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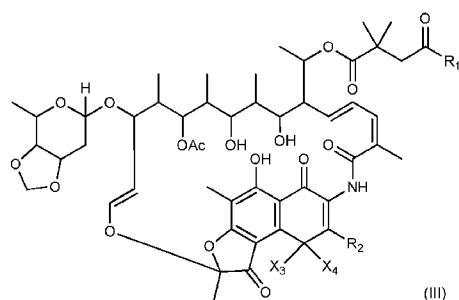
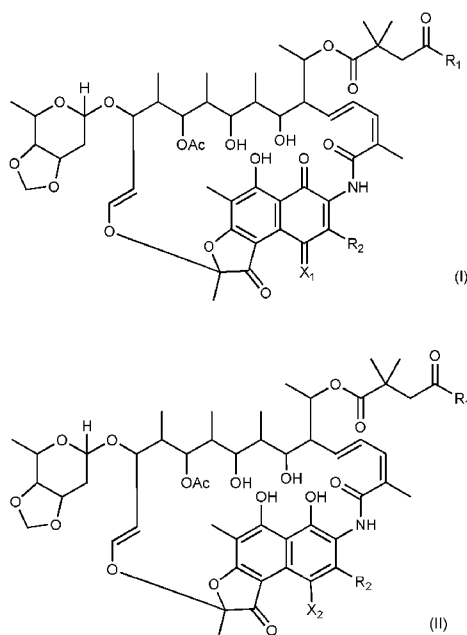
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(54) Title: COMPOUNDS FOR TREATING INFECTIONS CAUSED BY RIFAMPICIN-RESISTANT BACTERIA



(57) Abstract: Novel compounds of formulae (I)-(III) are provided, as well as pharmaceutical compositions comprising the novel compounds. Also described are therapeutic uses of the novel compounds, in particular in relation to the treatment of infections caused by rifampicin-resistant bacteria, e.g. rifampicin-resistant tuberculosis.

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COMPOUNDS FOR TREATING INFECTIONS CAUSED BY RIFAMPICIN-RESISTANT BACTERIA

INTRODUCTION

[0001] The present invention relates to certain compounds that are active against rifampicin-resistant RNA polymerases and rifampicin-resistant bacteria, as well as to pharmaceutical compositions comprising them, and to their use in the treatment of infections caused by rifampicin-resistant bacteria.

BACKGROUND OF THE INVENTION

[0002] Antibiotic resistance is on the increase, exacerbated by the fact that, in recent years, only a few new compounds have reached the clinic. RNA polymerase (RNAP) is an essential enzyme accomplishing transcription in all living organisms. At the same time, the sequence divergence between bacterial and human RNAPs, makes bacterial RNAP an excellent target for antibiotic development (Ho et al., 2009). In the last few years, details of the mode of action of a number of inhibitors of RNAP have been described (Bae et al., 2015; Degen et al., 2014; Maffioli et al., 2017; Molodtsov et al., 2015; Mukhopadhyay et al., 2008; Zhang et al., 2014a). However, most of these molecules have limited clinical utility, mainly due to their poor penetration of the bacterial cell envelope or strong binding to human plasma protein. Nevertheless, the search for new molecules that target RNAP and the analysis of their mode of action is a promising approach for the development of new antibiotics, as exemplified by the now clinically used fidaxomicin (trade name Dificid) for *Clostridium difficile*-associated diarrhea (Tupin et al., 2010).

[0003] The most studied class of antibiotics known to inhibit bacterial RNA transcription are the rifamycins, a family of mainly semisynthetic ansamycins derived from the natural product rifamycin S, of which rifampicin (RIF) is the most widely used (Aristoff et al., 2010). RIF (and the other rifamycins) binds in a pocket (the RIF-pocket) on the β subunit of RNAP in the vicinity of the catalytic site, and sterically blocks propagation of the growing RNA chain through the main channel of RNAP (Campbell et al., 2001; McClure and Cech, 1978). The collision of RNA and RIF happens when RNA reaches the length of 3-4 nucleotides, after which the RNA is released from the promoter complex as an abortive transcript.

[0004] The rifamycins are used, as part of the current combination therapy, for the first line treatment of tuberculosis (TB), the leading cause of death by infectious disease worldwide (WHO Global Tuberculosis report, 2017), as well as treatment for non-tuberculous mycobacterial infections (Ryu et al., 2016). One of the major problems with known rifamycins is the rapid selection for mutations in the RIF-binding pocket that lead to resistance. Multi-drug-resistant

strains of *Mycobacterium tuberculosis* (MDR-*M. tuberculosis*) presents a major clinical problem, as these strains are resistant to RIF, as well as several other first line drugs (such as isoniazid). In 2016, there were 600,000 new cases with resistance to rifampicin, of which 490,000 had MDR-TB. With a treatment success rate of only 54%, this highlights the requirement for improved treatment options. There are ~100 different amino acid substitutions in the RIF-pocket that have been found in RIF-resistant clinical isolates of *M. tuberculosis* (Sandgren et al., 2009), with mutations at three positions of the RIF-pocket that account for ~70% of the total substitutions (D516 – 7.4%, H526 – 20%, and S531 – 42%; *E. coli* numbering).

[0005] Previous efforts to probe the structure-activity relationships of the rifamycins, and to maximize their binding affinity for RNA polymerase, showed that even minor modifications of the *ansa*-chain resulted in decreased binding, due to changes in the spatial arrangement of the four hydroxyl groups (at C1, C8, C21 and C23) which form critical hydrogen bonds with the RIF pocket (Bacchi et al., 2008). Hence the production of clinically used semisynthetic rifamycins (rifampicin, rifabutin, rifapentine, rifalazil and rifaximin) has focused on the introduction of functionality at the C3 position to stabilize the oxidation state of the naphthoquinone core and to improve bioavailability (Floss and Yu, 2005; Perlman, 1977).

[0006] In spite of the advances to date, there remains a need for new compounds having potency against RIF-resistant RNAPs and RIF-resistant bacteria.

[0007] The present invention was devised with the foregoing in mind.

SUMMARY OF THE INVENTION

[0008] According to a first aspect of the present invention there is provided a compound of formula (I), (II) or (III) defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use in the treatment of infection caused by rifampicin-resistant bacteria.

[0009] According to a further aspect of the present invention there is provided a compound of formula (I), (II) or (III) as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof,

with the proviso that, in formula (I), when R₁ is hydroxy and R₂ is hydrogen, X₁ is not O.

[0010] According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula (I), (II) or (III) defined herein, or a pharmaceutically acceptable salt or solvate thereof, and one or more pharmaceutically acceptable excipients or carriers.

[0011] According to a further aspect of the present invention, there is provided a compound of

formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use in therapy.

[0012] According to a further aspect of the present invention, there is provided a compound of formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use as a medicament.

[0013] According to a further aspect of the present invention there is provided a method of inhibiting RIF-resistant RNA polymerase, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound of formula (I), (II) or (III) or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein.

[0014] According to a further aspect of the present invention, there is provided a method of inhibiting bacterial cell proliferation, *in vitro* or *in vivo*, said method comprising contacting a bacterial cell with an effective amount of a compound of formula (I), (II) or (III) or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein.

[0015] According to a further aspect of the present invention, there is provided a method of treating an infection caused by RIF-resistant bacteria in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of formula (I), (II) or (III) or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein.

[0016] According to a further aspect of the present invention, there is provided a use of a compound of formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the inhibition of RIF-resistant RNA polymerase.

[0017] According to a further aspect of the present invention, there is provided a use of a compound of formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of an infection caused by RIF-resistant bacteria.

[0018] Suitably, the infection caused by RIF-resistant bacteria is RIF-resistant tuberculosis.

[0019] Features, including optional, suitable, and preferred features in relation to one aspect of the invention may also be features, including optional, suitable and preferred features in relation to any other aspect of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0020] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0021] It is to be appreciated that references to “treating” or “treatment” include prophylaxis as well as the alleviation of established symptoms of a condition. “Treating” or “treatment” of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0022] A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0023] In this specification the term “alkyl” includes both straight and branched chain alkyl groups. References to individual alkyl groups such as “propyl” are specific for the straight chain version only and references to individual branched chain alkyl groups such as “isopropyl” are specific for the branched chain version only. For example, “(1-6C)alkyl” includes (1-4C)alkyl, (1-3C)alkyl, propyl, isopropyl and *t*-butyl.

[0024] The term “(m-nC)” or “(m-nC) group” used alone or as a prefix, refers to any group having m to n carbon atoms.

[0025] An “alkylene” group is an alkyl group that is positioned between and serves to connect two other chemical groups. Thus, “(1-6C)alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, for example, methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), 2-methylpropylene (-CH₂CH(CH₃)CH₂-), pentylene (-CH₂CH₂CH₂CH₂CH₂-), and the like.

[0026] “(3-10C)cycloalkyl” means a hydrocarbon ring containing from 3 to 10 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and bicyclo[2.2.1]heptyl.

[0027] “(3-10C)cycloalkenyl” means a hydrocarbon ring containing from 3 to 10 carbon atoms and at least one double bond, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl, such as 3-cyclohexen-1-yl, or cyclooctenyl.

[0028] The term “halo” or “halogeno” refers to fluoro, chloro, bromo and iodo, suitably fluoro, chloro and bromo, more suitably, fluoro and chloro.

[0029] The term “heterocyclyl”, “heterocyclic” or “heterocycle” means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system(s). Monocyclic heterocyclic rings contain from about 3 to 12 (suitably from 3 to 7) ring atoms, with from 1 to 5 (suitably 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Bicyclic heterocycles contain from 7 to 17 member atoms, suitably 7 to 12 member atoms, in the ring. Bicyclic heterocyclic(s) rings may be fused, spiro, or bridged ring systems. Examples of heterocyclic groups include cyclic ethers such as oxiranyl, oxetanyl, tetrahydrofuranyl, dioxanyl, and substituted cyclic ethers. Heterocycles containing nitrogen include, for example, azetidiny, pyrrolidiny, piperidiny, piperaziny, tetrahydrotriaziny, tetrahydropyrazoly, and the like. Typical sulfur containing heterocycles include tetrahydrothienyl, dihydro-1,3-dithiol, tetrahydro-2H-thiopyran, and hexahydrothiepine. Other heterocycles include dihydro-oxathioly, tetrahydro-oxazoly, tetrahydro-oxadiazoly, tetrahydrodioxazoly, tetrahydro-oxathiazoly, hexahydrotriaziny, tetrahydro-oxaziny, morpholiny, thiomorpholiny, tetrahydropyrimidiny, dioxoliny, octahydrobenzofuranyl, octahydrobenzimidazoly, and octahydrobenzothiazoly. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or SO₂ groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothienyl and thiomorpholiny such as tetrahydrothiene 1,1-dioxide and thiomorpholiny 1,1-dioxide. A suitable value for a heterocyclyl group which bears 1 or 2 oxo (=O) or thioxo (=S) substituents is, for example, 2-oxopyrrolidiny, 2-thioxopyrrolidiny, 2-oxoimidazolidiny, 2-thioxoimidazolidiny, 2-oxopiperidiny, 2,5-dioxopyrrolidiny, 2,5-dioxoimidazolidiny or 2,6-dioxopiperidiny. Particular heterocyclyl groups are saturated monocyclic 3 to 7 membered heterocyclyls containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur, for example azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidiny, morpholiny, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, thiomorpholiny, thiomorpholiny 1,1-dioxide, piperidiny, homopiperidiny, piperaziny or homopiperaziny. As the skilled person would appreciate, any heterocycle may be linked to another group via any suitable atom, such as via a carbon or nitrogen atom. In this specification, heterocycles are suitably linked to another group via a nitrogen atom.

[0030] By “spiro bi-cyclic heterocyclic ring systems” we mean that the two ring systems share one common spiro carbon atom, i.e. the heterocyclic ring is linked to a further cycloalkyl, cycloalkenyl or heterocyclic ring through a single common spiro carbon atom. Examples of spiro ring systems include 6-azaspiro[3.4]octane, 2-oxa-6-azaspiro[3.4]octane, 2-

azaspiro[3.3]heptanes, 2-oxa-6-azaspiro[3.3]heptanes, 7-oxa-2-azaspiro[3.5]nonane, 6-oxa-2-azaspiro[3.4]octane, 2-oxa-7-azaspiro[3.5]nonane and 2-oxa-6-azaspiro[3.5]nonane.

[0031] The term “heteroaryl” or “heteroaromatic” means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (for example 1-4, particularly 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur. The term heteroaryl includes both monovalent species and divalent species. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring, for example a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulfur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

[0032] Examples of heteroaryl include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, isoindolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiazolyl, indazolyl, purinyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl, pteridinyl, naphthyridinyl, carbazolyl, phenazinyl, benzisoquinolyl, pyridopyrazinyl, thieno[2,3-*b*]furanyl, 2H-furo[3,2-*b*]-pyranlyl, 5H-pyrido[2,3-*d*]-o-oxazinyl, 1H-pyrazolo[4,3-*d*]-oxazolyl, 4H-imidazo[4,5-*d*]thiazolyl, pyrazino[2,3-*d*]pyridazinyl, imidazo[2,1-*b*]thiazolyl, imidazo[1,2-*b*][1,2,4]triazinyl. “Heteroaryl” also covers partially aromatic bi- or polycyclic ring systems wherein at least one ring is an aromatic ring and one or more of the other ring(s) is a non-aromatic, saturated or partially saturated ring, provided at least one ring contains one or more heteroatoms selected from nitrogen, oxygen or sulfur. Examples of partially aromatic heteroaryl groups include for example, tetrahydroisoquinolyl, tetrahydroquinolyl, 2-oxo-1,2,3,4-tetrahydroquinolyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,3]dioxolyl, 2,2-dioxo-1,3-dihydro-2-benzothienyl, 4,5,6,7-tetrahydrobenzofuranyl, indolinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl and 3,4-dihydro-2H-pyrido[3,2-*b*][1,4]oxazinyl.

[0033] Examples of five membered heteroaryl groups include but are not limited to pyrrolyl, furanyl, thienyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.

[0034] Examples of six membered heteroaryl groups include but are not limited to pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.

[0035] A bicyclic heteroaryl group may be, for example, a group selected from:

a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyridine ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyrimidine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a pyrrole ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyrazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a pyrazine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an imidazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an oxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an isoxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a thiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an isothiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a thiophene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a furan ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a cyclohexyl ring fused to a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 ring heteroatoms; and

a cyclopentyl ring fused to a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 ring heteroatoms.

[0036] Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuranyl, benzthiophenyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benzisothiazolyl, isobenzofuranyl, indolyl, isoindolyl, indoliziny, indoliny, isoindoliny, puriny (e.g., adeniny, guaniny), indazolyl, benzodioxolyl and pyrazolopyridiny groups.

[0037] Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoliny, isoquinoliny, chromanyl, thiochromanyl, chromenyl, isochromenyl, chromanyl, isochromanyl, benzodioxanyl, quinoliziny, benzoxazinyl, benzodiaziny, pyridopyridiny, quinoxaliny, quinazoliny, cinnoliny, phthalazinyl, naphthyridiny and pteridiny groups.

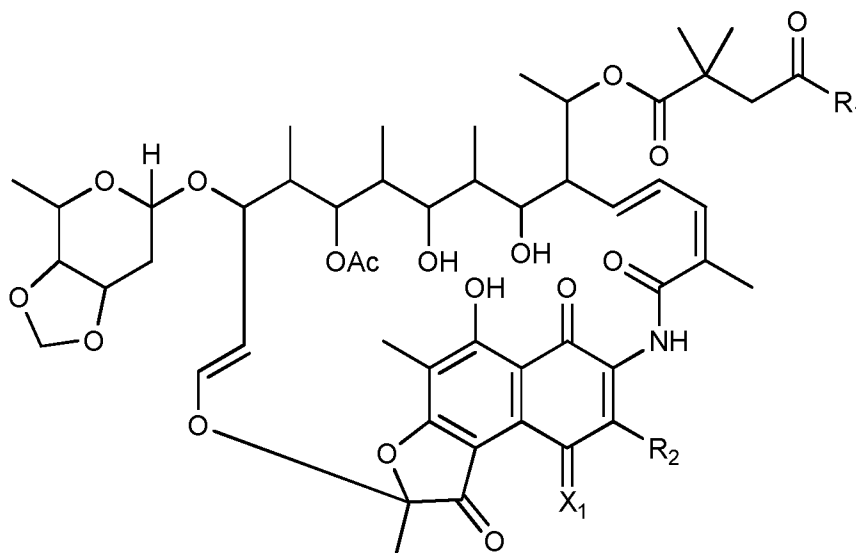
[0038] The term “aryl” means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. In a particular embodiment, an aryl is phenyl.

[0039] The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted.

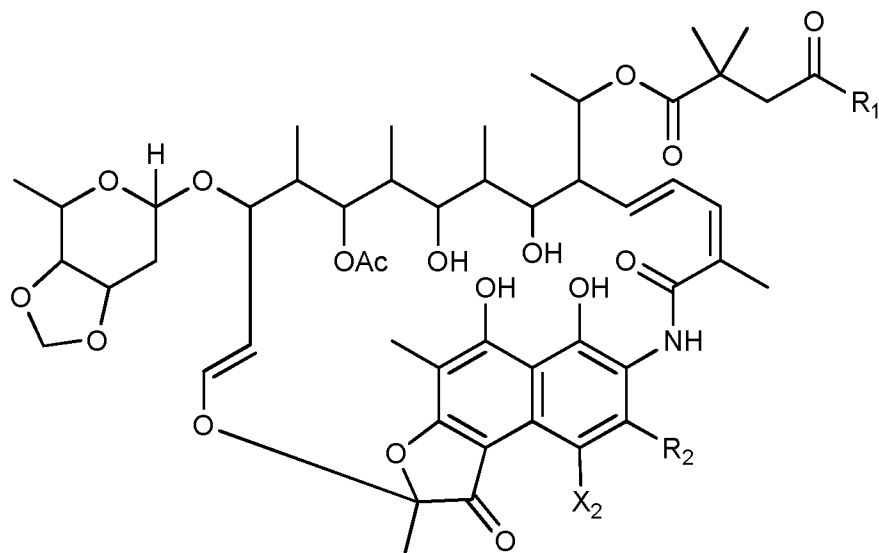
[0040] Where optional substituents are chosen from “one or more” groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

Therapeutic Uses and Applications

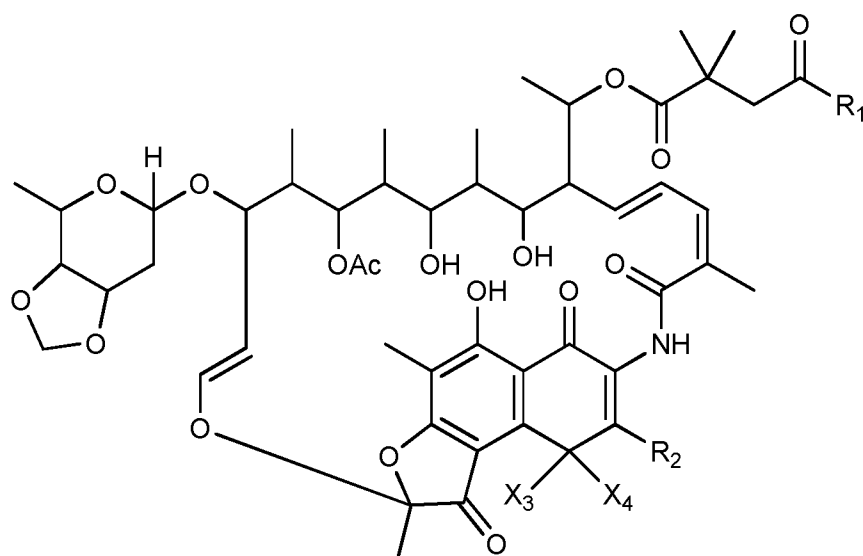
[0041] In one aspect, the present invention provides a compound of formula (I), (II) or (III) shown below, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use in the treatment of infection caused by rifampicin-resistant bacteria:



(1)



(II)



(III)

wherein,

R_1 is selected from hydrogen, halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_aR_b , OR_c , $OC(O)R_a$, $N(R_b)OR_a$,

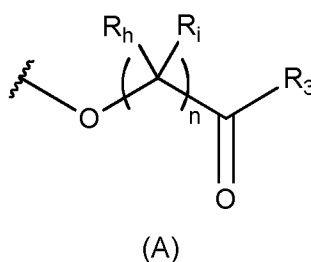
$N(R_b)C(O)OR_a$, $N(R_b)C(O)R_a$, $S(O)_pR_a$ (where p is 0, 1 or 2), $SO_2N(R_b)R_a$, and $N(R_b)SO_2R_a$;

R_2 is selected from hydrogen, halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_dR_e , OR_f , $C(O)R_d$, $C(O)OR_d$, $OC(O)R_d$, $C(R_d)=N(R_e)$, $N(R_d)OR_e$, $N(R_d)C(O)OR_e$, $C(O)N(R_d)R_e$, $N(R_d)C(O)R_e$, $S(O)_pR_d$ (where p is 0, 1 or 2), $SO_2N(R_d)R_e$, and $N(R_d)SO_2R_e$;

and wherein R_1 and R_2 are each independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, or (3-8C)cycloalkyl(1-2C)alkyl;

X_1 is selected from O and NR_g ;

X_2 is hydroxy or a group of formula (A) shown below:



wherein

n is 0, 1, 2, 3 or 4; and

R_3 is selected from hydrogen, halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_jR_k , OR_l , $C(O)R_j$, $C(O)OR_j$, $OC(O)R_j$, $C(R_j)=N(R_k)$, $N(R_j)OR_k$, $N(R_j)C(O)OR_k$, $C(O)N(R_j)R_k$, $N(R_j)C(O)R_k$, $S(O)_pR_j$ (where p is 0, 1 or 2), $SO_2N(R_j)R_k$, and $N(R_j)SO_2R_k$;

and wherein R_3 is independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, or (3-8C)cycloalkyl(1-2C)alkyl;

or R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 5-12 membered heteroaryl or heterocycle that is optionally substituted with one or more R_4 substituents;

and wherein each R_4 is independently selected from halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_mR_n , OR_o , $C(O)R_m$, $C(O)OR_m$, $OC(O)R_m$, $N(R_m)OR_n$, $N(R_m)C(O)OR_n$, $C(O)N(R_m)R_n$, $C(R_m)=N(R_n)$, $N(R_m)C(O)R_n$, $S(O)_pR_m$ (where p is 0, 1 or 2), $SO_2N(R_m)R_n$, and $N(R_m)SO_2R_n$;

and wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

X_3 and X_4 are independently selected from hydroxy, OR_p , NR_qR_r and a group of formula (A) shown above;

or X_3 and X_4 are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a 4-6 membered heterocycle that is optionally substituted with one or more R_5 substituents;

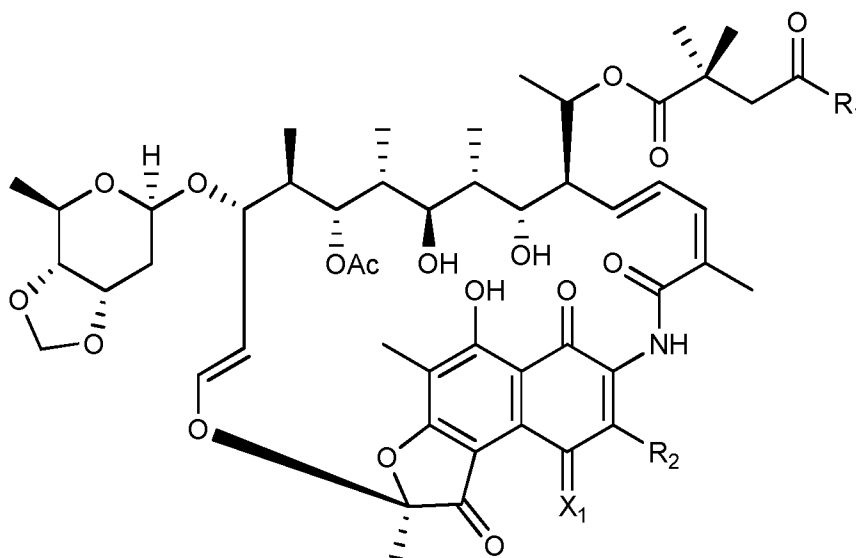
and wherein each R_5 is independently selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, oxo, amino, carboxy, carbamoyl, sulphamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-

6C)alkynyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

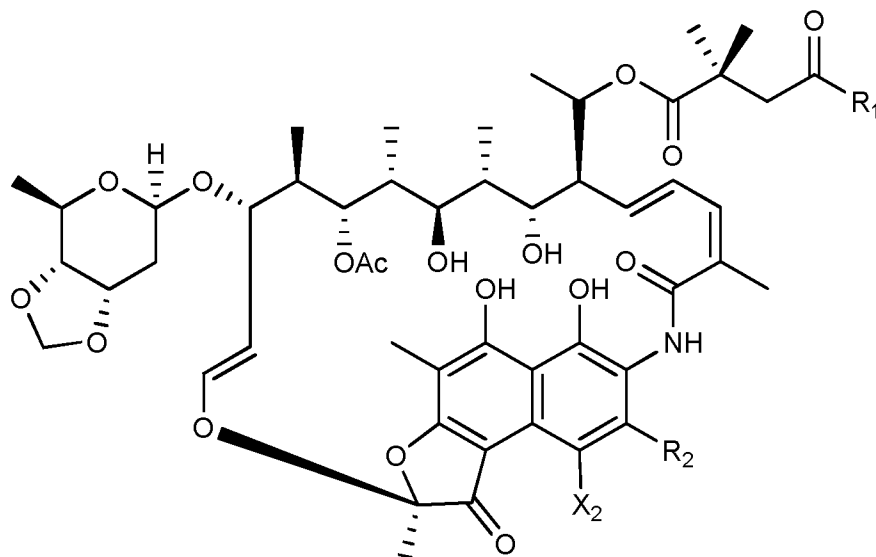
each R_a to R_r is independently selected from hydrogen, fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

and wherein each R_a to R_r is independently optionally substituted with one or more groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl.

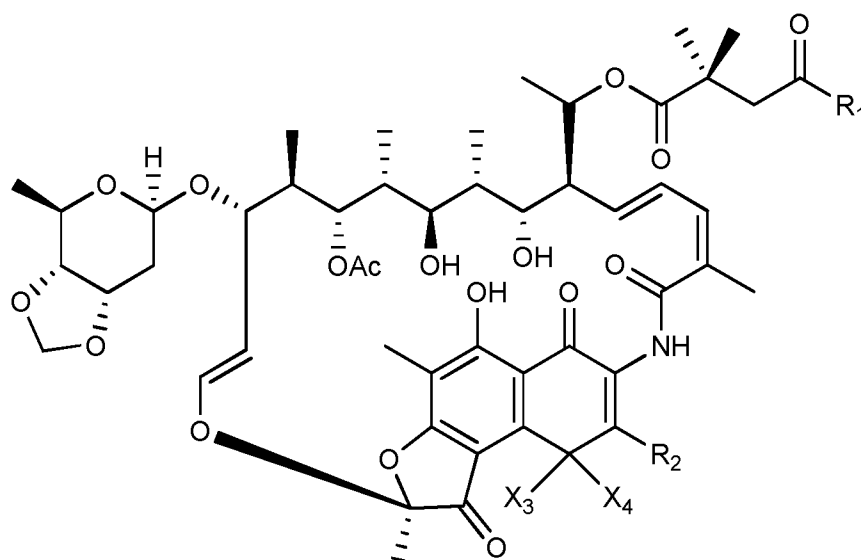
[0042] In an embodiment, the compound of formula (I), (II) or (III) has a structure according to formula (I'), (II') or (III') shown below:



(I')



(II')

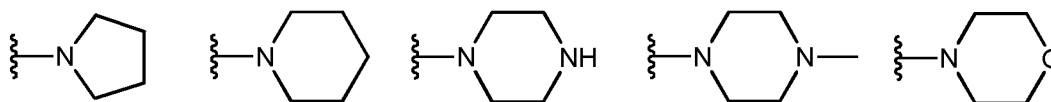


(III')

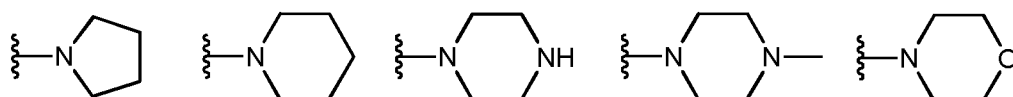
[0043] In particular compounds of formula (I), (II) or (III), or pharmaceutically acceptable salts, hydrates and/or solvates thereof, unless otherwise stated, each of R_1 , R_2 , X_1 , X_2 , X_3 and X_4 , and any of their associated substituents, has any of the meanings defined hereinbefore or in any of numbered paragraphs (1) to (87) hereinafter:

- (1) R_1 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl,

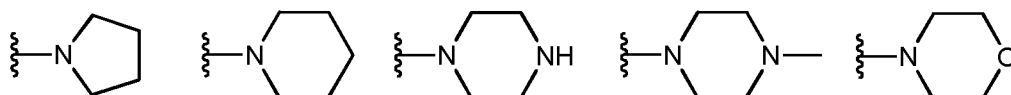
- (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_aR_b , OR_c , OC(O)R_a , $\text{N(R}_b\text{)OR}_a$, $\text{N(R}_b\text{)C(O)OR}_a$ and $\text{N(R}_b\text{)C(O)R}_a$, wherein R_1 is optionally substituted by one or more substituent groups selected from (1-4C)alkyl and (1-3C)alkoxy.
- (2) R_1 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_aR_b and OR_c , wherein R_1 is optionally substituted by one or more substituent groups selected from (1-4C)alkyl and (1-3C)alkoxy.
- (3) R_1 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_aR_b and OR_c , wherein R_1 is optionally substituted by one or more substituent groups selected from (1-2C)alkyl and (1-2C)alkoxy.
- (4) R_1 is selected from hydroxy, (1-6C)alkyl, aryl, heteroaryl, (3-8C)heterocyclyl, (3-8C)cycloalkyl, NR_aR_b and OR_c , wherein R_1 is optionally substituted by one or more substituent groups selected from (1-2C)alkyl and (1-2C)alkoxy.
- (5) R_1 is selected from hydroxy, (1-4C)alkyl, N-linked (3-8C)heterocyclyl, NR_aR_b and OR_c , wherein R_1 is optionally substituted by one or more (1-2C)alkyl.
- (6) R_1 is selected from hydroxy, N-linked (3-6C)heterocyclyl, NR_aR_b and OR_c , wherein the N-linked (3-6C)heterocyclyl contains 1 or 2 heteroatoms, wherein R_1 is optionally substituted by one or more (1-2C)alkyl.
- (7) R_1 is selected from hydroxy, NR_aR_b , OR_c or any one of the following:



- (8) R_1 is selected from hydroxy and OR_c (e.g. methoxy or ethoxy).
- (9) Each R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, (1-4C)alkoxy, aryl and (3-8C)heterocyclyl.
- (10) Each R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, aryl and N-linked (3-8C)heterocyclyl.
- (11) Each R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, phenyl and 5-6 membered N-linked heterocyclyl.
- (12) Each R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, phenyl or any one of the following:

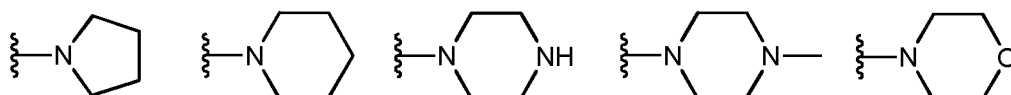


- (13) Each R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, amino, aryl, aryl(1-2C)alkyl, (3-8C)cycloalkyl or any one of the following



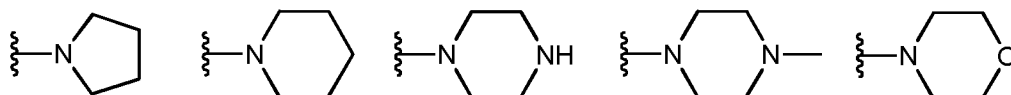
wherein each R_a and R_b is optionally substituted with one or more substituent groups selected from halo, hydroxy, (1-3C)alkyl and (1-3C)haloalkyl.

- (14) R_a is hydrogen or (1-6C)alkyl and R_b is selected from (1-6C)alkyl, amino, aryl, aryl(1-2C)alkyl, (3-8C)cycloalkyl or any one of the following



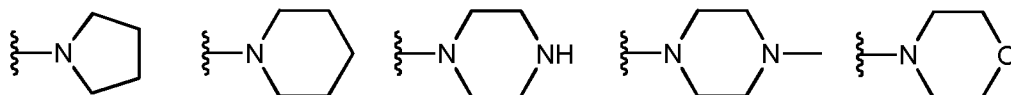
wherein each R_b is optionally substituted with one or more substituent groups selected from halo, hydroxy, (1-3C)alkyl and (1-3C)haloalkyl.

- (15) Each R_a and R_b are independently selected from hydrogen, (1-3C)alkyl, amino, aryl, aryl(1-2C)alkyl, (3-6C)cycloalkyl or any one of the following



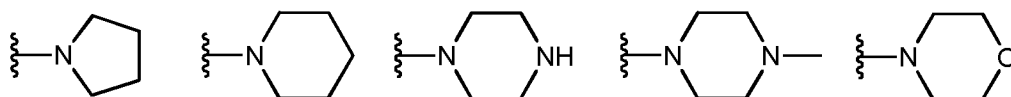
wherein each of the said amino, aryl and aryl(1-2C)alkyl groups is optionally substituted with one or more substituent groups selected from halo, hydroxy, (1-3C)alkyl and (1-3C)haloalkyl.

- (16) R_a is hydrogen or (1-3C)alkyl and R_b is selected from (1-3C)alkyl, amino, aryl, aryl(1-2C)alkyl, (3-6C)cycloalkyl or any one of the following



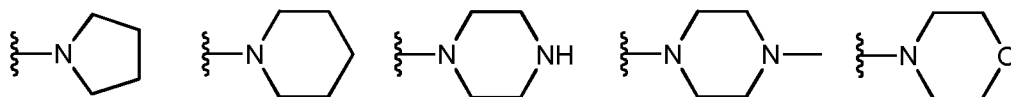
wherein each of the said amino, aryl and aryl(1-2C)alkyl groups is optionally substituted with one or more substituent groups selected from halo, hydroxy, (1-3C)alkyl and (1-3C)haloalkyl.

- (17) Each R_a and R_b are independently selected from hydrogen, (1-3C)alkyl, amino, phenyl, benzyl, (3-6C)cycloalkyl or any one of the following



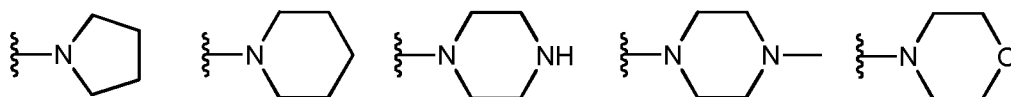
wherein each of the said phenyl and benzyl groups is optionally substituted with one or more substituent groups selected from fluoro, chloro hydroxy, (1-3C)alkyl and (1-3C)haloalkyl, and each of the said amino groups is optionally substituted with one or more substituent groups selected from (1-3C)alkyl.

- (18) R_a is hydrogen or (1-3C)alkyl and R_b is selected from (1-3C)alkyl, amino, phenyl, benzyl, (3-6C)cycloalkyl or any one of the following



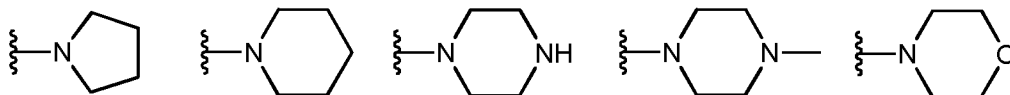
wherein each of the said phenyl and benzyl groups is optionally substituted with one or more substituent groups selected from fluoro, chloro hydroxy, (1-3C)alkyl and (1-3C)haloalkyl, and each of the said amino groups is optionally substituted with one or more substituent groups selected from (1-3C)alkyl.

- (19) Each R_a and R_b are independently selected from hydrogen, (1-2C)alkyl, NH_2 , $N(Me)_2$, $N(H)(Me)$, phenyl, benzyl, cyclopropyl or any one of the following



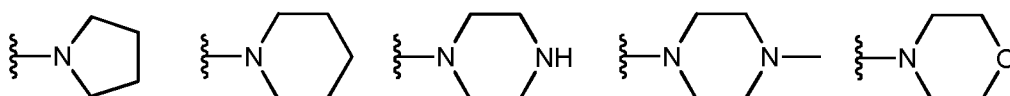
wherein each of the said phenyl and benzyl groups is optionally substituted with one or two substituent groups selected from fluoro, chloro, hydroxy and trifluoromethyl.

- (20) R_a is hydrogen or (1-2C)alkyl and R_b is selected from (1-2C)alkyl, NH_2 , $N(Me)_2$, $N(H)(Me)$, phenyl, benzyl, cyclopropyl or any one of the following



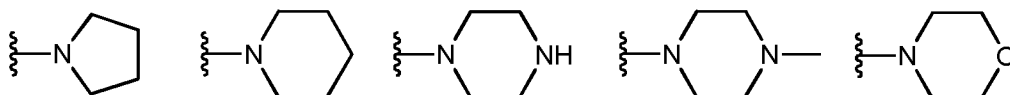
wherein each of the said phenyl and benzyl groups is optionally substituted with one or two substituent groups selected from fluoro, chloro, hydroxy and trifluoromethyl.

- (21) Each R_a and R_b are independently selected from hydrogen, (1-2C)alkyl, $N(Me)_2$, benzyl, cyclopropyl or any one of the following



wherein each of the said benzyl groups is optionally substituted with one substituent group selected from fluoro, chloro, hydroxy and trifluoromethyl.

- (22) R_a is hydrogen or (1-2C)alkyl and R_b is selected from (1-2C)alkyl, $N(Me)_2$, benzyl, cyclopropyl or any one of the following

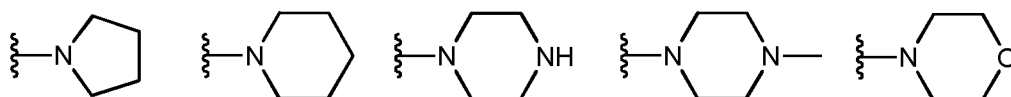


wherein each of the said benzyl groups is optionally substituted with one substituent group selected from fluoro, chloro, hydroxy and trifluoromethyl.

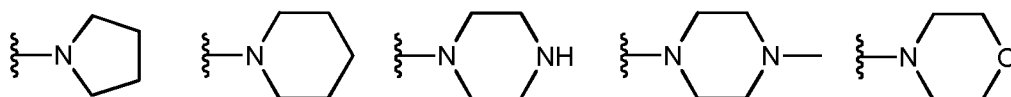
- (23) Each R_c is independently (1-6C)alkyl.
- (24) Each R_c is independently (1-3C)alkyl.
- (25) Each R_c is independently methyl or ethyl.
- (26) R_2 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_dR_e , OR_f , $C(O)R_d$, $C(O)OR_d$, $OC(O)R_d$, $C(R_d)=N(R_e)$, $N(R_d)OR_e$, $N(R_d)C(O)OR_e$, $C(O)N(R_d)R_e$ and $N(R_d)C(O)R_e$.
- (27) R_2 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_dR_e , OR_f , $C(O)R_d$, $C(O)OR_d$, $OC(O)R_d$ and $C(R_d)=N(R_e)$.
- (28) R_2 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_dR_e , OR_f , and $C(R_d)=N(R_e)$.

- (29) R_2 is selected from hydrogen, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
- (30) R_2 is selected from hydrogen, (1-6C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
- (31) R_2 is selected from hydrogen, (3-8C)heterocyclyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
- (32) R_2 is selected from hydrogen, N-pyrrolidinyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
- (33) Each R_d is independently selected from hydrogen and (1-6C)alkyl.
- (34) Each R_d is hydrogen.
- (35) Each R_e is independently selected from hydrogen, (1-6C)alkyl and (3-8C)heterocyclyl, any of which is optionally substituted with one or more substituent groups selected from (1-6C)alkyl and (3-8C)cycloalkyl.
- (36) Each R_e is independently selected from hydrogen, (1-4C)alkyl and (3-6C)heterocyclyl containing 1 or 2 heteroatoms selected from O and N, any of which is optionally substituted with one or more substituent groups selected from (1-4C)alkyl and (4-6C)cycloalkyl.
- (37) Each R_e is independently selected from hydrogen, (1-4C)alkyl and N-piperazinyl, any of which is optionally substituted with cyclopentyl.
- (38) Each R_e is N-piperazinyl, any of which is optionally substituted with cyclopentyl.
- (39) X_1 is O.
- (40) X_2 is hydroxy.
- (41) X_2 is a group of formula (A).
- (42) n is 1 or 2.
- (43) n is 1.
- (44) R_3 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_jR_k and OR_i , wherein R_3 is independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, amino, (1-4C)alkyl and (1-4C)alkoxy.
- (45) R_3 is selected from hydroxy, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_jR_k and OR_i , wherein R_3 is independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, amino, (1-4C)alkyl and (1-4C)alkoxy.

- (46) R_3 is selected from hydroxy, (1-6C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, NR_jR_k and OR_i , wherein R_3 is optionally substituted by one or more substituent groups selected from (1-4C)alkyl and (1-3C)alkoxy.
- (47) R_3 is selected from hydroxy, (1-3C)alkyl, (3-8C)heterocyclyl, NR_jR_k and OR_i , wherein R_3 is optionally substituted by one or more substituent groups selected from (1-2C)alkyl and (1-2C)alkoxy.
- (48) R_3 is selected from hydroxy, N-linked (3-8C)heterocyclyl, NR_jR_k and OR_i , wherein R_3 is optionally substituted by one or more (1-2C)alkyl.
- (49) R_3 is selected from hydroxy, NR_jR_k , OR_i or any one of the following:

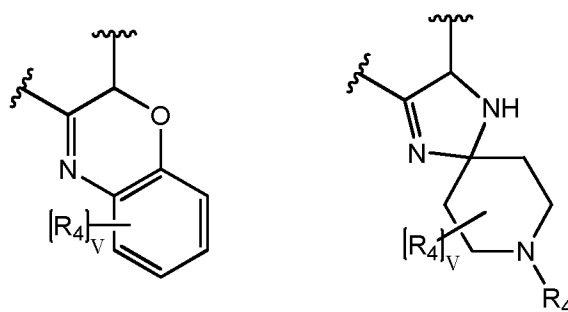


- (50) R_3 is selected from hydroxy or OR_i (e.g. methoxy).
- (51) Each R_h and R_i are independently selected from hydrogen and (1-6C)alkyl.
- (52) Each R_h and R_i are independently selected from hydrogen and (1-2C)alkyl.
- (53) Each R_h and R_i are hydrogen.
- (54) Each R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, (1-4C)alkoxy, aryl and (3-8C)heterocyclyl.
- (55) Each R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, aryl and N-linked (3-8C)heterocyclyl.
- (56) Each R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, phenyl and 5-6 membered N-linked heterocyclyl.
- (57) Each R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, phenyl or any one of the following:



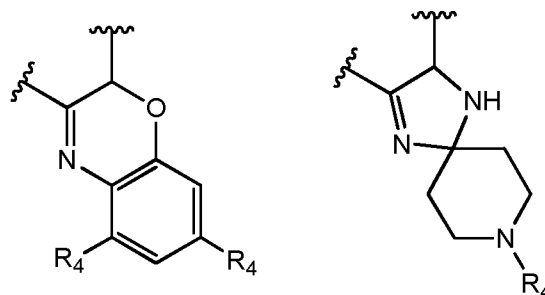
- (58) Each R_i is independently (1-6C)alkyl.
- (59) Each R_i is independently (1-3C)alkyl.
- (60) Each R_i is independently methyl or ethyl.
- (61) R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 5-12 membered heterocycle that is optionally substituted with one or more R_4 substituents.

- (62) R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 8-12 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system that is optionally substituted with one or more R_4 substituents.
- (63) R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 8-12 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system containing 1, 2 or 3 heteroatoms selected from O and N, wherein said 8-12 membered fused or spiro heterobicycle is optionally substituted with one or more R_4 substituents.
- (64) R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 9-11 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system containing 1, 2 or 3 heteroatoms selected from O and N, wherein said 9-11 membered fused or spiro heterobicycle is optionally substituted with one or more R_4 substituents.
- (65) R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 10 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system containing 1, 2 or 3 heteroatoms selected from O and N, wherein said 10 membered fused or spiro heterobicycle is optionally substituted with one or more R_4 substituents.
- (66) R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form either of the following groups:

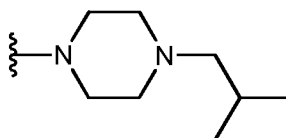


wherein v is a number 0, 1 or 2.

- (67) R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form either of the following groups:



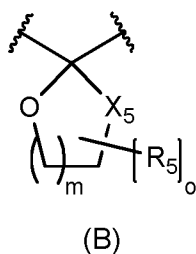
- (68) each R_4 is independently selected from halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_mR_n , OR_o , wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl.
- (69) each R_4 is independently selected from halo, hydroxy, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_mR_n , OR_o , wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, (1-4C)alkyl and (1-4C)alkoxy.
- (70) each R_4 is independently selected from halo, hydroxy, (1-6C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, NR_mR_n , OR_o , wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, (1-4C)alkyl and (1-4C)alkoxy.
- (71) each R_4 is independently selected from hydroxy, (1-6C)alkyl and (3-8C)heterocyclyl, wherein each R_4 is independently optionally substituted with one or more groups, (1-4C)alkyl.
- (72) each R_4 is independently selected from hydroxy, (1-4C)alkyl or a group:



- (73) X_3 and X_4 are independently selected from hydroxy, OR_p and NR_qR_r .
- (74) X_3 and X_4 are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a 4-6 membered heterocycle containing

1 or 2 heteroatoms selected from O and N, wherein the 4-6 membered heterocycle is optionally substituted with one or more R₅ substituents.

- (75) X₃ and X₄ are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a group having a structure according to formula (B) shown below:



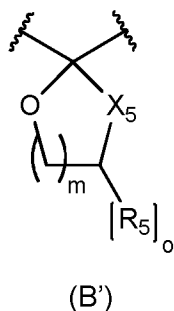
wherein,

X₅ is selected from O or NR_m;

m is a number selected from 1 and 2; and

o is a number selected from 1 and 2.

- (76) X₃ and X₄ are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a group having a structure according to formula (B') shown below:



wherein,

X₅ is selected from O or NR_m;

m is a number selected from 1 and 2; and

o is a number selected from 1 and 2.

- (77) X₅ is O.

- (78) m is 1.

- (79) o is 1.

- (80) Each R₅ is independently selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, amino, carboxy, (1-6C)alkyl, (1-4C)alkoxy, methylamino or dimethylamino,

aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl.

- (81) Each R_5 is independently selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, amino, carboxy, (1-6C)alkyl, (1-4C)alkoxy, methylamino and dimethylamino.
- (82) Each R_5 is independently selected from fluoro, chloro, hydroxy, oxo, amino, (1-3C)alkyl and (1-3C)alkoxy.
- (83) Each R_5 is independently selected from hydroxy, oxo and (1-4C)alkoxy.
- (84) R_5 is oxo.
- (85) $R_f, R_g, R_m, R_n, R_o, R_p, R_q, R_r$ are each independently selected from hydrogen and (1-6C)alkyl.
- (86) $R_f, R_g, R_m, R_n, R_o, R_p, R_q, R_r$ are each independently selected from hydrogen and (1-3C)alkyl.
- (87) $R_f, R_g, R_m, R_n, R_o, R_p, R_q, R_r$ are each hydrogen.

[0044] Suitably, the compound has a structure according to formula (I).

[0045] Suitably, the compound has a structure according to formula (II).

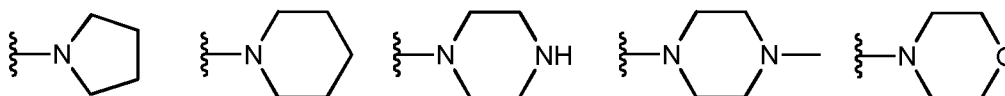
[0046] Suitably, the compound has a structure according to formula (III).

[0047] Suitably, the compound has a structure according to formula (I) or (II).

[0048] Suitably, the compound has a structure according to formula (I) or (III).

[0049] Suitably, the compound has a structure according to formula (II) or (III).

[0050] Suitably, (3-8)heterocycles are linked to the group to which they are attached via a nitrogen atom present within the heterocyclic ring (i.e. "N-linked"). More suitably, (3-8)heterocycles are 5-6 membered, containing 1-2 ring heteroatoms selected from N and O. Most suitably, (3-8)heterocycles are selected from the following:



[0051] Suitably an aryl group is phenyl.

[0052] Suitably, R_1 is as described in any of numbered paragraphs (3) to (8), wherein R_a and R_b are suitably as described in any of numbered paragraphs (10) to (12) and R_c is suitably as

described in any of numbered paragraphs (23) to (25). More suitably, R_1 is as described in any of numbered paragraphs (5) to (8), wherein R_a and R_b are suitably as described in any of numbered paragraphs (11) to (12) and R_c is suitably as described in any of numbered paragraphs (24) to (25). Yet more suitably, R_1 is as described in any of numbered paragraphs (7) to (8), wherein R_a and R_b are suitably as described in any of numbered paragraphs (11) to (12) and R_c is suitably as described in any of numbered paragraphs (24) to (25). Most suitably, R_1 is as described in numbered paragraph (8), wherein R_c is suitably as described in numbered paragraph (25).

[0053] Suitably, R_1 is as described in any of numbered paragraphs (3) to (8), wherein R_a and R_b are suitably as described in any of numbered paragraphs (13) to (22) and R_c is suitably as described in any of numbered paragraphs (23) to (25). More suitably, R_1 is as described in any of numbered paragraphs (5) to (8), wherein R_a and R_b are suitably as described in any of numbered paragraphs (17) to (22) and R_c is suitably as described in any of numbered paragraphs (24) to (25). Yet more suitably, R_1 is as described in any of numbered paragraphs (7) to (8), wherein R_a and R_b are suitably as described in any of numbered paragraphs (19) to (22) and R_c is suitably as described in any of numbered paragraphs (24) to (25). Most suitably, R_1 is as described in any of numbered paragraphs (7) to (8), wherein R_a and R_b are suitably as described in any of numbered paragraphs (21) to (22) and R_c is suitably as described in numbered paragraph (25)..

[0054] Suitably, R_2 is as described in any of numbered paragraphs (28) to (32), wherein R_d is suitably as described in any of numbered paragraphs (33) to (34) and R_e is suitably as described in any of numbered paragraphs (36) to (38). More suitably, R_2 is as described in any of numbered paragraphs (30) to (32), wherein R_d is suitably as described in numbered paragraph (34) and R_e is suitably as described in any of numbered paragraphs (37) to (38). Most suitably, R_2 is as described in numbered paragraph (32), wherein R_d is suitably as described in numbered paragraph (34) and R_e is suitably as described in numbered paragraph (38)

[0055] Suitably, X_2 is as described in numbered paragraph (41), wherein n is suitably as described in numbered paragraph (42) or (43), R_3 is suitably as described in any of numbered paragraphs (46) to (50), R_h and R_i are suitably as described in any of numbered paragraphs (52) to (53), R_j and R_k are suitably as described in any of numbered paragraphs (55) to (57) and R_l is suitably as described in any of numbered paragraphs (59) to (60). More suitably, X_2 is as described in numbered paragraph (41), wherein n is suitably as described in numbered paragraph (42) or (43), R_3 is suitably as described in any of numbered paragraphs (48) to (50), R_h and R_i are suitably as described in numbered paragraph (53), R_j and R_k are suitably as described in any of numbered paragraphs (56) to (57) and R_l is suitably as described in any of numbered paragraphs (59) to (60). Most suitably, X_2 is as described in numbered paragraph (41),

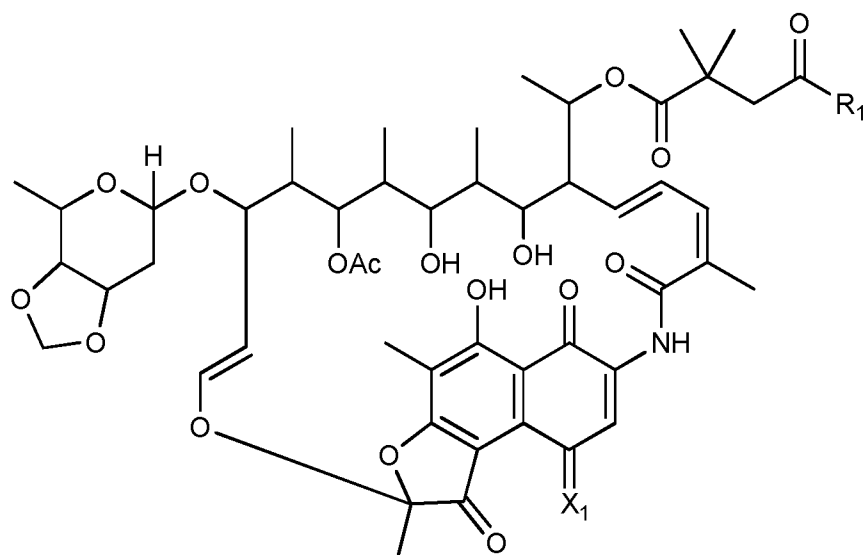
wherein n is suitably as described in numbered paragraph (43), R_3 is suitably as described in any of numbered paragraphs (49) to (50), R_h and R_i are suitably as described in numbered paragraph (53), R_j and R_k are suitably as described in numbered paragraph (57) and R_l is suitably as described in numbered paragraph (60).

[0056] Suitably, R_2 and X_1 or R_2 and X_2 are as described in any of numbered paragraphs (64) to (67), wherein R_4 is suitably as described in any of numbered paragraphs (69) to (72). More suitably, R_2 and X_1 or R_2 and X_2 are as described in any of numbered paragraphs (65) to (67), wherein R_4 is suitably as described in any of numbered paragraphs (70) to (72). Most suitably, R_2 and X_1 or R_2 and X_2 are as described in any of numbered paragraphs (66) to (67), wherein R_4 is suitably as described in paragraph (72).

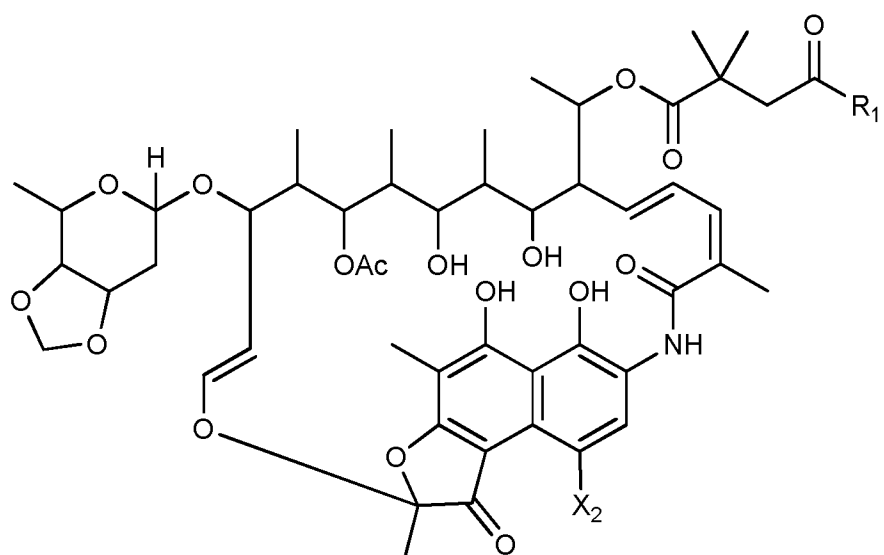
[0057] Suitably, X_3 and X_4 are as described in any of numbered paragraphs (75) to (76), wherein m is as described in numbered paragraph (78) and R_5 is as described in any of numbered paragraphs (81) to (84). More suitably, X_3 and X_4 are as described in any of numbered paragraphs (75) to (76), wherein m is as described in numbered paragraph (78), o is as described in numbered paragraph (79) and R_5 is as described in any of numbered paragraphs (81) to (84). Even more suitably, X_3 and X_4 are as described in any of numbered paragraphs (75) to (76), wherein X_5 is as described in numbered paragraph (77), m is as described in numbered paragraph (78), o is as described in numbered paragraph (79) and R_5 is as described in any of numbered paragraphs (82) to (84). Yet more suitably, X_3 and X_4 are as described in any of numbered paragraphs (75) to (76), wherein X_5 is as described in numbered paragraph (77), m is as described in numbered paragraph (78), o is as described in numbered paragraph (79) and R_5 is as described in any of numbered paragraphs (83) to (84). Most suitably, X_3 and X_4 are as described in numbered paragraph (76), wherein X_5 is as described in numbered paragraph (77), m is as described in numbered paragraph (78), o is as described in numbered paragraph (79) and R_5 is as described in any of numbered paragraphs (83) to (84).

[0058] Suitably, R_f , R_g , R_m , R_n , R_o , R_p , R_q , R_r are as described in numbered paragraph (86) or (87). Most suitably, R_f , R_g , R_m , R_n , R_o , R_p , R_q , R_r are as described in numbered paragraph (87).

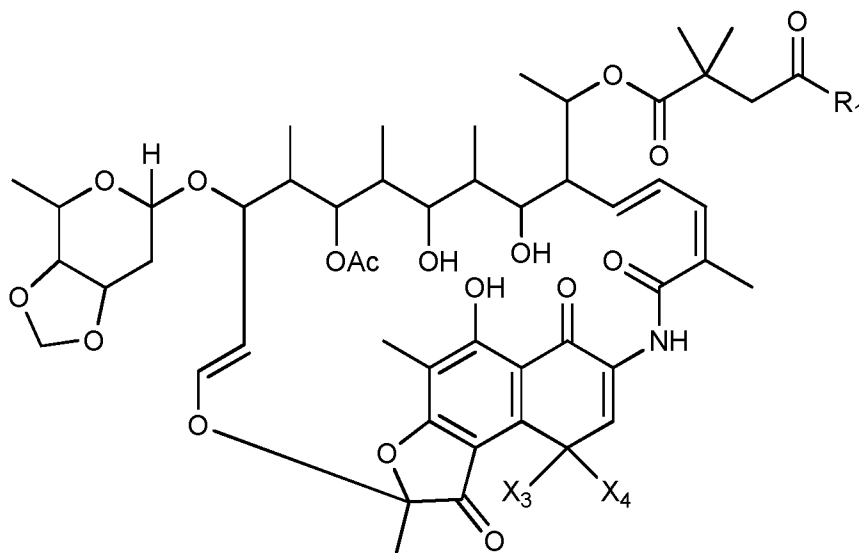
[0059] In a particular group of compounds having a structure according to formula (I), (II) or (III), R_2 is hydrogen, such that the compounds have a structure according to formula (Ia), (IIa) or (IIIa) shown below:



(Ia)



(IIa)



(IIIa)

wherein R₁, X₁, X₂, X₃ and X₄, and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0060] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (3) to (8);

R_a and R_b are as described in any of numbered paragraphs (10) to (12);

R_c is as described in any of numbered paragraphs (23) to (25); and

X₁, X₂, X₃ and X₄, and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0061] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (11) to (12);

R_c is as described in any of numbered paragraphs (24) to (25); and

X₁, X₂, X₃ and X₄, and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0062] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (11) to (12);

R_c is as described in any of numbered paragraphs (24) to (25);

X_1 is as described in numbered paragraph (39); and

X_2 , X_3 and X_4 , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0063] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R_1 is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (11) to (12);

R_c is as described in any of numbered paragraphs (24) to (25);

X_1 is as described in numbered paragraph (39);

X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R_3 is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60); and

X_3 and X_4 , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0064] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R_1 is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (11) to (12);

R_c is as described in any of numbered paragraphs (24) to (25);

X_1 is as described in numbered paragraph (39);

X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R_3 is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (81) to (84).

[0065] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (6) to (8);

R_a and R_b are as described in any of numbered paragraphs (11) to (12);

R_c is as described in any of numbered paragraphs (24) to (25);

X₁ is as described in numbered paragraph (39);

X₂ is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (43);

R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in numbered paragraph (53);

R_j and R_k are as described in any of numbered paragraphs (56) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[0066] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (7) to (8);

R_a and R_b are as described in numbered paragraph (12);

R_c is as described in numbered paragraph (25);

X₁ is as described in numbered paragraph (39);

X₂ is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (43);

R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in numbered paragraph (53);

R_j and R_k are as described in any of numbered paragraphs (56) to (57);

R₁ is as described in any of numbered paragraphs (59) to (60);

X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[0067] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in numbered paragraphs (8);

R_c is as described in numbered paragraph (25);

X₁ is as described in numbered paragraph (39);

X₂ is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (43);

R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in numbered paragraph (53);

R_j and R_k are as described in any of numbered paragraphs (56) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[0068] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (3) to (8);

R_a and R_b are as described in any of numbered paragraphs (13) to (22);

R_c is as described in any of numbered paragraphs (23) to (25); and

X₁, X₂, X₃ and X₄, and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0069] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (15) to (22);

R_c is as described in any of numbered paragraphs (24) to (25); and

X_1 , X_2 , X_3 and X_4 , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0070] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R_1 is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (15) to (22);

R_c is as described in any of numbered paragraphs (24) to (25);

X_1 is as described in numbered paragraph (39); and

X_2 , X_3 and X_4 , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0071] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R_1 is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (17) to (22);

R_c is as described in any of numbered paragraphs (24) to (25);

X_1 is as described in numbered paragraph (39);

X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R_3 is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60); and

X_3 and X_4 , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0072] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R_1 is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (19) to (22);

R_c is as described in any of numbered paragraphs (24) to (25);

X_1 is as described in numbered paragraph (39);

X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (46) to (50);
R_h and R_i are as described in any of numbered paragraphs (52) to (53);
R_j and R_k are as described in any of numbered paragraphs (55) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (82) to (84).

[0073] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (6) to (8);
R_a and R_b are as described in any of numbered paragraphs (19) to (22);
R_c is as described in any of numbered paragraphs (24) to (25);
X₁ is as described in numbered paragraph (39);
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (43);
R₃ is as described in any of numbered paragraphs (48) to (50);
R_h and R_i are as described in numbered paragraph (53);
R_j and R_k are as described in any of numbered paragraphs (56) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (83) to (84).

[0074] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R₁ is as described in any of numbered paragraphs (7) to (8);
R_a and R_b are as described in numbered paragraph (21) or (22);
R_c is as described in numbered paragraph (25);

X_1 is as described in numbered paragraph (39);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (43);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in numbered paragraph (53);
 R_j and R_k are as described in any of numbered paragraphs (56) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[0075] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R_1 , and any of its associated substituents, has any of the definitions appearing hereinbefore;
 X_1 is as described in numbered paragraph (39);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (42) or (43);
 R_3 is as described in any of numbered paragraphs (46) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60); and
 X_3 and X_4 , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0076] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

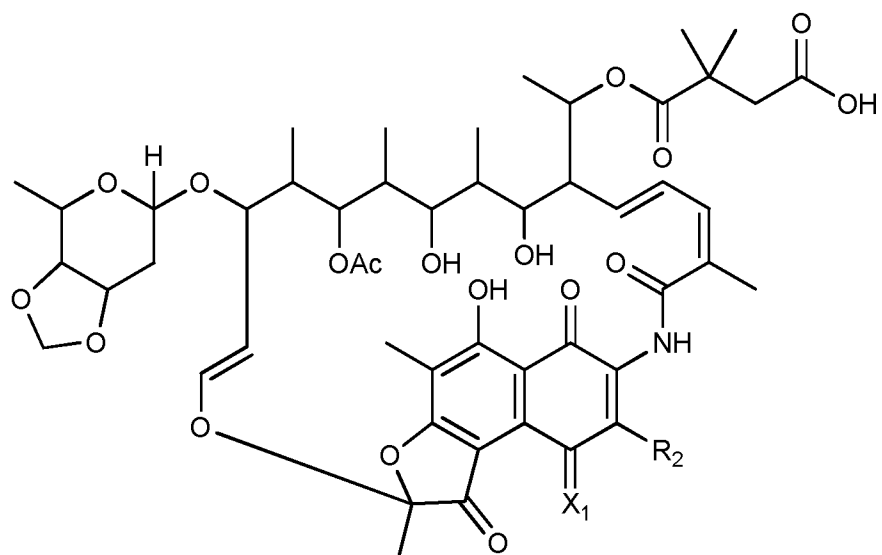
R_1 , and any of its associated substituents, has any of the definitions appearing hereinbefore;
 X_1 is as described in numbered paragraph (39);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (42) or (43);

R_3 is as described in any of numbered paragraphs (46) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (81) to (84).

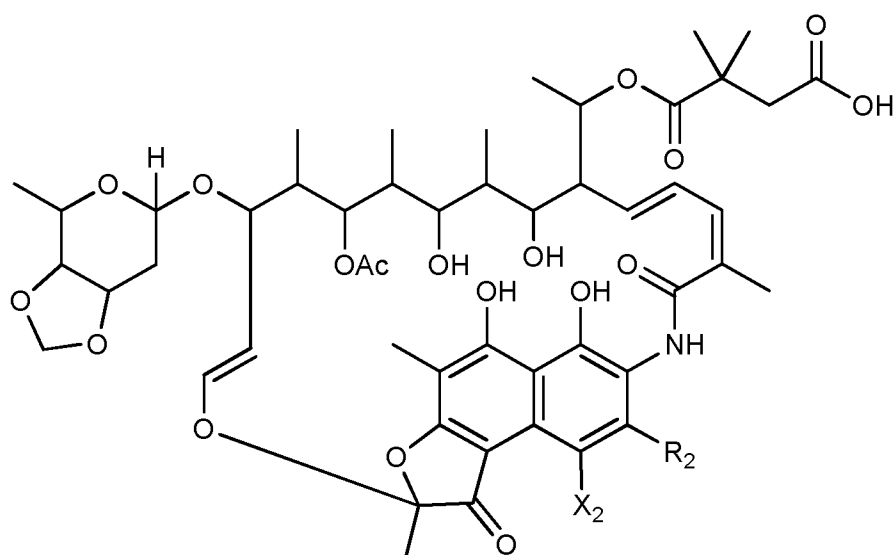
[0077] In an embodiment of the compounds of formula (Ia), (IIa) or (IIIa):

R_1 , and any of its associated substituents, has any of the definitions appearing hereinbefore;
 X_1 is as described in numbered paragraph (39);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (43);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in numbered paragraph (53);
 R_j and R_k are as described in any of numbered paragraphs (56) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

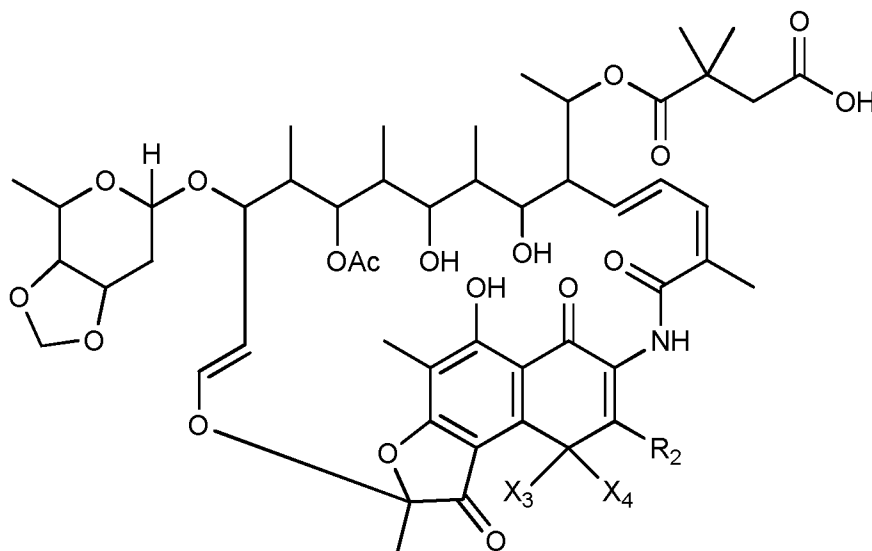
[0078] In a particular group of compounds having a structure according to formula (I), (II) or (III), R_1 is hydroxy, such that the compounds have a structure according to formula (Ib), (IIb) or (IIIb) shown below:



(Ib)



(IIb)



(IIIb)

wherein R₂, X₁, X₂, X₃ and X₄, and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0079] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R₂ is as described in any of numbered paragraphs (28) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (36) to (38);

X₁ is as described in numbered paragraph (39); and

X₂, X₃ and X₄, and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0080] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R₂ is as described in any of numbered paragraphs (30) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38);

X₁ is as described in numbered paragraph (39);

X₂ is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R₃ is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60); and

X_3 and X_4 , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0081] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R_2 is as described in numbered paragraph (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38);

X_1 is as described in numbered paragraph (39);

X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R_3 is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);

X_5 is as described in numbered paragraph (77);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R_5 is as described in any of numbered paragraphs (81) to (84).

[0082] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R_2 is as described in numbered paragraph (32);

R_d is as described in numbered paragraph (34);

R_e is as described in numbered paragraph (38);

X_1 is as described in numbered paragraph (39);

X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (43);

R_3 is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in numbered paragraph (53);
 R_j and R_k are as described in any of numbered paragraphs (56) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[0083] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R_2 is as described in numbered paragraph (32);
 R_d is as described in numbered paragraph (34);
 R_e is as described in numbered paragraph (38);
 X_1 is as described in numbered paragraph (39);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (43);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in numbered paragraph (53);
 R_j and R_k are as described in any of numbered paragraphs (56) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[0084] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R_2 is as described in any of numbered paragraphs (30) to (32);
 R_d is as described in any of numbered paragraphs (33) to (34);
 R_e is as described in any of numbered paragraphs (37) to (38);

X_1 is as described in numbered paragraph (39);

X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R_3 is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

or R_2 and X_1 or R_2 and X_2 are as described in any of numbered paragraphs (65) to (67), wherein R_4 is as described in any of numbered paragraphs (70) to (72);
and

X_3 and X_4 , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0085] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R_2 is as described in numbered paragraph (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38);

X_1 is as described in numbered paragraph (39);

X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R_3 is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

or R_2 and X_1 or R_2 and X_2 are as described in any of numbered paragraphs (65) to (67), wherein R_4 is as described in any of numbered paragraphs (70) to (72);

X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);

X_5 is as described in numbered paragraph (77);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (81) to (84).

[0086] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R₂ is as described in numbered paragraph (32);

R_d is as described in numbered paragraph (34);

R_e is as described in numbered paragraph (38);

X₁ is as described in numbered paragraph (39);

X₂ is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (43);

R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in numbered paragraph (53);

R_j and R_k are as described in any of numbered paragraphs (56) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

or R₂ and X₁ or R₂ and X₂ are as described in any of numbered paragraphs (66) to (67), wherein R₄ is as described in any of numbered paragraphs (71) to (72);

X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);

X₅ is as described in numbered paragraph (77);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[0087] In an embodiment of the compounds of formula (Ib), (IIb) or (IIIb):

R₂ is as described in numbered paragraph (32);

R_d is as described in numbered paragraph (34);

R_e is as described in numbered paragraph (38);

X₁ is as described in numbered paragraph (39);

X₂ is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (43);

R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in numbered paragraph (53);

R_j and R_k are as described in any of numbered paragraphs (56) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

or R_2 and X_1 or R_2 and X_2 are as described in any of numbered paragraphs (66) to (67), wherein R_4 is as described in any of numbered paragraphs (71) to (72);

X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);

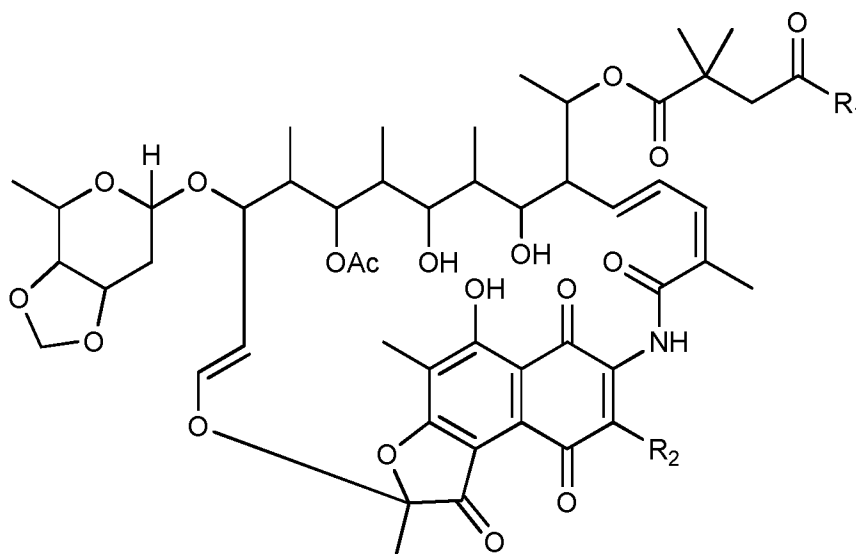
X_5 is as described in numbered paragraph (77);

m is as described in numbered paragraph (78);

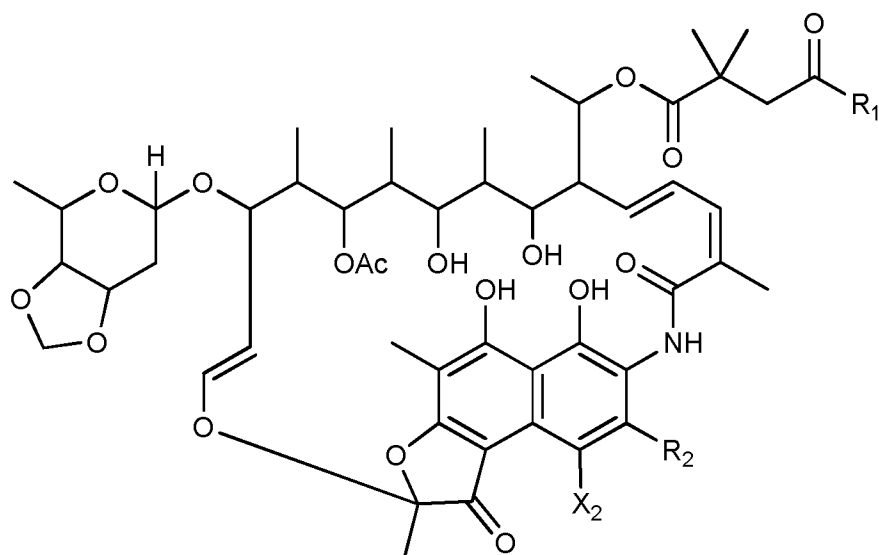
o is as described in numbered paragraph (79); and

R_5 is as described in any of numbered paragraphs (83) to (84).

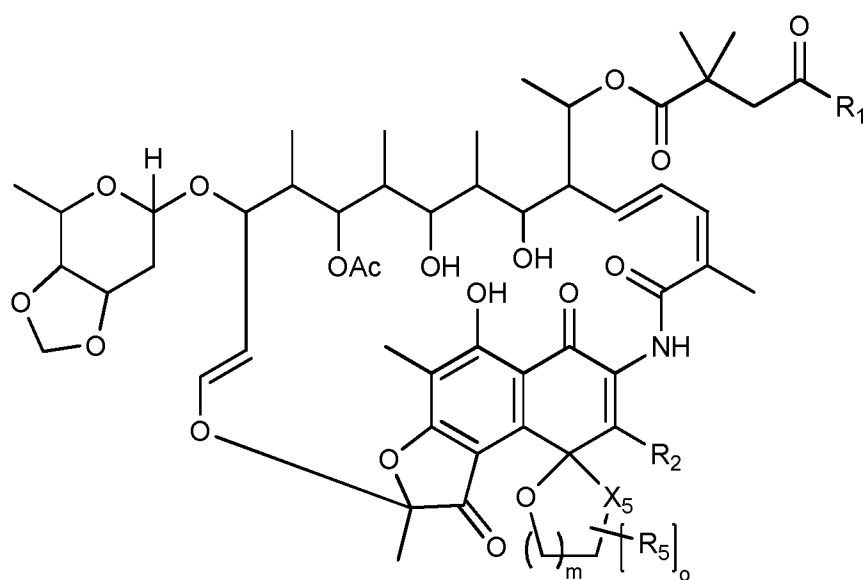
[0088] In a particular group of compounds having a structure according to formula (I), (II) or (III), X_1 is O and X_3 and X_4 are as defined in numbered paragraph (75), such that the compounds have a structure according to formula (Ic), (IIc) or (IIIc) shown below:



(Ic)



(IIc)



(IIIc)

wherein R_1 , R_2 , R_5 , X_2 , X_5 , m and o , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0089] In an embodiment of the compounds of formula (Ic), (IIc) or (IIIc):

R_1 , and any of its associated substituents, has any of the definitions appearing hereinbefore;

R_2 is as described in any of numbered paragraphs (30) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);
 R_e is as described in any of numbered paragraphs (37) to (38);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (42) or (43);
 R_3 is as described in any of numbered paragraphs (46) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (81) to (84).

[0090] In an embodiment of the compounds of formula (Ic), (IIc) or (IIIc):

R_1 , and any of their associated substituents, has any of the definitions appearing hereinbefore;
 R_2 is as described in any of numbered paragraphs (31) to (32);
 R_d is as described in any of numbered paragraphs (33) to (34);
 R_e is as described in any of numbered paragraphs (37) to (38);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (42) or (43);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[0091] In an embodiment of the compounds of formula (Ic), (IIc) or (IIIc):

R₁ is as described in any of numbered paragraphs (5) to (8);
R_a and R_b are as described in any of numbered paragraphs (11) to (12);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in any of numbered paragraphs (31) to (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38);
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (48) to (50);
R_h and R_i are as described in any of numbered paragraphs (52) to (53);
R_j and R_k are as described in any of numbered paragraphs (55) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (83) to (84).

[0092] In an embodiment of the compounds of formula (Ic), (IIc) or (IIIc):

R₁ is as described in any of numbered paragraphs (6) to (8);
R_a and R_b are as described in any of numbered paragraphs (11) to (12);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is hydrogen;
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (48) to (50);
R_h and R_i are as described in any of numbered paragraphs (52) to (53);
R_j and R_k are as described in any of numbered paragraphs (55) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);

X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (83) to (84).

[0093] In an embodiment of the compounds of formula (Ic), (IIc) or (IIIc):

R₁ is as described in numbered paragraph (8);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is hydrogen;
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (49) to (50);
R_h and R_i are as described in numbered paragraphs (53);
R_j and R_k are as described in any of numbered paragraphs (56) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (83) to (84).

[0094] In an embodiment of the compounds of formula (Ic), (IIc) or (IIIc):

R₁ is as described in any of numbered paragraphs (5) to (8);
R_a and R_b are as described in any of numbered paragraphs (13) to (22);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in any of numbered paragraphs (31) to (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38);
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[0095] In an embodiment of the compounds of formula (Ic), (IIc) or (IIIc):

R_1 is as described in any of numbered paragraphs (6) to (8);
 R_a and R_b are as described in any of numbered paragraphs (17) to (22);
 R_c is as described in any of numbered paragraphs (24) to (25);
 R_2 is hydrogen;
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (42) or (43);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[0096] In an embodiment of the compounds of formula (Ic), (IIc) or (IIIc):

R_1 is as described in any of numbered paragraphs (6) to (8);
 R_a and R_b are as described in any of numbered paragraphs (21) to (22);
 R_c is as described in any of numbered paragraphs (24) to (25);
 R_2 is hydrogen;
 X_2 is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_i is as described in any of numbered paragraphs (59) to (60);

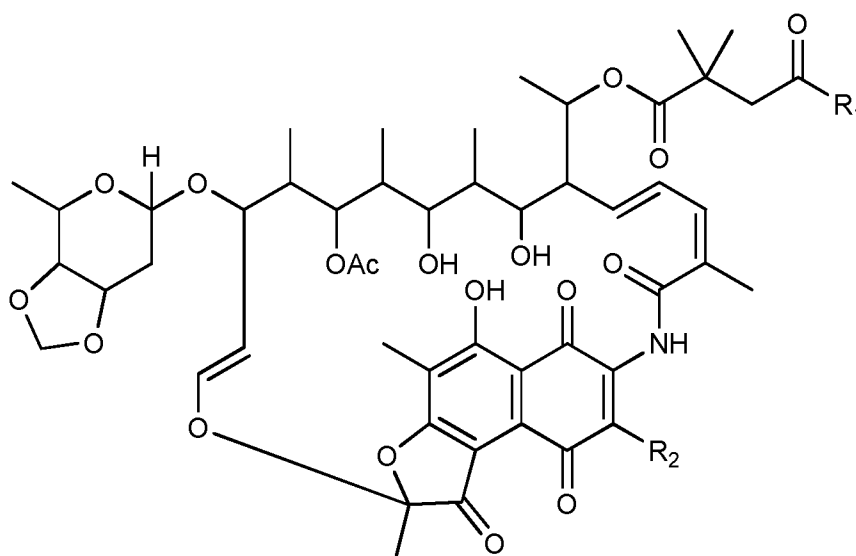
X₅ is as described in numbered paragraph (77);

m is as described in numbered paragraph (78);

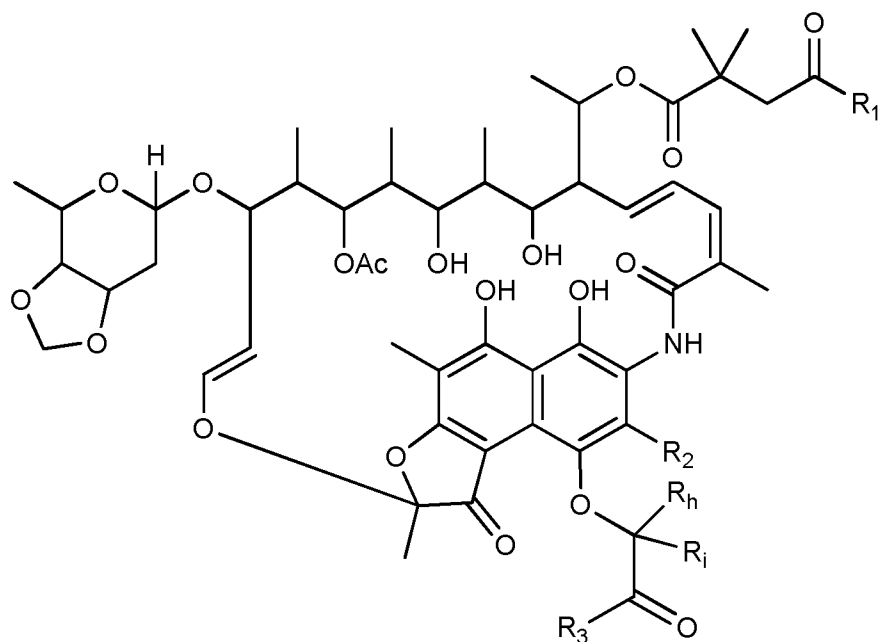
o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (83) to (84).

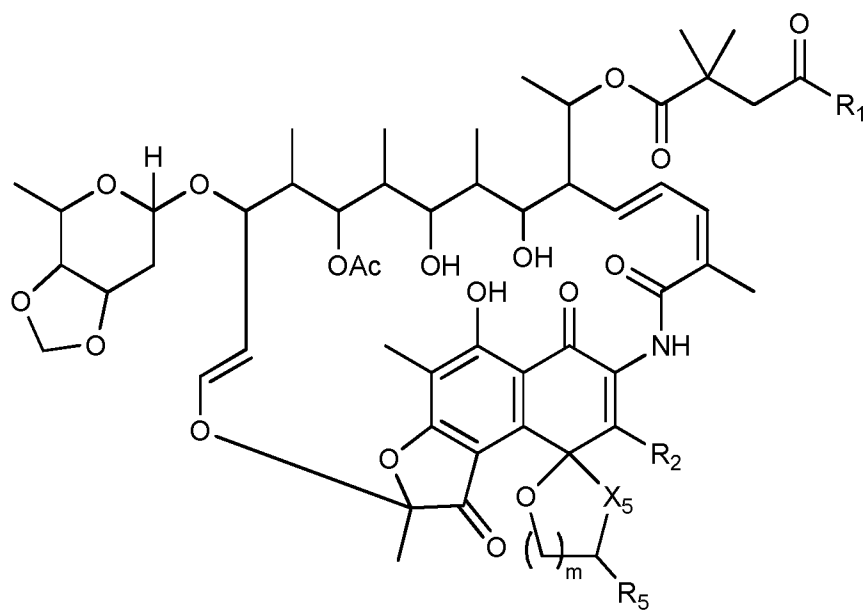
[0097] In a particular group of compounds having a structure according to formula (I), (II) or (III), X_1 is O, X_2 is as defined in numbered paragraph (41), n is 1, and X_3 and X_4 are as defined in numbered paragraph (76), such that the compounds have a structure according to formula (Id), (IIId) or (IIId) shown below:



(Id)



(IIId)



(IIIId)

wherein R_1 , R_2 , R_3 , R_5 , R_h , R_i , X_5 and m , and any of their associated substituents, have any of the definitions appearing hereinbefore.

[0098] In an embodiment of the compounds of formula (Id), (IIId) or (IIIId):

R₁, and any of its associated substituents, has any of the definitions appearing hereinbefore;

R₂ is as described in any of numbered paragraphs (30) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38);

R₃ is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X₅ is as described in numbered paragraph (77);

m is as described in numbered paragraph (78); and

R₅ is as described in any of numbered paragraphs (81) to (84).

[0099] In an embodiment of the compounds of formula (Id), (IId) or (IIId):

R₁, and any of its associated substituents, has any of the definitions appearing hereinbefore;

R₂ is as described in any of numbered paragraphs (31) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38);

R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X₅ is as described in numbered paragraph (77);

m is as described in numbered paragraph (78); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00100] In an embodiment of the compounds of formula (Id), (IId) or (IIId):

R₁ is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (11) to (12);

R_c is as described in any of numbered paragraphs (24) to (25);
 R_2 is as described in any of numbered paragraphs (31) to (32);
 R_d is as described in any of numbered paragraphs (33) to (34);
 R_e is as described in any of numbered paragraphs (37) to (38);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[00101]

In an embodiment of the compounds of formula (Id), (IId) or (IIId):
 R_1 is as described in any of numbered paragraphs (6) to (8);
 R_a and R_b are as described in any of numbered paragraphs (11) to (12);
 R_c is as described in any of numbered paragraphs (24) to (25);
 R_2 is hydrogen;
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[00102]

In an embodiment of the compounds of formula (Id), (IId) or (IIId):
 R_1 is as described in numbered paragraph (8);
 R_c is as described in any of numbered paragraphs (24) to (25);
 R_2 is hydrogen;
 R_3 is as described in any of numbered paragraphs (49) to (50);

R_h and R_i are as described in numbered paragraphs (53);
 R_j and R_k are as described in any of numbered paragraphs (56) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[00103]

In an embodiment of the compounds of formula (Id), (IId) or (IIId):
 R_1 is as described in any of numbered paragraphs (5) to (8);
 R_a and R_b are as described in any of numbered paragraphs (13) to (22);
 R_c is as described in any of numbered paragraphs (24) to (25);
 R_2 is as described in any of numbered paragraphs (31) to (32);
 R_d is as described in any of numbered paragraphs (33) to (34);
 R_e is as described in any of numbered paragraphs (37) to (38);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[00104]

In an embodiment of the compounds of formula (Id), (IId) or (IIId):
 R_1 is as described in any of numbered paragraphs (6) to (8);
 R_a and R_b are as described in any of numbered paragraphs (17) to (22);
 R_c is as described in any of numbered paragraphs (24) to (25);
 R_2 is hydrogen;
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X₅ is as described in numbered paragraph (77);

m is as described in numbered paragraph (78); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00105] In an embodiment of the compounds of formula (Id), (IId) or (IIId):

R₁ is as described in numbered paragraph (7) or (8);

R_a and R_b are as described in any of numbered paragraphs (21) to (22);

R_c is as described in any of numbered paragraphs (24) to (25);

R₂ is hydrogen;

R₃ is as described in any of numbered paragraphs (49) to (50);

R_h and R_i are as described in numbered paragraphs (53);

R_j and R_k are as described in any of numbered paragraphs (56) to (57);

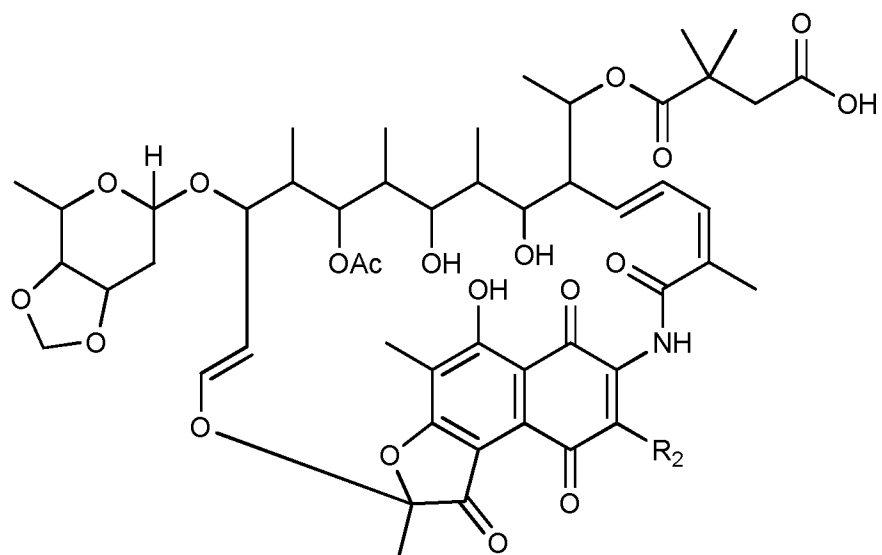
R_l is as described in any of numbered paragraphs (59) to (60);

X₅ is as described in numbered paragraph (77);

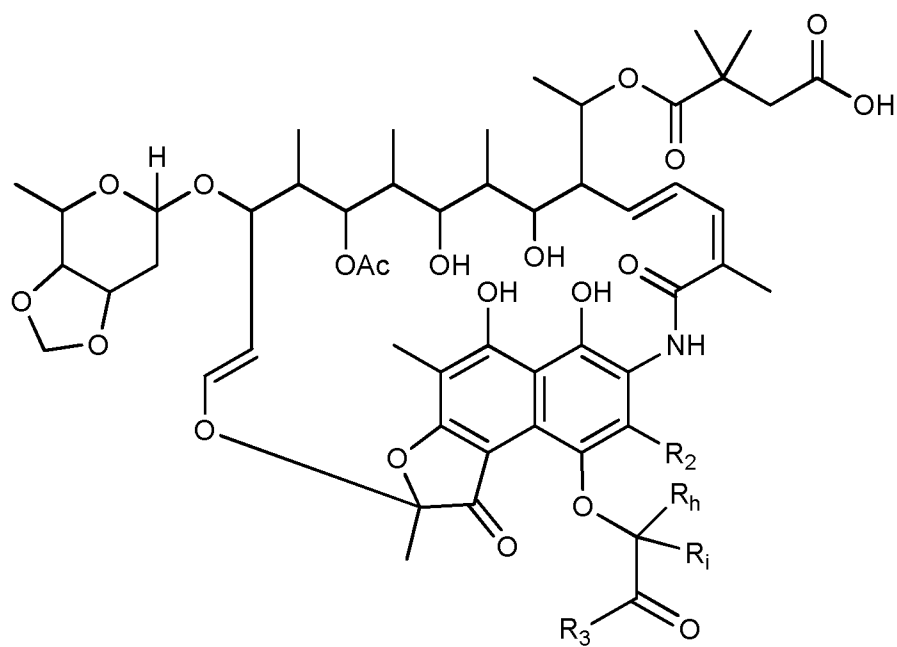
m is as described in numbered paragraph (78); and

R₅ is as described in any of numbered paragraphs (83) to (84).

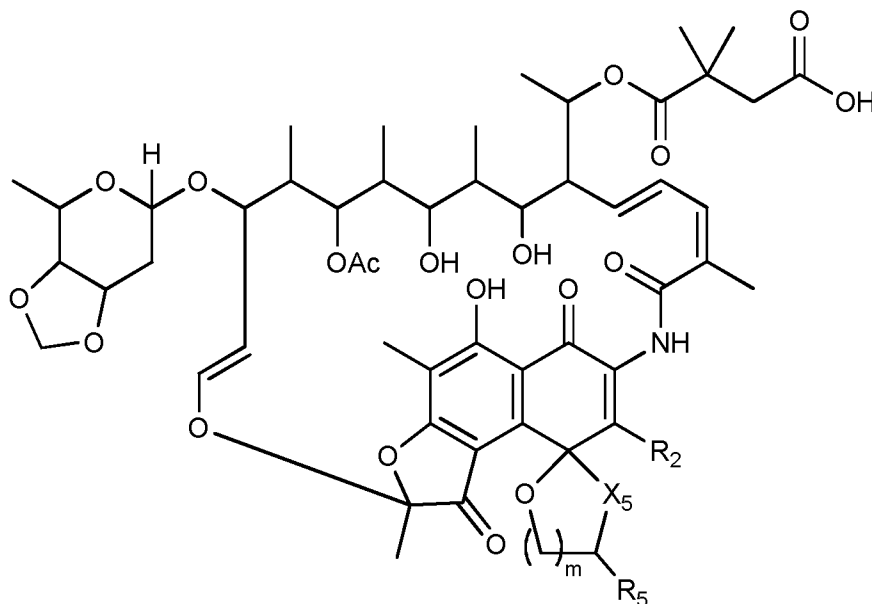
[00106] In a particular group of compounds having a structure according to formula (I), (II) or (III), R₁ is hydroxy, X₁ is O, X₂ is as defined in numbered paragraph (41), n is 1, and X₃ and X₄ are as defined in numbered paragraph (76), such that the compounds have a structure according to formula (Ie), (Ile) or (IIle) shown below:



(Ie)



(Ile)



(IIIe)

wherein R₂, R₃, R₅, R_h, R_i, X₅ and m, and any of their associated substituents, have any of the definitions appearing hereinbefore.

[00107] In an embodiment of the compounds of formula (Ie), (IIe) or (IIIe):

R₂ is as described in any of numbered paragraphs (30) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38);

R₃ is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X₅ is as described in numbered paragraph (77);

m is as described in numbered paragraph (78); and

R₅ is as described in any of numbered paragraphs (81) to (84).

[00108] In an embodiment of the compounds of formula (Ie), (IIe) or (IIIe):

R₂ is as described in any of numbered paragraphs (31) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38);

R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[00109]

In an embodiment of the compounds of formula (Ie), (Ile) or (IIIe):
 R_2 is as described in any of numbered paragraphs (31) to (32);
 R_d is as described in any of numbered paragraphs (33) to (34);
 R_e is as described in any of numbered paragraphs (37) to (38);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[00110]

In an embodiment of the compounds of formula (Ie), (Ile) or (IIIe):
 R_2 is hydrogen;
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

[00111]

In an embodiment of the compounds of formula (Ie), (Ile) or (IIIe):

R_2 is hydrogen;

R_3 is as described in any of numbered paragraphs (49) to (50);

R_h and R_i are as described in numbered paragraphs (53);

R_j and R_k are as described in any of numbered paragraphs (56) to (57);

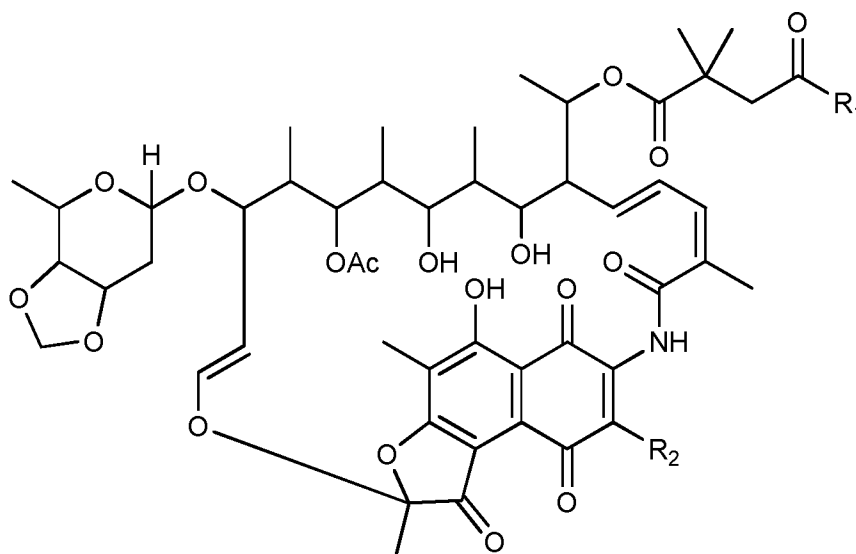
R_l is as described in any of numbered paragraphs (59) to (60);

X_5 is as described in numbered paragraph (77);

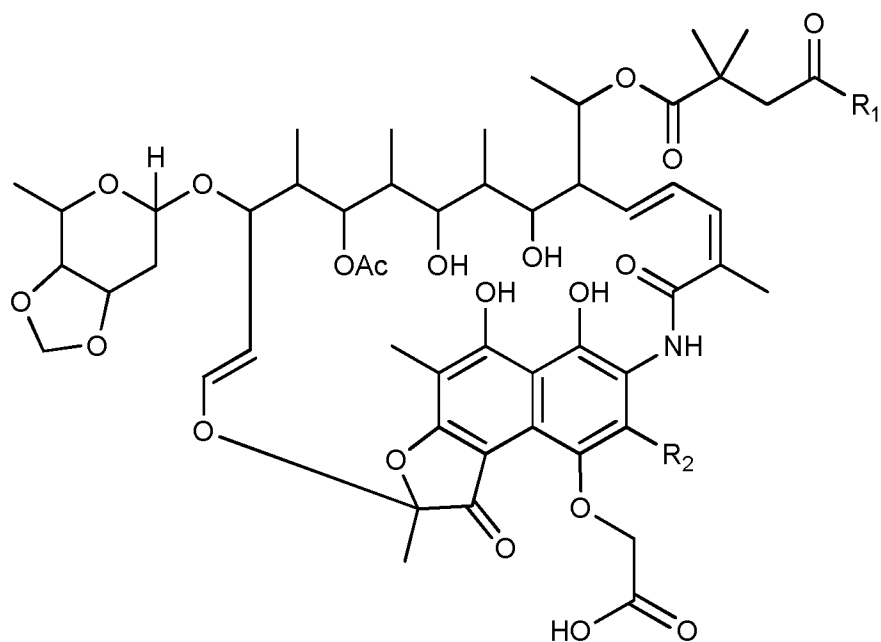
m is as described in numbered paragraph (78); and

R_5 is as described in any of numbered paragraphs (83) to (84).

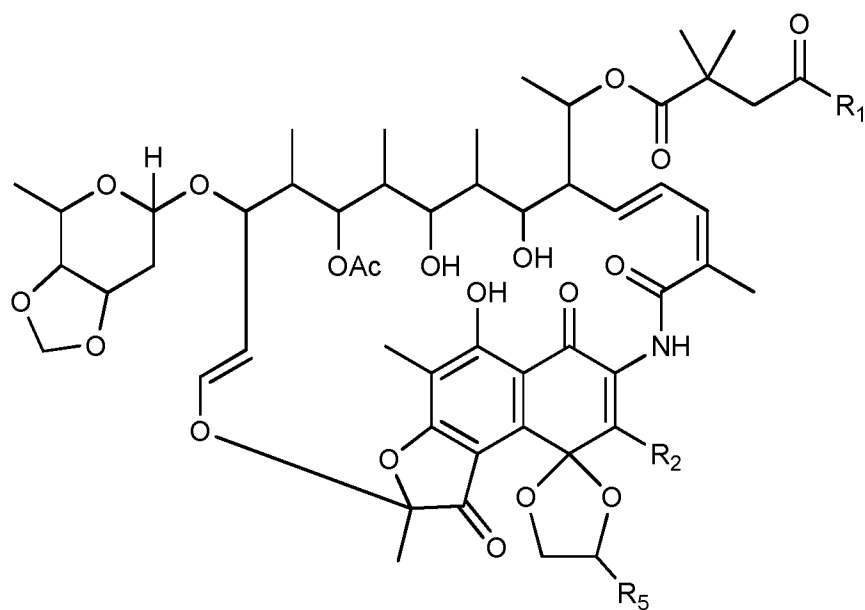
[00112] In a particular group of compounds having a structure according to formula (I), (II) or (III), X_1 is O, X_2 is as defined in numbered paragraph (41), n is 1, R_h and R_i are hydrogen, R_3 is hydroxy, X_3 and X_4 are as defined in numbered paragraph (76), X_5 is O, and m is 1, such that the compounds have a structure according to formula (If), (IIIf) or (IIIIf) shown below:



(If)



(11f)



(III f)

wherein R₁, R₂ and R₅, and any of their associated substituents, have any of the definitions appearing hereinbefore.

[00113] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁, and any of its associated substituents, has any of the definitions appearing hereinbefore;

R₂ is as described in any of numbered paragraphs (30) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38); and

R₅ is as described in any of numbered paragraphs (81) to (84).

[00114] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁, and any of its associated substituents, has any of the definitions appearing hereinbefore;

R₂ is as described in any of numbered paragraphs (31) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00115] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁ is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (11) to (12);

R_c is as described in any of numbered paragraphs (24) to (25);

R₂ is as described in any of numbered paragraphs (31) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00116] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁ is as described in any of numbered paragraphs (6) to (8);

R_a and R_b are as described in any of numbered paragraphs (11) to (12);

R_c is as described in any of numbered paragraphs (24) to (25);

R₂ is hydrogen; and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00117] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁ is as described in numbered paragraph (8);

R_c is as described in any of numbered paragraphs (24) to (25);

R₂ is hydrogen; and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00118] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁ is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (13) to (22);

R_c is as described in any of numbered paragraphs (24) to (25);

R₂ is as described in any of numbered paragraphs (31) to (32);

R_d is as described in any of numbered paragraphs (33) to (34);

R_e is as described in any of numbered paragraphs (37) to (38); and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00119] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁ is as described in any of numbered paragraphs (6) to (8);

R_a and R_b are as described in any of numbered paragraphs (17) to (22);

R_c is as described in any of numbered paragraphs (24) to (25);

R₂ is hydrogen; and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00120] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁ is as described in numbered paragraph (7) or (8);

R_a and R_b are as described in any of numbered paragraphs (19) to (22);

R_c is as described in any of numbered paragraphs (24) to (25);

R₂ is hydrogen; and

R₅ is as described in any of numbered paragraphs (83) to (84).

[00121] In an embodiment of the compounds of formula (If), (IIIf) or (IIIIf):

R₁ is as described in numbered paragraph (7) or (8);

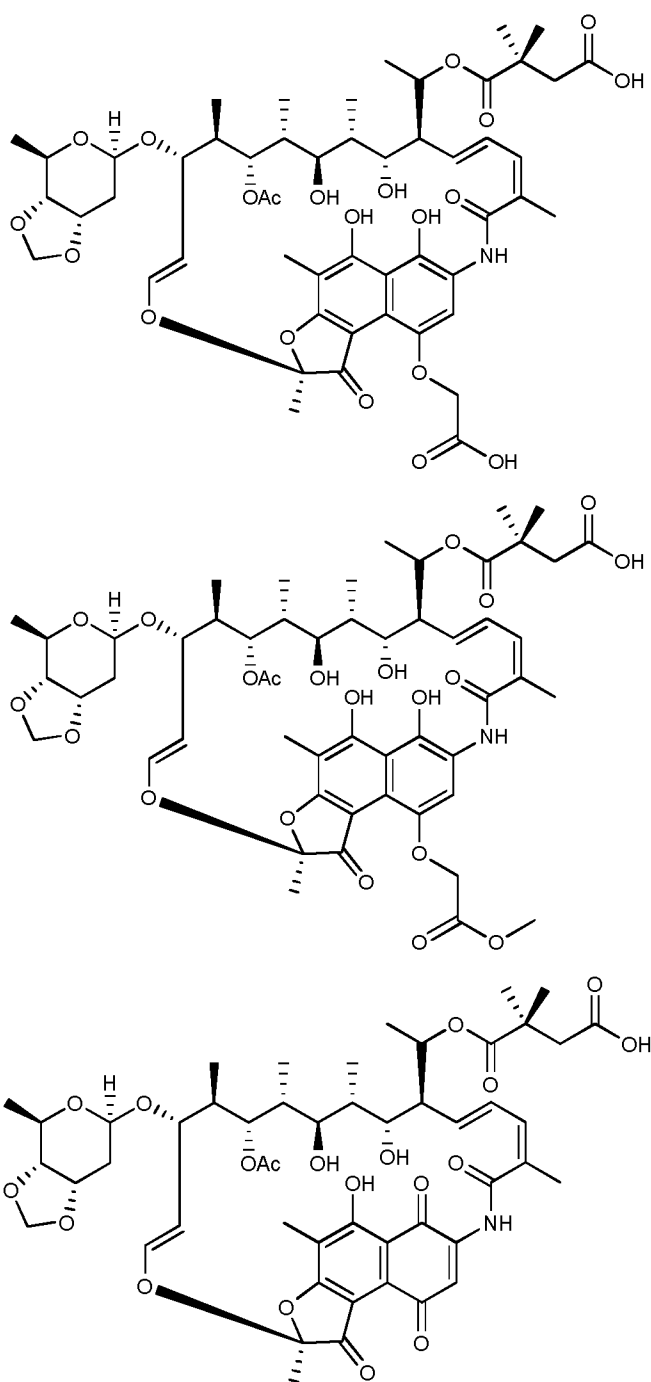
R_a and R_b are as described in any of numbered paragraphs (21) to (22);

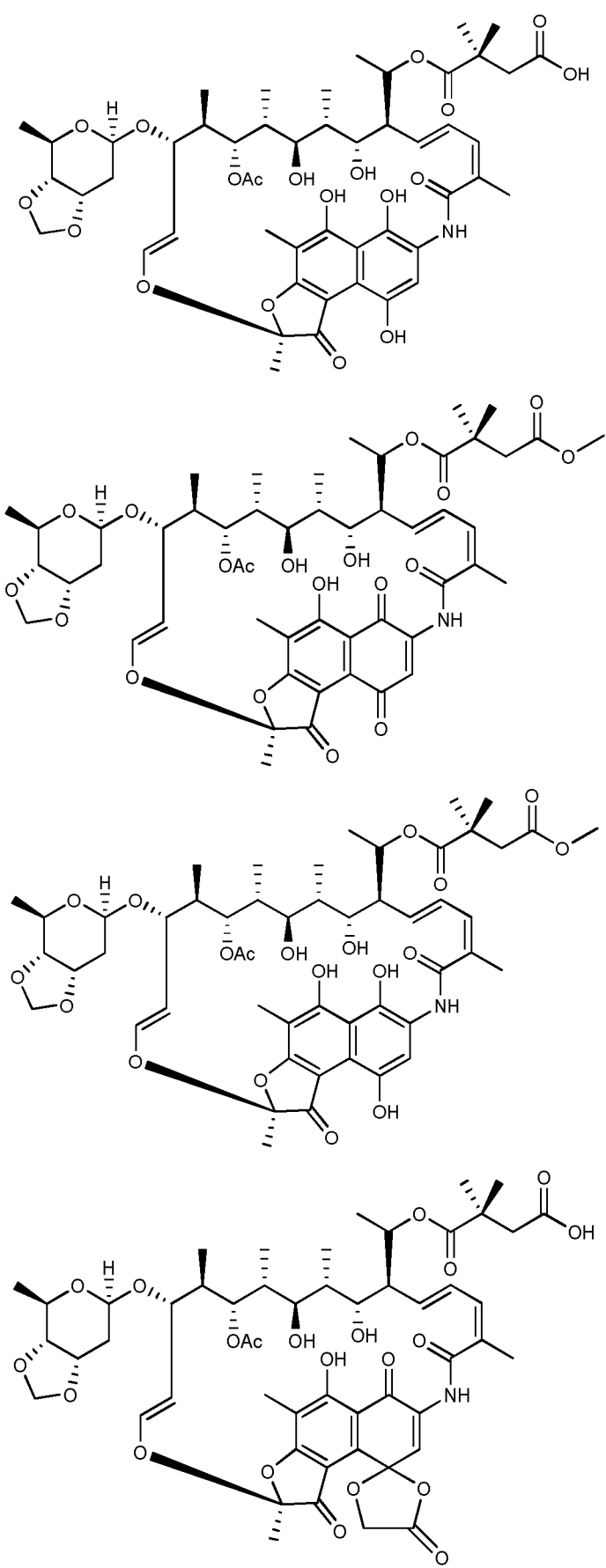
R_c is as described in any of numbered paragraphs (24) to (25);

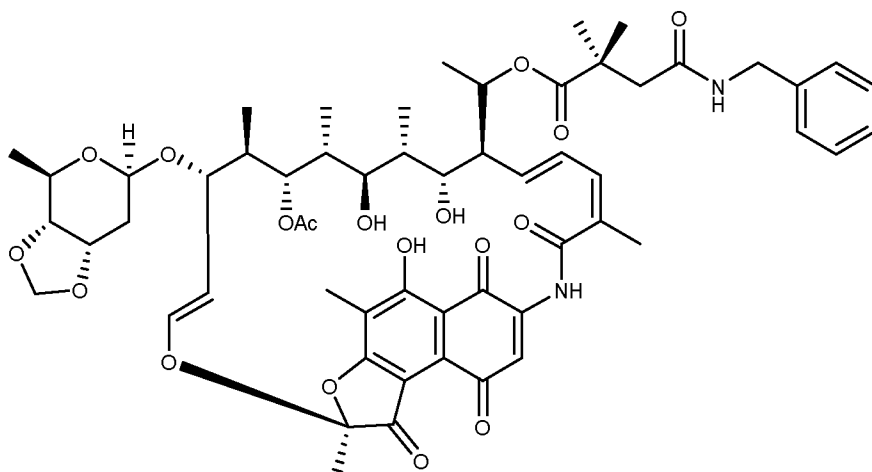
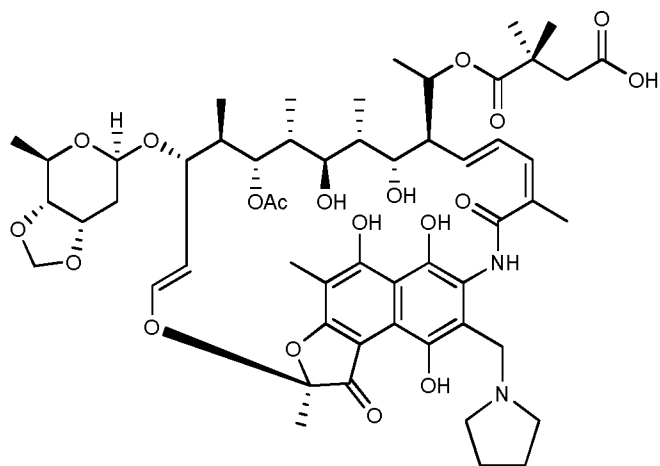
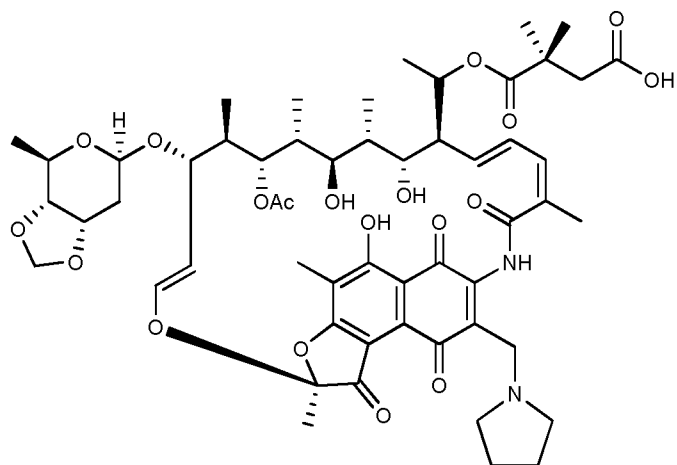
R₂ is hydrogen; and

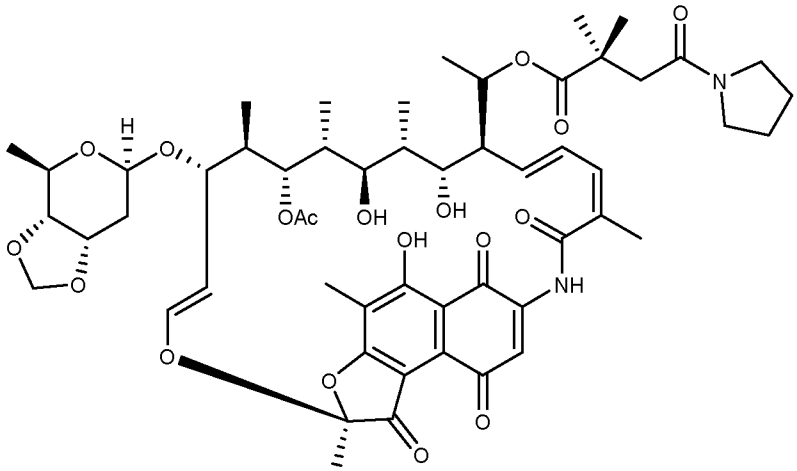
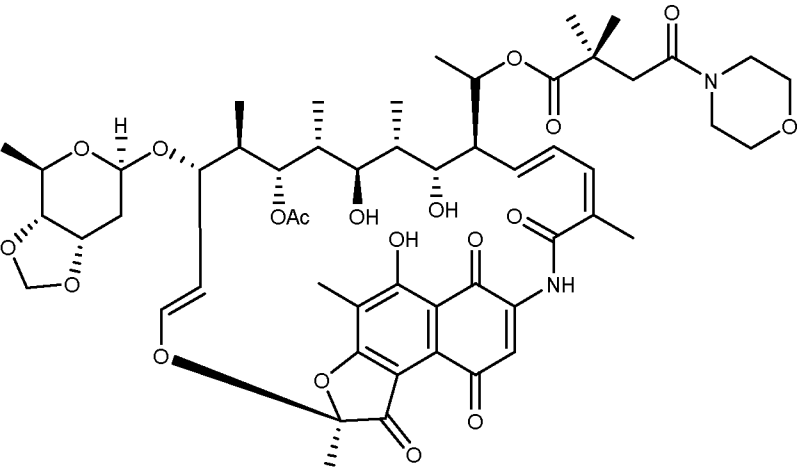
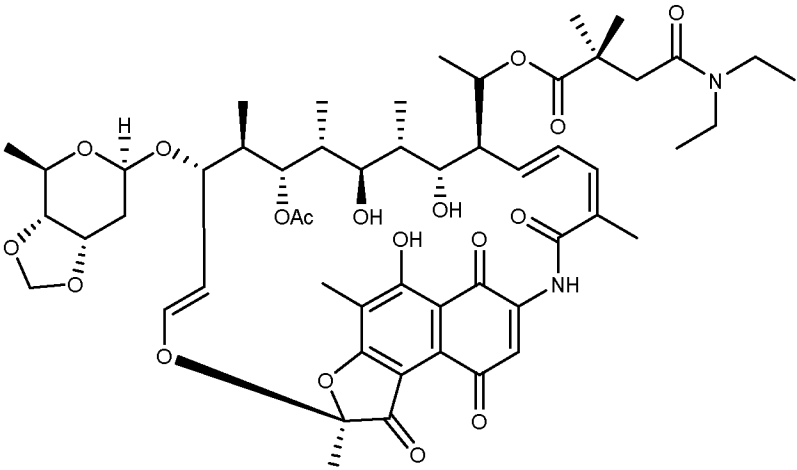
R₅ is as described in any of numbered paragraphs (83) to (84).

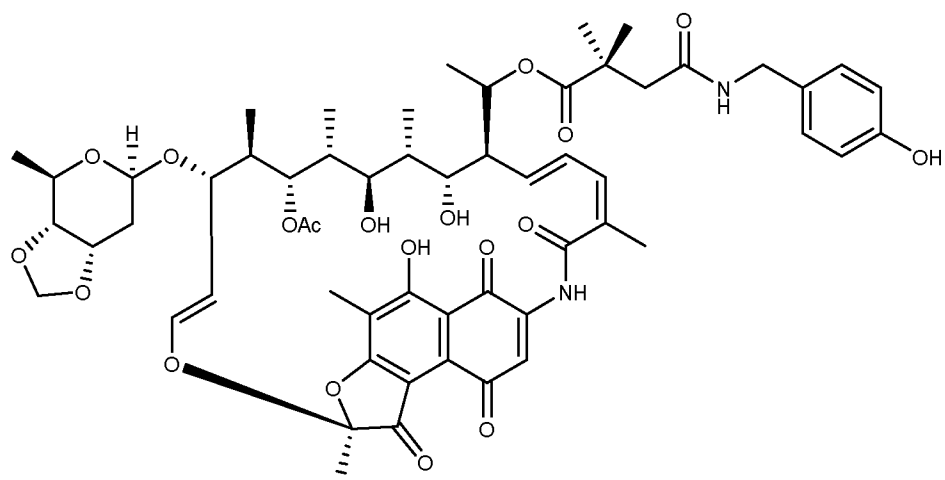
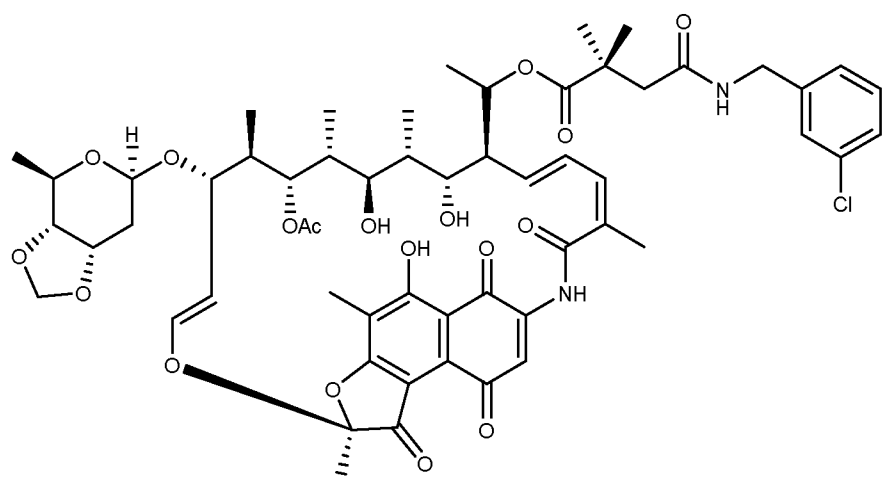
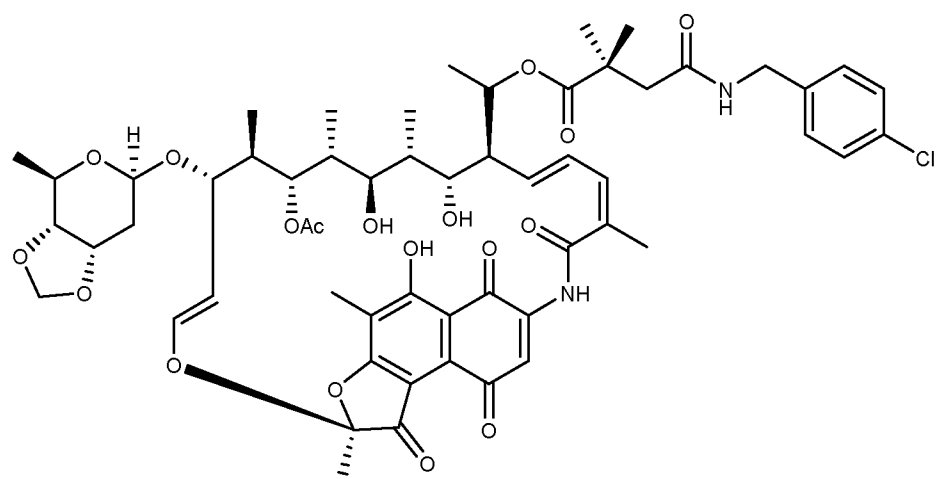
[00122] In a particular embodiment, the compound having a structure according to formula (I), (II) or (III) has any of the following structures:

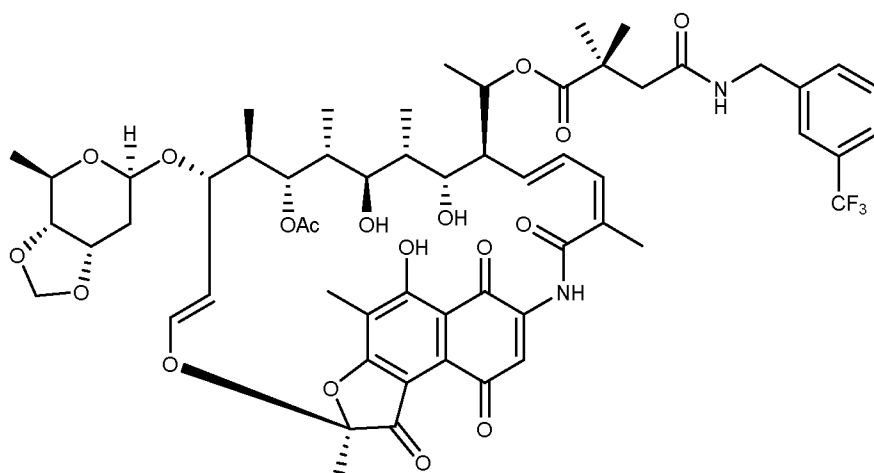
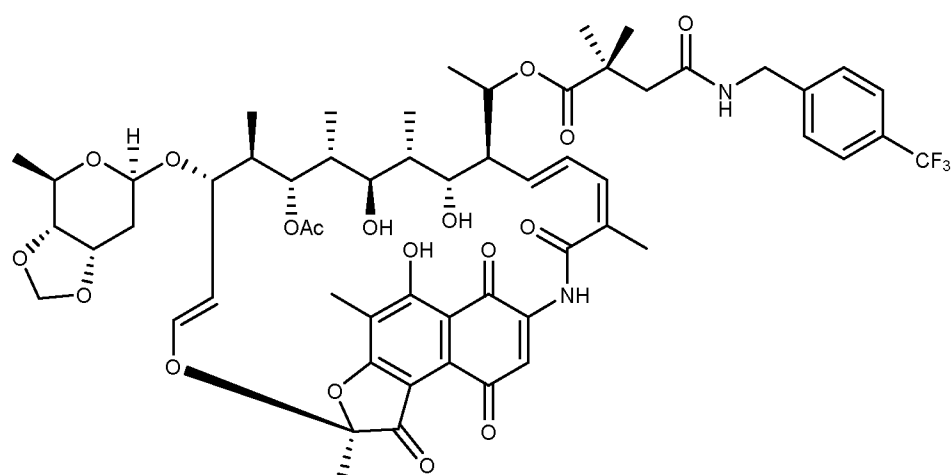
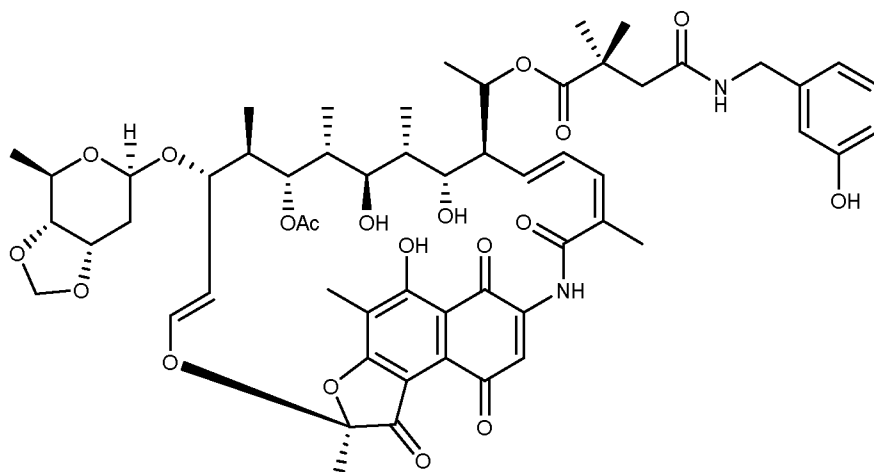


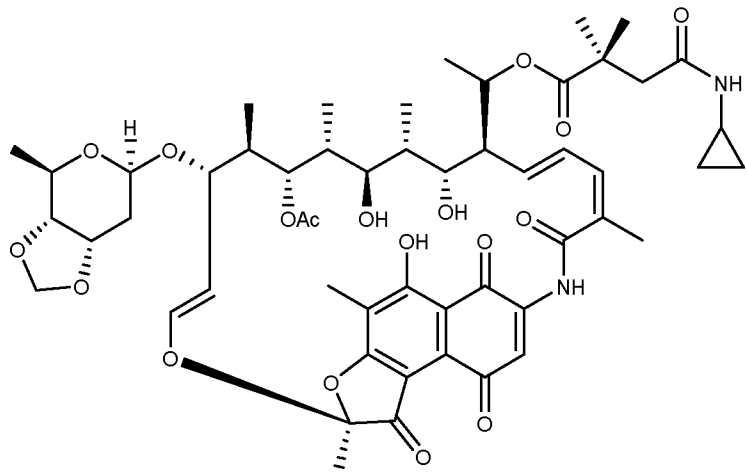
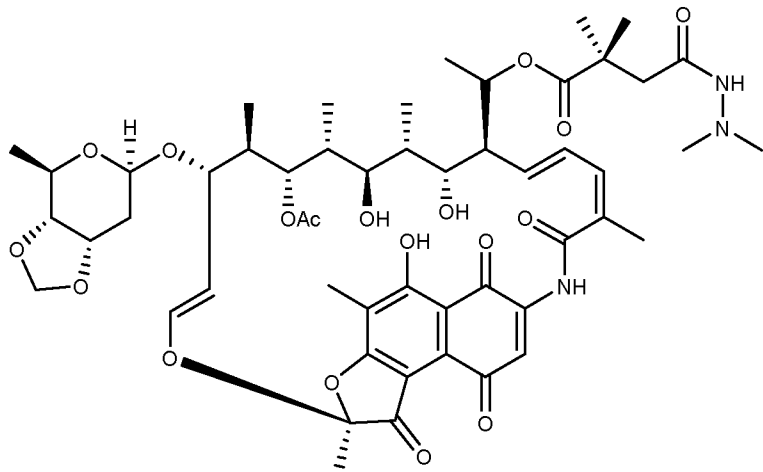
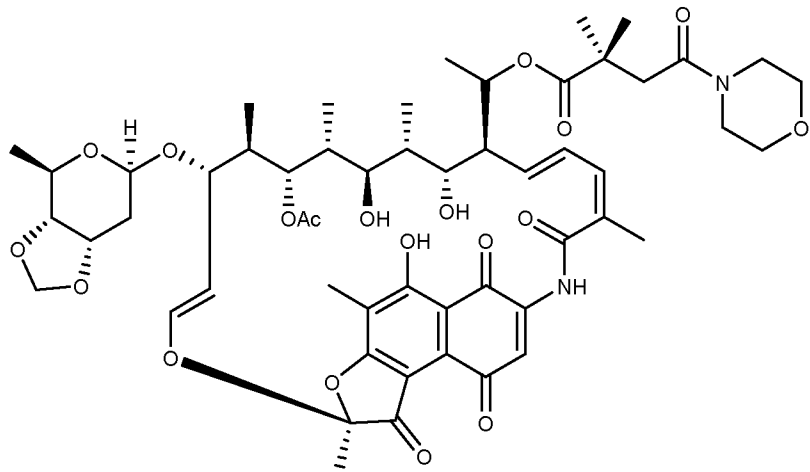


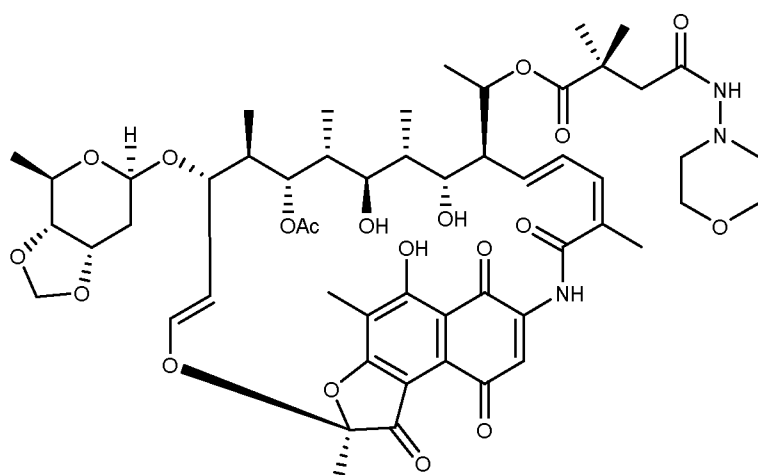
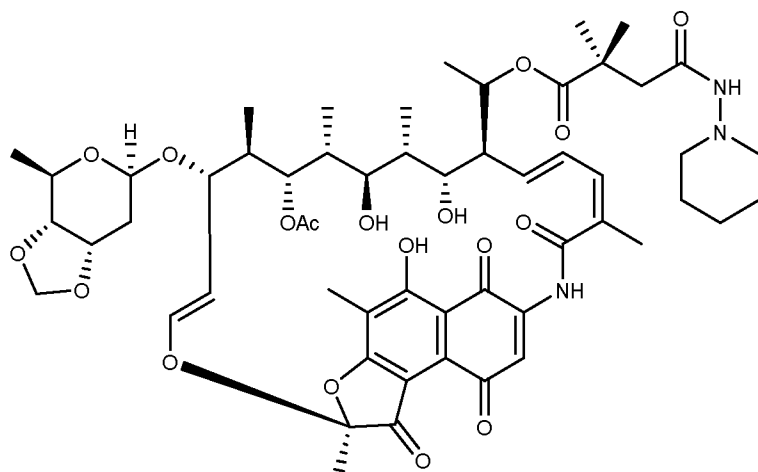




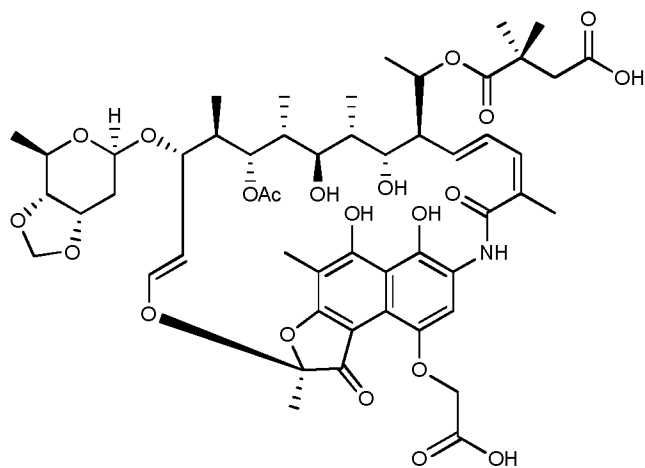


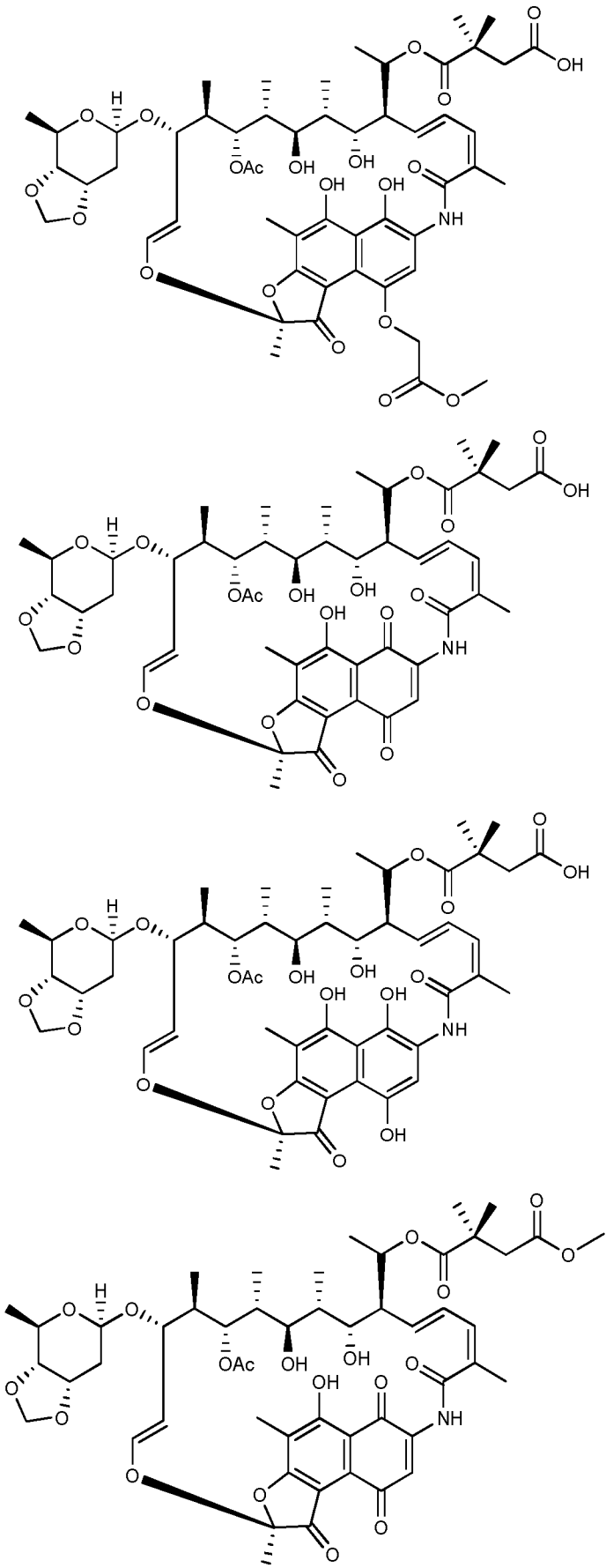


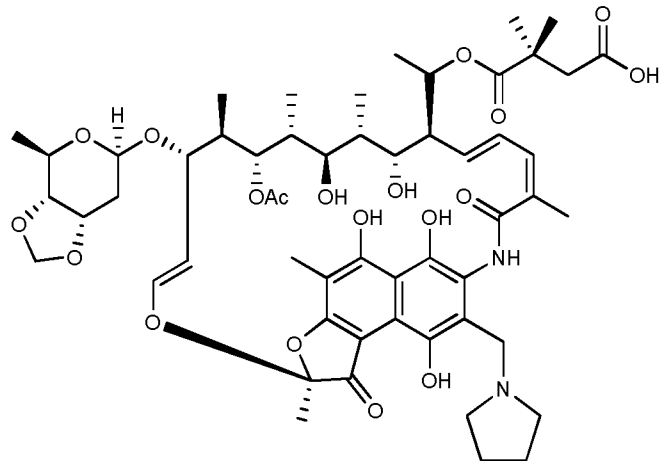
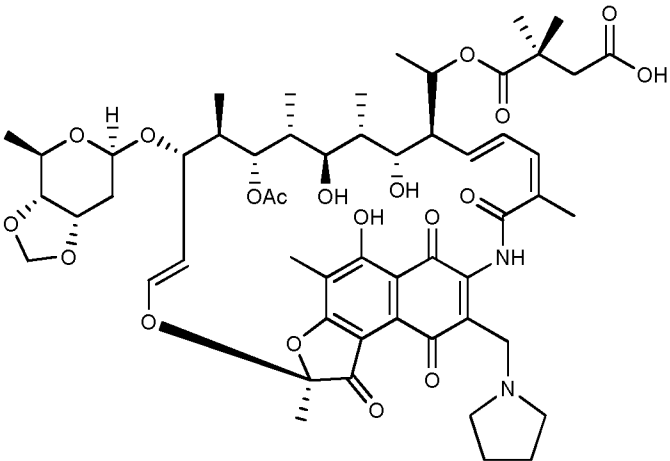
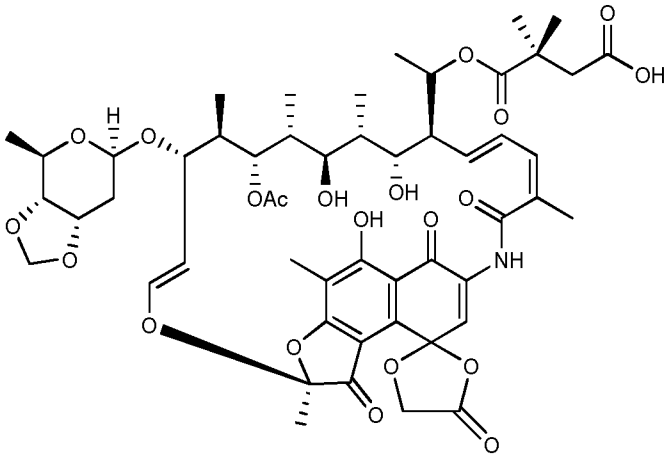
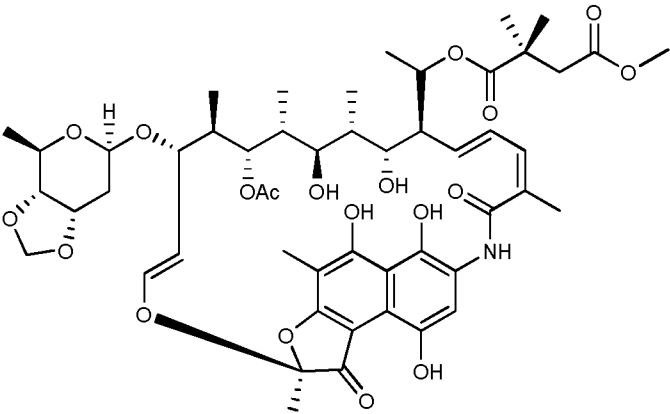




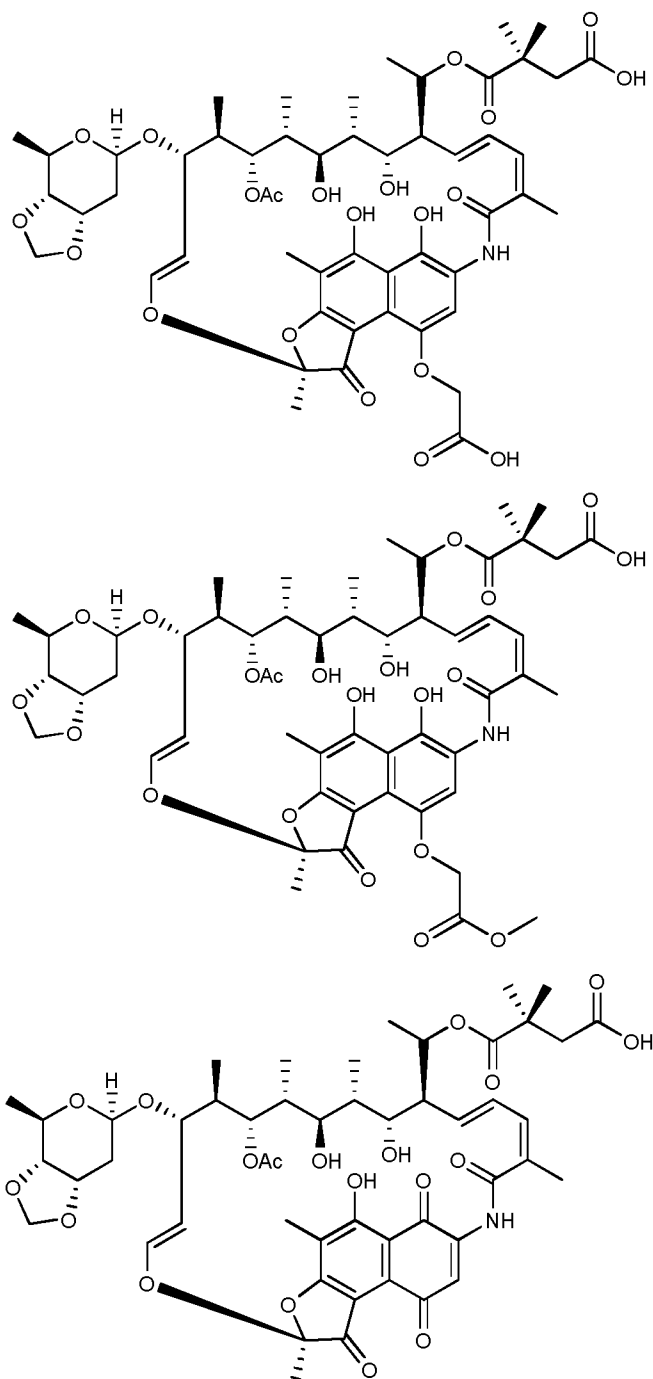
[00123] In a particular embodiment, the compound having a structure according to formula (I), (II) or (III) has any of the following structures:

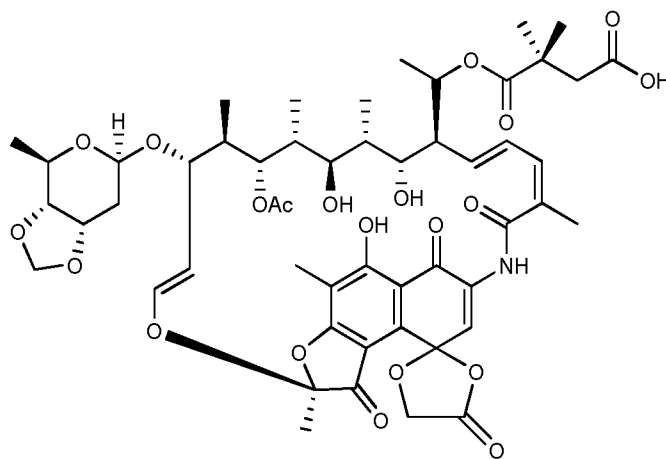
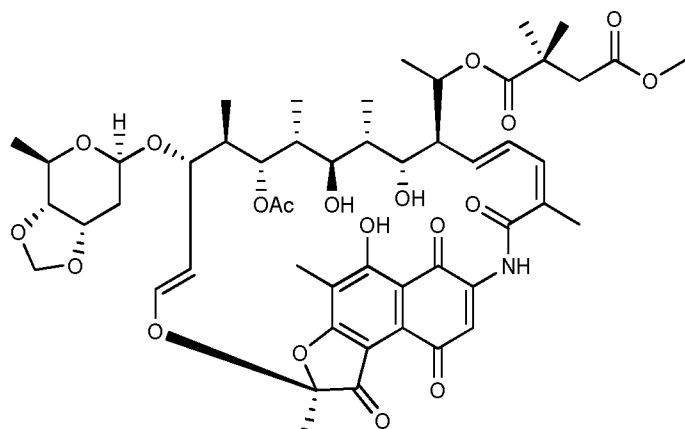




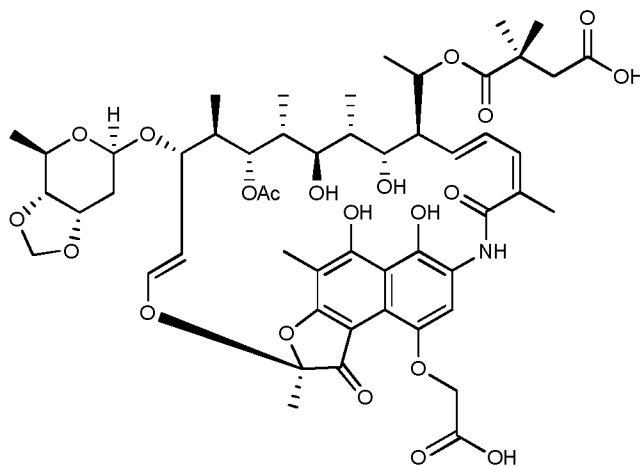


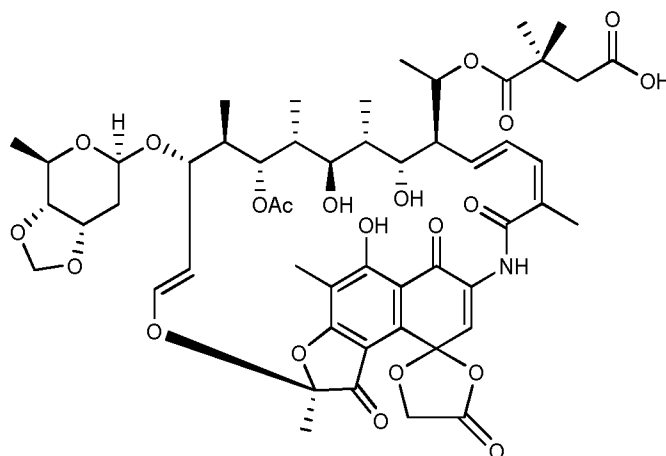
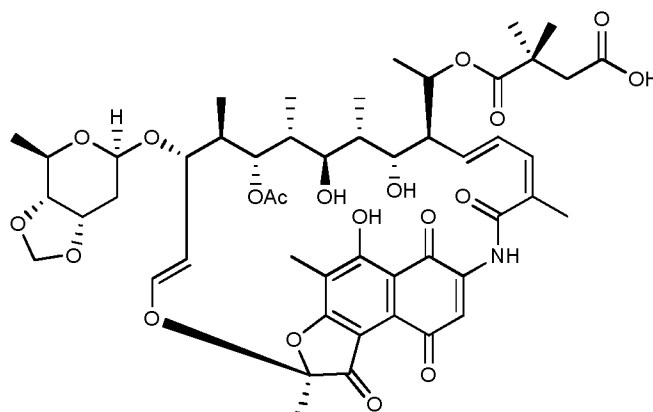
[00124] In a particular embodiment, the compound having a structure according to formula (I), (II) or (III) has any of the following structures:



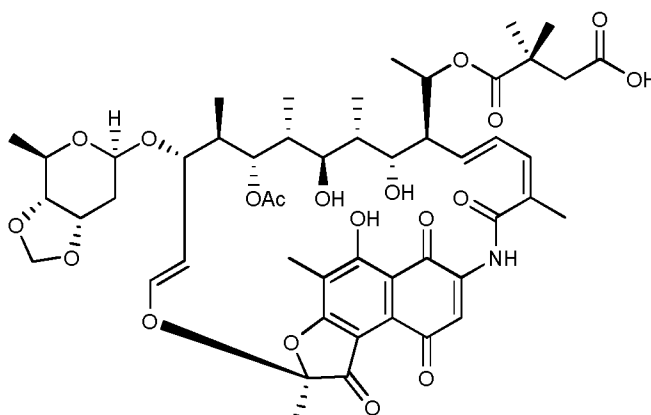


[00125] In a particular embodiment, the compound having a structure according to formula (I), (II) or (III) has any of the following structures:

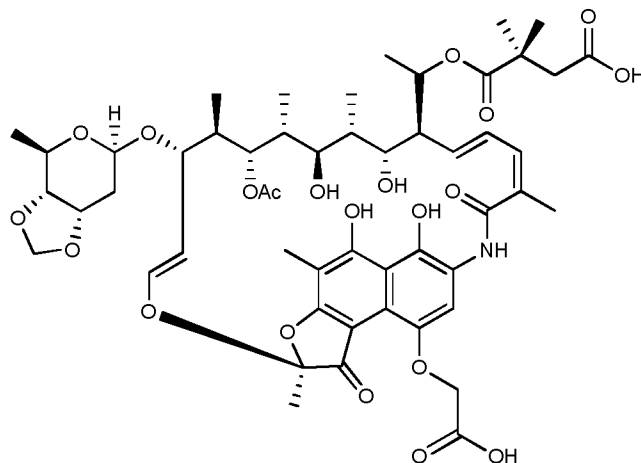




[00126] In a particular embodiment, the compound having a structure according to formula (I), (II) or (III) has the following structure:



[00127] In a particular embodiment, the compound having a structure according to formula (I), (II) or (III) has the following structure:



[00128] The present invention also provides a method of inhibiting RIF-resistant RNA polymerase, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound of formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein.

[00129] The present invention also provides a method of inhibiting bacterial cell proliferation, *in vitro* or *in vivo*, said method comprising contacting a bacterial cell with an effective amount of a compound of formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein.

[00130] The present invention also provides a method of treating an infection caused by RIF-resistant bacteria in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein, or a pharmaceutical composition as defined herein.

[00131] The present invention also provides a use of a compound of formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the inhibition of RIF-resistant RNA polymerase.

[00132] The present invention also provides a use of a compound of formula (I), (II) or (III), or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of an infection caused by RIF-resistant bacteria.

[00133] Suitably, the RIF-resistant bacteria is one or more RIF-resistant Gram positive bacteria.

[00134] Suitably, the RIF-resistant bacteria is RIF-resistant *S. aureus*.

[00135] Suitably, the RIF-resistant bacteria is RIF-resistant *M. tuberculosis*

[00136] Suitably, the infection caused by RIF-resistant bacteria is RIF-resistant tuberculosis.

[00137] For those aspects of the invention concerning therapy (e.g. medical uses, methods of treatment, etc), it will be appreciated that the compound of formula (I), (II) or (III) may be used (e.g. administered) in combination with one or more other active ingredients. Suitably, the one or more other active ingredients is rifampicin or a derivative thereof.

[00138] A suitable pharmaceutically acceptable salt of a compound of formula (I), (II) or (III) is, for example, an acid-addition salt of a compound of formula (I), (II) or (III) which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, formic, citric methane sulfonate or maleic acid. In addition, a suitable pharmaceutically acceptable salt of a compound of formula (I), (II) or (III) which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

[00139] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[00140] The compounds of formula (I), (II) or (III) may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of formula (I), (II) or (III) may have geometric isomeric centres (E- and Z- isomers). It is to be understood that the present invention encompasses all optical,

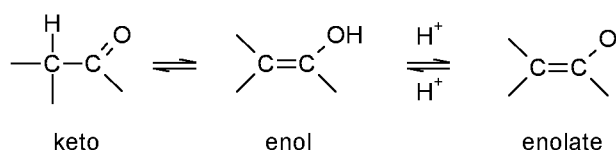
diastereoisomers and geometric isomers and mixtures thereof that possess antiproliferative activity.

[00141] The present invention also encompasses compounds of formula (I), (II) or (III) as defined herein which comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , $^2\text{H(D)}$, and $^3\text{H (T)}$; C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; and O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

[00142] It is also to be understood that certain compounds of formula (I), (II) or (III) may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms that possess activity towards RIF-resistant bacteria.

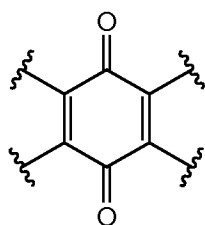
[00143] It is also to be understood that certain compounds of formula (I), (II) or (III) may exhibit polymorphism, and that the invention encompasses all such forms that possess activity towards RIF-resistant bacteria.

[00144] Compounds of formula (I), (II) or (III) may exist in a number of different tautomeric forms and references to compounds of formula (I), (II) or (III) include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by formula (I), (II) or (III). Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.

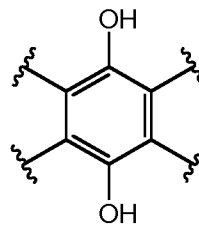


[00145] Compounds of formula (I), (II) or (III) containing an amine function may also form N-oxides. A reference herein to a compound of formula (I), (II) or (III) that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a *tertiary* amine or a nitrogen atom of a nitrogen-containing heterocycle. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with m-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

[00146] It will be understood that compound of formula (I), (II) or (III) containing a quinone moiety may readily convert into the corresponding hydroquinone form (see below), and *vice versa*. Both forms are encompassed by the present invention.



Quinone



Hydroquinone

[00147] The compounds of formula (I), (II) or (III) may be administered in the form of a pro-drug which is broken down in the human or animal body to release a compound of formula (I), (II) or (III). A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of formula (I), (II) or (III). A pro-drug can be formed when the compound formula (I), (II) or (III) contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of formula (I), (II) or (III), and *in-vivo* cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of formula (I), (II) or (III).

[00148] Accordingly, the present invention includes those compounds of formula (I), (II) or (III) as defined hereinbefore, when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of formula (I), (II) or (III) that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of formula (I), (II) or (III) may be a synthetically-produced compound or a metabolically-produced compound.

[00149] A suitable pharmaceutically acceptable pro-drug of a compound of formula (I), (II) or (III) is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

[00150] Various forms of pro-drug have been described, for example in the following documents :-

a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

- b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);
- c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);
- d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988);
- f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984);
- g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and
- h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[00151] A suitable pharmaceutically acceptable pro-drug of a compound of formula (I), (II) or (III) that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of formula (I), (II) or (III) containing a carboxy group is, for example, a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include C1-6alkyl esters such as methyl, ethyl and *tert*-butyl, C1-6alkoxymethyl esters such as methoxymethyl esters, C1-6alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, C3-8cycloalkylcarbonyloxy- C1-6alkyl esters such as cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters, 2-oxo-1,3-dioxolenylmethyl esters such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and C1-6alkoxycarbonyloxy- C1-6alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

[00152] A suitable pharmaceutically acceptable pro-drug of a compound of formula (I), (II) or (III) that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of formula (I), (II) or (III) containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C1-10alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C1-10alkoxycarbonyl groups such as ethoxycarbonyl, N,N -(C1-6)2carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C1-4alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether

forming groups for a hydroxy group include α -acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

[00153] A suitable pharmaceutically acceptable pro-drug of a compound of formula (I), (II) or (III) that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C1-4alkylamine such as methylamine, a (C1-4alkyl)2amine such as dimethylamine, N-ethyl-N-methylamine or diethylamine, a C1-4alkoxy- C2-4alkylamine such as 2-methoxyethylamine, a phenyl-C1-4alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

[00154] A suitable pharmaceutically acceptable pro-drug of a compound of formula (I), (II) or (III) that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C1-10alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C1-4alkyl)piperazin-1-ylmethyl.

[00155] The *in vivo* effects of a compound of formula (I), (II) or (III) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of formula (I), (II) or (III). As stated hereinbefore, the *in vivo* effects of a compound of formula (I), (II) or (III), may also be exerted by way of metabolism of a precursor compound (a pro-drug).

[00156] Though the present invention may relate to any compound or particular group of compounds defined herein by way of optional, preferred or suitable features or otherwise in terms of particular embodiments, the present invention may also relate to any compound or particular group of compounds that specifically excludes said optional, preferred or suitable features or particular embodiments.

[00157] Suitably, the present invention excludes any individual compounds not possessing the biological activity defined herein.

Routes of Administration

[00158] The compounds formula (I), (II) or (III) or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically, peripherally or topically (i.e., at the site of desired action).

[00159] Routes of administration include, but are not limited to, oral (e.g. by ingestion); buccal;

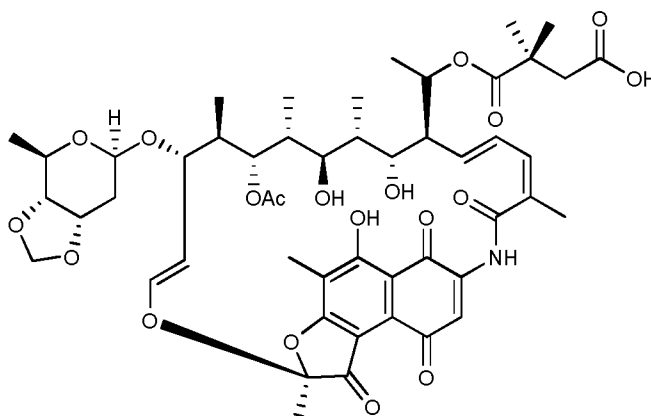
sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

Compounds of the invention

[00160] In one aspect of the present invention there is provided a compound of formula (I), (II) or (III) as hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof,

with the proviso that, in formula (I), when R_1 is hydroxy and R_2 is hydrogen, X_1 is not O.

[00161] The following compound is not a compound of the invention:



[00162] It will be understood that the compounds of the invention may have any of those definitions described hereinbefore in respect of formula (I), (II) or (III) – including all sub-formulae – subject to the aforementioned proviso.

[00163] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (I), (II) or (III), with the proviso that, in formula (I), R_1 is not hydroxy.

[00164] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (I'), (II') or (III'), with the proviso that, in formula (I'), R_1 is not hydroxy.

[00165] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (Ia), (IIa) or (IIIa), with the proviso that, in formula (Ia), R_1 is not hydroxy.

[00166] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (Ic), (IIc) or (IIIc), with the proviso that, in formula (Ic), R_1 is not hydroxy.

[00167] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (Id), (IIId) or (IIId), with the proviso that, in formula (Id), R_1 is not hydroxy.

[00168] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (If), (IIIf) or (IIIf), with the proviso that, in formula (If), R_1 is not hydroxy.

[00169] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (I), (II) or (III), with the proviso that, in formula (I), R_2 is not hydrogen.

[00170] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (I'), (II') or (III'), with the proviso that, in formula (I'), R_2 is not hydrogen.

[00171] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (Ib), (IIb) or (IIIb), with the proviso that, in formula (Ib), R_2 is not hydrogen.

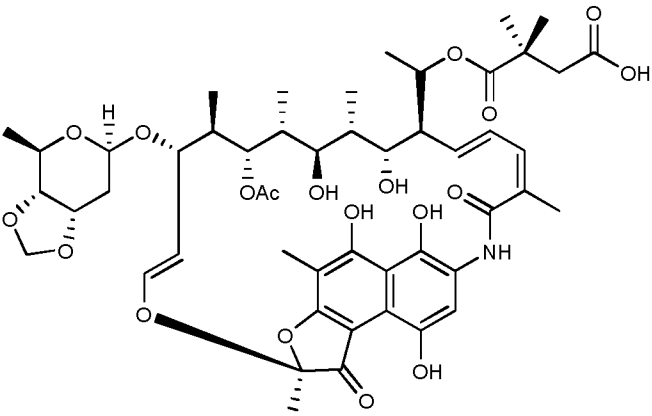
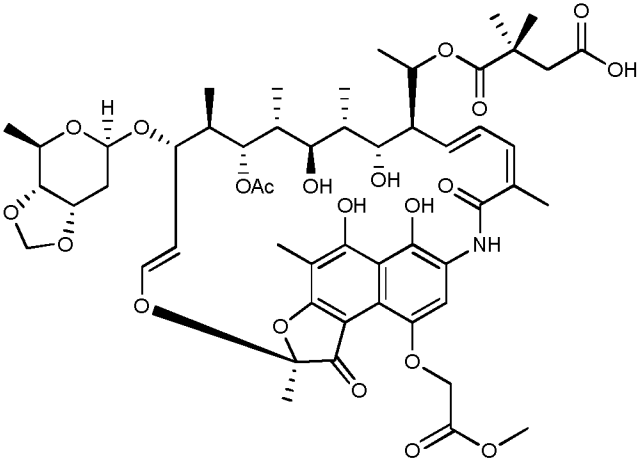
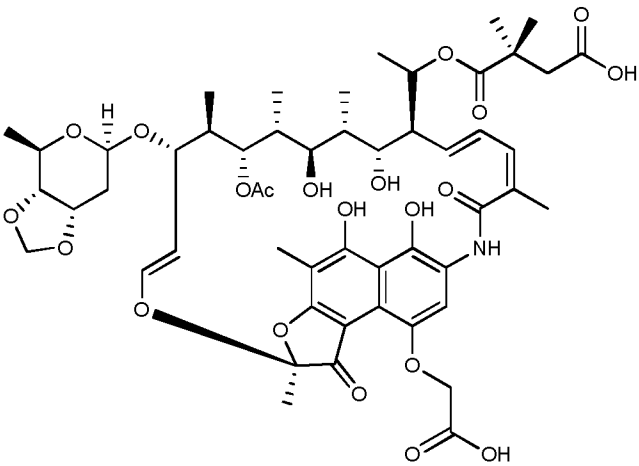
[00172] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (Ic), (IIc) or (IIIc), with the proviso that, in formula (Ic), R_2 is not hydrogen.

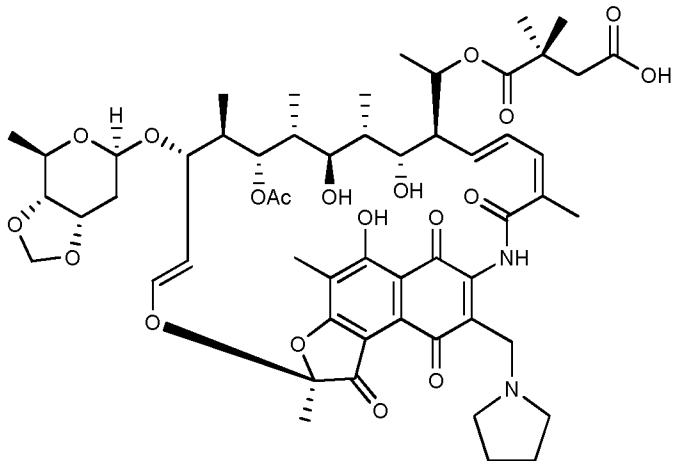
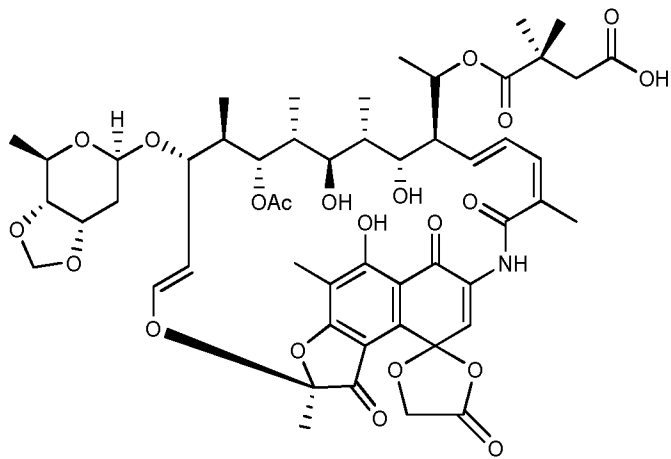
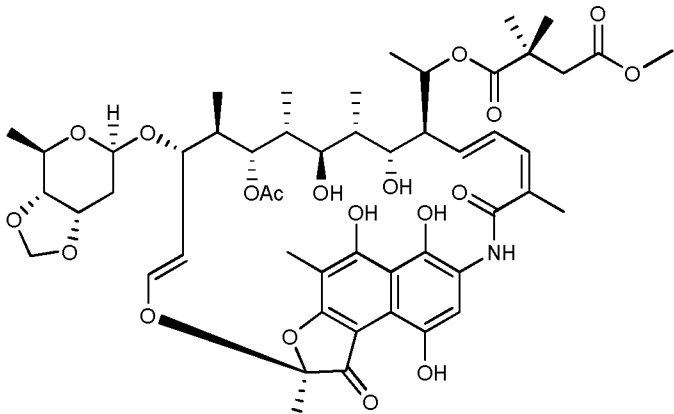
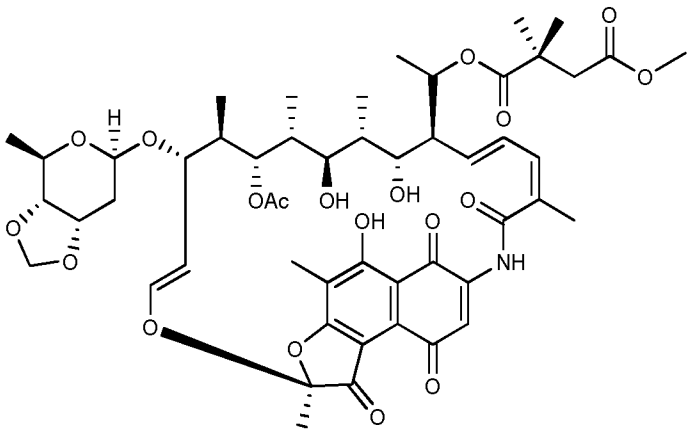
[00173] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (Id), (IIId) or (IIId), with the proviso that, in formula (Id), R_2 is not hydrogen.

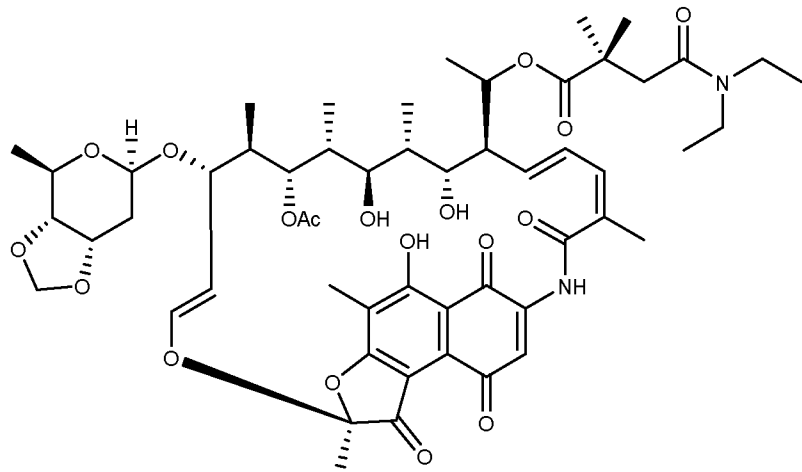
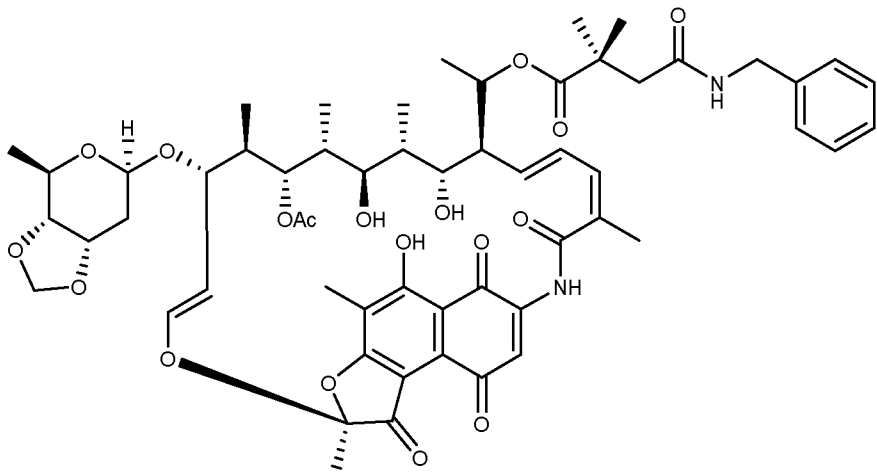
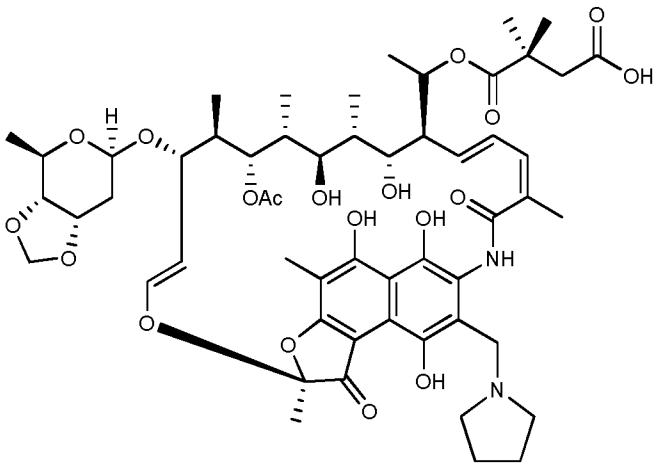
[00174] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (Ie), (IIe) or (IIIe), with the proviso that, in formula (Ie), R_2 is not hydrogen.

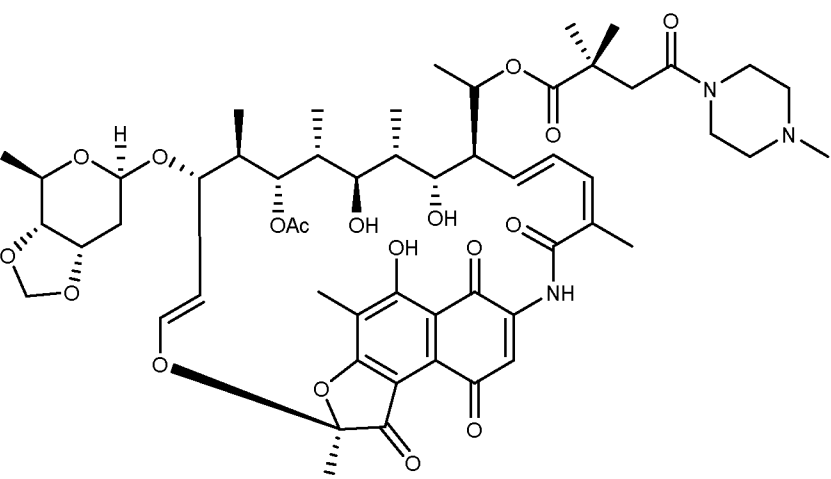
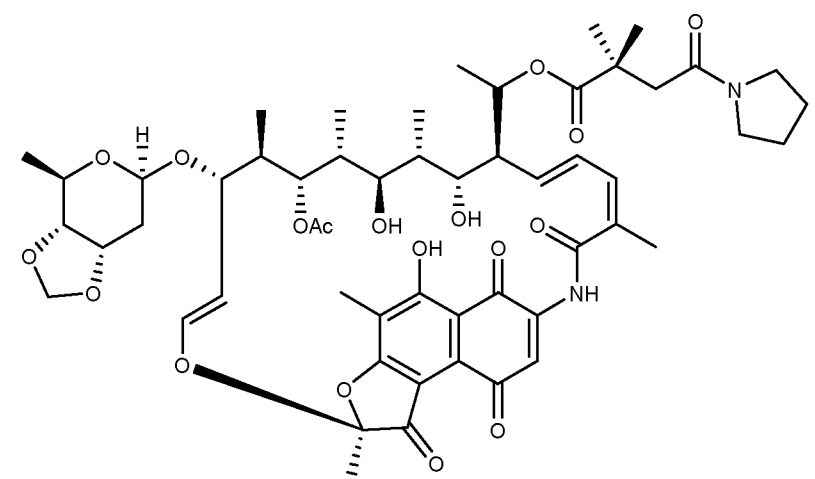
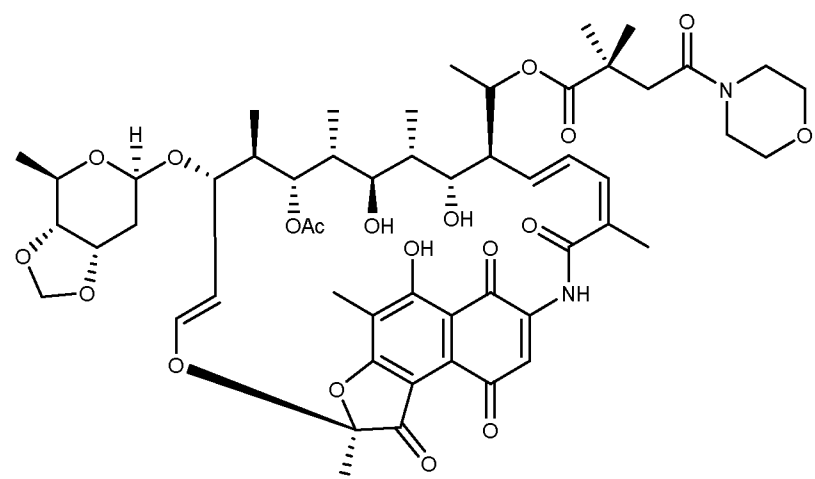
[00175] In an embodiment, the compound has any of those definitions appearing hereinbefore in relation to formula (If), (IIIf) or (IIIf), with the proviso that, in formula (If), R_2 is not hydrogen.

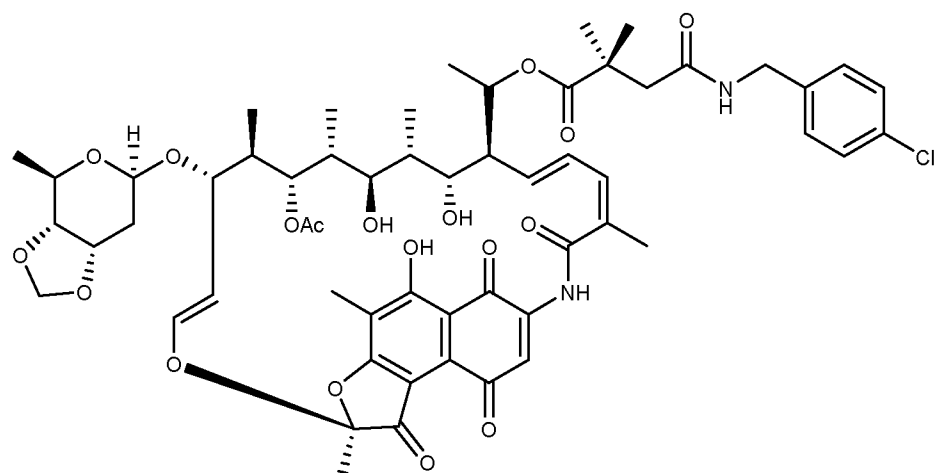
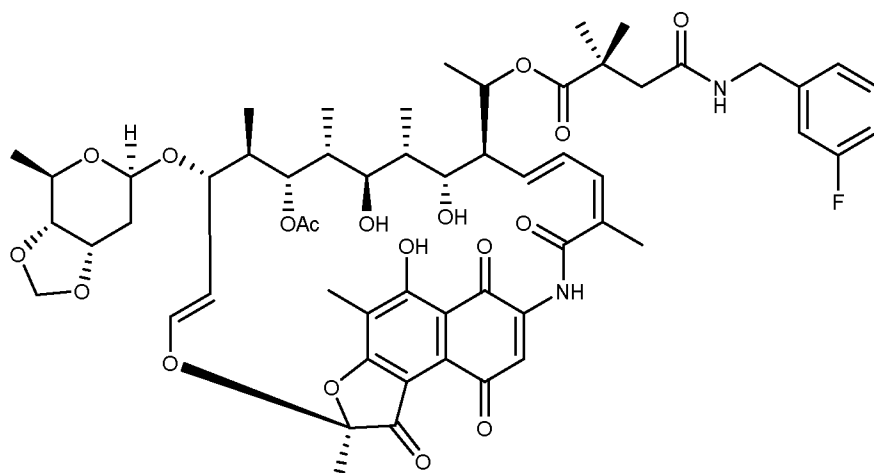
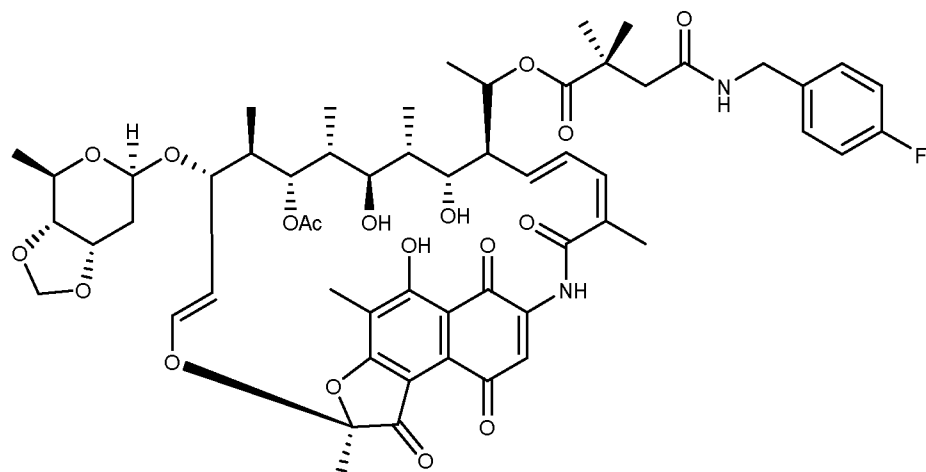
[00176] In a particular embodiment, the compound has any of the following structures:

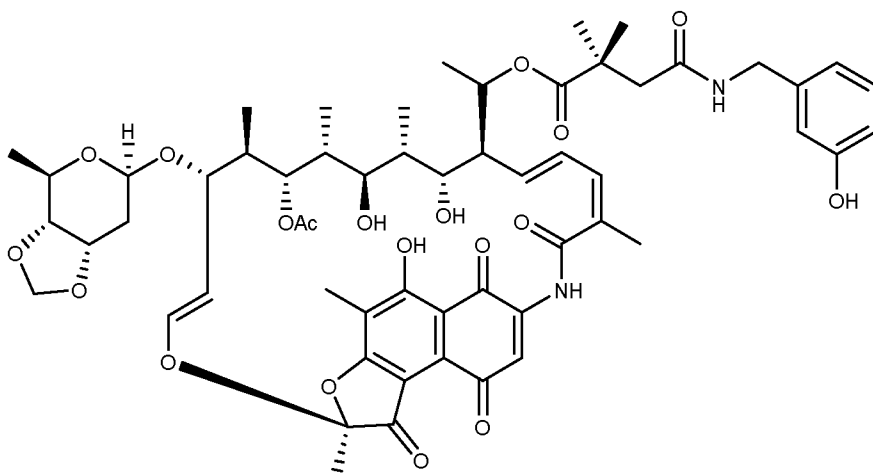
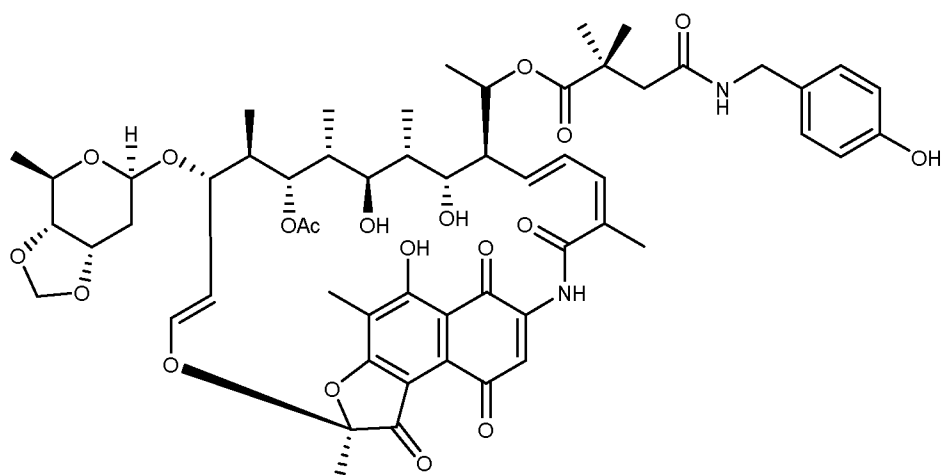
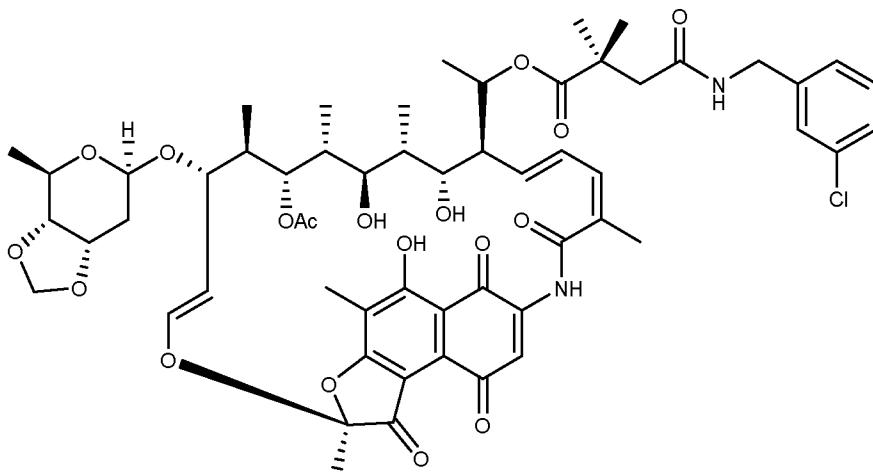


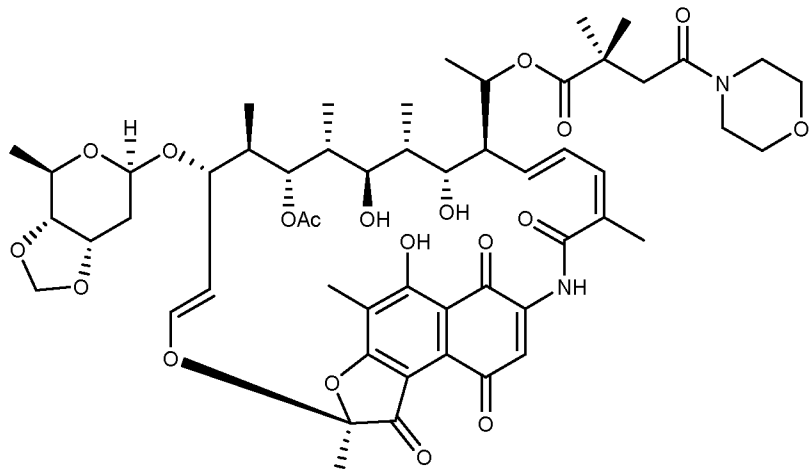
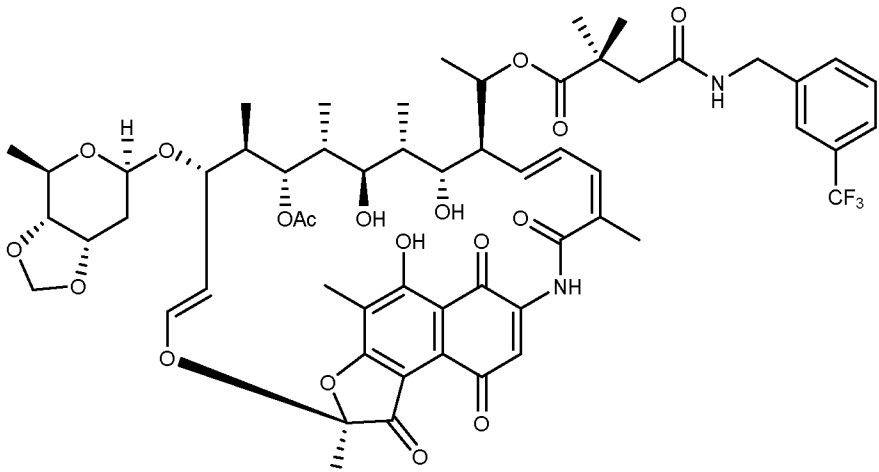
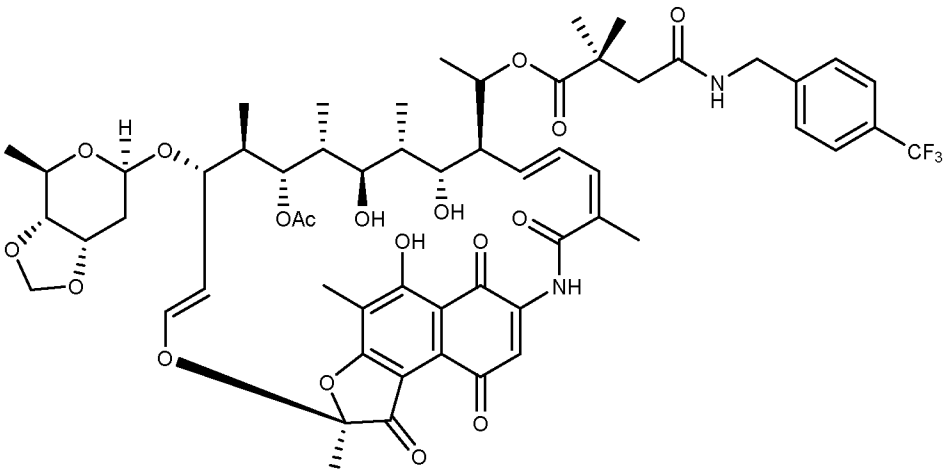


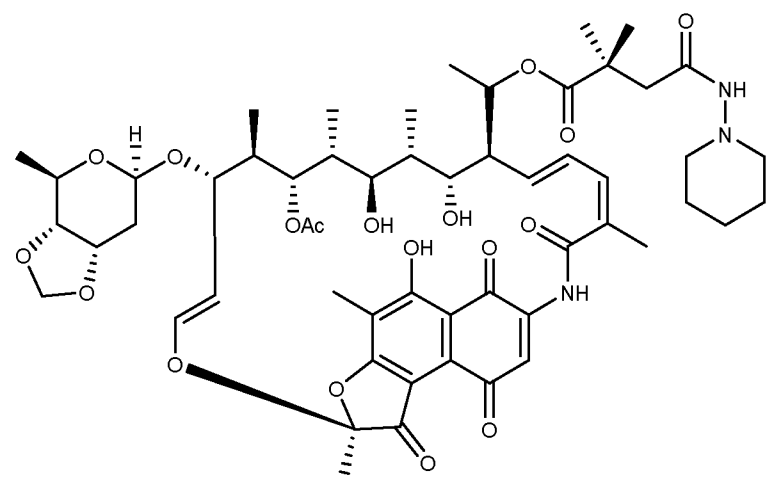
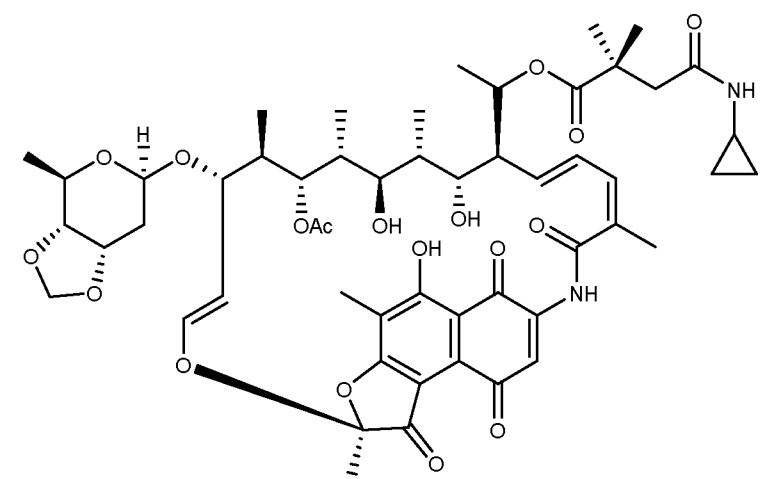
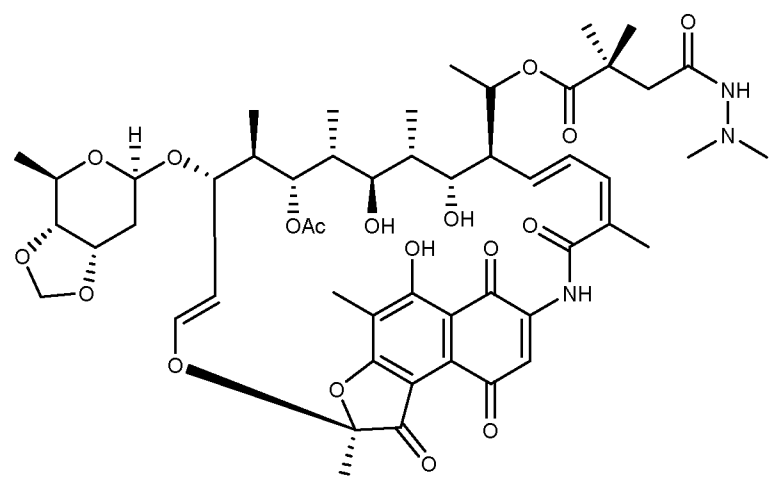


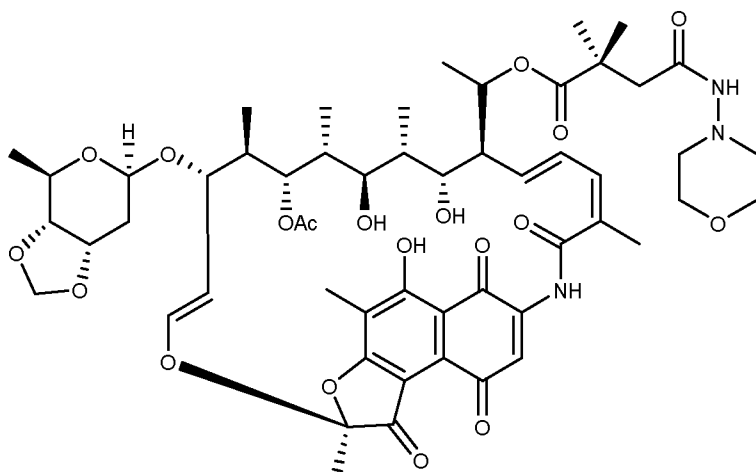




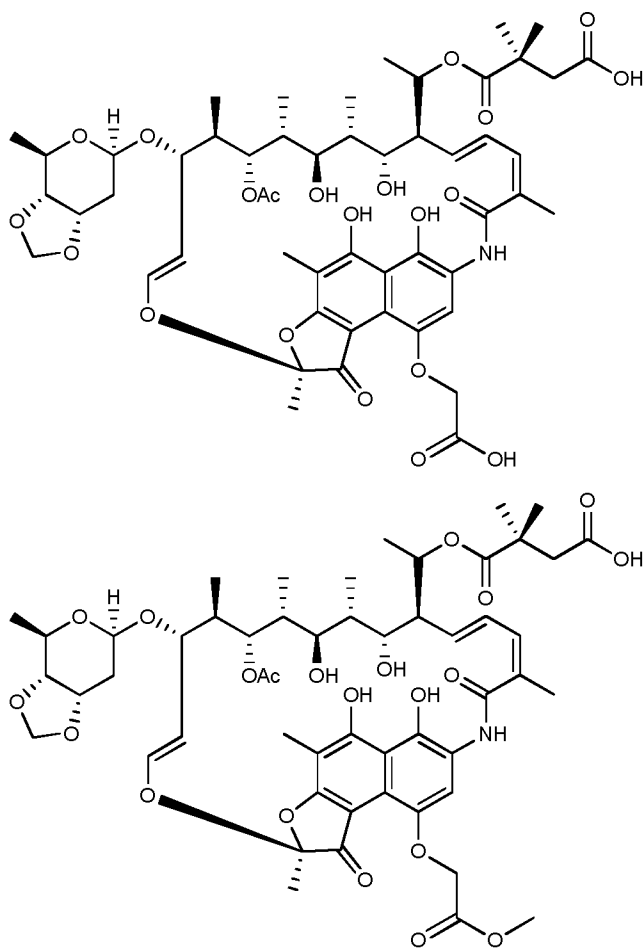


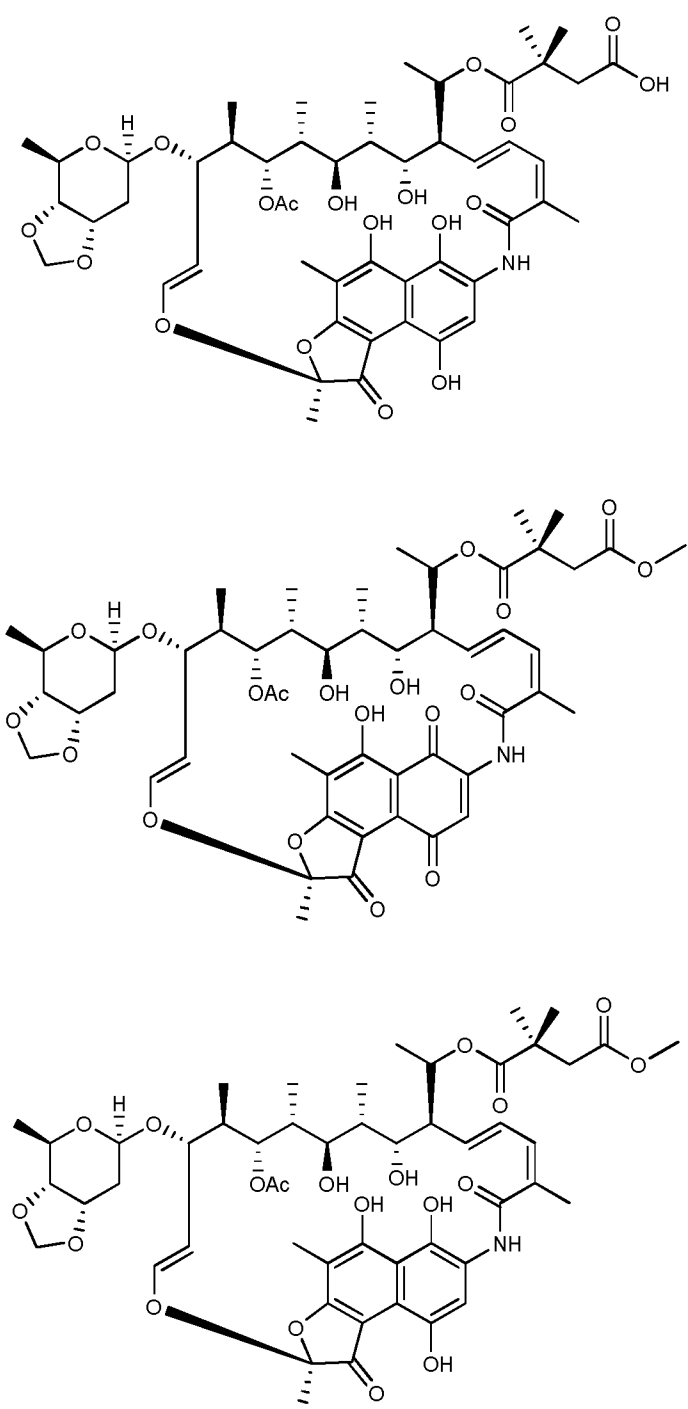


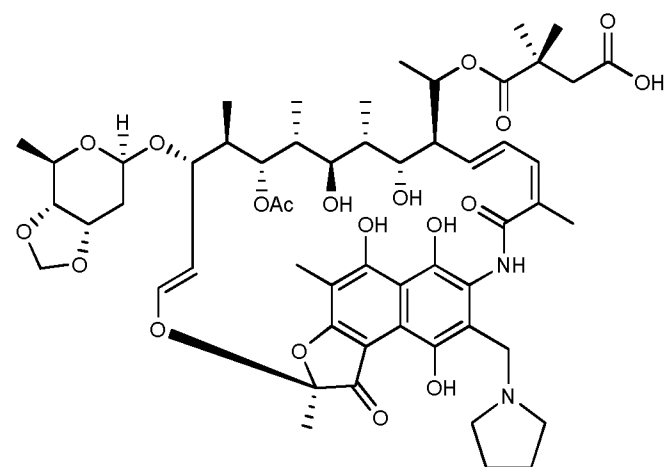
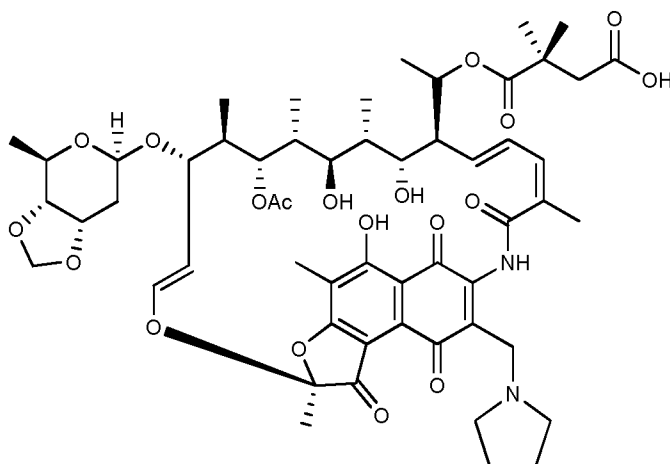
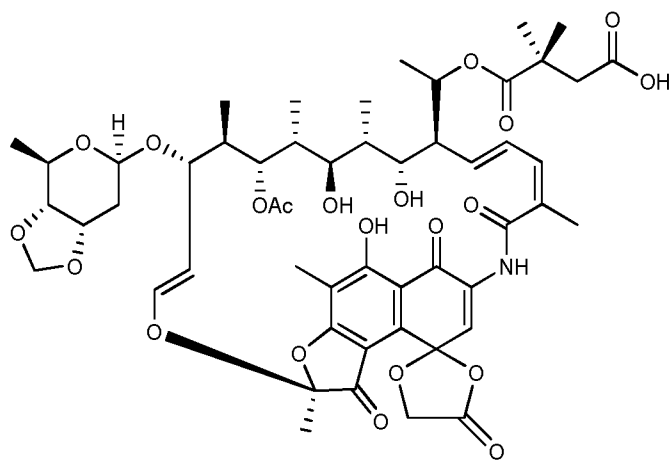




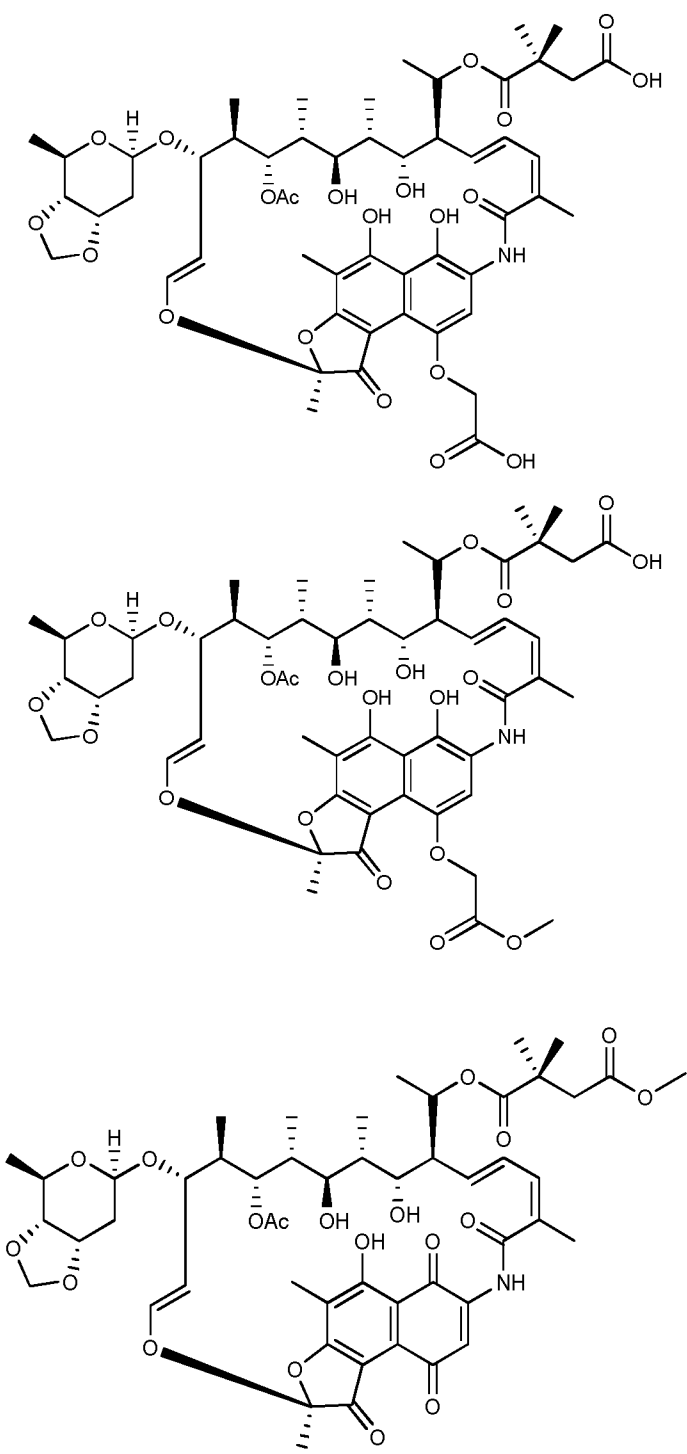
[00177] In a particular embodiment, the compound has any of the following structures:

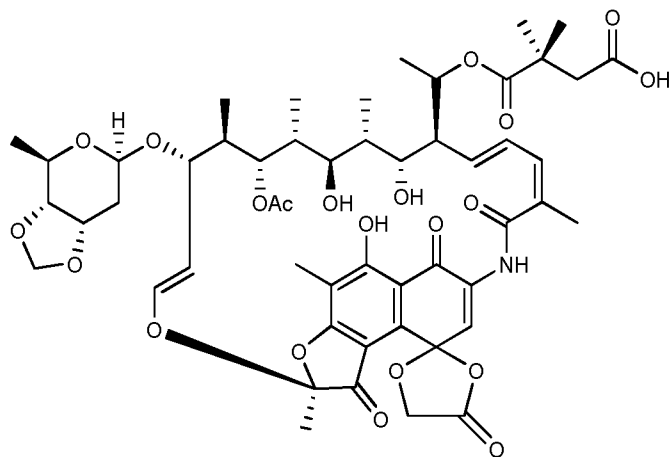




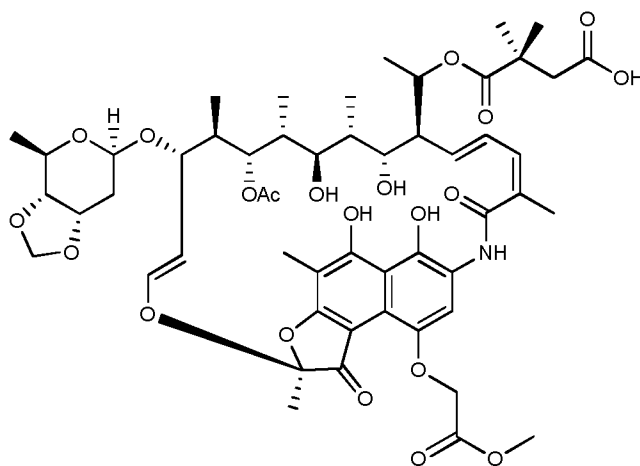
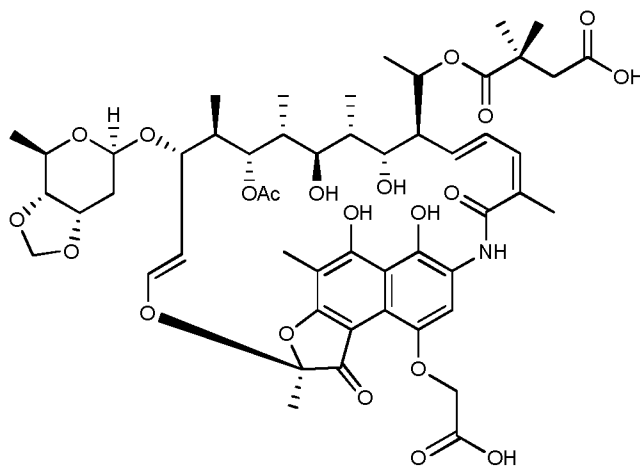


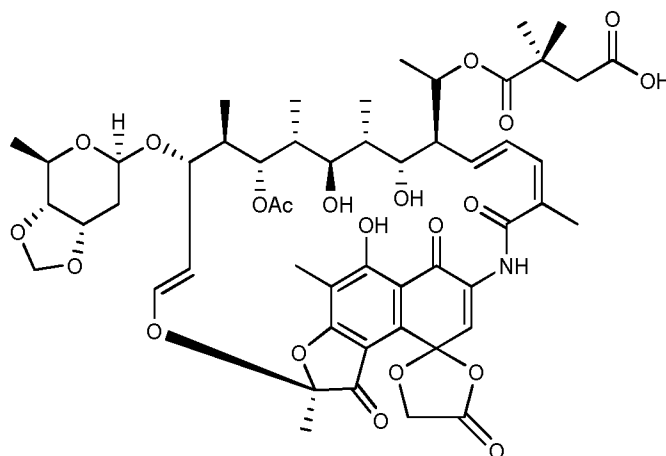
[00178] In a particular embodiment, the compound has any of the following structures:



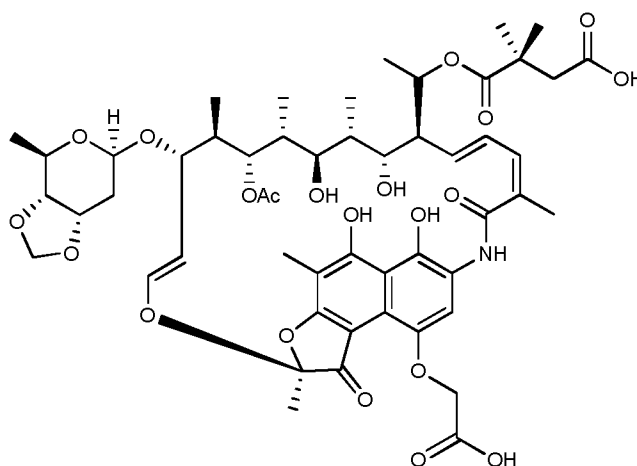


[00179] In a particular embodiment, the compound has any of the following structures:





[00180] In a particular embodiment, the compound has the following structure:



[00181] The present invention also provides a compound of the invention, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use in therapy.

[00182] The present invention also provides a compound of the invention, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein for use as a medicament.

[00183] The present invention also provides a method of treating a bacterial infection in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of the invention. The infection may be caused by RIF-resistant bacteria (e.g. RIF-resistant tuberculosis) or RIF-susceptible bacteria. When the infection is

caused by RIF-susceptible bacteria, the method of treatment may prevent the bacteria from becoming RIF-resistant.

[00184] For those aspects of the invention concerning therapy (e.g. medical uses, methods of treatment, etc), it will be appreciated that the compound of the invention may be used (e.g. administered) in combination with one or more other active ingredients. Suitably, the one or more other active ingredients is rifampicin or a derivative thereof.

Pharmaceutical Compositions

[00185] In one aspect of the present invention there is provided a pharmaceutical composition which comprises a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with a pharmaceutically acceptable diluent or carrier.

[00186] The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[00187] The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

[00188] An effective amount of a compound of the present invention for use in therapy is an amount sufficient to treat or prevent a proliferative condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

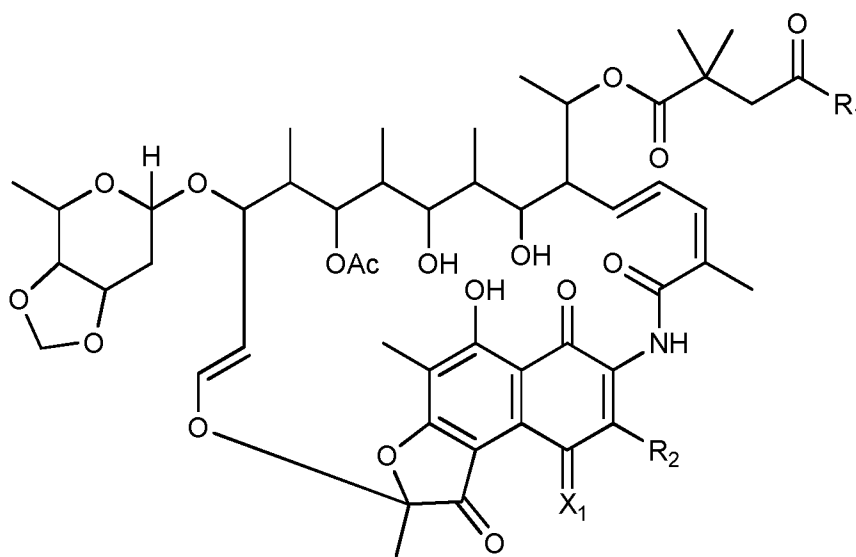
[00189] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

[00190] The size of the dose for therapeutic or prophylactic purposes of a compound of the formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

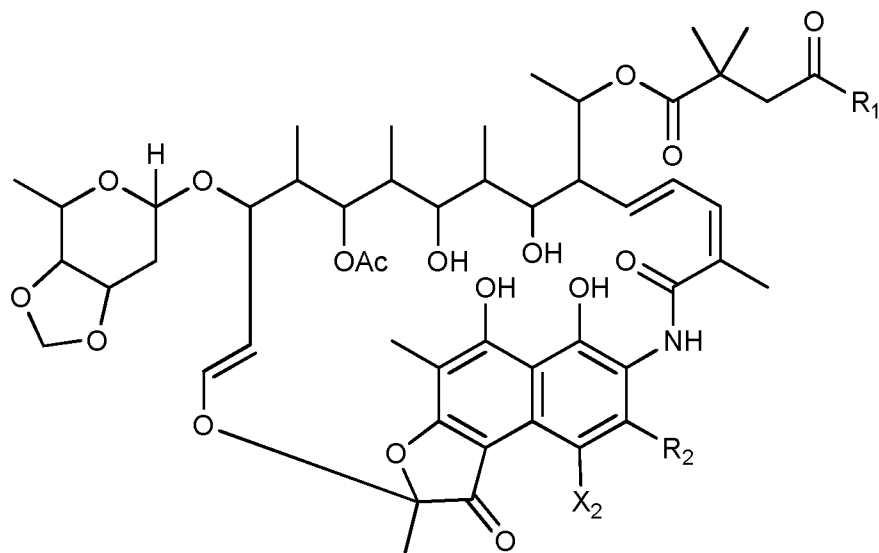
[00191] In using a compound of the invention for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous or intraperitoneal administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration may also be suitable, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

[00192] The following numbered statements 1 – 93 are not claims, but instead describe particular aspects and embodiments of the invention:

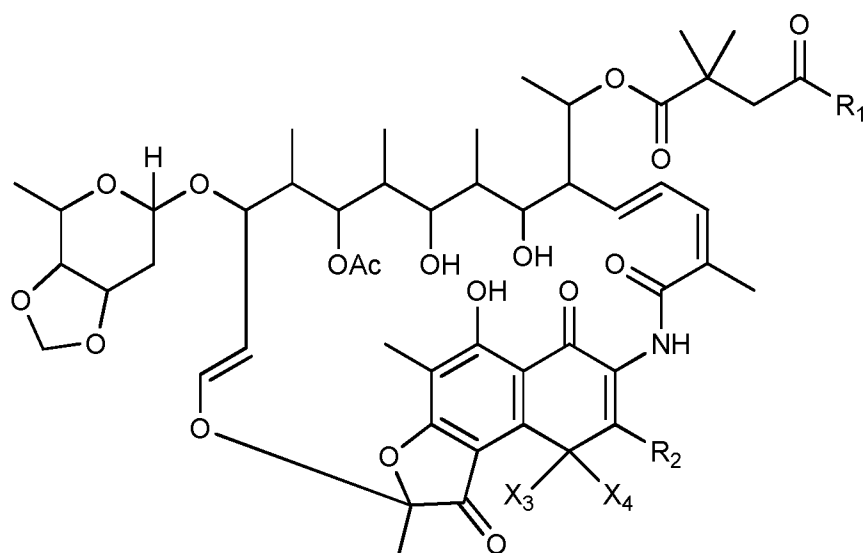
1. A compound of formula (I), (II) or (III) shown below, or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use in the treatment of infection caused by rifampicin-resistant bacteria:



(I)



(II)



(III)

wherein,

R_1 is selected from hydrogen, halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_aR_b , OR_c , $OC(O)R_a$, $N(R_b)OR_a$,

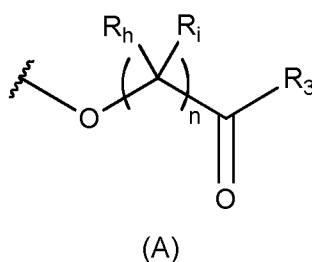
$N(R_b)C(O)OR_a$, $N(R_b)C(O)R_a$, $S(O)_pR_a$ (where p is 0, 1 or 2), $SO_2N(R_b)R_a$, and $N(R_b)SO_2R_a$;

R_2 is selected from hydrogen, halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_dR_e , OR_f , $C(O)R_d$, $C(O)OR_d$, $OC(O)R_d$, $C(R_d)=N(R_e)$, $N(R_d)OR_e$, $N(R_d)C(O)OR_e$, $C(O)N(R_d)R_e$, $N(R_d)C(O)R_e$, $S(O)_pR_d$ (where p is 0, 1 or 2), $SO_2N(R_d)R_e$, and $N(R_d)SO_2R_e$;

and wherein R_1 and R_2 are each independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, or (3-8C)cycloalkyl(1-2C)alkyl;

X_1 is selected from O and NR_g ;

X_2 is hydroxy or a group of formula (A) shown below:



wherein

n is 0, 1, 2, 3 or 4; and

R_3 is selected from hydrogen, halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_jR_k , OR_l , $C(O)R_j$, $C(O)OR_j$, $OC(O)R_j$, $C(R_j)=N(R_k)$, $N(R_j)OR_k$, $N(R_j)C(O)OR_k$, $C(O)N(R_j)R_k$, $N(R_j)C(O)R_k$, $S(O)_pR_j$ (where p is 0, 1 or 2), $SO_2N(R_j)R_k$, and $N(R_j)SO_2R_k$;

and wherein R_3 is independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, or (3-8C)cycloalkyl(1-2C)alkyl;

or R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 5-12 membered heteroaryl or heterocycle that is optionally substituted with one or more R_4 substituents;

and wherein each R_4 is independently selected from halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_mR_n , OR_o , $C(O)R_m$, $C(O)OR_m$, $OC(O)R_m$, $N(R_m)OR_n$, $N(R_m)C(O)OR_n$, $C(O)N(R_m)R_n$, $C(R_m)=N(R_n)$, $N(R_m)C(O)R_n$, $S(O)_pR_m$ (where p is 0, 1 or 2), $SO_2N(R_m)R_n$, and $N(R_m)SO_2R_n$;

and wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

X_3 and X_4 are independently selected from hydroxy, OR_p , NR_qR_r and a group of formula (A) shown above;

or X_3 and X_4 are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a 4-6 membered heterocycle that is optionally substituted with one or more R_5 substituents;

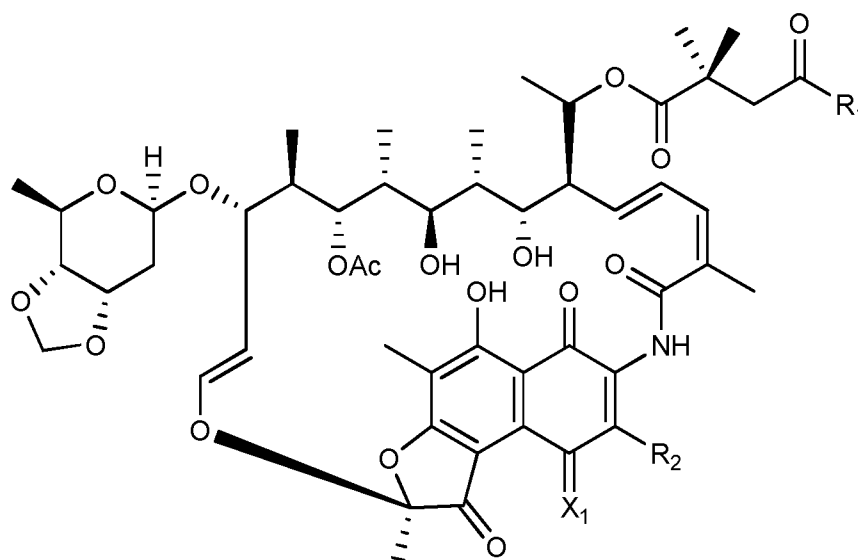
and wherein each R_5 is independently selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, oxo, amino, carboxy, carbamoyl, sulphamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-

6C)alkynyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

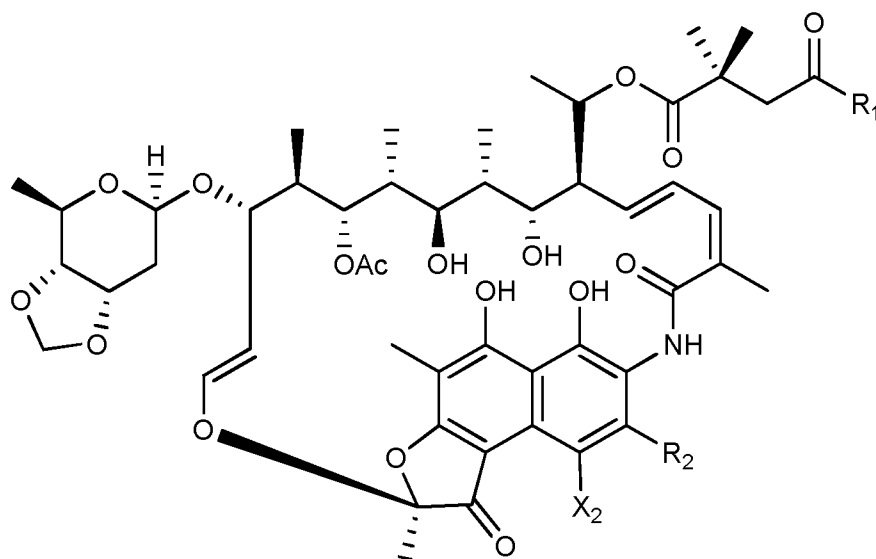
each R_a to R_r is independently selected from hydrogen, fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

and wherein each R_a to R_r is independently optionally substituted with one or more groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl.

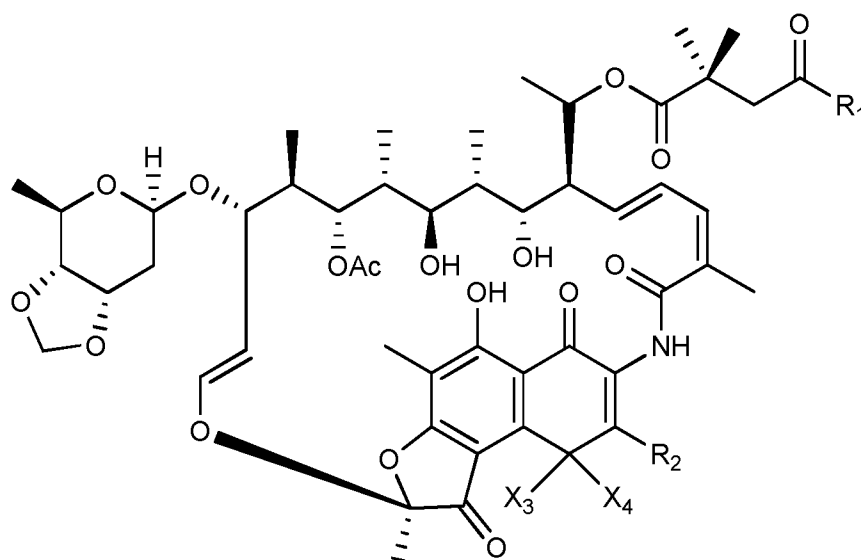
2. The compound for use according to statement 1, wherein the compound has a structure according to formula (I'), (II') or (III') shown below:



(I')



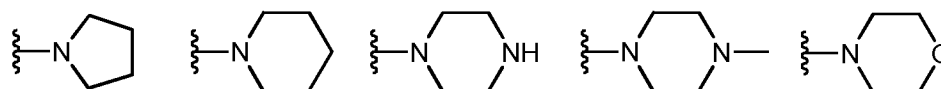
(II')



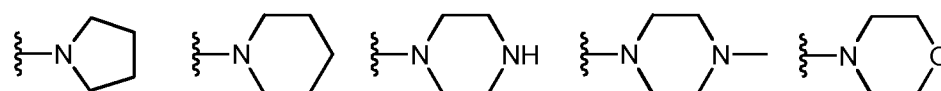
(III')

3. The compound for use according to statement 1 or 2, wherein R_1 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_aR_b , OR_c , $OC(O)R_a$, $N(R_b)OR_a$, $N(R_b)C(O)OR_a$ and $N(R_b)C(O)R_a$, wherein R_1 is optionally substituted by one or more substituent groups selected from (1-4C)alkyl and (1-3C)alkoxy.

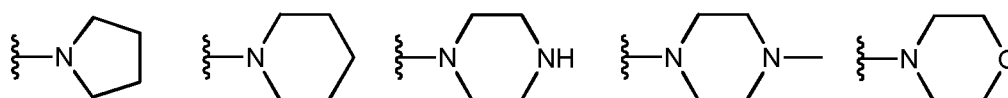
4. The compound for use according to statement 1, 2 or 3, wherein R_1 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_aR_b and OR_c ,
wherein R_1 is optionally substituted by one or more substituent groups selected from (1-4C)alkyl and (1-3C)alkoxy.
5. The compound for use according to any preceding statement, wherein R_1 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_aR_b and OR_c ,
wherein R_1 is optionally substituted by one or more substituent groups selected from (1-2C)alkyl and (1-2C)alkoxy.
6. The compound for use according to any preceding statement, wherein R_1 is selected from hydroxy, (1-6C)alkyl, aryl, heteroaryl, (3-8C)heterocyclyl, (3-8C)cycloalkyl, NR_aR_b and OR_c ,
wherein R_1 is optionally substituted by one or more substituent groups selected from (1-2C)alkyl and (1-2C)alkoxy.
7. The compound for use according to any preceding statement, wherein R_1 is selected from hydroxy, (1-4C)alkyl, N-linked (3-8C)heterocyclyl, NR_aR_b and OR_c ,
wherein R_1 is optionally substituted by one or more (1-2C)alkyl.
8. The compound for use according to any preceding statement, wherein R_1 is selected from hydroxy, (1-3C)alkyl, N-linked (3-6C)heterocyclyl, NR_aR_b and OR_c , wherein the N-linked (3-6C)heterocyclyl contains 1 or 2 heteroatoms,
wherein R_1 is optionally substituted by one or more (1-2C)alkyl.
9. The compound for use according to any preceding statement, wherein R_1 is selected from hydroxy, NR_aR_b , OR_c or any one of the following:



10. The compound for use according to any preceding statement, wherein R_1 is selected from hydroxy and OR_c (e.g. methoxy or ethoxy).
11. The compound for use according to any preceding statement, wherein R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, (1-4C)alkoxy, aryl and (3-8C)heterocyclyl.
12. The compound for use according to any preceding statement, wherein R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, aryl and N-linked (3-8C)heterocyclyl.
13. The compound for use according to any preceding statement, wherein R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, phenyl and 5-6 membered N-linked heterocyclyl.
14. The compound for use according to any preceding statement, wherein R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, phenyl or any one of the following:

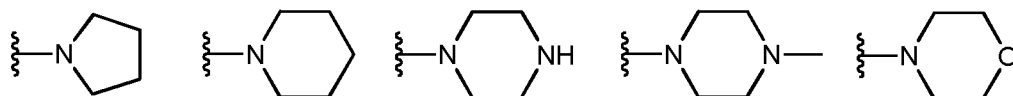


15. The compound for use according to any preceding statement, wherein R_a and R_b are independently selected from hydrogen, (1-6C)alkyl and phenyl.
16. The compound for use according to any one of statements 1 to 9, wherein each R_a and R_b are independently selected from hydrogen, (1-6C)alkyl, amino, aryl, aryl(1-2C)alkyl, (3-8C)cycloalkyl or any one of the following:



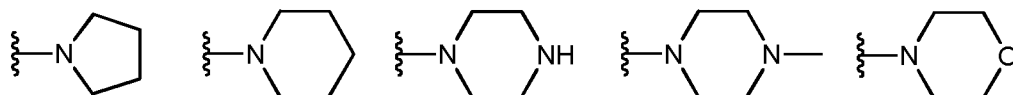
wherein each R_a and R_b is optionally substituted with one or more substituent groups selected from halo, hydroxy, (1-3C)alkyl and (1-3C)haloalkyl.

17. The compound for use according to any one of statements 1 to 9, wherein R_a is hydrogen or (1-6C)alkyl and R_b is selected from (1-6C)alkyl, amino, aryl, aryl(1-2C)alkyl, (3-8C)cycloalkyl or any one of the following:



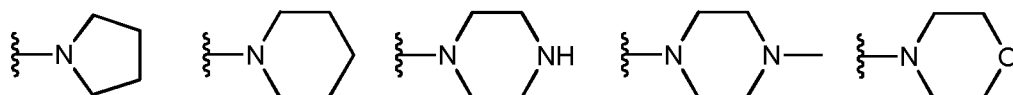
wherein each R_b is optionally substituted with one or more substituent groups selected from halo, hydroxy, (1-3C)alkyl and (1-3C)haloalkyl.

18. The compound for use according to any one of statements 1 to 9, wherein each R_a and R_b are independently selected from hydrogen, (1-3C)alkyl, amino, phenyl, benzyl, (3-6C)cycloalkyl or any one of the following:



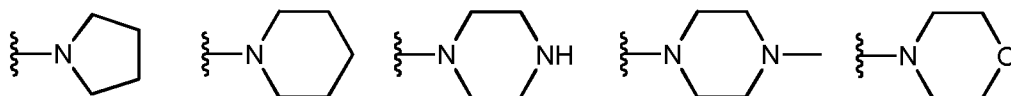
wherein each of the said phenyl and benzyl groups is optionally substituted with one or more substituent groups selected from fluoro, chloro hydroxy, (1-3C)alkyl and (1-3C)haloalkyl, and each of the said amino groups is optionally substituted with one or more substituent groups selected from (1-3C)alkyl.

19. The compound for use according to any one of statements 1 to 9, wherein R_a is hydrogen or (1-3C)alkyl and R_b is selected from (1-3C)alkyl, amino, phenyl, benzyl, (3-6C)cycloalkyl or any one of the following:



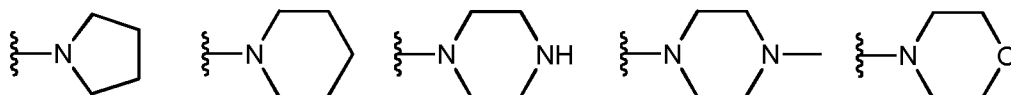
wherein each of the said phenyl and benzyl groups is optionally substituted with one or more substituent groups selected from fluoro, chloro hydroxy, (1-3C)alkyl and (1-3C)haloalkyl, and each of the said amino groups is optionally substituted with one or more substituent groups selected from (1-3C)alkyl.

20. The compound for use according to any one of statements 1 to 9, wherein each R_a and R_b are independently selected from hydrogen, (1-2C)alkyl, $N(Me)_2$, benzyl, cyclopropyl or any one of the following:



wherein each of the said benzyl groups is optionally substituted with one substituent group selected from fluoro, chloro, hydroxy and trifluoromethyl.

21. The compound for use according to any one of statements 1 to 9, wherein R_a is hydrogen or (1-2C)alkyl and R_b is selected from (1-2C)alkyl, $N(Me)_2$, benzyl, cyclopropyl or any one of the following:



wherein each of the said benzyl groups is optionally substituted with one substituent group selected from fluoro, chloro, hydroxy and trifluoromethyl.

22. The compound for use according to any preceding statement, wherein R_c is (1-6C)alkyl.

23. The compound for use according to any preceding statement, wherein R_c is (1-3C)alkyl.

24. The compound for use according to any preceding statement, wherein R_2 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_dR_e , OR_f , $C(O)R_d$, $C(O)OR_d$, $OC(O)R_d$, $C(R_d)=N(R_e)$, $N(R_d)OR_e$, $N(R_d)C(O)OR_e$, $C(O)N(R_d)R_e$ and $N(R_d)C(O)R_e$.

25. The compound for use according to any preceding statement, wherein R_2 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_dR_e , OR_f , $C(O)R_d$, $C(O)OR_d$, $OC(O)R_d$ and $C(R_d)=N(R_e)$.

26. The compound for use according to any preceding statement, wherein R_2 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_dR_e , OR_f , and $C(R_d)=N(R_e)$.
27. The compound for use according to any preceding statement, wherein R_2 is selected from hydrogen, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
28. The compound for use according to any preceding statement, wherein R_2 is selected from hydrogen, (1-6C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
29. The compound for use according to any preceding statement, wherein R_2 is selected from hydrogen, (3-8C)heterocyclyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
30. The compound for use according to any preceding statement, wherein R_2 is selected from hydrogen, N-pyrrolidinyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
31. The compound for use according to any preceding statement, wherein each R_d is independently selected from hydrogen and (1-6C)alkyl.
32. The compound for use according to any preceding statement, wherein each R_e is independently selected from hydrogen, (1-6C)alkyl and (3-8C)heterocyclyl, any of which is optionally substituted with one or more substituent groups selected from (1-6C)alkyl and (3-8C)cycloalkyl.
33. The compound for use according to any preceding statement, wherein each R_e is independently selected from hydrogen, (1-4C)alkyl and (3-6C)heterocyclyl containing 1 or 2 heteroatoms selected from O and N, any of which is optionally substituted with one or more substituent groups selected from (1-4C)alkyl and (4-6C)cycloalkyl.
34. The compound for use according to any preceding statement, wherein each R_e is independently selected from hydrogen, (1-4C)alkyl and N-piperazinyl, any of which is optionally substituted with cyclopentyl.

35. The compound for use according to any preceding statement, wherein each R_e is N-piperazinyl, which is optionally substituted with cyclopentyl.
36. The compound for use according to any preceding statement, wherein X_1 is O.
37. The compound for use according to any preceding statement, wherein X_2 is hydroxy or a group of formula (A), wherein
n is 1 or 2;
 R_3 is selected from hydrogen, halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_jR_k and OR_l ,
wherein R_3 is independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, amino, (1-4C)alkyl and (1-4C)alkoxy.
38. The compound for use according to any preceding statement, wherein X_2 is hydroxy or a group of formula (A), wherein
n is 1 or 2;
 R_3 is selected from hydroxy, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_jR_k and OR_l ,
wherein R_3 is independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, amino, (1-4C)alkyl and (1-4C)alkoxy.
39. The compound for use according to any preceding statement, wherein X_2 is hydroxy or a group of formula (A), wherein
n is 1;
 R_3 is selected from hydroxy, (1-6C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, NR_jR_k and OR_l ,
wherein R_3 is optionally substituted by one or more substituent groups selected from (1-4C)alkyl and (1-3C)alkoxy.
40. The compound for use according to any preceding statement, wherein X_2 is hydroxy or a group of formula (A), wherein

n is 1;

R₃ is selected from hydroxy, (1-3C)alkyl, (3-8C)heterocyclyl, NR_jR_k and OR_l,

wherein R₃ is optionally substituted by one or more substituent groups selected from (1-2C)alkyl and (1-2C)alkoxy.

41. The compound for use according to any preceding statement, wherein X₂ is a group of formula (A), wherein

n is 1; and

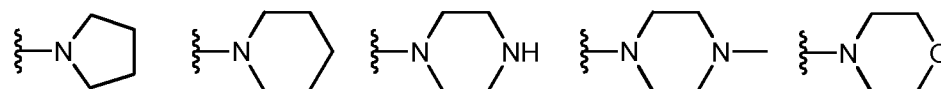
R₃ is selected from hydroxy, N-linked (3-8C)heterocyclyl, NR_jR_k and OR_l,

wherein R₃ is optionally substituted by one or more (1-2C)alkyl.

42. The compound for use according to any preceding statement, wherein X₂ is a group of formula (A), wherein

n is 1; and

R₃ is selected from hydroxy, NR_jR_k, OR_l (e.g. methoxy or ethoxy) or any one of the following:



43. The compound for use according to any preceding statement, wherein R_h and R_i are independently selected from hydrogen and (1-6C)alkyl.

44. The compound for use according to any preceding statement, wherein R_h and R_i are independently selected from hydrogen and (1-2C)alkyl.

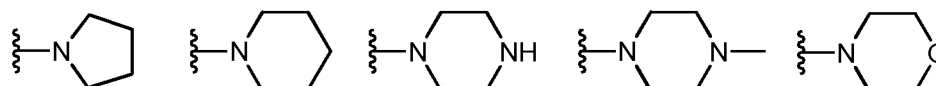
45. The compound for use according to any preceding statement, wherein R_h and R_i are hydrogen.

46. The compound for use according to any preceding statement, wherein R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, (1-4C)alkoxy, aryl and (3-8C)heterocyclyl.

47. The compound for use according to any preceding statement, wherein R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, aryl and N-linked (3-8C)heterocyclyl.

48. The compound for use according to any preceding statement, wherein R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, phenyl and 5-6 membered N-linked heterocyclyl.

49. The compound for use according to any preceding statement, wherein R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, phenyl or any one of the following:



50. The compound for use according to any preceding statement, wherein R_j and R_k are independently selected from hydrogen, (1-6C)alkyl and phenyl.

51. The compound for use according to any preceding statement, wherein R_l is (1-6C)alkyl.

52. The compound for use according to any preceding statement, wherein R_l is (1-3C)alkyl.

53. The compound for use according to any preceding statement, wherein X_2 is hydroxy.

54. The compound for use according to any preceding statement, wherein R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 5-12 membered heterocycle that is optionally substituted with one or more R_4 substituents.

55. The compound for use according to any preceding statement, wherein R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 8-12 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system that is optionally substituted with one or more R_4 substituents.

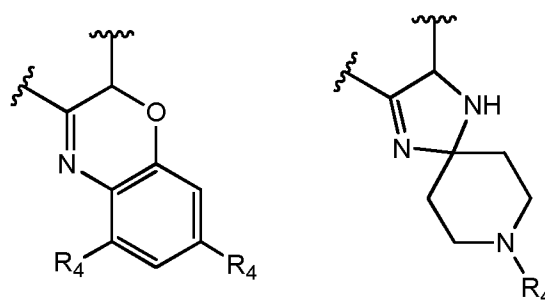
56. The compound for use according to any preceding statement, wherein R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 8-12 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system containing 1, 2 or 3 heteroatoms selected

from O and N, wherein said 8-12 membered fused or spiro heterobicycle is optionally substituted with one or more R_4 substituents.

57. The compound for use according to any preceding statement, wherein R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 9-11 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system containing 1, 2 or 3 heteroatoms selected from O and N, wherein said 9-11 membered fused or spiro heterobicycle is optionally substituted with one or more R_4 substituents.

58. The compound for use according to any preceding statement, wherein R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 10 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system containing 1, 2 or 3 heteroatoms selected from O and N, wherein said 10 membered fused or spiro heterobicycle is optionally substituted with one or more R_4 substituents.

59. The compound for use according to any preceding statement, wherein R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form either of the following groups:



60. The compound for use according to any preceding statement, wherein each R_4 is independently selected from halo, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_mR_n , OR_o ,

wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-

8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl.

61. The compound for use according to any preceding statement, wherein each R_4 is independently selected from halo, hydroxy, (1-6C)alkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_mR_n , OR_o ,

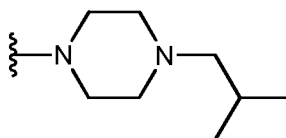
wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, (1-4C)alkyl and (1-4C)alkoxy.

62. The compound for use according to any preceding statement, wherein each R_4 is independently selected from halo, hydroxy, (1-6C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, NR_mR_n , OR_o ,

wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, (1-4C)alkyl and (1-4C)alkoxy.

63. The compound for use according to any preceding statement, wherein each R_4 is independently selected from hydroxy, (1-6C)alkyl and (3-8C)heterocyclyl, wherein each R_4 is independently optionally substituted with one or more groups, (1-4C)alkyl.

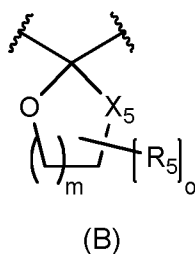
64. The compound for use according to any preceding statement, wherein each R_4 is independently selected from hydroxy, (1-4C)alkyl or a group:



65. The compound for use according to any preceding statement, wherein X_3 and X_4 are independently selected from hydroxy, OR_p and NR_qR_r .

66. The compound for use according to any preceding statement, wherein X_3 and X_4 are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a 4-6 membered heterocycle containing 1 or 2 heteroatoms selected from O and N, wherein the 4-6 membered heterocycle is optionally substituted with one or more R_5 substituents.

67. The compound for use according to any preceding statement, wherein X_3 and X_4 are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a group having a structure according to formula (B) shown below:



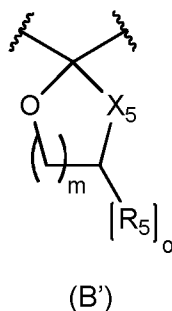
Wherein,

X_5 is selected from O or NR_m ;

m is a number selected from 1 and 2; and

o is a number selected from 1 and 2.

68. The compound for use according to any preceding statement, wherein X_3 and X_4 are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a group having a structure according to formula (B') shown below:



wherein,

X_5 is selected from O or NR_m ;

m is a number selected from 1 and 2; and

o is a number selected from 1 and 2.

69. The compound for use according to statement 61 or 62, wherein X_5 is O.

70. The compound for use according to statement 61, 62 or 63, wherein m is 1.
71. The compound for use according to any one of statement 61 to 64, wherein o is 1.
72. The compound for use according to any preceding statement, wherein each R₅ is independently selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, amino, carboxy, (1-6C)alkyl, (1-4C)alkoxy, methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl.
73. The compound for use according to any preceding statement, wherein each R₅ is independently selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, amino, carboxy, (1-6C)alkyl, (1-4C)alkoxy, methylamino and dimethylamino.
74. The compound for use according to any preceding statement, wherein each R₅ is independently selected from fluoro, chloro, hydroxy, oxo, amino, (1-3C)alkyl and (1-3C)alkoxy.
75. The compound for use according to any preceding statement, wherein each R₅ is independently selected from hydroxy, oxo and (1-4C)alkoxy.
76. The compound for use according to any preceding statement, wherein R₅ is oxo.
77. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ia), (IIa) or (IIIa) shown herein, wherein
- R₁ is as described in any of numbered paragraphs (5) to (8);
 - R_a and R_b are as described in any of numbered paragraphs (11) to (12);
 - R_c is as described in any of numbered paragraphs (24) to (25);
 - X₁ is as described in numbered paragraph (39);
 - X₂ is as described in numbered paragraph (40) or (41);
 - n is as described in numbered paragraph (42) or (43);
 - R₃ is as described in any of numbered paragraphs (46) to (50);
 - R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 - R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 - R_l is as described in any of numbered paragraphs (59) to (60);
 - X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);
 - m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (81) to (84)

78. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ia), (IIa) or (IIIa) shown herein, wherein

R₁ is as described in any of numbered paragraphs (5) to (8);

R_a and R_b are as described in any of numbered paragraphs (15) to (22);

R_c is as described in any of numbered paragraphs (24) to (25);

X₁ is as described in numbered paragraph (39);

X₂ is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (42) or (43);

R₃ is as described in any of numbered paragraphs (46) to (50);

R_h and R_i are as described in any of numbered paragraphs (52) to (53);

R_j and R_k are as described in any of numbered paragraphs (55) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (81) to (84)

79. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ia), (IIa) or (IIIa) shown herein, wherein

R₁ is as described in any of numbered paragraphs (7) to (8);

R_a and R_b are as described in numbered paragraph (12);

R_c is as described in numbered paragraph (25);

X₁ is as described in numbered paragraph (39);

X₂ is as described in numbered paragraph (40) or (41);

n is as described in numbered paragraph (43);

R₃ is as described in any of numbered paragraphs (48) to (50);

R_h and R_i are as described in numbered paragraph (53);

R_j and R_k are as described in any of numbered paragraphs (56) to (57);

R_l is as described in any of numbered paragraphs (59) to (60);

X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);

m is as described in numbered paragraph (78);

o is as described in numbered paragraph (79); and

R₅ is as described in any of numbered paragraphs (83) to (84).

80. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ia), (IIa) or (IIIa) shown herein, wherein

R₁ is as described in any of numbered paragraphs (7) to (8);
R_a and R_b are as described in any one of numbered paragraphs (19) to (22);
R_c is as described in numbered paragraph (25);
X₁ is as described in numbered paragraph (39);
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (43);
R₃ is as described in any of numbered paragraphs (48) to (50);
R_h and R_i are as described in numbered paragraph (53);
R_j and R_k are as described in any of numbered paragraphs (56) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (83) to (84).

81. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ib), (IIb) or (IIIb) shown herein, wherein

R₂ is as described in numbered paragraph (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38);
X₁ is as described in numbered paragraph (39);
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (46) to (50);
R_h and R_i are as described in any of numbered paragraphs (52) to (53);
R_j and R_k are as described in any of numbered paragraphs (55) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₃ and X₄ are as described in any of numbered paragraphs (75) to (76);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (81) to (84).

82. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ib), (IIb) or (IIIb) shown herein, wherein

R_2 is as described in numbered paragraph (32);
 R_d is as described in any of numbered paragraphs (33) to (34);
 R_e is as described in any of numbered paragraphs (37) to (38);
 X_1 is as described in numbered paragraph (39);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (42) or (43);
 R_3 is as described in any of numbered paragraphs (46) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
or R_2 and X_1 or R_2 and X_2 are as described in any of numbered paragraphs (65) to (67), wherein R_4 is as described in any of numbered paragraphs (70) to (72);
 X_3 and X_4 are as described in any of numbered paragraphs (75) to (76);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (81) to (84).

83. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ic), (IIc) or (IIIc) shown herein, wherein

R_1 is as described in any of numbered paragraphs (5) to (8);
 R_a and R_b are as described in any of numbered paragraphs (11) to (12);
 R_c is as described in any of numbered paragraphs (24) to (25);
 R_2 is as described in any of numbered paragraphs (31) to (32);
 R_d is as described in any of numbered paragraphs (33) to (34);
 R_e is as described in any of numbered paragraphs (37) to (38);
 X_2 is as described in numbered paragraph (40) or (41);
 n is as described in numbered paragraph (42) or (43);
 R_3 is as described in any of numbered paragraphs (48) to (50);
 R_h and R_i are as described in any of numbered paragraphs (52) to (53);
 R_j and R_k are as described in any of numbered paragraphs (55) to (57);
 R_l is as described in any of numbered paragraphs (59) to (60);
 X_5 is as described in numbered paragraph (77);
 m is as described in numbered paragraph (78);
 o is as described in numbered paragraph (79); and
 R_5 is as described in any of numbered paragraphs (83) to (84).

84. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ic), (IIc) or (IIIc) shown herein, wherein

R₁ is as described in any of numbered paragraphs (5) to (8);
R_a and R_b are as described in any of numbered paragraphs (15) to (22);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in any of numbered paragraphs (31) to (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38);
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (48) to (50);
R_h and R_i are as described in any of numbered paragraphs (52) to (53);
R_j and R_k are as described in any of numbered paragraphs (55) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (83) to (84).

85. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ic), (IIc) or (IIIc) shown herein, wherein

R₁ is as described in numbered paragraph (8);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in numbered paragraph (32);
R_d is as described in numbered paragraph (34);
R_e is as described in numbered paragraph (38);
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (49) to (50);
R_h and R_i are as described in numbered paragraphs (53);
R_j and R_k are as described in any of numbered paragraphs (56) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (83) to (84).

86. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ic), (IIc) or (IIIc) shown herein, wherein

R₁ is as described in numbered paragraph (7) or (8);
R_a and R_b are as described in any of numbered paragraphs (21) to (22);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in numbered paragraph (32);
R_d is as described in numbered paragraph (34);
R_e is as described in numbered paragraph (38);
X₂ is as described in numbered paragraph (40) or (41);
n is as described in numbered paragraph (42) or (43);
R₃ is as described in any of numbered paragraphs (49) to (50);
R_h and R_i are as described in numbered paragraphs (53);
R_j and R_k are as described in any of numbered paragraphs (56) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78);
o is as described in numbered paragraph (79); and
R₅ is as described in any of numbered paragraphs (83) to (84).

87. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Id), (IIId) or (IIIId) shown herein, wherein

R₁ is as described in any of numbered paragraphs (5) to (8);
R_a and R_b are as described in any of numbered paragraphs (11) to (12);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in any of numbered paragraphs (31) to (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38);
R₃ is as described in any of numbered paragraphs (48) to (50);
R_h and R_i are as described in any of numbered paragraphs (52) to (53);
R_j and R_k are as described in any of numbered paragraphs (55) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78); and
R₅ is as described in any of numbered paragraphs (83) to (84).

88. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Id), (IIId) or (IIIId) shown herein, wherein

R₁ is as described in any of numbered paragraphs (5) to (8);
R_a and R_b are as described in any of numbered paragraphs (19) to (22);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in any of numbered paragraphs (31) to (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38);
R₃ is as described in any of numbered paragraphs (48) to (50);
R_h and R_i are as described in any of numbered paragraphs (52) to (53);
R_j and R_k are as described in any of numbered paragraphs (55) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78); and
R₅ is as described in any of numbered paragraphs (83) to (84).

89. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Id), (IIId) or (IIIId) shown herein, wherein

R₁ is as described in numbered paragraph (8);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in numbered paragraph (32);
R_d is as described in numbered paragraph (34);
R_e is as described in numbered paragraph (38);
R₃ is as described in any of numbered paragraphs (49) to (50);
R_h and R_i are as described in numbered paragraphs (53);
R_j and R_k are as described in any of numbered paragraphs (56) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78); and
R₅ is as described in any of numbered paragraphs (83) to (84).

90. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Id), (IIId) or (IIIId) shown herein, wherein

R₁ is as described in numbered paragraph (7) or (8);
R_a and R_b are as described in any of numbered paragraphs (21) to (22);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in numbered paragraph (32);
R_d is as described in numbered paragraph (34);

R_e is as described in numbered paragraph (38);
R₃ is as described in any of numbered paragraphs (49) to (50);
R_h and R_i are as described in numbered paragraphs (53);
R_j and R_k are as described in any of numbered paragraphs (56) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78); and
R₅ is as described in any of numbered paragraphs (83) to (84).

91. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ie), (IIe) or (IIIe) shown herein, wherein

R₂ is as described in any of numbered paragraphs (31) to (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38);
R₃ is as described in any of numbered paragraphs (48) to (50);
R_h and R_i are as described in any of numbered paragraphs (52) to (53);
R_j and R_k are as described in any of numbered paragraphs (55) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78); and
R₅ is as described in any of numbered paragraphs (83) to (84).

92. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (Ie), (IIe) or (IIIe) shown herein, wherein

R₂ is as described in numbered paragraph (32);
R_d is as described in numbered paragraph (34);
R_e is as described in numbered paragraph (38);
R₃ is as described in any of numbered paragraphs (49) to (50);
R_h and R_i are as described in numbered paragraphs (53);
R_j and R_k are as described in any of numbered paragraphs (56) to (57);
R_l is as described in any of numbered paragraphs (59) to (60);
X₅ is as described in numbered paragraph (77);
m is as described in numbered paragraph (78); and
R₅ is as described in any of numbered paragraphs (83) to (84).

93. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (If), (IIIf) or (IIIIf) shown herein, wherein

R₁ is as described in any of numbered paragraphs (5) to (8);
R_a and R_b are as described in any of numbered paragraphs (11) to (12);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in any of numbered paragraphs (31) to (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38); and
R₅ is as described in any of numbered paragraphs (83) to (84).

94. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (If), (IIIf) or (IIIIf) shown herein, wherein

R₁ is as described in any of numbered paragraphs (5) to (8);
R_a and R_b are as described in any of numbered paragraphs (15) to (22);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in any of numbered paragraphs (31) to (32);
R_d is as described in any of numbered paragraphs (33) to (34);
R_e is as described in any of numbered paragraphs (37) to (38); and
R₅ is as described in any of numbered paragraphs (83) to (84).

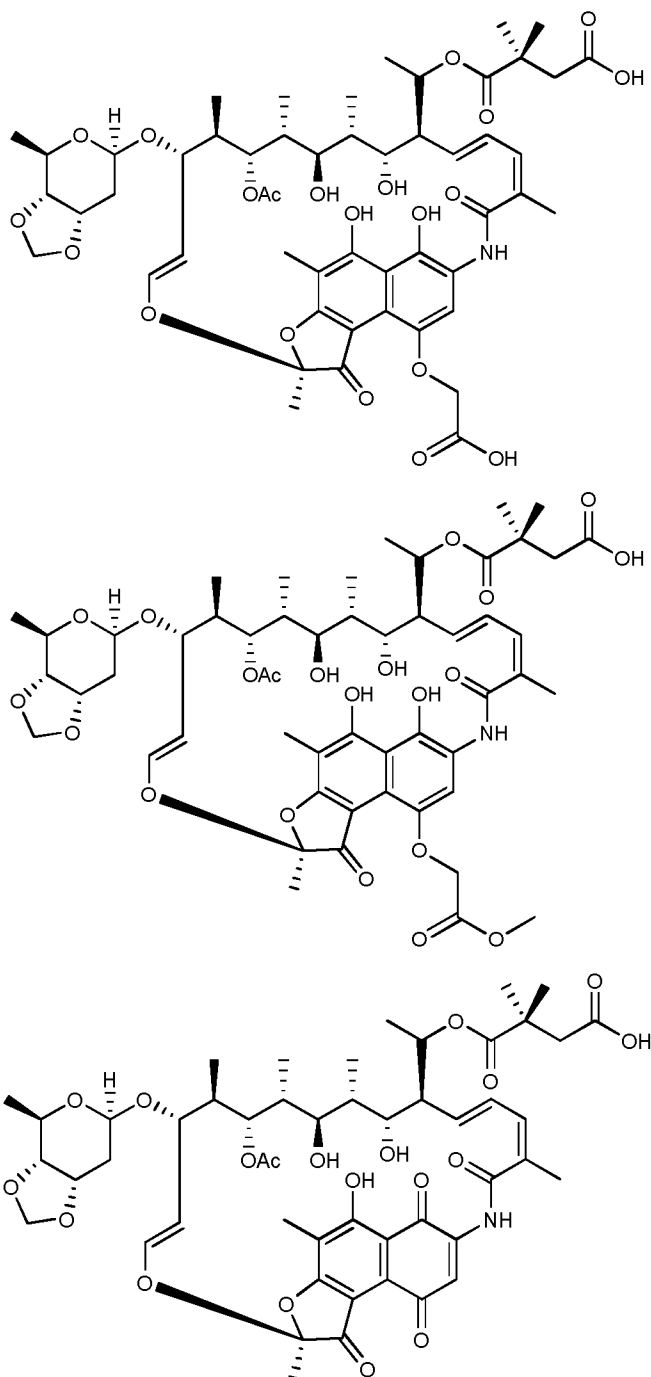
95. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (If), (IIIf) or (IIIIf) shown herein, wherein

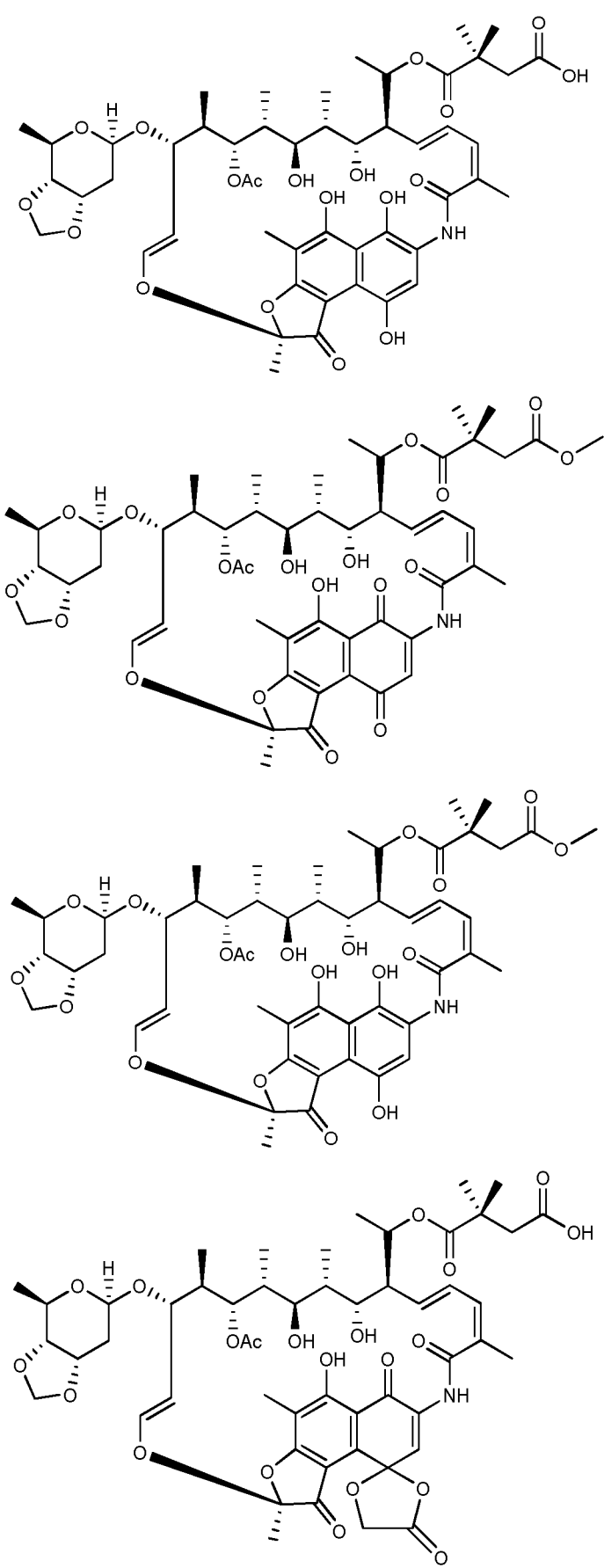
R₁ is as described in numbered paragraph (8);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in numbered paragraph (32);
R_d is as described in numbered paragraph (34);
R_e is as described in numbered paragraph (38); and
R₅ is as described in any of numbered paragraphs (83) to (84).

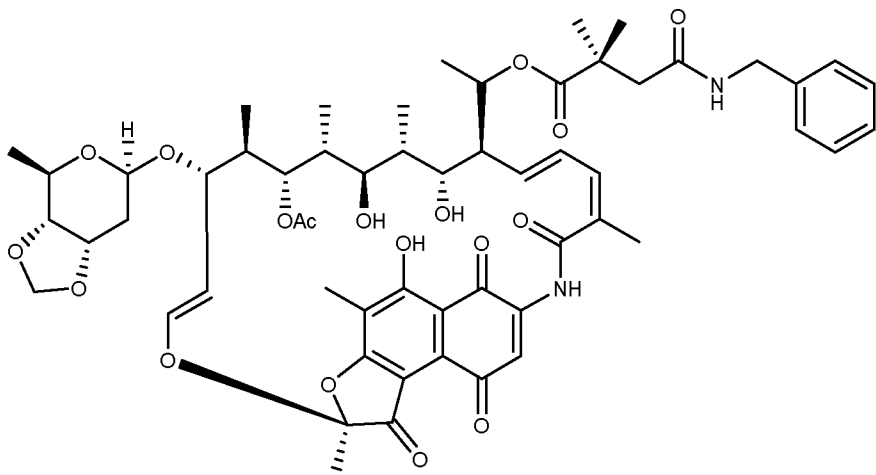
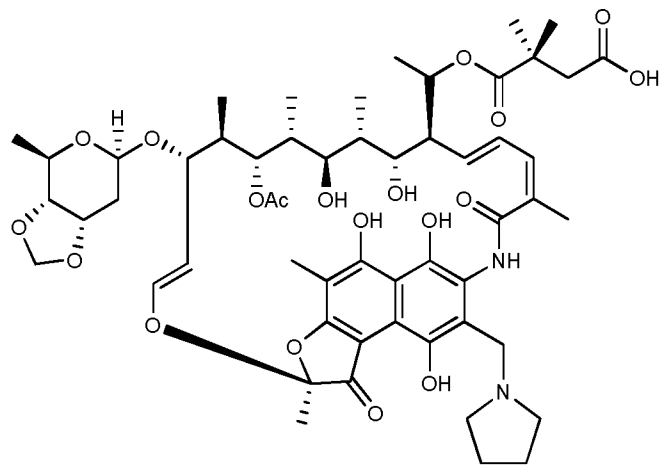
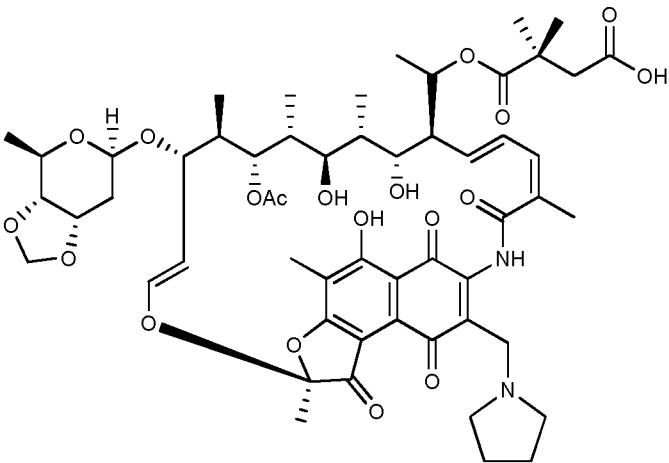
96. The compound for use according to any preceding statement, wherein the compound has a structure according to formula (If), (IIIf) or (IIIIf) shown herein, wherein

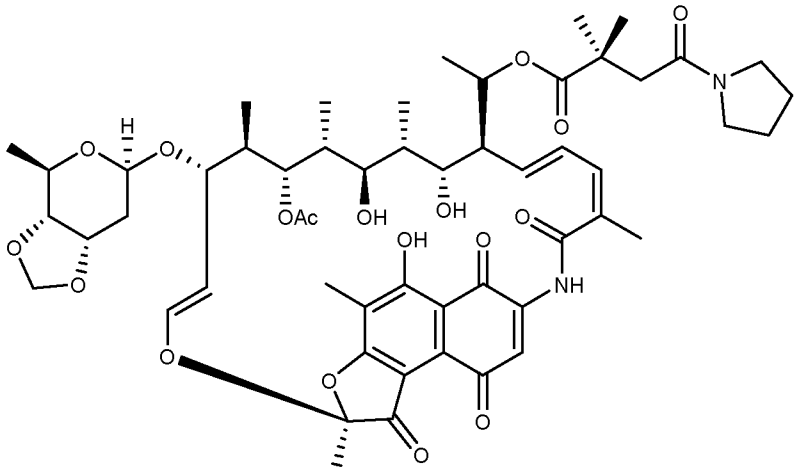
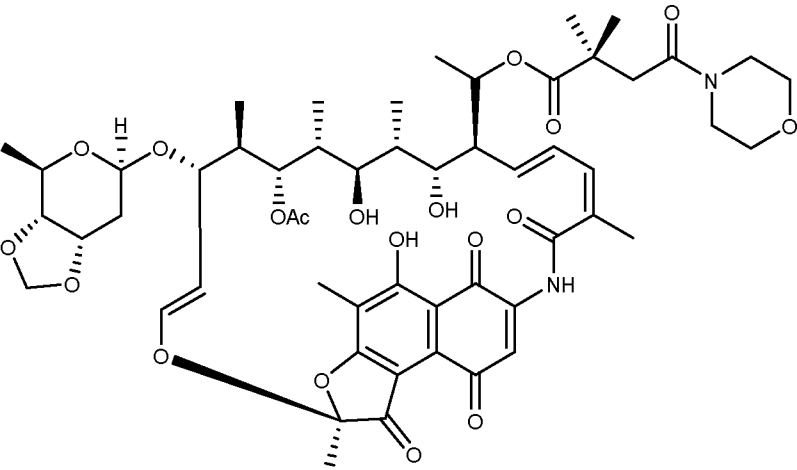
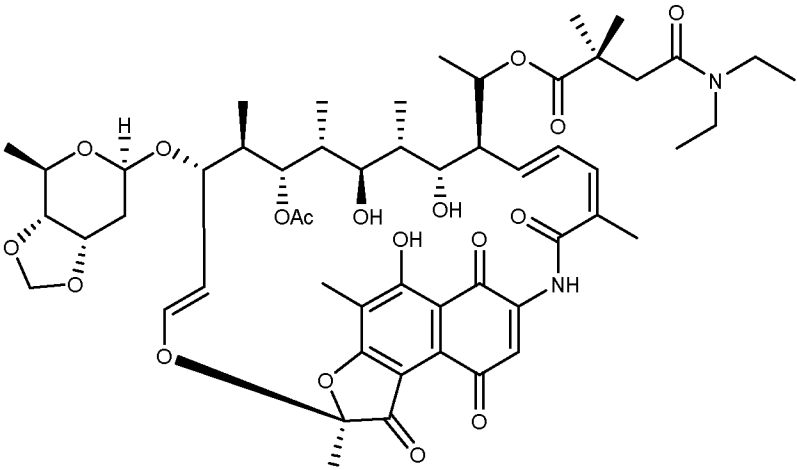
R₁ is as described in numbered paragraph (7) or (8);
R_a and R_b are as described in any of numbered paragraphs (21) to (22);
R_c is as described in any of numbered paragraphs (24) to (25);
R₂ is as described in numbered paragraph (32);
R_d is as described in numbered paragraph (34);
R_e is as described in numbered paragraph (38); and
R₅ is as described in any of numbered paragraphs (83) to (84).

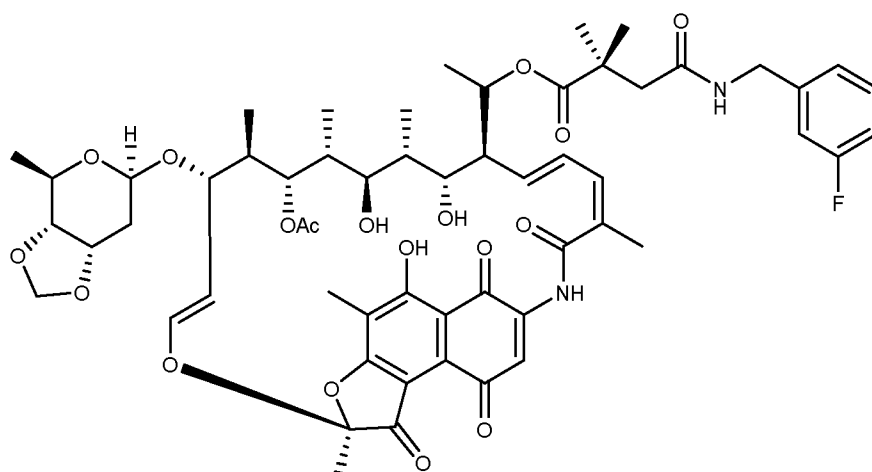
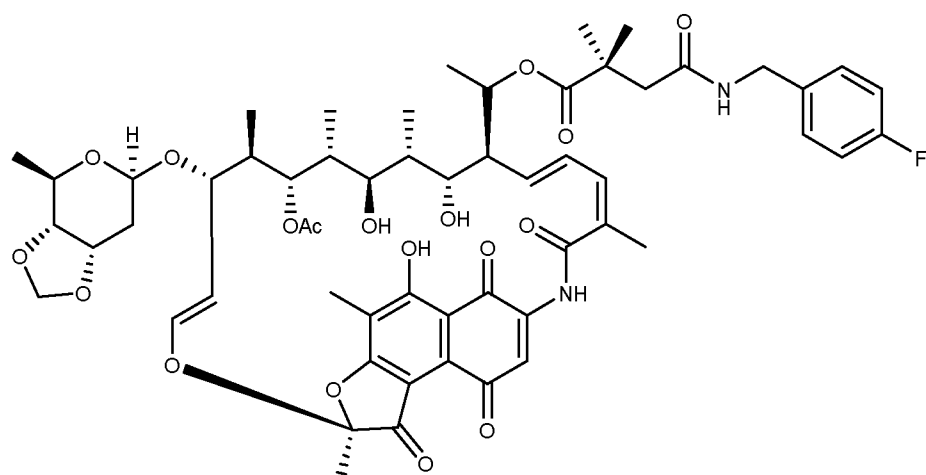
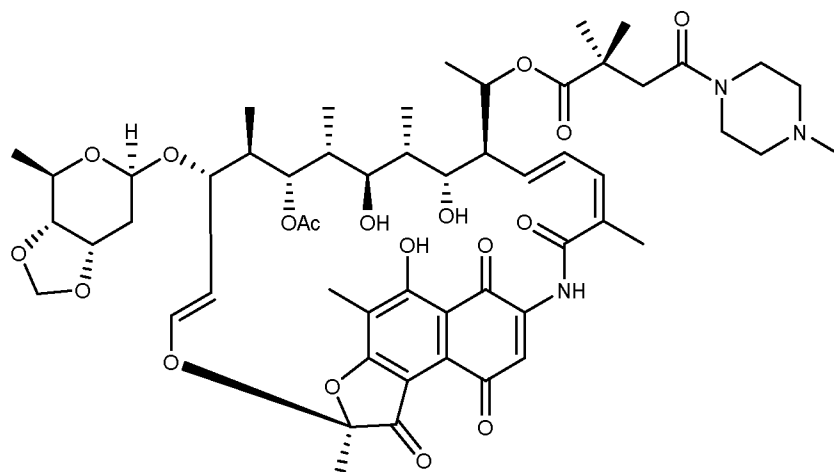
97. The compound for use according to any preceding statement, wherein the compound has any one of the following structures:

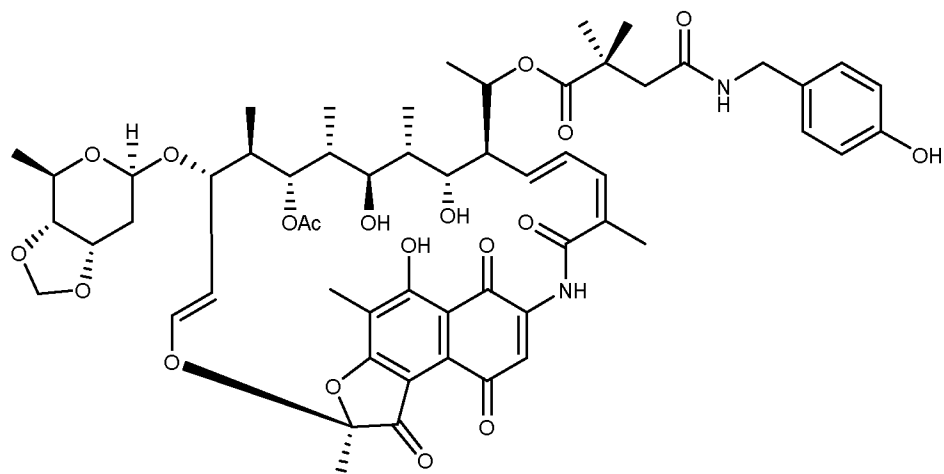
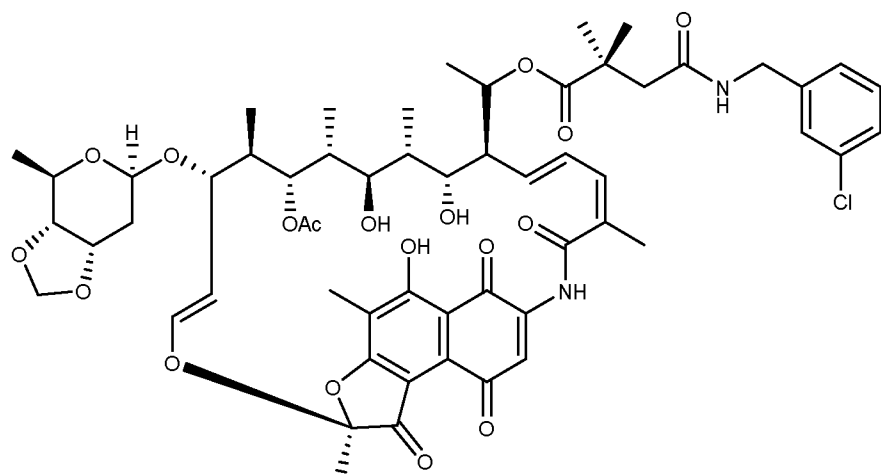
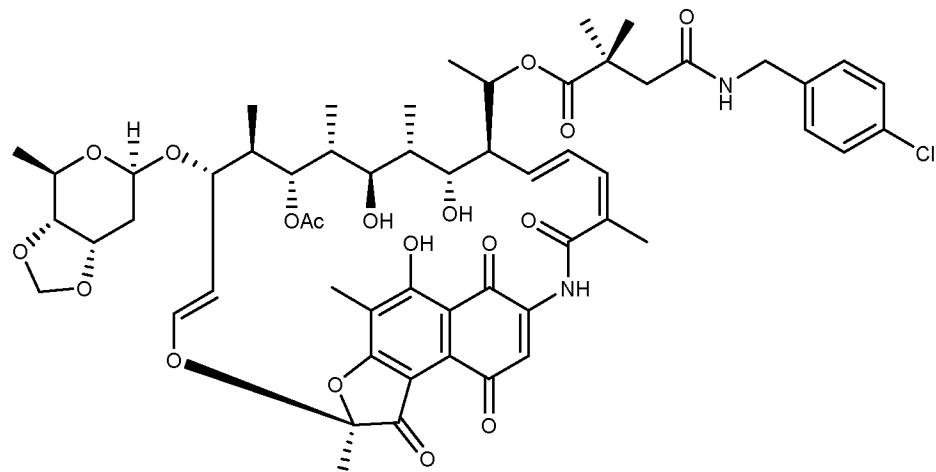


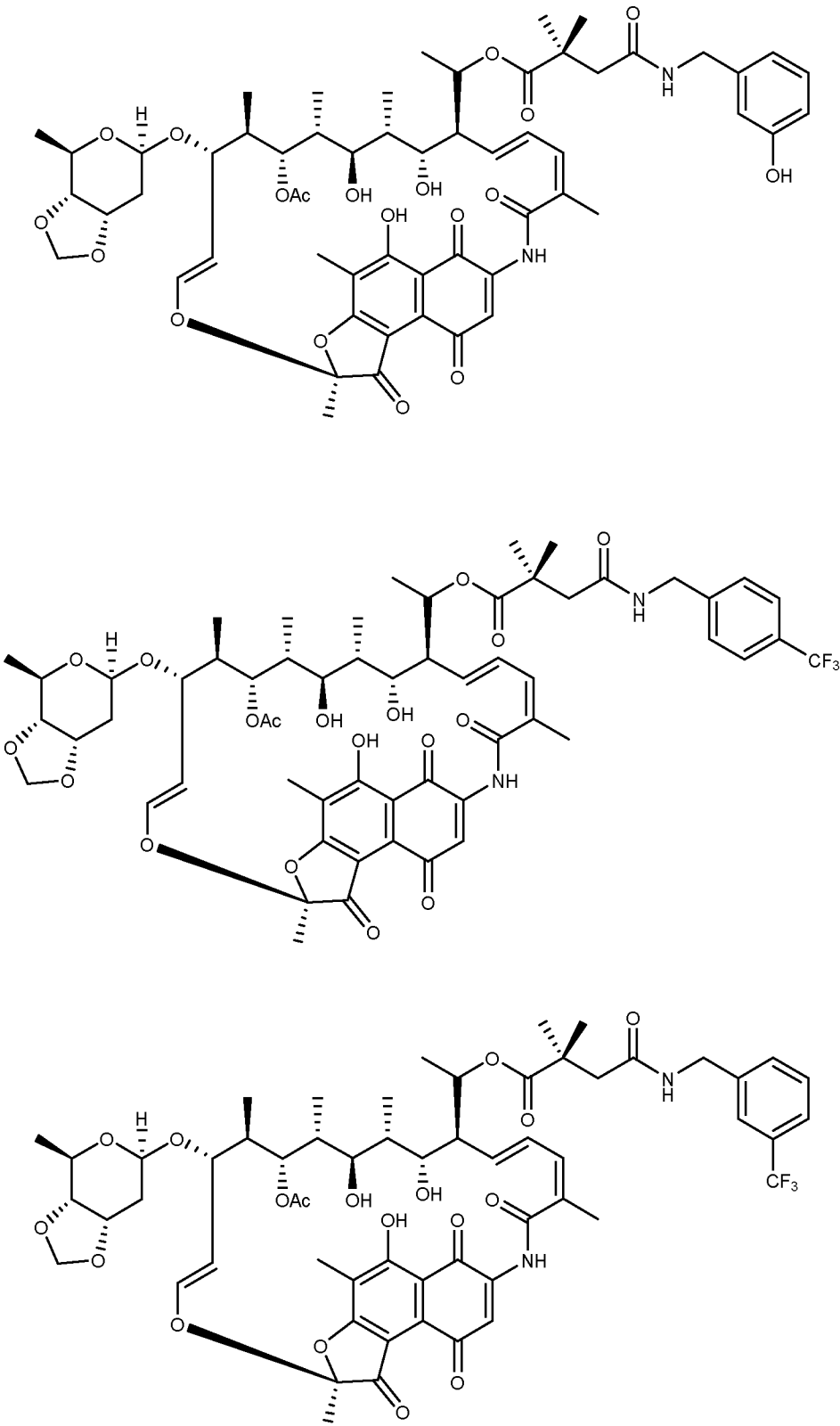


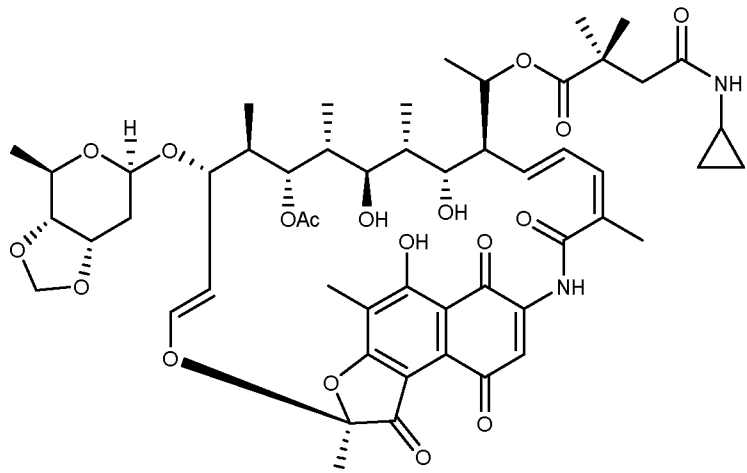
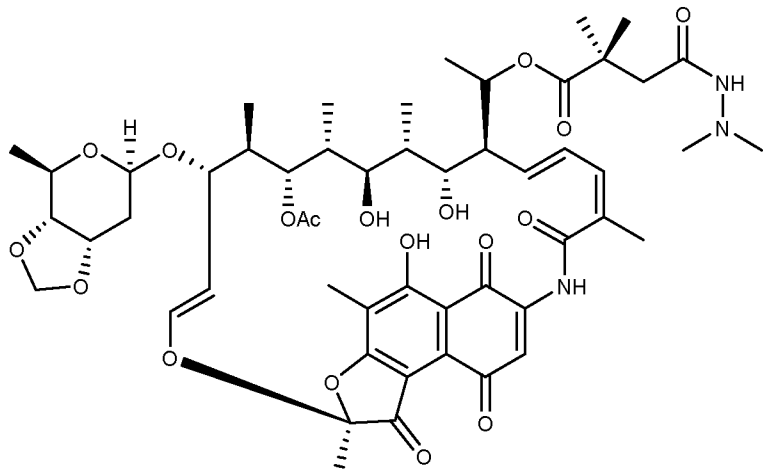
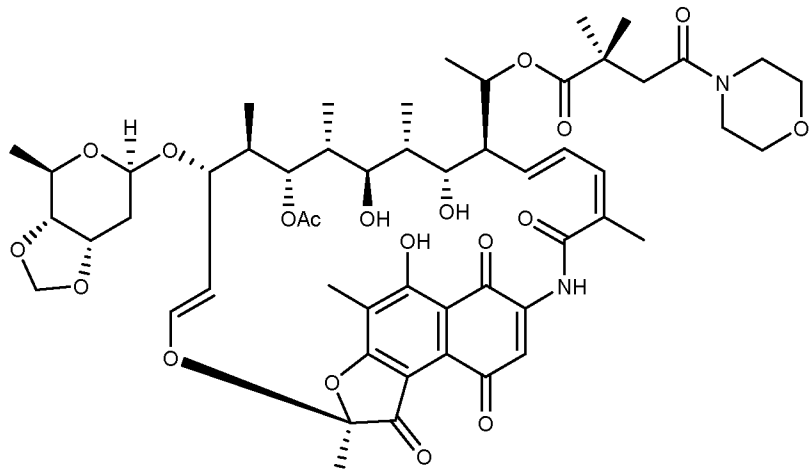


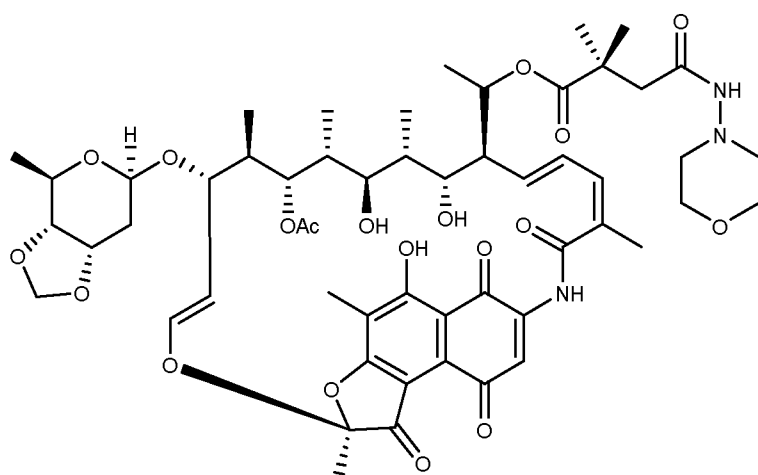
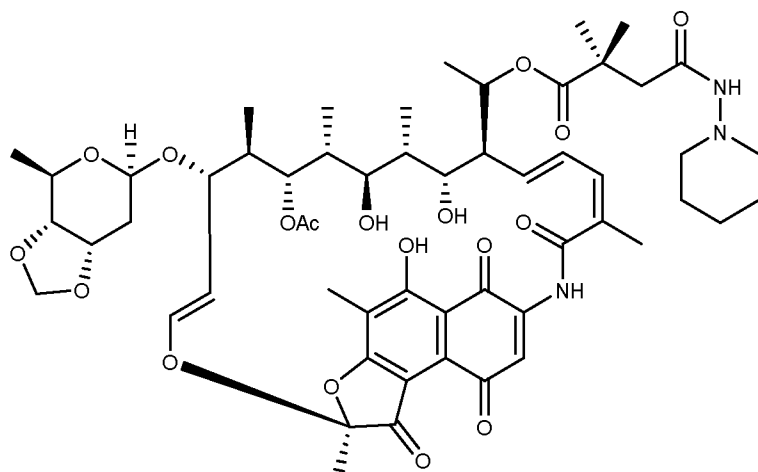




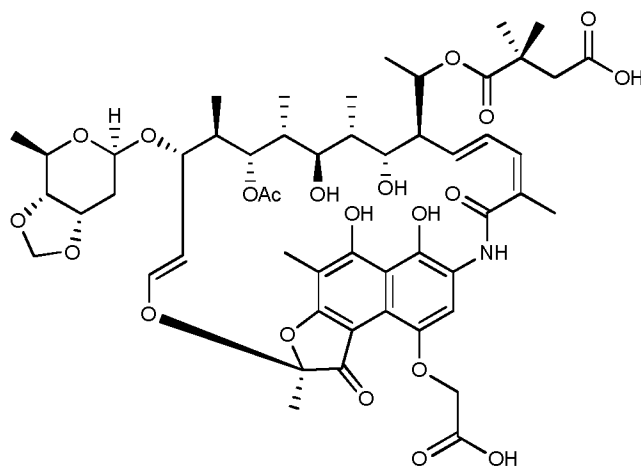


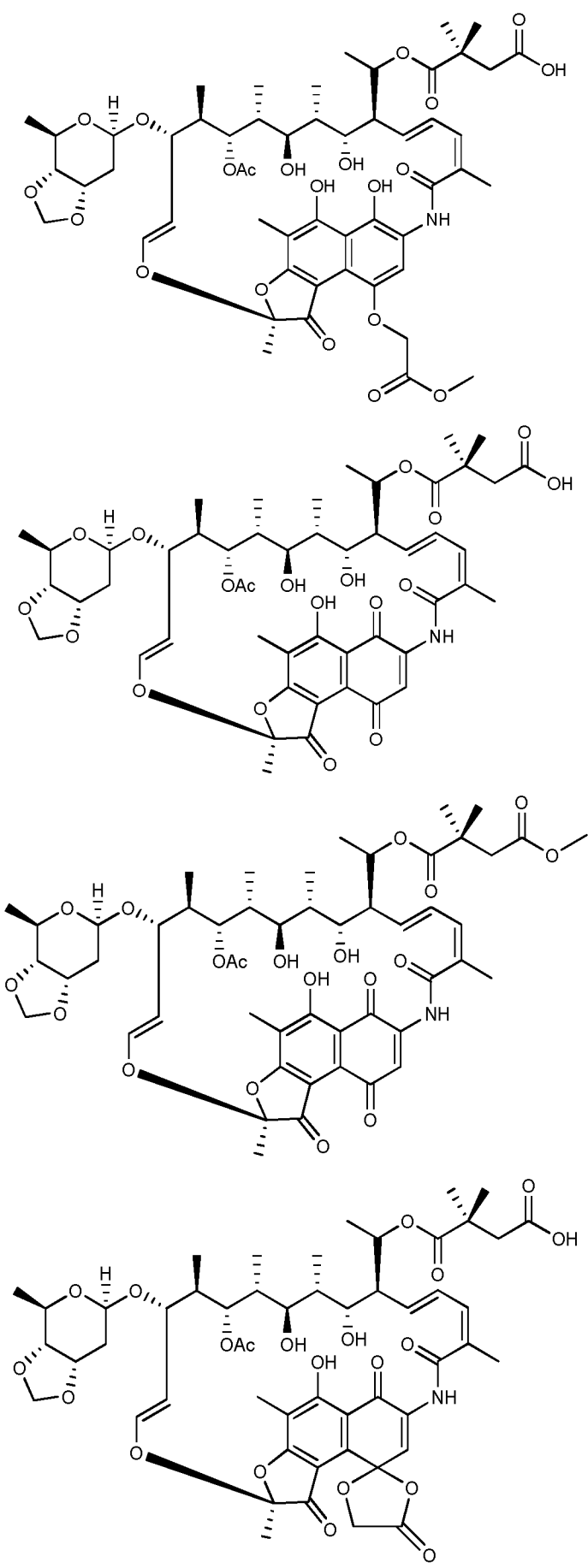


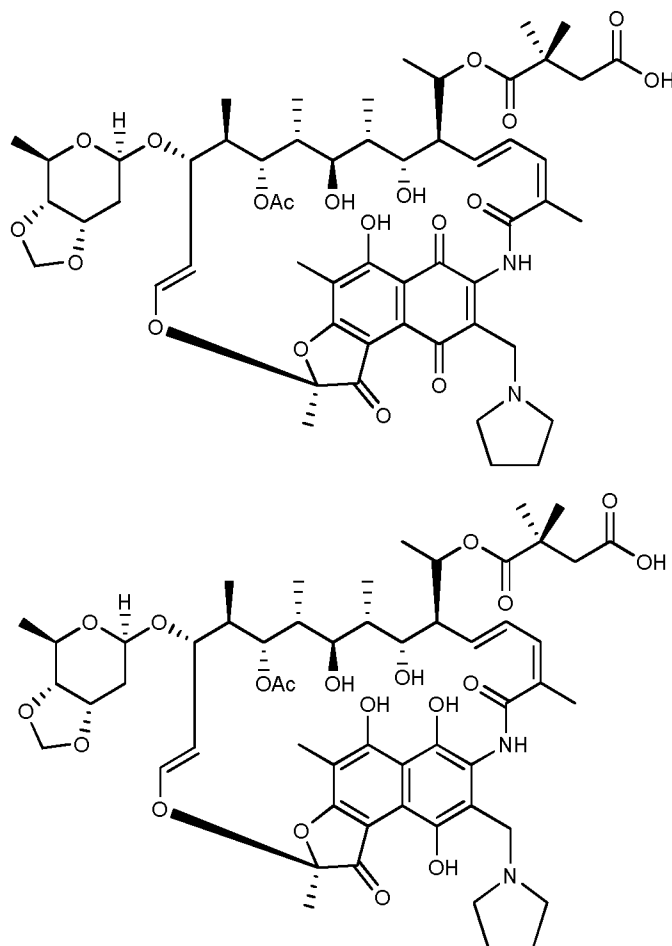




98. The compound for use according to any preceding statement, wherein the compound has any one of the following structures:







99. The compound for use according to any preceding statement, wherein the rifampicin-resistant bacteria is one or more rifampicin-resistant Gram positive bacteria.
100. The compound for use according to any preceding statement, wherein the rifampicin-resistant bacteria is rifampicin-resistant *S. aureus*.
101. The compound for use according to any preceding statement, wherein the rifampicin-resistant bacteria is rifampicin-resistant *M. tuberculosis*.
102. The compound for use according to any preceding statement, wherein the infection caused by rifampicin-resistant bacteria is tuberculosis.
103. A compound of formula (I), (II) or (III) as defined in any preceding statement, or a pharmaceutically acceptable salt, hydrate or solvate thereof, with the proviso that, in formula (I), when R₁ is hydroxy and R₂ is hydrogen, X₁ is not O.
104. The compound of statement 103, wherein, in formula (I), R₁ is not hydroxy.

105. The compound of statement 103 or 104, wherein, in formula (I), R_2 is not hydrogen.
106. A compound of any one of statements 103, 104 or 105 for use in therapy.
107. A compound of any one of statements 103, 104 or 105 for use as a medicament.
108. A pharmaceutical composition comprising a compound as defined in any one of statements 103, 104 or 105, or a pharmaceutically acceptable salt or solvate thereof, and one or more pharmaceutically acceptable excipients or carriers.

EXAMPLES

[00193] One or more examples of the invention will now be described, for the purpose of illustration only, with reference to the accompanying figures, in which:

Fig. 1 shows identification and mode of action of KglA. **A.** Disk diffusion assay with rifampicin (RIF), carbenicillin (Cb) and Kanglemycin A (KglA). The paper disks soaked with antibiotics were placed on the lawns of wild-type *B. subtilis* carrying *lacZ* gene under P_{helD} promoter, inducible during partial inhibition of transcription (left plate), and RIF-resistant *B. subtilis* (right plate). Note the blue halo around growth inhibition zones in the case of transcription inhibitors. **B.** Chemical structure of KglA in comparison with RIF. The *ansa*-chain modifications in KglA are highlighted. The semi-synthetic group of RIF is shown in purple. **C.** Transcription *in vitro* by *E. coli* RNAP on linear template containing T7A1 promoter. Run off, termination, and abortive tri- and tetra-nucleotides are marked. Note that tetra-nucleotide migrates faster than tri-nucleotide in these electrophoretic conditions. **D and E.** Inhibition of wild-type and RIF-resistant *E. coli* RNAPs by RIF and KglA. Error bars are $\pm$ SD. The brackets in the table contain $\pm$ SD, and Hill slope. **F.** Different ratio of the di- (pppApU) and the tri-nucleotide long (pppApUpC) abortive products in the presence of RIF and KglA. Transcription in the presence of nucleotides depicted (in the absence of CpA primer). Note that in 33% gel, run off and termination products remain in the well.

Fig. 2 shows **A.** Mass spectrum of KglA showing peaks at 1004.3866, 1020.3632 and 1985.7900 Da, assigned as $[M+Na]^+$, $[M+K]^+$ and $[2M+Na]^+$ respectively. **B.** Crystallographically determined structure of KglA (from synchrotron data). Non-H atoms are labelled. **C.** 500 MHz ^1H NMR spectra of KglA in $CDCl_3$. **D.** 125 MHz $^{13}C\{^1H\}$ NMR spectra of KglA in $CDCl_3$.

Fig. 3 shows the mass spectrum of DEMB1 showing peaks at 1042.42 and 1064.4074, assigned as $[M+H]^+$ and $[M+Na]^+$ respectively, which is the expected mass according to the DEMB1 structure.

Fig. 4 shows the mass spectrum of DEMB3 showing peaks at 1056.44 and 1078.42, assigned as $[M+H]^+$ and $[M+Na]^+$ respectively. Some contamination with DEMB1 was observed as $[M+H]^+=1042.42$.

Fig. 5 shows the mass spectrum of DEMB1C shown as $[M+H]^+ = 10062.3932$.

Fig. 6 shows the inhibition of RIF-resistant *E. coli* β S531L RNAP by DEMB1 shows very low IC₅₀ (for comparison IC₅₀[Rif] = 675 μ M=675 μ g/mL).

Fig. 7 shows the inhibition of RIF-resistant *E. coli* β S531L RNAP by DEMB3 shows very low IC₅₀ (for comparison IC₅₀[Rif] = 675 μ M=675 μ g/mL).

Fig. 8 shows the inhibition of RIF-resistant *E. coli* β S531L RNAP by DEMB1C shows relatively low IC₅₀ (for comparison IC₅₀[Rif] = 675 μ M=675 μ g/mL).

Analytical methods and assays

NMR analysis of Kanglemycin A (KglA)

[00194] All NMR spectra were recorded in CDCl₃ at 10°C. ¹H and ¹³C{¹H} NMR spectra were recorded directly with a Jeol Lambda 500 MHz spectrometer, whilst ¹H COSY; 45, 90 and 135 DEPT; HMQC and HMBC were recorded with a Jeol ECS 400 MHz spectrometer (not shown). Proton and carbon assignment was performed *de novo* from both 1D and 2D NMR experiments and was in close agreement with the literature (Wang et al., 1988).

Disk diffusion assay

[00195] Standard disc diffusion assay (Kirby-Bauer) was performed with the *B. subtilis* 168 *amyE::P_{helD}-lacZ cat* reporter strain or RIF-resistant *B. subtilis* 168 *rpoB_{H482R}* strain as described (Bauer et al., 1966). Briefly, disks were loaded with to 10 μ g of each drug, air-dried and placed on nutrient agar plates with embedded lawn of bacteria and x-gal (100 μ g/mL). Plates were incubated overnight at 37°C and scanned.

Purification of *E. coli* RNAP core and σ^{70} for transcription assays

[00196] RIF-resistant mutations were introduced in pETLRpoB plasmid (6xHis-tag on N-terminus of β subunit of *E. coli* RNAP) (Smith and Savery, 2005) by site-directed mutagenesis

using QuikChange II kit (Stratagene). Wild-type or mutant plasmids were transformed along with pRSFD2-rpoZ (encoding for ω subunit) in T7 Express strain (New England Biolabs). Expression and purification of core RNAP was performed as described (Kashlev et al., 1996) (with heparin chromatography used instead of gel filtration as suggested). N-terminal 6xHis-tagged *E. coli* σ^{70} subunit was purified as described (Zenkin et al., 2007).

In vitro transcription

[00197] One pmol of wild-type or mutant RNAP core and 3 pmols of σ^{70} and 0.1 pmols of linear template containing T7A1 promoter (Julius and Yuzenkova, 2017; Roghanian et al., 2015) were mixed in 7 μ L of transcription buffer (20 mM Tris HCl pH 7.9, 40 mM KCl, 10 mM MgCl₂). 1 μ L of DMSO containing or not containing antibiotics (concentrations specified in Figures) was added to the reaction. Transcription was initiated by the addition of 2 μ L of the mixture of nucleotides in transcription buffer, containing (final concentrations): 25 μ M CpA (or none in Fig. 1E), 100 μ M ATP, CTP and GTP and 10 μ M α -[³²P]UTP (20 Ci/mmol) (Hartmann Analytic). Reactions were stopped after 10-min incubation at 37°C by the addition of formamide-containing loading buffer. Products were separated on 20% or 33% denaturing (8M urea) polyacrylamide gels, revealed by PhosphorImaging (GE Healthcare), and analyzed using ImageQuant software (GE Healthcare). Activities (a sum of run off and termination products) were normalized to the activity without antibiotic, which was taken as 100%. The average activity of at least three replicates for each concentration of antibiotic was plotted (with their standard deviations as error bars) against concentration and fitted in four parameter logistic equation by nonlinear regression using SigmaPlot. The averages and standard deviations of the three individual IC₅₀s are reported in Fig 1E.

Determination of minimum inhibitory concentrations for bacteria

[00198] MICs were determined using the agar dilution method specified by the British Society for Antimicrobial Chemotherapy against a collection of 56 isolates (Andrews, 2001). Briefly, KglA was initially dissolved in a minimal volume of dimethyl sulfoxide and diluted in water before incorporation into IsoSensitest agar (Oxoid) at a final concentration range of 128 – 0.031 μ g/mL. A final inoculum of 10 000 CFU/spot was used for inoculation of plates. Cultures were incubated for 22 hours at 37 $\pm$ 0.5 °C. The MIC was recorded as the lowest concentration of KglA that achieved complete inhibition of visible growth. Inhibitor-free controls were also tested, including those containing equivalent solvent concentrations. All tests were performed at least twice on separate occasions to demonstrate reproducibility.

[00199] The collection included 16 isolates acquired from the National Collection of Type Cultures (NCTC; Colindale, UK), 3 isolates from the American Type Culture Collection (ATCC; Manassas, USA), and one from the National Collection of Pathogenic Fungi (NCPF; Colindale, UK). Also included were 36 strains of methicillin-resistant *Staphylococcus aureus* (MRSA) kindly supplied by Public Health England (Colindale, UK). These 36 strains were isolated from clinical samples in five European countries and included representatives of the major clones responsible for outbreaks of infection.

Example 1 – Kanglemycin A (“KglA”)

Isolation of KglA

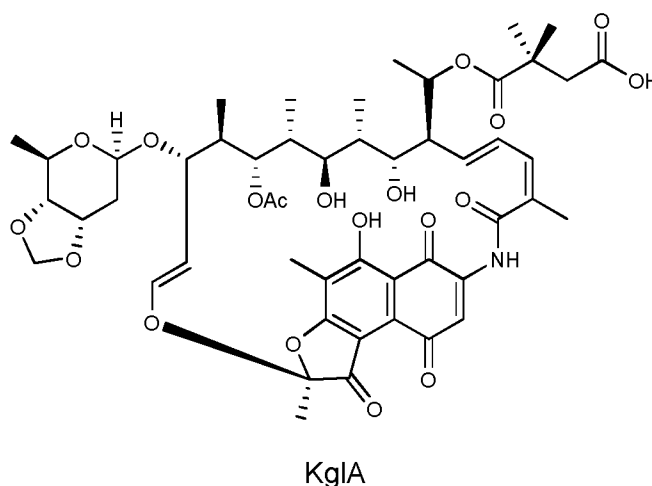
[00200] Actinomycete bacteria have historically been an excellent source of bioactive compounds, particularly antibiotics. To identify new antibiotics targeting transcription, a subset of strains from the Demuris collection of actinomycetes were screened for their ability to inhibit cell growth and to inhibit cellular transcription. As a reporter strain, previously described *B. subtilis* strain was used, which has a *lacZ* gene fused to the promoter of the bacterial helicase *helD*. This promoter is upregulated by the stress induced by partial inhibition of transcription resulting in a colorimetric response on an X-gal infused agar plate, thus indicating the presence of sub-inhibitory concentrations of an antibiotic targeting transcription (Fig. 1A left Petri dish; compare halos produced by RIF and carbenicillin, an inhibitor of cell wall synthesis) (Urban et al., 2007). The isolate *Amycolatopsis* DEM30355 was of particular interest as it produced a compound (identified as KglA, see below), which gave a blue halo at the edge of the zone of bacteria growth inhibition indicative of transcription inhibition (Fig. 1A, left Petri dish). Importantly, in contrast to RIF, this new compound inhibited RIF-resistant *B. subtilis* strain (β H482R; β H526R in *E. coli* numbering) (Fig. 1A, right Petri dish).

[00201] *Amycolatopsis* DEM30355 was cultivated as follows:

The fermentation of the *Amycolatopsis* sp. DEM303555 was conducted as previously described (Kepplinger et al., 2018). One kilogram of Amberlite XAD-16 resin was washed with deionized water and then applied to 50 L of filtered culture supernatant in batch absorption. The material was eluted with 32 L of 100% methanol and concentrated under reduced pressure (2.5 L). The concentrate was adjusted to pH 6.5 and extracted eight times with an equal amount of ethyl acetate. The organic extracts were combined and evaporated to dryness to yield 22.5 g of crude extract. A sample of the crude extract (3.91 g) was subjected to silica gel chromatography (eluent = 100% ethyl acetate, Biotage SNAP 100g cartridge). KglA-containing fractions were combined and the solvent was removed under reduced pressure to give 1.24 g of a dark coloured solid. This material was subjected to a second silica gel chromatography step (eluent = linear gradient

from diethyl ether to ethyl acetate. Evaporation of the KglA containing fractions yielded 806.2 mg as an orange solid.

[00202] The resulting orange crystalline compound retained the observed biological activity against both the reporter and RIF-resistant strains (Fig. 1A). ESI-MS revealed the mass $[M+Na]^+$ = 1004.3866 m/z (Fig. 2A), which corresponded to the mass of previously described kanglemycin A (KglA). ^1H and ^{13}C NMR, extensive 2-D NMR analysis, and, finally, single-crystal X-ray analysis (Fig. 2B, C, D) unambiguously confirmed the structure of the isolated compound to be KglA (Fig. 1B):



Mode of action and specificity of KglA

[00203] KglA is an antibiotic originally isolated from the fermentation broth of *Nocardia mediterranei* var. *kanglensis* 1741-64 (Wang et al., 1988), for which no mode of action has been previously proposed and only limited information on its biological activity has been reported. It is an ansamycin antibiotic which shares similarities with rifamycins, albeit with a number of unusual structural features. Most notably KglA differs from known rifamycins and their semisynthetic derivatives in that it contains two large *ansa*-bridge substituents, a pendant 2,2-dimethyl succinic acid side chain at C20 and a unique sugar moiety (β -O-3,4-O,O'-methylene digitoxose) at C27 (Fig. 1B). Furthermore, these modifications are unusual for bioactive natural and semi-synthetic rifamycins whose modifications are typically concentrated at the naphthoquinone core.

[00204] Activation of the *he/D* promoter and its structural similarity to the rifamycins suggested that KglA targets bacterial RNAP. Therefore, the effects of KglA on *in vitro* transcription by wild-type *E. coli* RNAP were analyzed. KglA efficiently inhibited transcription on a linear DNA template containing the strong T7A1 promoter (Fig. 1C). Inhibition of full-sized RNA products (run off or terminated) coincided with increased accumulation of short abortive tri- and tetra-nucleotide products (Fig. 1C; the reactions were started with the dinucleotide primer CpA). Such a mode of

action is characteristic of the rifamycins (Campbell et al., 2005; McClure and Cech, 1978), as can be seen from the pattern of inhibition of transcription by RIF (Fig. 1C). In this mode of action, the antibiotic binds in the pathway of the nascent RNA, physically blocking its extension and inducing the release of short RNAs as abortive products.

[00205] The IC_{50} 's of KglA and RIF were similar against wild-type RNAP (Fig 1D, E). However, despite having a similar mode of action to RIF, it was observed that KglA killed RIF-resistant bacteria (compare inhibition zones in Fig. 1A, right plate). To investigate this phenomenon, *E. coli* RNAPs carrying a series of rifampicin-resistant mutations were prepared, including $\beta S531L$, $\beta D516V$, $\beta D516Y$, $\beta H526Y$, $\beta H526P$, $\beta H526R$, and $\beta I572F$. These mutations correspond to the RIF-resistance mutations in *M. tuberculosis* most frequently observed in clinical isolates, with $\beta S531L$, $\beta D516V$ and $\beta H526Y$ accounting for 73% of all clinical RIF-resistant *M. tuberculosis* isolates (Gill and Garcia, 2011). Compared to RIF, KglA was much more potent against six out of seven RIF-resistant RNAPs (Fig. 1D, E); in particular the KglA was 10 times more active than RIF against $\beta S531L$ and $\beta D516V$ mutants. Note that while mutations at $\beta H526$ made RNAP insensitive to RIF (no inhibition at 2.5 mg/mL), KglA was still able to inhibit RNAPs with these mutations.

[00206] It was noted that the ratio of tri- (CpApU) and tetra-nucleotide (CpApUpC) products made, when transcription started with the dinucleotide primer CpA, was different for RIF and KglA (Fig. 1C; note the odd migration of abortive products in the gel described earlier (Borukhov et al., 1993)). Tetra-nucleotide production in the presence of KglA was inhibited as compared to RIF, suggesting that binding of KglA results in stronger steric hindrance towards RNA progression. To investigate this further, transcription starting with ATP (in the absence of CpA primer) was analyzed. As can be seen from Fig. 1F, KglA completely blocked the formation of triphosphorylated trinucleotide, pppApUpC, while RIF allowed some of its production (compare lanes 2 and, 5 and 6). Furthermore, KglA strongly diminished (70-fold inhibition) the formation of the first dinucleotide pppApU, while RIF had only moderate effect (3 fold inhibition). This further suggests that extra groups and/or the mode of binding of KglA sterically precludes translocation of the triphosphorylated 5' end of dinucleotide RNA and even interferes with the first phosphodiester bond formation, which both, conversely, are allowed in the case of RIF binding.

[00207] These results and *in vivo* data (Fig. 1A) suggest that KglA binds to RNAP in the RIF-binding pocket of β subunit, but in a manner different from known rifamycins, resulting in an increased resilience to the rifampicin-resistant amino acid substitutions in the RIF-binding pocket of RNAP. Furthermore, mode of action of KglA deviates from that of RIF, as KglA inhibits formation of the first phosphodiester bond, when transcription is started with nucleotide triphosphate.

KglA potency against Gram-positive pathogens

[00208] The results discussed above suggest that KglA may be effective against RIF-resistant bacteria. Thus, KglA was tested against 20 clinically relevant pathogenic species, 8 Gram-positive, 10 Gram-negative and 2 eukaryotes (Table 1). Amongst the eight Gram-positive pathogens tested, KglA was highly active against six species, and had somewhat lower activity against the remaining two. Out of 10 Gram-negative pathogens, KglA was active against only *Providencia rettgeri*. No activity was observed towards the two strains of eukaryotic microorganisms (yeast): *Candida albicans* and *Candida glabrata*. The antibacterial potential of KglA was further tested against 38 MRSA strains. 35 of these strains showed low MICs (0.025–2 µg/mL). Only three MRSA strains had relatively high MICs of KglA (32-128 µg/mL), however these were still significantly lower than the comparable MICs for RIF (>128 µg/ml). The results suggest that KglA has potential as a Gram-positive-specific antimicrobial, and, importantly, against RIF-resistant species.

Table 1. Minimum inhibitory concentrations (MICs) of KglA against bacterial and eukaryotic pathogens (*Andrews, J.M. (2001). Determination of minimum inhibitory concentrations. The Journal of antimicrobial chemotherapy 48 Suppl 1, 5-16.).

	Organism/isolate	Strain Reference	KglA, µg/mL	RIF, µg/mL
Gram Negative	<i>Acinetobacter baumannii</i>	ATCC 19606	>128	-
	<i>Burkholderia cepacia</i>	ATCC 25416	>128	-
	<i>Enterobacter cloacae</i>	NCTC 11936	>128	-
	<i>Escherichia coli</i>	NCTC 10418	>128	16*
	<i>Klebsiella pneumoniae</i>	NCTC 9528	>128	-
	<i>Providencia rettgeri</i>	NCTC 7475	64	-
	<i>Pseudomonas aeruginosa</i>	NCTC 10662	>128	-
	<i>Salmonella typhimurium</i>	NCTC 74	>128	-
	<i>Serratia marcescens</i>	NCTC 10211	>128	-
	<i>Yersinia enterocolitica</i>	NCTC 11176	>128	-
Gram Positive	<i>Bacillus subtilis</i>	NCTC 9372	1	-
	<i>Enterococcus faecalis</i>	NCTC 775	64	-
	<i>Enterococcus faecium</i>	NCTC 7171	128	-
	<i>Listeria monocytogenes</i>	NCTC 11994	8	-
	<i>Staphylococcus epidermidis</i>	NCTC 11047	1	-
	<i>Staphylococcus aureus</i>	NCTC 6571	0.25	0.004*
	<i>Staphylococcus aureus</i> (MRSA)	NCTC 11939	1	-
	<i>Streptococcus pyogenes</i>	NCTC 8306	0.031	-
Yeast	<i>Candida albicans</i>	ATCC 90028	>128	-
	<i>Candida glabrata</i>	NCPF 9725	>128	-
	Bel	97597	2	2

<i>S. aureus</i>	Bel	97598	64	>128
	Fin	37481	0.5	≤0.008
	Fin	54511	32	>128
	Fin	54518	128	>128
	Fra	462	0.5	≤0.008
	Fra	920	1	≤0.008
	Fra	95035	1	0.016
	Ger	131/98 (Sger 11d2)	0.5	0.016
	Ger	1966/97 (Han 111c)	0.5	≤0.008
	Ger	2594-1/97 (Sger 11a)	1	0.016
	Ger	2594-2/97 (Sger 11b)	0.25	≤0.008
	EMRSA 15	1729/98	0.5	≤0.008
	EMRSA 15	1758/98	0.5	≤0.008
	EMRSA 15	14956	0.5	≤0.008
	EMRSA 15	12484/98	0.5	≤0.008
	EMRSA 15	14185/98	0.5	≤0.008
	EMRSA 15	16822/98	0.5	≤0.008
	EMRSA 15	19972/98	0.5	≤0.008
	EMRSA 15	20460/98	0.5	0.016
	EMRSA 15	21268/98	0.5	≤0.008
	EMRSA 15	21698/98	0.5	≤0.008
	EMRSA 15	2501/98	0.5	≤0.008
	EMRSA 15	6323/98	0.5	≤0.008
	EMRSA 16	00036/95	1	0.016
	EMRSA 16	00998/95	1	≤0.008
	EMRSA 16	03732/95	1	0.016
	EMRSA 16	07121/95	1	≤0.008
	EMRSA 16	07924/95	0.5	≤0.008
	EMRSA 16	18200/95	0.5	≤0.008
	EMRSA 16	18205/95	0.5	≤0.008
	EMRSA 16	21354/95	1	0.016
	EMRSA 16	23728/98	1	≤0.008
	EMRSA 16	23729/98	1	≤0.008
	EMRSA 16	32010/96	1	0.016
	EMRSA 16	34256/96	1	≤0.008
	MRSA	NCTC 11939	1	≤0.008
	<i>Staphylococcus aureus</i>	NCTC 6571	0.25	≤0.008

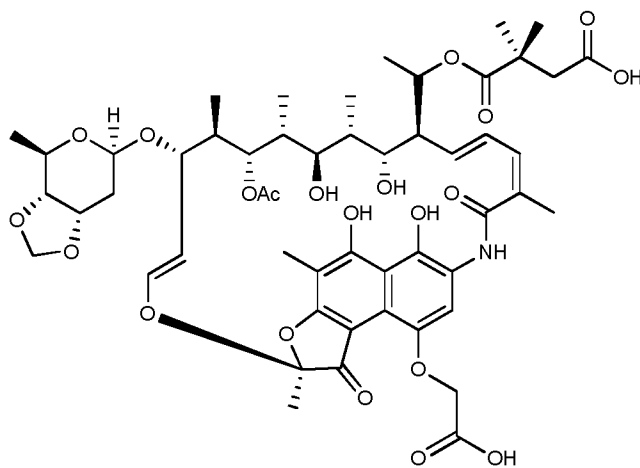
Example 2 – DEMB1 (“B1”), DEMB3 (“B3”) and DEMB1C (“B1C”)

Isolation of B1, B3 and B1C

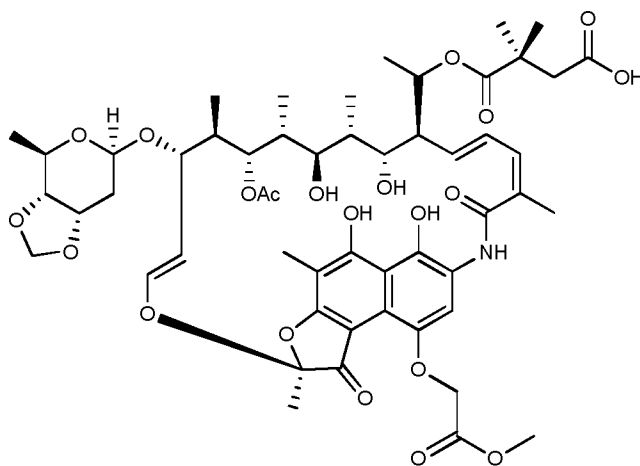
[00209] B1 was isolated from *Amycolatopsis* DEM30355 in a similar manner to KglA (Example 1). In the process of B1 purification, two new compounds with the accurate masses of 1055.44 Da and 1061.39Da were identified, presumed to be the methyl ester and cyclized/oxidised derivatives of B1 correspondingly. The new compounds were named B3 (methyl ester) and B1C

(cyclized/oxidised). To further investigate the hypothesis, 10 mg of B1 was dissolved in 0.5 mL of methanol, stored at -20 °C and analysed by LC-MS every 24 hour. The time kinetic experiment confirmed the conversion of B1 to B3 where about half of B1 was converted to B3 after 7 days. The time kinetic experiment did not show any changes in the proportion of B1C after storage in methanol. However, it was observed that conversion to B1C is increased in aqueous solutions of B1

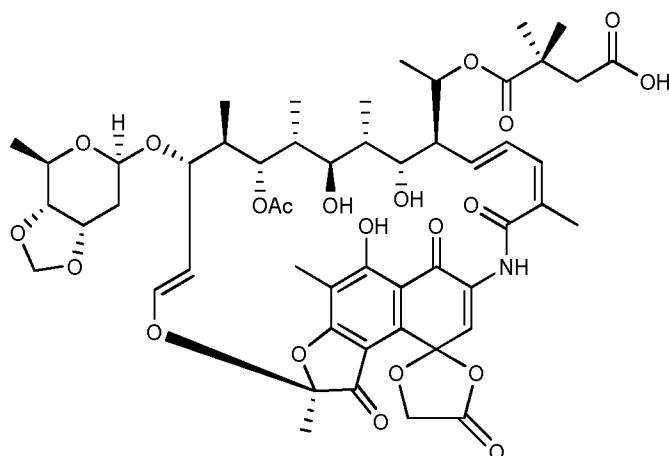
[00210] The mixture containing B1, B3 and B1C was then evaporated to dryness and dissolved in 20% Acetonitrile:H₂O. To purify the two derivatives of B1, the reaction mixture was subjected to the C18 column and separated by reversed-phase chromatography (eluent=linear gradient 20% Acetonitrile in H₂O to 100% acetonitrile). Fractions containing the B1, B3 and B1C were collected and analysed separately by LC-MS (Figs 3, 4 and 5).



B1



B3

B1C

Potency against RIF-resistant RNAPs

[00211] To investigate the efficacy of B1, B3 and B1C against rifampicin-resistant RNA polymerase (RNAP), they were tested against the *E.coli* RNAP carrying β S531L (the most frequently observed RIF-resistant mutation in clinical isolates). The IC₅₀ of B3 against β S531L RNAP (2 μ g/mL) was similar to that of B1 (3 μ g/mL) suggesting that methylation of carboxylic group does not affect the RNAP binding. (Figs 6 and 7) The inhibition of β S531L RNAP by B1C was weaker than the other two compounds (30 μ g/mL). Compared to Rif, all three derivatives are very potent inhibitors of Rif-resistant β S531L RNAP (IC₅₀[Rif] = 675 μ g/mL).

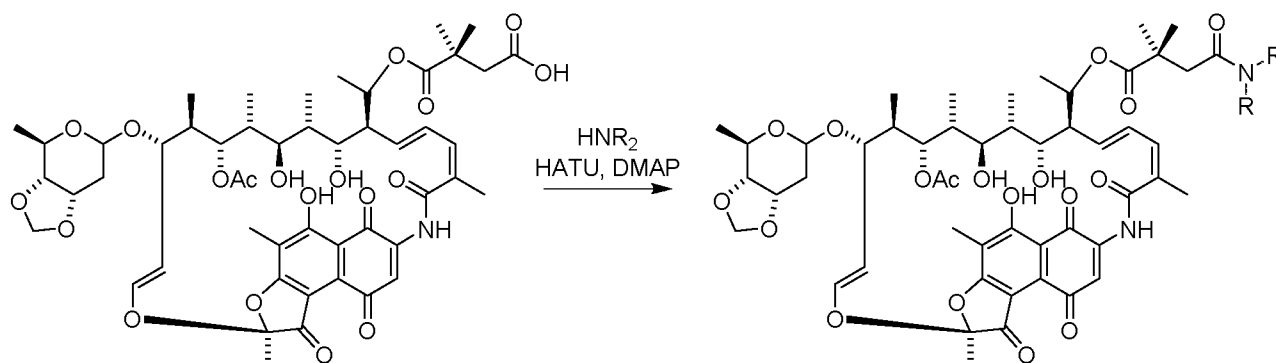
[00212] The potency of B1 against other *E. coli* RNAPs carrying rifampicin-resistant mutations, including β S531L, β D516V, β D516Y, β H526Y, β H526P, β H526R, and β I572F, was analysed. Table 2 below compares the potency of B1 against various RIF-resistant RNAPs with that of RIF and rifamycin B ("rifB"):

Table 2 – IC₅₀ of inhibition of RIF-resistant RNAPs by B1, RIF and rifB (μg/ml)

<i>RNAP</i>	<i>RIF</i>	<i>DEMB1</i>	<i>rifB</i>
WT	0.49	0.70	0.4
D516V	320	0.32	10.9
D516Y	80	0.26	NA
I572F	93	0.17	0.6
S531L	623	1.08	22
H526Y	>2500	22.60	707
H526P	>2500	128.90	NA
H526R	>2500	460.00	NA

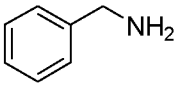
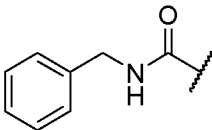
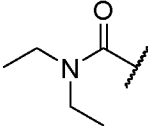
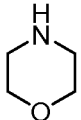
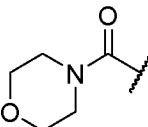
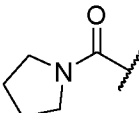
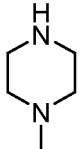
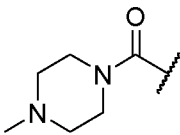
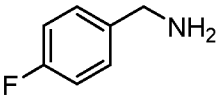
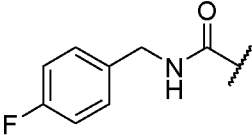
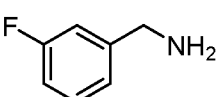
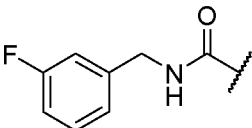
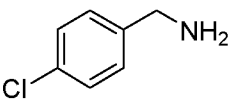
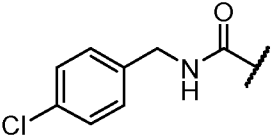
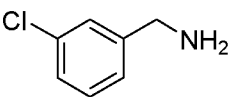
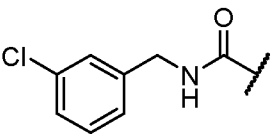
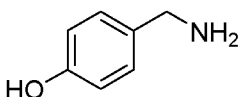
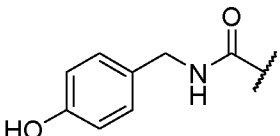
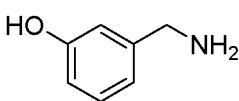
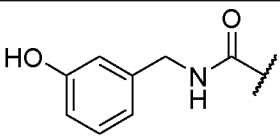
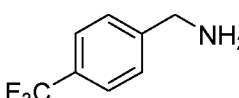
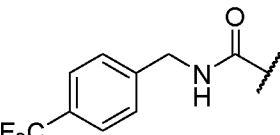
Example 3 – c17b-001 to c17b-018Preparation of compounds

[00213] Compounds c17b-001 to c17b-018 were prepared by reaction of KglA (Example 1) with a series of different amines (see Table 3) according to the reaction scheme below:



[00214] To a round bottom flask, under an atmosphere of nitrogen, was added KglA (1 eq.), 4-dimethylaminopyridine (6 eq.), hexafluorophosphate azabenzotriazole tetramethyl uronium (3 eq.), amine (10 eq.) and DMF (55 mL/mmol of KglA). The reaction mixture was stirred at room temperature, until the reaction was complete (typically 2-8 hours). The reaction sample then underwent solid phase extraction using increasing amounts of methanol (20%, 50%, 75%, 100%). The fraction in 75% methanol was then ran on HPLC. Peaks produced by the sample were collected and analysed by LCMS. The fraction containing the desired product was made up to a concentration of 1mg/mL and froze in 100% methanol.

Table 3 – Preparation of compounds c17b-001 to c17b-018 – reagents and reaction times

Compound	Amine	Resulting amide moiety	Reaction time/ h
c17b-001			4
c17b-002	HNEt ₂		8
c17b-003			2.5
c17b-004			4
c17b-005			4
c17b-006			2
c17b-007			2
c17b-008			2
c17b-009			2
c17b-010			2.5
c17b-011			2
c17b-012			2

c17b-013			2
C17b-014			2
C17b-015			2
C17b-016			2
C17b-017			2
C17b-018			2

LCMS

[00215] Compounds c17b-001 to c17b-018, as purified by HPLC, were analysed by LCMS according to the following protocol:

Solvent: Water, MeCN, 0.1% formic acid

Column flow rate: 0.2 µL/ min

Gradient:

Time/ min	Water / %	MeCN / %
0	80	20
20	0	100
25	0	100
26	80	20
30	80	20

[00216] Tables 4 and 5 below show the theoretical and observed mass of compounds c17b-001 to c17b-018, as determined by LCMS.

Table 4 – Theoretical mass of compounds c17b-001 to c17b-018

	[M+H] ⁺	[M+Na] ⁺	[2M+H] ⁺	[2M+Na] ⁺	[M-H+2Na] ⁺	[M+3H] ⁺	[M+2H+Na] ⁺	[M-sugar] ⁺
KglA	982.4067	1004.3886	1963.8061	1985.7881	2007.77	984.4224	1006.4043	822.3331
C17b-001	1071.4696	1093.4516	2141.932	2163.9139	-	1073.4853	1095.4672	911.3961
C17b-002	1037.4853	1059.4672	2073.9633	2095.9452	-	1039.5009	1061.4829	877.4117
C17b-003	1051.4646	1073.4465	2101.9218	2123.9038	-	1053.4802	1075.4621	891.391
C17b-004	1035.4696	1057.4516	2069.932	2091.9139	-	1037.4853	1059.4672	875.3961
C17b-005	1064.4962	1086.4781	2127.9851	2149.967	-	1066.5118	1088.4938	904.4226
C17b-006	1089.4602	1111.4422	2177.9132	2199.8951	-	1091.4759	1113.4578	929.3867
C17b-007	1089.4602	1111.4422	2177.9132	2199.8951	-	1091.4759	1113.4578	929.3867
C17b-008	1105.4307	1127.4126	2209.8541	2231.836	-	1107.4463	1129.4283	945.3571
C17b-009	1105.4307	1127.4126	2209.8541	2231.836	-	1107.4463	1129.4283	945.3571
C17b-010	1087.4646	1109.4465	2173.9218	2195.9038	-	1089.4802	1111.4621	927.391
C17b-011	1087.4646	1109.4465	2173.9218	2195.9038	-	1089.4802	1111.4621	927.391
C17b-012	C17b-001	1161.439	2277.9068	2299.8887	-	1141.4727	1163.4546	979.3835
C17b-013	1139.457	1161.439	2277.9068	2299.8887	-	1141.4727	1163.4546	979.3835
C17b-014	1049.4853	1071.4672	2097.9633	2119.9452	-	1051.5009	1073.4829	889.4117
C17b-015	1024.4649	1046.4468	2047.9225	2069.9044	-	1026.4805	1048.4625	864.3913
C17b-016	1021.4540	1043.4359	2041.9007	2063.8826	-	1023.4696	1045.4516	862.3877
C17b-017	1064.4962	1086.4781	2127.9851	2149.9670	-	1066.5118	1088.4938	904.4226
C17b-018	1066.4755	1088.4574	2131.9436	2153.9256	-	1068.4911	1090.4730	906.4019

Table 5 – Observed mass of compounds c17b-001 to c17b-018 as determined by LCMS

	[M+H] ⁺	[M+Na] ⁺	[2M+H] ⁺	[2M+Na] ⁺	[M-H+2Na] ⁺	[M+3H] ⁺	[M+2H+Na] ⁺	[M-sugar] ⁺
KglA								
C17b-001	1071.4608	1093.442		2163.896				911.387
C17b-002	1037.467	1059.4476		2096.9084				877.3945
C17b-003	1051.4449			2124.8666				891.374
C17b-004	1035.4546	1057.4348						875.3843
C17b-005	1064.4809	1086.461				1066.4961		904.4073
C17b-006	1089.4386	1111.4202		2200.853				929.3679
C17b-007	1089.4423	1111.4321		2200.8585				929.3699
C17b-008	1105.4108	1127.3929						945.3404
C17b-009	1105.4417	1127.4214						945.3663
C17b-010	1087.4454	1109.4267						927.3751
C17b-011	1087.4780	1109.4605						927.4032
C17b-012	1139.4742	1161.4569						979.3972
C17b-013	1139.4517	1161.4395						979.3748
C17b-014	1049.4932	1071.4810						889.4236
C17b-015	1024.4684	1046.4538						
C17b-016	1021.4551							
C17b-017	1064.5016	1086.4813						904.4290
C17b-018								

Minimum inhibitory concentration (MIC)

[00217] To test the MIC, the following dilution was performed. A sample of 1:9 *Staphylococcus aureus* strain RN4220: LB (Luria broth growth media) was made up and incubated for 4 hours. An optical density of a 1:9 sample was 0.120 at 600nm. The amount of 1:9 *Staphylococcus aureus*: LB was calculated in the following way:

$$OD_{(600nm)} \times 10 = 0.120 \times 10 = 1.20$$

$$C_1V_1 = C_2V_2$$

$$0.05 \text{ (desired concentration)} \times 20\text{mL (desired volume)} = 1.20 \times V_2$$

$$V_2 = 0.83\text{mL} = 833.88 \mu\text{L of 1:9 1:9 } Staphylococcus aureus: LB \text{ in 20mL of LB.}$$

180 µL of the 20mL diluted *Staphylococcus aureus*: LB was added to each column to make the volume up to 200 µL. The plates were left overnight in a shaking incubator.

[00218] The MIC results are shown in Table 6:

Table 6 – MIC for compounds c17b-001 to c17b-018 against *Staphylococcus aureus* strain RN4220

Compound	MIC (µg/mL)
c17b-001	1.00
c17b-002	0.50
c17b-003	0.25
c17b-004	0.25
c17b-005	
c17b-006	
c17b-007	
c17b-008	
c17b-009	0.25
c17b-010	1.00
c17b-011	0.25
c17b-012	
c17b-013	0.50
C17b-014	0.50
C17b-015	
C17b-016	
C17b-017	0.25
C17b-018	

[00219] While specific embodiments of the invention have been described herein for the purpose of reference and illustration, various modifications will be apparent to a person skilled in the art without departing from the scope of the invention as defined by the appended claims.

REFERENCES

- Andrews, J.M. (2001). Determination of minimum inhibitory concentrations. *The Journal of antimicrobial chemotherapy* 48 Suppl 1, 5-16.
- Aristoff, P.A., Garcia, G.A., Kirchhoff, P.D., and Showalter, H.D. (2010). Rifamycins – Obstacles and Opportunities. *Tuberculosis* 90, 94-118.
- Bacchi, A., Carcelli, M., and Pelizzi, G. (2008). Sampling rifamycin conformational variety by cruising through crystal forms: implications for polymorph screening and for biological models. *New J Chem* 32, 1725-1735.
- Bae, B., Nayak, D., Ray, A., Mustaev, A., Landick, R., and Darst, S.A. (2015). CBR antimicrobials inhibit RNA polymerase via at least two bridge-helix cap-mediated effects on nucleotide addition. *Proc Natl Acad Sci U S A* 112, E4178-4187.
- Bauer, A.W., Kirby, W.M., Sherris, J.C., and Turck, M. (1966). Antibiotic susceptibility testing by a standardized single disk method. *American journal of clinical pathology* 45, 493-496.
- Borukhov, S., Sagitov, V., Josaitis, C.A., Gourse, R.L., and Goldfarb, A. (1993). Two modes of transcription initiation in vitro at the *rrnB* P1 promoter of *Escherichia coli*. *J Biol Chem* 268, 23477-23482.
- Campbell, E.A., Korzheva, N., Mustaev, A., Murakami, K., Nair, S., Goldfarb, A., and Darst, S.A. (2001). Structural mechanism for rifampicin inhibition of bacterial rna polymerase. *Cell* 104, 901-912.
- Campbell, E.A., Pavlova, O., Zenkin, N., Leon, F., Irschik, H., Jansen, R., Severinov, K., and Darst, S.A. (2005). Structural, functional, and genetic analysis of sorangicin inhibition of bacterial RNA polymerase. *The EMBO journal* 24, 674-682.
- Degen, D., Feng, Y., Zhang, Y., Ebright, K.Y., Ebright, Y.W., Gigliotti, M., Vahedian-Movahed, H., Mandal, S., Talaue, M., Connell, N., *et al.* (2014). Transcription inhibition by the depsipeptide antibiotic salinamide A. *Elife* 3, e02451.
- Floss, H.G., and Yu, T.W. (2005). Rifamycin-mode of action, resistance, and biosynthesis. *Chemical reviews* 105, 621-632.
- Gill, S.K., and Garcia, G.A. (2011). Rifamycin inhibition of WT and Rif-resistant *Mycobacterium tuberculosis* and *Escherichia coli* RNA polymerases in vitro. *Tuberculosis (Edinb)* 91, 361-369.
- Ho, M.X., Hudson, B.P., Das, K., Arnold, E., and Ebright, R.H. (2009). Structures of RNA polymerase-antibiotic complexes. *Curr Opin Struct Biol* 19, 715-723.
- Julius, C., and Yuzenkova, Y. (2017). Bacterial RNA polymerase caps RNA with various cofactors and cell wall precursors. *Nucleic acids research* 45, 8282-8290.
- Kashlev, M., Nudler, E., Severinov, K., Borukhov, S., Komissarova, N., and Goldfarb, A. (1996). Histidine-tagged RNA polymerase of *Escherichia coli* and transcription in solid phase. *Methods in enzymology* 274, 326-334.

Kepplinger, B., Morton-Laing, S., Seistrup, K.H., Marrs, E.C.L., Hopkins, A.P., Perry, J.D., Strahl, H., Hall, M.J., Errington, J., and Ellis Allenby, N.E. (2018). Mode of Action and Heterologous Expression of the Natural Product Antibiotic Vancoremycin. *ACS chemical biology* 13, 207-214.

Lambert, R.J., and Pearson, J. (2000). Susceptibility testing: accurate and reproducible minimum inhibitory concentration (MIC) and non-inhibitory concentration (NIC) values. *Journal of applied microbiology* 88, 784-790.

Maffioli, S.I., Zhang, Y., Degen, D., Carzaniga, T., Del Gatto, G., Serina, S., Monciardini, P., Mazzetti, C., Gugliera, P., Candiani, G., *et al.* (2017). Antibacterial Nucleoside-Analog Inhibitor of Bacterial RNA Polymerase. *Cell* 169, 1240-1248 e1223.

McClure, W.R., and Cech, C.L. (1978). On the mechanism of rifampicin inhibition of RNA synthesis. *The Journal of biological chemistry* 253, 8949-8956.

Molodtsov, V., Fleming, P.R., Eyermann, C.J., Ferguson, A.D., Foulk, M.A., McKinney, D.C., Masse, C.E., Buurman, E.T., and Murakami, K.S. (2015). X-ray crystal structures of Escherichia coli RNA polymerase with switch region binding inhibitors enable rational design of squaramides with an improved fraction unbound to human plasma protein. *J Med Chem* 58, 3156-3171.

Mukhopadhyay, J., Das, K., Ismail, S., Koppstein, D., Jang, M., Hudson, B., Sarafianos, S., Tuske, S., Patel, J., Jansen, R., *et al.* (2008). The RNA polymerase "switch region" is a target for inhibitors. *Cell* 135, 295-307.

Perlman, D. (1977). *Structure-activity relationships among the semisynthetic antibiotics* (New York: Academic Press).

Roghanian, M., Zenkin, N., and Yuzenkova, Y. (2015). Bacterial global regulators DksA/ppGpp increase fidelity of transcription. *Nucleic acids research* 43, 1529-1536.

Ryu, Y.J., Koh, W.J., and Daley, C.L. (2016). Diagnosis and Treatment of Nontuberculous Mycobacterial Lung Disease: Clinicians' Perspectives. *Tuberculosis and respiratory diseases* 79, 74-84.

Sandgren, A., Strong, M., Muthukrishnan, P., Weiner, B.K., Church, G.M., and Murray, M.B. (2009). Tuberculosis drug resistance mutation database. *PLoS medicine* 6, e2.

Smith, A.J., and Savery, N.J. (2005). RNA polymerase mutants defective in the initiation of transcription-coupled DNA repair. *Nucleic acids research* 33, 755-764.

Tupin, A., Gualtieri, M., Leonetti, J.P., and Brodolin, K. (2010). The transcription inhibitor lipiarmycin blocks DNA fitting into the RNA polymerase catalytic site. *The EMBO journal* 29, 2527-2537.

Urban, A., Eckermann, S., Fast, B., Metzger, S., Gehling, M., Ziegelbauer, K., Rubsamen-Waigmann, H., and Freiberg, C. (2007). Novel whole-cell antibiotic biosensors for compound discovery. *Applied and environmental microbiology* 73, 6436-6443.

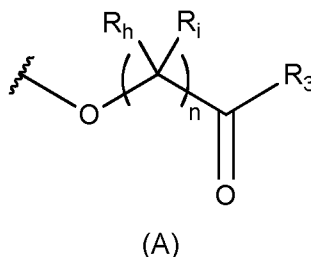
Wang, N.J., Fu, Y., Yan, G.H., Bao, G.H., Xu, C.F., and He, C.H. (1988). Isolation and structure of a new ansamycin antibiotic kanglemycin A from a Nocardia. *The Journal of antibiotics* 41, 264-267.

Zenkin, N., Kulbachinskiy, A., Yuzenkova, Y., Mustaev, A., Bass, I., Severinov, K., and Brodolin, K. (2007). Region 1.2 of the RNA polymerase sigma subunit controls recognition of the -10 promoter element. *The EMBO journal* 26, 955-964.

Zhang, Y., Degen, D., Ho, M.X., Sineva, E., Ebright, K.Y., Ebright, Y.W., Mekler, V., Vahedian-Movahed, H., Feng, Y., Yin, R., *et al.* (2014a). GE23077 binds to the RNA polymerase 'i' and 'i+1' sites and prevents the binding of initiating nucleotides. *Elife* 3, e02450.

X_1 is selected from O and NR_g ;

X_2 is hydroxy or a group of formula (A) shown below:



wherein

n is 0, 1, 2, 3 or 4; and

R_3 is selected from hydrogen, halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_jR_k , OR_i , $C(O)R_j$, $C(O)OR_j$, $OC(O)R_j$, $C(R_j)=N(R_k)$, $N(R_j)OR_k$, $N(R_j)C(O)OR_k$, $C(O)N(R_j)R_k$, $N(R_j)C(O)R_k$, $S(O)_pR_j$ (where p is 0, 1 or 2), $SO_2N(R_j)R_k$, and $N(R_j)SO_2R_k$;

and wherein R_3 is independently optionally substituted by one or more substituent groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (1-4C)alkoxy, $S(O)_qCH_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, or (3-8C)cycloalkyl(1-2C)alkyl;

or R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 5-12 membered heteroaryl or heterocycle that is optionally substituted with one or more R_4 substituents;

and wherein each R_4 is independently selected from halo, cyano, isocyano, nitro, hydroxy, (1-6C)alkyl, (1-6C)haloalkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-8C)heteroalkyl, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl,

(3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl, NR_mR_n , OR_o , $\text{C(O)}\text{R}_m$, $\text{C(O)}\text{OR}_m$, $\text{OC(O)}\text{R}_m$, $\text{N(R}_m\text{)OR}_n$, $\text{N(R}_m\text{)C(O)OR}_n$, $\text{C(O)N(R}_m\text{)R}_n$, $\text{C(R}_m\text{)=N(R}_n\text{)}$, $\text{N(R}_m\text{)C(O)R}_n$, $\text{S(O)}_p\text{R}_m$ (where p is 0, 1 or 2), $\text{SO}_2\text{N(R}_m\text{)R}_n$, and $\text{N(R}_m\text{)SO}_2\text{R}_n$;

and wherein each R_4 is independently optionally substituted with one or more groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, $\text{S(O)}_q\text{CH}_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

X_3 and X_4 are independently selected from hydroxy, OR_p , NR_qR_r and a group of formula (A) shown above;

or X_3 and X_4 are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a 4-6 membered heterocycle that is optionally substituted with one or more R_5 substituents;

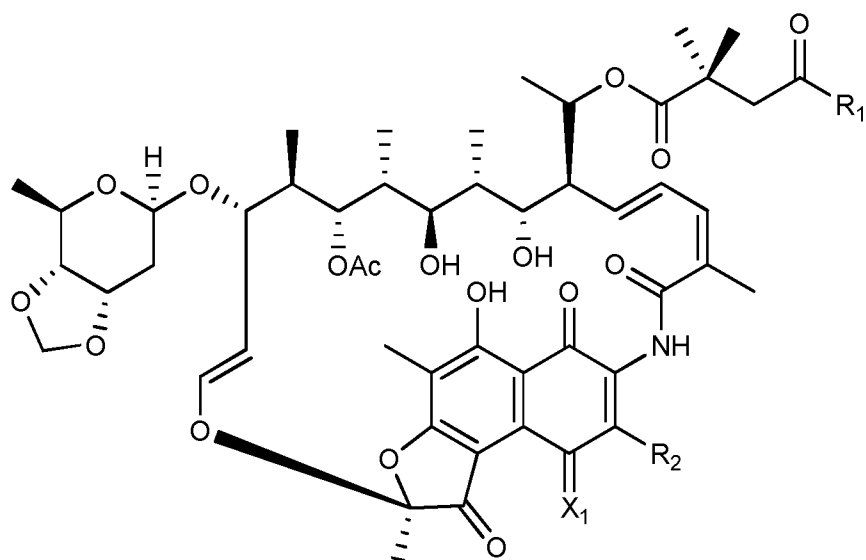
and wherein each R_5 is independently selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, oxo, amino, carboxy, carbamoyl, sulphamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-4C)alkoxy, $\text{S(O)}_q\text{CH}_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

each R_a to R_r is independently selected from hydrogen, fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-4C)alkoxy, $\text{S(O)}_q\text{CH}_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl;

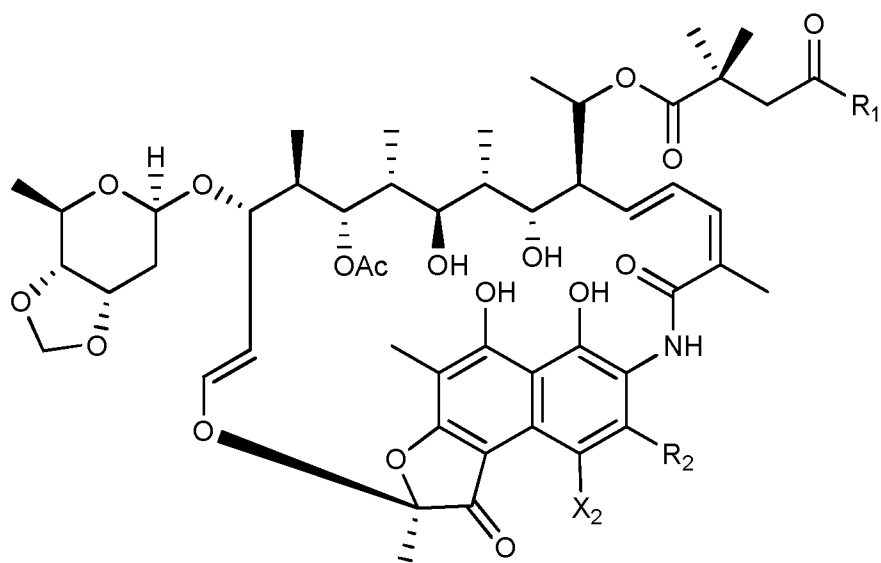
and wherein each R_a to R_r is independently optionally substituted with one or more groups selected from fluoro, chloro, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, $\text{S(O)}_q\text{CH}_3$ (where q is 0, 1 or 2), methylamino or dimethylamino, aryl, aryl(1-2C)alkyl, heteroaryl, heteroaryl(1-2C)alkyl, (3-8C)heterocyclyl, (3-

8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, and (3-8C)cycloalkyl(1-2C)alkyl.

2. The compound for use according to claim 1, wherein the compound has a structure according to formula (I'), (II') or (III') shown below:

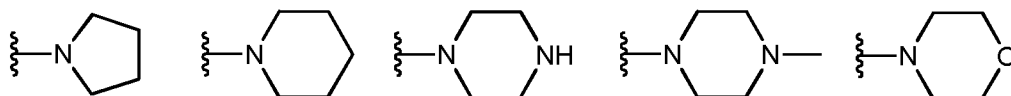


(I')



(II')

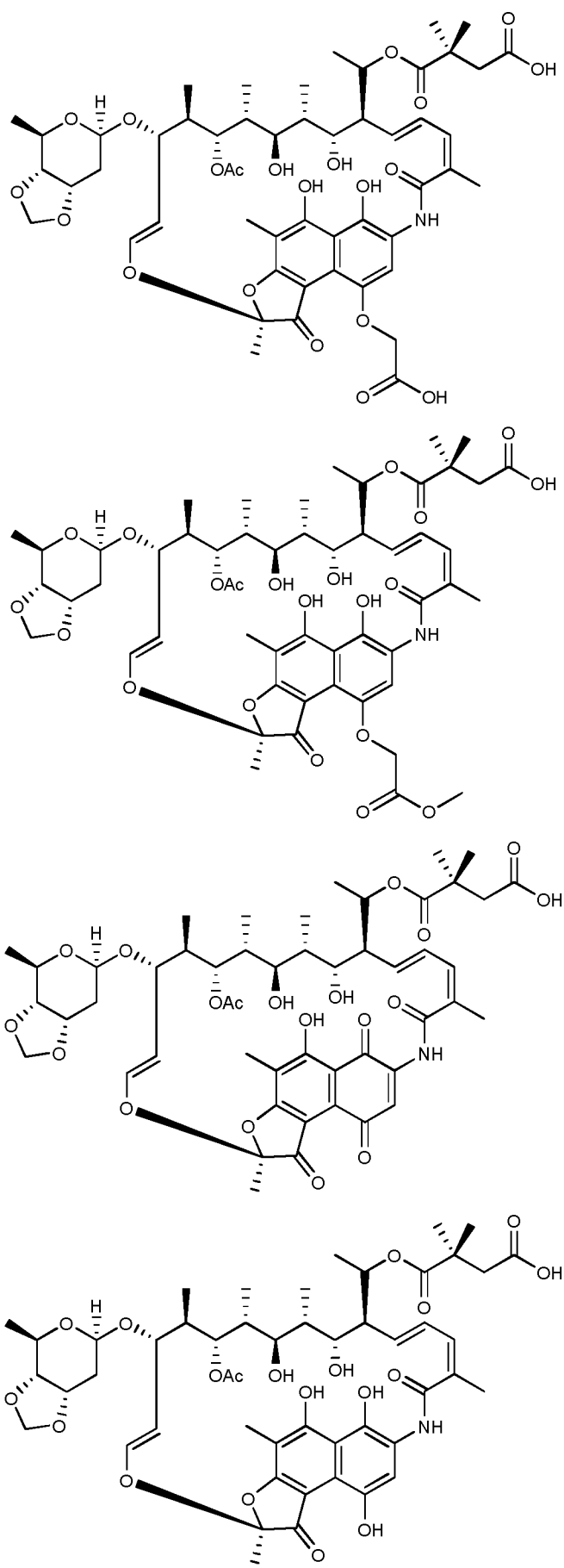
6. The compound for use according to any one of claims 1 to 4, wherein R_a is hydrogen or (1-2C)alkyl and R_b is selected from (1-2C)alkyl, $N(Me)_2$, benzyl, cyclopropyl or any one of the following:

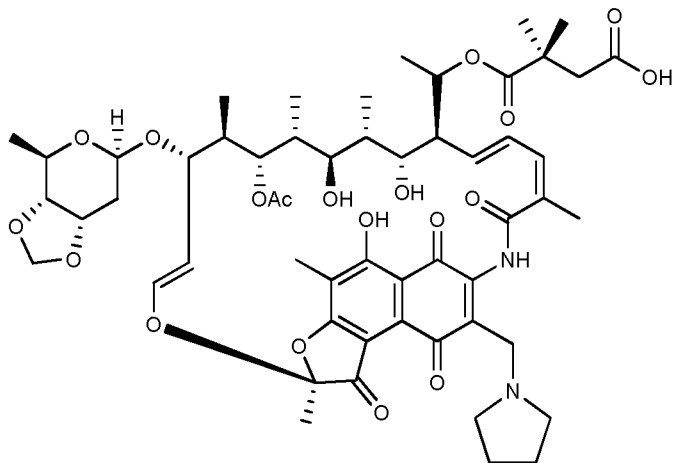
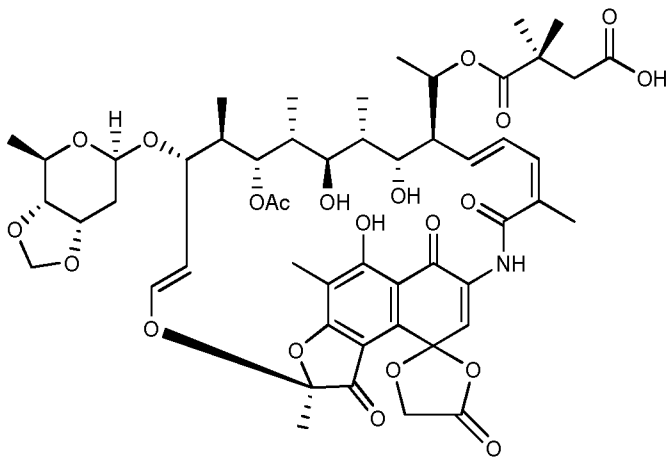
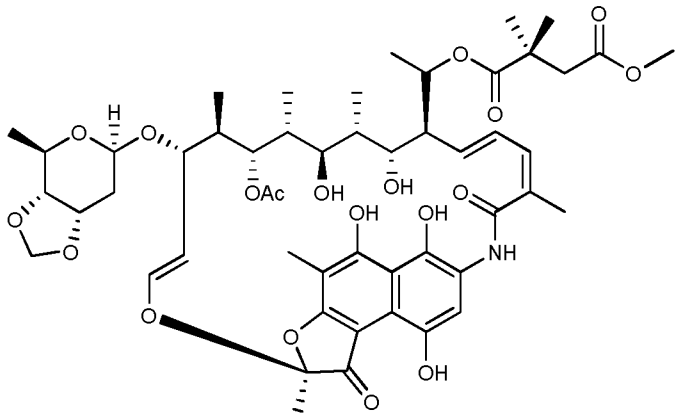
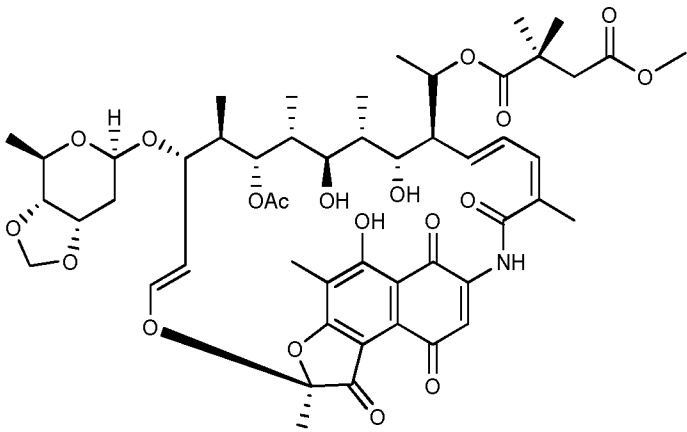


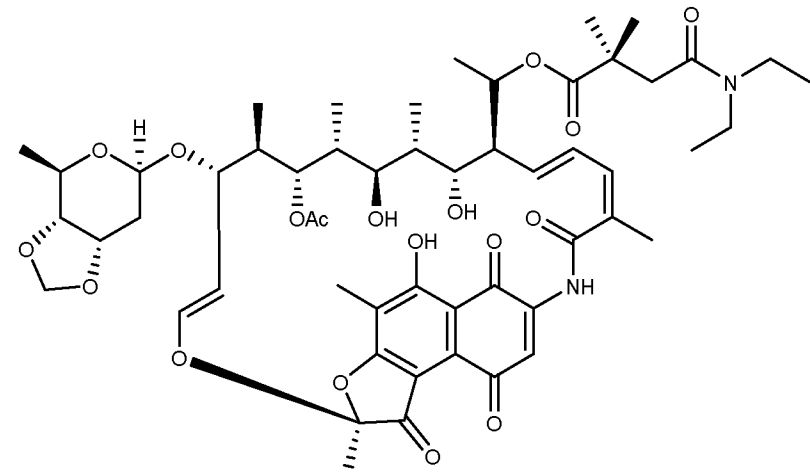
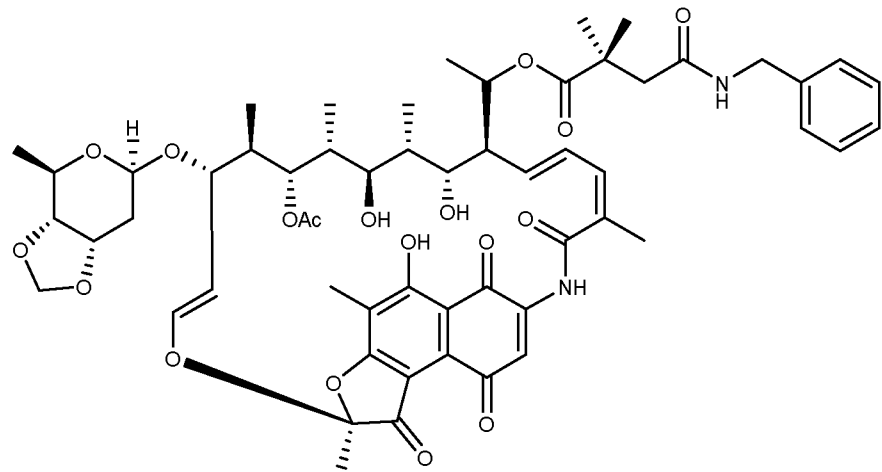
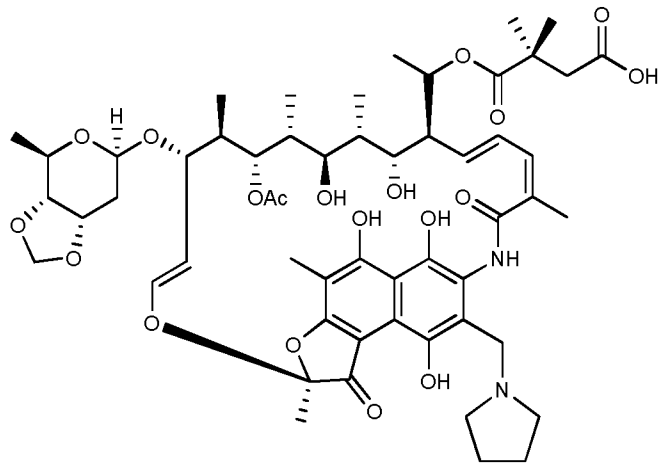
wherein each of the said benzyl groups is optionally substituted with one substituent group selected from fluoro, chloro, hydroxy and trifluoromethyl.

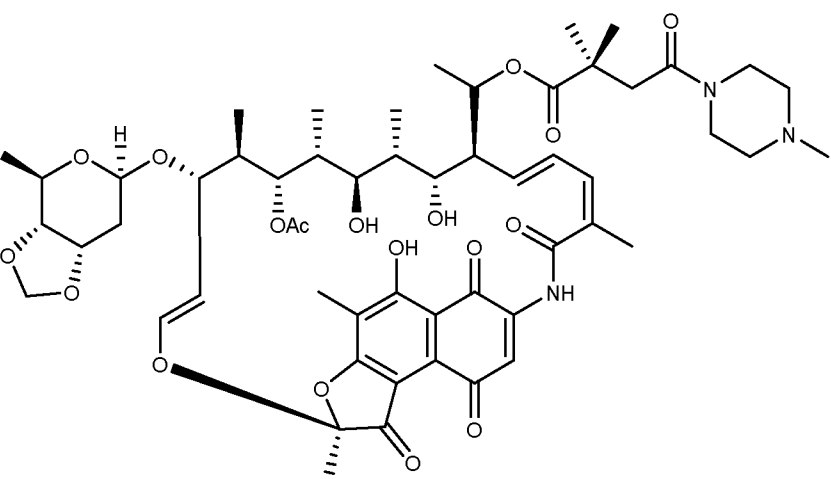
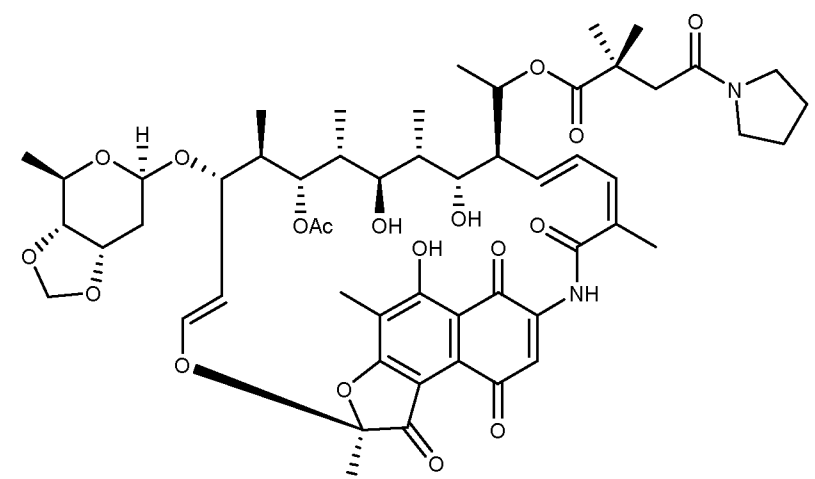
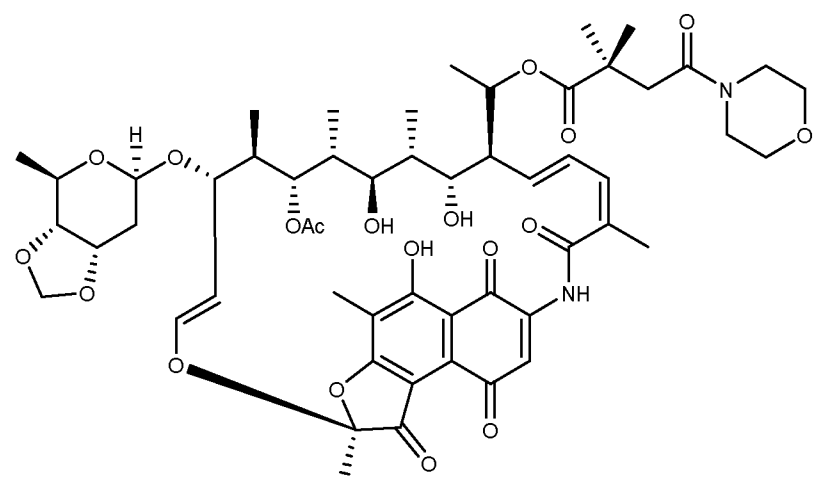
7. The compound for use according to any preceding claim, wherein R_c is (1-6C)alkyl.
8. The compound for use according to any preceding claim, wherein R_2 is selected from hydrogen, (1-6C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl(1-2C)alkyl and $C(R_d)=N(R_e)$.
9. The compound for use according to any preceding claim, wherein each R_d is independently selected from hydrogen and (1-6C)alkyl.
10. The compound for use according to any preceding claim, wherein each R_e is independently selected from hydrogen, (1-4C)alkyl and N-piperazinyl, any of which is optionally substituted with cyclopentyl.
11. The compound for use according to any preceding claim, wherein X_1 is O.
12. The compound for use according to any preceding claim, wherein X_2 is hydroxy or a group of formula (A), wherein
 n is 1;
 R_h and R_i are independently selected from hydrogen and (1-2C)alkyl;
 R_3 is selected from hydroxy, (1-6C)alkyl, (3-8C)heterocyclyl, (3-8C)heterocyclyl(1-2C)alkyl, NR_jR_k and OR_l ,
 wherein R_3 is optionally substituted by one or more substituent groups selected from (1-4C)alkyl and (1-3C)alkoxy.

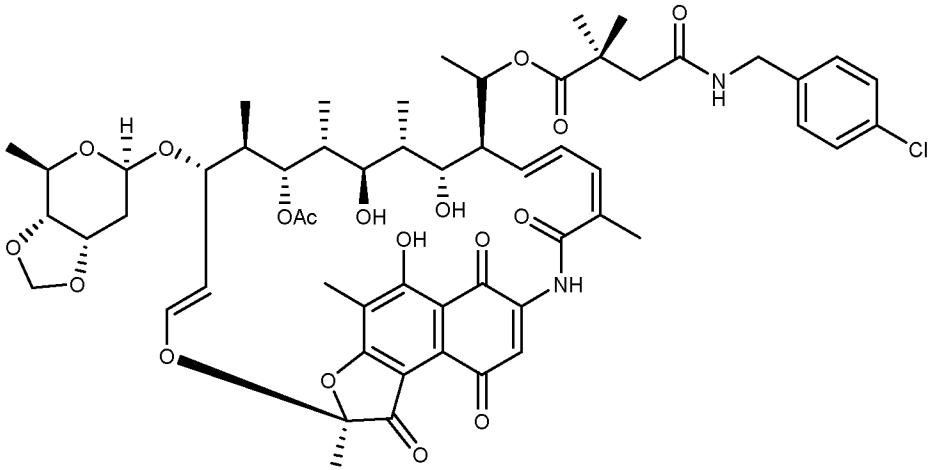
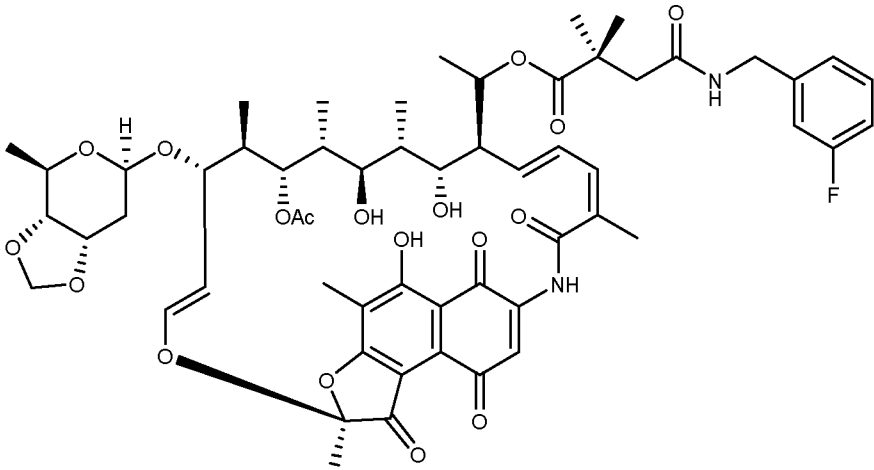
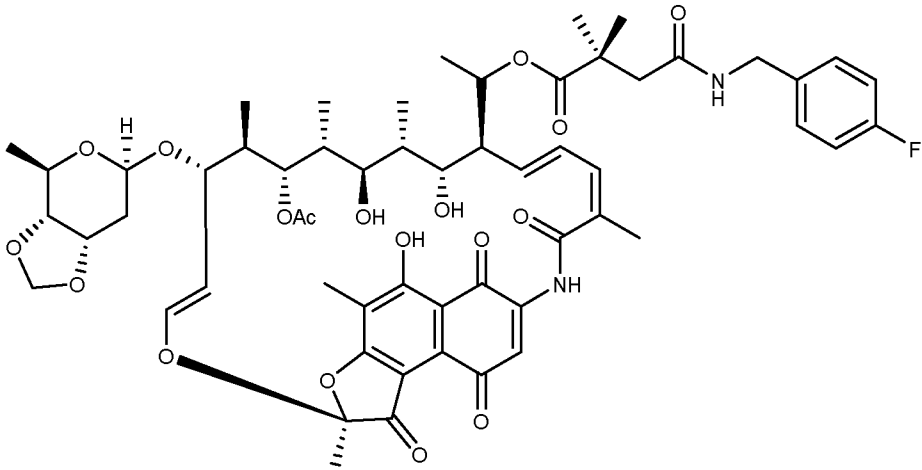
13. The compound for use according to any preceding claim, wherein R_j and R_k are independently selected from hydrogen, (1-6C)alkyl, phenyl and 5-6 membered N-linked heterocyclyl.
14. The compound for use according to any preceding claim, wherein R_i is (1-6C)alkyl.
15. The compound for use according to any preceding claim, wherein R_2 and X_1 or R_2 and X_2 are linked, such that when they are taken in combination with the carbon atoms to which they are attached, they collectively form a 9-11 membered fused heterobicycle or spiro bi-cyclic heterocyclic ring system containing 1, 2 or 3 heteroatoms selected from O and N, wherein said 9-11 membered fused or spiro heterobicycle is optionally substituted with one or more R_4 substituents.
16. The compound for use according to any preceding claim, wherein each R_4 is independently selected from hydroxy, (1-6C)alkyl and (3-8C)heterocyclyl, wherein each R_4 is independently optionally substituted with one or more groups, (1-4C)alkyl.
17. The compound for use according to any preceding claim, wherein X_3 and X_4 are linked, such that when they are taken in combination with the carbon atom to which they are attached, they collectively form a 4-6 membered heterocycle containing 1 or 2 heteroatoms selected from O and N, wherein the 4-6 membered heterocycle is optionally substituted with one or more R_5 substituents.
18. The compound for use according to any preceding claim, wherein each R_5 is independently selected from fluoro, chloro, hydroxy, oxo, amino, (1-3C)alkyl and (1-3C)alkoxy.
19. The compound for use according to any preceding claim, wherein the compound has any one of the following structures:

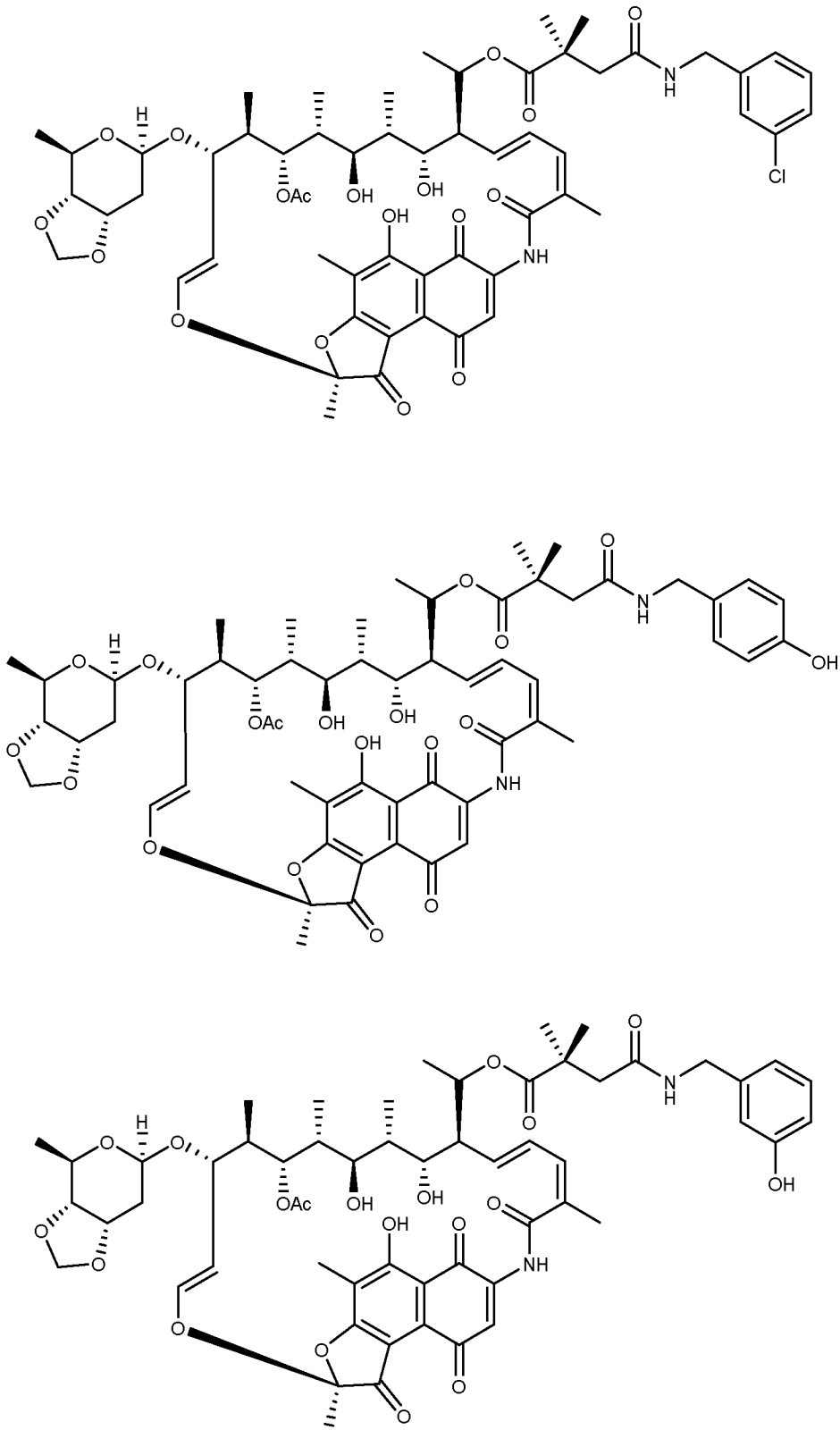


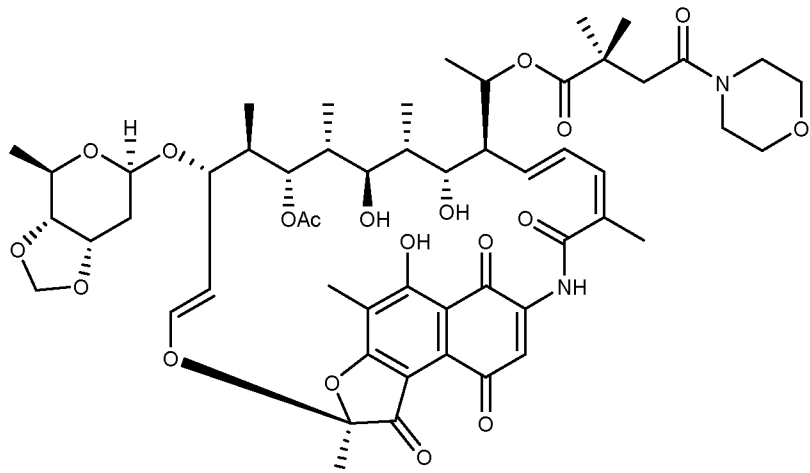
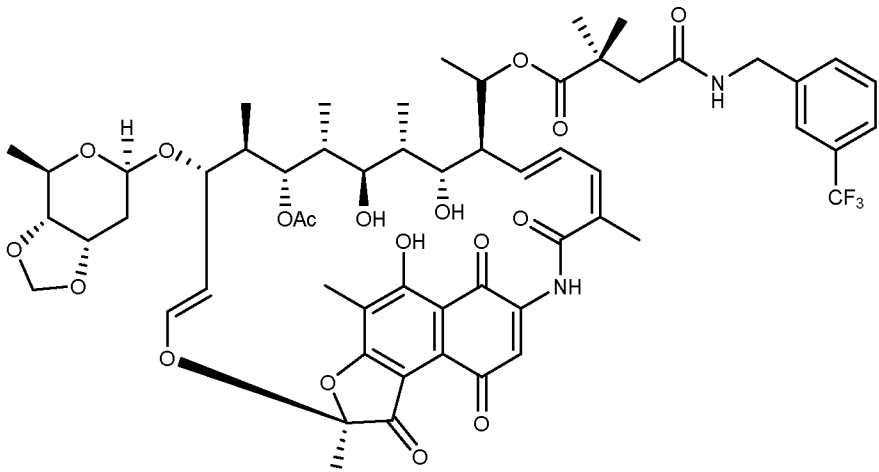
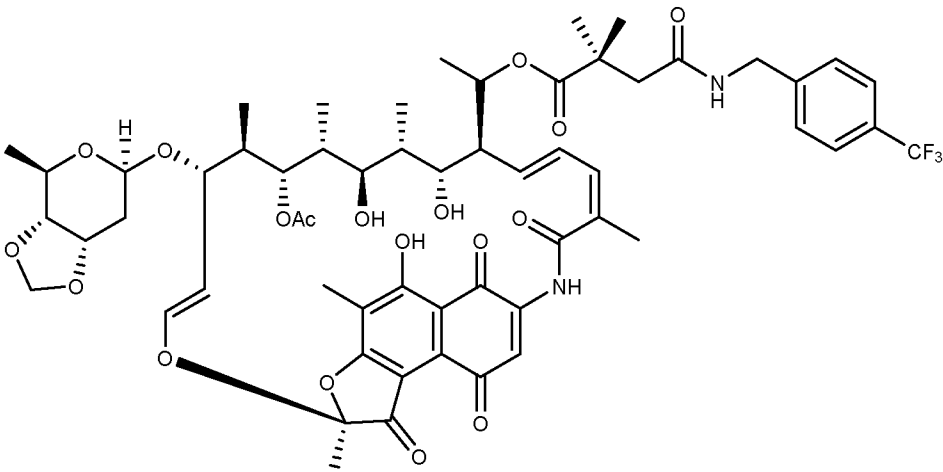


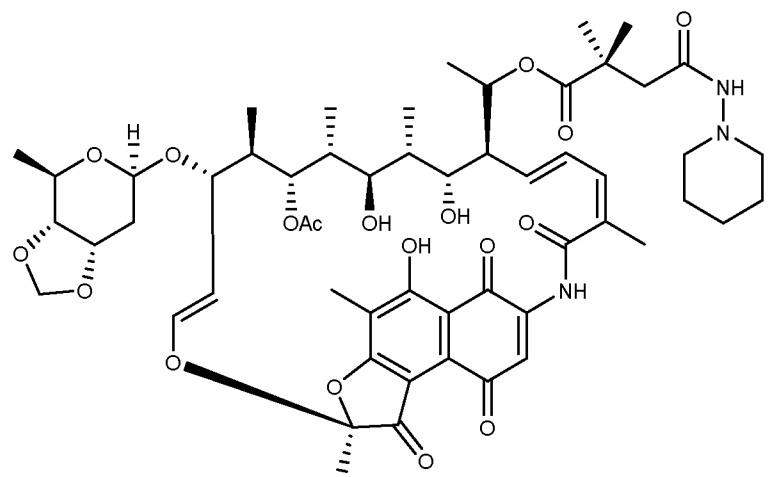
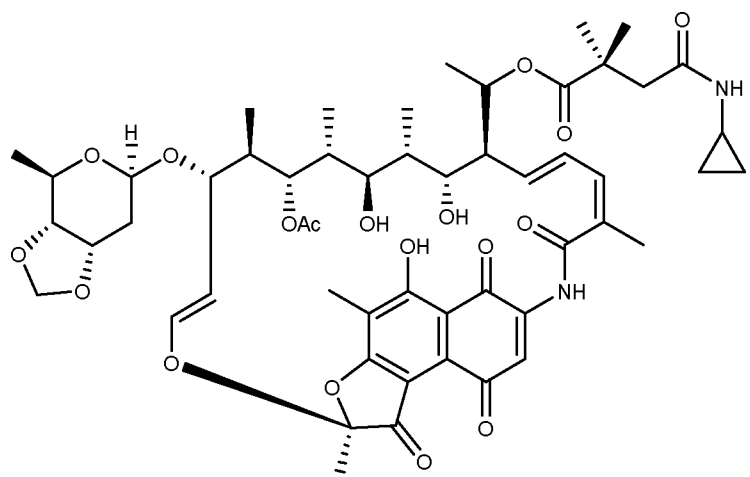
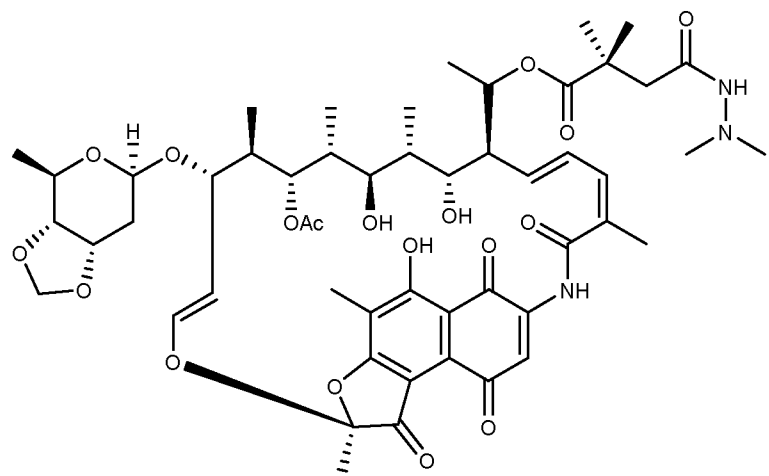


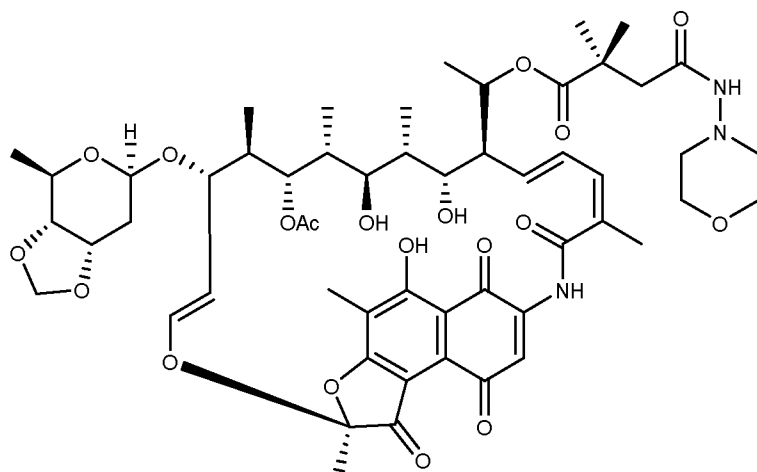












20. The compound for use according to any preceding claim, wherein the infection caused by rifampicin-resistant bacteria is tuberculosis.
21. A compound of formula (I), (II) or (III) as defined in any preceding claim, or a pharmaceutically acceptable salt, hydrate or solvate thereof, with the proviso that, in formula (I), when R_1 is hydroxy and R_2 is hydrogen, X_1 is not O.
22. A pharmaceutical composition comprising a compound as claimed in claim 21, or a pharmaceutically acceptable salt or solvate thereof, and one or more pharmaceutically acceptable excipients or carriers.

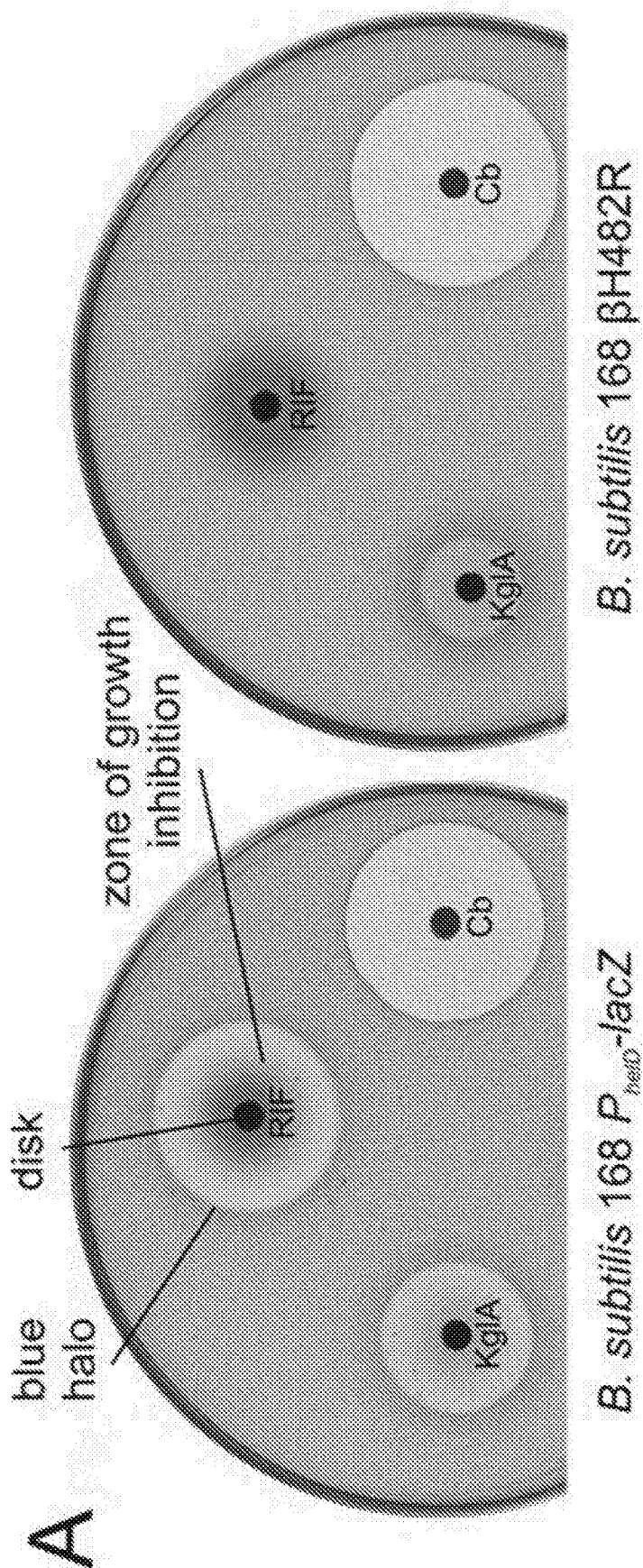


FIGURE 1

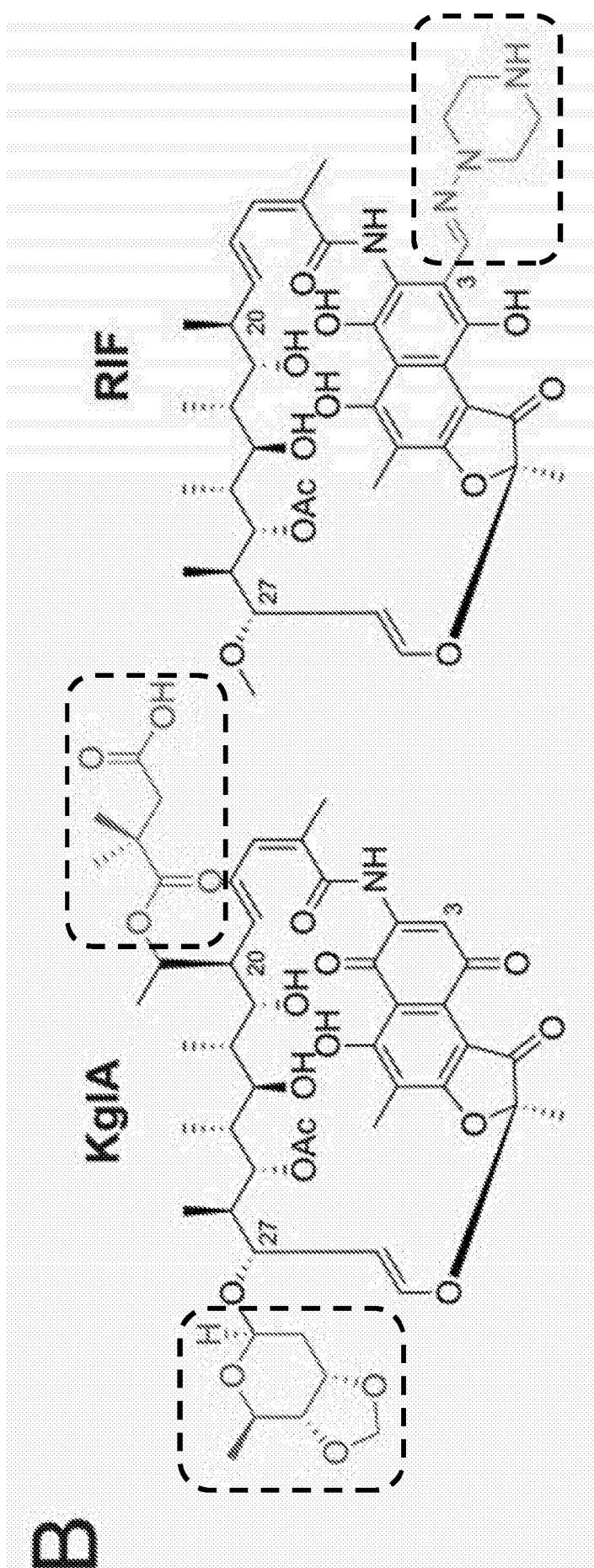


FIGURE 1

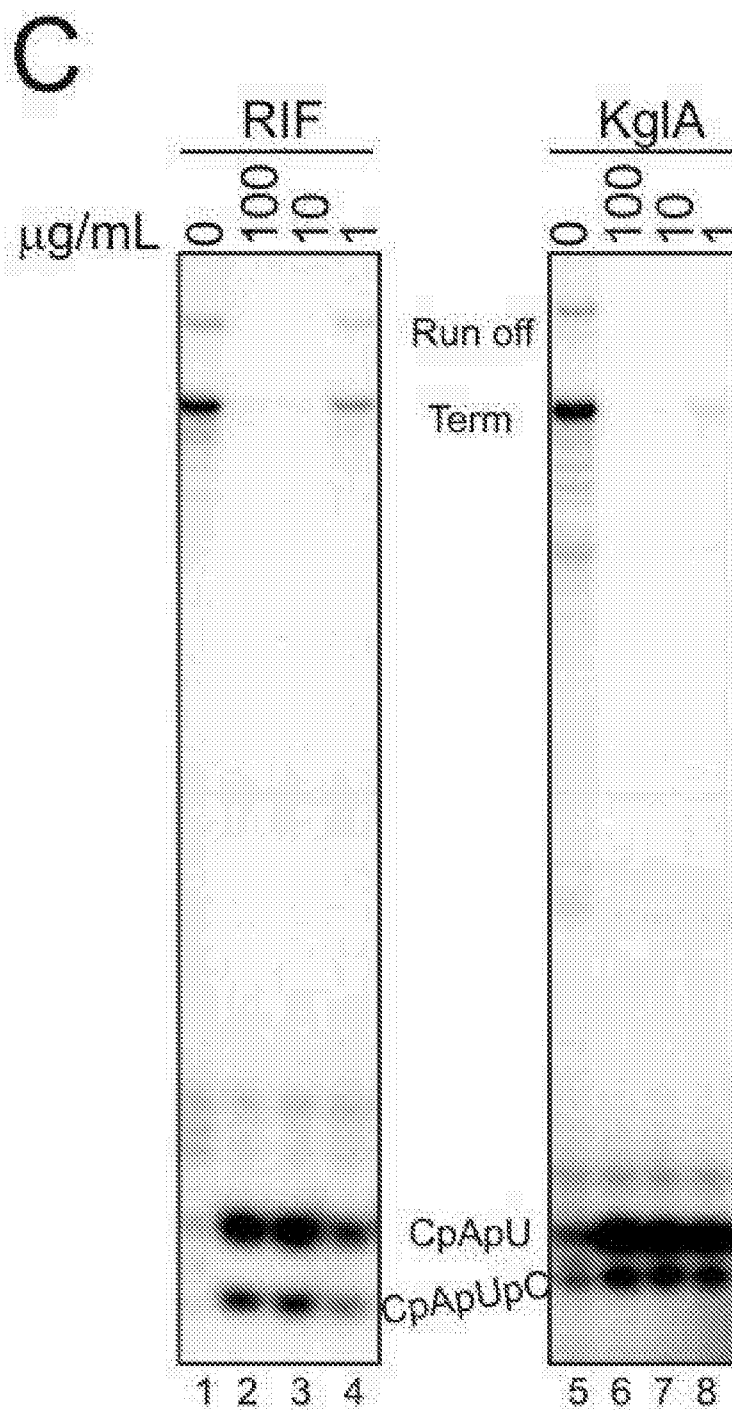


FIGURE 1

D

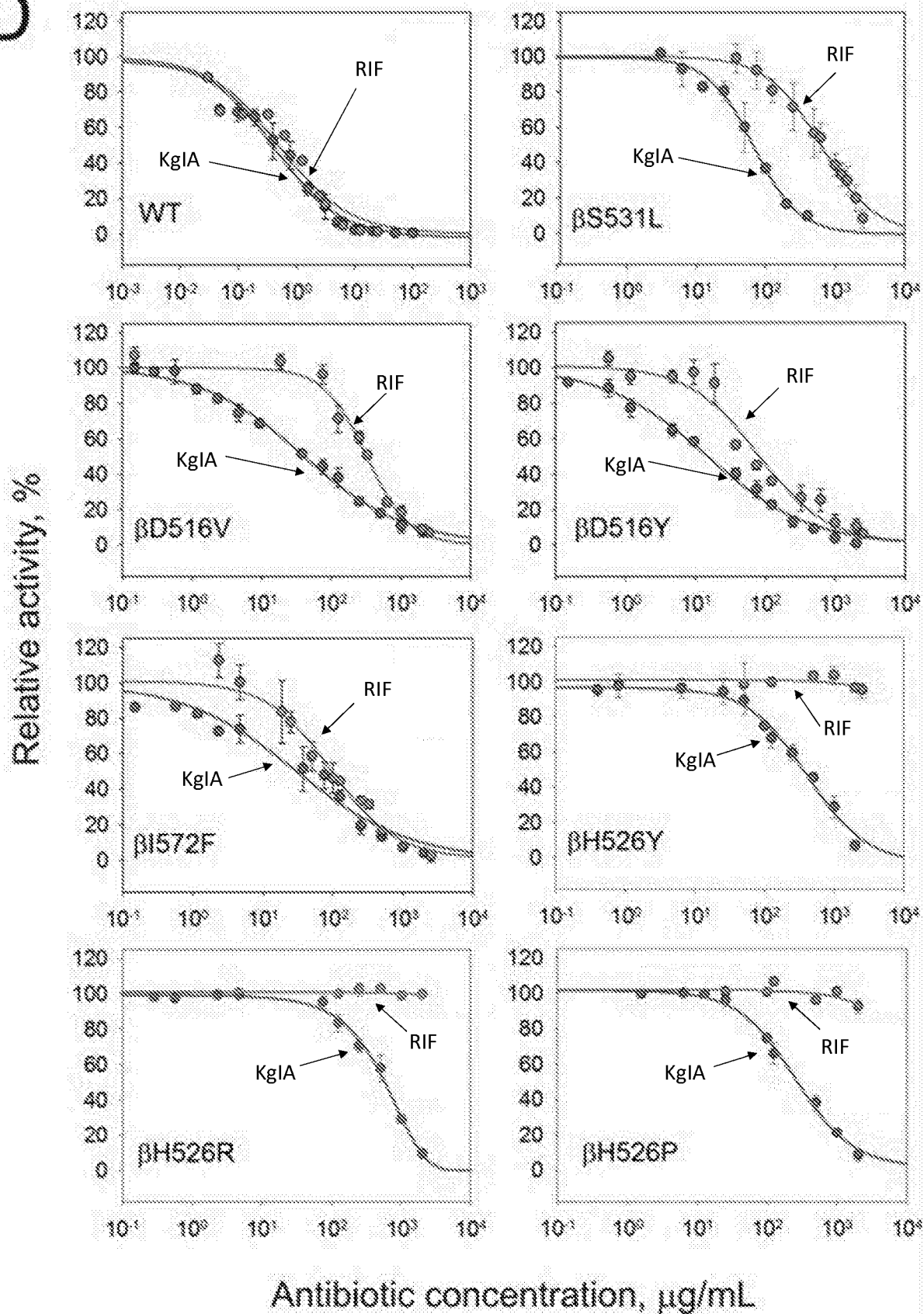


FIGURE 1

E

RNAP	IC ₅₀ (KglA), µg/mL	IC ₅₀ (RIF), µg/mL
WT	0.42 (±0.04, 0.79)	0.49 (±0.07, 0.72)
βS531L	67 (±5, 1.32)	623 (±48, 1.13)
βD516V	39 (±3, 0.59)	320 (±19, 1.42)
βD516Y	14.7 (±1.2, 0.58)	80 (±10, 0.87)
βH526Y	403 (±50, 1.01)	>2500
βH526P	253 (±25, 1.05)	>2500
βH526R	572 (±38, 1.44)	>2500
βI572F	101 (±5, 0.61)	93 (±10, 0.93)

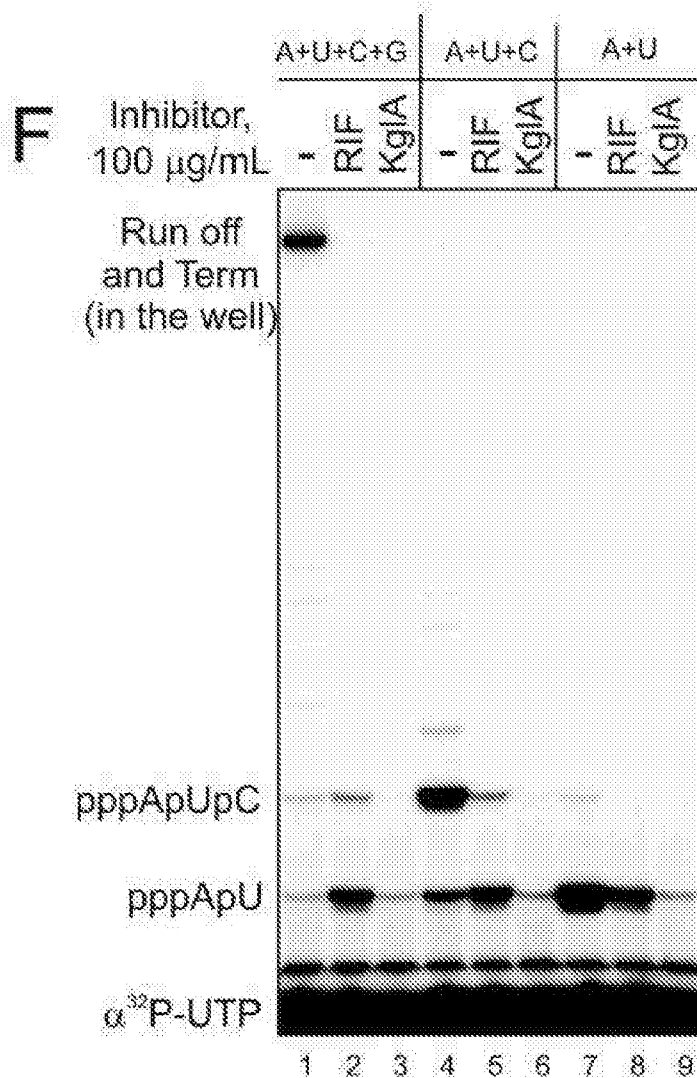


FIGURE 1

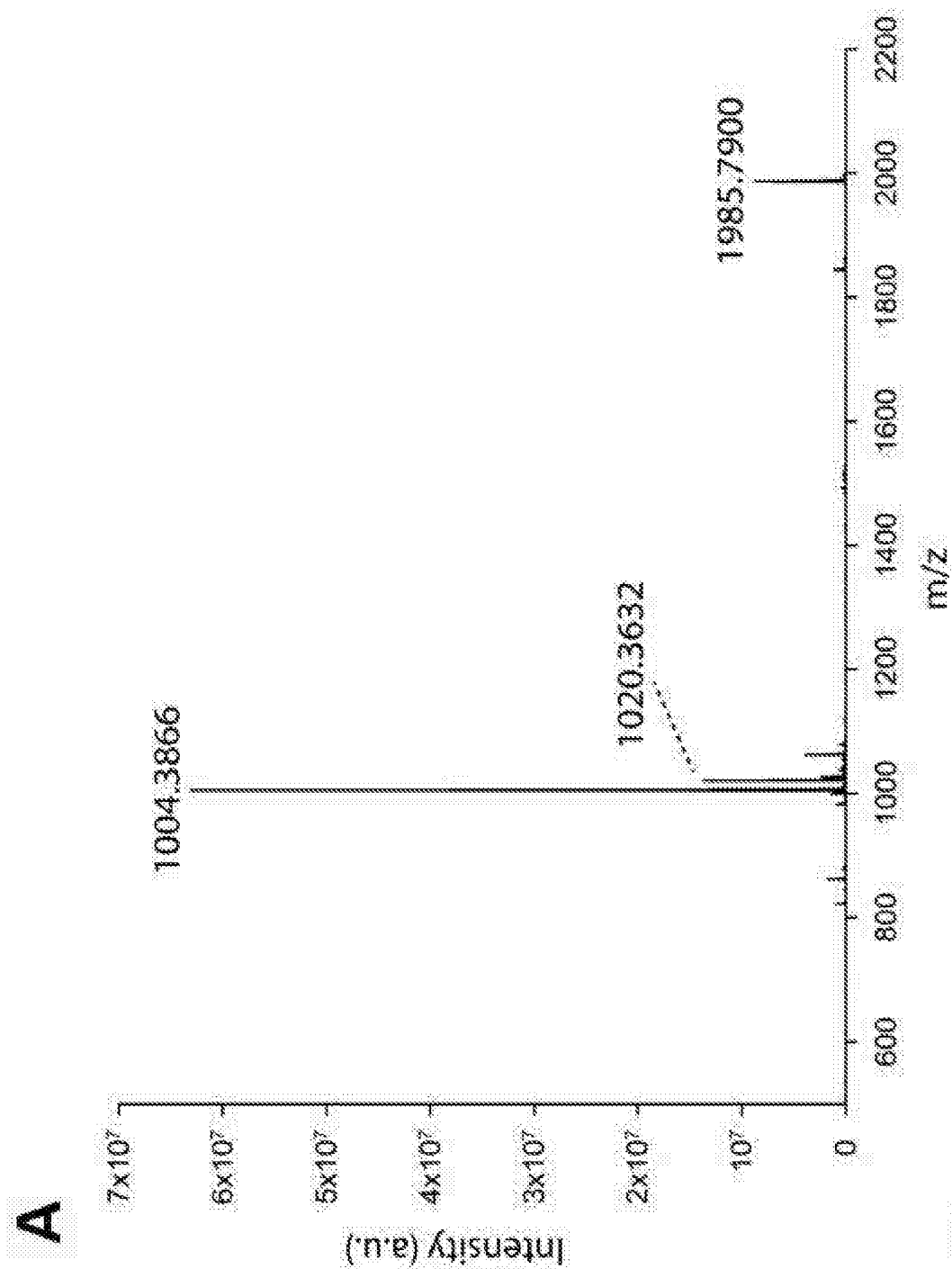


FIGURE 2

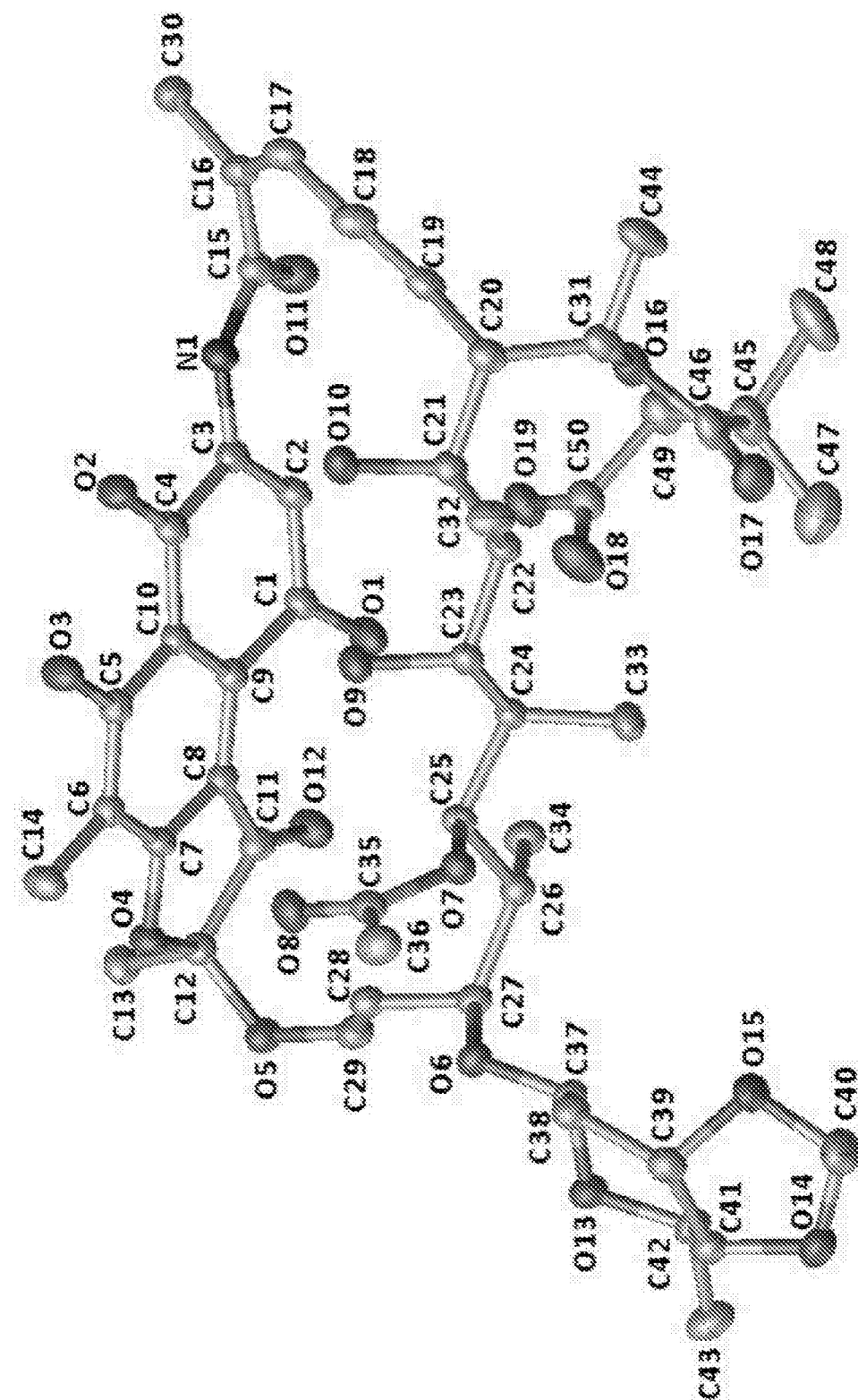


FIGURE 2

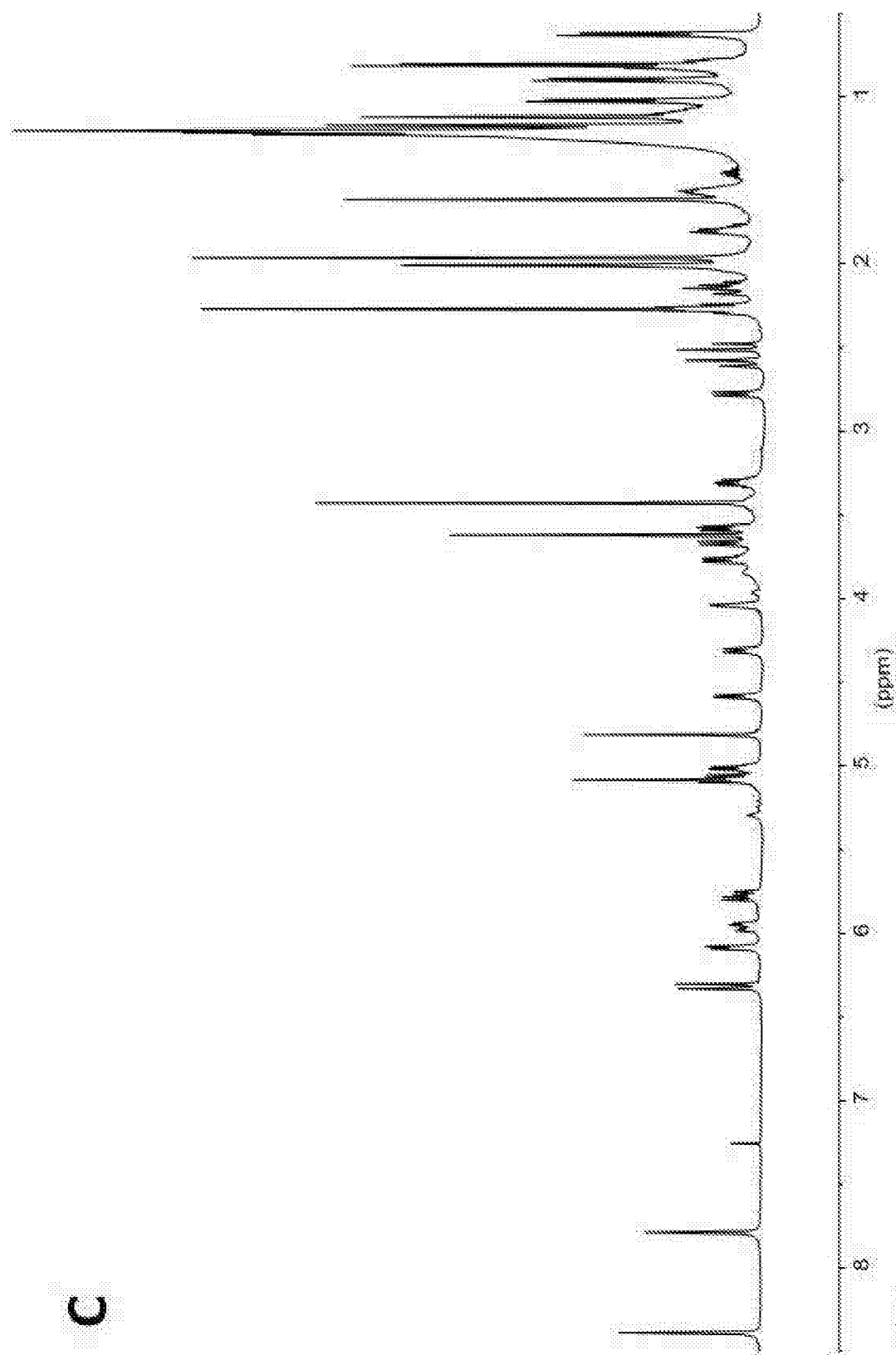


FIGURE 2

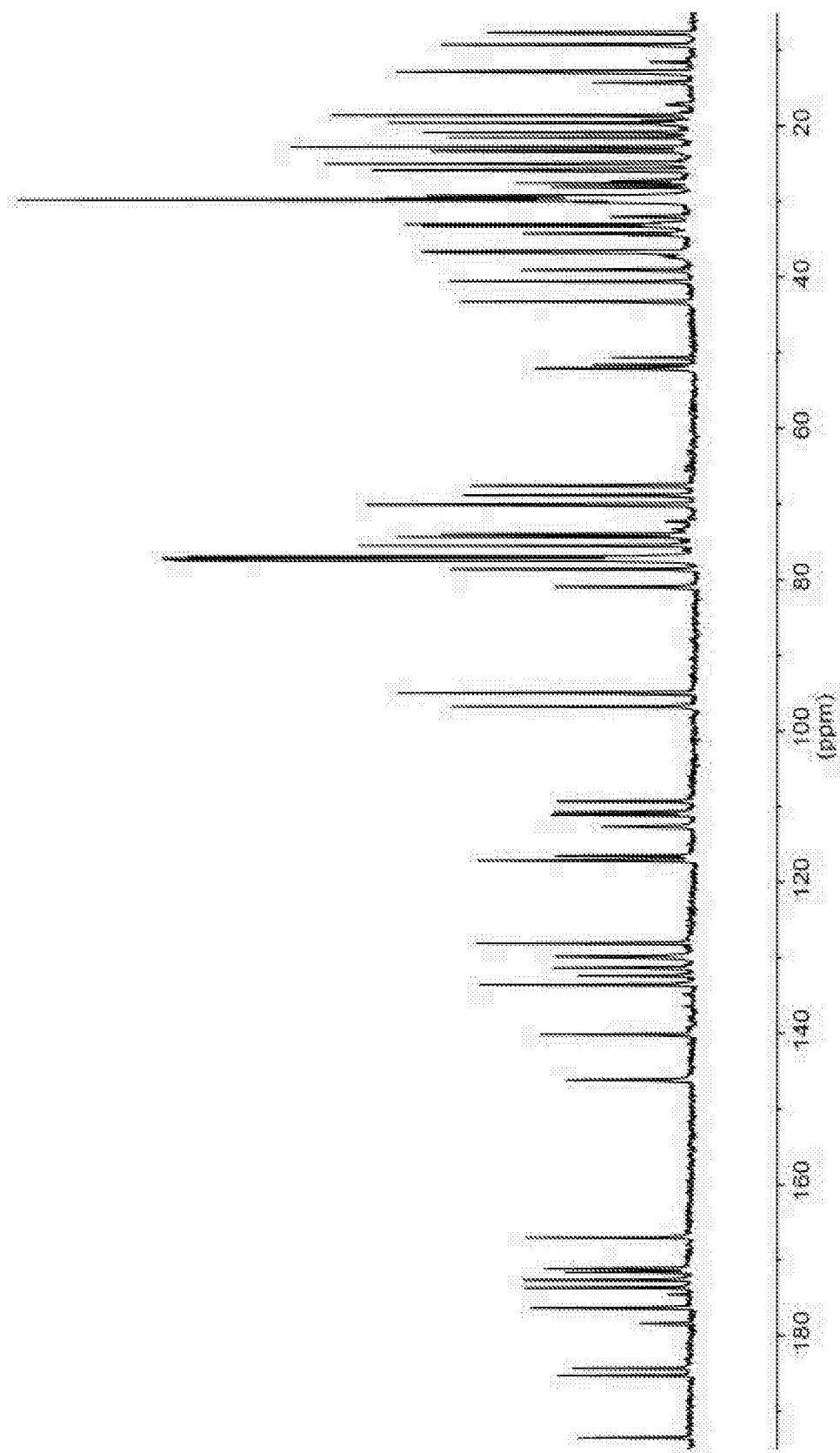
D

FIGURE 2

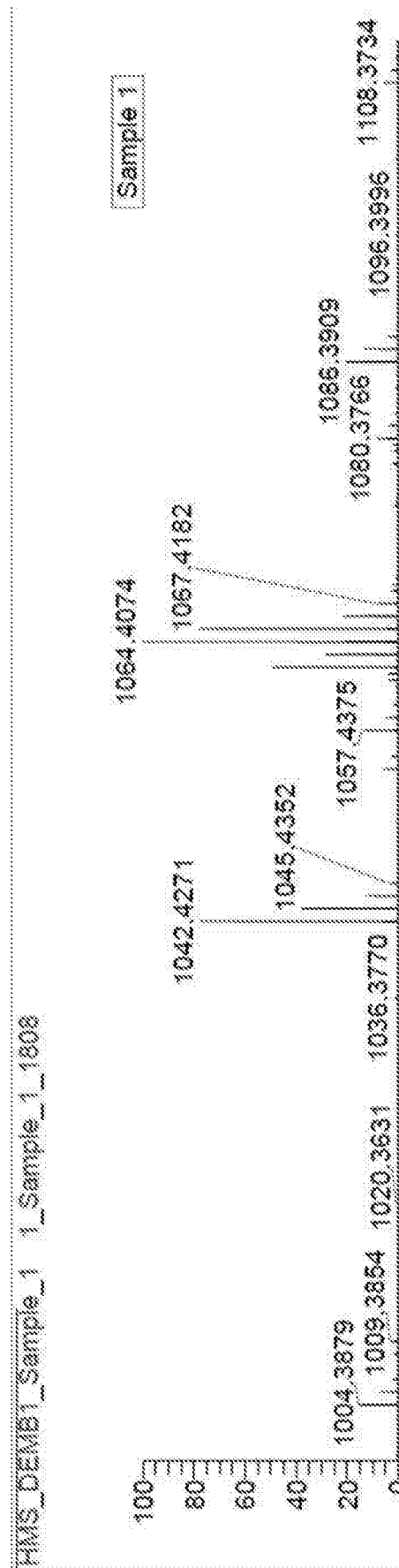


FIGURE 3

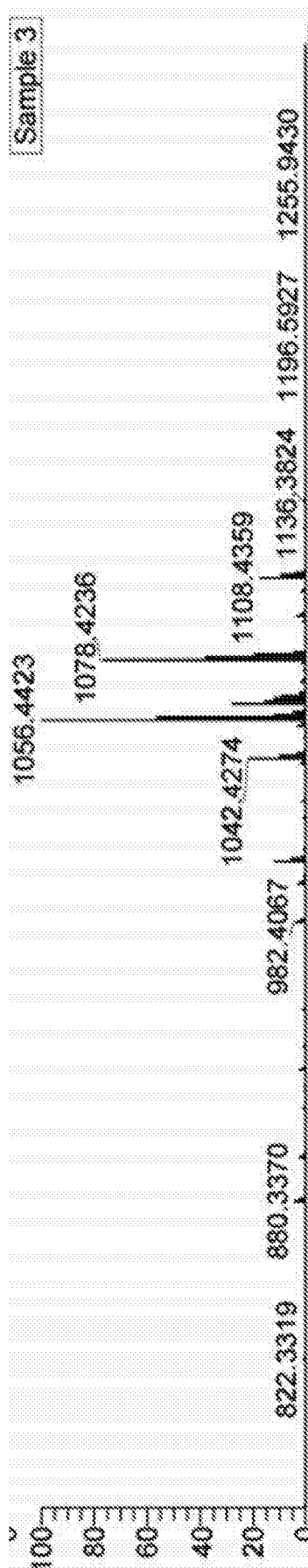


FIGURE 4

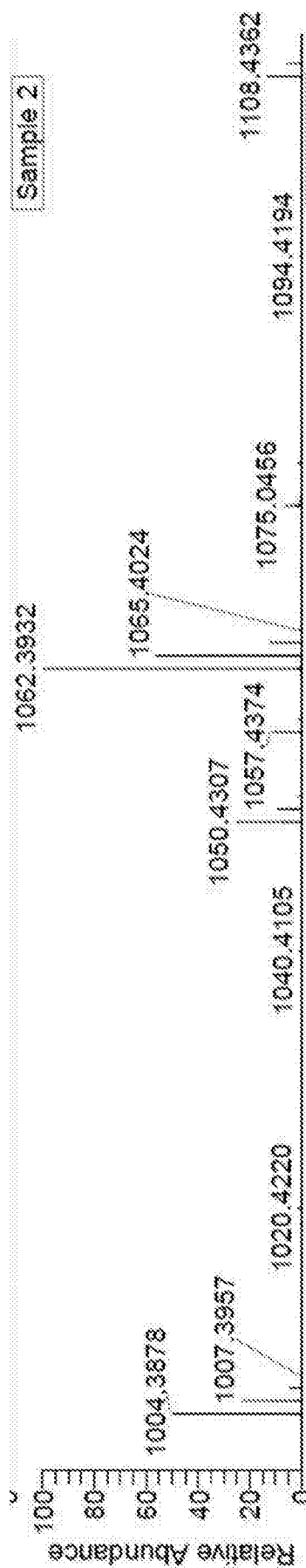


FIGURE 5

DEM30355 B1-S531L

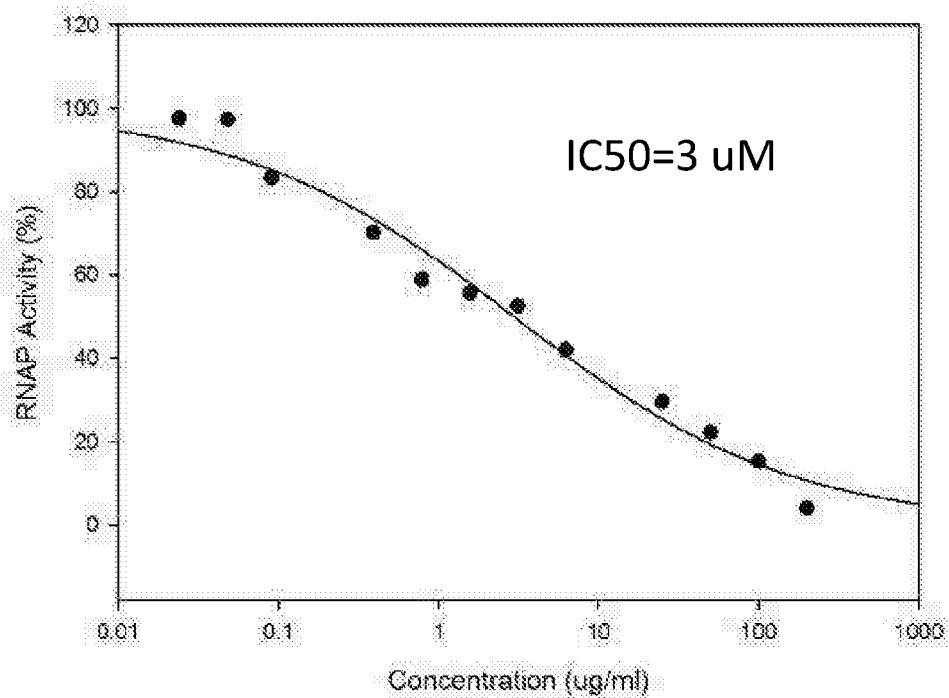


FIGURE 6

DEM30355 B3-S531L

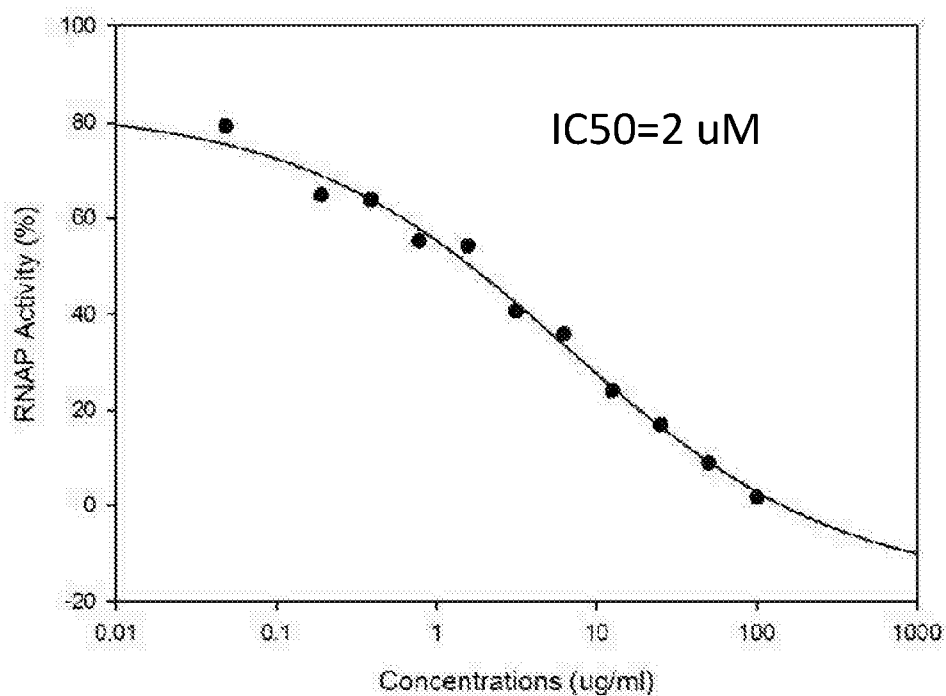


FIGURE 7

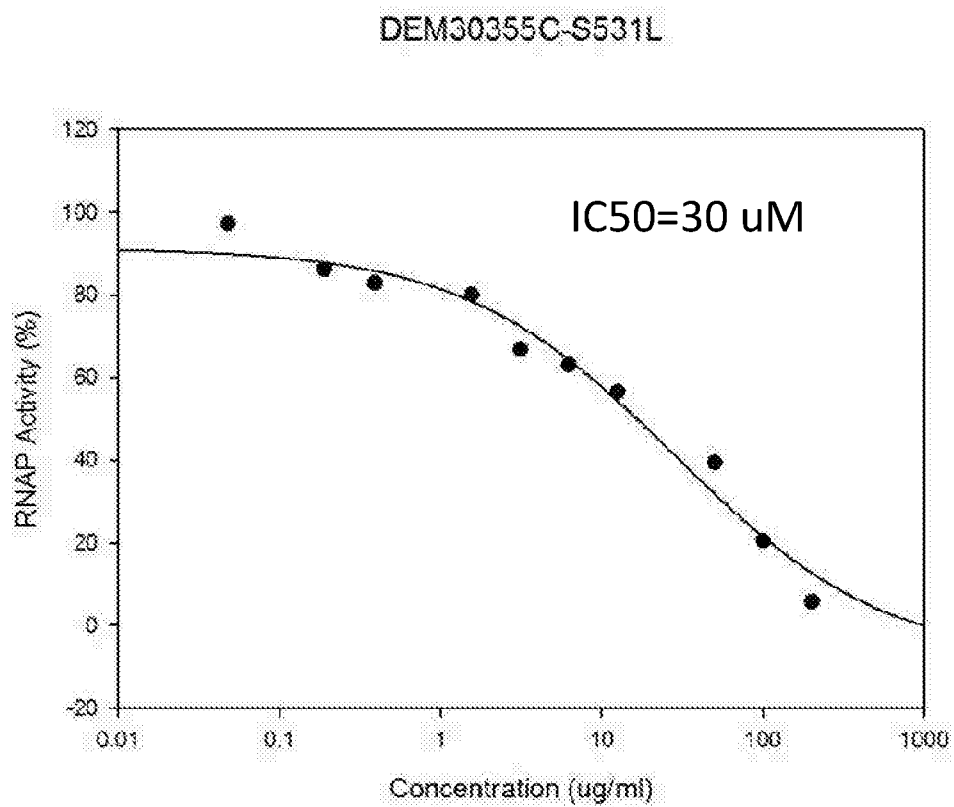


FIGURE 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/052061

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P31/04 A61K31/395 A61P31/06 C07D498/08
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P A61K C07D

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

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

EP0-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WANG N-J ET AL: "Isolation and structure of a new ansamycin antibiotic kanglemycin A from A Nocardia", THE JOURNAL OF ANTIBIOTICS, vol. 41, no. 2, February 1988 (1988-02), pages 264-267, XP055614098, ISSN: 0021-8820, DOI: 10.7164/antibiotics.41.264 cited in the application the whole document ----- -/--	1-22

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

☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

4 September 2019

Date of mailing of the international search report

23/09/2019

Name and mailing address of the ISA/

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Authorized officer

Elliott, Adrian

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2019/052061

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	MOSAEI H ET AL: "Mode of Action of Kanglemycin A, an Ansamycin Natural Product that Is Active against Rifampicin-Resistant Mycobacterium tuberculosis", MOLECULAR CELL, vol. 72, no. 2, 20 September 2018 (2018-09-20), page 263, XP085531571, ISSN: 1097-2765, DOI: 10.1016/J.MOLCEL.2018.08.028 the whole document	1-22
E	----- WO 2019/147753 A1 (THE ROCKEFELLER UNIVERSITY) 1 August 2019 (2019-08-01) see the whole document and, in particular, claims 40 and 41	1-22
X,P	----- PEEK J ET AL: "Rifamycin congeners kanglemycins are active against rifampicin-resistant bacteria via a distinct mechanism", NATURE COMMUNICATIONS, vol. 9, 8 October 2018 (2018-10-08), pages 1-15, XP055618088, DOI: 10.1038/s41467-018-06587-2 the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2019/052061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019147753 A1	01-08-2019	NONE	