* 429.34 (M+H). **S8-7-5**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.48 (d, *J* = 8.8 Hz, 1 H), 6.82 (d, *J* = 8.8 Hz, 1 H), 3.88 (s, 1 H), 3.34-3.18 (m, 2 H), 3.03-2.94 (m, 1 H), 2.85 (d, *J* = 12.8 Hz, 1 H), 2.30 (t, *J* = 15.2 Hz, 1 H), 2.24-2.20 (m, 1 H), 1.82-1.72 (m, 2 H), 1.60-1.50 (m, 1 H), 1.02 (t, *J* = 7.6 Hz, 3 H); MS (ESI) *m/z* 463.31 (M+H). **S8-7-6**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.50 (d, *J* = 9.2 Hz, 1 H), 6.84 (d, *J* = 9.2 Hz, 1 H), 4.24 (s, 1 H), 3.53-3.45 (m, 1 H), 3.41-3.25 (m, 3 H), 3.22-3.16 (m, 1 H), 3.09-2.99 (m, 1 H), 2.95-2.92 (m, 1 H), 2.33 (t, *J* = 14.8 Hz, 1 H), 2.21 (ddd, *J* = 13.2, 4.4, 2.8 Hz, 1 H), 1.89-1.74 (m, 4 H), 1.68-1.59 (m, 1 H), 1.03 (t, *J* = 7.6 Hz, 3 H), 0.99 (t, *J* = 7.6 Hz, 3 H); MS (ESI) *m/z* 505.35 (M+H).



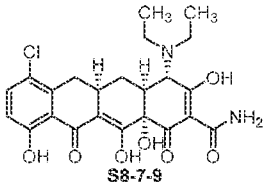
S8-7-7

Compound **S8-7-7** was prepared from compound **S8-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.48 (d, *J* = 8.4 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 3.88 (s, 1 H), 3.46-3.41 (m, 1 H), 3.37-3.32 (m, 1 H), 3.30-3.25 (m, 1 H), 3.03-2.95 (m, 1 H), 2.85-2.82 (m, 1 H), 2.30 (t, *J* = 15.2 Hz, 1 H), 2.24-2.20 (m, 1 H), 1.60-1.51 (m, 1 H), 1.36 (t, *J* = 7.6 Hz, 3 H); MS (ESI) *m/z* 449.26 (M+H).



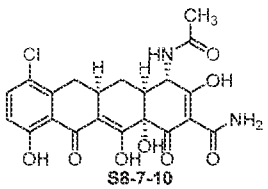
S8-7-8

Compound **S8-7-8** was prepared from compound **S8-4** with CH_3CHO by using General Procedure **B-1** (at 0 °C), then **B-1** again with HCHO, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.50 (d, *J* = 8.8 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 1 H), 4.23 (s, 0.5 H), 4.14 (s, 0.5 H), 3.51-3.43 (m, 1 H), 3.37-3.30 (m, 2 H), 3.08-2.89 (m, 5 H), 2.34 (t, *J* = 15.2 Hz, 1 H), 2.28-2.19 (m, 1 H), 1.71-1.58 (m, 1 H), 1.42 (t, *J* = 7.2 Hz, 1.5 H), 1.38 (t, *J* = 7.2 Hz, 1.5 H); MS (ESI) *m/z* 463.28 (M+H).



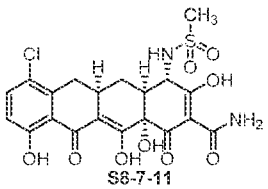
S8-7-9

Compound **S8-7-9** was prepared from compound **S8-4** with CH_3CHO by using General Procedures **B-1**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.50 (d, *J* = 8.8 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 1 H), 4.23 (s, 1 H), 3.65-3.56 (m, 1 H), 3.50-3.44 (m, 2 H), 3.36-3.29 (m, 2 H), 3.08-3.01 (m, 1 H), 2.93-2.90 (m, 1 H), 2.36-2.23 (m, 2 H), 1.69-1.59 (m, 1 H), 1.42 (t, *J* = 7.6 Hz, 6 H), 0.99 (t, *J* = 7.6 Hz, 3 H); MS (ESI) *m/z* 477.30 (M+H).



S8-7-10

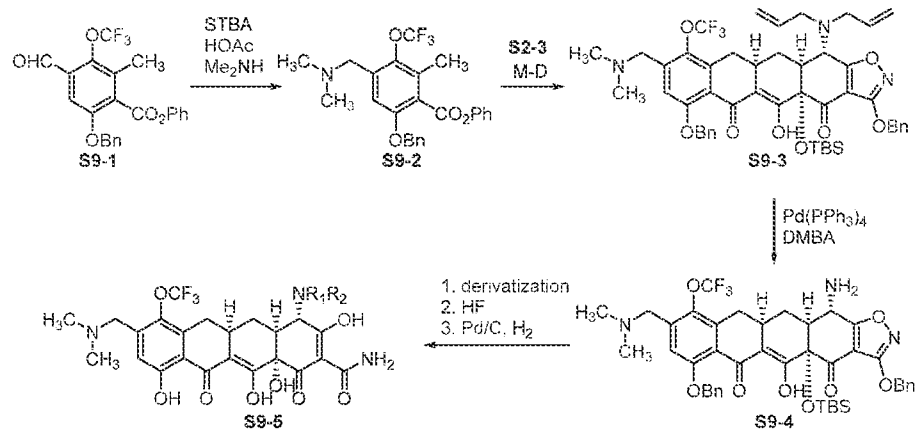
Compound **S8-7-10** was prepared from compound **S8-4** with Ac_2O by using General Procedures **B-2**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 9.2 Hz, 1 H), 6.80 (d, *J* = 9.2 Hz, 1 H), 4.68 (d, *J* = 6.4 Hz, 1 H), 3.22 (dd, *J* = 16.0, 4.4 Hz, 1 H), 3.01-2.93 (m, 1 H), 2.52 (t, *J* = 15.6 Hz, 1 H), 2.46-2.42 (m, 1 H), 2.39-2.32 (m, 1 H), 2.04 (s, 3 H), 1.64-1.56 (m, 1 H); MS (ESI) *m/z* 463.27 (M+H).



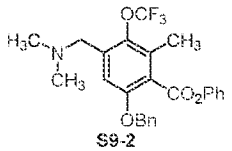
S8-7-11

Compound **S8-7-11** was prepared from compound **S8-4** with Ms_2O by using General Procedures **B-2**, **C** and **D-1**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (d, *J* = 9.2 Hz, 1 H), 6.79 (d, *J* = 9.2 Hz, 1 H), 4.10 (d, *J* = 4.4 Hz, 1 H), 3.25 (dd, *J* = 16.0, 4.4 Hz, 1 H), 3.14 (s, 3 H), 3.01-2.92 (m, 1 H), 2.53-2.48 (m, 2 H), 2.30-2.24 (m, 1 H), 1.69-1.61 (m, 1 H); MS (ESI) *m/z* 499.22 (M+H).

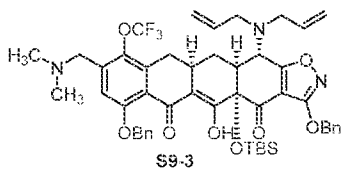
Scheme 9



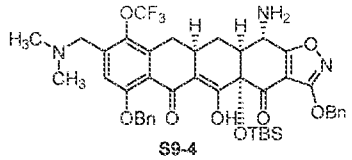
The following compounds were prepared per Scheme 9.



Compound **S9-1** (0.15 g, 0.35 mmol, 1.0 eq, prepared per literature procedures including WO 2014036502 A2) was dissolved in DCM (2 mL). Dimethylamine (0.12 mL, 5.6 M in EtOH, 0.70 mmol, 2.0 eq) and acetic acid (60 µL, 1.14 mmol, 3.0 eq) were added under a nitrogen atmosphere. Then sodium triacetoxyborohydride (148 mg, 0.70 mmol, 2.0 eq) was added. After 10 min, LC/MS indicated that the starting material was consumed. Saturated $NaHCO_3$ solution was added and extracted with DCM. The organic phase was concentrated under reduced pressure. The residue was purified by flash column chromatography (Biotage 10 g silica gel column, 10%→30% EtOAc in hexanes gradient), yielding 100 mg (62%) of the compound **S9-2** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2 H), 7.38-7.34 (m, 5 H), 7.26-7.22 (m, 1 H), 7.20 (s, 1 H), 7.09-7.06 (m, 2 H), 5.17 (s, 2 H), 3.49 (s, 2 H), 2.40 (s, 3 H), 2.23 (s, 6 H); MS (ESI) *m/z* 460.23 (M+H).

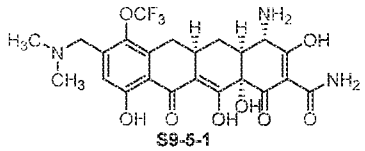


Compound **S9-3** was prepared from compound **S9-2** and diallyenone **S2-3** by using General Procedure E: MS (ESI) *m/z* 900.41 (M+H).



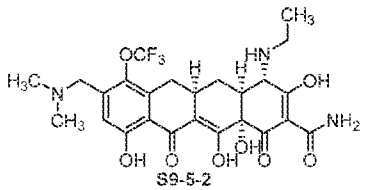
S9-4

Compounds **S9-4** was prepared from compound **S9-3** by using General Procedure **A**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.52 (s, 1 H), 7.49-7.44 (m, 6 H), 7.41-7.29 (m, 6 H), 7.25 (s, 1 H), 5.40, 5.36 (ABq, J = 12.0 Hz, 2 H), 5.31, 5.22 (ABq, J = 12.0 Hz, 2 H), 3.92 (d, J = 2.0 Hz, 1 H), 3.49, 3.43 (ABq, J = 14.4 Hz, 2 H), 3.02 (dd, J = 16.0, 4.4 Hz, 1 H), 2.79-2.71 (m, 1 H), 2.64-2.61 (m, 1 H), 2.28-2.20 (m, 1 H), 2.20 (s, 6 H), 2.13-2.08 (m, 1 H), 1.58-1.49 (m, 1 H), 0.74 (s, 9 H), 0.22 (s, 3 H), 0.10 (s, 3 H); MS (ESI) *m/z* 820.33 (M+H).



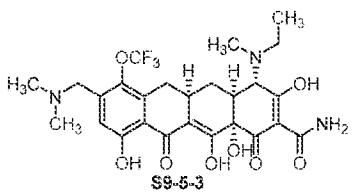
S9-5-1

Compound **S9-5-1** was prepared from compound **S9-4** by using General Procedures **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.24 (s, 1 H), 4.45 (s, 2 H), 3.90 (s, 1 H), 3.19 (dd, J = 15.6, 3.6 Hz, 1 H), 3.04-2.96 (m, 1 H), 2.94 (s, 3 H), 2.86 (s, 3 H), 2.68 (br d, J = 12.8 Hz, 1 H), 2.41 (t, J = 14.4 Hz, 1 H), 2.27-2.24 (m, 1 H), 1.64-1.54 (m, 1 H); MS (ESI) *m/z* 528.18 (M+H).



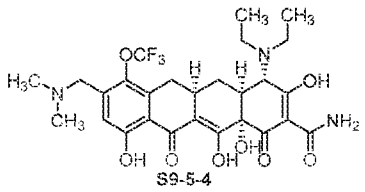
S9-5-2

Compound **S9-5-2** was prepared from compound **S9-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.20 (s, 1 H), 4.45 (s, 2 H), 3.88 (s, 1 H), 3.46-3.39 (m, 1 H), 3.37-3.30 (m, 1 H), 3.18 (dd, J = 15.6, 4.4 Hz, 1 H), 3.05-2.97 (m, 1 H), 2.94 (s, 3 H), 2.86 (s, 3 H), 2.86-2.83 (m, 1 H), 2.41 (t, J = 14.8 Hz, 1 H), 2.24 (ddd, J = 14.0, 5.6, 2.8 Hz, 1 H), 1.64-1.54 (m, 1 H), 1.36 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 556.2 (M+H).



S9-5-3

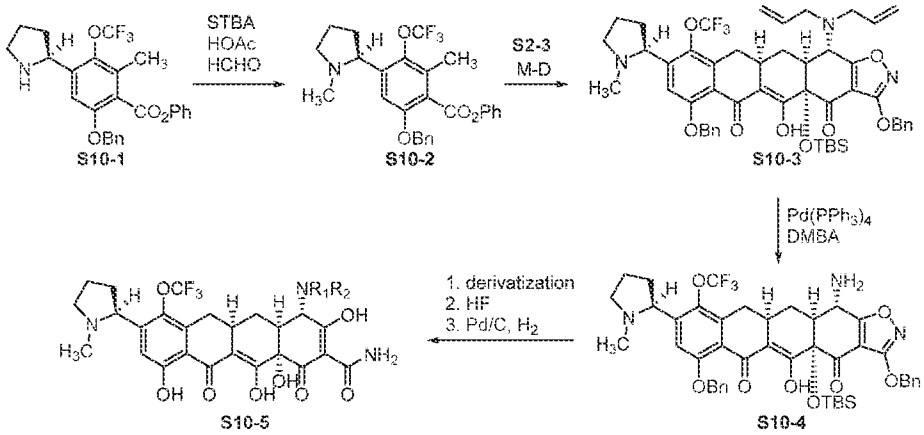
Compound **S9-5-3** was prepared from compound **S9-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **B-1** again with HCHO, **C** and **D-2**: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.22 (s, 1 H), 4.46 (s, 2 H), 4.24 (s, 0.5 H), 4.15 (s, 0.5 H), 3.53-3.44 (m, 1 H), 3.38-3.30 (m, 1 H), 3.22-3.18 (m, 1 H), 3.11-2.94 (m, 8 H), 2.86 (s, 3 H), 2.42 (t, J = 14.4 Hz, 1 H), 2.29-2.23 (m, 1 H), 1.68-1.60 (m, 1 H), 1.44-1.34 (m, 3 H); MS (ESI) *m/z* 570.2 (M+H).



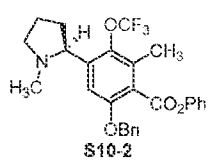
S9-5-4

Compound **S9-5-4** was prepared from compound **S9-4** with CH_3CHO by using General Procedures **B-1**, **C** and **D-2**: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.28 (s, 1 H), 4.47 (s, 2 H), 4.28 (s, 1 H), 3.65-3.56 (m, 1 H), 3.54-3.43 (m, 2 H), 3.41-3.34 (m, 1 H), 3.21 (br d, J = 15.6 Hz, 1 H), 3.13-3.05 (m, 1 H), 2.99-2.96 (m, 1 H), 2.96 (s, 3 H), 2.86 (s, 3 H), 2.41 (t, J = 14.8 Hz, 1 H), 2.28 (br d, J = 12.8 Hz, 1 H), 1.69-1.60 (m, 1 H), 1.42 (t, J = 7.2 Hz, 6 H); MS (ESI) *m/z* 584.20 (M+H).

Scheme 10

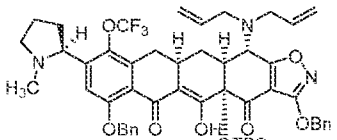


The following compounds were prepared per Scheme 10.



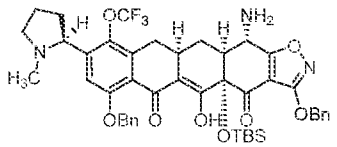
S10-2

Compound **S10-2** was prepared from **S10-1** (prepared according to literature procedures including WO 2014036502 A2) with HCHO by using General Procedure **B-1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2 H), 7.38-7.33 (m, 5 H), 7.26 (s, 1 H), 7.26-7.22 (m, 1 H), 7.09-7.06 (m, 2 H), 5.19, 5.15 (ABq, J = 11.6 Hz, 2 H), 3.49 (t, J = 8.4 Hz, 1 H), 3.26-3.21 (m, 1 H), 2.33 (q, J = 9.2 Hz, 1 H), 2.29-2.20 (m, 1 H), 2.15 (s, 3 H), 1.97-1.88 (m, 1 H), 1.86-1.78 (m, 1 H), 1.60-1.50 (m, 1 H); MS (ESI) *m/z* 486.15 (M+H).



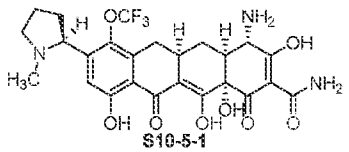
S10-3

Compound **S10-3** was prepared from compound **S10-2** and diallyenone **S2-3** by using General Procedure **E**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.99 (s, 1 H), 7.51-7.47 (m, 4 H), 7.40-7.31 (m, 5 H), 7.28-7.26 (m, 2 H), 5.83-5.73 (m, 2 H), 5.36 (s, 2 H), 5.23 (s, 2 H), 5.23-5.18 (m, 2 H), 5.09 (d, J = 10.4 Hz, 2 H), 4.09 (d, J = 10.4 Hz, 1 H), 3.43 (t, J = 8.0 Hz, 1 H), 3.35-3.30 (m, 2 H), 3.22-3.16 (m, 3 H), 3.12 (dd, J = 15.2, 4.0 Hz, 1 H), 2.95-2.88 (m, 1 H), 2.66 (t, J = 15.6 Hz, 1 H), 2.52-2.48 (m, 1 H), 2.45-2.40 (m, 1 H), 2.30 (q, J = 8.4 Hz, 1 H), 2.23-2.10 (m, 1 H), 2.06 (s, 3 H), 1.96-1.89 (m, 1 H), 1.85-1.77 (m, 1 H), 1.59-1.51 (m, 1 H), 0.82 (s, 9 H), 0.25 (s, 3 H), 0.13 (s, 3 H); MS (ESI) *m/z* 926.37 (M+H).



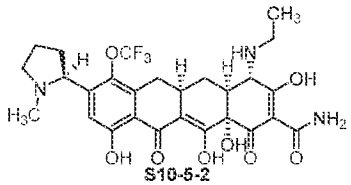
S10-4

Compound **S10-4** was prepared from compound **S10-3** by using General Procedure **A**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.51 (s, 1 H), 7.55-7.53 (m, 2 H), 7.49-7.47 (m, 2 H), 7.41-7.28 (m, 7 H), 5.40, 5.36 (ABq, J = 12.4 Hz, 2 H), 5.28, 5.22 (ABq, J = 12.0 Hz, 2 H), 3.92 (d, J = 2.4 Hz, 1 H), 3.43 (t, J = 8.0 Hz, 1 H), 3.23-3.19 (m, 1 H), 3.02 (dd, J = 15.2, 3.6 Hz, 1 H), 2.80-2.71 (m, 1 H), 2.64-2.61 (m, 1 H), 2.34-2.10 (m, 3 H), 2.09 (s, 3 H), 1.96-1.79 (m, 3 H), 1.58-1.49 (m, 2 H), 0.74 (s, 9 H), 0.22 (s, 3 H), 0.10 (s, 3 H); MS (ESI) *m/z* 846.37 (M+H).



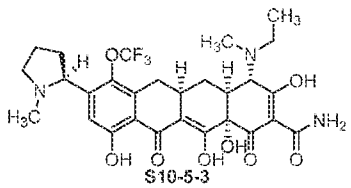
S10-5-1

Compound **S10-5-1** was prepared from compound **S10-4** by using General Procedures **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.27 (s, 1 H), 4.85-4.74 (m, 1 H), 3.88 (s, 1 H), 3.88-3.83 (m, 1 H), 3.42-3.33 (m, 1 H), 3.21 (dd, J = 16.0, 3.6 Hz, 1 H), 3.03-2.94 (m, 1 H), 2.77 (s, 3 H), 2.66-2.54 (m, 2 H), 2.54-2.23 (m, 5 H), 1.65-1.55 (m, 1 H); MS (ESI) *m/z* 554.14 (M+H).



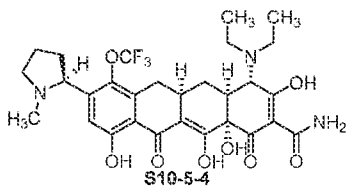
S10-5-2

Compound **S10-5-2** was prepared from compound **S10-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.33 (s, 1 H), 4.82-4.75 (m, 1 H), 3.89 (s, 1 H), 3.89-3.83 (m, 1 H), 3.47-3.33 (m, 3 H), 3.21 (dd, J = 16.0, 4.0 Hz, 1 H), 3.06-2.98 (m, 1 H), 2.87 (d, J = 12.8 Hz, 1 H), 2.77 (s, 3 H), 2.61-2.52 (m, 1 H), 2.43-2.44 (m, 5 H), 1.64-1.54 (m, 1 H), 1.37 (t, J = 7.2 Hz, 3 H); MS (ESI) *m/z* 582.16 (M+H).



S10-5-3

Compound **S9-5-3** was prepared from compound **S9-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **B-1** again with HCHO, **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.38 (s, 1 H), 4.80-4.75 (m, 1 H), 4.26 (s, 0.5 H), 4.18 (s, 0.5 H), 3.89-3.85 (m, 1 H), 3.56-3.46 (m, 1 H), 3.43-3.32 (m, 2 H), 3.23 (d, J = 15.6 Hz, 1 H), 3.13-2.95 (m, 5 H), 2.77 (s, 3 H), 2.62-2.55 (m, 1 H), 2.44-2.26 (m, 5 H), 1.70-1.60 (m, 1 H), 1.44-1.37 (m, 3 H); MS (ESI) *m/z* 596.18 (M+H).

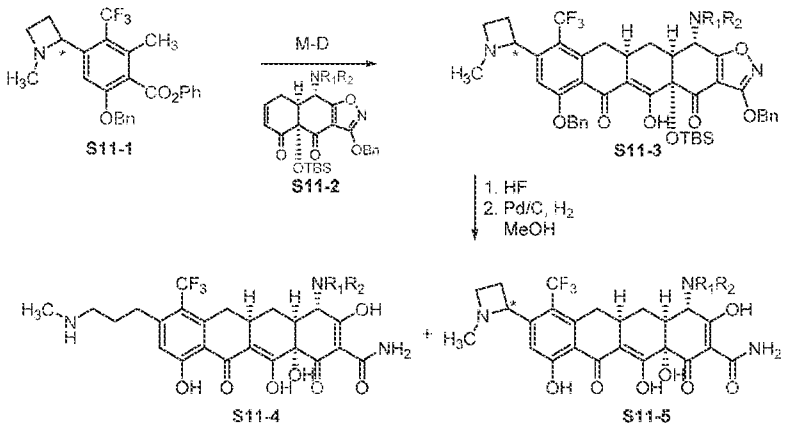


S10-5-4

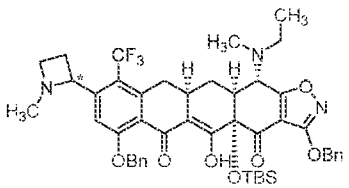
Compound **S9-5-4** was prepared from compound **S9-4** with CH_3CHO by using General Procedures **B-1**, **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.40 (s, 1 H), 4.79-4.77 (m, 1 H), 4.27 (s, 1 H), 3.89-3.86 (m, 1 H), 3.63-3.56 (m, 1 H), 3.48-3.35 (m, 4

H), 3.23 (br d, J = 15.6 Hz, 1 H), 3.09 (br s, 1 H), 2.97 (br d, J = 13.6 Hz, 1 H), 2.76 (s, 3 H), 2.60-2.54 (m, 1 H), 2.42-2.27 (m, 5 H), 1.68-1.60 (m, 1 H), 1.41 (t, J = 6.4 Hz, 6 H); MS (ESI) *m/z* 610.19 (M+H).

Scheme 11

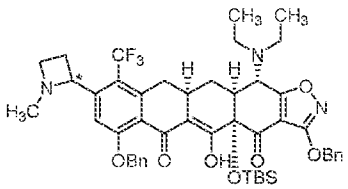


The following compounds were prepared per Scheme 11.



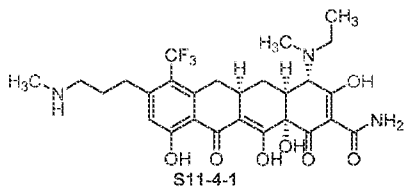
Compound **S11-3-1** was prepared from **S11-1** (prepared according to literature procedures including WO 2012021712 A1) and C-4 methylethylaminoenone **S11-2-1**

(prepared according to literature procedures including WO 2014036502 A2) by using General Procedure **E**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.84 (s, 1 H), 7.59 (s, 1 H), 7.51-7.49 (m, 4 H), 7.39-7.32 (m, 5 H), 7.28-7.24 (m, 1 H), 5.39, 5.34 (ABq, *J* = 12.8 Hz, 2 H), 5.36 (s, 2 H), 4.24 (br s, 1 H), 4.02 (d, *J* = 9.6 Hz, 1 H), 3.43-3.39 (m, 1 H), 3.20 (d, *J* = 15.6 Hz, 1 H), 2.94-2.80 (m, 3 H), 2.74-2.60 (m, 2 H), 2.56-2.44 (m, 3 H), 3.36 (s, 3 H), 2.26-2.14 (m, 1 H), 2.21 (s, 3 H), 1.97-1.90 (m, 1 H), 1.05 (t, *J* = 7.2 Hz, 3 H), 0.84 (s, 9 H), 0.28 (s, 3 H), 0.16 (s, 3 H); MS (ESI) *m/z* 858.3 (M+H).

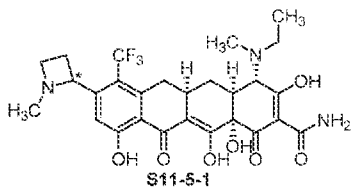


S11-3-2

Compound **S11-3-2** was prepared from **S11-1** and C-4 diethylaminoenone **S11-2-2** (prepared according to literature procedures including WO 2014036502 A2) by using General Procedure **E**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.83 (s, 1 H), 7.60 (s, 1 H), 7.51-7.47 (m, 4 H), 7.39-7.31 (m, 5 H), 7.28-7.24 (m, 1 H), 5.42-5.30(m, 4 H), 4.24-4.19 (m, 1 H), 4.03 (d, *J* = 10.4 Hz, 1 H), 3.42-3.38 (m, 1 H), 3.23-3.19 (m, 1 H), 2.95-2.86 (m, 2 H), 2.75-2.68 (m, 5 H), 2.51-2.44 (m, 3 H), 2.23-2.20 (m, 1 H), 2.20 (s, 3 H), 1.97-1.90 (m, 1 H), 1.08 (t, *J* = 7.2 Hz, 3 H), 0.84 (s, 9 H), 0.28 (s, 3 H), 0.16 (s, 3 H); MS (ESI) *m/z* 872.3 (M+H).

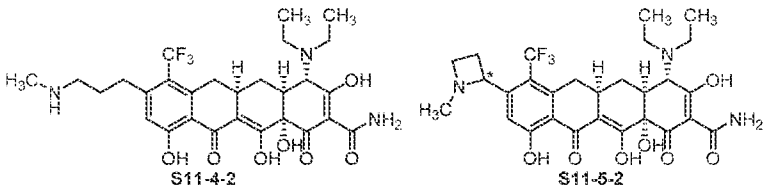


S11-4-1



S11-5-1

Compounds **S11-4-1** and **S11-5-1** were prepared from compound **S11-3-1** by using General Procedures **C** and **D-2**. **S11-4-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) *δ* 6.89 (s, 1 H), 4.16 (s, 1 H), 3.39 (br s, 2 H), 3.29-3.22 (m, 1 H), 3.08-2.86 (m, 9 H), 2.70 (s, 3 H), 2.53 (t, *J* = 15.1 Hz, 1 H), 2.21-2.18 (m, 1 H), 2.02-1.92 (m, 2 H), 1.67-1.61 (m, 1 H), 1.37 (t, *J* = 7.3 Hz, 3 H); MS (ESI) *m/z* 568.18 (M+H). **S11-5-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) *δ* 7.05 (s, 1 H), 5.94 (t, *J* = 8.2 Hz, 1 H), 4.17-4.10 (m, 3 H), 3.40 (br s, 2 H), 3.22-3.18 (m, 1 H), 3.12-2.90 (m, 8 H), 2.72-2.58 (m, 3 H), 2.24-2.21 (m, 1 H), 1.69-1.60 (m, 1 H), 1.39 (t, *J* = 7.3 Hz, 3 H); MS (ESI) *m/z* 566.16 (M+H).



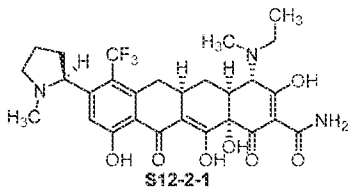
S11-4-2 S11-5-2

Compounds **S11-4-2** and **S11-5-2** were prepared from compound **S11-3-1** by using General Procedures **C** and **D-2**. **S11-4-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 6.89 (s, 1 H), 4.24 (s, 1 H), 3.53-3.47 (m, 2 H), 3.42-3.34 (m, 2 H), 3.27-3.22 (m, 1 H), 3.08-3.04 (m, 2 H), 2.99-2.86 (m, 4 H), 2.70 (s, 3 H), 2.53 (t, J = 15.2 Hz, 1 H), 2.20 (ddd, J = 14.0, 5.2, 2.8 Hz, 1 H), 2.00-1.93 (m, 2 H), 1.67-1.57 (m, 1 H), 1.40 (t, J = 7.2 Hz, 6 H); MS (ESI) m/z 582.2 (M+H). **S11-5-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.05 (s, 1 H), 5.94 (t, J = 8.2 Hz, 1 H), 4.24-4.10 (m, 3 H), 3.51 (br s, 2 H), 3.40 (br s, 2 H), 3.23-3.19 (m, 1 H), 3.12-2.89 (m, 6 H), 2.72-2.54 (m, 2 H), 2.22 (ddd, J = 13.7, 4.6, 2.7 Hz, 1 H), 1.68-1.59 (m, 1 H), 1.40 (t, J = 7.3 Hz, 6 H); MS (ESI) m/z 580.2 (M+H).

Scheme 12

S12-1 S12-2

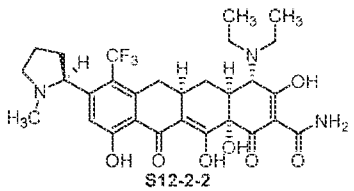
The following compounds were prepared per Scheme 12.



S12-2-1

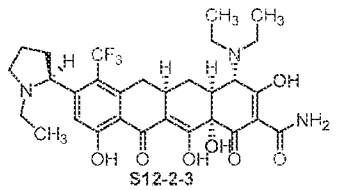
To a solution of compound **S12-1-1** (R_1,R_2 = CH_3,CH_3CH_2, 26 mg, 0.041 mmol, 1 eq, prepared per literature procedures including WO 2014036502 A2) in CH_3OH (1 mL) was added HCHO solution (9 µL, 0.12 mmol, 3.0 eq). Pd-C (10wt%, 10 mg) was added under nitrogen. The reaction vessel was sealed and purged with hydrogen by briefly evacuating the flask followed by flushing with hydrogen gas (1 atm). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt overnight. The reaction was filtered through a small Celite

pad. The cake was washed with CH_3OH. The filtrate was concentrated. The residue was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 µ RP-γ 100A column [10 µm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 3.0 mL (0.05 *N* HCl/water); gradient: 5→35% B in A over 20 min; mass-directed fraction collection]. Fractions containing the desired product were collected and freeze-dried to yield compound **S12-2-1** (15.6 mg): ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.49 (s, 1 H), 4.75 (t, *J* = 8.0 Hz, 1 H), 4.26 (s, 0.5 H), 4.18 (s, 0.5 H), 3.94-3.89 (m, 1 H), 3.55-3.48 (m, 1 H), 3.43-3.26 (m, 3 H), 3.04-2.95 (m, 5 H), 2.75-2.61 (m, 5 H), 2.36-2.24 (m, 4 H), 1.70-1.61 (m, 1 H), 1.42-1.389 (m, 3 H); MS (ESI) *m/z* 580.23 (M+H).



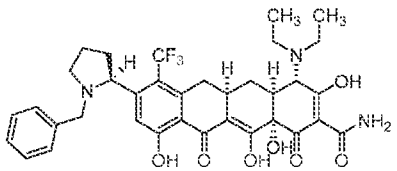
S12-2-2

Compound **S12-2-2** was prepared from compound **S12-1-2** (R_1R_2 = Et_2, prepared according to literature procedures including WO 2014036502 A2) by using a similar procedure for compound **S12-2-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.50 (s, 1 H), 4.74 (t, *J* = 8.0 Hz, 1 H), 4.26 (s, 1 H), 3.94-3.89 (m, 1 H), 3.64-3.56 (m, 1 H), 3.53-3.45 (m, 2 H), 3.42-3.34 (m, 2 H), 3.29-3.26 (m, 1 H), 3.06-2.96 (m, 2 H), 2.74 (s, 3 H), 2.71-2.61 (m, 5 H), 2.36-2.22 (m, 4 H), 1.69-1.59 (m, 1 H), 1.41 (t, *J* = 7.2 Hz, 6 H); MS (ESI) *m/z* 594.06 (M+H).



S12-2-3

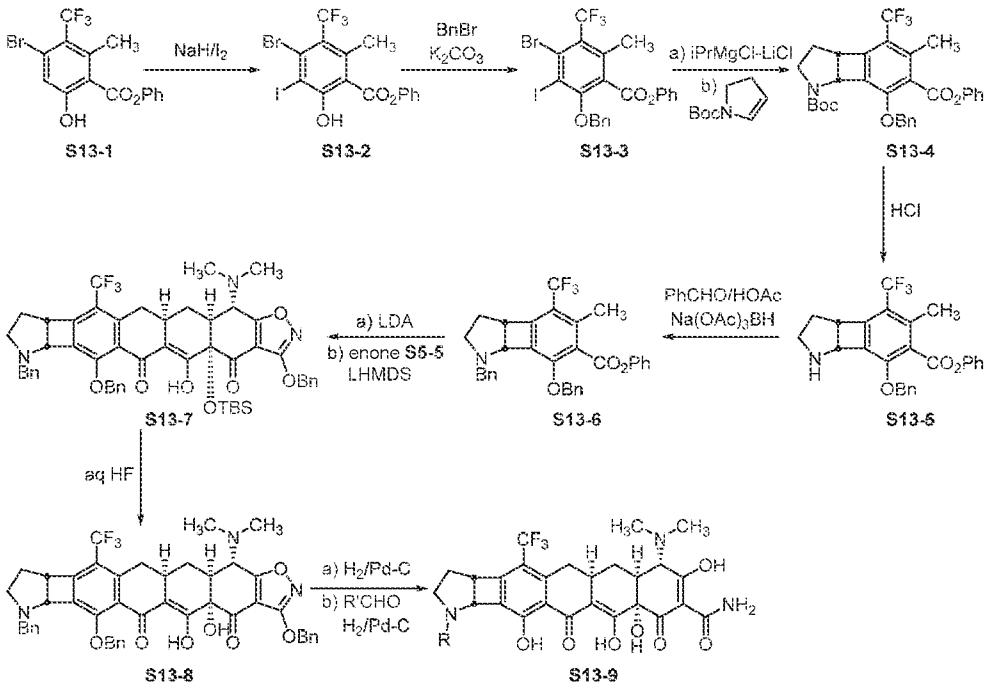
Compound **S12-2-3** was prepared from compound **S12-1-2** (R_1R_2 = Et_2) and CH_3CHO by using a similar procedure for compound **S12-2-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.56 (s, 1 H), 4.75 (t, *J* = 8.0 Hz, 1 H), 4.26 (s, 1 H), 3.99-3.93 (m, 1 H), 3.63-3.56 (m, 1 H), 3.53-3.43 (m, 2 H), 3.39-3.32 (m, 2 H), 3.29-3.25 (m, 1 H), 3.10-2.95 (m, 4 H), 2.70-2.62 (m, 2 H), 2.34-2.20 (m, 4 H), 1.69-1.59 (m, 1 H), 1.41 (t, *J* = 7.2 Hz, 6 H), 1.24 (t, *J* = 7.2 Hz, 3 H); MS (ESI) *m/z* 608.07 (M+H).



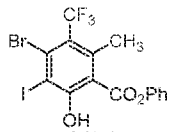
S12-2-4

To a solution of compound **S12-1-2** (R_1R_2 = Et_2, 266 mg, 0.41 mmol, 1 eq) in CH_3OH (3 mL) was added PhCHO (100 μL, 0.99 mmol, 2.4 eq) and $NaBH(OAc)_3$ (110 mg, 0.52 mmol, 1.3 eq) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 15 min. Then the cold was removed and the reaction was stirred at rt for 15 min. Concentrated HCl (4 drops) was added and the resulting reaction was concentrated to ~2 mL. The residue was dropped into stirring MTBE (70 mL) to give a suspension. The solid was collected by filtration, dried under vacuum. Then the solid was dissolved in 0.05 *N* HCl/water. The resulting solution was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 μ RP-γ 100A column [10 μm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 3.0 mL (0.05 *N* HCl/water); gradient: 10→60% B in A over 20 min; mass-directed fraction collection]: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.32-7.31 (m, 6 H), 4.89 (t, *J* = 8.0 Hz, 1 H), 4.47 (d, *J* = 12.8 Hz, 1 H), 4.27 (s, 1 H), 4.22 (d, *J* = 12.8 Hz, 1 H), 3.88-3.83 (m, 1 H), 3.64-3.37 (m, 5 H), 3.19-3.15 (m, 1 H), 3.03-2.95 (m, 2 H), 2.77-2.68 (m, 1 H), 2.57 (t, *J* = 14.8 Hz, 1 H), 2.24-2.12 (m, 4 H), 1.67-1.58 (m, 1 H), 1.43 (t, *J* = 7.2 Hz, 6 H); MS (ESI) *m/z* 670.32 (M+H).

Scheme 13

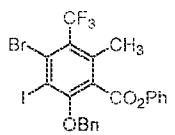


The following compounds were prepared per Scheme 13.



S13-2

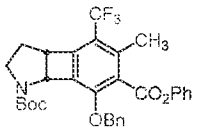
To compound **S13-1** (1.04 g, 2.77 mmol, 1 eq) in toluene (8 mL) was added NaH (444 mg, 60% in mineral oil, 11.09 mmol, 4 eq). The white suspension was stirred at rt for 8 min. Iodine (2.81 g, 11.09 mmol, 4 eq) was added. The reaction mixture was stirred at rt for overnight. Water and 1 N HCl (11 mL) were added, followed by the addition of 10% aqueous Na_2SO_3. The mixture was extracted with EtOAc. The organic phase was washed with brine and concentrated under reduced pressure to give the desired product **S13-2**: MS (ESI) *m/z* 498.9 (M-H).



S13-3

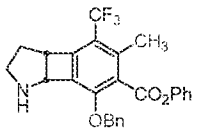
The above product **S13-2** (2.77 mmol, crude, 1 eq) was dissolved in DMF (5 mL). BnBr (0.40 mL, 3.32 mmol, 1.2 eq) and K_2CO_3 (0.57 g, 4.16 mmol, 1.5 eq) were added. The

suspension was stirred at rt for overnight. The reaction mixture was diluted with EtOAc, washed with water (50 mL x 2) and brine (30 mL x 1). The organic phase was concentrated under reduced pressure and the residue was purified on silica gel with 0 to 3% EtOAc/hexane to yield the desired product **S13-3**: MS (ESI) *m/z* 589.0 (M-H).



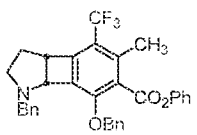
S13-4

To compound **S13-3** (632 mg, 1.07 mmol, 1 eq) in THF (5 mL) cooled at -78 °C was added *i*PrMgCl-LiCl (1.07 mL, 1.3 M/THF, 1.39 mmol, 1.3 eq) dropwise while maintaining reaction internal temperature between -72 to -75 °C. The reaction was stirred at -78 °C for 30 min. 1-*N*-Boc-2,3-dihydropyrrole (0.92 mL, 5.33 mmol, 5 eq) was added dropwise. The reaction was gradually warmed up from -78 °C to rt over 2 h with stirring. The reaction was further stirred at rt for 48 hrs. EtOAc (100 mL) was added. The reaction mixture was washed with saturated aqueous ammonium chloride (50 mL x 2) and brine (50 mL x 1), dried over magnesium sulfate, and concentrated under reduced pressure. Column chromatography on silica gel with 0 to 8% EtOAc/hexane yielded the desired product **S13-4** as a pale oil (224 mg, 38%): MS (ESI) *m/z* 576.4 (M+Na).



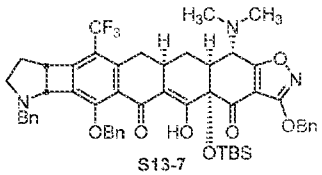
S13-5

Compound **S13-4** (224 mg, 0.40 mmol) was treated with 4 N HCl in dioxane at rt for 1 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the reaction mixture was extracted with EtOAc (50 mL x 3). The combined EtOAc extracts were dried over magnesium sulfate and concentrated under reduced pressure to give compound **S13-5** as a pale solid (165 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.60 (m, 8 H), 7.10 (d, J = 7.3 Hz, 2 H), 5.56 (ABq, J = 12.2, 28.1 Hz, 2 H), 4.76 (d, J = 3.6 Hz, 1 H), 4.03 (br d, J = 8.0 Hz, 1 H), 3.10-3.20 (m, 1 H), 2.65-2.80 (m, 1 H), 2.49 (s, 3 H), 1.90-2.00 (m, 1 H), 1.55-1.70 (m, 1 H); MS (ESI) *m/z* 454.4 (M+H).



S13-6

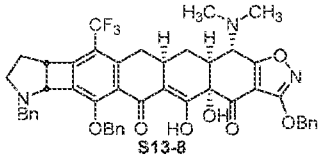
To compound **S13-5** (165 mg, 0.36 mmol, 1 eq) in 1,2-dichloroethane (4 mL) was added HOAc (0.033mL, 0.55 mmol, 1.5 eq), benzaldehyde (0.055 mL, 0.54 mmol, 1.5 eq), and $Na(OAc)_3BH$ (116 mg, 0.55 mmol, 1.5 eq) at rt. The reaction mixture was stirred at rt for overnight, added with aqueous sodium bicarbonate (50 mL), and extracted with EtOAc (50 mL x 3). The combined EtOAc extracts were dried over sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel with 0-8% EtOAc/hexane yielded the desired product **S13-6** as a pale oil (178 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.70 (m, 13 H), 7.07 (d, J = 7.4 Hz), 5.48 (br d, J = 12.2 Hz, 1 H), 5.18 (br d, J = 12.2 Hz, 1 H), 4.62 (br s, 1 H), 4.23 (br s, 1 H), 3.85 (br s, 1 H), 3.64 (d, J = 12.8 Hz, 1 H), 3.01 (br s, 1 H), 2.82 (br s, 1 H), 2.49 (s, 3 H), 2.04 (br s, 1 H), 1.87 (br s, 1 H); MS (ESI) m/z 544.4 (M+H).



S13-7

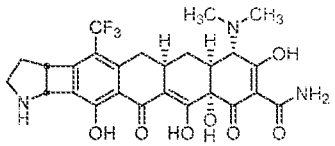
To diisopropylamine (0.058 mL, 0.41 mmol, 1.25 eq) in THF (2 mL) at -78 °C was added nBuLi (0.164 mL, 2.5 M/hexane, 0.41 mmol, 1.25 eq) dropwise. The reaction was stirred at 0 °C for 10 min and cooled to -78 °C. Compound **S13-6** (178 mg, 0.33 mmol, in 4 mL THF) was added dropwise while maintaining the reaction internal temperature between -70 to -78 °C. The resulting deep red solution was stirred at -78 °C for 30 min. LHMDS (0.41 mL, 1 M/THF, 0.41 mmol, 1.25 eq) and enone **S5-5** (198 mg, 0.41 mmol, in 2 mL THF) were added dropwise while maintaining the reaction internal temperature between -70 to -78 °C. The reaction was gradually warmed up from -78 to 0 °C over 2 h with stirring. Saturated aqueous sodium bicarbonate (50 mL) was added. The reaction mixture was extracted with EtOAc (50 mL x 3). The combined EtOAc extracts were dried over magnesium sulfate. Column chromatography on silica gel with 0 to 25% EtOAc/hexane yielded the two diastereomers of desired product as yellow foams. **S13-7A**, diastereomer A (125 mg, 41%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.01 (s, 1 H), 7.18-7.50 (m, 11 H), 6.80-6.90 (m, 4 H), 5.49 (br s, 2 H), 5.36 (s, 2 H), 4.97 (s, 2 H), 4.50 (br s, 1 H), 4.13 (br s, 1 H), 3.94 (d, J = 13.0 Hz, 1 H), 3.76 (br s, 1 H), 3.62 (d, J = 13.4 Hz, 1 H), 3.19 (br d, J = 16.5 Hz, 1 H), 2.90-3.05 (m, 2 H), 2.40-3.80 (m, 4 H), 2.48 (s, 6 H), 2.11 (br d, J = 14.7 Hz, 1 H), 0.85 (s, 9 H), 0.28 (s, 3 H), 0.16 (s, 3 H); MS (ESI) m/z 932.6 (M+H). **S13-7B**, diastereomer B (136 mg, 44%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.87 (s, 1 H), 6.85-7.45 (m, 15 H), 6.05 (d, J = 10.4 Hz, 1 H), 5.35 (br s, 1 H), 5.25-5.35 (m,

1 H), 5.30 (d, J = 10.2 Hz, 2 H), 4.51 (br s, 1 H), 4.07 (br s, 1 H), 3.90 (d, J = 13.1 Hz, 1 H), 3.70-3.80 (m, 1 H), 3.75 (d, J = 13.0 Hz, 1 H), 3.55-3.65 (m, 1 H), 3.08-3.18 (m, 1 H), 2.00-2.95 (m, 6 H), 2.40 (s, 6 H), 0.80 (s, 9 H), 0.00-0.25 (m, 6 H); MS (ESI) *m/z* 932.6 (M+H).

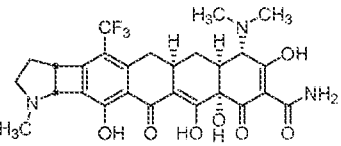


S13-8

Compound **S13-7A** (125 mg, 0.134 mmol) in dioxane (4 mL) was treated with 48% aqueous HF (4 mL) at rt for overnight. The reaction mixture was slowly added into a vigorously stirred saturated aqueous K_2HPO_4 solution (160 mL). The mixture was extracted with EtOAc (50 mL x 3). The EtOAc extracts were combined, dried over magnesium sulfate, and concentrated under reduced pressure to yield the crude product **S13-8A** as a yellow foam: MS (ESI) *m/z* 818.5 (M+H). Similarly, compound **S13-7B** (136 mg, 0.146 mmol) was desilylated to give compound **S13-8B** as a yellow foam: MS (ESI) *m/z* 818.5 (M+H).



S13-9-1



S13-9-2

Compound **S13-8A** (0.134 mmol, crude) was dissolved in dioxane:methanol (3:1, v/v, 4 mL). HCl (0.5 M/aqueous methanol, 1 mL) and 10% Pd-C (29 mg, 0.014 mmol, 0.1 eq) were added. The reaction mixture was then stirred under H_2 (1 atm) for 4 hrs. Half of the reaction mixture (2.5 mL) was removed from the reaction vessel and filtered through a small Celite pad. The Celite pad was washed with methanol (2 mL x 3). The combined filtrates were concentrated under reduced pressure. The crude product was purified by preparative HPLC with a gradient of 5% acetonitrile/0.05 N HCl to 40% acetonitrile/0.05 N HCl over 20 min to yield the desired product **S13-9-1A** as a yellow solid after lyophilization (22 mg, bis-HCl salt, 53%): ^{1}H NMR (400 MHz, CD_3OD) δ 5.31 (d, J = 3.7 Hz, 1 H), 4.40 (br d, J = 5.5 Hz, 1 H), 4.13 (s, 1 H), 3.64 (dd, J = 6.7, 11.6 Hz, 1 H), 2.90-3.20 (m, 4 H), 3.05 (s, 3 H), 2.95 (s, 3 H), 2.50-2.62 (m, 1 H), 2.10-2.30 (m 3 H), 1.55-1.70 (m, 1 H); MS (ESI) *m/z* 550.4 (M+H).

One half of the above reaction mixture (2.5 mL) was added with formaldehyde (0.10 mL, 37% in water, 1.33 mmol, 20 eq). The reaction mixture was stirred under H_2 (1 atm) at rt for 72 h and filtered through a small Celite pad. The Celite pad was washed with methanol (2 mL x 3) and the combined filtrates were concentrated under reduced pressure. The crude

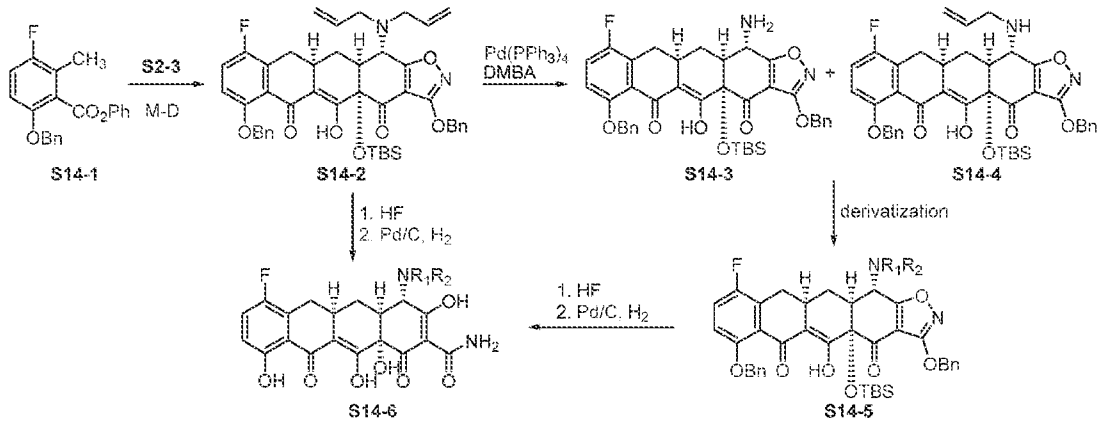
product was purified by preparative HPLC with a gradient of 5% acetonitrile/0.05 N HCl to 40% acetonitrile/0.05 N HCl over 20 min to yield the desired product **S13-9-2A** as an orange solid after lyophilization (16 mg, bis-HCl salt, 38%): ^{1}H NMR (400 MHz, CD_3OD) δ 5.42 (d, J = 3.0 Hz, 1 H), 4.40 (br s, 1 H), 4.13 (s, 1 H), 3.70-3.80 (m, 1 H), 2.94-3.15 (m, 4 H), 3.08 (s, 3 H), 3.05 (s, 3 H), 2.95 (s, 3 H), 2.55-2.65 (m, 1 H), 2.20-2.35 (m, 3 H), 1.58-1.70 (m, 1 H); MS (ESI) *m/z* 564.3 (M+H).

Compound **S13-8B** (0.146 mmol, crude) was similarly treated as **S13-8A** to yield the following desired compounds:

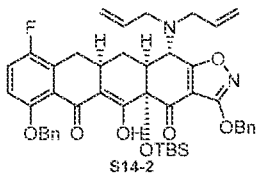
S13-9-1B (19 mg, bis-HCl salt, yellow solid, 42%): ^{1}H NMR (400 MHz, CD_3OD) δ 5.30 (d, J = 3.0 Hz, 1 H), 4.40 (br d, J = 5.5 Hz, 1 H), 4.13 (s, 1 H), 3.63 (dd, J = 6.3, 11.6 Hz, 1 H), 2.90-3.22 (m, 4 H), 3.04 (s, 3 H), 2.94 (s, 3 H), 2.52-2.61 (m, 1 H), 2.08-2.30 (m, 3 H), 1.56-1.68 (m, 1 H); MS (ESI) *m/z* 550.4 (M+H).

S13-9-2B (18 mg, bis-HCl salt, yellow solid, 39%): ^{1}H NMR (400 MHz, CD_3OD) δ 5.41 (d, J = 2.8 Hz, 1 H), 4.39 (br s, 1 H), 4.14 (s, 1 H), 3.70-3.78 (m, 1 H), 2.90-3.25 (m, 4 H), 3.11 (s, 3 H), 3.04 (s, 3 H), 2.95 (s, 3 H), 2.54-2.63 (m, 1 H), 2.20-2.35 (m, 3 H), 1.58-1.69 (m, 1 H); MS (ESI) *m/z* 564.3 (M+H).

Scheme 14

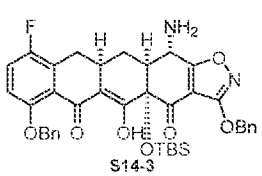


The following compounds were prepared per Scheme 14.

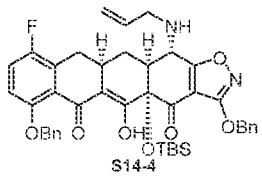


S14-2

Compound **S14-2** was prepared from compound **S14-1** (obtained via standard benzylation of the corresponding phenol, which was prepared according to literature procedures including WO2012/021712 A1) and diallylenone **S2-3** by using General Procedure **E**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.05 (s, 1H), 7.52-7.42 (m, 4H), 7.41-7.25 (m, 6H), 7.13-7.07 (m, 1H), 6.83 (dd, J = 9.4, 4.1 Hz, 1H), 5.85-5.73 (m, 2H), 5.36 (s, 2H), 5.24-5.07 (m, 6H), 4.08 (d, J = 10.1 Hz, 1H), 3.36-3.27 (m, 2H), 3.25-3.10 (m, 3H), 3.04-2.9 (m, 1H), 2.68-2.57 (m, 1H), 2.54-2.39 (m, 2H), 2.15-2.08 (m, 1H), 0.816 (s, 9H), 0.25 (s, 3H), 0.12 (s, 3H); MS (ESI) *m/z* 777.58 (M+H).

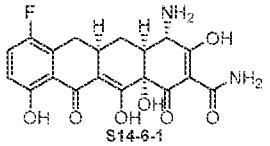


S14-3



S14-4

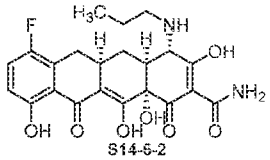
Compound **S14-3** and **S14-4** were prepared from compound **S14-2** by using General Procedure **A**. **S14-3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.61 (s, 1H), 7.54-7.42 (m, 4H), 7.42-7.26 (m, 6H), 7.08 (t, J = 8.4 Hz, 1H), 6.83 (dd, J = 9.0, 4.0 Hz, 1H), 5.39, 5.35 (ABq, J = 12.2 Hz, 2H), 5.23, 5.14 (ABq, J = 12.2 Hz, 2H), 3.92 (d, J = 2.4 Hz, 1H), 3.02 (dd, J = 16.0, 3.6 Hz, 1H), 2.87-2.75 (m, 1H), 2.64-2.57 (m, 1H), 2.19 (t, J = 16.0 Hz, 1H), 2.15-2.05 (m, 2H), 0.73 (s, 9H), 0.20 (s, 3H), 0.09 (s, 3H); MS (ESI) 697.53 *m/z* (M+H). **S14-4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.66 (s, 1H), 7.54-7.42 (m, 4H), 7.42-7.25 (m, 6H), 7.10-7.04 (m, 1H), 6.83 (dd, J = 9.2, 4.5 Hz, 1H), 5.93-5.78 (m, 1H), 5.41-5.34 (m, 2H), 5.30-5.08 (m, 4H), 4.69 (d, J = 6.1 Hz, 1H), 3.76-3.70 (m, 1H), 3.58-3.50 (m, 1H), 3.46-3.37 (m, 1H), 3.02-2.94 (m, 1H), 2.83-2.67 (m, 2H), 2.15 (t, J = 15.0 Hz, 1H), 2.06-1.98 (m, 1H), 0.72 (s, 9H), 0.20 (s, 3H), 0.07 (s, 3H); MS (ESI) *m/z* 737.51 (M+H).



S14-6-1

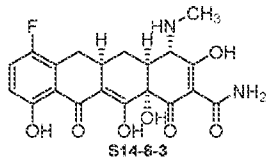
Compound **S14-6-1** was prepared from compound **S14-3** by using General Procedures **C** and **D-2**: **S14-6-1**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.26 (t, J = 8.9 Hz,

1H), 6.80 (dd, *J* = 9.2 4.0 Hz, 1H), 3.87 (s, 1H), 3.15 (dd, *J* = 15.3, 4.9 Hz, 1H), 2.97 (qd, *J* = 9.8, 4.9 Hz, 1H), 2.61 (dt, *J* = 12.6, 2.1 Hz, 1H), 2.29 (t, *J* = 10.4 Hz, 1H), (qd, *J* = 13.7, 2.4 Hz, 1H), 1.59 (td, *J* = 13.3, 10.6 Hz, 1H); MS (ESI) *m/z* 405.25 (M+H).

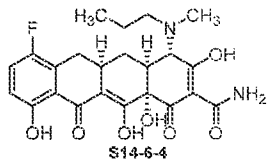


S14-6-2

Compound **S14-6-2** was prepared from compound **S14-2** by using General Procedures **C** and **D-2**: **S14-6-2** ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.26 (t, *J* = 9.2 Hz, 1H), 6.81 (dd, J = 9.2, 4.0 Hz, 1H), 3.86 (s, 1H), 3.27-3.17 (m, 2H), 3.16-3.09 (m, 1H), 3.04-2.92 (m, 1H), 2.82 (d, *J* = 12.8 Hz, 1H), 2.27 (t, *J* = 14.6 Hz, 1H), 2.19 (dq, *J* = 13.6, 2.6 Hz, 1H), 1.76 (td, *J* = 15.6, 7.7 Hz, 2H), 1.57 (td, *J* = 13.4, 11.0 Hz, 1H), 1.03 (t, *J* = 7.3 Hz, 3H); MS (ESI) *m/z* 447.33 (M+H).

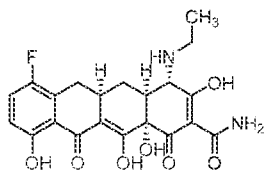


S14-6-3



S14-6-4

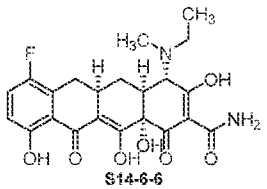
Compounds **S14-6-3** and **S14-6-4** were prepared from compound **S14-4** with HCHO by using General Procedures **B-1**, **C**, and **D2**. **S14-6-3**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.27 (t, *J* = 8.9 Hz, 1H), 6.81 (dd, J = 9.2, 4.0 Hz, 1H), 3.78 (s, 1H), 3.14 (dd, *J*= 15.0, 4.6 Hz, 1H), 3.04-2.93 (m, 2H), 2.90 (s, 3H), 2.80-2.73 (m, 1H), 2.28 (t, *J* = 14.6 Hz, 1H), 2.18 (dq, *J* = 13.6, 2.6 Hz, 1H), 1.62-1.50 (m, 1H), MS (ESI) *m/z* 419.32 (M+H). **S14-6-4**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.27 (t, *J* = 9.2 Hz, 1H), 6.81 (dd, J = 9.2, 4.0 Hz, 1H), 4.19 (s, 0.5H), 4.09 (s, 0.5H), 3.39-3.31 (m, 1H) 3.22-3.09 (m, 2H), 3.08-2.86 (m, 5H), 2.34-2.13 (m, 2H), 1.90-1.56 (m, 3H), 1.08-0.95 (m, 3H); MS (ESI) *m/z* 461.32 (M+H).



S14-6-5

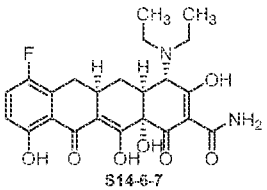
Compound **S14-6-5** was prepared from compound **S14-3** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **C**, and **D2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.26 (t, *J* = 8.9 Hz, 1H), 6.81 (dd, J = 9.2, 4.0 Hz, 1H), 3.84 (s, 1H), 3.48-3.30 (m, 2H), 3.14

(dd, *J* = 14.6, 4.3 Hz, 1H), 3.03-2.92 (m, 1H), 2.79 (d, *J* = 12.2 Hz, 1H), 2.27 (t, *J* = 14.4 Hz, 1H), 2.19 (qd, *J* = 11.2, 3.2 Hz, 1H), 1.62-1.50 (m, 1H), 1.35 (t, *J* = 7.3 Hz, 3H); MS (ESI) *m/z* 433.31 (M+H).



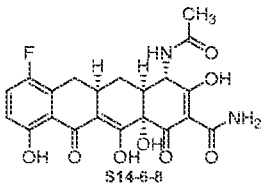
S14-6-6

Compound **S14-6-6** was prepared from compound **S14-3** with CH_3CHO by using General Procedures **B-1** (at 0 °C), then **B-1** again with HCHO, **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.27 (t, *J* = 8.9 Hz, 1H), 6.81 (dd, J = 9.2, 4.0 Hz, 1H), 4.21 (s, 0.5H). 4.10 (s, 0.5H), 3.52-3.41 (m, 1H), 3.38-3.29 (m, 1h), 3.19-3.11 (m, 1H), 3.09-2.85 (m, 5H), 2.34-2.15 (m, 2H), 1.71-1.56 (m, 1H), 1.44-1.33 (m, 3H); MS (ESI) *m/z* 447.29 (M+H).



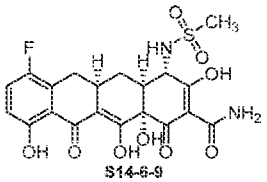
S14-6-7

Compound **S14-6-7** was prepared from compound **S14-3** with CH_3CHO by using General Procedures **B-1**, **C**, and **D2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.27 (t, *J* = 9.2 Hz, 1H), 6.81 (dd, J = 9.2, 4.0 Hz, 1H), 4.23 (s, 1H), 3.63-3.52 (m, 1H), 3.80-3.40 (m, 2H), 3.35-3.24 (m, 1H), 3.19-3.11 (m, 1H), 3.07-2.96 (m, 1H), 2.88 (d, *J* = 12.8 Hz, 1H), 2.32-2.16 (m, 2), 1.69-1.56 (m, 1H), 1.40 (t, *J* = 7.0 Hz, 6H); MS (ESI) *m/z* 461.32 (M+H).



S14-6-8

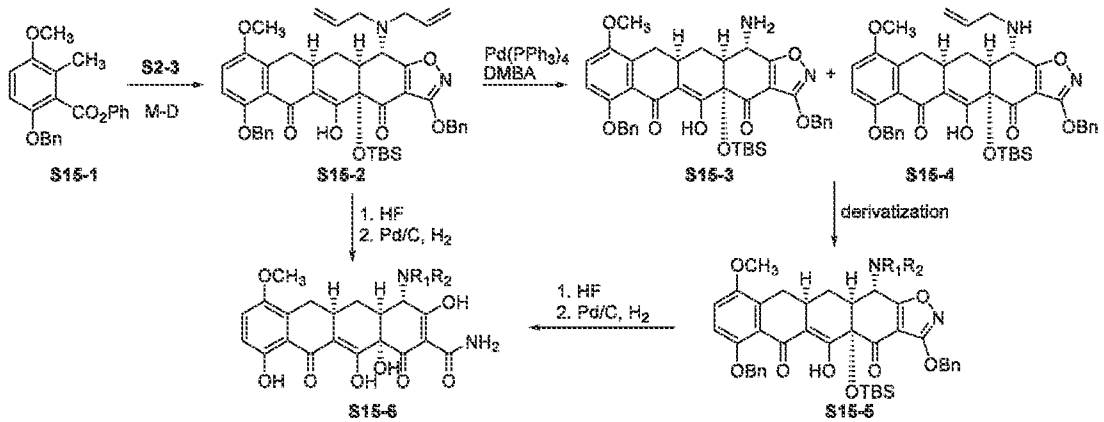
Compound **S14-6-8** was prepared from compound **S14-3** with Ac_2O using General Procedures **B-2**, **C**, and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.23 (t, *J* = 9.2 Hz, 1H), 6.76 (dd, J = 9.2, 3.7 Hz, 1H), 4.70-4.59 (m, 1H), 3.10-3.03 (m, 1H), 3.02-2.91 (m, 1H), 2.53-2.30 (m, 2H), 2.03 (s, 3H), 1.65-1.56 (m, 1H); MS (ESI) *m/z* 447.24 (M+H).



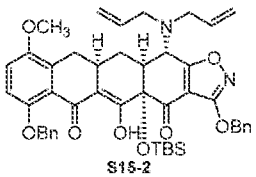
S14-6-9

Compound **S14-6-9** was prepared from compound **S14-3** with Ms_2O using General Procedures **B-2**, **C**, and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.24 (t, J = 8.9 Hz, 1H), 6.77 (dd, J = 8.9, 4.0 Hz, 1H), 4.09 (d, J = 4.3 Hz, 1H), 3.16-3.08 (m, 4H), 3.04-2.92 (m, 1H), 2.53-2.40 (m, 2H), 2.31-2.23 (m, 1H), 1.72-1.61 (m, 1H); MS (ESI) *m/z* 483.1 (M+H).

Scheme 15

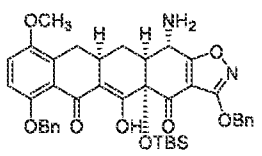


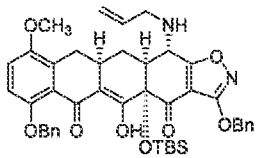
The following compounds were prepared per Scheme 15.



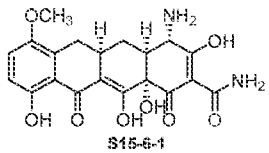
S15-2

Compound **S15-2** was prepared from compound **S15-1** (prepared according to literature procedures including WO2011/025982 A2) and diallylenone **S2-3** by using General Procedure **E**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.07 (s, 1H), 7.51-7.43 (m, 4H), 7.40-7.25 (m, 6H), 6.92, 6.82 (ABq, J = 8.8 Hz, 2H), 5.88-5.73 (m, 2H), 5.35 (s, 2H), 5.23-5.06 (m, 6H), 4.11 (d, J = 9.8 Hz, 1H), 3.80 (s, 3H), 3.36-3.15 (m, 5H), 3.00-2.77 (m, 1H), 2.56-2.34 (m, 3H), 2.15-2.08 (m, 1H), 0.81 (s, 9H), 0.25 (s, 3H), 0.12 (s, 3H); MS (ESI) *m/z* 789.55 (M+H).

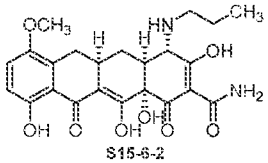

S15-3

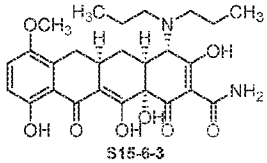

S15-4

Compound **S15-3** and **S15-4** were prepared from compound **S15-2** by using General Procedure **A**. **S15-3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.63 (s, 1H), 7.53-7.46 (m, 4H), 7.41-7.27 (m, 6H), 6.93 (d, J = 9.2 Hz, 1H), 6.85 (d, J = 9.2 Hz, 1H), 5.41, 5.36 (ABq, J = 12.1 Hz, 2H), 5.22, 5.12 (ABq, J = 12.1 Hz, 2H), 3.96-3.92 (m, 1H), 3.66 (s, 3H), 3.16 (dd, J = 15.9, 4.3 Hz, 1H), 2.84-2.72 (m, 1H), 2.64-2.57 (m, 1H), 2.13-2.06 (m, 3H), 0.75 (s, 9H), 0.22 (s, 3H), 0.12 (s, 3H); MS (ESI) *m/z* 709.49 (M+H). **S15-3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.70 (s, 1H), 7.54-7.46 (m, 4H), 7.41-7.28 (m, 6H), 6.93 (d, J = 9.2, 1H), 6.85 (d, J = 9.2 Hz, 1H), 5.95-5.84 (m, 1H), 5.42, 5.37 (ABq, J = 12.2 Hz, 2H), 5.32-5.08 (m, 4H), 3.77 (s, 3H), 3.56 (dd, J = 13.2, 6.7 Hz, 1H), 3.47-3.39 (m, 1H), 3.11 (dd, J = 15.9, 4.9 Hz, 1H), 2.80-2.68 (m, 2H), 2.61-2.45 (m, 1H), 2.08-1.98 (m, 2H), 1.51-1.39 (m, 1H), 0.73 (s, 9H), 0.22 (s, 3H), 0.10 (s, 3H); MS (ESI) *m/z* 749.48 (M+H).


S15-6-1

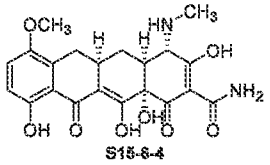
Compound **S15-6-1** was prepared from compound **S15-3** by using General Procedures **C** and **D-2**: **S15-6-1**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.21 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 9.2 Hz, 1H), 3.83 (s, 1H), 3.77 (s, 3H), 2.93-2.82 (m, 1H), 2.60-2.52 (m, 1H), 2.22-2.07 (m, 2H), 1.63-1.50 (m, 1H); MS (ESI) *m/z* 417.25 (M+H).

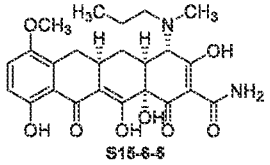

S15-6-2


S15-6-3

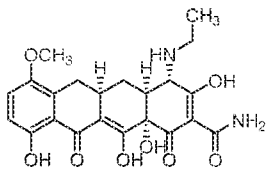
Compounds **S15-6-2** and **S15-6-3** were prepared from compound **S15-2** by using General Procedures **C** and **D-2**. **S15-6-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.21 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 9.2 Hz, 1H), 3.85 (s, 1H), 3.77 (s, 3H), 3.28-3.14 (m, 3H), 2.96-2.84 (m, 1H), 2.80 (d, J = 12.2 Hz, 1H), 2.20-2.05 (m, 2H), 1.81-1.65 (m, 2H), 1.60-1.48 (m, 1H), 1.02 (t. J = 7.3 Hz, 3H); MS (ESI) *m/z* 459.4 (M+H). **S15-6-3**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.22 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 9.2 Hz, 1H), 4.18 (s, 1H),

3.77 (s, 3H), 3.39-3.14 (m, 5H), 3.04-2.64 (m, 2H), 2.20-2.08 (m, 2H), 1.90-1.74 (m, 2H), 1.70-1.52 (m, 1H), 1.08-0.98 (m, 6H); MS (ESI) *m/z* 501.3 (M+H).

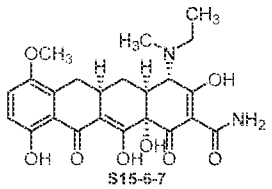

S15-6-4


S15-6-5

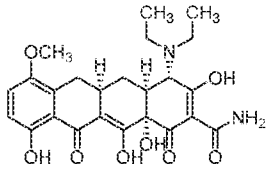
Compounds **S14-6-4** and **S14-6-5** were prepared from compound **S15-4** with HCHO by using General Procedures **B-1**, **C**, and **D2**. **S15-6-4**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.21 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 9.2 Hz, 1H), 3.80-3.76 (m, 4H), 3.26-3.20 (m, 1H), 2.95-2.84 (m, 4H), 2.78-2.71 (m, 1H), 2.19-2.04 (m, 2H), 1.60-1.47 (m, 1H); MS (ESI) *m/z* 431.2 (M+H). **S15-6-5**: ^{1}H NMR (400 MHz, CD_3OD, , hydrochloride salt, rotamers) δ 7.21 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 9.2 Hz, 1H), 4.18 (s, 0.5H), 4.08 (s, 0.5H), 3.78 (s, 3H), 3.40-3.23 (m, 3H), 3.22-3.10 (m, 1H), 3.04-2.85 (m, 4H), 2.23-2.06 (m, 2H), 1.90-1.69 (m, 2H), 1.69-1.54 (m, 1H), 1.07-0.96 (m, 3H); MS (ESI) *m/z* 473.2 (M+H).


S15-6-6

Compound **S15-6-6** was prepared from compound **S15-3** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **C**, and **D2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.21 (d, J = 9.2 Hz, 1H), 6.77 (d, J = 9.2 Hz, 1H), 3.84 (s, 1H), 3.77 (s, 3H), 3.45-3.20 (m, 2H), 2.96-2.83 (m. 1H), 2.78 (d, J = 12.8 Hz, 1H), 2.21-2.00 (m, 2H), 1.59-1.46 (m, 1H), 1.35 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 445.2 (M+H).

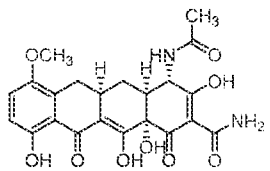

S15-6-7

Compound **S15-6-7** was prepared from compound **S15-3** with CH_3CHO by using General Procedures **B-1** (at 0 °C), then **B-1** again with HCHO, **C** and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt, rotamers) δ 7.22 (d, J = 9.2 Hz, 1H), 6.77 (d, J = 9.2 Hz, 1H), 4.20 (s, 0.5H), 4.09 (s, 0.5H), 3.77 (s, 3H), 3.52-3.40 (m, 1H), 3.38-3.22 (m, 2H), 3.04-2.83 (m, 5H), 2.23-2.06 (m, 2H), 1.70-1.53 (m, 1H), 1.44-1.33 (m, 3H); MS (ESI) *m/z* 459.2 (M+H).



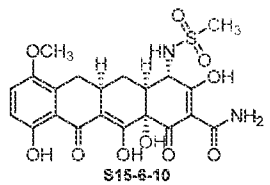
S15-6-8

Compound **S15-6-8** was prepared from compound **S15-3** with CH_3CHO by using General Procedures **B-1**, **C**, and **D2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 7.21 (d, J = 9.2 Hz, 1H), 6.77 (d, J = 9.2 Hz, 1H), 4.22 (s, 1H), 3.77 (s, 3H), 3.64-3.52 (m, 1H), 3.48-3.37 (m, 2H), 3.30-3.23 (m, 2H), 3.01-2.81 (m, 2H), 2.23-2.05 (m, 2H), 1.66-1.53 (m, 1H), 1.39 (t, J = 7.3 Hz, 6H); MS (ESI) *m/z* 473.2 (M+H).



S15-6-9

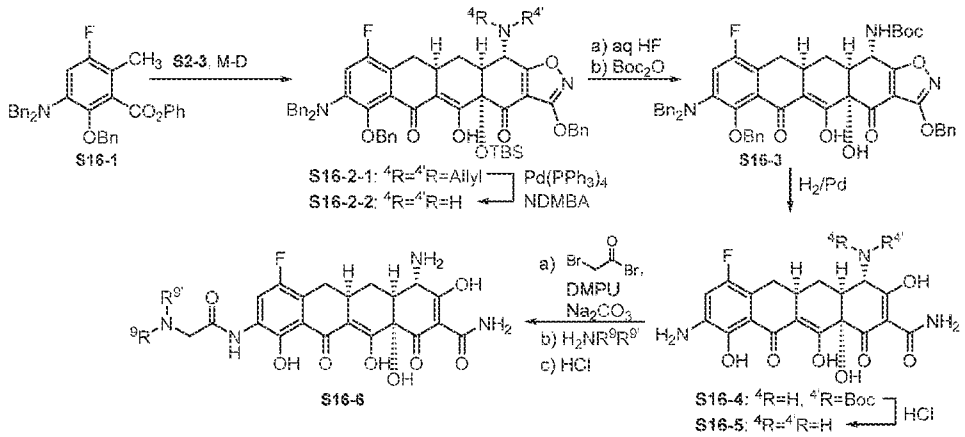
Compound **S15-6-9** was prepared from compound **S15-3** with Ac_2O using General Procedures **B-2**, **C**, and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt, rotamers) δ 7.18 (d, J = 9.2 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 4.71-4.64 (m, 1H), 3.77 (s, 3H), 3.20 (dd, J = 16.5, 4.9 Hz, 1H), 2.94-2.84 (m, 1H), 2.46-2.22 (m, 3H), 2.03 (s, 3H), 1.63-1.52 (m, 1H); MS (ESI) *m/z* 459.2 (M+H).



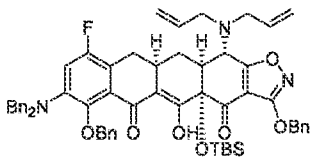
S15-6-10

Compound **S15-6-10** was prepared from compound **S15-3** with Ms_2O using General Procedures **B-2**, **C**, and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt, rotamers) δ 7.18 (d, J = 9.2 Hz, 1H), 6.74 (d, J = 9.2 Hz, 1H), 4.71-4.64 (m, 1H), 4.08 (d, J = 4.3 Hz, 1H), 3.77 (s, 3H), 3.23 (dd, J = 15.9, 4.9 Hz, 1H), 3.13 (s, 3H), 2.95-2.84 (m, 1H), 2.48 (td, J = 7.2, 3.5 Hz, 1H), 2.33-2.18 (m, 2H), 1.69-1.58 (m, 1H); MS (ESI) *m/z* 495.18 (M+H).

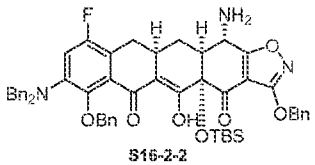
Scheme 16



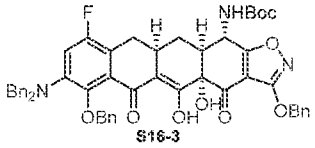
The following compounds were prepared per Scheme 16.



Compound **S16-2-1** was prepared from **S16-1** (6.574 g, 12.36 mmol, 2.1 eq) and C-4 ethylmethylamino enone **S2-3** (3.149 g, 5.89 mmol, 1 eq) by using General Procedure **E**. Product **S16-2-1** (1.321 g, 23%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.17 (s, 1H), 7.55-7.50 (m, 4H), 7.41-7.30 (m, 8 H), 7.29-7.22 (m, 4H), 7.18-7.11 (m, 4H), 6.68 (d, J = 11.0 Hz, 1H), 5.88-5.76 (m, 2H), 5.37 (s, 2H), 5.27-5.10 (m, 5H), 5.00 (d, J = 9.5 Hz, 1H), 4.33 (d, J = 14.6 Hz, 2H), 4.19 (d, J = 14.0 Hz, 2H), 3.38-3.19 (m, 4H), 3.13-2.95 (m, 2H), 2.17-2.10 (m, 1H), 0.83 (s, 9H), 0.26 (s, 3H), 0.15 (s, 3H); MS (ESI) *m/z* 972.55 (M+H).

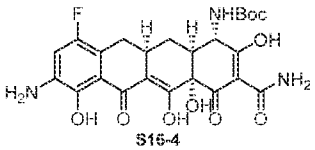


Compound **S16-2-2** was prepared from compound **S16-2-1** (1.321 g, 1.36 mmol, 1 eq) by using General Procedure **A**. **S16-2-2** (884 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.52 (s, 1H), 7.40-7.33 (m, 4H), 7.30-7.20 (m, 6H), 7.20-7.13 (m, 2H), 7.09-7.02 (m, 4H), 6.56 (d, J = 10.4 Hz, 1H), 5.31, 5.26 (ABq, J = 16.8 Hz, 2H), 5.17, 5.04 (ABq, J = 10.4 Hz, 2H), 4.26, 4.11 (ABq, J = 14.0 Hz, 2H), 3.82 (s, 1H), 2.82 (dd, J = 15.3, 4.3 Hz, 1H), 2.64-2.52 (m, 1H), 2.52-2.44 (m, 1H), 2.08-1.92 (m, 4H), 0.67 (s, 9H), 0.12 (s, 3H), 0.00 (s, 3H); MS (ESI) *m/z* 892.56 (M+H).



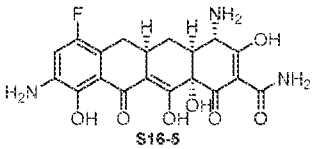
S16-3

Compound **S16-3** was prepared from compound **S16-2-2** (884 mg, 0.99 mmol, 1 eq) using General Procedure **C**, followed by treatment with Boc_2O (227 mg, 1.04 mmol, 1.05 eq) in DCM (10 mL) at 0 °C, followed by warming to ambient temperature until complete by LCMS analysis. The reaction solution was diluted with saturated aqueous ammonium chloride (30 mL) and extracted with EtOAc (2 x 35 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude product was purified via flash column chromatography on silica gel using 8%-50% EtOAc/hexanes to yield the desired product **S16-3** (750 mg, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.03 (s, 1H), 7.50-7.21 (m, 15H), 7.18-7.11 (m, 5 H), 6.68 (d, J = 10.4 Hz, 1H), 5.83-5.77 (m, 1H), 5.35 (s, 2H), 5.23 (d, J = 9.7 Hz, 1H), 5.13-5.03 (m, 2H), 4.57 (s, 1H), 4.33 (d, J = 14.6 Hz, 2H), 4.22 (d, J = 14.0 Hz, 2H), 2.92-2.85 (m, 1H), 2.70-2.57 (m, 2H), 2.16-2.05 (m, 2H), 1.57 (s, 9H); MS (ESI) *m/z* 878.61 (M+H).



S16-4

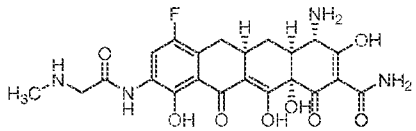
Compound **S16-4** was prepared by dissolving **S16-3** (750 mg, 0.854 mmol, 1 eq) in methanol:dioxane (1:1, 8 mL) with 1 N aqueous HCl (854 µL, 1 eq). Pd-C (10wt%, 106 mg) was added in one portion and the reaction vessel was sealed and purged with hydrogen by briefly evacuating the flask followed by flushing with hydrogen gas (1 atm). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 6.5 hr. The reaction was filtered through a small Celite pad. The cake was washed with CH_3OH. The filtrate was concentrated and the resulting orange foam was used without further purification. **S16-4**: MS (ESI) *m/z* 518.26 (M-H).



S16-5

To a solution of **S16-4** (20mg, 0.038 mmol, 1 eq) in CH_3OH (750 µL) was added concentrated HCl (12N, 200 µL). The reaction was stirred at room temperature for 4 hr. The

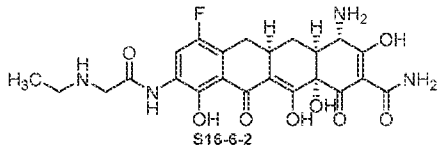
solution was concentrated under reduced pressure and the residue was dissolved in 0.05 *N* HCl in water and the resulting solution was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 µ RP-γ 100A column [10 µm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 2.0 mL (0.05 *N* HCl/water); gradient: 5→30% B in A over 20 min; mass-directed fraction collection]. Fractions containing the desired product were collected and freeze-dried to yield compound **S16-5**: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.38 (d, J = 8.6 Hz, 1H), 3.88 (s, 1H), 3.23-3.10 (m, 1H), 3.09-2.95 (m, 1H), 2.64 (d, J = 12.2 Hz, 1H), 2.42-2.30 (m, 1H), 2.29-2.19 (m, 1H), 2.68-2.45 (m, 1H); MS (ESI) *m/z* 420.2 (M+H).



S16-6-1

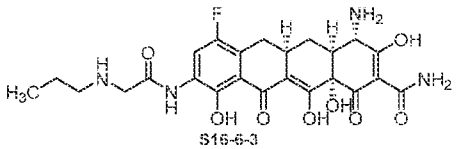
General Procedure H (acylation/amine addition): To a solution of **S16-4** (32 mg, 0.62 mmol, 1 eq) in DMPU:CH_3CN (400 µL:1.6 mL) was added Na_2CO_3 (32 mg, 0.302 mmol, 5 eq) and bromoacetylbromide (6.5 µL, 0.72 mmol, 1.2 eq). This mixture was stirred under an atmosphere of nitrogen for 1.5 hr. A solution of methylamine (2.0 M in THF, 335 µL, 0.62 mmol, 10 eq) was added and the reaction was stirred at room temperature for 17 hr. The reaction solution was concentrated under reduced pressure, then dissolved in CH_3OH (400 µL) and added dropwise to rapidly stirring MTBE (15 mL). The resulting green precipitate was filtered off on a Celite pad and washed with MTBE. The solid was washed off the Celite pad with CH_3OH containing several drops of concentrated HCl. The resulting orange solution was concentrated in vacuo. The crude residue was dissolved in CH_3OH (1 mL), to which was added 0.05 *N* HCl in water (300 µL) and concentrated HCl (200 µL). The reaction solution was stirred at room temperature for 1.5 hr. The solution was concentrated under reduced pressure and the resulting residue was dissolved in CH_3OH (800 µL) and added to rapidly stirring MTBE (15 mL). The resulting orange precipitate was filtered through a Celite pad and washed as before, then washed off the Celite pad with CH_3OH. The solution was concentrated under reduced pressure. The residue was dissolved in 0.05 *N* HCl in water and the resulting solution was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 µ RP-γ 100A column [10 µm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 2.0 mL (0.05 *N* HCl/water); gradient: 5→30% B in A over 20 min; mass-directed fraction collection]. Fractions

containing the desired product were collected and freeze-dried to yield compound **S16-6-1** (4.9 mg, 4%): ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.06 (s, 2H), 3.88 (s, 1H), 3.18-3.10 (m, 1H), 3.07-2.93 (m, 1H), 2.77 (s. 3H), 2.62 (d, J = 12.8 Hz, 1H), 2.33-2.18 (m, 2H), 1.64-1.56 (m, 1H); MS (ESI) *m/z* 491.21 (M+H).



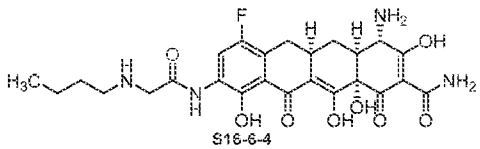
S16-6-2

Compound **S16-6-2** was prepared from compound **S16-4** with ethylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.07 (s, 2H), 3.88 (s, 1H), 3.18-3.10 (m, 3H), 3.07-2.93 (m, 1H), 2.67-2.60 (m. 1H), 2.33-2.20 (m, 2H), 1.64-1.56 (m, 1H) 1.35 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 565.19 (M+H).



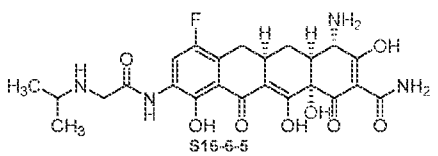
S16-6-3

Compound **S16-6-3** was prepared from compound **S16-4** with propylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.08 (s, 2H), 3.89 (s, 1H), 3.17-2.92 (m, 4H), 2.66 (d, J = 12.2 Hz, 1H), 2.33-2.20 (m, 2H), 1.85-1.72 (m, 2H), 1.64-1.56 (m, 1H), 1.04 (t, J = 7.6 Hz, 3H); MS (ESI) *m/z* 519.26 (M+H).



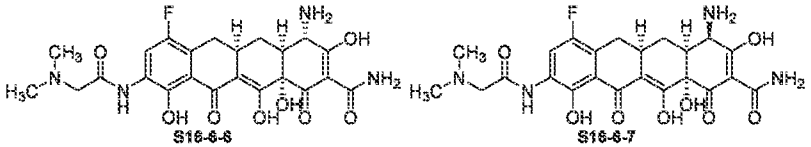
S16-6-4

Compound **S16-6-4** was prepared from compound **S16-4** with butylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.08 (s, 2H), 3.88 (s, 1H), 3.18-2.94 (m, 4H), 2.66 (d, J = 12.2 Hz, 1H), 2.33-2.20 (m, 2H), 1.78-1.68 (m, 2H), 1.64-1.52 (m, 1H), 1.48-1.38 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H); MS (ESI) *m/z* 533.32 (M+H).

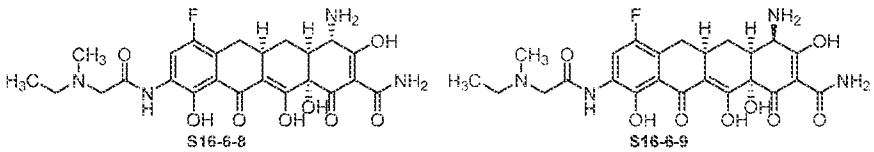


S15-6-5

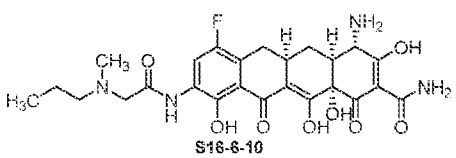
Compound **S16-6-5** was prepared from compound **S16-4** with isopropylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.08 (s, 2H), 3.88 (s, 1H), 3.52-3.43 (m, 1H), 3.18-3.10 (m, 1H), 3.05-2.95 (m, 1H), 2.63 (d, J = 12.8 Hz, 1H), 2.35-2.20 (m, 2H), 1.64-1.56 (m, 1H), 1.37 (d, J = 6.8 Hz, 6H); MS (ESI) *m/z* 519.19 (M+H).



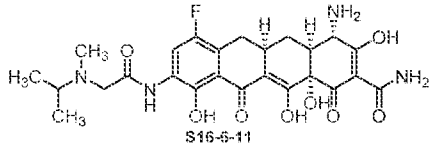
Compounds **S16-6-6** and **S16-6-7** were prepared from compound **S16-4** with dimethylamine using General Procedure **H**. **S16-6-6**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.22 (s, 2H), 3.87 (s, 1H), 3.18-3.10 (m, 1H), 3.07-2.93 (m, 7H), 2.77 (s. 3H), 2.64-2.60 (m, 1H), 2.33-2.18 (m, 2H), 1.64-1.56 (m, 1H); MS (ESI) 505.27 *m/z* (M+H). **S16-6-7**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.78-4.74 (m, 1H), 4.22 (s, 2H), 3.18-3.08 (m, 1H), 2.99 (s, 6H), 2.92-2.74 (m, 2H), 2.36-2.27 (s. 1H), 2.14-2.05 (m, 1H), 1.52-1.42 (m, 1H); MS (ESI) *m/z* 505.27 (M+H).



Compounds **S16-6-8** and **S16-6-9** were prepared from compound **S16-4** with dimethylamine using General Procedure **H**. **S16-6-8**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.28 (d, J = 17.7 Hz, 1H), 4.16 (d, J = 17.7 Hz, 1H), 3.88 (s, 1H), 3.50-3.23 (m, 2H), 3.17-3.10 (m, 1H), 3.03-2.94 (m. 4H), 2.64-2.60 (m, 1H) 2.36-2.19 (m, 2H), 1.66-1.55 (m, 1H), 1.38 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 519.26 (M+H). **S16-6-9**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.78-4.74 (m, 1H), 4.28 (d, J = 17.7 Hz, 1H), 4.16 (d, J = 17.7 Hz, 1H), 3.50-3.23 (m, 2H), 3.17-3.10 (m, 1H), 3.03-3.73 (m, 6H), 2.37-2.26 (m, 1H), 2.15-2.05 (m, 1H), 1.51-1.35 (m, 4H); MS (ESI) *m/z* 519.26 (M+H).

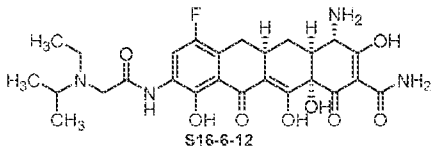


Compound **S16-6-10** was prepared from compound **S16-4** with *N*-methylpropylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.29 (d, J = 16.5 Hz, 1H), 4.18 (d, J = 18.9 Hz, 1H), 3.30-3.12 (m, 2H), 3.15-2.92 (m, 4H), (d, J = 12.2 Hz, 1H), 2.36-2.20 (m, 2H), 1.86-1.76 (m, 2H), 1.64-1.56 (m, 1H), 1.03 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 533.23 (M+H).



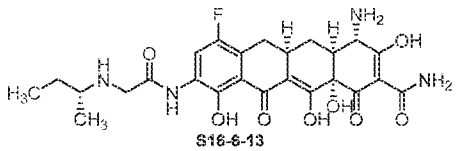
S16-6-11

Compound **S16-6-11** was prepared from compound **S16-4** with *N*-methylisopropylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.30 (d, J = 15.9 Hz, 1H), 4.09 (d, J = 15.9 Hz, 1H), 3.88 (s, 1H), 3.72-3.65 (m, 1H), 3.18-3.10 (m, 1H), 3.05-2.93 (m, 1H), 2.90 (s, 3H), 2.66-2.61 (m, 1H), 2.35-2.18 (m, 2H), 1.59-1.52 (m, 1H), 1.43-1.32 (m, 6H); MS (ESI) *m/z* 533.25 (M+H).



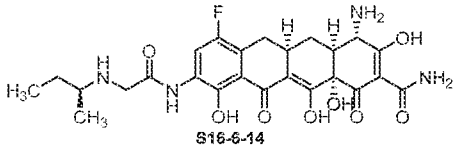
S16-6-12

Compound **S16-6-12** was prepared from compound **S16-4** with *N*-ethylisopropylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.31 (d, J = 17.1 Hz, 1H), 4.08 (d, J = 16.5 Hz, 1H), 3.88 (s, 1H), 3.82-3.72 (m, 1H), 3.41-3.32 (m, 1H), 3.21-3.10 (m, 1H), 3.17-2.93 (m, 1H), 2.66-2.61 (m, 1H), 2.35-2.18 (m, 2H), 1.64-1.52 (m, 1H), 1.44-1.30 (m, 9H); MS (ESI) *m/z* 547.26 (M+H).



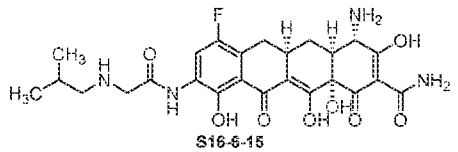
S16-6-13

Compound **S16-6-13** was prepared from compound **S16-4** with *R*-(-)-*sec*-butylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.24 (d, J = 11.0 Hz, 1H), 4.10 (s, 2H), 3.88 (s, 1H), 3.72-3.65 (m, 1H), 3.31-3.25 (m, 2H), 3.18-3.10 (m, 1H), 3.05-2.93 (m, 1H), 2.90 (s, 3H), 2.66-2.61 (m, 1H), 2.35-2.18 (m, 2H), 1.88-1.82 (m, 1H), 1.65-1.52 (m, 1H), 1.38-1.25 (m, 3H), 1.04 (t, J = 7.9 Hz, 3H); MS (ESI) *m/z* 533.23 (M+H).



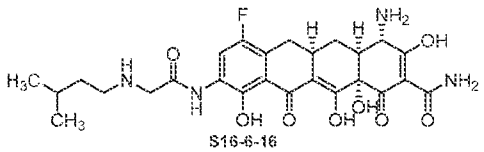
S16-6-14

Compound **S16-6-14** was prepared from compound **S16-4** with *S*-(+)-*sec*-butylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.09 (s, 2H), 3.87 (s, 1H), 3.18-3.10 (m, 1H), 3.05-2.92 (m, 1H), 2.65-2.60 (m, 1H), 2.36-2.18 (m, 2H), 1.94-1.80 (m, 1H), 1.66-1.53 (m, 2H), 1.33 (d, J = 6.7 Hz, 3H), 1.03 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 533.23 (M+H).



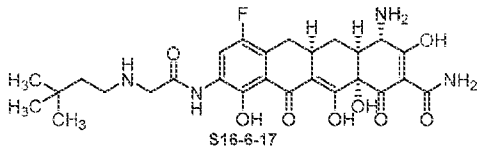
S16-6-15

Compound **S16-6-15** was prepared from compound **S16-4** with isobutylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.24 (d, J = 11.0 Hz, 1H), 4.09 (s, 2H), 3.89 (s, 1H), 3.18-3.10 (m, 1), 3.15-2.92 (m, 3H), 2.67-2.60 (m, 1H), 2.34-2.19 (m, 2H), 2.13-2.00 (m, 1H), 1.66-1.52 (m, 1H), 1.06 (d, J = 6.7 Hz, 6H); MS (ESI) *m/z* 533.32 (M+H).



S16-6-16

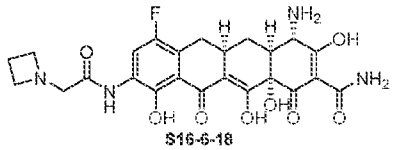
Compound **S16-6-16** was prepared from compound **S16-4** with isoamylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.08 (s, 2H), 3.88 (s, 1H), 3.20-3.08 (m, 3H), 3.15-2.92 (m, 1H), 2.68-2.62 (m, 1H), 2.36-2.20 (m, 2H), 1.78-1.52. (m, 3H), 0.99 (d, J = 6.1 Hz, 6H); MS (ESI) *m/z* 547.25 (M+H).



S16-6-17

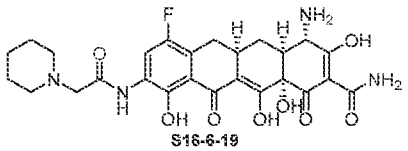
Compound **S16-6-17** was prepared from compound **S16-4** with 3,3-dimethylbutylamine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.10 (s, 2H), 3.89 (s, 1H), 3.19-3.09 (m, 3H),

3.15-2.92 (m, 1H), 2.68-2.62 (m, 1H), 2.35-2.20 (m, 2H), 1.68-1.56 (m, 3H), 0.99 (s, 9H); MS (ESI) *m/z* 561.27 (M+H).



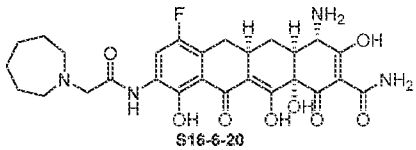
S16-6-18

Compound **S16-6-18** was prepared from compound **S16-4** with azetidine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.18 (d, J = 11.0 Hz, 1H), 4.42-4.30 (m, 4H), 4.27-4.10 (m, 2H), 3.87 (s, 1H), 3.19-3.10 (m, 1H), 3.02-2.92 (m, 1H), 2.71-2.59 (m, 2H), 2.53-2.40 (m, 1H), 2.34-2.17 (m, 2H), 1.64-1.52 (m, 1H); MS (ESI) *m/z* 517.27 (M+H).



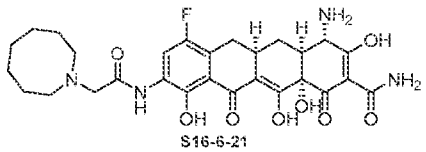
S16-6-19

Compound **S16-6-19** was prepared from compound **S16-4** with piperidine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.19 (s, 2H), 3.88 (s, 1H), 3.77-3.58 (m, 2H), 3.20-3.08 (m, 3H), 3.07-2.94 (m, 1H), 2.68-2.62 (m, 1H), 2.35-2.20 (m, 2H), 2.00-1.82 (m, 5H), 1.65-1.52 (m, 2H); MS (ESI) *m/z* 545.25 (M+H).

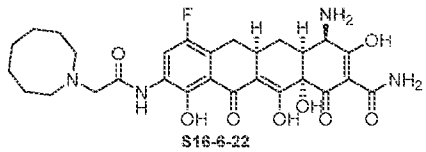


S16-6-20

Compound **S16-6-20** was prepared from compound **S16-4** with hexamethyleneimine using General Procedure **H**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.24 (d, J = 11.0 Hz, 1H), 4.27 (s, 2H), 3.89 (s, 1H), 3.61-3.51 (m, 2H), 3.41-3.32 (m, 2H), 3.19-3.09 (m, 1H), 3.07-2.94 (m, 1H), 2.66-2.61 (m, 1H), 2.35-2.20 (m, 2H), 2.06-1.90 (m, 4H), 1.86-1.69 (m, 4H), 1.67-1.53 (m, 1H); MS (ESI) *m/z* 559.56 (M+H).



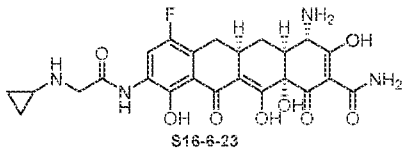
S16-6-21



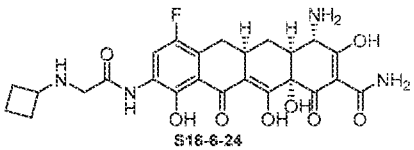
S16-6-22

Compound **S16-6-21** and **S16-6-22** were prepared from compound **S16-4** with heptamethyleneimine using General Procedure **H**. **S16-6-21**: ^{1}H NMR (400 MHz, CD_3OD,

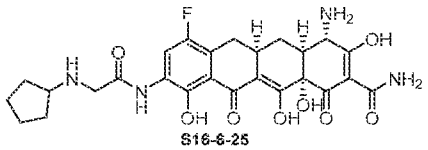
dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.27 (s, 2H), 3.88 (s, 1H), 3.58-3.45 (m, 2H), 3.43-3.32 (m, 2H), 3.18-3.09 (m, 1H), 3.05-2.92 (m, 1H), 2.68-2.59 (m, 1H), 2.36-2.18 (m, 2H), 2.10-1.90 (m, 4H), 1.88-1.52 (m, 7H); MS (ESI) *m/z* 573.59 (M+H). **S16-6-22**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.74 (d, J = 4.9 Hz, 1H), 4.25 (s, 2H), 3.56-3.45 (m, 2H), 3.41-3.31 (m, 2H), 3.16-3.07 (m, 1H), 2.92-2.74 (m, 2H), 2.37-2.26 (m, 1H), 2.12-1.89 (m, 5H), 1.86-1.61 (m, 5H), 1.51-1.40 (m, 1H); MS (ESI) *m/z* 573.59 (M+H).


S16-6-23

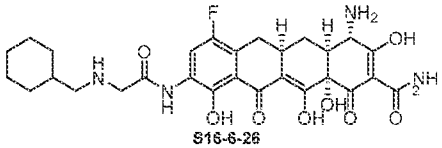
Compound **S16-6-23** was prepared from compound **S16-4** with cyclopropylamine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.21 (d, J = 11.0 Hz, 1H), 4.18 (s, 2H), 3.88 (s, 1H), 3.18-3.08 (m, 1H), 3.05-2.93 (m, 1H), 2.90-2.81 (m, 1H), 2.67-2.62 (m, 1H), 2.33-2.19 (m, 2H), 1.64-1.53 (m, 1H), 0.98-0.89 (m, 4H); MS (ESI) *m/z* 517.27 (M+H).


S16-6-24

Compound **S16-6-24** was prepared from compound **S16-4** with cyclobutylamine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 3.96 (s, 2H), 3.91-3.79 (m, 2H), 3.19-3.09 (m, 1H), 3.05-2.92 (m, 1H), 2.68-2.60 (m, 1H), 2.40-2.19 (m, 6H), 2.00-1.88 (m, 2H), 1.65-1.53 (m, 1H); MS (ESI) *m/z* 531.37 (M+H).

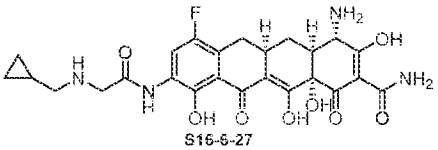

S16-6-25

Compound **S16-6-25** was prepared from compound **S16-4** with cyclopentylamine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.25 (d, J = 11.0 Hz, 1H), 4.09 (s, 2H), 3.88 (m, 2H), 3.68-3.58 (m, 1H), 3.19-3.09 (m, 1H), 3.05-2.92 (m, 1H), 2.68-2.60 (m, 1H), 2.38-2.12 (m, 4H), 1.91-1.54 (m, 7H); MS (ESI) *m/z* 545.23 (M+H).



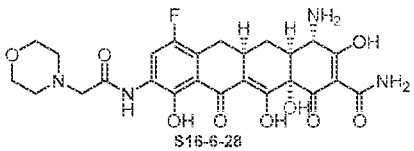
S16-6-26

Compound **S16-6-26** was prepared from compound **S16-4** with cyclohexanemethylamine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.07 (s, 2H), 3.87 (m, 2H), 3.19-3.09 (m, 1H), 3.03-2.90 (m, 3H), 2.68-2.60 (m, 1H), 2.38-2.20 (m, 2H), 1.91-1.71 (m, 6H), 1.65-1.55 (m, 1H), 1.42-1.20 (m, 3H), 1.13-1.00 (m, 2H); MS (ESI) *m/z* 573.26 (M+H).



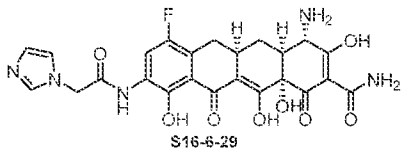
S16-6-27

Compound **S16-6-27** was prepared from compound **S16-4** with cyclopropanemethylamine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.10 (s, 2H), 3.87 (m, 2H), 3.19-3.10 (m, 1H), 3.04-2.92 (m, 3H), 2.65-2.60 (m, 1H), 2.34-1.97 (m, 2H), 1.65-1.55 (m, 1H), 1.16-1.08 (m, 1H), 0.78-0.70 (m, 2H), 0.46-0.40 (m, 2H); MS (ESI) *m/z* 531.21 (M+H).



S16-6-28

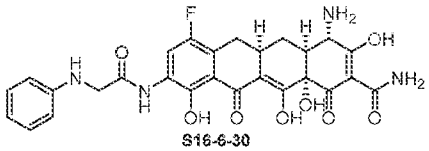
Compound **S16-6-28** was prepared from compound **S16-4** with morpholine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.21 (d, J = 11.0 Hz, 1H), 4.26 (s, 2H), 4.13-3.97 (m, 2H), 3.95-3.81 (m, 3H), 3.67-3.51 (m, 2H), 3.38-3.33 (m, 2H), 3.19-3.10 (m, 1H), 3.04-2.92 (m, 3H), 2.65-2.58 (m, 1H), 2.34-1.97 (m, 2H), 1.65-1.55 (m, 1H); MS (ESI) *m/z* 547.3 (M+H).



S16-6-29

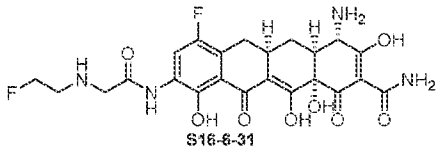
Compound **S16-6-29** was prepared from compound **S16-4** with imidazole using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.99 (s, 1H), 8.16 (d, J = 10.8 Hz, 1H), 7.67 (s, 1H), 7.60 (s, 1H), 5.32 (s, 2H), 3.87 (s, 1H), 3.17-3.10 (m, 1H),

3.05-2.92 (m, 1H), 2.65-2.58 (m, 1H), 2.34-2.15 (m, 2H), 1.65-1.52 (m, 1H); MS (ESI) *m/z* 528.15 (M+H).

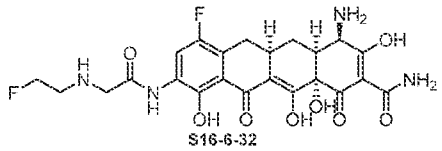


S16-6-30

Compound **S16-6-30** was prepared from compound **S16-4** with aniline using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.29 (d, J = 11.0 Hz, 1H), 7.40-7.32 (m, 2H), 7.11-7.00 (m, 3H), 4.14 (s, 2H), 3.86 (s, 1H), 3.19-3.09 (m, 1H), 3.02-2.90 (m, 1H), 2.65-2.55 (m, 1H), 2.34-2.16 (m, 2H), 1.62-1.52 (m, 1H); MS (ESI) *m/z* 551.21 (M-H).

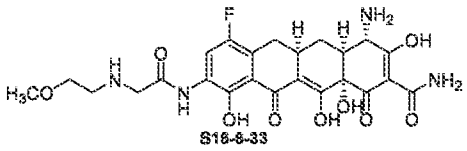


S16-6-31



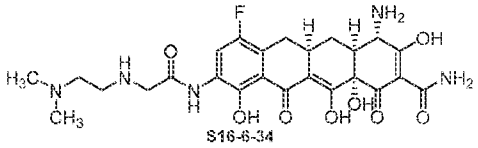
S16-6-32

Compound **S16-6-31** and **S16-6-32** were prepared from compound **S16-4** with 2-fluoroethylamine hydrochloride (4 eq) using General Procedure **H**. **S16-6-31**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.88-4.83 (m, 1H), 4.76-4.70 (m, 1H), 4.16 (s, 2H), 3.87 (s, 1H), 3.56-3.44 (m, 2H), 3.19-3.09 (m, 1H), 3.06-2.94 (m, 1H), 2.67-2.57 (m, 1H), 2.34-2.16 (m, 2H), 1.62-1.52 (m, 1H); MS (ESI) 523.27 *m/z* (M+H). **S16-6-32**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.25 (d, J = 11.0 Hz, 1H), 4.89-4.81 (m, 1H), 4.78-4.72 (m, 2H), 4.17 (s, 2H), 3.56-3.44 (m, 2H), 3.19-3.09 (m, 1H), 2.98-2.78 (m, 1H), 2.39-2.24-2.67 (m, 1H), 2.14-2.08 (m, 1H), 1.55-1.42 (m, 1H); MS (ESI) *m/z* 523.27 (M+H).



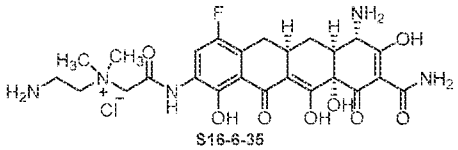
S16-6-33

Compound **S16-6-33** was prepared from compound **S16-4** with 2-methoxyethylamine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.10 (s, 2H), 3.87 (s, 1H), 3.72-3.67 (m, 2H), 3.42 (s, 3H), 3.35-3.31 (m, 2H), 3.19-3.09 (m, 1H), 3.04-2.92 (m, 1H), 2.65-2.60 (m, 1H), 2.34-2.18 (m, 2H), 1.64-1.52 (m, 1H); MS (ESI) *m/z* 535.24 (M+H).



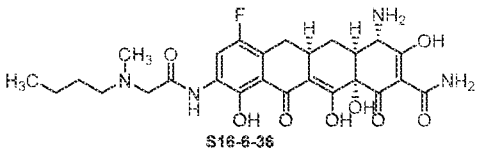
S16-6-34

Compound **S16-6-34** was prepared from compound **S16-4** with *N,N*-dimethylethylenediamine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.21 (s, 2H), 3.87 (s, 1H), 3.67-3.55 (m, 4H), 3.19-3.09 (m, 1H), 3.05-2.92 (m, 7H), 2.65-2.60 (m, 1H), 2.35-2.18 (m, 2H), 1.64-1.52 (m, 1H); MS (ESI) *m/z* 548.24 (M+H).

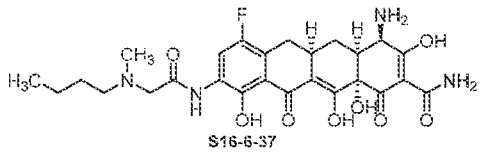


S16-6-35

Side-product **S16-6-35** was also obtained from the reaction to produce **S16-6-34**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.18 (d, J = 10.4 Hz, 1H), 4.54 (s, 2H), 4.10-4.02 (m, 2H), 3.87 (s, 1H), 3.60-6.52 (m, 2H), 3.46 (s, 6H), 3.19-3.10 (m, 1H), 3.04-2.93 (m, 1H), 2.66-2.59 (m, 1H), 2.35-2.17 (m, 2H), 1.65-1.43 (m, 1H); MS (ESI) *m/z* 548.5 (M+H).

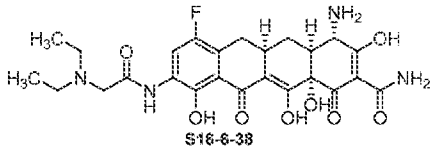


S16-6-36



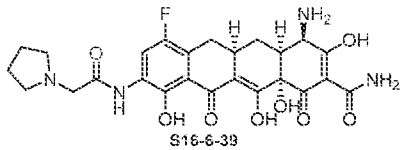
S16-6-37

Compounds **S16-6-36** and **S16-6-37** were prepared from compound **S16-4** with *N*-methylbutylamine using General Procedure **H**. **S16-6-36**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.31, 4.19 (ABq, J = 16.5 Hz, 2H), 3.88 (s, 1H), 3.34-3.25 (m, 1H), 3.23-3.11 (m, 2H), 3.05-2.94 (m, 4H), 2.67-2.60 (m, 1H), 2.36-2.18 (m, 2H), 1.82-1.71 (m, 2H), 1.66-1.54 (m, 1H), 1.50-1.39 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 547.26 (M+H). **S16-6-37**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.24 (d, J = 11.0 Hz, 1H), 4.76 (d, J = 4.9 Hz, 1H), 4.29, 4.19 (ABq, J = 16.8 Hz, 2H), 3.41-3.24 (m, 2H), 3.21-3.10 (m, 1H), 2.99 (s, 3H), 2.94-2.70 (m, 2H), 2.38-2.28 (m, 1H), 2.13-2.05 (m, 1H), 1.82-1.71 (m, 2H), 1.52-1.39 (m, 3H), 1.02 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 547.26 (M+H).



S16-6-38

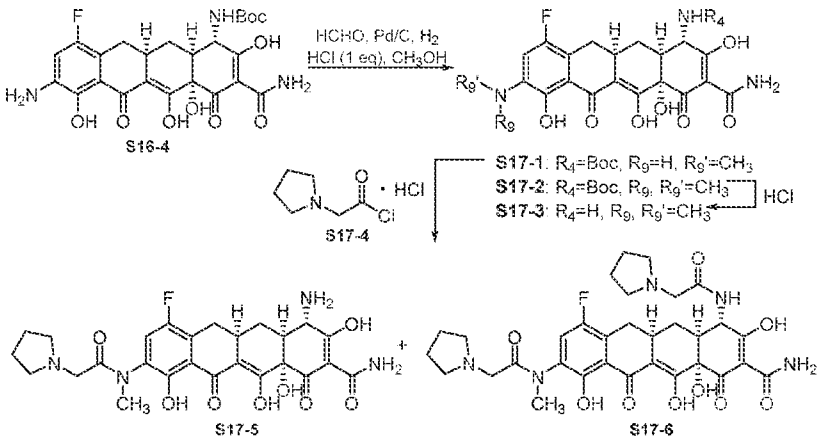
Compound **S16-6-38** was prepared from compound **S16-4** with diethylamine using General Procedure **H**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.21 (d, J = 11.0 Hz, 1H), 4.24 (s, 2H), 3.88 (s, 1H), 3.39-3.30 (m, 4H), 3.14 (dd, J = 15.3, 4.3 Hz, 1H), 3.05-2.93 (m, 1H), 2.64 (d, J = 12.8 Hz, 1H), 2.35-2.18 (m, 2H), 1.64-1.51 (m, 1H), 1.36 (t, J = 7.3 Hz, 6H); MS (ESI) *m/z* 533.36 (M+H).



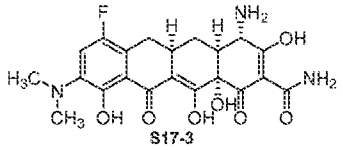
S16-6-39

Compound **S16-6-39** was prepared from 7-fluoro-9-pyrrolidinoacetamido-6-demethyl-6-deoxytetracycline (*J. Med. Chem.*, **2012**, 597-605) in a manner similar to **S1-6-2**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.74 (d, J = 4.9 Hz, 1H), 4.31 (s, 2H), 3.82-3.72 (m, 2H), 3.23-3.06 (m, 3H), 2.94-2.74 (m, 2H), 2.37-2.26 (m, 1H), 2.23-1.99 (m, 5H), 1.52-1.39 (m, 1H); MS (ESI) *m/z* 531.35 (M+H).

Scheme 17

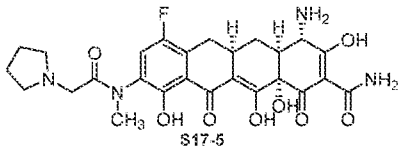


The following compounds were prepared per Scheme 17.

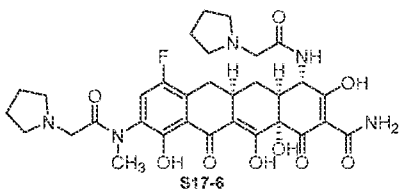


S17-3

To a solution of **S16-4** (26.7 mg, 0.051 mmol, 1 eq) in CH_3OH (1 mL) was added 1*N* aqueous HCl (51 μL, 0.051 mmol, 1 eq), HCHO (aqueous, 37wt%, 5.7 μL, 0.77 mmol, 1.5 eq) and Pd-C (10wt%, 15 mg). The reaction vessel was sealed and purged with hydrogen by briefly evacuating the flask followed by flushing with hydrogen gas (1 atm). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 2 h 30 min. The reaction was filtered through a small Celite pad. The cake was washed with CH_3OH. The filtrate was concentrated and the crude residue was dissolved in CH_3OH (1 mL), to which was added 0.05 *N* HCl in water (300 μL) and concentrated HCl (200 μL). The reaction solution was stirred at room temperature for 1.5 hr. The solution was concentrated under reduced pressure and the resulting residue was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 μ RP-γ 100A column [10 μm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 3.0 mL (0.05 *N* HCl/water); gradient: 5→30% B in A over 15 min; mass-directed fraction collection]. Fractions containing the desired product were collected and freeze-dried to yield compound **S17-3** (10.8 mg, 40%): ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.91 (d, J = 9.8 Hz, 1H), 3.91 (s, 1H), 3.31-3.30 (m, 6H). 3.26-3.18 (m, 1H), 3.12-3.01 (m, 1H), 2.69 (d, J = 12.2 Hz, 1H), 2.45-2.34 (m, 1H), 2.32-2.23 (m, 1H), 1.69-1.55 (m, 1H); MS (ESI) *m/z* 448.25 (M+H).



S17-5

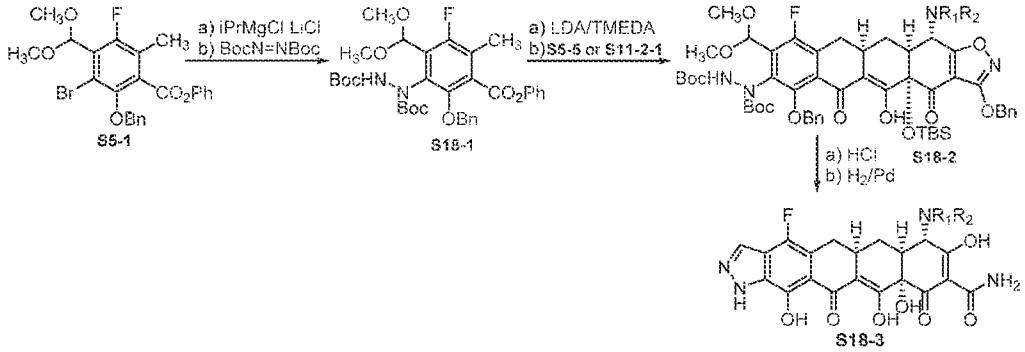


S17-6

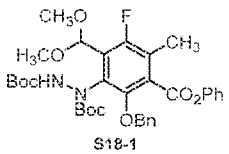
To a solution of **S16-4** (17.6 mg, 0.034 mmol, 1 eq) in CH_3OH (1 mL) was added 1*N* aqueous HCl (34 μL, 0.034 mmol, 1 eq), HCHO (aqueous, 37wt%, 25 μL of a 10% volume solution in CH_3OH, 0.034 mmol, 1 eq), and Pd-C (10wt%, 10 mg). The reaction vessel was sealed and purged with hydrogen by briefly evacuating the flask followed by flushing with hydrogen gas (1 atm). The reaction mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 1 h 30 min. The reaction was filtered through a small Celite pad. The cake was washed with CH_3OH. The filtrate was concentrated. The crude residue was dissolved in NMP under

nitrogen atmosphere and charged with **S17-4** (prepared per literature procedure *Org. Process Res. Dev.*, 2013, *17*, 838-845; 10 eq). The reaction solution was added dropwise to rapidly stirring MTBE (15 mL). The resulting tan precipitate was filtered off on a Celite pad and washed with MTBE. The solid was washed off the Celite pad with CH_3OH. The resulting orange solution was concentrated in vacuo. The crude residue was dissolved in CH_3OH (1 mL), to which was added 0.05 *N* HCl in water (300 μL) and concentrated HCl (200 μL). The reaction solution was stirred at room temperature for 15 hr. The solution was concentrated under reduced pressure and the resulting residue was dissolved in CH_3OH (800 μL) and added to rapidly stirring MTBE (15 mL). The resulting orange precipitate was filtered through a Celite pad and washed as before, then washed off the Celite pad with CH_3OH. The solution was concentrated under reduced pressure. The residue was dissolved in 0.05 *N* HCl in water and the resulting solution was purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 μ RP-γ 100A column [10 μm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 2.0 mL (0.05 *N* HCl/water); gradient: 5→30% B in A over 20 min; mass-directed fraction collection]. Fractions containing the desired product and those containing a corresponding diacylated compound were collected and freeze-dried to yield compounds **S17-5** (5 mg, 24%) and **S17-6** (3 mg, 12%). **S17-5**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.53-7.48 (m, 1H), 4.10, 4.05 (ABq, 10.5 Hz, 1H), 3.93-3.83 (m, 2H), 3.79-3.62 (m, 2H), 3.27-3.13 (m, 4H), 3.10-2.93 (m, 3H), 2.70-2.61 (m, 1H), 2.43-1.91 (m, 6H), 1.68-1.52 (m, 1H); MS (ESI) *m/z* 545.33 (M+H). **S17-6**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.72 (at, J = 7.3 Hz, 1H), 7.49 (dd, J = 8.5, 2.4 Hz, 1H), 4.78-4.68 (m, 1H), 4.21-4.01 (m, 2H), 3.89, 3.84 (ABq, 8.0 Hz, 1H), 3.81-3.61 (m, 4H), 3.23 (d, J = 7.6 Hz, 3H), 3.21-3.10 (m, 3H), 3.10-2.92 (m, 3H), 2.61-2.31 (m, 2H), 2.22-1.92 (m, 9H), 1.73-1.52 (m, 1H); MS (ESI) *m/z* 656.30 (M+H).

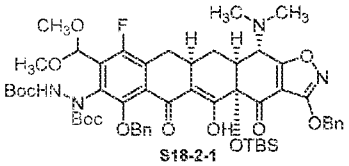
Scheme 18

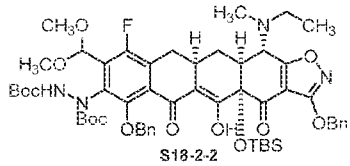


The following compounds were prepared per Scheme 18.

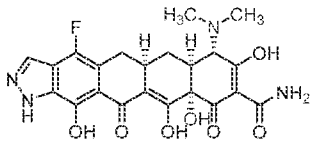


A flame-dried flask was charged with **S5-1** (748 mg, 1.53 mmol, 1 eq) under N_2, dissolved in THF (24 mL) and cooled to -78 °C. Isopropyl magnesium chloride lithium chloride complex (1.3*N* in THF, 5.88 mL, 7.64 mmol, 5 eq) was added dropwise to the reaction solution over 15 min, maintaining the internal temperature below -70 °C. The anion mixture was allowed to warm slowly to 0 °C over one hour, and was then re-cooled to -78 °C. A flame-dried flask was charged with di-*tert*-butyl azodicarboxylate (1.76 g, 7.63 mmol, 5 eq), evacuated and back-filled with N_2, then dissolved in THF (5 mL). This solution was added dropwise over 30 min to the cold anion solution with a THF rinse forward (1 mL), maintaining the internal temperature below -70 °C. The resulting reaction mixture was allowed to warm slowly to room temperature overnight. Saturated aqueous ammonium chloride (12 mL), then water (10 mL) were added and the mixture extracted three times with EtOAc (50 mL, 2x20 mL). The combined organic layers were dried over Na_2SO_4, were filtered, and were concentrated under reduced pressure. The resulting residue was purified via flash column chromatography on silica gel with 2%-25% EtOAc in hexanes as eluent to provide the desired compound **S18-1** (746 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.44-7.23 (m, 8 H), 7.09-6.76 (m, 2H), 5.99 (m, 0.5H), 5.88 (m, 0.5H), 5.10-5.94 (m, 2H), 3.60-3.43 (m, 6H), 2.40-2.33 (m, 3H), 1.57-1.38 (m, 18H);); MS (ESI) *m/z* 641.26 (M+H).

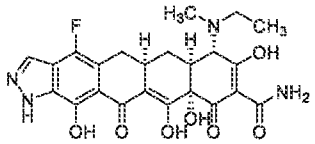

S18-2-1


S18-2-2

Compounds **S18-2-1** and **S18-2-2** were prepared from compound **S18-1** and dimethylenone **S5-5** and ethylmethylenone **S11-2-1**, respectively, by using General Procedure **E**. **S18-2-1**: MS (ESI) *m/z* 1029.22 (M+H). **S18-2-2**: MS (ESI) *m/z* 1043.41 (M+H).

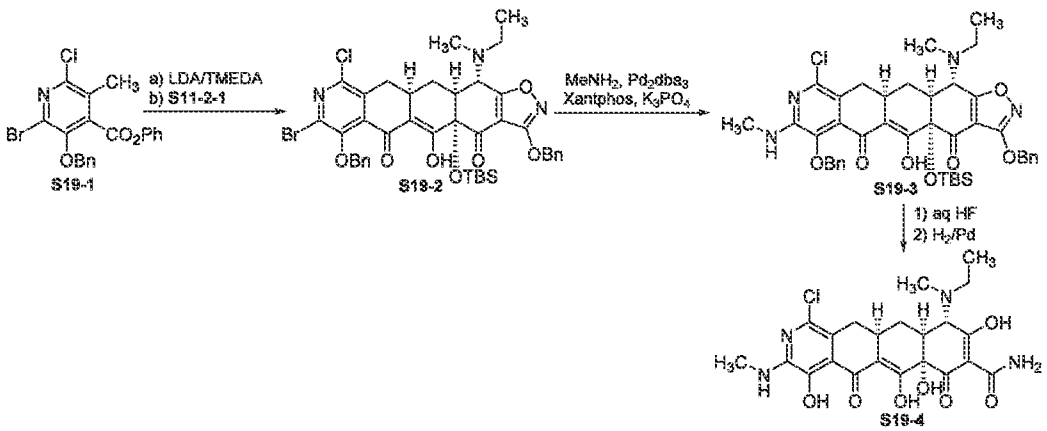

S18-3-1

A solution of **S18-2-1** (33 mg, 0.032 mmol, 1 eq) in THF (500 μL) and 4*N* aqueous HCl (500 μL) was stirred at room temperature overnight, then heated at 50 °C for 3.5 hr. The solution was neutralized via the addition of pH 7 phosphate buffer and the solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was deprotected using General Procedure **D-2** to provide desired compound **S18-3-1**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.05 (s, 1H), 4.08 (s, 1H), 3.39-3.22 (m, 1H), 3.09-2.91 (m, 8H), 2.34-2.17 (m, 2H), 1.70-1.57 (m, 1H); MS (ESI) *m/z* 472.98 (M+H).

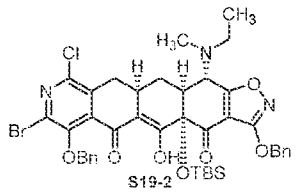

S18-3-2

A solution of **S18-2-2** (207 mg, 0.198 mmol, 1 eq) in THF (3 mL) and 4*N* aqueous HCl (3 mL) was stirred and heated at 50 °C for 3 hr. The solution was neutralized via careful addition of 6*N* aqueous NaOH and the solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was deprotected using General Procedure **D-2** to provide desired compound **S18-3-2**: ^{1}H NMR (400 MHz, CD_3OD, rotamers, dihydrochloride salt) δ 8.06 (s, 1H), 4.22 (s, 0.5H), 4.12 (s, 0.5H), 3.54-3.42 (m, 1H), 3.40-3.19 (m, 2H), 3.08-2.87 (m, 5H), 2.34-2.17 (m, 2H), 1.72-1.57 (m, 1H), 1.54-1.34 (m, 3H). MS (ESI) *m/z* 487.09 (M+H).

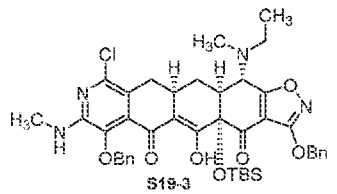
Scheme 19



The following compounds were prepared per Scheme 19.

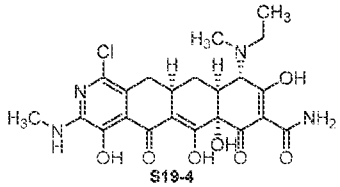


Compound **S19-1** (prepared per literature procedures including WO2010/129055 A1; 518 mg, 1.20 mmol, 1 eq) and ethylmethylenone **S11-2-1** (600 mg, 1.21 mmol, 1 eq) were placed under N_2, dissolved in THF (12 mL), and cooled to -73 °C. LHMDS (1.0 M in THF, 3.6 mL, 3.6 mmol, 3 eq) was added dropwise over 26 min, maintaining internal temperature below -70 °C. The reaction solution was allowed to warm to 0 °C over 1 hr. The solution was neutralized via the addition of pH 7 phosphate buffer (20 mL) and the solution was allowed to warm to room temperature. The solution was extracted with DCM (3x40 mL) and the combined organic layers were washed with 1*N* NaOH (2x25 mL) and brine, then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography on silica gel with 2%-25% EtOAc in hexanes as eluent to provide the desired compound **S19-2** (812 mg, 81%) : ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 15.45 (brs, 1H), 7.54-7.45 (m, 4H), 7.43 7.30 (m, 6H), 5.40-5.30 (m, 2H), 5.03 (aq, J = 9.4 Hz, 2H), 3.97-3.86 (m, 1H), 3.24 (dd, J = 16.2, 5.2 Hz, 1H), 3.12-3.02 (m, 1H), 2.90-2.75 (m, 1H), 2.72-2.56 (m, 2H), 2.55-2.32 (m, 5H), 2.23-2.11 (m, 1H), 1.19-1.06 (m, 3H), 0.81 (s, 9H), 0.288-0.20 (brm, 3H), 0.13 (s, 3H); MS (ESI) *m/z* 836.16 (M+H).



S19-3

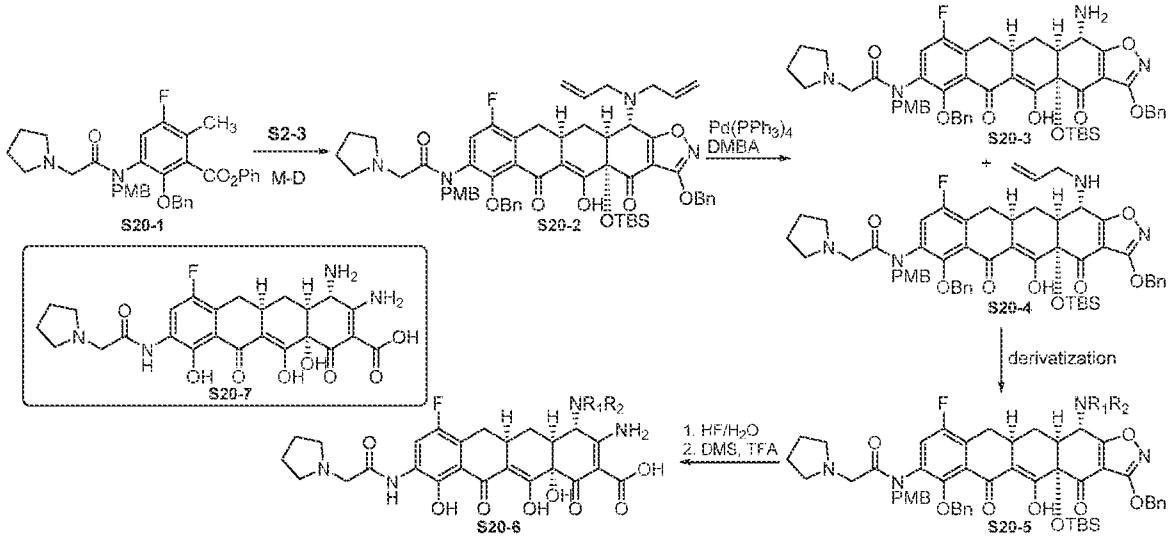
A sealable vessel was charged with **S19-2** (290 mg, 0.317 mmol, 1 eq), Pd_2dba_3 (13.5 mg, 0.015 mmol, 0.05 eq), Xantphos (30.3 mg, 0.052 mmol, 0.15 eq), K_3PO_4 (202 mg, 0.952 mmol, 3 eq). The vessel was capped and sealed, then evacuated and back-filled with N_2 (g) three times. The vessel was charged with 1,4-dioxane (3.2 mL) and methylamine solution (2.0 M in THF, 475 µL, 0.951 mmol, 3 eq) and then placed in a 100 °C bath for 2 hr. The resulting mixture was filtered through a Celite pad with an EtOAc wash. The filtrate was concentrated under reduced pressure. Purification of the resulting residue by preparative reverse phase HPLC on a Waters Autopurification system using a Sunfire Prep C18 OBD column [5 µm, 19 × 50 mm; flow rate, 20 mL/min; Solvent A: H_2O with 0.1% HCO_2H; Solvent B: CH_3CN with 0.1% HCO_2H; gradient: 5→100% B in A over 20 min; mass-directed fraction collection]. Fractions with the desired MW also contained starting material. Lyophilization of these fractions provided a mixture of **S19-2** and **S19-3** in a ratio of 1:0.43 (ratio determined via ^1H NMR in $CDCl_3$; 99 mg total, 28.5 mg desired product, 11%). This mixture was used without further purification. **S19-3**: MS (ESI) *m/z* 785.18 (M+H).



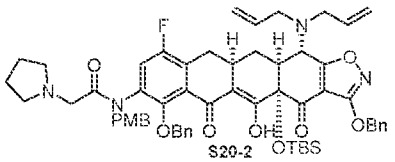
S19-4

Compound **S19-4** was prepared from **S19-3** using General Procedures **C**, and **D-2** (in CH_3OH:dioxane 1:1 with no HCl/water). ^1H NMR (400 MHz, CD_3OD, rotamers, dihydrochloride salt) δ 4.22 (s, 0.5H), 4.12 (s, 0.5H), 3.53-3.41 (m, 1H), 3.37-3.29 (m, 1H), 3.10-2.87 (m, 9H), 2.31-2.15 (m, 2H), 1.69-1.53 (m, 1H), 1.45-1.33 (m, 3H). MS (ESI) *m/z* 493.05 (M+H).

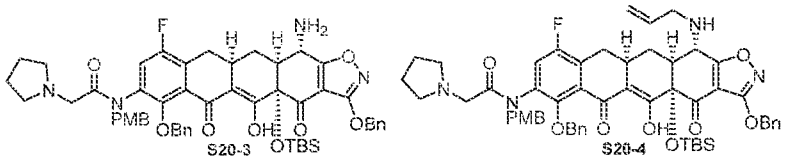
Scheme 20



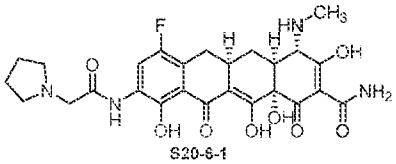
The following compounds were prepared per Scheme 20.



Compound **S20-2** was prepared from known D-ring precursor **S20-1** (prepared per literature procedure: *J. Org. Chem.*, 2017, *82*, 936-943) and **S2-3** (observed as a mixture of rotamers via ^{1}HNMR spectral analysis in $CDCl_3$) using General Procedure **E**. **S20-2**: MS (ESI) *m/z* 1023.74 (M+H).

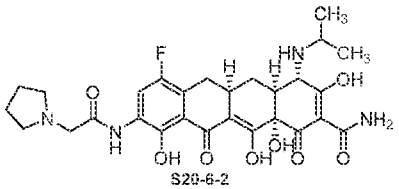


Compounds **S20-3** and **S20-4** were prepared from compound **S20-2** by using General Procedure **A**. **S20-3**: MS (ESI) *m/z* 943.67 (M+H). **S20-4**: MS (ESI) *m/z* 983.67 (M+H).

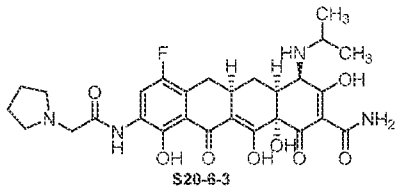


Compound **S20-6-1** was prepared from compound **S20-3** by using General Procedures **B-1** with HCHO, **C**, and **D-1**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.21 (d, *J*

= 10.6 Hz, 1 H), 4.31 (s, 2 H), 3.75-3.83 (m, 3 H), 3.10-3.25 (m, 4 H), 2.95-3.04 (m, 2 H), 2.90 (s, 3 H), 2.05-2.30 (m, 5 H), 1.63-1.71 (m, 1 H); MS (ESI) *m/z* 545.3 (M+H).

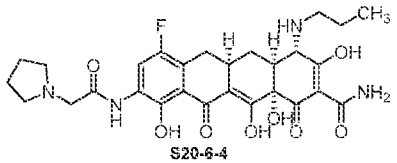


S20-6-2



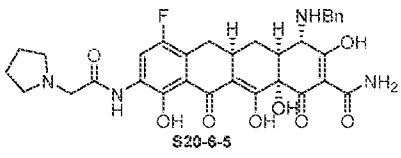
S20-6-3

Compounds **S20-6-2** and **S20-6-3** were prepared from compound **S20-3** by using General Procedures **B-1** with acetone, **C**, and **D-1**. **S20-6-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.21 (d, *J* = 10.6 Hz, 1 H), 4.30 (s, 2 H), 3.75-3.85 (m, 3 H), 3.10-3.25 (m, 3 H), 2.95-3.04 (m, 1 H), 2.80-2.85 (m, 1 H), 2.05-2.27 (m, 5 H), 1.80-1.90 (m, 2 H), 1.53-1.62 (m, 1 H), 1.35-1.45 (m, 6 H); MS (ESI) *m/z* 573.3 (M+H). **S20-6-3**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.21 (d, *J* = 10.6 Hz, 1 H), 4.30 (s, 2 H), 3.75-3.82 (m, 3 H), 3.63-3.70 (m, 1 H), 3.08-3.22 (m, 3 H), 2.81-2.98 (m, 2 H), 2.05-2.21 (m, 7 H), 1.40-1.46 (m, 6 H); MS (ESI) *m/z* 573.3 (M+H).



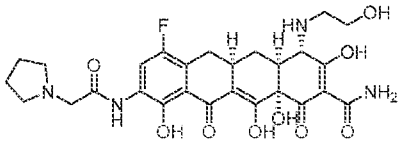
S20-6-4

Compound **S20-6-4** was prepared from compound **S20-3** by using General Procedures **B-1** with propionaldehyde, **C**, and **D-1**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.20 (d, *J* = 10.6 Hz, 1 H), 4.30 (s, 2 H), 3.72-3.81 (m, 3 H), 3.10-3.25 (m, 3 H), 2.95-3.04 (m, 2 H), 2.80-2.87 (m, 2 H), 2.05-2.25 (m, 6 H), 1.80-1.90 (m, 2 H), 1.55-1.60 (m, 1 H), 0.98-1.05 (t, *J* = 7.8 Hz, 3 H); MS (ESI) *m/z* 573.2 (M+H).



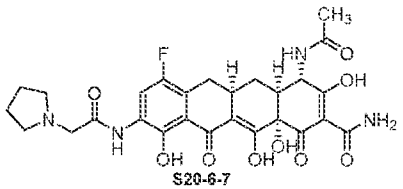
S20-6-5

Compound **S20-6-5** was prepared from compound **S20-3** by using General Procedures **B-1** with benzaldehyde, **C**, and **D-1**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.21 (d, *J* = 10.6 Hz, 1 H), 7.56-7.60 (m, 2 H), 7.45-7.51 (m, 3 H), 4.46-4.51 (m, 1 H), 4.31 (s, 2 H), 3.72-3.83 (m, 5 H), 2.90-3.20 (m, 3 H), 1.97-2.25 (m, 7 H), 1.25-1.30 (m, 1 H); MS (ESI) *m/z* 621.2 (M+H).



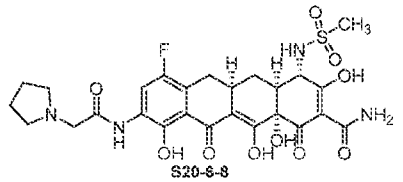
S20-6-6

Compound **S20-6-6** was prepared from compound **S20-3** by using General Procedures **B-1** with 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde, **C**, and **D-1**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.20 (d, J = 10.6 Hz, 1 H), 4.32 (s, 2 H), 3.75-3.95 (m, 5 H), 3.40-3.45 (m, 1 H), 2.95-3.25 (m, 5 H), 2.80-2.90 (m, 1 H), 2.03-2.30 (m, 6 H), 1.53-1.62 (m, 1 H); MS (ESI) *m/z* 575.2 (M+H).



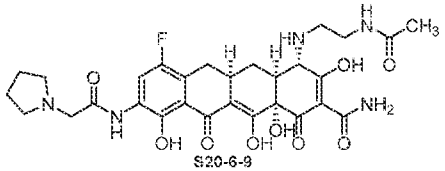
S20-6-7

Compound **S20-6-7** was prepared from compound **S20-3** by using General Procedures **B-2** with Ac_2O, **C**, and **D-1**. ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 8.20 (d, J = 10.6 Hz, 1 H), 4.69-4.72 (m, 1 H), 4.41 (s, 2 H), 3.75-3.81 (m, 2 H), 3.15-3.21 (m, 3 H), 2.90-3.10 (m, 2 H), 2.30-2.45 (m, 3 H), 2.05-2.20 (m, 3 H), 2.01 (s, 3 H), 1.55-1.63 (m, 1 H); MS (ESI) *m/z* 573.2 (M+H).



S20-6-8

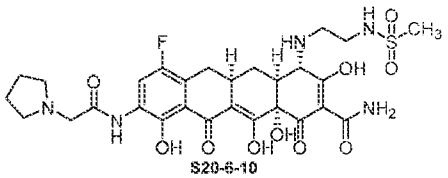
Compound **S20-6-8** was prepared from compound **S20-3** by using General Procedures **B-2** with Ms_2O, **C**, and **D-1**. ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 8.20 (d, J = 10.6 Hz, 1 H), 4.41 (s, 2 H), 4.08-4.11 (m, 1 H), 3.75-3.82 (m, 3 H), 3.09-3.21 (m, 4 H), 2.95-3.03 (m, 1 H), 2.55-2.61 (m, 3 H), 2.02-2.30 (m, 5 H), 1.66-1.72 (m, 1 H); MS (ESI) *m/z* 609.2 (M+H).



S20-6-9

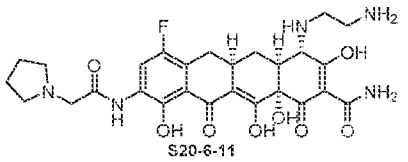
Compound **S20-6-9** was prepared from compound **S20-3** by using General Procedures **B-1** with *N*-Boc-2-aminoacetaldehyde, treatment with HCl (4*N* aqueous) in dioxane, **B-2** with

Ac_2O, **C**, and **D-1**. ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.31 (s, 2H), 3.96 (s, 1H), 3.83-3.73 (m, 2H), 3.65-3.52 (m, 1H), 3.52-3.42 (m, 2H), 3.24-3.08 (m, 3H), 3.06-2.96 (m, 1H), 2.82-2.75 (m, 1H), 2.32-1.96 (m, 10H), 1.63-1.50 (m, 1H); MS (ESI) *m/z* 616.5 (M+H).



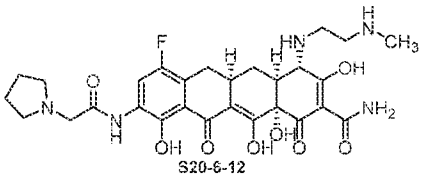
S20-6-10

Compound **S20-6-10** was prepared from compound **S20-3** by using General Procedures **B-1** with *N*-Boc-2-aminoacetaldehyde, treatment with HCl (4*N* aqueous) in dioxane, **B-2** with Ms_2O, **C**, and **D-1**. ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.47 (s, 2H), 4.30 (s, 2H), 4.02 (s, 1H), 3.83-3.71 (m, 2H), 3.54-3.43 (m, 3H), 3.28-3.11 (m, 4H), 3.12 (s, 3H), 3.00 (s, 3H), 2.87-2.79 (m, 1H), 2.32-2.00 (m, 5H), 1.63-1.50 (m, 1H); MS (ESI) *m/z* 652.3 (M+H).

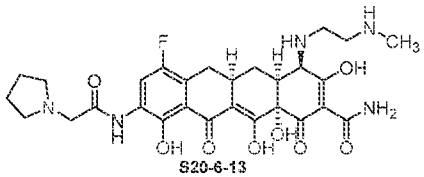


S20-6-11

Compound **S20-6-11** was prepared from compound **S20-3** by using General Procedures **B-1** with *N*-Boc-2-aminoacetaldehyde, **C**, and **D-1**.^1H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 8.24 (d, J = 11.0 Hz, 1H), 4.31 (s, 2H), 4.01 (s, 1H), 3.83-3.71 (m, 3H), 3.66-3.54 (m, 1H), 3.45-3.35 (m, 2H), 3.34-3.28 (m, 1H), 3.34-2.91 (m, 7H), 2.34-2.03 (m, 7H), 1.65-1.50 (m, 1H); MS (ESI) *m/z* 574.2 (M+H).



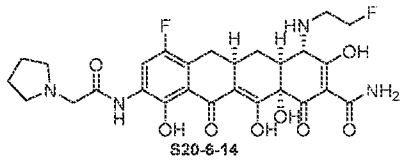
S20-6-12



S20-6-13

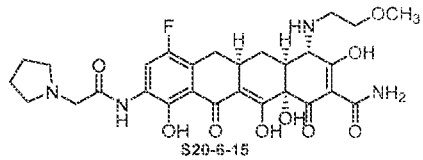
Compounds **S20-6-12** and **S20-6-13** were prepared from known compound **S20-7** (prepared using literature procedure including WO 2014/036502 A2) by using General Procedure **B-1** with *N*-Boc-2-methylaminoacetaldehyde, treatment with HCl (4*N* aqueous) in dioxane and purification via reverse phase preparative HPLC as described in General Procedure **D-1**. **S20-6-12**: ^1H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.31 (s, 2H), 4.03 (s, 1H), 3.86-3.72 (m, 3H), 3.72-3.61 (m, 1H), 3.46 (t, J = 7.0

Hz, 1H), 3.24-3.09 (m, 5H), 2.79 (m, 3H), 2.32-2.01 (m, 6H), 1.63-1.50 (m, 1H); MS (ESI) *m/z* 588.4 (M+H). **S20-6-13**: ^{1}H NMR (400 MHz, CD_3OD, trihydrochloride salt) δ 8.22 (d, J = 11.0 Hz, 1H), 4.83 (d, J = 4.9 Hz, 1H), 4.31 (s, 2H), 3.87-3.72 (m, 3H), 3.70-3.59 (m, 1H), 3.57-3.42 (m, 2H), 3.24-3.09 (m, 3H), 309-3.01 (m, 1H), 3.01-2.89 (m, 1H), 2.82 (s, 3H), 2.36-1.99 (m, 6H), 1.56-1.43 (m, 1H); MS (ESI) *m/z* 588.4 (M+H).



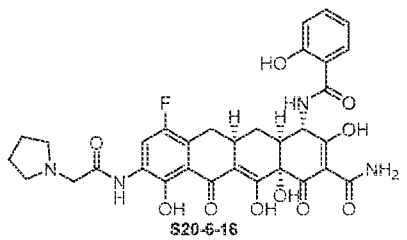
S20-6-14

Compound **S20-6-14** was prepared from compound **S20-3** by using General Procedures **B-1** with FCH_2CHO (prepared from the corresponding alcohol according to the literature procedure in WO 2011146089 Al), **C**, and **D-1**.^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.88-4.72 (m, 2H), 4.32 (s, 2H), 4.00 (s, 1H), 3.85-3.58 (m, 4H), 3.27-3.08 (m, 3H), 3.07-2.94 (m, 4H), 2.89 (d, J = 13.4 Hz, 1H), 2.34-1.99 (m, 6H), 1.65-1.51 (m, 1H); MS (ESI) *m/z* 577.3 (M+H).



S20-6-15

Compound **S20-6-15** was prepared from compound **S20-3** by using General Procedures **B-1** with CH_3OCH_2CHO (prepared from the corresponding alcohol per the literature procedure in WO 2011146089 Al), **C**, and **D-1**. ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.23 (d, J = 11.0 Hz, 1H), 4.31 (s, 2H), 3.96 (s, 1H), 3.83-3.62 (m, 4H), 3.54-3.44 (m, 2H), 3.40 (s, 3H), 3.24-3.09 (m, 3H), 3.05-2.93 (m, 1H), 2.85 (ad, J = 12.8 Hz, 1H), 2.33-2.00 (m, 6H), 1.65-1.52 (m, 1H).

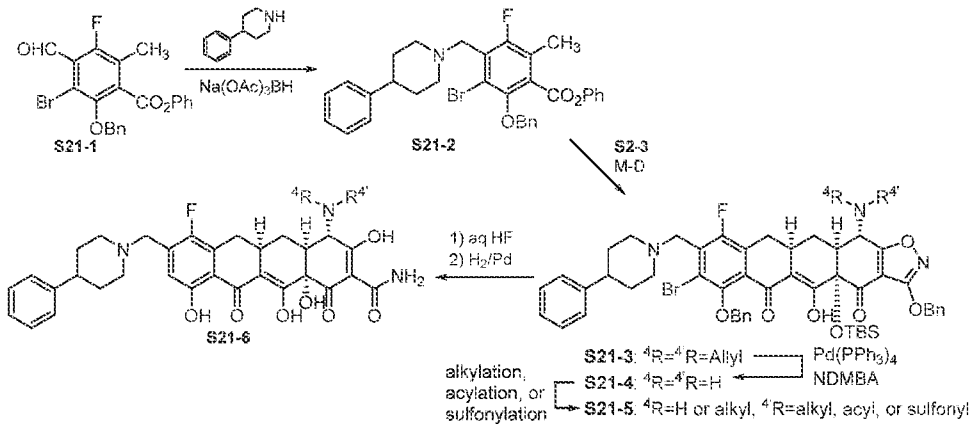


S20-6-16

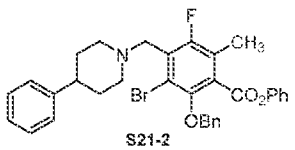
A flask was charged with **S20-7** (51 mg, 0.096 mmol, 1 eq, (prepared using literature procedure including WO 2014/036502 A2), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (29.8 mg, 0.16 mmol, 1.1 eq) and 1-hydroxybenzotriazole (19.7 mg, 0.15 mmol,

1.5 eq) and placed under N_2. To the vessel was added DMF (2 mL) and DIEA (26.6 μL, 0.15 mmol, 1.6 eq). The mixture was stirred at room temperature for 1 h, then purified by preparative reverse phase HPLC on a Waters Autopurification system using a Phenomenex Polymerx 10 μ RP-γ 100A column [10 μm, 150 × 21.20 mm; flow rate, 20 mL/min; Solvent A: 0.05 *N* HCl/water; Solvent B: CH_3CN; injection volume: 2.0 mL (0.05 *N* HCl/water); gradient: 0→85% B in A over 30 min; mass-directed fraction collection]. Fractions containing the desired product were collected and freeze-dried to yield compound **S20-6-16**. ^{1}H NMR (400 MHz, CD_3OD, hydrochloride salt) δ 8.18 (d, J = 11.0 Hz, 1H), 7.92 (dd, J = 7.9, 1.8 Hz, 1H), 7.43-7.35 (m, 1H), 6.96-6.88 (m, 2H), 5.69-5.60 (m, 1H), 4.29 (s, 2H), 3.91-3.58 (m, 2H), 3.12-3.04 (m, 1H), 2.96-2.87 (m, 1H), 2.85-2.73 (m, 1H), 2.30-2.00 (m, 7H), 1.49-1.35 (m, 1H); MS (ESI) *m/z* 651.3 (M+H).

Scheme 21

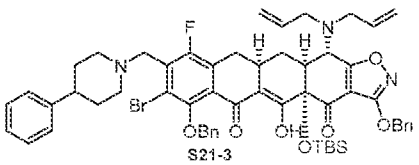


The following compounds were prepared per Scheme 21.



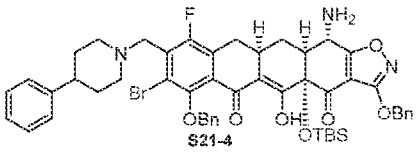
To a solution of **S21-1** (1.65 g, 3.72 mmol, 1 eq, prepared per literature procedure: *J. Med. Chem.*, 2013, *56*, 8112–8138) in DCM (37 mL) was added 4-phenylpiperidine (2.99 g, 18.6 mmol, 5 eq), followed by HOAc (1 mL, 18.6 mmol, 5 eq). After one hour, STAB (2.37 g, 11.18 mmol, 3 eq was added. After 1 h, the reaction mixture was diluted with EtOAc (150 mL) and washed with saturated, aqueous $NaHCO_3$ (2x90 mL), 1N NaOH (30 mL) and brine (30

mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography on silica gel with CH_3OH in DCM, 0.5%-3% to provide **S21-2** (1.42 g, 65%). ^1H NMR (400 MHz, $CDCl_3$) δ 13.35 (brs, 1H), 7.53-7.45 (m, 2H), 7.43-7.18 (m, 11H), 7.09-7.02 (m, 2H), 5.14 (s, 2H), 4.60 (s, 2H), 3.85-3.75 (m, 2H), 2.92-2.55 (m, 4H), 2.42 (s, 3H), 2.04-1.94 (m, 2H). MS (ESI) *m/z* 588.37 (M+H).



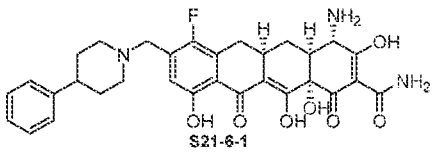
S21-3

Compound **S21-3** was prepared from **S21-2** (and **S2-3** using General Procedure **E**. ^1H NMR (400 MHz, $CDCl_3$) δ 15.92 (s, 1H), 7.62-7.48 (m, 4H), 7.43-7.14 (m, 11H), 5.89-5.76 (m, 2H), 5.38 (s, 2H), 5.23 (d, J = 17.1 Hz, 2H), 5.15 (d, J = 9.58 Hz, 2H), 5.04-4.94 (m, 2H), 4.07 (d, J = 10.4 Hz, 1H), 3.79 (brs, 1H), 3.39-3.30 (m, 2H), 3.28-3.14 (m, 3H), 3.13-2.98 (m, 2H), 5.67-2.42 (m, 4H), 2.39-2.25 (m, 1H), 2.15 (d, J = 17.7 Hz, 1H), 1.8 (brs, 1H), 0.83 (s, 9H), 0.27 (s, 3H), 0.13 (s, 3H). MS (ESI) *m/z* 1028.69 (M+H).



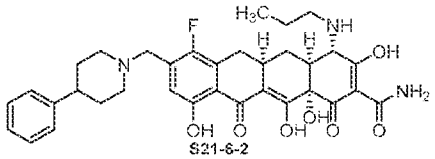
S21-4

Compound **S21-4** was prepared from compound **S21-3** by using General Procedure **A**. ^1H NMR (400 MHz, $CDCl_3$, rotamers, all peaks are broadened) δ 16.19 (m, 1H), 13.19 (brs, 1H), 7.54-7.17 (m, 15H), 5.42-4.91 (m, 5H), 4.61-4.35 (m, 2H), 4.09-3.99 (m, 1H), 3.90-3.60 (m, 2H), 3.29-2.44 (m, 7H), 2.36-1.82 (m, 4H), 0.87-0.59 (m, 9H), 0.22- -0.04 (m, 6H). MS (ESI) *m/z* 948.60 (M+H).



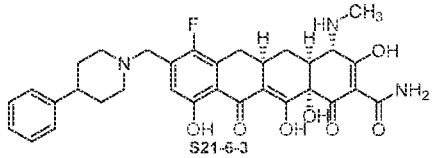
S21-6-1

Compound **S21-6-1** was prepared from compound **S21-4** by using General Procedures **C** and **D-2**.^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.35-7.18 (m, 5H), 7.09 (d, J = 6.4 Hz, 1H), 4.40 (s, 2H), 3.87 (s, 1H), 3.69-3.56 (m, 2H), 3.28-3.17 (m, 3H), 3.07-2.95 (m, 1H), 2.94-2.83 (m, 1H), 2.63 (d, J = 12.8 Hz, 1H), 2.43-2.31 (m, 1H), 2.28-2.20 (m, 1H), 2.15-1.91 (m, 4H), 1.67-1.54 (m, 1H); MS (ESI) *m/z* 578.46 (M+H).



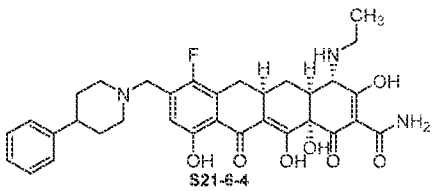
S21-6-2

Compound **S21-6-2** was prepared from compound **S21-3** by using General Procedures **C** and **D-2**.^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.36-7.19 (m, 5H), 7.13-7.07 (m, 1H), 4.42 (s, 2H), 3.86 (s, 1H), 3.69-3.59 (m, 2H), 3.28-3.14 (m, 5H), 3.09-2.96 (m, 1H), 2.93-2.81 (m, 2H), 2.41-2..31 (m, 1H), 2.26-2.18 (m, 1H), 2.15-1.91 (m, 4H), 1.83-1.70 (m, 2H), 1.65-1.53 (m, 1H), 1.03 (t, J = 8 Hz, 3H). MS (ESI) *m/z* 620.50 (M+H).



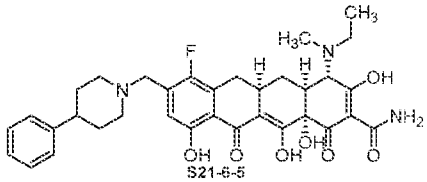
S21-6-3

To a solution of **S21-4** in THF was added allylbromide (4 eq), potassium carbonate (8 eq) and a catalytic amount of NaI. This mixture was headed at 40 °C for 5 h. The solution was diluted with brine and extracted with EtOAc. The organic layers were concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel with 10%-80% EtOAc in hexanes. The resulting product was subjected to General Procedures **B-1**, **C** and **D-2** to provide **S21-6-3**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.38-7.20 (m, 5H), 7.15-7.07 (m, 1H), 4.42 (s, 2H), 3.80 (s, 1H), 3.70-3.59 (m, 2H), 3.28-3.15 (m, 3H), 3009-2.98 (m, 1H), 2.95-2.73 (m, 5H), 2.42-2.30 (m, 1H), 2.26-2.17 (m, 1H), 2.16-1.91 (m, 4H), 1.67-1.54 (m, 1H); MS (ESI) *m/z* 592.4 (M+H).



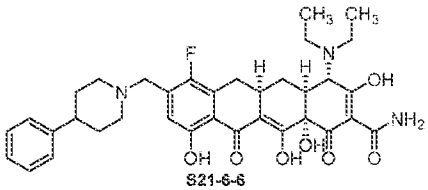
S21-6-4

Compound **S21-6-4** was prepared from compound **S21-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **C**, and **D2**: ^{1}H NMR (400 MHz, CD_3OD dihydrochloride salt) δ 7.39-7.19 (m, 5H), 7.13-7.06 (m, 1H), 4.41 (s, 2H), 3.85 (s, 1H), 3.70-3.60 (m, 2H), 3.44-3.14 (m, 3H), 3.07-2.98 (m, 1H), 2.95-2.71 (m, 4H), 2.41-2.30 (m, 1H), 2.26-2.18 (m, 1H), 2.16-1.89 (m, 4H), 1.64-1.51 (m, 1H), 1.35 (t, J = 7.3 Hz, 3H); MS (ESI) *m/z* 606.47 (M+H).



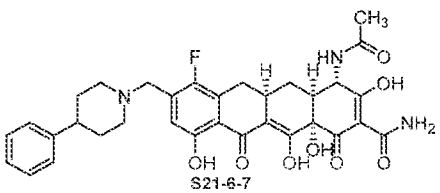
S21-6-5

Compound **S21-6-5** was prepared from compound **S21-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **B-1** with HCHO, **C**, and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.38-7.17 (m, 5H), 7.14-7.09 (m, 1H), 4.42 (s, 2H), 4.22 (s, 0.5H), 4.13 (s, 0.5H), 3.71-3.60 (m, 2H), 3.54-3.40 (m, 1H), 3.29-3.17 (m, 2H), 3.16-2.83 (m, 6H), 2.41-2.30 (m, 1H), 2.30-2.20 (m, 1H), 2.15-1.94 (m, 4H), 1.73-1.59 (m, 1H), 1.46-1.33 (m, 3H); MS (ESI) *m/z* 620.50 (M+H).



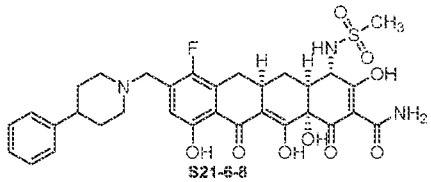
S21-6-6

Compound **S21-6-6** was prepared from compound **S21-4** with CH_3CHO by using General Procedures **B-1** (at 0 °C), **B-1** again with CH_3CHO, **C**, and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.38-7.18 (m, 5H), 7.13-7.08 (m, 1H), 4.42 (s, 2H), 4.24 (s, 1H), 3.70-3.53 (m, 3H), 3.50-3.40 (m, 2H), 3.29-3.17 (m, 4H), 3.14-3.02 (m, 1H), 2.95-2.84 (m, 2H), 2.41-2.30 (m, 1H), 2.28-2.20 (m, 1H), 2.15-1.92 (m, 4H), 1.72-1.58 (m, 1H), 1.40 (t, J = 7.2 Hz, 6H); MS (ESI) *m/z* 634.49 (M+H).



S21-6-7

Compound **S21-6-7** was prepared from compound **S21-4** by using General Procedures **B-2** with Ac_2O, **C**, and **D-2**: ^{1}H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 8.39-8.31 (m, 1H), 7.37-7.19 (m, 5H), 7.09-7.03 (m, 1H), 4.76-4.69 (m, 1H), 4.42 (s, 2H), 3.71-3.61 (m, 2H), 3.28-3.21 (m, 1H), 3.19-3.11 (m, 1H), 3.08-2.98 (m, 1H), 2.95-2.84 (m, 1H), 2.65-2.53 (m, 1H), 2.47-2.34 (m, 2H), 2.28-2.20 (m, 1H), 2.18-1.91 (m, 7H), 1.68-1.58 (m, 1H); MS (ESI) *m/z* 620.3 (M+H).



S21-6-8

Compound **S21-6-8** was prepared from compound **S21-4** by using General Procedures **B-2** with Ms_2O, **C**, and **D-2**: ^1H NMR (400 MHz, CD_3OD, dihydrochloride salt) δ 7.35-7.17 (m, 5H), 7.03 (d, J = 5.6 Hz, 1H), 4.37 (s, 2H), 4.14-4.09 (m, 1H), 3.66-3.55 (m, 2H), 3.27-3.09 (m, 6H), 3.08-2.98 (m, 1H), 2.92-2.82 (m, 1H), 2.67-2.54 (m, 1H), 2.53-2.44 (m, 1H), 2.37-2.26 (m, 1H), 2.13-2.88 (m, 4H), 1.79-1.69 (m, 1H); MS (ESI) *m/z* 656.3 (M+H).

Example 4: Antibacterial Activity

The antibacterial activities for the compounds of the invention were studied according to the following protocols.

Minimum Inhibitory Concentration (MIC) Assay

MICs were determined according to the Clinical and Laboratory Standards Institute (CLSI) guidances (e.g., CLSI. Performance standards for antimicrobial susceptibility testing; nineteenth information supplement. CLSI document M100-S19, CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA, 2009). Briefly, frozen bacterial strains were thawed and subcultured onto Mueller Hinton Broth (MHB) or other appropriate media (*Streptococcus* requires blood and *Haemophilus* requires hemin and NAD). Following incubation overnight, the strains were subcultured onto Mueller Hinton Agar and again incubated overnight. Colonies were observed for appropriate colony morphology and lack of contamination. Isolated colonies were selected to prepare a starting inoculum equivalent to a 0.5 McFarland standard. The starting inoculum was diluted 1:125 (this is the working inoculum) using MHB for further use. Test compounds were prepared by dilution in sterile water to a final concentration of 5.128 mg/mL. Antibiotics (stored frozen, thawed and used within 3 hours of thawing) and compounds were further diluted to the desired working concentrations.

The assays were run as follows. Fifty µL of MHB was added to wells 2 – 12 of a 96-well plate. One hundred µL of appropriately diluted antibiotics was added to well 1. Fifty µL of antibiotics was removed from well 1 and added to well 2 and the contents of well 2 mixed by pipetting up and down five times. Fifty µL of the mixture in well 2 was removed

and added to well 3 and mixed as above. Serial dilutions were continued in the same manner through well 12. Fifty µL was removed from well 12 so that all contained 50 µL. Fifty µL of the working inoculum was then added to all test wells. A growth control well was prepared by adding 50 µL of working inoculum and 50 µL of MHB to an empty well. The plates were then incubated at 37 °C overnight, removed from the incubator and each well was read on a plate reading mirror. The lowest concentration (MIC) of test compound that inhibited the growth of the bacteria was recorded.

Example:

	1	2	3	4	5	6	7	8	9	10	11	12
[Abt]	32	16	8	4	2	1	0.5	0.25	0.125	0.06	0.03	0.015
Growth	-	-	-	-	-	+	+	+	+	+	+	+

[abt] = antibiotic concentration in the well in µg/ml Growth = bacterial growth (cloudiness)

Interpretation: MIC = 2 µg/mL

Protocol for Determining Inoculum Concentration (Viable Count)

Fifty 50µl of the inoculum was pipetted into well 1. Ninety µl of sterile 0.9% NaCl was pipetted into wells 2–6 of a 96-well microtiter plate. Ten µL from was removed from well 1 and added it to well 2 followed by mixing. Ten µL was removed from well two and mixed with the contents of well 3 and so on creating serial dilutions through well 6. Ten µL was removed from each well and spotted onto an appropriate agar plate. The plate was placed into an incubator overnight. The colonies in spots that contain distinct colonies were counted. Viable count was calculated by multiplying the number of colonies by the dilution factor.

Spot from Well	1	2	3	4	5	6
Dilution Factor	10^2	10^3	10^4	10^5	10^6	10^7

Bacterial Strains

The following bacterial strains, listed below, were examined in minimum inhibitory concentration (MIC) assays.

ORGANISM	STRAIN DESIGNATION	KEY PROPERTIES
Staphylococcus aureus	SA100	ATCC 13709, MSSA, Smith strain

ORGANISM	STRAIN DESIGNATION	KEY PROPERTIES
Staphylococcus aureus	SA101	ATCC 29213, CLSI quality control strain, MSSA
Staphylococcus aureus	SA191	HA-MRSA, tetracycline-resistant, lung infection model isolate
Staphylococcus aureus	SA161	HA-MRSA, tetracycline-resistant, *tet*(M)
Staphylococcus aureus aaaureusaureus	SA158	Tetracycline-resistant *tet*(K)
Staphylococcus epidermidis	SE164	ATCC 12228, CLSI quality control strain, tetracycline-resistant
Enterococcus faecalis	EF103	ATCC 29212, tet-I/R, control strain
Enterococcus faecalis	EF159	Tetracycline-resistant, *tet*(M)
Enterococcus faecalis	EF327	Wound isolate (US) *tet*(M)
Enterococcus faecium	EF404	Blood isolate (US) *tet*(M)
Streptococcus pneumoniae	SP106	ATCC 49619, CLSI quality control strain
Streptococcus pneumoniae	SP160	Tetracycline-resistant, *tet*(M)
Streptococcus pyogenes	SP312	2009 clinical isolate, *tet*(M)
Streptococcus pyogenes	SP193	*S. pyogenes* for efficacy models; tetS; sensitive to sulfonamides
Haemophilus influenzae	HI262	Tetracycline-resistant, ampicillin-resistant
Moraxella catarrhalis	MC205	ATCC 8176, CLSI quality control strain
Escherichia coli	EC107	ATCC 25922, CLSI quality control strain
Escherichia coli	EC155	Tetracycline-resistant, *tet*(A)
Enterobacter cloacae	EC108	ATCC 13047, wt
Enterobacter cloacae	EC603	Urine isolate (Spain)
Escherichia coli	EC878	MG1655 *tolC::kan*
Klebsiella pneumoniae	KP109	ATCC 13883, wt
Klebsiella pneumoniae	KP153	Tetracycline-resistant, *tet*(A), MDR, $ESBL^+$
Klebsiella pneumoniae	KP457	2009 $ESBL^+$, CTX-M, OXA
Proteus mirabilis	PM112	ATCC 35659

ORGANISM	STRAIN DESIGNATION	KEY PROPERTIES
Proteus mirabilis	PM385	Urine ESBL+ isolate
Pseudomonas aeruginosa	PA111	ATCC 27853, wt, control strain
Pseudomonas aeruginosa	PA169	Wt, parent of PA170-173
Pseudomonas aeruginosa	PA173	PA170 Δ*mexX*; MexXY-(missing a functional efflux pump)
Pseudomonas aeruginosa	PA555	ATCC BAA-47, wild type strain PAO1
Pseudomonas aeruginosa	PA556	Multiple-Mex efflux pump knockout strain
Pseudomonas aeruginosa	PA673	2009 urine isolate from catheter in male from East North Central US
Pseudomonas aeruginosa	PA669	2009 clinical isolate from tracheal aspirate
Pseudomonas aeruginosa	PA693	2009 isolate from corneal scraping of female from Pacific US
Pseudomonas aeruginosa	PA1145	Strain used in murine pneumonia model
Acinetobacter baumannii	AB110	ATCC 19606, wt
Acinetobacter baumannii	AB250	Cystic fibrosis isolate, MDR
Stenotrophomonas maltophilia	SM256	Cystic fibrosis isolate, MDR
Burkholderia cenocepacia	BC240	Cystic fibrosis isolate, MDR

*MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; HA-MRSA, hospital-associated MRSA; *tet*(K), major gram-positive tetracycline efflux mechanism; *tet*(M), major gram-positive tetracycline ribosome-protection mechanism; ESBL+, extended spectrum β-lactamase

Results

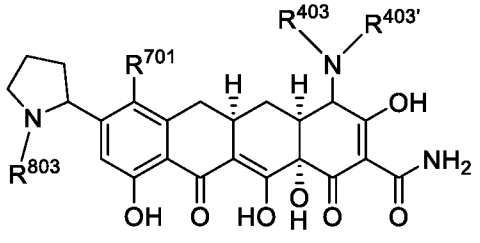
Values of minimum inhibition concentration (MIC) for tested compounds of the invention are provided in the table represented in FIG. 14A through FIG. 14E, collectively. MIC values are reported in μg/mL.

The relevant teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS:

1. A method of treating an Acute Myeloid Leukemia (AML), said method comprising administering to a subject in need of treatment an effective amount of a compound having Structural Formula (XX):



(XX)

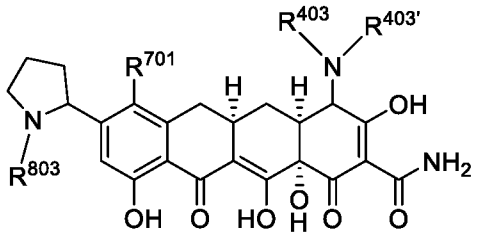
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof, wherein:

R^{803} is H, a C_{1-6} alkyl, a C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, a C_{3-12} carbocyclyl-(C_{0-3})alkylenyl, an amino-(C_1-C_4) alkyl, a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-4})alkyl, or a (4-13 member)heterocyclyl-(C_0-C_3)alkylenyl, wherein the heterocyclyl portion is optionally substituted with a C_{1-3} alkyl;

R^{701} is H, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl, C_{1-4} haloalkoxy; and

R^{403} and $R^{403'}$, each independently, is H; a C_{1-4} alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl-, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; or a $H_2NC(O)$-(C_1-C_3)alkylenyl-.

2. Use of a compound having Structural Formula (XX):



(XX)

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof, wherein:

R^{803} is H, a C_{1-6} alkyl, a C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, a C_{3-12} carbocyclyl-(C_{0-3})alkylenyl, an amino-(C_1-C_4) alkyl, a mono- or di- (C_1-C_4 alkyl)amino-(C_{1-}

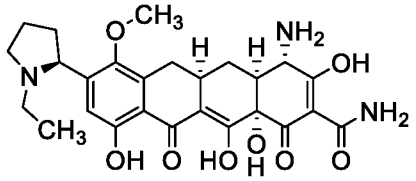
$_4$)alkyl, or a (4-13 member)heterocyclyl-(C_0-C_3)alkylenyl, wherein the heterocyclyl portion is optionally substituted with a C_{1-3} alkyl;

R^{701} is H, a C_{1-4} alkyloxy, -OH, C_{1-4} alkyl, a C_{1-4} haloalkyl, or C_{1-4} hydroxyalkyl, C_{1-4} haloalkoxy; and

R^{403} and $R^{403'}$, each independently, is H; a C_{1-4} alkyl; a C_{3-12} carbocyclyl-(C_0-C_3)alkylenyl-, wherein the carbocyclyl portion is optionally substituted with a hydroxyl group; or a $H_2NC(O)$-(C_1-C_3)alkylenyl-,

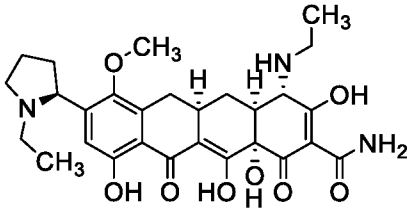
in the manufacture of a medicament for treating an Acute Myeloid Leukemia (AML).

3. The method of claim 1 or the use of claim 2, wherein the compound is selected from:



compound 3A/K4

, and



,

or a pharmaceutically acceptable salt thereof.

4. The method of claim 1 or the use of claim 2, wherein R^{701} is $-OCH_3$, and R^{803} is ethyl.

5. The method of claim 1 or the use of claim 2, wherein R^{701} is $-OCH_3$, and R^{403} and $R^{403'}$ each is hydrogen.

6. The method of claim 1 or the use of claim 2, wherein R^{803} is ethyl and R^{403} and $R^{403'}$ each is hydrogen.

7. The method of claim 1 or the use of claim 2, wherein R^{701} is a $-OCF_3$, and R^{803} is methyl.

8. The method of claim 1 or the use of claim 2, wherein R^{701} is $-CF_3$, and R^{803} is a C_{1-4} alkyl or a (C_3-C_6)carbocyclyl-(C_0-C_3)alkylenyl.

9. The method of claim 1 or the use of claim 2, wherein the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

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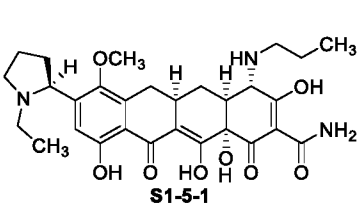
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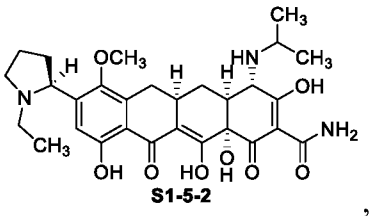
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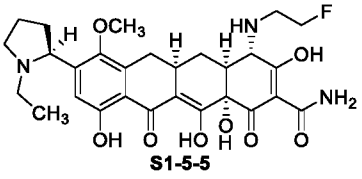
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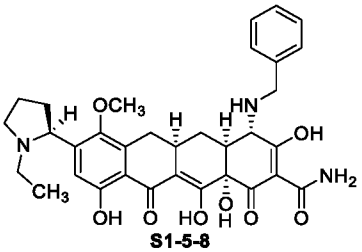
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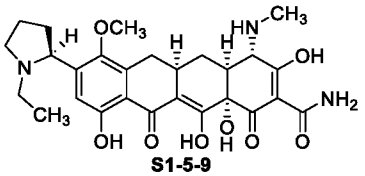
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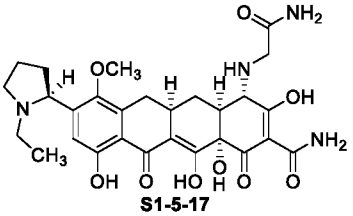
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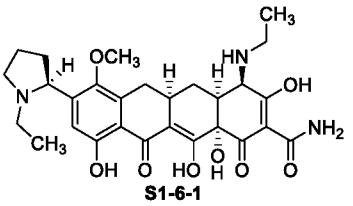
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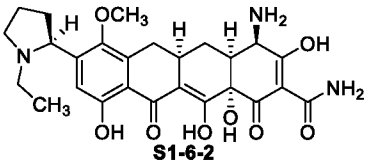
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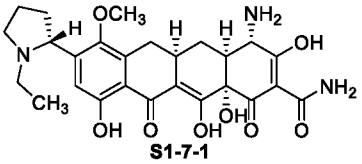
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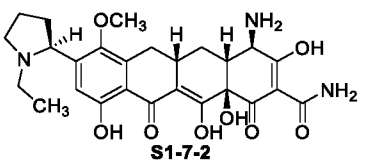
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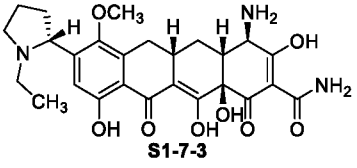
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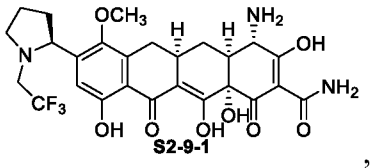
10. The method of claim 1 or the use of claim 2, wherein the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof: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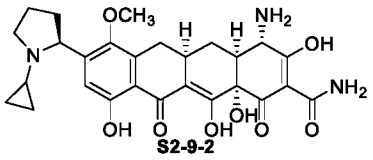
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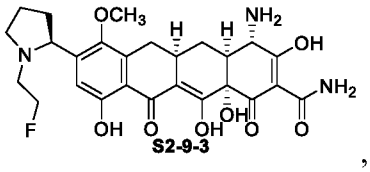
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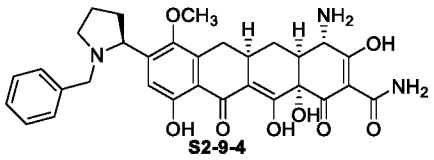
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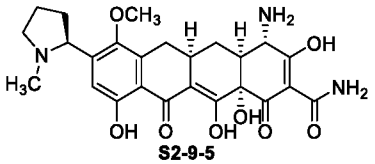
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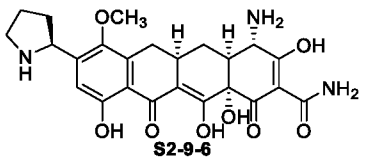
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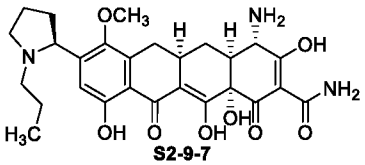
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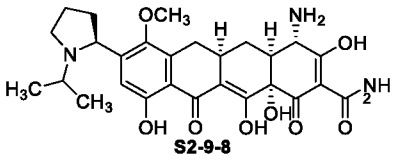
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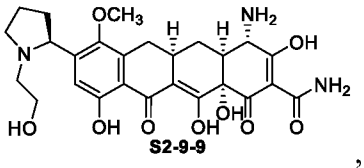
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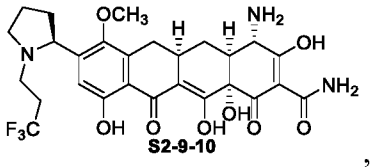
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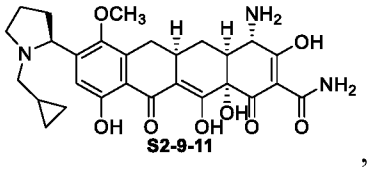
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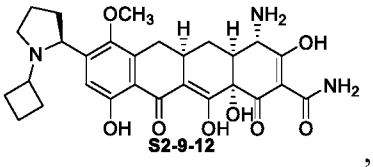
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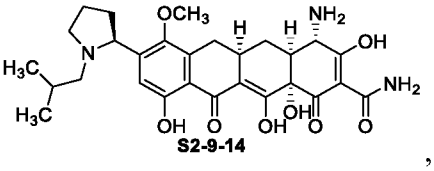
S2-9-13 ,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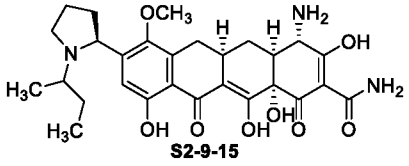
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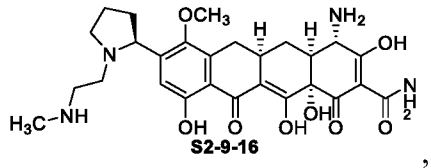
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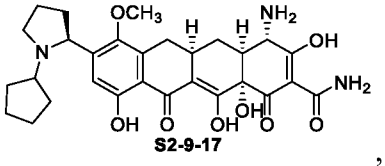
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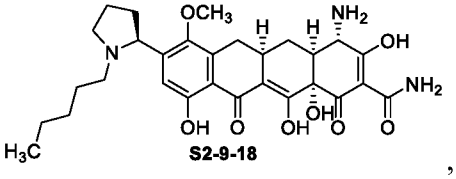
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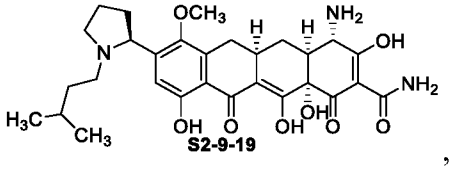
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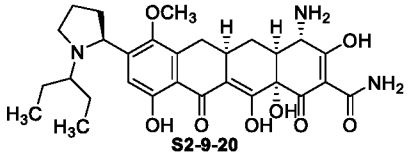
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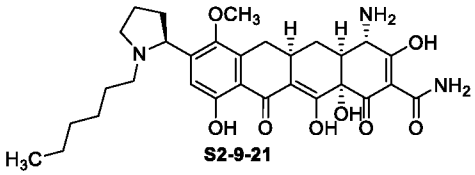
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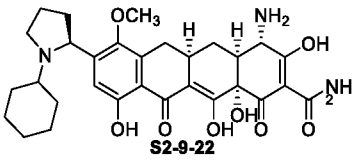
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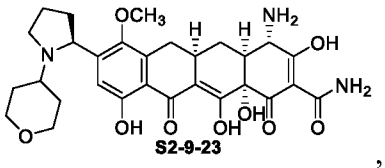
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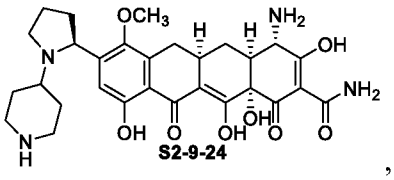
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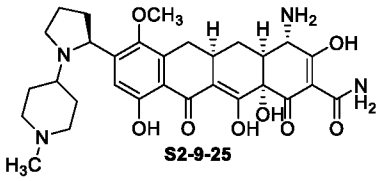
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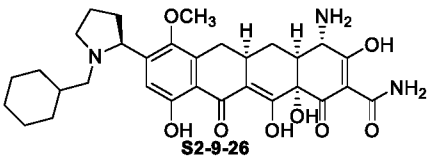
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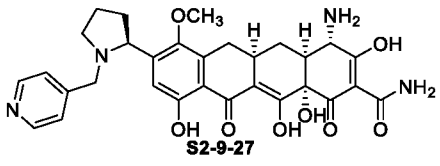
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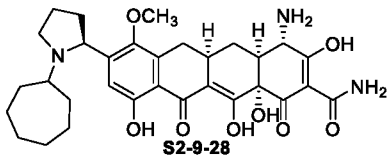
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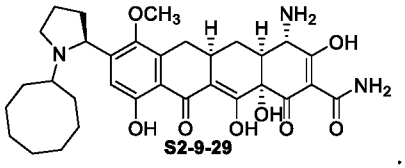
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11. The method of claim 1 or the use of claim 2, wherein the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

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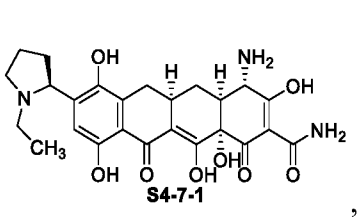

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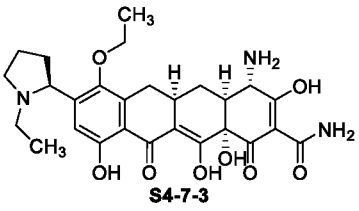

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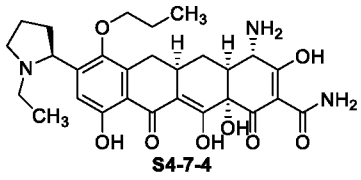

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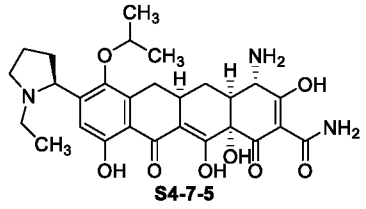

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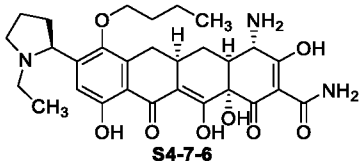
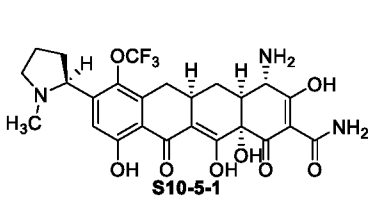


.

12. The method of claim 1 or the use of claim 2, wherein the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:



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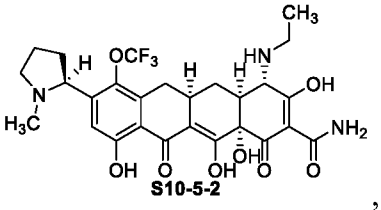

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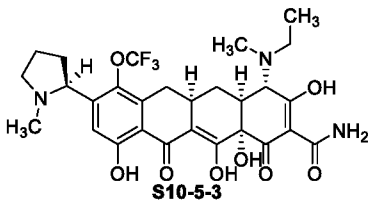

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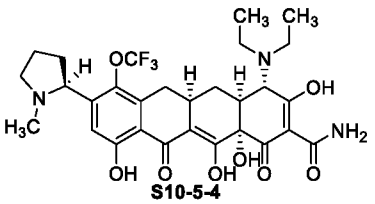

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13. The method of claim 1 or the use of claim 2, wherein the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

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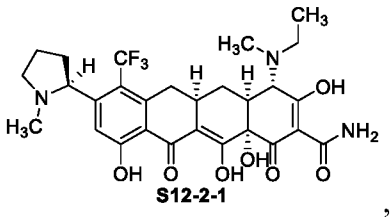
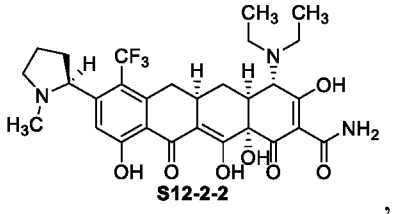


S12-2-1,



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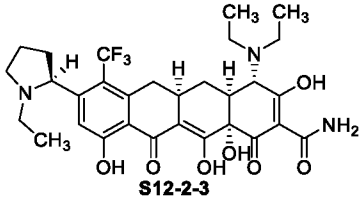
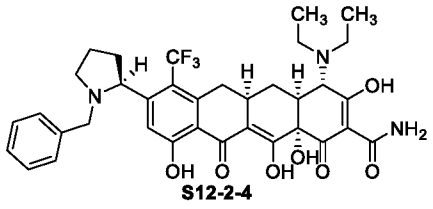
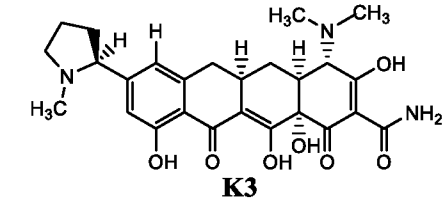


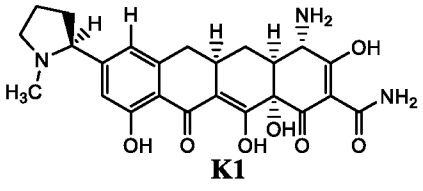
S12-2-3

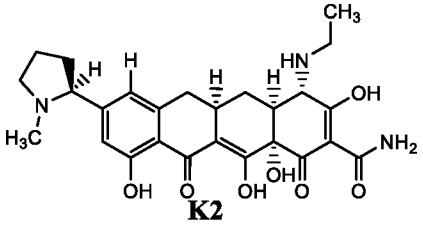


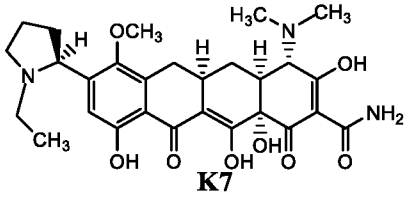
S12-2-4.

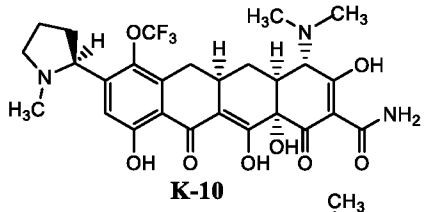
14. The method of claim 1 or the use of claim 2, wherein the compound is represented by any one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

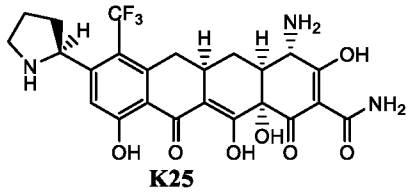

K3

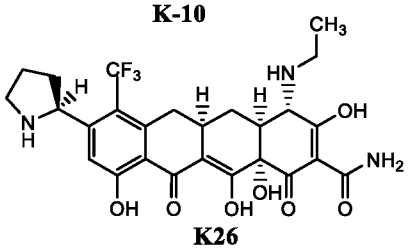

K1

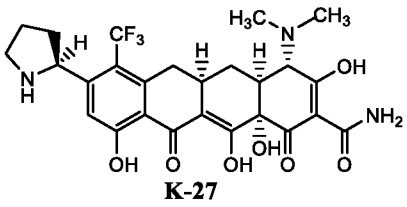

K2

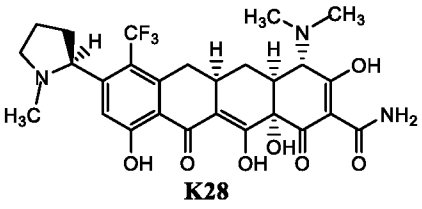

K7


K-10


K25


K26


K-27


K28

15. The method of claim 1 or the use of claim 2, further comprising administration of one or more additional therapeutic agents.

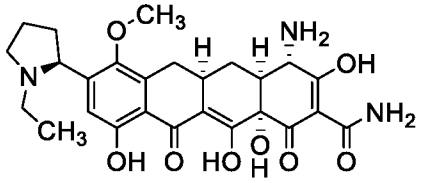
16. The method or use of claim 15, wherein the additional therapeutic agents are cytarabine and an anthracycline drug.

17. The method or use of claim 16, wherein the anthracycline drug is selected from daunorubicin or idarubicin.

18. The method or use of claim 15 or claim 16, further including administration of cladribine.

19. The method or use of any one of claims 1 to 14, wherein the subject is a human.

20. The method of claim 1 or the use of claim 2, wherein the compound is represented by the following structural formula

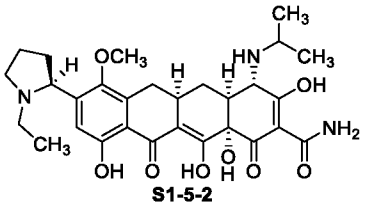


compound 3A/K4

,

or a pharmaceutically acceptable salt thereof.

21. The method of claim 1 or the use of claim 2, wherein the compound is represented by any one of the following structural formulas:



S1-5-2

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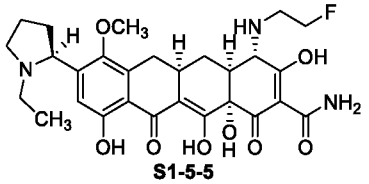

S1-5-5

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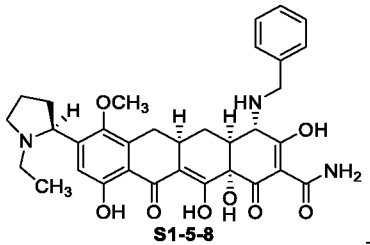

S1-5-8

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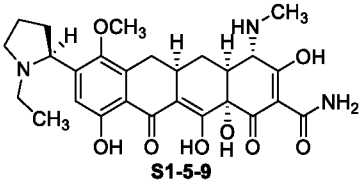

S1-5-9

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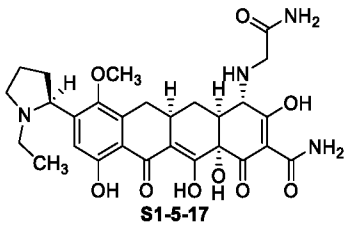

S1-5-17

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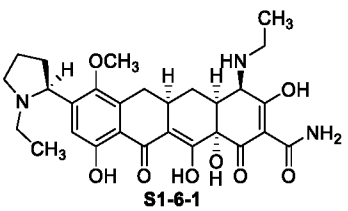

S1-6-1

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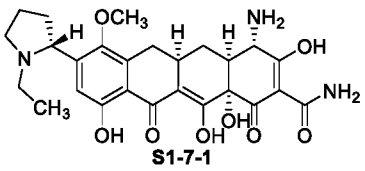

S1-7-1

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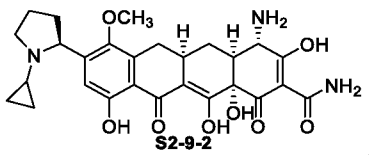

S2-9-2

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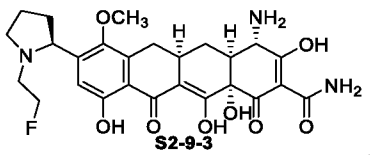

S2-9-3

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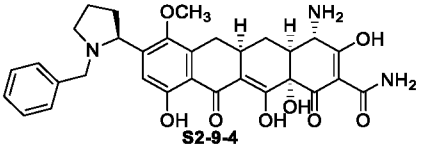

S2-9-4

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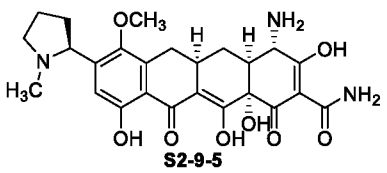

S2-9-5

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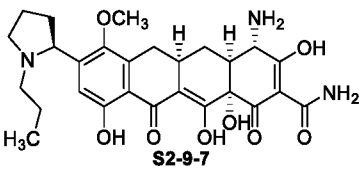

S2-9-7

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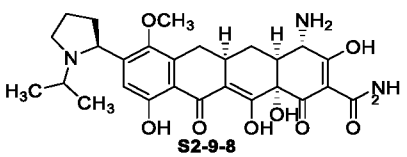

S2-9-8

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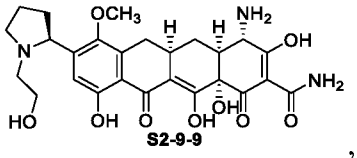
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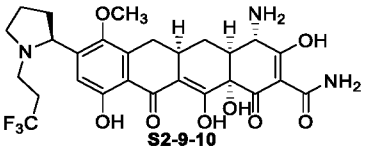
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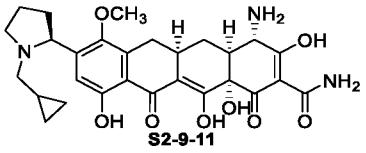
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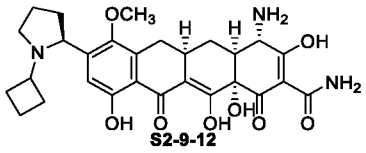
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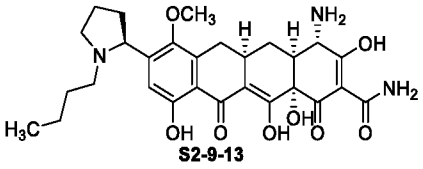
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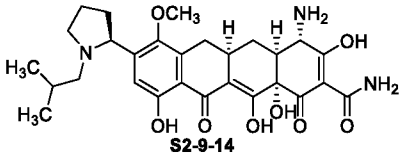
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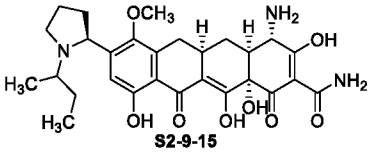
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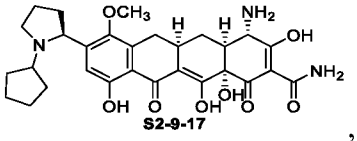
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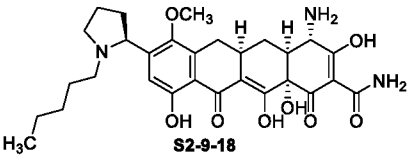
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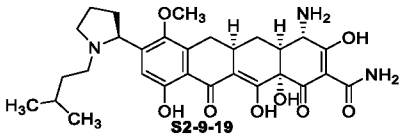
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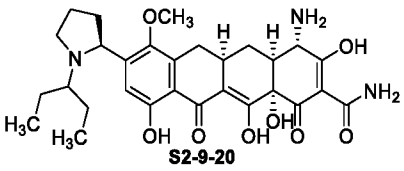
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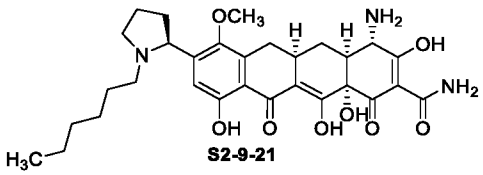
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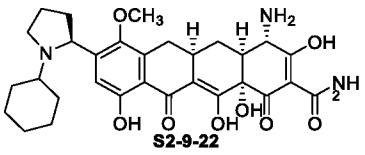
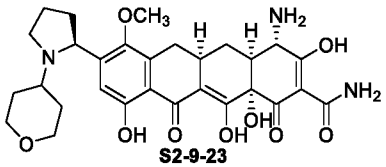
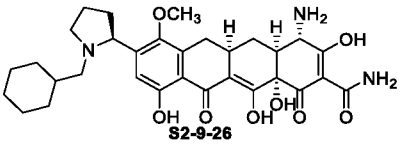
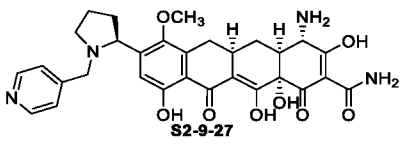
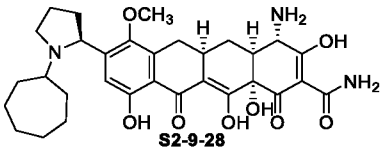
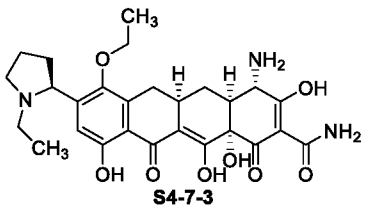

S2-9-22


S2-9-23


S2-9-26


S2-9-27


S2-9-28


S4-7-3

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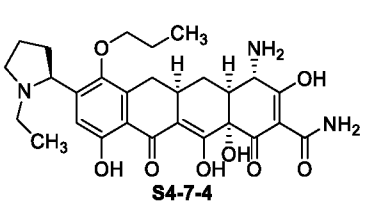
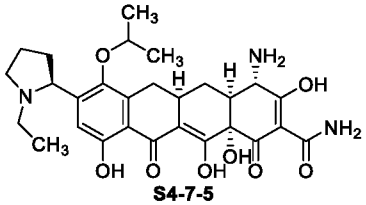
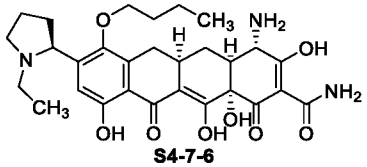
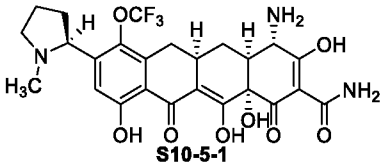
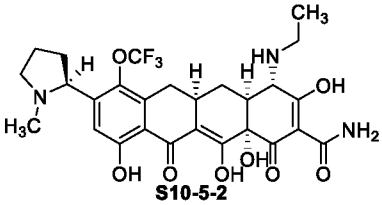
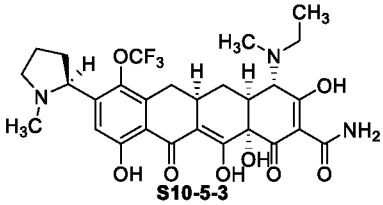

S4-7-4 ,

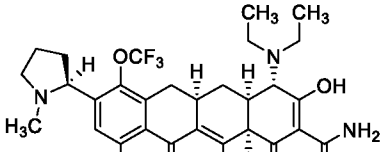

S4-7-5 ,

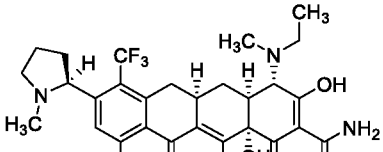

S4-7-6 ,

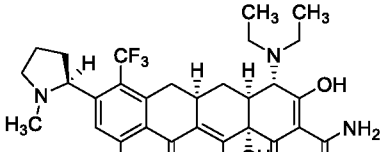

S10-5-1 ,

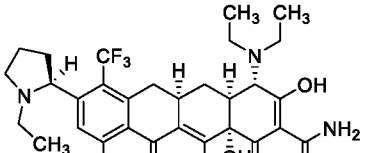

S10-5-2 ,

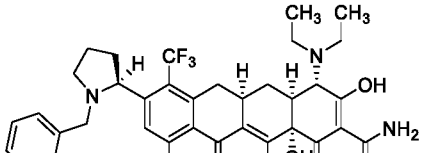

S10-5-3 ,

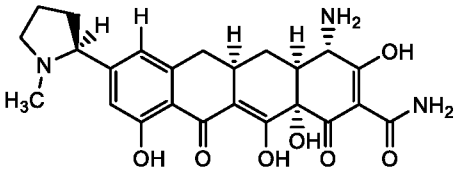

S10-5-4 ,

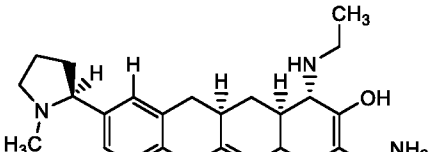

S12-2-1 ,

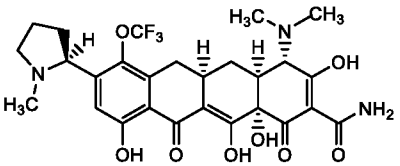

S12-2-2 ,

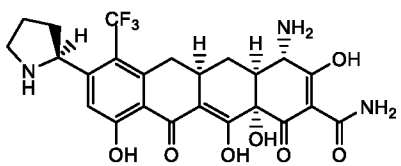

S12-2-3 ,


S12-2-4 ,


K1 ,


K2 ,


K-10 ,


K25 ,

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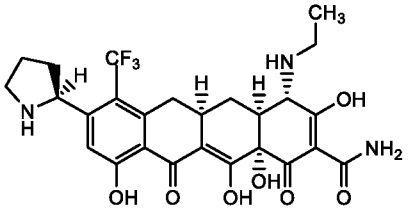

K26

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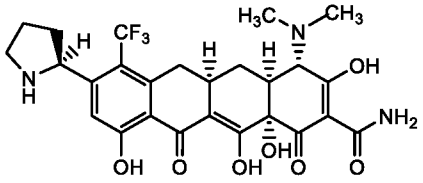

K-27

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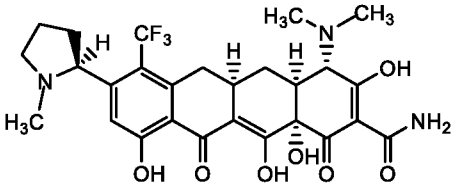

K28

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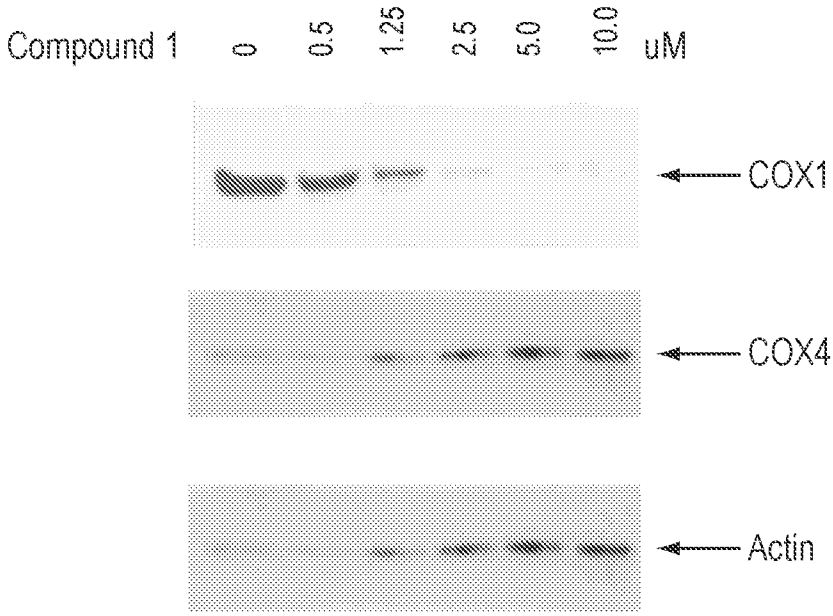

Compound 1
0
0.5
1.25
2.5
5.0
10.0
uM
COX1
COX4
Actin

FIG. 1

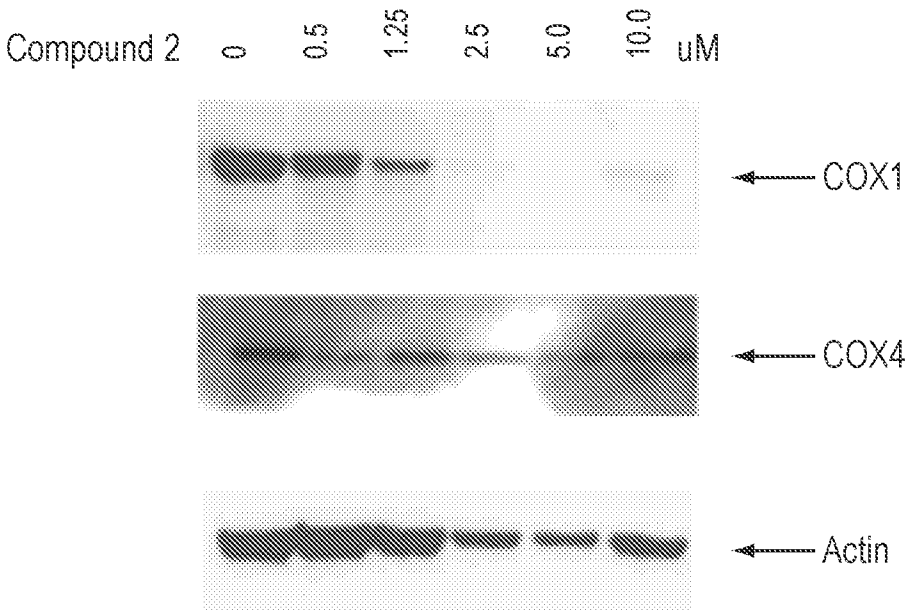

Compound 2
0
0.5
1.25
2.5
5.0
10.0
uM
COX1
COX4
Actin

FIG. 2

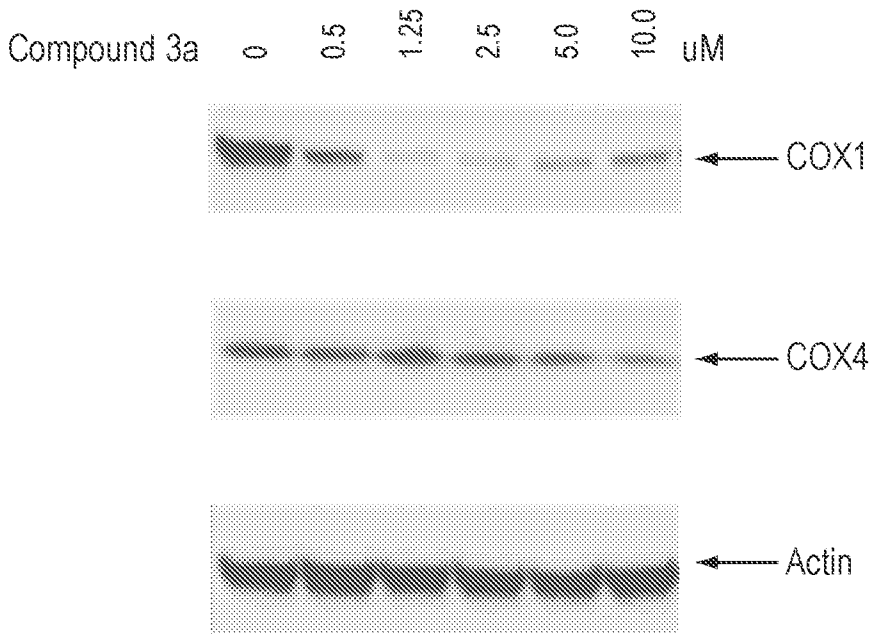

Compound 3a
0
0.5
1.25
2.5
5.0
10.0
uM
COX1
COX4
Actin

FIG. 3

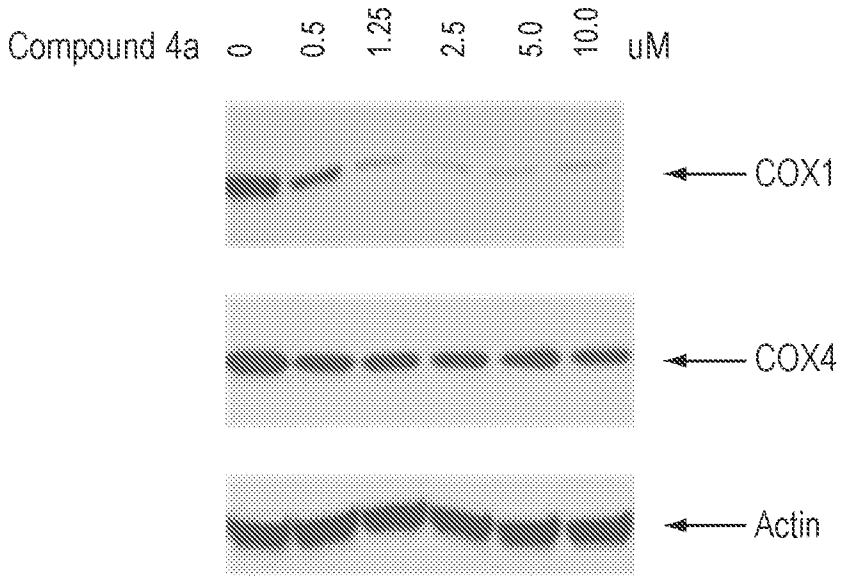

Compound 4a
0
0.5
1.25
2.5
5.0
10.0
uM
COX1
COX4
Actin

FIG. 4

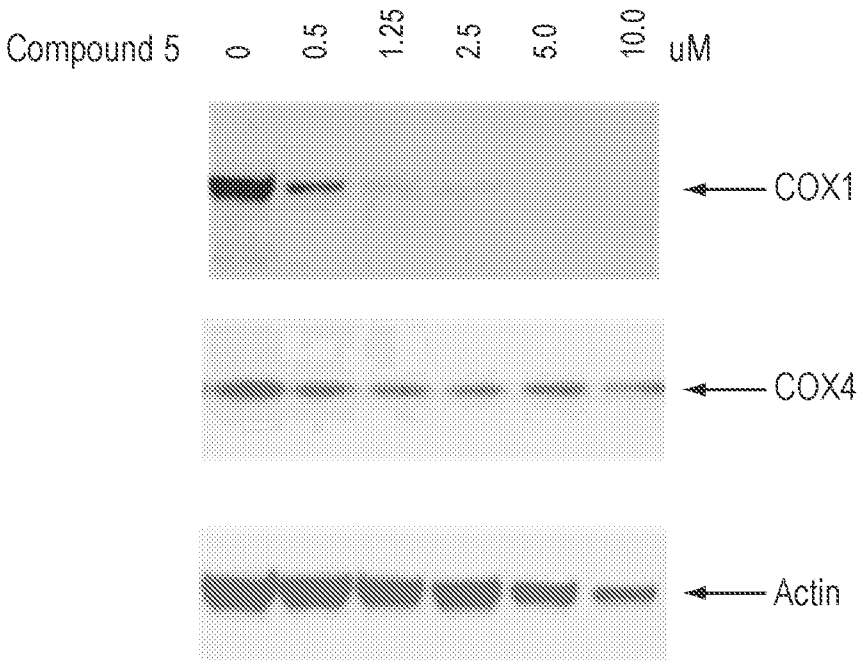

Compound 5
0
0.5
1.25
2.5
5.0
10.0
uM
COX1
COX4
Actin

FIG. 5

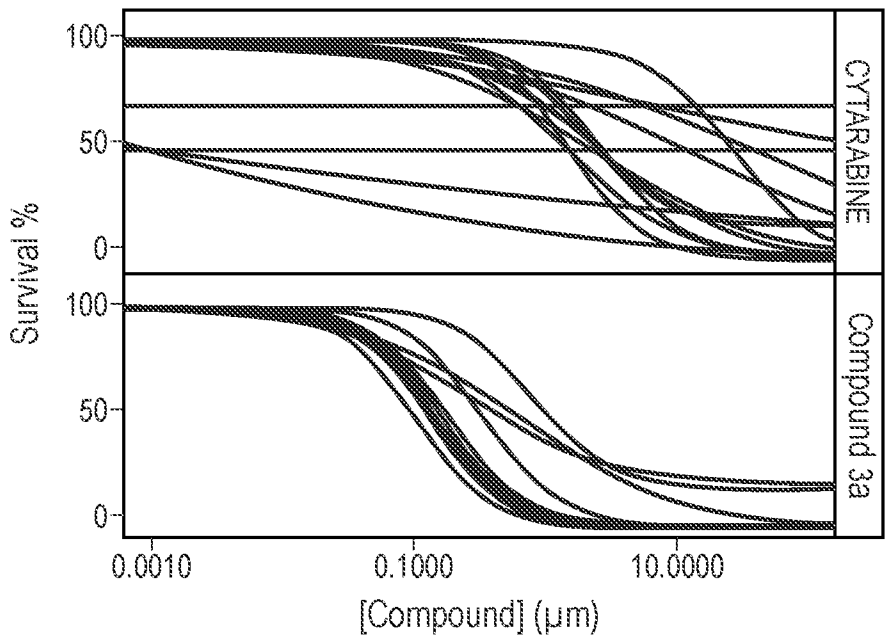

100
50
0
Survival %
CYTARABINE
Compound 3a
0.0010
0.1000
10.0000
[Compound] (μm)

FIG. 6

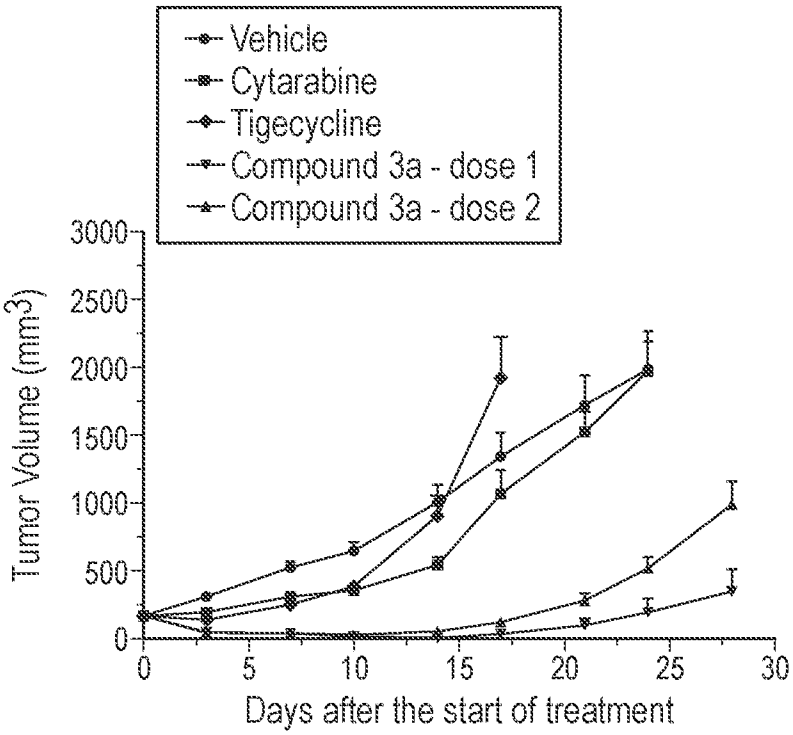

Vehicle
Cytarabine
Tigecycline
Compound 3a - dose 1
Compound 3a - dose 2
Tumor Volume (mm3)
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
Days after the start of treatment

FIG. 7A

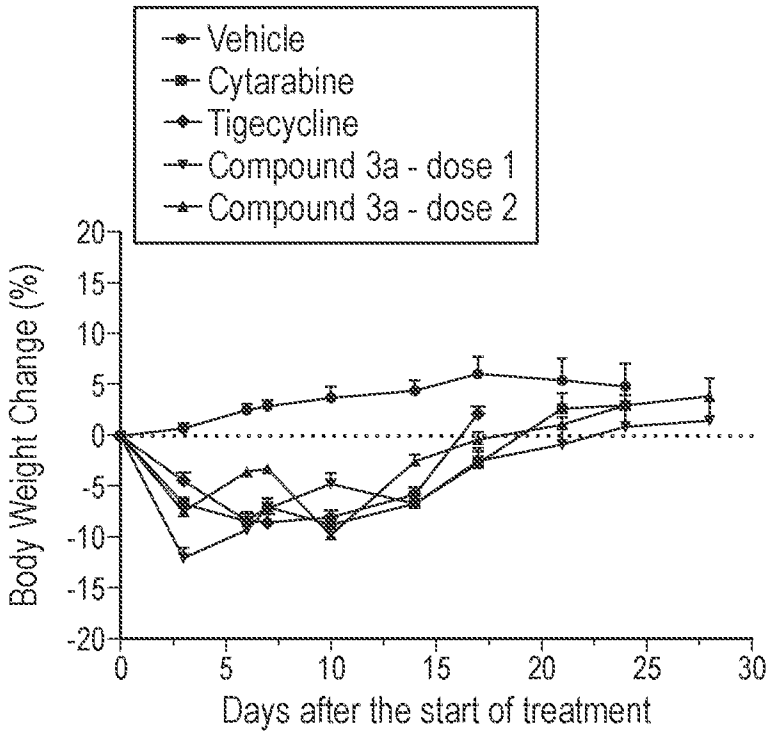

Vehicle
Cytarabine
Tigecycline
Compound 3a - dose 1
Compound 3a - dose 2
Body Weight Change (%)
20
15
10
5
0
-5
-10
-15
-20
0
5
10
15
20
25
30
Days after the start of treatment

FIG. 7B

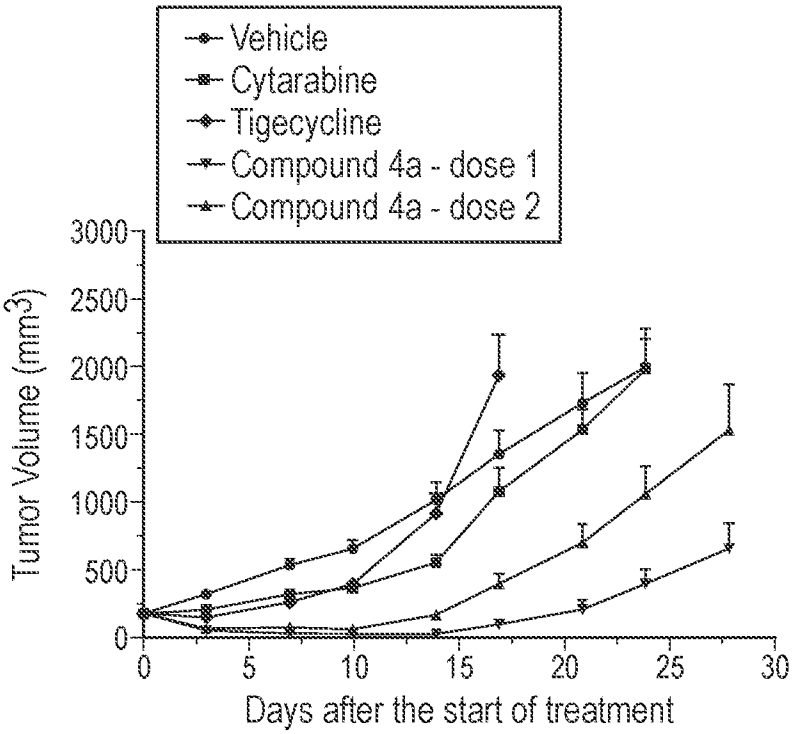

Vehicle
Cytarabine
Tigecycline
Compound 4a - dose 1
Compound 4a - dose 2
Tumor Volume (mm3)
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
Days after the start of treatment

FIG. 7C

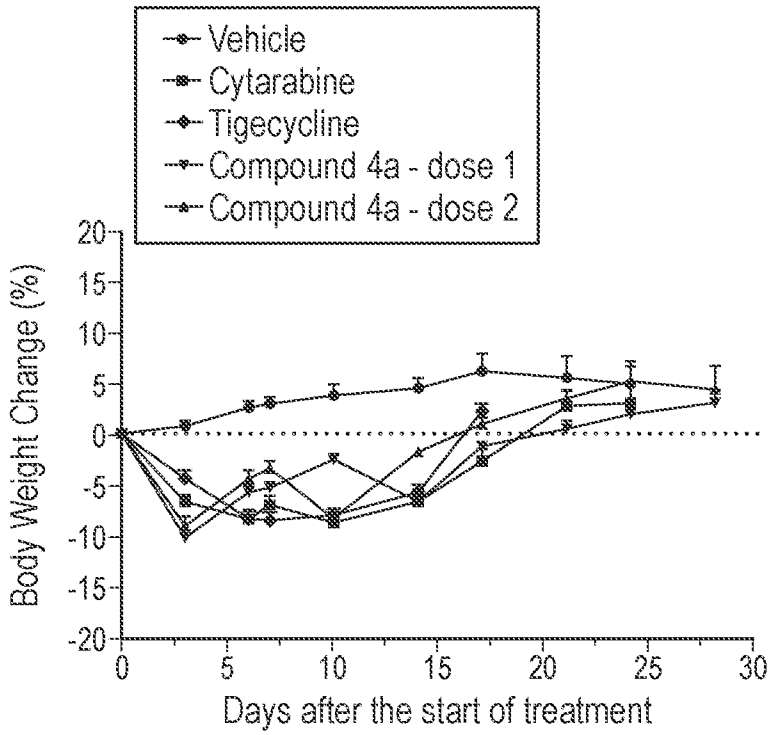

Vehicle
Cytarabine
Tigecycline
Compound 4a - dose 1
Compound 4a - dose 2
Body Weight Change (%)
20
15
10
5
0
-5
-10
-15
-20
0
5
10
15
20
25
30
Days after the start of treatment

FIG. 7D

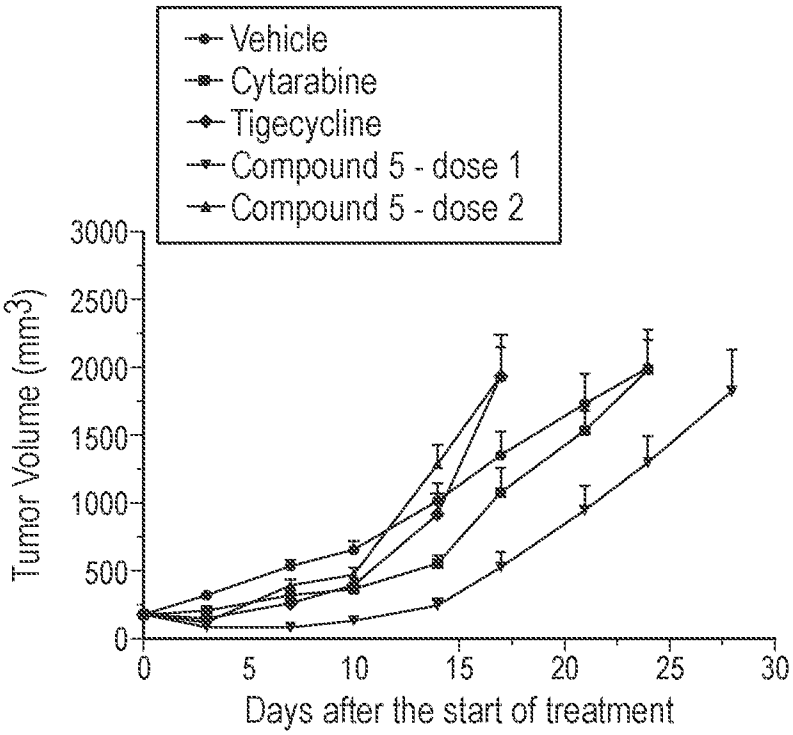

Vehicle
Cytarabine
Tigecycline
Compound 5 - dose 1
Compound 5 - dose 2
Tumor Volume (mm3)
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
Days after the start of treatment

FIG. 7E

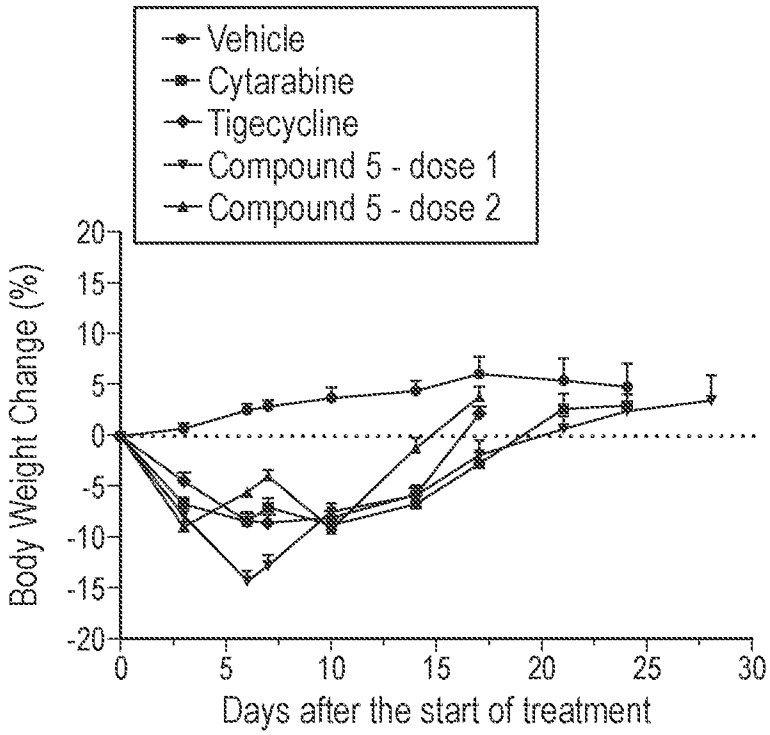

Vehicle
Cytarabine
Tigecycline
Compound 5 - dose 1
Compound 5 - dose 2
Body Weight Change (%)
20
15
10
5
0
-5
-10
-15
-20
0
5
10
15
20
25
30
Days after the start of treatment

FIG. 7F

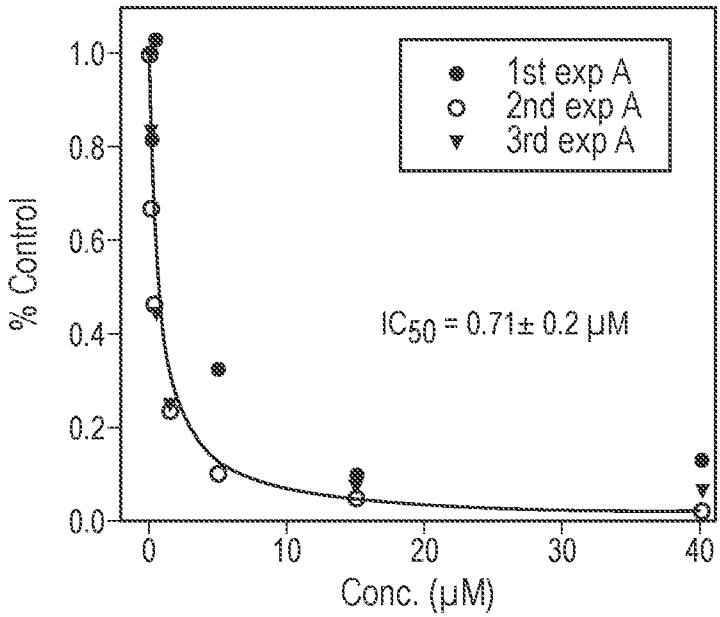

1st exp A
2nd exp A
3rd exp A
% Control
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Conc. (μM)
IC50 = 0.71± 0.2 μM

FIG. 8

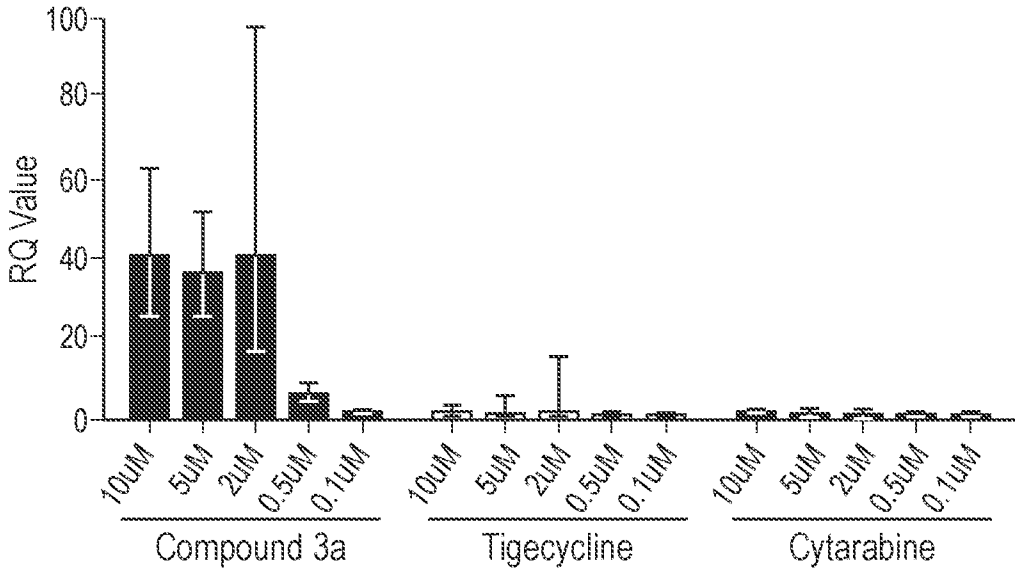

RQ Value
100
80
60
40
20
0
10uM
5uM
2uM
0.5uM
0.1uM
Compound 3a
Tigecycline
Cytarabine

FIG. 9

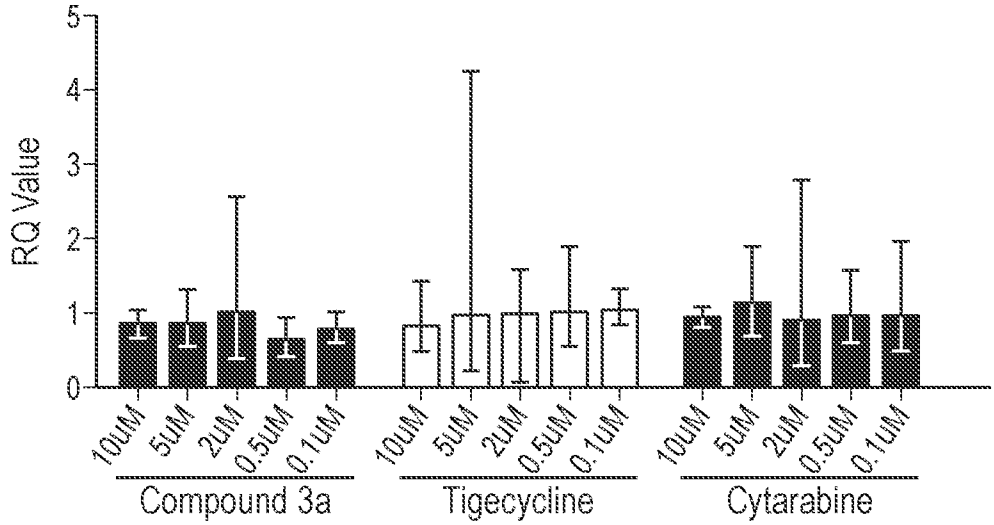


FIG. 10

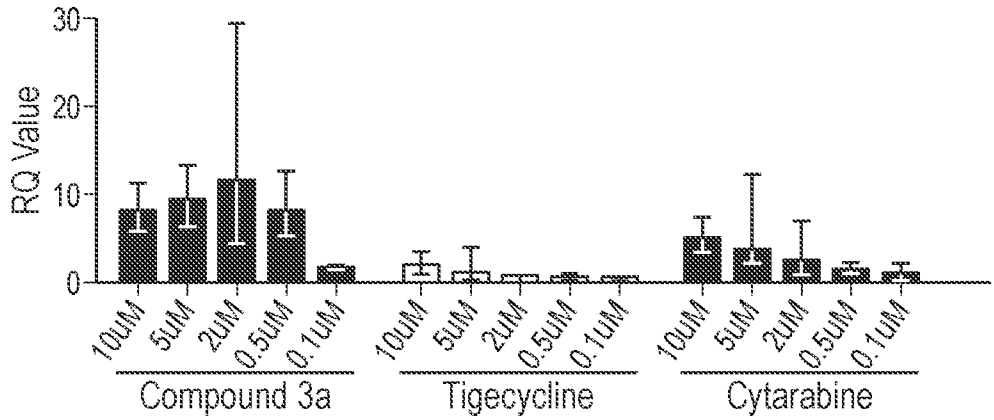


FIG. 11

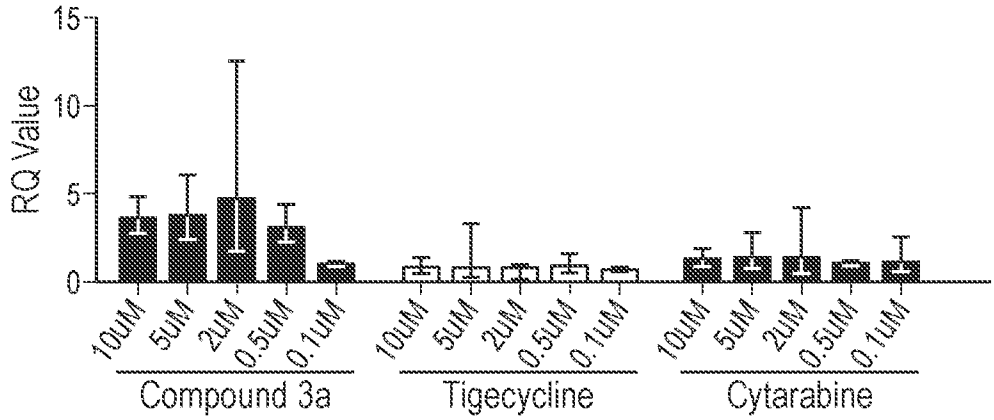


FIG. 12

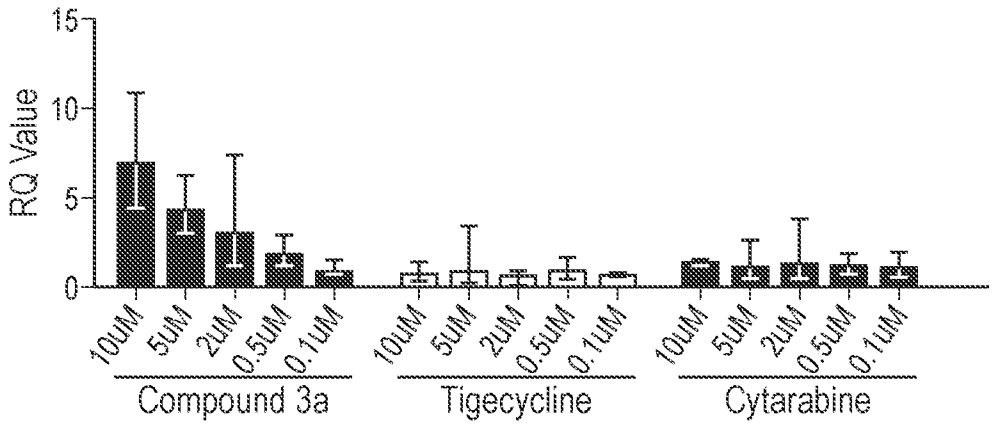

15
10
5
0
RQ Value
10uM
5uM
2uM
0.5uM
0.1uM
Compound 3a
Tigecycline
Cytarabine

FIG. 13

Compound Number	MIC(ug/mL)																				
	SA101	SA161	SA158	EF327	EF404	SP160	EC107	EC155	EC878	KP457	PM385	PA555	PA556	PA1145	PA669	PA673	PA693	EC603	AB250	SM256	BC240
	29213	tetM	tetK	tetM	tetM	tetM	25922	tetA	tolC	CTX-M-15		BAA-47	Vivisource					tetA			
S12-2-3	1	2	0.125	0.5	0.625	≤0.0156	0.0625	0.25	0.25	2	4	32	4	32	>32	>32	>32	4	1	1	8
S12-2-2	0.5	2	0.0312	1	0.25	≤0.0156	≤0.0156	0.125	0.0312	2	2	32	2	32	32	32	32	4	0.5	0.25	4
S12-2-1	0.125	2	≤0.0156	2	0.25	≤0.0156	≤0.0156	0.0625	≤0.0156	1	2	16	1	16	32	32	32	2	0.25	0.125	8
S9-5-1	4	32	0.125	16	8	2	0.0625	16	0.0312	1	1	4	0.125	4	8	8	8	16	4	2	8
S9-5-3	0.25	16	≤0.0156	8	4	0.125	≤0.0156	0.5	≤0.0156	1	4	16	0.25	16	32	32	>32	4	0.5	0.125	8
S9-5-2	2	16	0.25	8	8	1	≤0.0156	8	≤0.0156	1	4	16	0.25	16	32	32	32	8	1	2	8
S9-5-4	1	8	0.25	8	4	0.5	≤0.0156	0.5	≤0.0156	2	4	32	0.5	32	>32	>32	>32	4	1	0.5	16
S10-5-1	2	16	0.125	4	2	≤0.0156	≤0.0156	8	0.0312	2	2	16	1	8	16	16	16	4	0.5	2	4
S10-5-2	1	4	0.0312	4	1	≤0.0156	≤0.0156	2	≤0.0156	1	2	16	1	16	32	32	32	4	0.125	0.125	4
S10-5-3	0.125	4	≤0.0156	2	0.5	≤0.0156	≤0.0156	0.5	≤0.0156	2	4	16	2	16	32	32	>32	2	0.5	0.0625	8
S10-5-4	1	4	0.0625	4	1	≤0.0156	≤0.0156	0.5	≤0.0156	2	4	32	4	32	>32	>32	>32	4	1	0.5	8
S11-5-1	0.5	4	≤0.0156	4	4	0.25	≤0.0156	2	≤0.0156	4	8	32	2	32	>32	>32	>32	4	0.25	0.125	8
S11-4-1	4	>32	1	>32	32	8	1	32	0.25	8	16	>32	0.5	>32	>32	>32	>32	32	16	16	>32
S11-5-2	0.5	2	0.0625	2	2	0.25	0.0312	1	0.0312	2	4	32	2	32	>32	>32	>32	4	0.25	0.5	8
S11-4-2	8	32	1	32	16	4	0.5	16	0.0625	4	16	>32	1	32	>32	>32	>32	32	16	8	>32
S18-3-2	0.0625	1	0.5	2	0.5	0.25	0.125	16	≤0.0156	2	1	8	0.25	16	>32	32	>32	>32	0.5	0.25	1
S19-4	≤0.0156	0.5	0.125	2	0.25	0.25	0.0625	16	0.0312	1	8	16	0.25	16	16	16	16	>32	2	0.125	0.5
S1-6-2	16	>32	8	32	32	2	2	>32	1	8	32	32	0.5	32	>32	>32	>32	32	>32	>32	>32
S16-6-39	>32	>32	>32	>32	>32	16	8	>32	4	>32	>32	>32	2	>32	>32	>32	>32	>32	>32	>32	>32
S1-6-1	32	>32	4	16	16	4	0.5	8	1	2	16	>32	1	>32	>32	>32	>32	4	>32	16	>32
S6-6-5	4	2	1	2	2	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S6-6-4	0.5	0.5	1	0.5	0.5	2	8	>32	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	2	>32
S21-6-2	8	2	1	0.5	0.5	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	4	>32

TO FIG. 14A-2

FIG. 14A-1

FROM FIG. 14A-1

S21-6-1	16	16	4	2	2	8	16	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	1	>32
S6-6-6	1	2	2	1	0.5	4	2	4	4	16	>32	>32	32	>32	>32	>32	16	16	2	4
S6-6-7	0.125	1	0.125	2	1	2	1	4	2	8	16	>32	8	>32	>32	>32	>32	4	2	2
S6-6-8	0.5	1	0.5	2	1	4	1	4	4	32	16	>32	16	>32	>32	>32	>32	4	2	4
S6-6-1	2	2	2	2	1	8	2	2	2	8	>32	8	8	8	16	16	8	4	32	0.25	2
S6-6-2	1	2	2	1	0.5	4	2	4	2	4	>32	32	8	16	16	32	16	8	32	0.25	2
S6-6-3	1	1	0.5	2	2	8	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	32	8	>32
S14-6-2	0.5	1	1	0.5	0.5	2	1	8	2	8	>32	>32	16	>32	>32	>32	>32	16	8	1	4
S14-6-3	2	4	4	2	2	4	1	16	0.5	2	>32	8	2	8	8	16	8	32	>32	2	4
S14-6-4	1	2	0.5	4	4	8	4	>32	2	>32	>32	>32	8	>32	>32	>32	>32	>32	8	8	16
S14-6-1	4	4	4	2	1	8	1	4	1	8	8	2	1	2	2	4	2	16	>32	0.25	2
S14-6-5	1	2	4	0.5	0.5	2	0.5	16	0.5	4	>32	32	4	32	32	32	32	32	4	4	4
S7-6-7	1	8	1	16	1	4	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S7-6-4	16	32	4	8	1	1	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S7-6-5	32	32	32	32	16	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S7-6-8	8	16	1	8	4	2	32	>32	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S7-6-1	32	32	2	16	2	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	2	>32	>32
S7-6-6	16	16	1	2	0.5	1	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	>32
S7-6-2	8	16	2	2	1	4	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	2	>32	>32
S7-6-3	16	32	8	32	2	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S6-6-9	16	16	16	16	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	>32
S14-6-6	0.5	1	0.5	2	2	4	0.5	8	0.125	4	16	>32	2	>32	>32	>32	>32	8	1	8	2
S14-6-7	0.5	1	1	2	2	4	0.5	8	0.125	8	16	>32	2	>32	>32	>32	>32	4	1	4	2
S6-6-10	4	4	4	8	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	8	>32	>32
S7-6-10	32	>32	32	32	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	1	>32	>32

FIG. 14A-2

Compound Number	MIC(ug/mL)																					
	SA101 29213	SA161 tetM	SA158 tetK	EF327 tetM	EF404 tetM	SP160 tetM	EC107 25922	EC155 tetA	EC878 tdiC	KP457 CTX-M-15	PM385	PA555 BAA-47	PA556	PA1145	PA669	PA673	PA693	EC603 tetA	AB250	SM256	BC240
													Vivisource								
S8-7-5	0.25	0.5	2	0.125	0.25	1	4	8	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	16	>32	8
S8-7-6	1	2	1	2	1	>32	0.5	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S8-7-2	4	8	8	4	4	32	>32	32	2	16	32	16	4	16	16	32	16	32	>32	8	8
S8-7-3	0.5	0.5	0.25	1	1	4	4	>32	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	8	4	32
S8-7-1	2	2	2	0.5	0.5	4	1	2	1	4	32	2	2	4	4	8	4	4	32	0.0625	2
S8-7-7	0.5	1	2	0.25	0.25	2	2	8	2	4	>32	32	8	>32	>32	>32	>32	8	8	2	4
S8-7-9	0.25	0.5	4	0.5	0.5	4	1	8	1	8	16	>32	8	>32	>32	>32	>32	>32	2	2	4
S8-7-8	0.5	0.5	1	0.5	0.5	2	1	8	1	8	32	>32	16	>32	>32	>32	>32	>32	4	1	4
S8-7-10	16	16	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S8-7-11	4	8	4	32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	16	>32
S7-6-9	8	32	8	16	8	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S8-7-4	2	2	4	2	2	4	2	8	2	8	32	>32	8	>32	>32	>32	>32	16	32	2	8
S21-6-4	8	4	4	2	2	4	32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	8	>32
S21-6-5	1	2	0.5	1	1	2	4	8	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	8	8
S21-6-6	2	1	0.5	1	1	1	4	8	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	4	4
S21-6-3	16	16	16	8	8	16	32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	8	>32
S14-6-8	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	>32	>32	>32	8	>32	>32	>32	>32	>32	>32	>32
S5-9-1A	4	16	1	16	4	2	2	>32	0.5	4	2	32	0.25	>32	>32	>32	>32	>32	>32	>32	>32
S5-9-1B	1	4	0.25	2	1	0.5	0.5	>32	0.25	2	0.5	32	0.125	>32	>32	>32	>32	16	>32	>32	>32
S5-9-2A	2	32	0.5	16	8	1	2	32	1	8	16	32	0.5	32	>32	>32	>32	>32	32	16	>32
S5-9-2B	2	4	0.125	0.5	0.5	0.0312	1	16	0.25	4	8	32	0.25	32	>32	>32	>32	16	16	32	>32
S5-9-3A	1	16	0.25	8	4	1	0.5	4	0.5	4	16	32	0.25	32	>32	>32	>32	8	16	8	>32
S5-9-3B	0.25	0.5	0.5	0.25	0.125	0.0312	0.5	8	0.125	4	16	32	0.125	8	>32	>32	>32	8	16	16	>32

TO FIG. 14B-2

FIG. 14B-1

FROM FIG. 14B-1

S5-9-4A	0.5	8	0.25	8	4	1	1	4	0.5	8	16	>32	1	>32	>32	>32	16	16	4	32
S5-9-4B	0.25	1	0.125	0.125	0.125	≥0.0156	0.5	8	0.25	8	32	>32	0.5	>32	>32	>32	>32	16	4	>32
S5-9-5A	4	>32	1	4	2	2	8	16	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	4	>32
S5-9-5B	2	>32	0.5	1	0.5	0.125	8	16	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	4	>32
S1-5-12	32	0.25	8	8	4	16	>32	>32	32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32
S6-6-2	2	8	1	4	4	4	0.5	16	0.0625	2	16	8	0.5	32	4	8	4	32	32	2
S15-6-3	4	8	2	4	4	>32	>32	>32	16	>32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32
S15-6-2	1	8	1	2	2	4	2	32	0.5	16	32	>32	4	32	>32	>32	>32	16	2	8
S15-6-4	2	16	4	8	16	16	1	32	0.25	8	>32	32	0.5	32	32	32	>32	>32	4	4
S15-6-5	2	8	0.5	8	8	16	4	>32	0.5	>32	>32	>32	2	>32	>32	>32	>32	16	8	16
S15-6-6	2	4	4	2	4	16	1	32	0.125	8	>32	>32	0.5	>32	>32	>32	32	>32	4	8
S15-6-7	0.5	8	0.25	8	8	8	0.5	32	0.0625	8	>32	>32	1	>32	>32	>32	>32	16	2	4
S14-6-9	16	32	32	>32	>32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	32	>32
S15-6-9	>32	>32	>32	>32	>32	>32	>32	>32	4	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32
S15-6-10	32	>32	>32	>32	>32	>32	>32	>32	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S21-6-7	>32	>32	32	8	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S21-6-8	>32	>32	8	4	2	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S20-6-16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S15-6-8	2	8	0.5	8	8	8	0.5	16	0.0625	16	32	>32	1	>32	>32	>32	>32	8	2	8
S5-9-6A	32	>32	16	32	16	8	2	16	2	8	16	>32	1	>32	>32	>32	32	>32	32	>32
S5-9-6B	32	32	8	8	8	1	2	16	0.5	8	16	32	>32	>32	32	>32	2	>32	>32	>32
S5-9-7	16	32	16	16	16	4	16	>32	4	>32	>32	>32	>32	>32	>32	>32	32	>32	>32	>32
S5-9-8B	>32	>32	32	>32	>32	32	4	>32	1	32	>32	>32	>32	>32	4	>32	1	>32	>32	>32
S5-9-9A	8	>32	4	>32	16	4	4	>32	0.5	16	8	>32	0.25	>32	>32	>32	>32	>32	>32	>32
S5-9-9B	32	>32	8	8	8	2	4	>32	0.5	16	8	>32	0.5	>32	>32	>32	>32	>32	>32	>32

FIG. 14B-2

Compound Number	MIC(ug/mL)																				
	SA101 29213	SA161 tetM	SA158 tetK	EF327 tetM	EF404 tetM	SP160 tetM	EC107 25922	EC155 tetA	EC876 tetC	KP457 CTX-M-15	PM385	PA555 BAA-47	PA556	PA1145	PA669	PA673	PA693	EC603 tetA	AB250	SM256	BC240
													Vivisource								
S5-9-10A	16	>32	4	32	32	8	4	>32	0.5	8	4	>32	0.5	>32	>32	32	>32	4	>32	32	>32
S5-9-10B	32	32	8	8	8	2	4	32	0.25	8	4	32	0.25	32	32	8	32	4	>32	16	>32
S5-9-11A	16	>32	4	32	16	2	2	>32	0.25	4	8	>32	0.25	>32	>32	>32	>32	>32	>32	>32	>32
S5-9-11B	16	>32	8	8	8	1	2	32	0.25	8	16	>32	0.5	>32	>32	>32	>32	>32	32	32	>32
S5-9-12A	2	32	2	16	8	2	2	2	1	8	32	>32	0.5	>32	>32	>32	>32	>32	32	16	>32
S5-9-12B	0.5	2	0.5	0.5	0.25	0.0312	0.5	4	0.125	4	8	>32	0.125	>32	>32	>32	>32	4	8	8	32
S5-9-13A	8	32	4	16	8	2	1	16	0.5	8	32	>32	1	>32	>32	>32	>32	>32	16	16	>32
S5-9-13B	4	8	2	1	1	0.125	0.5	2	0.125	4	16	>32	0.25	>32	>32	>32	>32	8	4	4	32
S1-5-1	0.5	32	0.25	8	2	0.25	0.0312	0.0625	0.0312	0.25	2	32	0.25	>32	>32	>32	>32	0.5	2	1	16
S1-5-2	0.5	32	0.25	4	1	0.0625	0.0312	0.125	0.0312	0.25	2	16	0.25	32	>32	>32	>32	0.5	4	1	16
S1-5-9	0.25	8	0.125	4	1	0.125	0.125	2	0.0625	0.5	2	8	0.125	16	32	32	32	2	8	4	32
S2-9-5	0.5	>32	0.25	32	8	2	0.25	2	0.125	1	1	8	0.0625	16	32	32	32	4	32	16	>32
S20-6-1	0.25	0.5	0.25	0.125	0.0625	≤0.0156	0.125	4	≤0.0156	1	2	8	0.0625	8	16	16	16	8	8	8	16
S20-6-4	4	4	2	1	0.5	≤0.0156	0.0312	1	≤0.0156	1	4	32	0.5	32	>32	>32	>32	2	4	4	16
S20-6-7	>32	>32	>32	>32	>32	>32	>32	>32	4	>32	>32	>32	16	>32	>32	>32	>32	>32	>32	>32	>32
S20-6-8	32	>32	32	32	32	32	>32	>32	2	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32
S20-6-5	8	4	2	2	2	0.125	8	16	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	16	0.5
S20-6-4	4	8	4	1	0.5	0.0312	0.0625	1	≤0.0156	2	4	8	4	32	4	>32	0.5	>32	>32	>32	>32
S20-6-4	8	8	8	4	4	0.25	0.5	8	0.5	4	8	32	16	>32	32	32	1	32	>32	32	>32
S20-6-6	>32	>32	32	32	32	8	16	>32	4	>32	>32	>32	2	>32	>32	>32	>32	>32	>32	>32	>32
S1-5-10	32	>32	8	>32	>32	32	8	16	1	32	>32	>32	1	>32	>32	>32	>32	>32	>32	>32	>32
S1-5-11	16	>32	2	>32	>32	16	2	4	0.25	16	32	>32	1	>32	>32	>32	>32	>32	>32	>32	>32
S1-5-8	2	2	0.5	2	2	0.25	0.125	1	0.25	4	16	>32	2	>32	>32	>32	>32	8	4	4	>32

TO FIG. 14C-2

FIG. 14C-1

FROM FIG. 14C-1

S1-5-4	4	>32	2	>32	16	2	2	32	0.5	4	16	>32	0.5	>32	>32	>32	>32	32	>32	>32	>32	>32	>32
S1-5-7	>32	>32	>32	>32	>32	32	>32	>32	16	>32	>32	>32	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S1-5-18	8	>32	2	>32	32	8	1	8	0.5	8	>32	>32	2	>32	>32	>32	>32	32	>32	>32	>32	8	>32
S1-5-16	16	>32	8	>32	>32	16	8	16	2	16	>32	>32	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S1-5-17	4	>32	2	>32	16	4	1	4	0.5	4	8	>32	0.5	>32	>32	>32	>32	16	>32	>32	>32	>32	>32
S1-5-14	>32	>32	32	>32	>32	32	8	32	4	32	>32	>32	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S1-5-15	>32	>32	32	>32	>32	32	16	>32	4	>32	>32	>32	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S1-5-3	>32	>32	32	>32	>32	32	32	>32	16	>32	>32	>32	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S1-5-5	2	32	0.25	16	4	0.25	0.0312	0.25	0.0625	1	4	>32	2	>32	>32	>32	>32	2	2	2	4	4	32
S1-5-6	2	>32	0.25	32	8	0.5	0.0625	0.25	0.0625	1	4	>32	2	>32	>32	>32	>32	2	8	4	4	4	>32
S20-6-9	>32	>32	>32	>32	>32	>32	>32	>32	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S20-6-10	>32	>32	>32	>32	>32	>32	>32	>32	16	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S20-6-11	>32	>32	32	32	32	4	32	>32	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S20-6-13	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S20-6-14	8	16	8	8	8	0.0625	0.25	2	0.0625	4	16	>32	1	>32	>32	>32	>32	16	8	4	16	16	16
S2-9-3	4	16	0.5	8	4	1	0.25	8	0.0625	2	4	8	1	8	16	16	8	8	4	4	8	8	8
S2-9-4	2	4	0.5	2	0.5	2	0.5	2	1	4	16	32	16	>32	>32	>32	>32	4	2	4	8	8	8
S20-6-15	16	32	16	16	2	0.125	0.25	2	0.125	4	16	>32	1	>32	>32	>32	>32	16	32	16	32	32	32
S20-6-12	>32	>32	>32	>32	>32	16	>32	>32	32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S2-9-7	2	16	0.125	8	2	0.125	0.0312	0.125	0.0312	0.5	2	16	0.0625	16	32	32	32	1	8	4	16	16	16
S2-9-8	0.5	8	0.125	4	2	0.125	0.125	0.25	0.125	0.5	2	8	0.125	8	32	16	32	1	16	16	>32	>32	>32
S2-9-11	1	32	0.125	8	4	0.25	0.0625	0.25	0.0625	0.5	2	8	0.125	8	16	16	16	2	8	8	16	16	16
S2-9-14	1	3	0.0625	2	1	0.0625	≤0.0156	0.125	0.0625	1	2	16	1	16	16	16	16	1	1	1	1	1	8
S2-9-17	0.5	8	0.0625	2	1	0.0312	≤0.0156	0.0625	0.0312	0.5	2	8	0.125	8	32	16	16	1	4	4	4	4	16
S2-9-13	1	16	0.125	4	2	0.125	≤0.0156	0.125	0.0312	1	2	8	0.5	8	16	16	16	1	4	4	4	4	8

FIG. 14C-2

Compound Number	MIC(ug/mL)																				
	SA101	SA161	SA158	EF327	EF404	SP160	EC107	EC155	EC878	KP457	PM385	PA555	PA556	PA1145	PA669	PA673	PA693	EC603	AB250	SM256	BC240
	29213	tetM	tetK	tetM	tetM	tetM	25922	tetA	tolC	CTX-M-15		BAA-47	Vivisource					tetA			
S2-9-19	2	4	0.25	4	2	0.125	0.0312	0.25	0.125	2	4	16	4	16	32	32	16	2	2	4	16
S2-9-26	2	2	1	2	2	0.5	0.5	1	2	8	8	32	16	32	16	32	32	8	4	2	16
S2-9-27	8	>32	4	16	16	4	2	16	0.5	8	>32	>32	4	>32	>32	>32	>32	16	8	16	>32
S2-9-6	32	>32	16	>32	>32	32	8	>32	8	32	16	>32	4	>32	>32	>32	>32	>32	>32	>32	>32
S2-9-21	2	4	1	4	2	1	0.25	0.5	0.5	4	8	>32	8	16	32	32	32	2	4	2	8
S16-6-28	>32	>32	>32	>32	>32	>32	32	>32	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	8	>32
S2-9-2	2	8	0.25	2	1	0.125	0.0312	1	0.0625	1	4	8	1	8	16	16	16	2	1	2	8
S2-9-22	0.5	8	0.125	2	0.5	0.0312	≤0.0156	0.0312	0.0312	0.5	2	8	0.5	16	32	32	32	1	2	2	16
S2-9-12	0.5	8	0.125	2	1	0.0625	0.0312	0.0625	0.0312	0.25	1	16	0.0625	8	16	16	16	0.5	4	8	16
S2-9-24	2	>32	1	>32	>32	32	0.25	0.25	1	8	16	>32	16	>32	>32	>32	>32	0.25	>32	16	8
S2-9-23	1	32	0.25	4	2	0.125	0.25	0.5	0.0312	2	8	16	0.125	16	32	32	32	4	16	16	32
S1-6-5	8	32	16	16	8	8	1	>32	0.25	32	8	16	0.25	16	16	8	16	>32	>32	2	8
S3-7-2	8	8	2	4	4	4	8	8	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	4	>32
S2-9-10	4	4	2	2	2	1	2	4	1	8	32	32	2	>32	>32	>32	>32	16	8	4	>32
S2-9-18	2	8	0.25	4	2	0.0625	0.0312	0.25	0.0625	2	4	8	2	>32	16	32	16	2	2	4	8
S2-9-1	4	4	2	2	1	2	8	8	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	16	4	>32
S2-9-28	1	4	0.125	2	1	≤0.0156	≤0.0156	0.125	0.0312	2	4	16	1	16	32	32	32	2	4	4	16
S2-9-15	0.5	8	0.0625	2	1	≤0.0156	≤0.0156	0.0625	≤0.0156	0.25	2	16	0.125	16	32	32	32	0.5	4	4	16
S2-9-25	32	>32	8	>32	>32	8	16	32	2	>32	>32	>32	1	>32	>32	>32	>32	>32	>32	>32	>32
S2-9-29	16	32	8	16	8	2	1	8	1	8	>32	>32	8	>32	>32	>32	>32	16	32	16	>32
S2-9-16	>32	>32	>32	>32	>32	>32	>32	>32	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S2-9-20	32	32	16	32	32	4	2	8	2	8	32	>32	8	>32	>32	>32	>32	8	32	32	>32
S2-9-9	16	>32	4	>32	>32	16	16	32	2	>32	>32	>32	1	>32	>32	>32	>32	>32	>32	>32	>32

TO FIG. 14D-2

FIG. 14D-1

FROM FIG. 14D-1

S16-6-30	>32	>32	>32	>32	>32	>32	16	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	1	>32
S16-6-8	8	16	4	2	8	0.0625	0.25	4	≤0.0156	2	2	4	0.25	8	8	8	8	4	16	8	16		
S16-6-9	>32	>32	>32	>32	>32	16	16	>32	2	>32	>32	>32	4	>32	>32	>32	>32	>32	>32	>32	>32		
S16-6-19	4	8	4	4	4	0.125	0.5	1	0.25	8	4	8	2	8	8	8	8	2	8	4	16		
S16-6-33	>32	>32	>32	>32	>32	8	16	32	0.5	>32	>32	>32	0.5	>32	>32	32	>32	>32	>32	32	>32		
S16-6-5	32	32	8	8	8	1	2	4	0.125	8	4	32	0.125	32	32	16	32	16	>32	>32	>32		
S1-5-13	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32		
S16-6-38	8	8	2	2	4	0.0625	0.25	2	0.0625	2	4	8	1	4	8	16	8	2	8	4	8		
S16-6-11	8	8	2	2	4	0.0312	0.125	1	0.0312	1	4	8	0.5	4	8	16	8	2	8	4	8		
S16-6-23	32	>32	>32	>32	32	8	8	16	0.5	>32	>32	16	1	16	16	16	16	32	>32	16	>32		
S4-7-1	8	32	4	16	16	16	4	8	2	16	8	16	2	16	32	16	16	16	8	8	16		
S16-6-18	4	16	4	2	4	0.5	0.5	4	0.125	2	2	32	0.0625	32	32	32	32	8	>32	32	>32		
S4-7-2	0.5	16	0.125	1	0.5	0.0312	0.25	1	0.5	0.25	4	32	0.5	32	32	>32	32	1	8	8	32		
S16-6-1	8	>32	32	8	8	8	4	8	2	16	8	32	0.5	32	32	32	32	16	>32	>32	>32		
S16-6-3	8	32	16	4	2	1	1	2	0.125	4	4	16	0.0625	16	16	8	16	8	>32	16	>32		
S16-6-4	16	16	8	2	2	1	0.5	1	0.0625	2	4	8	0.125	8	8	4	8	8	32	8	32		
S16-6-6	2	16	4	1	0.5	0.25	0.25	8	0.0312	2	1	8	0.0312	16	32	16	16	8	32	32	32		
S16-6-7	>32	>32	>32	>32	>32	16	16	>32	4	>32	32	>32	2	>32	>32	32	>32	>32	>32	>32	>32		
S16-6-15	16	16	8	4	2	1	0.5	2	0.125	2	4	8	0.5	8	8	8	8	4	32	4	16		
S16-6-31	>32	>32	>32	>32	>32	16	16	>32	1	>32	32	>32	1	>32	>32	32	>32	>32	>32	>32	>32		
S16-6-32	>32	>32	>32	>32	>32	>32	>32	>32	32	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	>32	>32		
S1-7-1	1	>32	0.25	16	16	2	0.25	1	0.125	1	2	16	0.125	16	32	16	32	4	32	16	>32		
S1-7-2	32	>32	16	32	32	8	16	32	8	32	>32	32	4	32	32	32	>32	>32	>32	>32	>32		
S3-7-1	1	>32	0.5	>32	32	4	0.5	1	0.25	2	4	32	0.125	32	>32	>32	>32	16	>32	32	>32		
S4-7-3	0.5	32	0.125	8	2	0.25	0.125	0.25	0.0625	0.5	2	8	0.125	8	16	16	16	2	16	8	32		

FIG. 14D-2

Compound Number	MIC(ug/mL)																				
	SA101 29213	SA161 tetM	SA158 tetK	EF327 tetM	EF404 tetM	SP160 tetM	EC107 25922	EC155 tetA	EC878 tolC	KP457 CTX-M-15	PM385	PA555 BAA-47	PA556	PA1145 Vivisource	PA669	PA673	PA693	EC603 tetA	AB250	SM256	BC240
S16-6-24	16	32	>32	8	4	1	1	4	0.0625	4	4	16	0.125	16	16	8	16	8	>32	16	>32
S16-6-25	0.5	32	0.25	8	2	0.25	0.125	0.25	≤0.0156	0.5	2	8	0.125	8	16	32	32	1	16	8	32
S16-6-27	1	>32	0.5	>32	>32	4	1	1	0.125	4	4	32	0.125	32	>32	>32	>32	8	>32	32	>32
S2-9-6	8	8	4	4	4	1	1	1	0.25	8	8	8	4	8	8	8	4	4	32	4	8
S16-6-34	>32	>32	>32	>32	>32	>32	>32	>32	8	>32	>32	>32	32	>32	>32	>32	>32	>32	>32	32	>32
S16-6-16	16	16	8	4	4	1	0.5	1	0.0312	4	4	4	1	4	8	8	8	4	>32	8	16
S4-7-4	0.5	16	0.125	4	1	0.0625	0.0312	0.25	≤0.0156	2	4	16	2	16	32	32	32	2	2	4	16
S4-7-6	0.5	32	0.125	4	2	0.125	0.0312	0.125	≤0.0156	1	2	16	0.25	16	32	32	32	1	4	4	16
S16-6-2	8	>32	32	8	4	4	1	4	0.125	>32	4	32	0.125	32	32	16	32	16	>32	32	>32
S16-6-13	32	32	8	8	4	1	2	4	0.0312	8	4	16	0.25	16	16	8	16	8	>32	16	>32
S16-6-14	32	32	8	4	4	0.5	1	4	0.0312	4	4	16	0.25	16	16	8	16	8	>32	16	>32
S4-7-5	0.5	8	0.125	4	1	0.0625	0.125	0.25	0.0312	0.5	2	16	0.125	16	32	32	32	2	32	16	32
S16-6-35	32	32	32	32	32	32	4	>32	1	>32	32	32	1	32	32	16	32	32	>32	16	16
S16-6-26	8	8	4	4	4	2	2	4	4	32	16	16	8	16	16	>32	32	32	>32	2	4
S16-6-20	4	8	4	2	2	0.5	1	4	1	8	8	32	8	16	16	>32	16	8	32	4	4
S16-6-22	16	16	8	16	8	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	4	>32
S16-6-21	4	4	2	2	2	4	32	8	32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	2	>32
S1-7-3	>32	>32	>32	>32	>32	32	>32	>32	16	>32	>32	>32	8	>32	>32	>32	>32	>32	>32	>32	>32
S16-6-29	>32	>32	>32	>32	>32	>32	32	>32	4	>32	>32	>32	4	>32	>32	>32	>32	>32	>32	>32	>32
S17-3	16	16	8	8	4	16	8	16	8	32	>32	16	8	16	16	32	16	32	>32	4	
S16-6-10	4	8	4	2	1	0.125	0.25	2	0.125	2	4	8	2	8	8	16	8	2	8	8	
S16-6-12	4	8	4	2	1	0.125	0.5	1	0.5	4	16	32	4	32	32	>32	32	4	16	4	
S17-5	>32	>32	>32	>32	>32	32	16	>32	4	>32	>32	>32	8	>32	>32	>32	>32	>32	>32	>32	

TO FIG. 14E-2

FIG. 14E-1

FROM FIG. 14E-1

S17-6	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S13-9-1A	1	4	1	0.125	0.5	0.125	0.25	>32	0.0312	2	4	16	0.125	16	32	32	32	32	16	16	32	16	16	32
S13-9-1B	32	>32	32	32	32	32	32	>32	4	>32	>32	>32	4	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S13-9-2A	4	2	0.5	0.125	0.5	0.125	0.5	16	0.5	8	32	>32	2	>32	>32	>32	>32	>32	>32	4	2	2	>32	>32
S13-9-2B	16	16	8	8	16	16	32	>32	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
S18-3-1	0.0625	2	1	2	0.5	0.5	0.0625	32	≤0.0156	1	2	16	0.125	32	>32	32	16	>32	2	0.5	0.5	0.5	0.5	0.5
S12-2-4																								
S16-6-36																								
S16-6-37																								
Sancycline	0.5	2	4	4	4	8	8	32	1	8	8	32	1	32	>32	>32	>32	32	16	1	4	4	2	4
Minocycline	0.0625	8	0.0312	32	8	2	0.5	8	0.25	8	16	16	0.125	32	>32	>32	>32	>32	8	0.5	8	8	4	8
Tigecycline	0.0625	0.125	0.0625	0.0625	0.0312	≤0.0156	0.0312	0.5	0.0312	1	4	16	0.25	16	32	32	>32	2	8	1	16	16	8	16

FIG. 14E-2

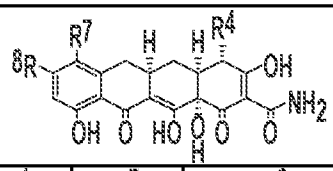
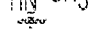
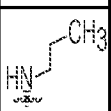
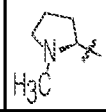
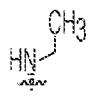
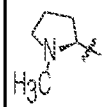
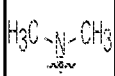
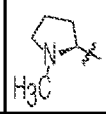
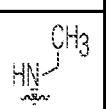
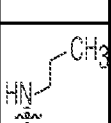
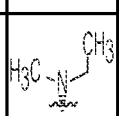
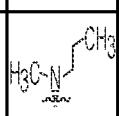
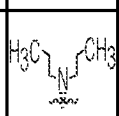
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S8-7-2				4.2						
S8-7-4				2.1						
K1				0.23		1.96				
K2				0.60		2.70				
K3				1.3		13.75				
S15-6-1				1.6						
S15-6-4				5.5						
S15-6-6				3.8						
S15-6-2				1.9						
S15-6-7				4.2						
S15-6-8				4.0						
S15-6-5				3.8						
S15-6-3				2.0						
S15-6-9				15						

FIG. 15A

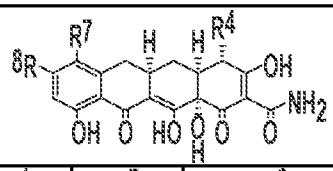
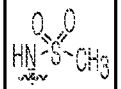
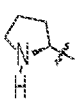
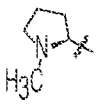
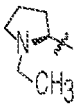
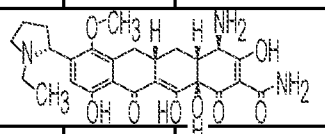
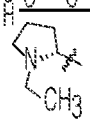
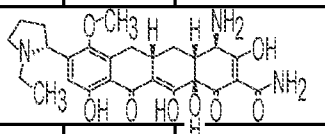
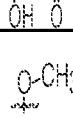
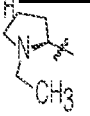
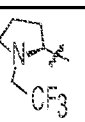
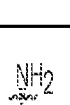
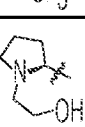
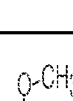
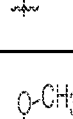
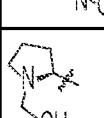
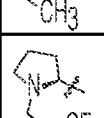
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S15-6-10				8.0						
S2-9-6				1.6						
K2-9-5				0.11	0.14	0.38	0.24			
K4				0.07	0.11	0.5	0.21	0.13	0.11	0.15
S1-7-3				>5						
S1-7-1				0.09	0.23	0.83	0.92	0.25	0.20	0.37
S1-7-2				3.5						
S1-6-2				3.1						
S2-9-3				0.12	0.29	0.57	0.48			
S2-9-1				3.2						
S2-9-9				0.88						
S2-9-16				20						
S2-9-7				0.10	0.24	0.28	0.6			
S2-9-10				0.47						

FIG. 15B

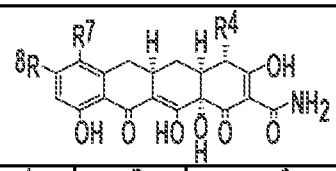
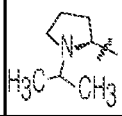
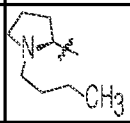
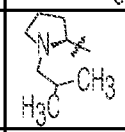
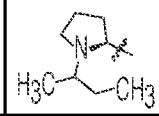
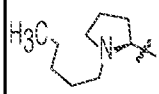
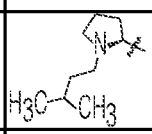
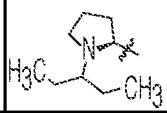
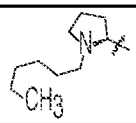
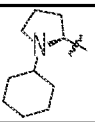
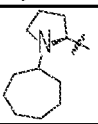
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S2-9-8	NH_2	$O-CH_3$		0.04	0.09	0.28	0.2	0.11	0.07	0.12
S2-9-13	NH_2	$O-CH_3$		0.10	0.15	0.48	0.31			
S2-9-14	NH_2	$O-CH_3$		0.11	0.14	0.09	0.31			
S2-9-11	NH_2	$O-CH_3$		0.13	0.17	0.27	0.38			
S2-9-15	NH_2	$O-CH_3$		0.07	0.16	0.44	0.30			
S2-9-18	NH_2	$O-CH_3$		0.09	0.17	0.55	1.4			
S2-9-19	NH_2	$O-CH_3$		0.13	0.18	0.39	0.60			
S2-9-20	NH_2	$O-CH_3$		0.76						
S2-9-21	NH_2	$O-CH_3$		0.14	0.34	0.51	0.38			
S2-9-2	NH_2	$O-CH_3$		0.10	0.19	0.35	0.22			
S2-9-12	NH_2	$O-CH_3$		0.10	0.08	0.29	0.19	0.12	0.01	0.11
S2-9-17	NH_2	$O-CH_3$		0.06	0.09	0.39	0.21			
S2-9-22	NH_2	$O-CH_3$		0.07	0.11	0.34	0.12	0.07	0.06	0.09
S2-9-28	NH_2	$O-CH_3$		0.07	0.11	0.32	0.30			

FIG. 15C

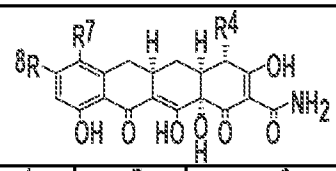
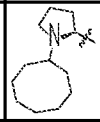
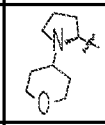
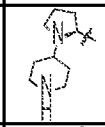
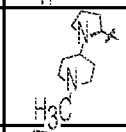
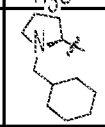
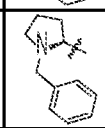
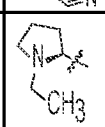
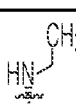
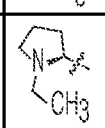
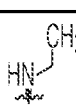
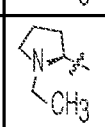
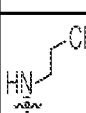
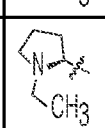
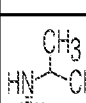
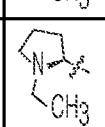
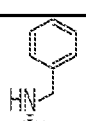
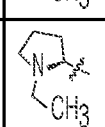
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S2-9-29				2.8						
S2-9-23				0.11	0.15	0.29	0.15	0.24	0.15	0.15
S2-9-24				3.7						
S2-9-25				1.9						
S2-9-26				0.14	0.33	0.55	0.62			
S2-9-4				0.25						
S2-9-27				0.95						
S1-5-9				0.17	0.19	0.48	0.26			
K5				0.15	0.18	0.54	0.68			
S1-6-1				0.91						
S1-5-1				2.2						
S1-5-2				0.10	0.19	0.28	0.23			
S1-5-8				0.44						
K6				6.5						

FIG. 15D

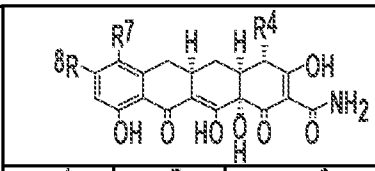
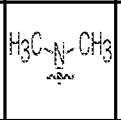
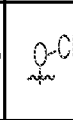
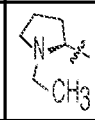
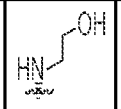
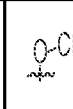
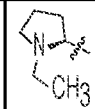
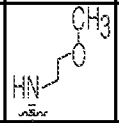
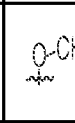
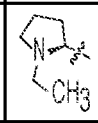
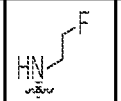
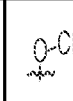
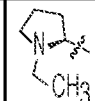
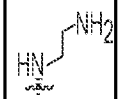
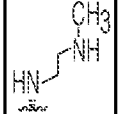
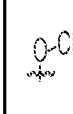
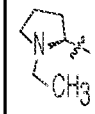
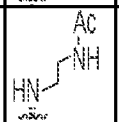
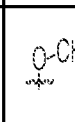
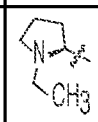
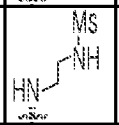
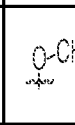
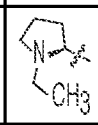
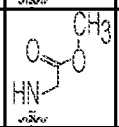
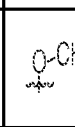
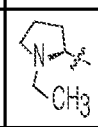
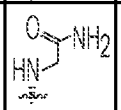
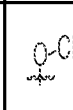
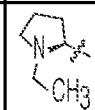
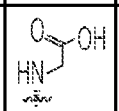
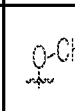
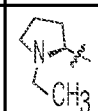
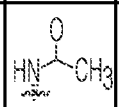
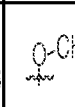
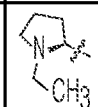
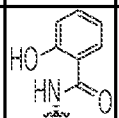
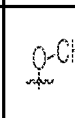
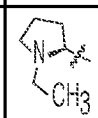
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
K7				0.55		5.45				
S1-5-4				7.2						
S1-5-6				2.5						
S1-5-5				0.93						
S1-5-3				3.6						
S1-5-7				>20						
S1-5-14				2.6						
S1-5-15				4.6						
S1-5-18				7						
S1-5-17				0.28						
S1-5-16				2.9						
S1-5-10				18						
S1-5-12				1.2						
S1-5-11				15						

FIG. 15E

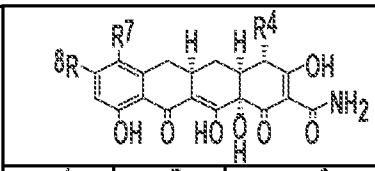
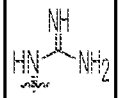
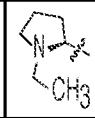
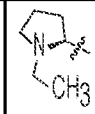
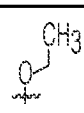
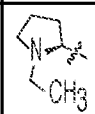
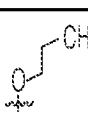
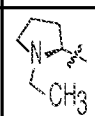
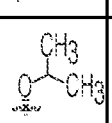
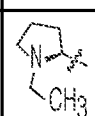
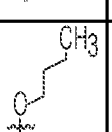
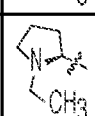
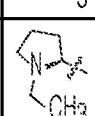
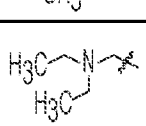
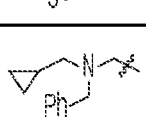
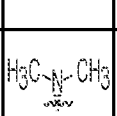
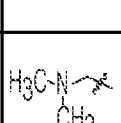
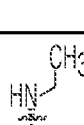
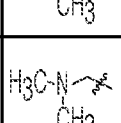
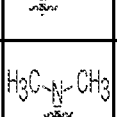
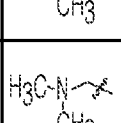
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S1-5-13				>5						
S4-7-1				3.0						
S4-7-3				0.05	0.21	0.87	0.72			
S4-7-4				0.09	0.16	0.46	0.55	0.17	0.12	0.14
S4-7-5				0.04	0.35	0.72	1.1			
S4-7-6				0.05	0.19	0.56	0.83			
S4-7-2				0.04	0.12	0.77	0.51			
S3-7-1				0.10	0.28	0.9				
S3-7-2				0.90						
K8				3.2		15.68				
S9-5-1				0.22		0.87				
S9-5-2				0.23		3.00				
K9				1.6		12.64				
S9-5-3						7.23				

FIG. 15F

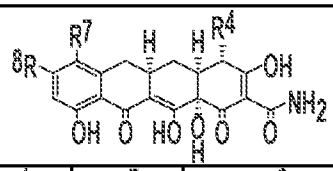
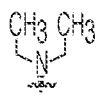
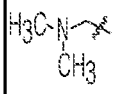
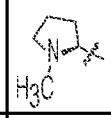
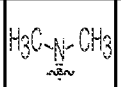
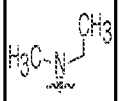
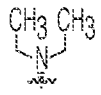
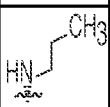
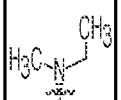
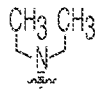
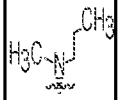
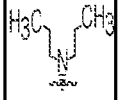
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S9-5-4						9.36				
S10-5-1				0.21		1.33				
S10-5-2				0.09	0.22	0.44	0.29			
K10				0.40		3.69				
S10-5-3						2.69				
S10-5-4						3.34				
S8-7-1				1.4						
S8-7-7				1.0						
S8-7-5				0.52						
S8-7-8				0.93						
S8-7-9				0.86						
S8-7-3				1.1						
S8-7-6				1.2						
S8-7-10				20						

FIG. 15G

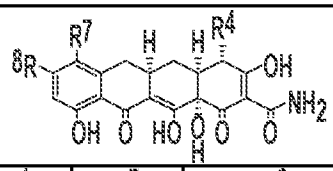
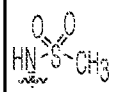
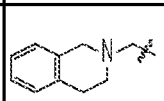
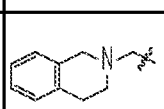
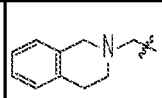
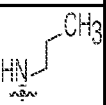
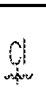
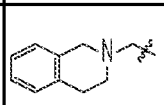
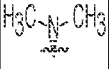
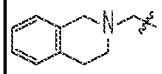
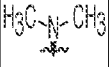
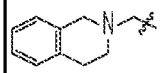
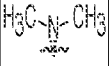
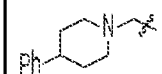
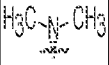
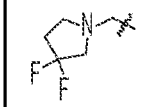
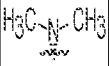
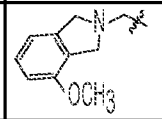
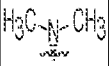
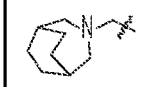
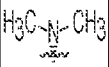
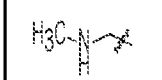
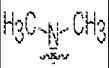
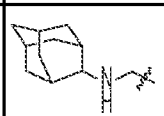
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S8-7-11				15						
S7-6-1				1.0						
S7-6-2				1.8						
S7-6-6				0.45						
S7-6-4				0.15						
K11				0.30		0.45				
K12				0.4						
K13				0.45		0.92				
K14				0.40		0.64				
K15				0.58		0.87				
K16				0.27		0.40				
K17				1.6		12.28				
K18				0.39		0.84				
K19				0.39		0.75				

FIG. 15H

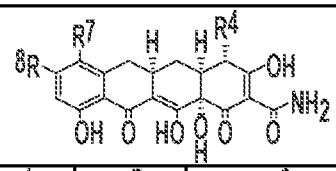
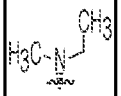
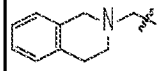
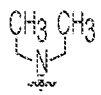
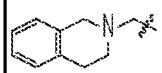
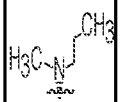
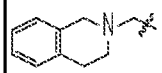
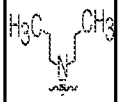
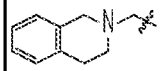
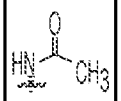
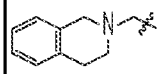
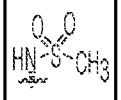
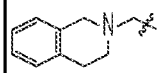
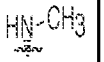
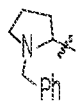
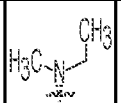
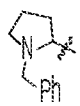
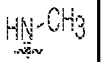
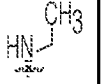
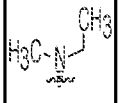
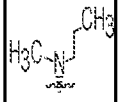
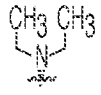
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S7-6-7		Cl		0.34						
S7-6-8		Cl		0.28						
S7-6-3		Cl		0.25						
S7-6-5		Cl		0.40						
S7-6-9		Cl		>10						
S7-6-10		Cl		>10						
K20		Cl		0.43		0.55				
K21		Cl		0.38		0.51				
S6-6-1		CF_3		1.7						
S6-6-2		CF_3		1.2						
S6-6-6		CF_3		0.96						
S6-6-7		CF_3		0.97						
S6-6-3		CF_3		1.8						
S6-6-8		CF_3		0.90						

FIG. 15I

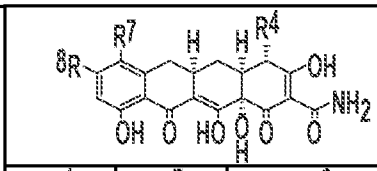
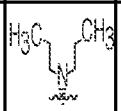
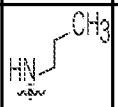
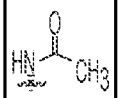
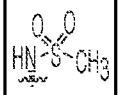
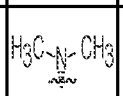
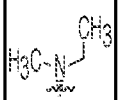
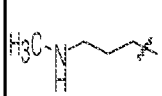
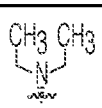
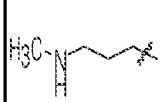
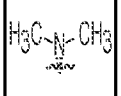
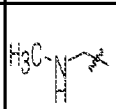
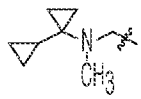
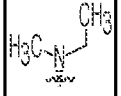
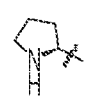
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S6-6-5				0.91						
S6-6-4				0.31						
S6-6-9				>20						
S6-6-10				25						
K22				3.6						
S11-4-1				2.8						
S11-4-2				4.9						
K23				1.6		19.18				
K24				0.24		1.66				
S11-5-1			 diastereomer A	0.62						
S11-5-2			 diastereomer A	0.57						
K25				0.25		3.02				
K26				0.22		1.16				
K27				0.56		6.89				

FIG. 15J

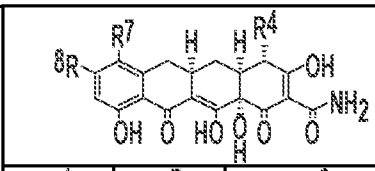
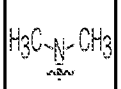
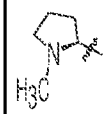
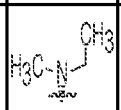
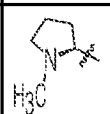
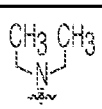
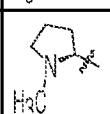
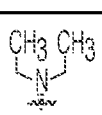
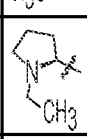
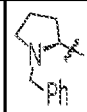
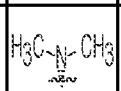
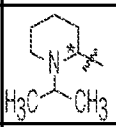
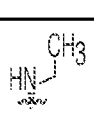
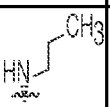
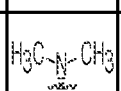
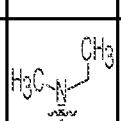
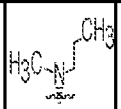
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
K28				0.41		2.63				
S12-2-1				1.1		2.05				
S12-2-2						4.18				
S12-2-3						3.47				
S12-2-4				0.96						
K29				0.50		2.05				
S14-6-1				1.0						
S14-6-3				2.1						
S14-6-5				1.1						
S14-6-2				1.1						
K30				2.0		2.71				
S14-6-6				2.0						
S14-6-4				2.7						
S14-6-7				1.7						

FIG. 15K

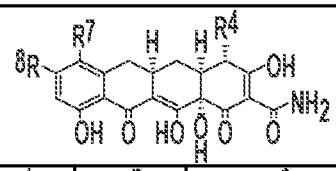
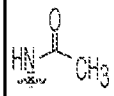
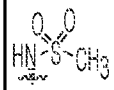
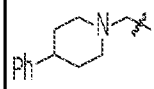
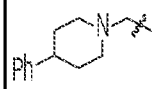
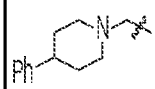
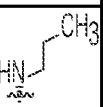
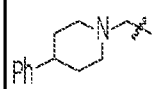
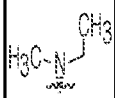
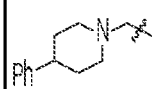
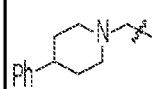
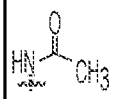
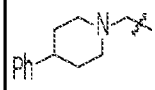
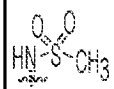
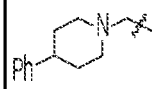
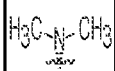
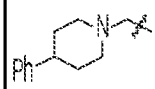
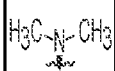
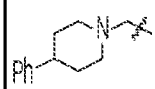
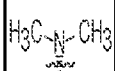
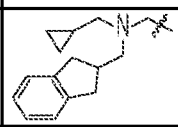
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S14-6-8				21						
S14-6-9				19						
S21-6-1				0.34						
S21-6-3				2.8						
S21-6-4				0.8						
S21-6-2				0.26						
S21-6-5				0.4						
S21-6-6				0.39						
S21-6-7				4.0						
S21-6-8				16						
K31				0.32		0.94				
K32				0.78						
K33				0.50		0.71				
K34				2.1		26.26				

FIG. 15L

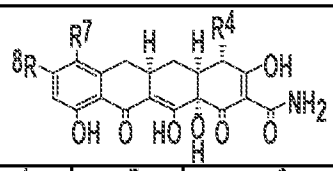
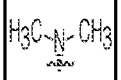
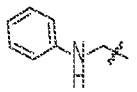
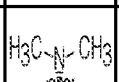
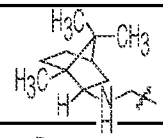
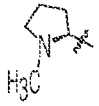
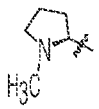
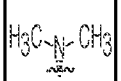
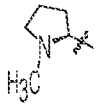
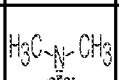
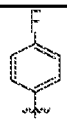
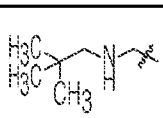
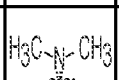
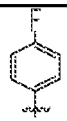
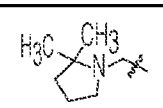
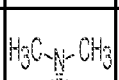
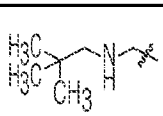
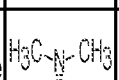
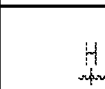
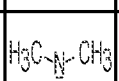
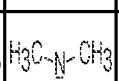
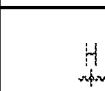
Compound Number				IC_{50} (μM)						
				Liquid Tumor						
	R^4	R^7	R^8	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
K35				0.65		0.57				
K36				0.52		0.87				
K37				0.19		0.90				
K38				0.38		1.36				
K39				1.2		6.58				
K40				0.57		1.54				
K41				6.0		9.92				
K42				0.51		2.33				
Sancycline				inactive		4.94				
Minocycline				6.44		30.88				

FIG. 15M

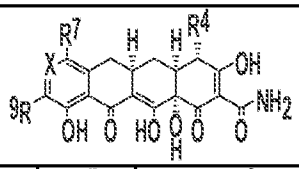
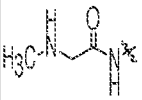
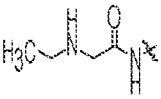
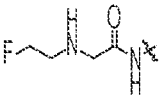
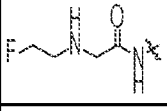
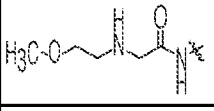
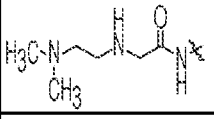
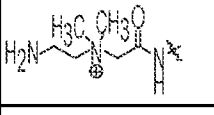
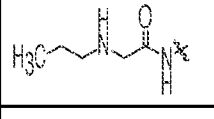
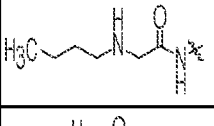
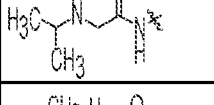
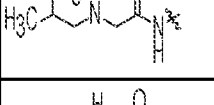
Compound Number					IC_{50} (μM)						
					Liquid Tumor Cell Line						
	R^4	R^7	R^9	X	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S16-5				CH	2.3						
S17-3				CH	3.3						
S16-6-1				CH	0.63						
S16-6-2				CH	0.45						
S16-6-31				CH	6.8						
S16-6-32				CH	>20						
S16-6-33				CH	1.1	1.9	>10				
S16-6-34				CH	>20						
S16-6-35				CH	2.2						
S16-6-3				CH	0.26						
S16-6-4				CH	0.28						
S16-6-5				CH	0.12	0.33	2.5	2.5			
S16-6-15				CH	0.26						
S16-6-13				CH	0.22						

FIG. 16A

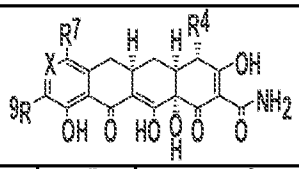
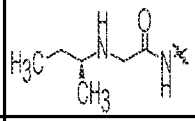
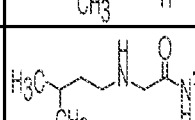
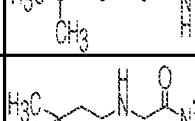
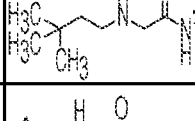
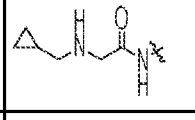
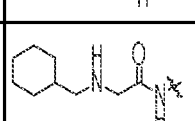
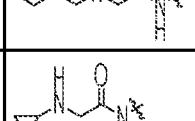
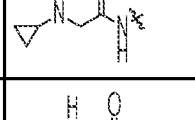
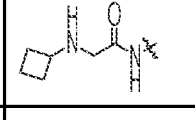
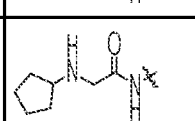
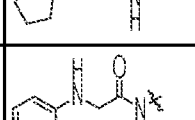
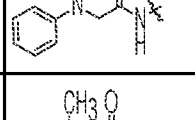
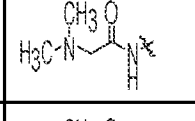
Compound Number					IC_{50} (μM)						
					Liquid Tumor Cell Line						
	R^4	R^7	R^9	X	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S16-6-14				CH	0.22						
S16-6-16				CH	0.55						
S16-6-17				CH	0.45						
S16-6-27				CH	0.32						
S16-6-26				CH	0.45						
S16-6-23				CH	1.0						
S16-6-24				CH	0.27						
S16-6-25				CH	0.22						
S16-6-30				CH	>20						
S16-6-6				CH	0.07	0.20	0.68	2.4	0.17	0.24	0.22
S16-6-7				CH	4.2						
S16-6-8				CH	0.12	0.28	1.9	1.3			
S16-6-9				CH	4.1						
S16-6-10				CH	0.16						

FIG. 16B

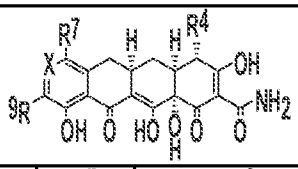
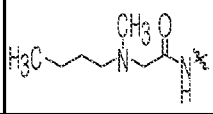
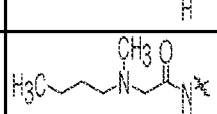
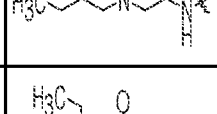
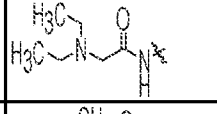
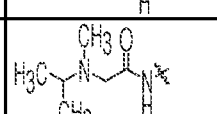
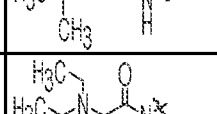
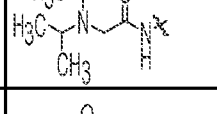
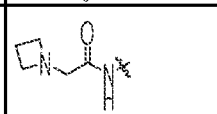
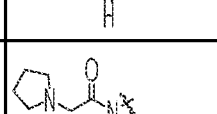
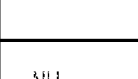
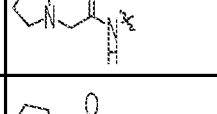
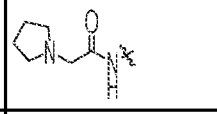
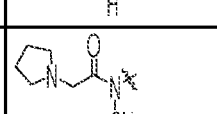
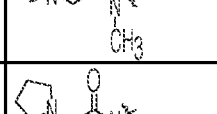
Compound Number					IC_{50} (μM)						
					Liquid Tumor Cell Line						
	R^4	R^7	R^9	X	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S16-6-36				CH							
S16-6-37											
S16-6-38				CH	0.07	0.23	0.89	1.2	0.28	0.14	0.16
S16-6-11				CH	0.05	0.11	0.70	0.80	0.15	0.17	0.28
S16-6-12				CH	0.21						
S16-6-18				CH	0.08	0.21	1.0	0.75	0.20	0.41	0.39
K43				CH	0.10	0.13	0.54	0.53	0.10	0.15	0.25
S16-6-39				CH	>10						
S17-5				CH	6.0						
S17-6				CH	>20						
S16-6-29				CH	3.9						
S16-6-19				CH	0.04	0.13	0.95	1.6	0.28	0.40	0.52
S16-6-28				CH	>20						
S16-6-20				CH	0.13	0.48	1.5				

FIG. 16C

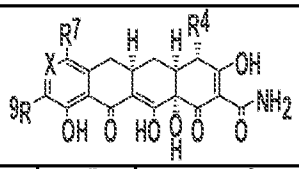
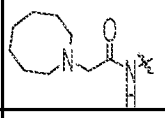
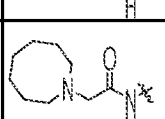
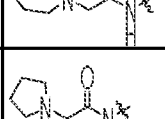
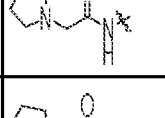
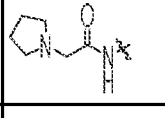
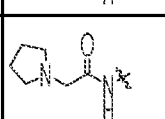
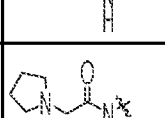
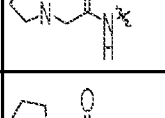
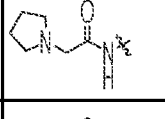
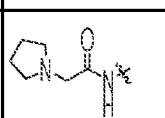
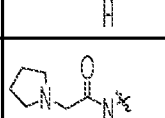
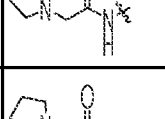
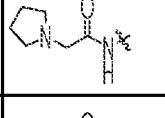
Compound Number					IC_{50} (μM)						
					Liquid Tumor Cell Line						
	R^4	R^7	R^9	X	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S16-6-21				CH	0.47						
S16-6-22				CH	3.1						
S20-6-1				CH	0.21	0.48	1.4	0.94	0.32	0.31	0.80
K44				CH	0.26		1.44				
S20-6-4				CH	0.14						
S20-6-2				CH	0.55						
S20-6-3				CH	8.9						
S20-6-5				CH	0.93						
S20-6-7				CH	>25						
S20-6-16				CH	3.4						
S20-6-8				CH	>25						
S20-6-14				CH	1.9						
S20-6-6				CH	7.4						
S20-6-15				CH	0.59						

FIG. 16D

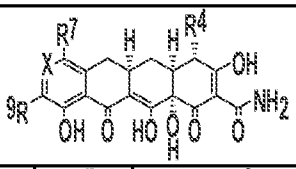
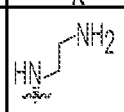
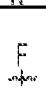
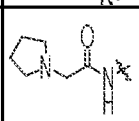
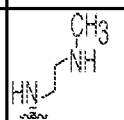
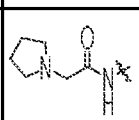
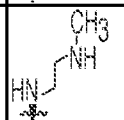
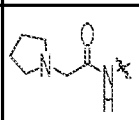
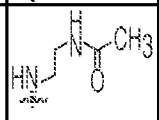
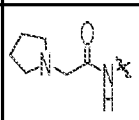
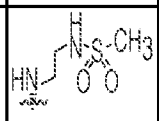
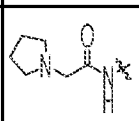
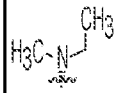
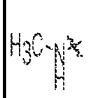
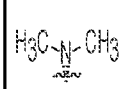
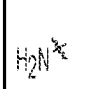
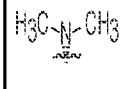
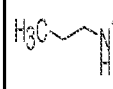
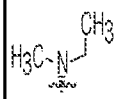
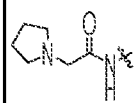
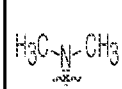
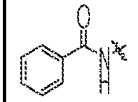
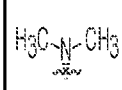
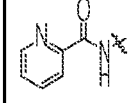
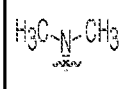
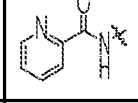
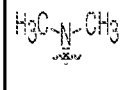
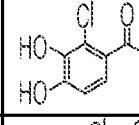
Compound Number					IC_{50} (μM)						
					Liquid Tumor Cell Line						
	R^4	R^7	R^9	X	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
S20-6-11				CH	>5						
S20-6-12				CH	>20						
S20-6-13				CH	>20						
S20-6-9				CH	≥20						
S20-6-10				CH	>5						
S19-4				N	>5						
K45				N			>40				
K46				N			2.88				
K47				CH	0.91		5.81				
K48				CH	inactive		16.83				
K49				CH	0.51		1.71				
K50				CH	8.9		37.24				
K51				CH	inactive		>40				
K52				CH	0.55		1.06				

FIG. 16E

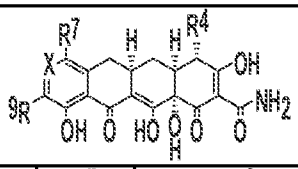
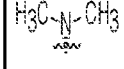
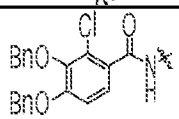
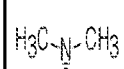
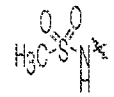
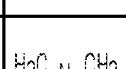
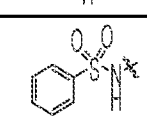
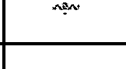
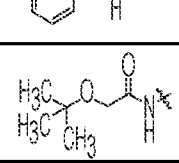
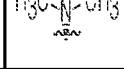
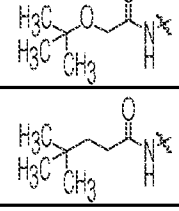
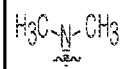
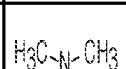
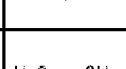
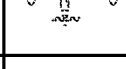
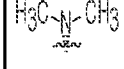
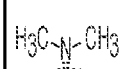
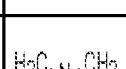
Compound Number					IC_{50} (μM)						
					Liquid Tumor Cell Line						
	R^4	R^7	R^9	X	MV4-11	MOLT-4	THP-1	K-562	KG-1	KU812	MEG-01
K53				CH	inactive		>40				
K54				CH	inactive		>40				
K55				CH	1.1		1.11				
K56				CH	8.3		4.01				
K57				CH	0.84		1.00				
K58				CH	0.34		3.04				
K59				CH	inactive		>40				
K60				CH	inactive		>40				
K61				CH	3.5		10.71				
K62				CH	1.3		0.75				
K63				CH	1.2		0.67				
K64				CH	0.40		0.83				
K65				CH	inactive		4.09				
Tigecycline				CH	1.7	2.3	6.5	3.2	2.7		

FIG. 16F

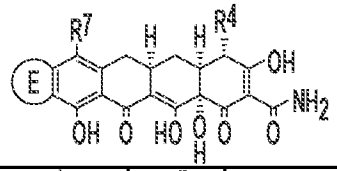
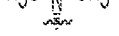
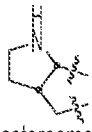
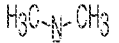
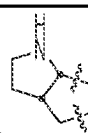
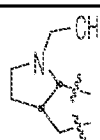
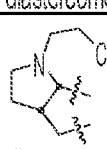
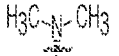
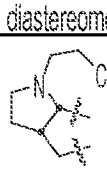
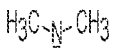
Compound Number				IC_{50} (μM)	
	R^4	R^7	E	MV4-11	THP-1
S5-9-1A			 diastereomer A	11	
S5-9-1B			 diastereomer B	7.3	
S5-9-2A			 diastereomer A	7.0	
S5-9-2B			 diastereomer B	3.6	
S5-9-3A			 diastereomer A	11	
S5-9-3B			 diastereomer B	5.5	
S5-9-4A			 diastereomer A	8.1	
S5-9-4B			 diastereomer B	2.4	
S5-9-5A			 diastereomer A	0.94	

FIG. 17A

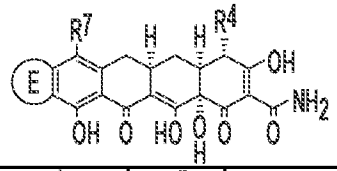
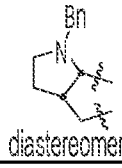
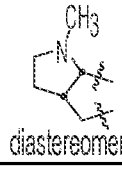
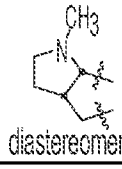
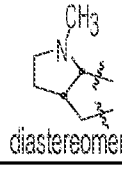
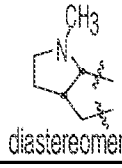
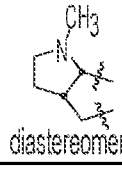
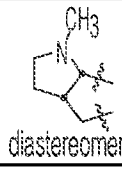
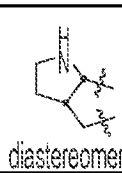
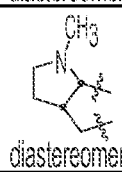
Compound Number				IC_{50} (μM)	
	R^4	R^7	E	MV4-11	THP-1
S5-9-5B			 diastereomer B	0.40	
S5-9-10A			 diastereomer A	1.0	
S5-9-10B			 diastereomer B	0.90	
S5-9-9A			 diastereomer A	2.3	
S5-9-9B			 diastereomer B	7.9	
S5-9-11A			 diastereomer A	2.8	
S5-9-11B			 diastereomer B	1.7	
S5-9-8B			 diastereomer B	6.9	
S5-9-6A			 diastereomer A	2.4	

FIG. 17B

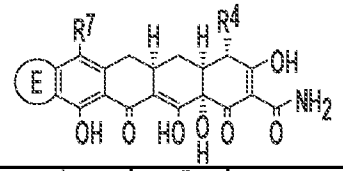
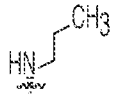
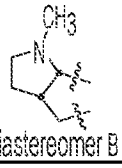
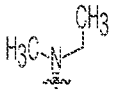
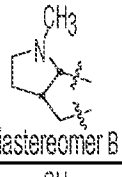
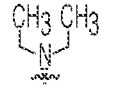
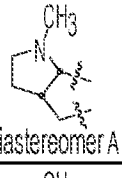
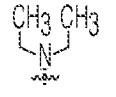
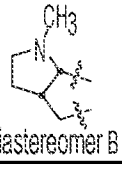
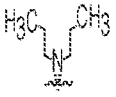
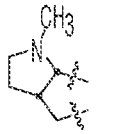
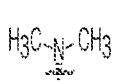
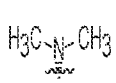
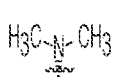
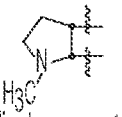
Compound Number				IC_{50} (μM)	
	R^4	R^7	E	MV4-11	THP-1
S5-9-6B			 diastereomer B	1.4	
S5-9-12A			 diastereomer A	6.5	
S5-9-12B			 diastereomer B	3.4	
S5-9-13A			 diastereomer A	7.2	
S5-9-13B			 diastereomer B	2.2	
S5-9-7				4.4	
S13-9-1A			 diastereomer A	2.8	
S13-9-1B			 diastereomer B	18	
S13-9-2A			 diastereomer A	5.0	

FIG. 17C

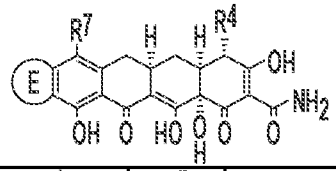
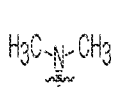
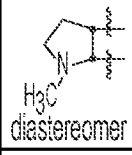
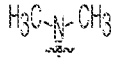
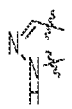
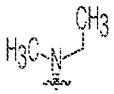
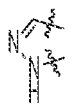
Compound Number				IC_{50} (μM)	
	R^4	R^7	E	MV4-11	THP-1
S13-9-2B			 diastereomer B	3.0	
S18-3-1					>40
S18-3-2				2.4	

FIG. 17D