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(54) Title: PROCESSES FOR PREPARING MACROLIDES AND KETOLIDES AND INTERMEDIATES THEREFOR

(57) Abstract: The invention described herein pertains to processes for the preparation of macrolide antibacterial agents. In particular, the invention pertains to processes for preparing macrolides and ketolides from erythromycin A.



WO 2011/146829 A1

PROCESSES FOR PREPARING MACROLIDES AND KETOLIDES AND  
INTERMEDIATES THEREFOR

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of United States provisional application  
61/346,664, filed 20 May 2010, which is incorporated by reference herein.

TECHNICAL FIELD

The invention described herein pertains to processes for the preparation of  
macrolide antibacterial agents. In particular, the invention pertains to processes for preparing  
macrolides and ketolides from erythromycin A.

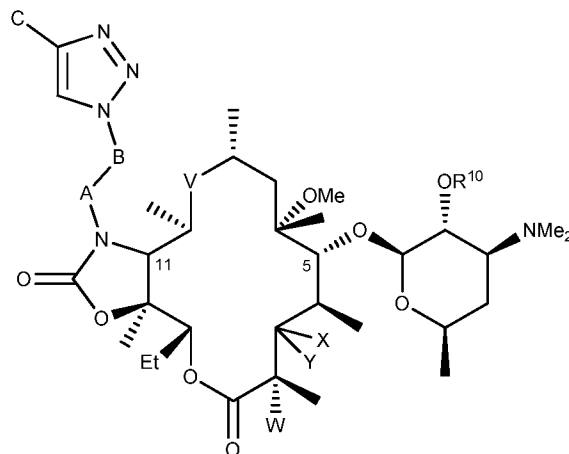
10 BACKGROUND AND SUMMARY OF THE INVENTION

Macrolide antibiotics, characterized by a large lactone ring to which are  
attached one or more deoxy sugars, usually cladinose and desosamine, are antimicrobial  
drugs that are active against aerobic and anaerobic gram positive cocci and are prescribed for  
the treatment of respiratory tract and soft tissue infections. The macrolides, which belong to  
15 the polyketide class of natural products, function by reversibly binding to the 50S subunit of  
the bacterial ribosome, blocking protein synthesis and preventing bacterial growth and  
reproduction. Although this action is primarily bacteriostatic, at higher concentrations,  
macrolides can be bactericidal. Erythromycin and the semi-synthetic derivatives  
azithromycin and clarithromycin are among the marketed macrolide antibiotics.

20 Ketolides, which are semi-synthetic derivatives of the 14-membered macrolide  
erythromycin A, belong to this class of drugs used to treat respiratory tract infections. These  
drugs are effective against macrolide-resistant bacteria because of their ability to bind to two  
sites on the bacterial ribosome. Telithromycin and cethromycin belong to this group of  
antibiotics.

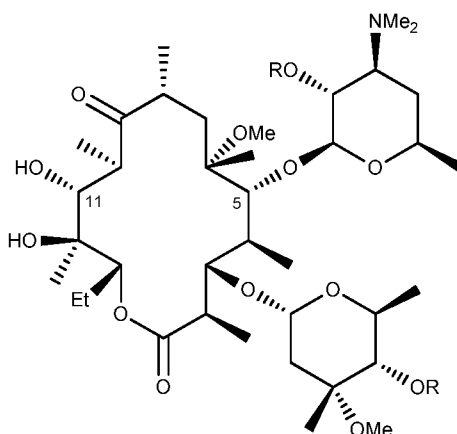
25 Acquired bacterial resistance to macrolides occurs primarily through post-  
transcriptional methylation of the 23S bacterial ribosome. This results in cross-resistance to  
macrolides, lincosamides and streptogramins. Although rare, acquired resistance also can  
result from the production of drug-inactivating enzymes such as esterases or kinases, as well  
as the production of active ATP-dependent efflux proteins that transport macrolides out of the  
30 cell. A significant fraction of pneumococci are resistant to currently available antibiotics.  
Accordingly, new macrolide and ketolide antibiotics are needed, along with processes for  
preparing them.

In particular, international patent application publication No. WO 2004/080391, and its counterpart publication US 2006/0100164, the disclosures of which are incorporated herein by reference, describes a family of macrolide and ketolide antibiotics, including fluoroketolide antibiotics, of formula (I)



(I)

and pharmaceutically acceptable salts thereof, wherein  $R^{10}$ , X, Y, V, W, A, B, and C are as described herein, and Me indicates methyl, and Et indicates ethyl. One notable, but non-limiting example compound of formula (I) is solithromycin, also referred to as OP-1068 and/or CEM-101. The preparation of CEM-101 and related compounds is described in WO 2009/055557, the disclosure of which is incorporated herein by reference. A starting material used in WO 2009/055557 A1 for the preparation of the macrolide antibacterial agents is clarithromycin. In the processes described therein, clarithromycin is converted into a clarithromycin derivative in which the hydroxyl groups of the sugar moieties are protected with acyl groups, such as clarithromycin dibenzoate, also known as 2',4''-di-O-benzoyl-6-O-methylerythromycin A, to form compounds of formula (II).



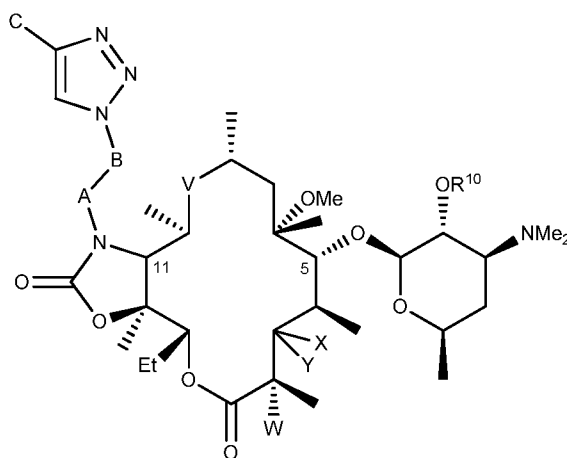
(II)

and pharmaceutically acceptable salts thereof, wherein R is as described herein.

Clarithromycin is a semisynthetic antibacterial agent in which the 6-hydroxy group of erythromycin A has been converted into a 6-methoxy group to eliminate undesired interaction with the carbonyl group at the 9-position of the macrolide ring, thereby stabilizing the antibiotic. Clarithromycin has been prepared by various processes. The most widely used processes begin with erythromycin A, which is converted to its oxime and then to a protected erythromycin A 9-oxime derivative as an intermediate, and variously involve protection and deprotection of the hydroxyl and dimethyl groups of the pendant sugar moieties before and after methylation of the 6-hydroxy group of the macrolide ring (see, for example, US 6,515,116 for a review of the reported processes; an alternative approach including protection of the desosaminyl amino group as an N-oxide is described in US 6,809,188). For the efficient production of a clarithromycin derivative in which the hydroxyl groups of the sugar moieties are protected with acyl groups and, subsequently, of a final macrolide antibacterial agent, there is needed a preparation of the diprotected derivative from erythromycin A which avoids the protecting and deprotecting steps used in the prior methodology for the preparation of clarithromycin. Described herein are processes for the direct production from erythromycin A of clarithromycin derivatives of formula (II) in which the hydroxyl groups of the sugar moieties are protected with acyl groups with a reduced number of steps. Also described herein are processes for preparing compounds of formula (I) from compounds of formula (II).

## DETAILED DESCRIPTION

In one illustrative embodiment of the invention, processes are described for preparing compounds of formula (I)



(I)

and pharmaceutically acceptable salts thereof, wherein:

R<sup>10</sup> is hydrogen, acyl or a prodrug moiety;

X is H; and Y is  $OR^7$ ; where  $R^7$  is monosaccharide, disaccharide, alkyl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted, or acyl or  $C(=O)NR^8R^9$ ; where  $R^8$  and  $R^9$  are each independently selected from the group consisting of hydrogen, hydroxy, alkyl, heteroalkyl, alkoxy, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted, and dimethylaminoalkyl, acyl, sulfonyl, ureido, and carbamoyl; or  $R^8$  and  $R^9$  are taken together with the attached nitrogen to form an optionally substituted heterocycle; or X and Y are taken together with the attached carbon to form carbonyl;

V is  $C(=O)$ ,  $C(=NR^{11})$ ,  $CH(NR^{12}, R^{13})$ , or  $N(R^{14})CH_2$ ; where  $N(R^{14})$  is attached to the C-10 carbon; where  $R^{11}$  is hydroxy or alkoxy;  $R^{12}$  and  $R^{13}$  are each independently selected from the group consisting of hydrogen, hydroxy, alkyl, alkoxy, heteroalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted, and dimethylaminoalkyl, acyl, sulfonyl, ureido, and carbamoyl;  $R^{14}$  is hydrogen, hydroxy, alkyl, alkoxy, heteroalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, each of which is optionally substituted, or dimethylaminoalkyl, acyl, sulfonyl, ureido, or carbamoyl;

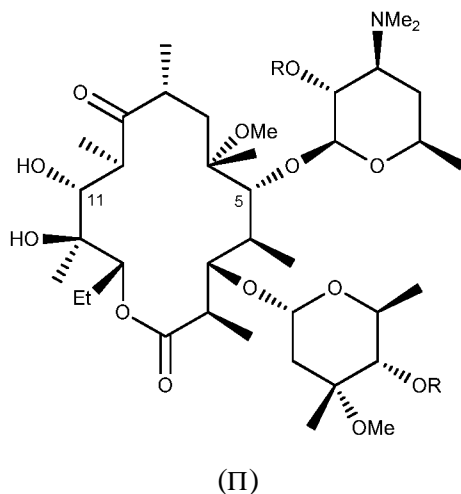
W is H, F, Cl, Br, I, or OH;

A is  $CH_2$ ,  $C(=O)$ ,  $C(=O)O$ ,  $C(=O)NH$ ,  $S(=O)_2$ ,  $S(=O)_2NH$ , or  $C(=O)NHS(=O)_2$ ;

B is  $(CH_2)_n$  where n is an integer from 0 to 10; or an unsaturated carbon chain of 2 to 10 carbons; and

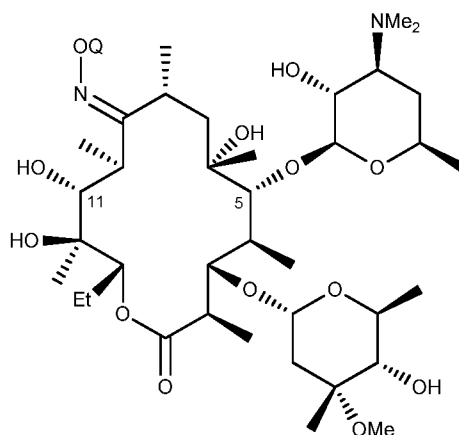
C is hydrogen, hydroxy, alkyl, alkoxy, heteroalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, each of which is optionally substituted, or acyl, acyloxy, sulfonyl, ureido, or carbamoyl.

In another illustrative embodiment, processes are described for preparing compounds of formula (II)



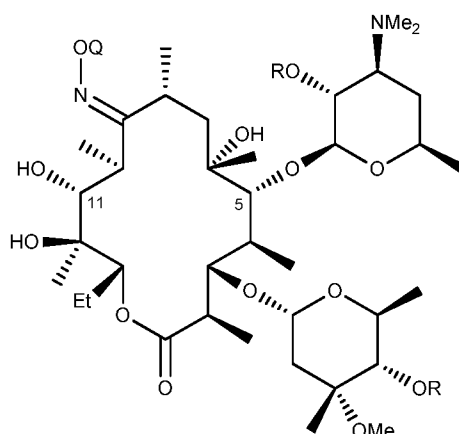
and pharmaceutically acceptable salts thereof, wherein R is an acyl group. In another embodiment, R is a hindered acyl group, such as benzoyl.

In another embodiment, processes are described herein comprising the step of (a) contacting a compound of formula (III)



(III)

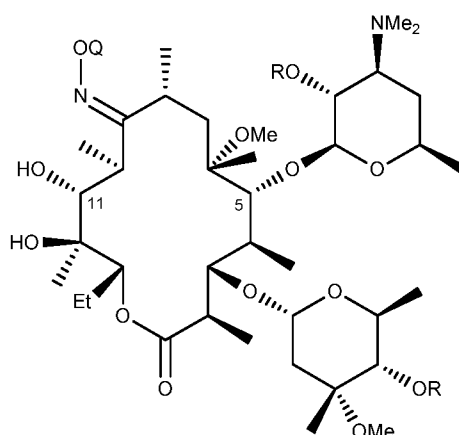
or an acid addition salt thereof, with an acylating agent to prepare a compound of formula (IV)



(IV)

or an acid addition salt thereof; where in each instance Q in combination with the oxime oxygen forms an acetal or a ketal, or Q is troyl, and R is an acyl group. In another embodiment, the step (a) of the processes includes a base.

In another illustrative embodiment, processes are described herein comprising the step of (b) contacting a compound of formula (IV), as described herein, or an acid addition salt thereof, with a methylating agent to prepare a compound of formula (V)

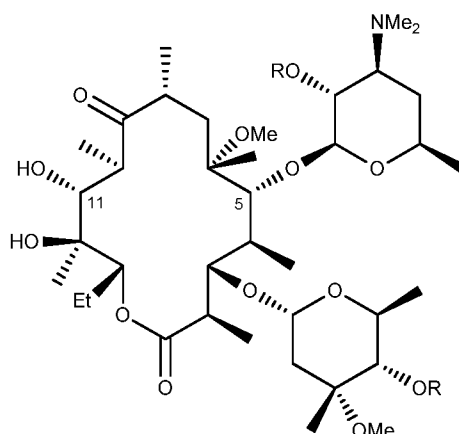


(V)

or an acid addition salt thereof, where Q and R are as described in the alternative embodiments herein. In another embodiment, the step (b) of the processes includes a base.

- 5 In another embodiment, the step (b) of the processes includes an aprotic polar solvent.

In another illustrative embodiment, processes are described herein comprising the step of (c) contacting a compound of formula (V), as described herein, or an acid addition salt thereof, with a deoximating agent to form the compound of formula (II),



(II)

or an acid addition salt thereof, where R is described in the alternative embodiments herein.

It is to be understood that each of the steps (a), (b), and (c) may be combined in additional embodiments. It is further to be understood that the variations of each of the steps (a), (b), and (c) described herein may be combined without limitation in additional  
 15 embodiments. For example, another illustrative process comprises acylating step (a) and further comprises methylating step (b), and further comprises deoximating step (c). Another illustrative process comprises methylating step (b) and further comprises deoximating step (c). Another illustrative process comprises acylating step (a) and further comprises methylating step (b), and further comprises deoximating step (c), and further comprises steps

described in WO 2009/055557 for converting compounds of formula (II) into compounds of formula (I).

In another embodiment, processes for preparing compounds of formula (IV), such as compounds of formula (IV) where R is benzoyl, or an acid addition salt thereof, are described herein, where the processes comprise the step of contacting a compound of formula (III), as described herein, or an acid addition salt thereof, with an acylating agent, such as benzoyl anhydride, also referred to as benzoic anhydride, to form a compound of formula (IV), or an acid addition salt thereof. In one variation, the step is performed in the presence of a base.

In another embodiment, processes for preparing compounds of formula (V), or an acid addition salt thereof, as described herein, where the processes comprise the step of contacting a compound of formula (IV), as described herein, or an acid addition salt thereof, with a methylating agent, to form a 6-O-methyl compound of formula (V), as described herein, or an acid addition salt thereof. In one variation, the step is performed in the presence of a base. In another variation, the step is performed in an aprotic polar solvent. In another variation, the step is performed in the presence of a base and in an aprotic polar solvent.

In another embodiment, processes for preparing compounds of formula (II), including compounds of formula (II) where R is benzoyl, or an acid addition salt of any of the foregoing, are described herein, where the processes comprise the step of contacting a compound of formula (V), as described herein, or an acid addition salt thereof, with a deoximating agent to form a compound of formula (II), or an acid addition salt thereof.

In another illustrative embodiment of any of the foregoing processes, Q is an O-protecting group. In one variation, Q in combination with the oxime oxygen forms an acetal or ketal, or Q is troyl. In another illustrative embodiment, R is an acyl group. In another illustrative embodiment, Q is an O-protecting group. In one variation, Q in combination with the oxime oxygen forms an acetal or ketal, or Q is troyl, and R is an acyl group.

In another illustrative embodiment of any of the foregoing processes, Q is  $C(R^A)(R^C)(OR^B)$ , wherein

$R^A$  is a group of the formula  $CH_2R^D$ , where  $R^D$  is hydrogen, (1-3C)alkyl or (1-6C)alkoxy;

$R^B$  is (1-6C)alkyl, (5-7C)cycloalkyl; phenyl or arylalkyl; and

$R^C$  is hydrogen, (1-4C)alkyl, phenyl or arylalkyl; or alternatively in any of the foregoing



$R^B$  and  $R^D$  together form an ethylene, propylene or trimethylene group; or  
 $R^B$  and  $R^D$  together form a (3-5C)alkanediyl group which may be further substituted with one to three (1-3C)alkyl substituents; or

$R^B$  and  $R^C$  together form a (3-4C)alkanediyl group.

5 In another embodiment of any of the foregoing processes, Q is 2-methoxy-2-propyl, 1-methoxycyclohexyl, or 1-isopropoxycyclohexyl. In another embodiment of any of the foregoing processes, Q is 2-methoxy-2-propyl.

Compounds of formula (III), as described herein, may be prepared by contacting erythromycin A 9-oxime with a corresponding compound of formula

10  $R^E-C(R^A)(R^C)(OR^B)$  in which  $R^E$  is (1-6C)alkoxy or in which  $R^A$  and  $R^E$  together form a group of formula  $CHR^D$  connected by a double bond. The step may be carried out in the presence of an acidic catalyst, for example in the presence of pyridine hydrochloride. In another variation, the step is performed using 2-methoxypropene to form a compound of formula (III) in which Q is 2-methoxy-2-propyl. In another variation, the step is performed,  
15 in dichloromethane at about 0 °C to about room temperature in the presence of pyridine hydrochloride using excess 2-methoxypropene. In another variation, Q is tropyl, and the compounds of formula (III) may be prepared by reacting erythromycin A 9-oxime with tropylum tetrafluoroborate in an aprotic polar solvent.

In another embodiment of any of the processes described herein, R is a  
20 sterically hindered acyl group, such as a benzoyl group. In another embodiment of any of the processes described herein, R is not acetyl. Without being bound by theory, it is believed herein that the use of a sterically hindered group R may improve the processes and/or the purity of the isolated product of the processes. It has been discovered that unhindered acyl groups, such as acetyl groups, present on the C-5 saccharide may migrate to other positions  
25 on the macrolide, for example from the 2'-hydroxy group of the desosamine moiety to an amino group of a side chain. Use of a sterically hindered group R decreases and/or precludes such a migration leading to improved processes and/or improved purities of the isolated product of the processes

In another embodiment of any of the processes described herein, R is benzoyl.

30 In another embodiment of any of the processes described herein, step (a) is performed with an acylating agent is the anhydride, acid halide, or an activated ester of the corresponding acyl group R. In another embodiment of any of the processes described herein, the acylating agent is the anhydride of the acyl group R. In another embodiment of any of the processes described herein, about 2 to about 6 equivalents of acylating agent to an

equivalent of the compound of formula (III) is employed. In another embodiment of any of the processes described herein, a base is included in step (a), such as a tertiary amine. In another embodiment of any of the processes described herein, the base is triethylamine, diisopropylethylamine, or 4-methylmorpholine, or a combination thereof. In another embodiment of any of the processes described herein, about 1 to about 4 equivalents of base to an equivalent of the compound of formula of formula (III) is employed. In another embodiment of any of the processes described herein, the acylation is performed in the presence of about 0.5 to about 2.5 equivalents of an acylation catalyst to an equivalent of the compound of formula of formula (III). In another embodiment of any of the processes described herein, the acylation catalyst is 4-dimethylaminopyridine.

In another embodiment of any of the processes described herein, the methylating agent is methyl bromide, methyl iodide, dimethyl sulfate, methyl p-toluenesulfonate, or methyl methanesulfonate. In another embodiment, the methylating agent is methyl iodide. In another embodiment of a process described herein, a base is used in combination with the methylating agent, such as sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, or potassium t-butoxide, or a mixture thereof. In another embodiment the base used with the methylating agent is potassium hydroxide. In another embodiment the methylation step is performed in an aprotic polar solvent, such as dimethyl sulfoxide, dimethylformamide, 1-methyl-2-pyrrolidone, a mixture thereof, or a mixture of any of these solvents with one or more of tetrahydrofuran, 2-methyltetrahydrofuran, 1,2-dimethoxyethane, acetonitrile or ethyl acetate. In another embodiment of any of the processes described herein, the methylating step is performed at a temperature from about -15 °C to about 60 °C. Another embodiment of processes described herein for the methylation of a compound of formula (IV) is one wherein the methylating step is performed at a temperature from about 0 °C to about 30 °C.

It has been unexpectedly discovered herein that the methylation step of compounds of formula (IV), where R is benzoyl, is performed without, any or substantially any, cleavage of the benzoate ester present on compounds of formula (IV).

Illustratively, removal of the group Q, such as by O-deprotection, and/or removal of the oxime group at C-9 to form a ketone, such as by deoximation, may be performed using any of a number of conventional processes and/or reagents. Illustrative deoximation methods include, but are not limited to, hydrolytic, oxidative and reductive conditions. In one embodiment, the deoximating agent comprises a reducing agent. Illustrative embodiments of deoximating agents include, but are not limited to, inorganic

sulfur oxide compounds such as sodium hydrogen sulfite, sodium pyrosulfate, sodium thiosulfate, sodium sulfite, sodium hydrosulfite, sodium metabisulfite, sodium bisulfite, sodium dithionate, potassium hydrogen sulfite, potassium thiosulfate and potassium metabisulfite, and mixtures thereof. In another embodiment of any of the processes described  
 5 herein, the deoximating agent is sodium metabisulfite or sodium bisulfite, or a combination thereof. It is to be understood that O-deprotection may be performed prior to deoximation; or O-deprotection and deoximation may be performed in a single ("one-pot") step by treatment, either sequentially, concurrently, contemporaneously, or simultaneously by using acid, such as formic acid, and a deoximating agent.

10 In another embodiment of any of the processes described herein, the step of converting the C-9 oxime into a carbonyl is performed by contacting the compound of formula (V) wherein the deoximating agent comprises formic acid and sodium metabisulfite in an aqueous alcoholic solution at a temperature ranging from ambient temperature to about the boiling point of the solvent.

15 It has been unexpectedly discovered that removing the O-protecting group Q and removing the oxime from a compound of formula (V) in which R is benzoyl may be performed without, any or substantially any, cleavage of the benzoate ester present on compounds of formula (V).

20 It is to be understood that the various subgenera, species, and compounds described herein may be made by the various embodiments of the processes described herein. For example, in another embodiment of any of the processes herein, V is C(O); and/or

R<sup>7</sup> is an aminosugar or a halosugar; or

R<sup>7</sup> is 4-nitro-phenylacetyl or 2-pyridylacetyl; or

X and Y are taken together with the attached carbon to form carbonyl; and/or

25 A is CH<sub>2</sub>; and/or

B is alkenylene; and/or

B is (C<sub>n</sub>H<sub>2n</sub>)<sub>n</sub>; where n is 2 to 6, 2 to 5, or 2 to 4, or 2 to 3, or 3; and/or

C is aminophenyl; or

C is 3-aminophenyl; and/or

30 W is fluoro; or

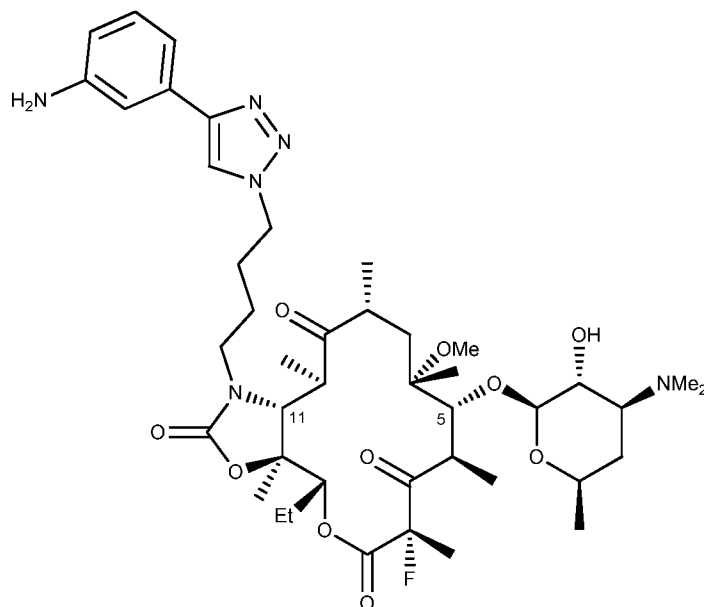
W is hydrogen; and/or

R<sup>10</sup> is hydrogen or acyl; or

R<sup>10</sup> is hydrogen; or

R<sup>10</sup> is benzoyl.

In another embodiment of any of the processes described herein, the compound of formula (I) is CEM-101, or a pharmaceutically acceptable salt, solvate or hydrate thereof. The compound CEM-101 has Chemical Abstracts Registry Number 760981-83-7, and structure of the compound is as follows:



5

As used herein, the term "alkyl", alone or in combination, refers to an optionally substituted straight-chain, optionally substituted branched-chain, or optionally substituted cyclic alkyl radical having from 1 to about 30 carbons, more preferably 1 to 12 carbons. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like. A "lower alkyl" is a shorter alkyl, e.g., one containing from 1 to about 6 carbon atoms.

10

The term "alkoxy," alone or in combination, refers to an alkyl ether radical, alkyl-O, wherein the term alkyl is defined as above. Examples of alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

15

The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain, optionally substituted branched-chain, or optionally substituted cyclic alkenyl hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 30 carbon atoms, more preferably 2 to about 18 carbons. Examples of alkenyl radicals include ethenyl, propenyl, butenyl, 1,4-butadienyl and the like. The term can also embrace cyclic alkenyl structures. A "lower alkenyl" refers to an alkenyl having from 2 to about 6 carbons.

20

The term "acyloxy" refers to the ester group OC(O)-R, where R is H, alkyl, alkenyl, alkynyl, aryl, or arylalkyl, wherein the alkyl, alkenyl, alkynyl and arylalkyl groups may be optionally substituted.

5 The term "acyl" includes alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl substituents attached to a compound via a carbonyl functionality (e.g., CO-alkyl, CO-aryl, CO-arylalkyl or CO-heteroarylalkyl, etc.).

The term "heteroalkyl" generally refers to a chain of atoms that includes both carbon and at least one heteroatom. Illustrative heteroatoms include nitrogen, oxygen, and sulfur.

10 As used herein, the term "aryl" includes monocyclic and polycyclic aromatic carbocyclic and aromatic heterocyclic groups, each of which may be optionally substituted. As used herein, the term "heteroaryl" includes aromatic heterocyclic groups, each of which may be optionally substituted. Illustrative carbocyclic aromatic groups described herein include, but are not limited to, phenyl, naphthyl, and the like. Illustrative heterocyclic  
15 aromatic groups include, but are not limited to, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, quinolinyl, quinazolinyl, quinoxalinyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzisoxazolyl, benzisothiazolyl, and the like.

The term "arylalkyl" refers to an alkyl group substituted with one or more  
20 unsubstituted or substituted monocyclic or polycyclic aryl groups. Illustrative arylalkyl groups include benzyl, diphenylmethyl, trityl, 2-phenylethyl, 1-phenylethyl, 2-pyridylmethyl, 4,4'-dimethoxytrityl, and the like.

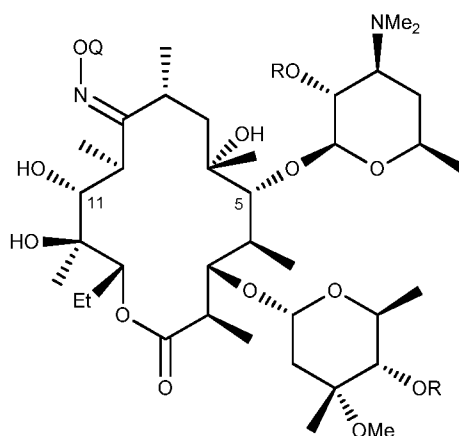
The term "alkylaryl" refers to an aryl group substituted with an alkyl group.

The term "sulfonyl" refers to SO<sub>2</sub>-R where R is H, alkyl or aryl.

25 The term "saccharide" includes monosaccharides, disaccharides, and polysaccharides, each of which is optionally substituted. The term also includes sugars and deoxysugars optionally substituted with amino, amido, ureyl, halogen, nitrile, or azido groups. Illustrative examples include, glucosamine, N-acetylglucosamine, desosamine, forosamine, sialic acid, and the like.

30 The term "activated ester" includes carboxylic acid derivatives in which the hydrogen of the hydroxy group has been replaced with a residue which results in the formation of a good leaving group, including the 4-nitrophenyl ester and an activated ester or anhydride derived from a coupling reagent.

In another embodiment, compounds of formula (IV) are described

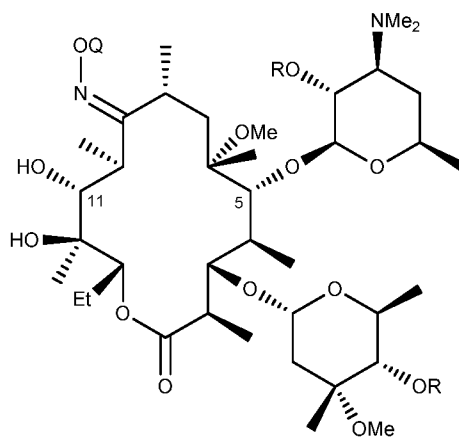


(IV)

and acid addition salts thereof; wherein Q and R are as described in the various embodiments herein.

5

In another embodiment, compounds of formula (V) are described



(V)

and acid addition salts thereof; wherein Q and R are as described in the various embodiments herein.

10

It is appreciated herein that because compounds of formulae (I), (II), (III), (IV), and (V) each contain a dimethylamino group on the desosaminyl moiety, the compounds may form acid addition salts. Accordingly, it is to be understood that any acid addition salt of a compound of formulae (I), (II), (III), (IV), and (V) suitable for use in pharmaceutical manufacturing or for providing a free base which is suitable for use in pharmaceutical manufacturing is described herein and to be included in the invention described herein.

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In each of the foregoing and following embodiments, it is to be understood that the formulae include and represent not only all pharmaceutically acceptable salts of the compounds, but also include any and all hydrates and/or solvates of the compound formulae.

It is appreciated that certain functional groups, such as the hydroxy, amino, and like groups form complexes and/or coordination compounds with water and/or various solvents, in the various physical forms of the compounds. Accordingly, the above formulae are to be understood to include and represent those various hydrates and/or solvates. In each of the foregoing and following embodiments, it is also to be understood that the formulae include and represent each possible isomer, such as stereoisomers and geometric isomers, both individually and in any and all possible mixtures. In each of the foregoing and following embodiments, it is also to be understood that the formulae include and represent any and all crystalline forms, partially crystalline forms, and non crystalline and/or amorphous forms of the compounds. For example, Illustrative crystal morphologies are described in co-pending PCT international application No. PCT/US20 11/029424, the disclosure of which is incorporated herein in its entirety.

### EXAMPLES

The following examples further illustrate specific embodiments of the invention; however, the following illustrative examples should not be interpreted in any way to limit the invention. Abbreviations used in the examples include the following: DCM, dichloromethane; DMAP, 4-dimethylaminopyridine; DMSO; dimethyl sulfoxide; EA, ethyl acetate; <sup>1</sup>H-NMR, proton nuclear magnetic resonance spectroscopy; MeOH, methanol; Mw, molecular weight; RT, room (ambient) temperature; THF, tetrahydrofuran; TLC, thin layer chromatography.

EXAMPLE. Synthesis of erythromycin A 9-oxime (1). A mixture of erythromycin A (15 g, 20.4 mmol), NH<sub>2</sub>OH.HCl (7.3 g, 105 mmol) and triethylamine (7 g, 69 mmol) in MeOH (23 mL) is heated to reflux overnight. A white solid forms during the reaction. The reaction mixture is concentrated to a small volume. To the obtained residue is added dilute aqueous NH<sub>4</sub>OH solution at 0 °C until the pH of the mixture reaches about 10 to 11. Additional solid precipitates out from the mixture. The mixture is filtered, the collected solid is washed with water and dried under vacuum to give 14.2 g of 1 as white granular solid in 93% yield. TLC analysis (DCM:MeOH:NH<sub>4</sub>OH = 90:10:1) of the obtained 1 shows a small amount of an additional compound (lower spot), corresponding to the Z-isomer. Mass analysis of the obtained 1 showsd a peak with Mw = 749, corresponding to the title compound. <sup>1</sup>H-NMR analysis of the product is consistent with the title compound, and also shows a mixture of the (1) and the HCl salt thereof. The product is used without purification.

EXAMPLE. Large Scale Preparation of (1). Erythromycin (250 g, 0.34 mol) and hydroxylamine hydrochloride (80.3 g, 1.15 mol) in methanol (325 ml) are heated under reflux in the presence of triethylamine (45 g, 0.44 mol). The reaction is monitored by TLC using toluene/triethylamine (8:2) as eluent. After completion (ca. 24 h), the reaction mass is gradually cooled and stirred at 0-5 °C for 1 h, filtered and washed with cooled methanol (100 mL). The wet solid (265 g) is suspended in isopropyl alcohol (350 mL) and heated to 50-55 °C followed by the addition of aqueous ammonia (650 mL) over a period of 2h. The solution is stirred for 1 h at 50-55 °C and gradually cooled to 10-15 °C and maintained for 2 h. The solid was filtered and washed with water and dried at 80-85 °C for 12 h to isolate 186 g. About 3% of the corresponding Z-oxime isomer is observed by HPLC. The preparation is repeated as follows with the corresponding scale of other reagents.

No.	Batch Size	Product	Yield (%)	Purity by HPLC
1	100g	73 g	74%	93% + 3% of Z-oxime
2	250 g	186 g	73%	95% + 3% of Z-oxime
3	250 g	187 g	73%	95% + 3% of Z-oxime

EXAMPLE. Synthesis of a Compound of Formula (III), Q = 2-methoxy-2-propyl (9). To a solution of (1) (3 g, 4 mmol) in anhydrous dichloromethane (DCM, 21 mL) is added 2-methoxypropene (1.5 g, 20.8 mmol), followed by pyridine hydrochloride (0.72 g, 6.2 mmol) at 0 °C. After the addition, the reaction mixture is stirred at 0 °C at RT for 30 min. Conversion is monitored by TLC analysis of the reaction mixture (DCM:MeOH:NH<sub>4</sub>OH = 90:10:1). If conversion is incomplete, the mixture is cooled back to 0 °C, and another 0.5 g of 2-methoxypropene (6.9 mmol) is added. The mixture is stirred at 0 °C for another 0.5 h. If conversion is incomplete, another 0.5 g of 2-methoxypropene (6.9 mmol), followed with another 0.1 g of pyridine hydrochloride (0.86 mmol) is added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for another 15 min. Upon complete conversion, the reaction mixture is diluted with saturated aqueous NaHCO<sub>3</sub> solution. The DCM layer is separated and the aqueous layer is extracted with DCM. The combined DCM layers are washed with brine, dried over MgSO<sub>4</sub>, concentrated to dryness to give 3.3 g crude product as a white foam in quantitative yield. Mass analysis of the product shows Mw = 821, corresponding to the title compound, and a very minor peak with molecular weight of 861. <sup>1</sup>H-NMR of the product is consistent with the title compound, and a small amount 2-methoxypropan-2-ol and pyridine. The product is used without further purification.



EXAMPLE. Synthesis of a Compound of Formula (IV), Q = 2-methoxy-2-propyl, R = benzoyl (10). To a solution of (9) (4.1g, 5 mmol) in ethyl acetate (65 mL) is added benzoyl anhydride (4.5 g, 20 mmol), followed by triethylamine (1.26 g, 12.5 mmol) and DMAP (0.9 g, 7.4 mmol) at RT. The resulting mixture is stirred at RT for 36 h. The reaction mixture is diluted with saturated aqueous NaHCO<sub>3</sub> solution. The EA layer is separated and the aqueous layer is extracted with EA. The combined EA layers are washed with brine, dried over MgSO<sub>4</sub>, filtered to remove the drying agent, and concentrated to dryness. The obtained residue is subjected to silica gel column chromatography (DCM:MeOH:NH<sub>4</sub>OH = 97:3:0.3) to give 4.2 g of 10 in 80% yield as a white solid. Mass analysis of the purified product shows Mw = 1029, corresponding to the title compound. <sup>1</sup>H-NMR is consistent with the title compound.

EXAMPLE. Large Scale Preparation of (9). Erythromycin Oxime (1) (200 g, 0.26 mol) is dissolved in DCM (1.4 L) and the volume is reduced to 1 L by distillation under atmospheric pressure. After cooling the reaction mass to 0-5°C, 2-methoxypropene (80 g, 1.1 mol) and pyridine hydrobromide (50 g, 0.31 mol) are added and stirred for 3 h at 20-25 °C. Mass analysis confirmed the presence of (9). Without isolation, benzoic anhydride (211 g, 0.93 mol), triethylamine (54 g, 0.53 mol), DMAP (48.8 g, 0.40 mol) are added and the reaction is continued for 24 h at 30°C. The reaction is monitored by TLC and analyzed by mass spectrometry. After completion, saturated sodium bicarbonate (1 L) is added and stirred for 15 min and allowed to settle. The layers are separated and the organic layer is concentrated. The material is isolated to 190 g with a purity of 48-51%. The preparation is repeated as follows with the corresponding scale of other reagents.

No.	Batch Size	Unpurified Product	Purity
1	200 g	190 g	48%
2	200 g	186 g	50%
3	200 g	184 g	51%

The unpurified product from successive batches is combined (450 g) and dissolved in EA (4.5 L) to a clear solution that is washed with saturated sodium bicarbonate (2.2 L), water (2.2 L), and brine (2.2 L), and concentrated. The isolated product is crystallized from IPE/n-Hexane to 360 g (84%).

EXAMPLE. Synthesis of a Compound of Formula (V), Q = 2-methoxy-2-propyl, R = benzoyl (11). A solution of (10) (3.8 g, 3.7 mmol) in anhydrous THF (15 mL) and anhydrous DMSO (15 mL) is cooled to 0 °C. Powdered KOH (0.46 g, 8.2 mmol) is

added, followed by methyl iodide (1.06 g, 7.5 mmol) at 0 °C. The resulting reaction mixture is stirred at 0°C for 5 min, subsequently becoming a thick paste and stopping the stirring. The mixture is warmed to RT for 5 min, remaining a thick paste, and diluted with 15 mL of THF and 15 mL of DMSO, to a free flowing suspension. The mixture is stirred at RT for another 0.5 hr, diluted with saturated aqueous NaHCCl<sub>3</sub> solution, and extracted with ethyl acetate. The ethyl acetate extract is washed with brine, dried over MgSO<sub>4</sub> and concentrated to dryness. The isolated residue is purified by silica gel column chromatography (DCM:MeOH:NH<sub>4</sub>OH = 97:3:0.3) to 2.83 g of (11) as a white solid in 73% yield. Mass analysis shows Mw = 1043), corresponding to the title compound, along with a minor peak Mw = 1057. <sup>1</sup>H-NMR is consistent with the title compound.

EXAMPLE. Large Scale Preparation of (11). Benzoylated oxime (10) (100 g, 0.09 mol) is dissolved in toluene (1.8 L) and the solution is distilled under vacuum to remove toluene (300 mL), cooled to 15°C, and diluted with DMSO (1.5 L). After cooling to 5°C, methyl iodide (20.5 g, 0.14 mol) is added followed by KOH (10.8g, 0.19 mol) and the reaction is continued for 3 h. The reaction is stopped by the addition of 40% dimethylamine (22 g) and the temperature of the reaction mass is raised to RT and diluted with water (500 mL) with stirring. The layers are separated and the aqueous layer is extracted with toluene (500 mL). The combined organic layers are washed with water (2 L) and the organic layer is concentrated by distillation under vacuum. The isolated product is stirred in IPE (500 mL) for 5 h and filtered to 82g of the title compound, which is used without further purification. The preparation is repeated as follows with the corresponding scale of other reagents.

No.	Batch Size	Product	Yield (%)
1	100 g	82 g	-
2	100 g	78 g	-
3	100 g	84 g	-
4	90 g	71 g	80%

EXAMPLE. Synthesis of a Clarithromycin Dibenzoate, Formula (II), R = benzoyl. To a solution of (11) (800 mg, 0.78 mmol) in ethanol (8 mL) and water (8 mL) is added sodium metabisulfite (740 mg, 3.89 mmol) at RT. The resulting mixture is adjusted to pH 2-3 by adding formic acid (1.5 mL). The mixture is heated at 60 °C for 1 h. Conversion is monitored by mass spectrometry. If incomplete, or showing a large amount of the deprotected oxime intermediate (Mw = 971), another 2 g of sodium metabisulfite (10.5 mmol) is added. The mixture is stirred at 60 °C for another 7 h, then cooled to RT. A white solid precipitate forms as the reaction progresses. The reaction mixture is neutralized with

dilute aqueous  $\text{NaHCO}_3$  solution to pH of 8-9 and the resulting mixture is filtered. The isolated white solid is dried under vacuum to 760 mg of clarithromycin dibenzoate. The unpurified product is combined with material obtained from other preparations (ca. 200 mg) and purified by silica gel column chromatography to 730 mg of clarithromycin dibenzoate in 79% yield. Mass analysis shows  $M_w = 956$ , corresponding to the title compound, with a minor peak of  $M_w = 970$ , which is attributed to the carryover impurity in (11).  $^1\text{H-NMR}$  is consistent with the title compound.

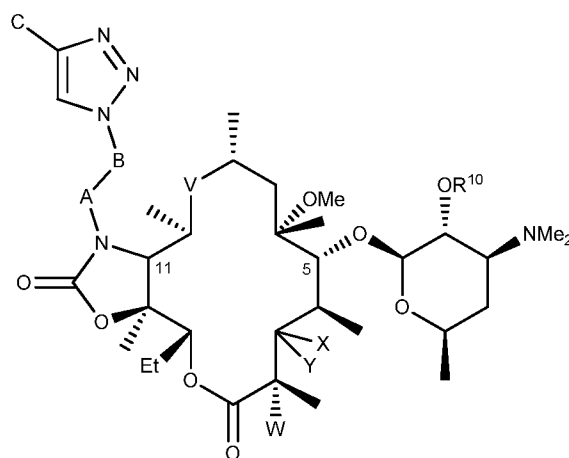
EXAMPLE. Large Scale Preparation of Clarithromycin Dibenzoate.

Methylated oxime (11) (80 g, 0.07 mol) is dissolved in absolute alcohol (400 mL). Water (400 mL) is added, followed by sodium bisulfite (72 g, 0.69 mol) and formic acid (21 g). The reaction mass is heated to reflux for 6 h, cooled to RT, and diluted with water (400 mL). The reaction mass is cooled to 10-15°C, and 25% NaOH (160 ml) is added slowly. The mixture is stirred for 2 h and filtered. The isolated solid is washed with water (500 mL) and dissolved in ethylacetate (400 mL). The organic layer is washed with water (400 mL), then brine (400 mL), then concentrated. The isolated material is crystallized from ethyl acetate (1.7 T) to 40.8 g (95% purity). Alternatively, the isolated material is crystallized from IPA/IPE 89-90% purity. The preparation is repeated as follows with the corresponding scale of other reagents.

No.	Batch Size	Product	Yield (%)
1	80 g	40.8 g	95%
2	70 g	37.8 g	90%
3	70 g	45 g	89%

WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein:

$R^{10}$  is hydrogen, acyl or a prodrug moiety;

X is H; and Y is  $OR^7$ ; where  $R^7$  is monosaccharide, disaccharide, alkyl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted, or acyl or  $C(=O)NR^8R^9$ ; where  $R^8$  and  $R^9$  are each independently selected from the group consisting of hydrogen, hydroxy, alkyl, heteroalkyl, alkoxy, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted, and dimethylaminoalkyl, acyl, sulfonyl, ureido, and carbamoyl; or  $R^8$  and  $R^9$  are taken together with the attached nitrogen to form an optionally substituted heterocycle; or X and Y are taken together with the attached carbon to form carbonyl;

V is  $C(=O)$ ,  $C(=NR^{11})$ ,  $CH(NR^{12}, R^{13})$ , or  $N(R^{14})CH_2$ ; where  $N(R^{14})$  is attached to the C-10 carbon; where  $R^{11}$  is hydroxy or alkoxy;  $R^{12}$  and  $R^{13}$  are each independently selected from the group consisting of hydrogen, hydroxy, alkyl, alkoxy, heteroalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, each of which is optionally substituted, and dimethylaminoalkyl, acyl, sulfonyl, ureido, and carbamoyl;  $R^{14}$  is hydrogen, hydroxy, alkyl, alkoxy, heteroalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, each of which is optionally substituted, or dimethylaminoalkyl, acyl, sulfonyl, ureido, or carbamoyl;

W is H, F, Cl, Br, I, or OH;

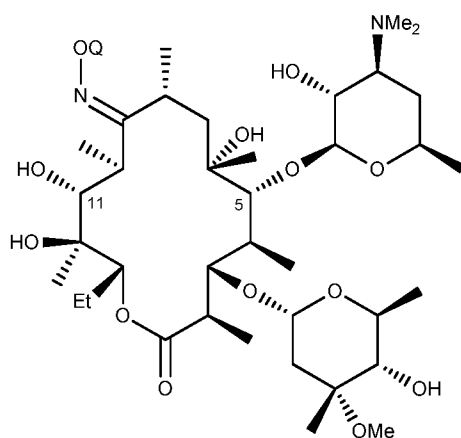
A is  $CH_2$ ,  $C(=O)$ ,  $C(=O)O$ ,  $C(=O)NH$ ,  $S(=O)_2$ ,  $S(=O)_2NH$ , or  $C(=O)NHS(=O)_2$ ;

B is  $(CH_2)_n$  where n is an integer from 0 to 10; or an unsaturated carbon chain of 2 to 10 carbons; and

C is hydrogen, hydroxy, alkyl, alkoxy, heteroalkyl, aryl, arylalkyl, heteroaryl,

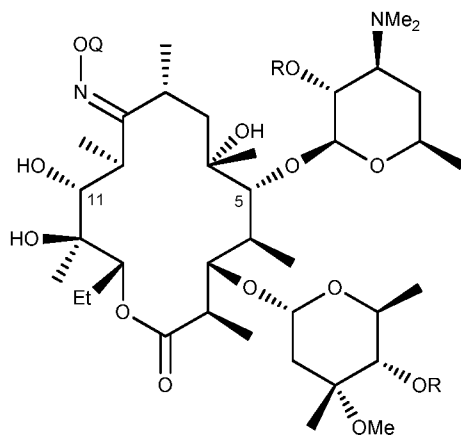
or heteroarylalkyl, each of which is optionally substituted, or acyl, acyloxy, sulfonyl, ureido, or carbamoyl;

the process comprising (a) the step of contacting a compound of formula (III),



(III)

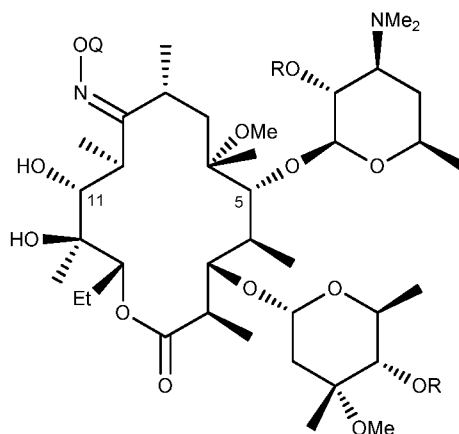
or an acid addition salt thereof, wherein Q in combination with the oxime oxygen forms an acetal or ketal, or Q is troyl, with an acylating agent to form a compound of formula (IV)



(IV)

or an acid addition salt thereof, wherein R is an acyl group; or

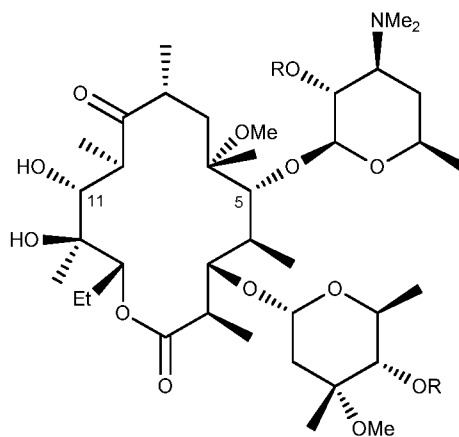
the process comprising (b) the step of contacting a compound of formula (IV), or an acid addition salt thereof, with a methylating agent, to form a compound of formula (V)



(V)

or an acid addition salt thereof; or

the process comprising (c) the step of contacting a compound of formula (V), or an acid addition salt thereof, with a deoximating agent to form a compound of formula (II)



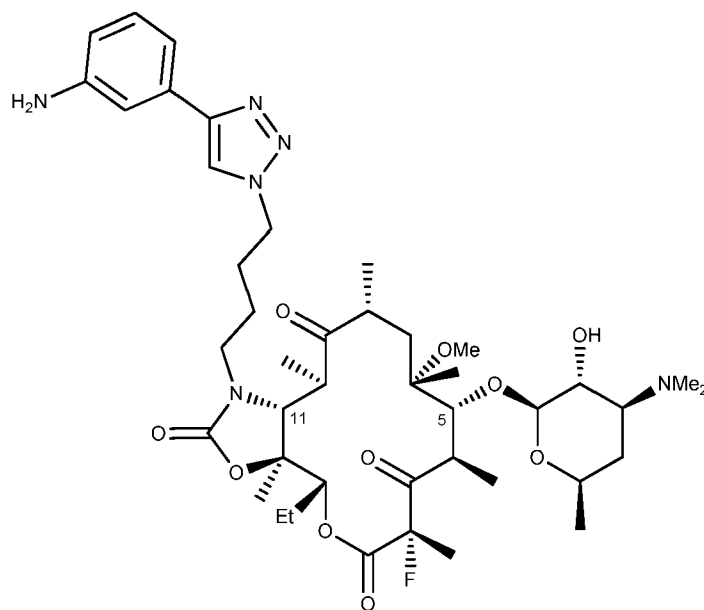
(II)

or an acid addition salt thereof; or

the process comprising any combination of (a), (b), and (c).

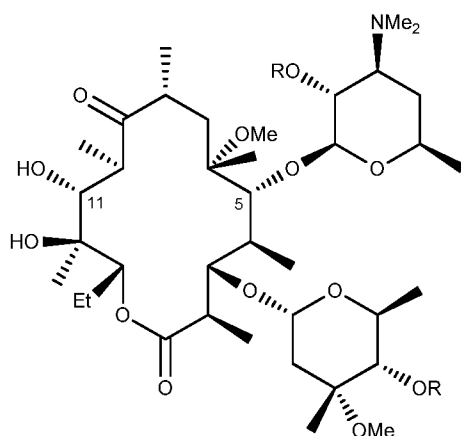
2. The process of claim 1 comprising (a) and (b).
3. The process of claim 1 comprising (a) and (c).
4. The process of claim 1 comprising (b) and (c).
5. The process of claim 1 comprising (a), (b), and (c).
6. The process of any one of claims 1 to 5 wherein step (a) is performed in the presence of a base.
7. The process of any one of claims 1 to 5 wherein step (b) is performed in the presence of a base.
8. The process of any one of claims 1 to 5 wherein step (b) is performed in an aprotic polar solvent.

9. The process of any one of claims 1 to 5 wherein V is C(O).
10. The process of any one of claims 1 to 5 wherein W is fluoro.
11. The process of any one of claims 1 to 5 wherein W is hydrogen.
12. The process of any one of claims 1 to 5 wherein X and Y are taken together with the attached carbon to form carbonyl.
13. The process of any one of claims 1 to 5 wherein A is CH<sub>2</sub>.
14. The process of any one of claims 1 to 5 wherein B is alkenylene.
15. The process of any one of claims 1 to 5 wherein B is (CF<sub>3</sub>)<sub>n</sub>, where n is an integer from 2 to 4.
16. The process of any one of claims 1 to 5 wherein C is 3-aminophenyl.
17. The process of any one of claims 1 to 5 wherein R<sup>10</sup> is benzoyl.
18. The process of any one of claims 1 to 5 wherein R<sup>10</sup> is hydrogen.
19. The process of any one of claims 1 to 5 wherein the compound of formula (I) is of the formula



or a pharmaceutically acceptable salt thereof.

20. A process for preparing a compound of formula (II);

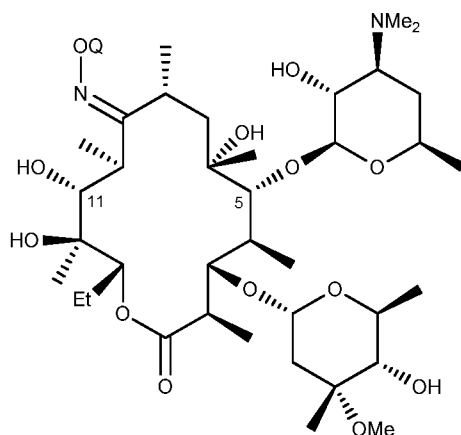


(II)

or a pharmaceutically acceptable salt thereof, wherein:

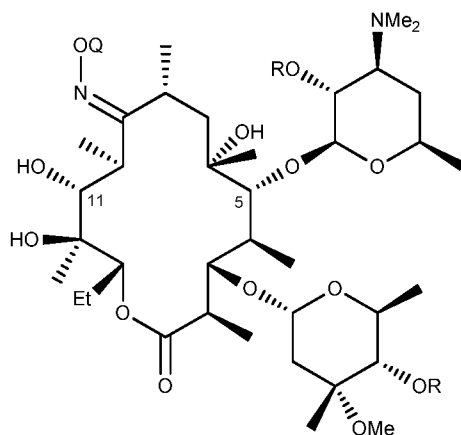
R is an acyl group;

the process comprising (a) the step of contacting a compound of formula (III),



(III)

or an acid addition salt thereof, wherein Q in combination with the oxime oxygen forms an acetal or ketal, or Q is troyl, with an acylating agent to form a compound of formula (IV)

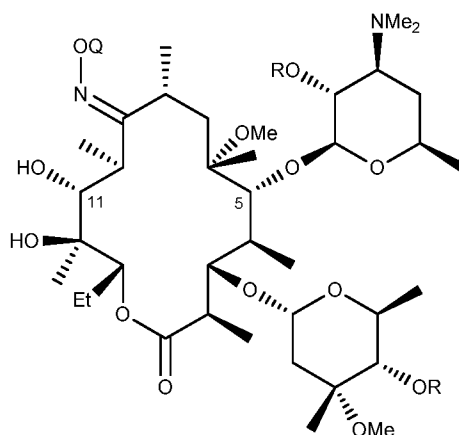


(IV)

or an acid addition salt thereof, wherein R is an acyl group; or



the process comprising (b) the step of contacting a compound of formula (IV), or an acid addition salt thereof, with a methylating agent, to form a compound of formula (V)



(V)

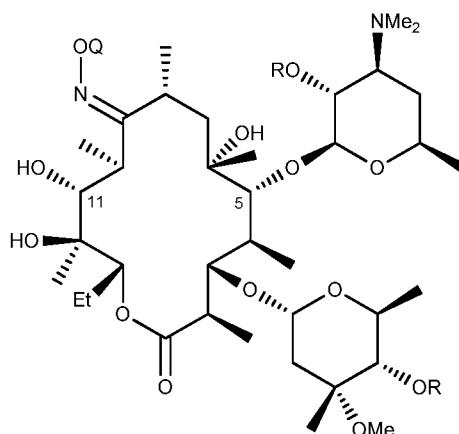
or an acid addition salt thereof; or

the process comprising (c) the step of contacting a compound of formula (V), or an acid addition salt thereof, with a deoximating agent to form a compound of formula (II); or

the process comprising any combination of (a), (b), and (c).

21. The process of claim 20 comprising (a) and (b).
22. The process of claim 20 comprising (a) and (c).
23. The process of claim 20 comprising (b) and (c).
24. The process of claim 20 comprising (a), (b), and (c).
25. The process of any one of claims 20 to 24 wherein step (a) is performed in the presence of a base.
26. The process of any one of claims 20 to 24 wherein step (b) is performed in the presence of a base.
27. The process of any one of claims 20 to 24 wherein step (b) is performed in an aprotic polar solvent.

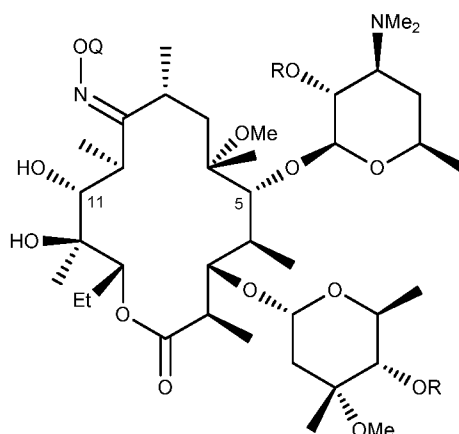
28. A compound of formula (IV)



(IV)

or an acid addition salt thereof, wherein Q in combination with the oxime oxygen forms an acetal or ketal, or Q is troyl, and R is an acyl group.

29. A compound of formula (V)



(V)

or an acid addition salt thereof, wherein Q in combination with the oxime oxygen forms an acetal or ketal, or Q is troyl, and R is an acyl group.

30. The process or compound of any one of claims 1 to 5, 20 to 24, or 28 to 29 wherein Q is 2-methoxy-2-propyl, 1-methoxycyclohexyl or 1-isopropoxycyclohexyl.

31. The process or compound of any one of claims 1 to 5, 20 to 24, or 28 to 29 wherein Q is 2-methoxy-2-propyl.

32. The process or compound of any one of claims 1 to 5, 20 to 24, or 28 to 29 wherein R is a sterically hindered acyl group.

33. The process or compound of any one of claims 1 to 5, 20 to 24, or 28 to 29 wherein R is benzoyl.

34. The process of any one of claims 1 to 5 or 20 to 24 wherein the acylating agent is the anhydride.

35. The process of any one of claims 1 to 5 or 20 to 24 wherein the base in step (a) is a tertiary amine.

36. The process of any one of claims 1 to 5 or 20 to 24 wherein step (a) is performed in the presence of 4-dimethylaminopyridine.

37. The process of any one of claims 1 to 5 or 20 to 24 wherein the methylating agent in step (b) is methyl bromide, methyl iodide, dimethyl sulfate, methyl p-toluenesulfonate or methyl methanesulfonate.

38. The process of any one of claims 1 to 5 or 20 to 24 wherein the base in step (b) is sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride or potassium t-butoxide or a mixture thereof.

39. The process of any one of claims 1 to 5 or 20 to 24 wherein the aprotic polar solvent in step (b) is dimethyl sulfoxide, dimethylformamide, 1-methyl-2-pyrrolidone, a mixture thereof, optionally further forming a mixture with one or more of tetrahydrofuran, 2-methyltetrahydrofuran, 1,2-dimethoxyethane, acetonitrile, or ethyl acetate.

40. The process of any one of claims 1 to 5 or 20 to 24 wherein the deoximating agent in step (c) comprises a reducing agent.

41. The process of any one of claims 1 to 5 or 20 to 24 wherein the deoximating agent in step (c) comprises formic acid and sodium metabisulfite.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/37330

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61 K 31/70 (201 1.01 )

USPC - 514/29

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)

USPC - 514/29 (see search terms below)

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

USPC - 514/28; 536/7.2; 536/7.4 (see search terms below)

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

USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: macrolides, ketolides, [1,2,3]-triazole, 4-(3-aminophenyl), aminosugars, sterically hindered acyl group, benzoyl, benzoic anhydride, DMAP, 9-oxime, 9-O-tropyloxime, formic acid, sodium bisulfite, methylating agent, methyl iodide, C9 ketone, oximes, 11,12-carbamate, Erythromycin A, spacer, A-B. INTERNE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/055557 A1 (PEREIRA et al.) 30 April 2009 (30.04.2009), pg 1 - pg 5; pg 12 - pg 13.	1-41
Y	US 6,515,116 B2 (SUH et al.) 04 February 2003 (04.02.2003), col 3, ln 7 - col 4, ln 44; col 7, ln 47-67; col 9, ln 11-50.	1-41
Y	WO 03/004509 A2 (CHU et al.) 16 January 2003 (16.01.2003), pg 1, ln 7-12; pg 4, ln 14 - pg 15, ln 22; pg 36, ln 22 - pg 37, ln 2; pg 38, ln 12-15.	30-31

Further documents are listed in the continuation of Box C.

\* 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

"&amp;"

document member of the same patent family

Date of the actual completion of the international search

10 August 2011 (10.08.201 1)

Date of mailing of the international search report

26 AUG 2011

Name and mailing address of the ISA/US

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