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(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(71) Applicant (for US only): **POLJAK, Tanja** [HR/HR]; c/o GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ALIHODZIC, Sulejman** [HR/HR]; c/o GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB). **ELENKOV, Ivaylo, Jivkov** [HR/HR]; c/o GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(74) Agent: **CRAWLEY, Karen, A.**; GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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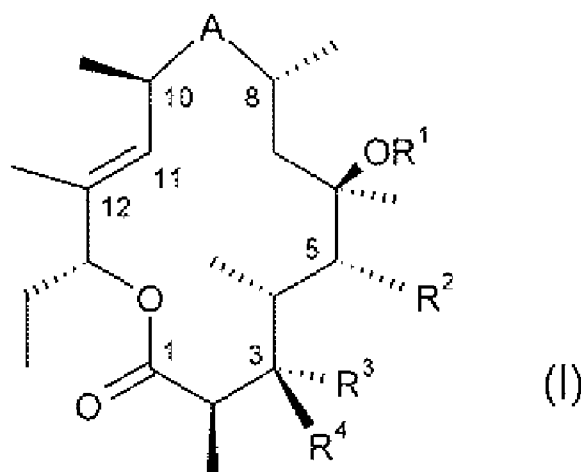
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(54) Title: NEW 14 AND 15 MEMBERED MACROLIDES FOR THE TREATMENT OF NEUTROPHIL DOMINATED INFLAMMATORY DISEASES



(57) Abstract: (*E*)-11,12-Didehydro-11,12-dideoxy 14-membered macrolides and 15-membered azalide macrolides represented by Formula (I): useful in the treatment of neutrophil dominated inflammatory diseases, especially in the treatment of neutrophil dominated inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils, to intermediates for their preparation, to methods for their preparation, to their use as therapeutic agents, and to salts thereof.

NEW 14 AND 15 MEMBERED MACROLIDES FOR THE TREATMENT OF NEUTROPHIL DOMINATED INFLAMMATORY DISEASES

Technical Field

The present invention relates to 11,12-didehydro-11,12-dideoxy 14-membered macrolides and 15-membered azalide macrolides useful in the treatment of inflammatory diseases. More particularly, the invention relates to (E)-11,12-didehydro-11,12-dideoxy 14-membered macrolides and 15-membered azalide macrolides useful in the treatment of neutrophil dominated inflammatory diseases, especially in the treatment of neutrophil dominated inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils, to intermediates for their preparation, to methods for their preparation, to their use as therapeutic agents, and to salts thereof.

Background

Inflammation is the final common pathway of various insults, such as infection, trauma, and allergies to the human body. It is characterized by activation of the immune system with recruitment and activation of inflammatory cells and production of pro-inflammatory mediators.

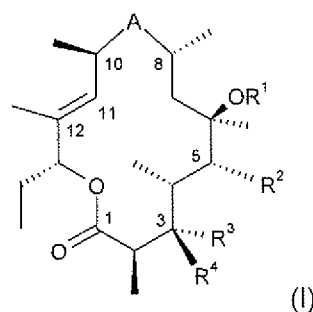
Most inflammatory diseases are characterized by enhanced accumulation of differing proportions of inflammatory cells, including monocytes/macrophages, granulocytes, plasma cells, lymphocytes and platelets. Along with tissue endothelial cells and fibroblasts, these inflammatory cells release a complex array of lipids, growth factors, cytokines and destructive enzymes that cause local tissue damage.

One form of inflammatory response is neutrophilic inflammation which is characterized by infiltration of the inflamed tissue by neutrophilic polymorphonuclear leukocytes (PMN, i.e. neutrophils), which are a major component of host defence. Neutrophils are activated by a great variety of stimuli and are involved in a number of clinical conditions and diseases where they play a pivotal role. Such diseases may be classified according to the major neutrophil-activating event (Table 3, page 638 of V. Witko-Sarsat et al., *Laboratory Investigation* (2000) 80(5), 617-653). Tissue infection by extracellular bacteria represents the prototype of this inflammatory response. On the other hand, various non-infectious diseases are characterized by extravascular recruitment of neutrophils. These non-infectious inflammatory diseases may be the result of an intermittent resurgence (e.g. flare in autoimmune diseases such as rheumatoid arthritis), or continuous generation (e.g. chronic obstructive pulmonary disease (COPD)) of inflammatory signals arising from underlying immune dysfunction. Non-infectious inflammatory diseases include chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diffuse panbronchiolitis (DPB), bronchiolitis obliterans (BOS), bronchitis, bronchiectasis, emphysema, adult respiratory distress syndrome (ARDS, known also as acute respiratory distress syndrome

or respiratory distress syndrome, RDS), as well as glomerulonephritis, rheumatoid arthritis, gouty arthritis, ulcerative colitis, certain dermatoses such as psoriasis and vasculitis. In these conditions neutrophils are thought to play a crucial role in the development of tissue injury which, when persistent, can lead to the irreversible destruction of the normal tissue architecture with consequent organ dysfunction. Consequently, correlation between neutrophil number in sputum or bronchoalveolar lavage fluid and disease severity and decline in lung function is demonstrated in patients with chronic obstructive pulmonary disease (Di Stefano et al., *Am J Respir Crit Care Med.* (1998), 158(4): 1277-1285), cystic fibrosis (Sagel SD et al., *J Pediatr.* (2002), 141(6): 811-817), diffuse panbronchiolitis (Yanagihara K et al., *Int J Antimicrob Agents.* (2001), 18 Suppl 1: S83-87), bronchiolitis obliterans (Devouassoux G et al., *Transpl Immunol.* (2002), 10(4): 303-310), bronchitis (Thompson AB et al., *Am Rev Respir Dis.* (1989), 140(6): 1527-1537), bronchiectasis (Sepper R et al., *Chest* (1995), 107(6): 1641-1647), adult respiratory distress syndrome (Weiland JE et al., *Am Rev Respir Dis.* (1986), 133(2): 218-225), to name a few. In addition, there is increasing evidence of neutrophil inflammation in asthmatics, particularly in patients with severe disease and patients who smoke (Chalmers GW et al., *Chest* (2001), 120: 1917-1922). Evidence of the importance of neutrophils in several lung diseases has prompted a search for drugs that inhibit neutrophilic infiltration into lungs and consequent inflammation (reviewed in Barnes PJ, *J Allergy Clin Immunol.* (2007), 119(5): 1055-1062).

Summary of the Invention

25 The present invention relates to (*E*)-11,12-didehydro-11,12-dideoxy 14-membered macrolides and 15-membered azalide macrolides represented by Formula (I):

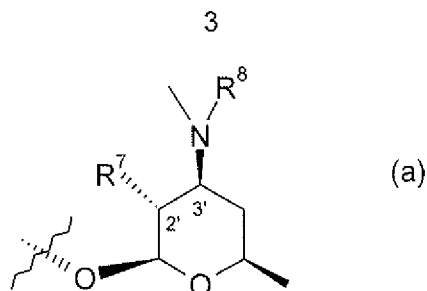


wherein,

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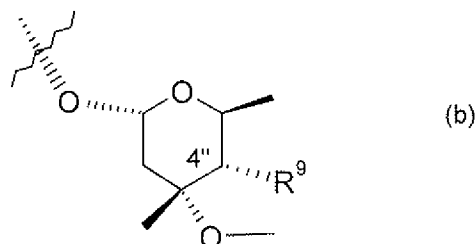
R^1 is hydrogen or CH_3 ;

R² is a β-D-desosaminy group of Formula (a);



R³ is:

i) an α -L-cladinosyl group of Formula (b)



5 and A is a bivalent radical -C(O)-, -N(R⁵)CH₂-, -CH₂N(R⁵)-, -C(=NOR⁶)-, -CH(OH)-, -NHC(O)- or -C(O)NH-, or

ii) hydroxyl and A is a bivalent radical -N(R⁵)CH₂-, -CH₂N(R⁵)-, -NHC(O)- or -C(O)NH-;

10

R⁴ is hydrogen;

R⁵ is hydrogen or -C₁₋₄alkyl;

15 R⁶ is hydrogen or -C₁₋₄alkyl, wherein -C₁₋₄alkyl may be optionally interrupted by one or two oxygen atoms, and/or is unsubstituted or substituted by one or two substituents independently selected from -C₁₋₄alkoxy or -C₃₋₇cycloalkyl, with the proviso that when the -C₁₋₄alkyl is interrupted by two oxygen atoms, the two oxygen atoms are not adjacent one another;

20

R⁷ is hydroxyl, hydroxyl protecting group or -O-(CH₂)₂CN;

R⁸ is independently selected from:

- 25 ai) hydrogen,
 bi) -C₁₋₆alkyl, unsubstituted or substituted at the terminal carbon atom by a substituent selected from the group consisting of:
- (aii) hydroxyl,
 - (bii) -(5-oxotetrahydro-2-furanyl),
 - (cii) -C₁₋₃alkoxy, and
 - (dii) -C(O)C₁₋₃alkyl, or
- 30 ci) -C(=O)-R¹⁰;

R⁹ is hydroxyl or hydroxyl protecting group;

R¹⁰ is independently selected from:

- 5 (a) -C₁₋₄alkyl, unsubstituted or substituted at the terminal carbon atom by a substituent selected from the group consisting of hydroxyl, -C₁₋₄alkoxy, -C(O)OC₁₋₄alkyl, -N(R⁵)(R¹¹) and -S-R¹²,
- (b) a 5-6 membered heteroaromatic ring, unsubstituted or substituted by one or two substituents independently selected from the group consisting of halo, hydroxyl, -C₁₋₃alkyl, -C₁₋₃alkoxy, -CF₃, -OCF₃ and -NH₂,
- 10 (c) phenyl, unsubstituted or substituted by one or two substituents independently selected from the group consisting of halo, hydroxyl, -C₁₋₃alkyl, -C₁₋₃alkoxy, -CF₃, -OCF₃ and -NH₂,
- 15 (d) a 4-6-membered heterocyclic ring, unsubstituted or substituted by one or two -C₁₋₃alkyl, or
- (e) -C₃₋₇cycloalkyl, unsubstituted or substituted by one or two substituents independently selected from the group consisting of hydroxy, -C₁₋₃alkoxy and -C(O)OC₁₋₃alkyl;
- 20

R¹¹ is -C₁₋₄alkyl;

R¹² is a 5-6 membered heteroaromatic ring, unsubstituted or substituted by one or two substituents independently selected from the group consisting of halo, hydroxyl, -C₁₋₃alkyl, -C₁₋₃alkoxy, -CF₃, -OCF₃ and -NH₂;

25

or a salt thereof.

The present invention also relates to pharmaceutical compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

30

Furthermore, the present invention also relates to methods of treating neutrophil dominated inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils comprising administration of a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof to a subject in need thereof.

35

According to another aspect, the invention relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in human or veterinary medical therapy.

40

In another aspect, the invention relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of neutrophil dominated

inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils.

- 5 In another aspect, the invention relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of neutrophil dominated inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils.

Brief Description of the Figures

- 10 Figure 1 shows correlation of inhibition of IL-6 production *in vitro* and inhibition of cell infiltration into BALF *in vivo*.

Description of the Embodiments

- 15 It will be understood that the present invention covers all combinations of aspects, suitable, convenient and preferred groups described herein.

The term "alkyl" as used herein, refers to a saturated, straight or branched-chain hydrocarbon radical containing the stated number of carbon atoms, for example, C₁₋₄alkyl contains between one and four carbon atoms. Examples of "C₁₋₃alkyl" radicals include: methyl, ethyl, propyl and isopropyl. Examples of "C₁₋₄alkyl" radicals include: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. Examples of "C₁₋₆alkyl" radicals include: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl and the like.

25 The term "alkoxy" as used herein, refers to an -O-alkyl group wherein alkyl is as defined above. Examples of "-C₁₋₃alkoxy" radicals include: methoxy, ethoxy, propoxy and isopropoxy. Examples of "-C₁₋₄alkoxy" radicals include: methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, and the like.

30 The term "-C₁₋₄alkyl substituted by phenyl" as used herein, refers to alkyl as defined above, substituted by phenyl. Examples of "-C₁₋₄alkyl substituted by phenyl" radicals include benzyl, phenyl-2-ethyl, phenyl-1-ethyl, phenyl-3-propyl, phenyl-2-propyl and the like.

35 The term "aryl" as used herein refers to a C₆₋₁₀ monocyclic or bicyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthyl, tetrahydronaphthalenyl and the like.

- 40 The term "comprise", and variations such as "comprises" and "comprising", throughout the specification and the claims which follow, unless the context requires otherwise, will be

understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

5 The term "cycloalkyl" as used herein, refers to a saturated monocyclic hydrocarbon ring containing the stated number of carbon atoms, for example, 3 to 7 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

10 The term "halogen" or "halo" refers to a fluorine, chlorine, bromine or iodine atom.

The term "heteroaromatic ring" or "heteroaryl ring" as used herein refers to a 5-6
15 membered monocyclic aromatic ring containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen and sulphur. Examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, furazanyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl and the like.

20 The term "heterocyclic ring" refers to a 4-6 membered monocyclic ring which may be saturated or partially unsaturated containing 1 to 2 heteroatoms independently selected from oxygen, nitrogen or sulphur. Examples of such monocyclic rings include pyrrolidinyl, azetidiny, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, pyranyl, morpholinyl, thiomorpholinyl, thiazolidinyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and
25 the like.

The term "hydroxyl protecting group" refers to a substituent on an functional hydroxyl group which prevent undesired reactions and degradations during synthetic procedures, and which may be selectively removed after certain synthetic step. Examples of "hydroxyl
30 protecting group" include: ester and ether hydroxyl protecting group. Examples of ester hydroxyl protecting group include: formyl, $-OC(O)C_{1-4}alkyl$ such as acetyl (Ac or $-C(O)CH_3$), methoxyacetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, triphenylmethoxyacetyl, phenoxyacetyl, benzoylformyl, benzoyl (Bz or $-C(O)C_6H_5$), benzyloxycarbonyl (Cbz or $-C(O)-O-CH_2C_6H_5$), methoxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl or 2-(trimethylsilyl)ethoxycarbonyl and the like. Examples of ether hydroxyl protecting group include: alkyl silyl groups such as trimethylsilyl (TMS), tert-butyldimethylsilyl, triethylsilyl, triisopropylsilyl and the like. Examples of suitable "hydroxyl protecting group" include: $-OC(O)C_{1-4}alkyl$ such as acetyl (Ac or $-C(O)CH_3$), benzoyl (Bz), benzyloxycarbonyl (Cbz) and trimethylsilyl (TMS).
35 Suitably, "hydroxyl protecting group" is: acetyl (Ac or $-C(O)CH_3$), benzoyl (Bz) or benzyloxycarbonyl (Cbz). Conveniently, "hydroxyl protecting group" is: acetyl (Ac or $-C(O)CH_3$).

The term "inert solvent" or "solvent inert to the reaction", as used herein, refers to a solvent that cannot react with the dissolved compounds including non-polar solvents such as hexane, toluene, diethyl ether, diisopropylether, chloroform, ethyl acetate, THF, dichloromethane; polar aprotic solvents such as acetonitrile, acetone, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, pyridine, and polar protic solvents such as lower alcohol, acetic acid, formic acid and water.

The term "lower alcohol", as used herein, refers to a C₁₋₄alcohol, such as for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like.

In one aspect the present invention relates to a compound of Formula (I) or a salt thereof wherein the salt is a pharmaceutically acceptable salt. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci. (1977) 66: 1-19. Suitable pharmaceutically acceptable salts can include acid or base addition salts.

Suitable addition salts are formed from inorganic or organic acids which form non-toxic salts and examples are hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, trifluoroacetate, maleate, malate, fumarate, lactate, tartrate, citrate, formate, gluconate, succinate, salicylate, propionate, pyruvate, hexanoate, oxalate, oxaloacetate, trifluoroacetate, saccharate, glutamate, aspartate, benzoate, alkyl or aryl sulphonates (eg methanesulphonate, ethanesulphonate, benzenesulphonate or p-toluenesulphonate) and isethionate. For example, hydrochloride or acetate salt.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compounds of the invention are within the scope of the invention. The salts of compounds of Formula (I) may form solvates (e.g. hydrates) and the invention also includes all such solvates.

In one aspect, compounds of the present invention may be in the form of pharmaceutically acceptable salts, solvates or solvates of salts. In a further aspect, a compound of Formula (I) of the present invention may be in the form of a pharmaceutically acceptable salt.

References hereinafter to "a compound according to the invention" or "compounds of the present invention" include both a compound of Formula (I) or its pharmaceutically acceptable salts.

With regard to stereoisomers, the compounds of Formula (I) have more than one asymmetric carbon atom. In the general Formula (I) as drawn, the solid wedge shaped

bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

5 It will be appreciated that the substituents on the macrolide may also have one or more asymmetric carbon atoms. Thus, the compounds of Formula (I) may occur as individual diastereomers or mixtures thereof. All such isomeric forms are included within the present invention, including mixtures thereof.

10 Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. An individual stereoisomer may also be prepared from a corresponding optically pure intermediate or by resolution, such as H.P.L.C., of the corresponding mixture using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding mixture with a suitable optically active acid or base, as appropriate.

15 It will be appreciated that compounds of the invention may exist as geometric isomers (cis/trans or (E)/(Z)). The present invention includes the individual geometric isomers of the compounds of the invention and, where appropriate, mixtures thereof, unless otherwise stated.

20 The compounds of Formula (I) may be in crystalline or amorphous form. Furthermore, some of the crystalline forms of the compounds of Formula (I) may exist as polymorphs, which are included in the present invention.

25 In one aspect of the invention A is a bivalent radical $-N(R^5)CH_2-$ wherein R^5 is $-C_{1-4}$ alkyl and R^1 is hydrogen. In a further aspect of the invention A is a bivalent radical $-N(R^5)CH_2-$ wherein R^5 is methyl and R^1 is hydrogen.

30 In one aspect of the invention A is a bivalent radical $-NHC(O)-$ and R^1 is CH_3 .

In one aspect of the invention A is a bivalent radical $-N(R^5)CH_2-$ wherein R^5 is methyl and R^1 is hydrogen or A is a bivalent radical $-NHC(O)-$ and R^1 is CH_3 .

35 In one aspect of the invention R^1 is hydrogen.

In one aspect of the invention R^1 is CH_3 .

In one aspect of the invention R^3 is α -L-cladinosyl group of Formula (b).

40 In one aspect of the invention R^3 is hydroxyl.

In one aspect of the invention R^3 is α -L-cladinosyl group of Formula (b) or hydroxyl and A is a bivalent radical $-N(R^5)CH_2-$, $-CH_2N(R^5)-$, $-NHC(O)-$ or $-C(O)NH-$. In a further aspect of

the invention R^3 is α -L-cladinosyl group of Formula (b) or hydroxyl and A is a bivalent radical $-N(R^5)CH_2-$ or $-NHC(O)-$. In even further aspect of the invention R^3 is α -L-cladinosyl group of Formula (b) and A is a bivalent radical $-N(R^5)CH_2-$ or $-NHC(O)-$.

5 In one aspect of the invention R^5 is methyl.

In one aspect of the invention R^7 is hydroxyl.

10 In one aspect of the invention R^7 is a hydroxyl protecting group. In a further aspect of the invention the hydroxyl protecting group is $-OC(O)C_{1-4}alkyl$. In another aspect of the invention the hydroxyl protecting group is $-OC(O)CH_3$ (acetyl).

In one aspect of the invention R^8 is hydrogen.

15 In one aspect of the invention R^8 is unsubstituted $-C_{1-6}alkyl$. In a further aspect of the invention R^8 is unsubstituted methyl.

20 In one aspect of the invention R^8 is $-C_{1-6}alkyl$ substituted at the terminal carbon atom by hydroxyl. In a further aspect of the invention R^8 is ethyl or n-propyl substituted at the terminal carbon atom by hydroxyl.

25 In one aspect of the invention R^8 is $-C_{1-6}alkyl$ substituted at the terminal carbon atom by $-[(2R)-5-oxotetrahydro-2-furanyl]$ or $-[(2S)-5-oxotetrahydro-2-furanyl]$. In a further aspect of the invention R^8 is methyl substituted at the terminal carbon atom by $-[(2R)-5-oxotetrahydro-2-furanyl]$. In another aspect of the invention R^8 is methyl substituted at the terminal carbon atom by $-[(2S)-5-oxotetrahydro-2-furanyl]$.

30 In one aspect of the invention R^8 is $-C(=O)-R^{10}$ and R^{10} is $-C_{1-4}alkyl$ substituted at the terminal carbon atom by $-C_{1-4}alkoxy$. In a further aspect of the invention R^{10} is methyl, ethyl or n-propyl substituted at the terminal carbon atom by methoxy. In another aspect of the invention R^{10} is methyl substituted by methoxy.

35 In one aspect of the invention R^8 is $-C(=O)-R^{10}$ and R^{10} is $-C_{1-4}alkyl$ substituted at the terminal carbon atom by $-C(O)OC_{1-4}alkyl$. In a further aspect of the invention R^{10} is methyl, ethyl or n-propyl substituted at the terminal carbon atom by $-C(O)OCH_3$. In another aspect of the invention R^{10} is ethyl substituted at the terminal carbon atom by $-C(O)OCH_3$.

40 In one aspect of the invention R^8 is $-C(=O)-R^{10}$ and R^{10} is $-C_{1-4}alkyl$ substituted at the terminal carbon atom by $-N(R^5)(R^{11})$. In a further aspect of the invention R^{10} is methyl, ethyl or n-propyl substituted at the terminal carbon atom by $-N(CH_3)_2$. In another aspect of the invention R^{10} is methyl substituted by $-N(CH_3)_2$.

In one aspect of the invention R^8 is $-C(=O)-R^{10}$ and R^{10} is $-C_{1-4}$ alkyl substituted at the terminal carbon atom by $-S-R^{12}$. In a further aspect of the invention R^{10} is methyl, ethyl or n-propyl substituted at the terminal carbon atom by a six membered unsubstituted heteroaromatic ring. In another aspect of the invention R^{10} is methyl and R^{12} is pyridyl. In a yet further aspect R^{12} is 4-pyridyl.

In one aspect of the invention R^8 is $-C(=O)-R^{10}$ and R^{10} is 5-6 membered unsubstituted heteroaromatic ring. In a further aspect of the invention R^{10} is six membered monocyclic unsubstituted heteroaromatic ring containing two heteroatoms. In another aspect of the invention R^{10} is pyrazinyl. In a yet further aspect of the invention R^{10} is 2-pyrazinyl.

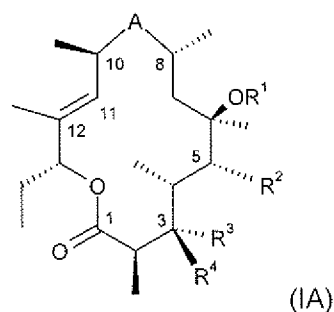
In one aspect of the invention R^9 is hydroxyl.

In one aspect of the invention R^9 is a hydroxyl protecting group. In a further aspect of the invention the hydroxyl protecting group is $-OC(O)C_{1-4}$ alkyl. In another aspect of the invention the hydroxyl protecting group is $-OC(O)CH_3$ (acetyl).

In one aspect of the invention R^{11} is methyl, ethyl or n-propyl. In a further aspect of the invention R^{11} is methyl.

In one aspect of the invention R^{12} is 5-6 membered unsubstituted heteroaromatic ring. In a further aspect of the invention R^{12} is six membered unsubstituted heteroaromatic ring containing one heteroatom. In another aspect of the invention R^{12} is pyridyl. In a yet further aspect R^{12} is 4-pyridyl.

In a further aspect of the invention, there is provided a compound of Formula (I) represented by Formula (IA):

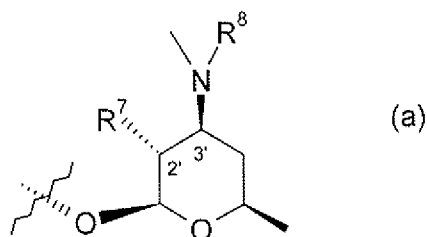


wherein,

A is a bivalent radical $-N(R^5)CH_2-$, $-CH_2N(R^5)-$, $-NHC(O)-$ or $-C(O)NH-$;

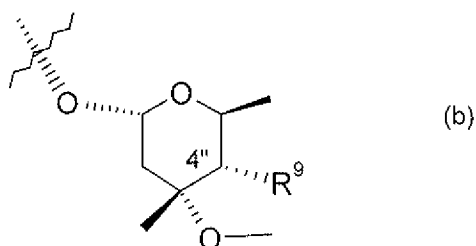
R^1 is hydrogen or CH_3 ;

R² is a β-D-desosaminyI group of Formula (a);



5

R³ is an α-L-cladinosyl group of Formula (b) or hydroxyl;



10 R⁴ is hydrogen;

R⁵ is hydrogen or -C₁₋₄alkyl;

R⁷ is hydroxyl, hydroxyl protecting group or -O-(CH₂)₂CN;

15

R⁸ is independently selected from:

- ai) hydrogen,
- bi) -C₁₋₆alkyl, unsubstituted or substituted at the terminal carbon atom by hydroxyl or -(5-oxotetrahydro-2-furanyl), or
- ci) -C(=O)-R¹⁰;

20

R⁹ is hydroxyl or hydroxyl protecting group;

R¹⁰ is independently selected from:

- 25 (aiii) -C₁₋₄alkyl, unsubstituted or substituted at the terminal carbon atom by a substituent selected from the group consisting of hydroxyl, -C₁₋₄alkoxy, -C(O)OC₁₋₄alkyl, -N(R⁵)(R¹¹) and -S-R¹², or
- (biii) 5-6 membered unsubstituted heteroaromatic ring;

30 R¹¹ is -C₁₋₄alkyl;

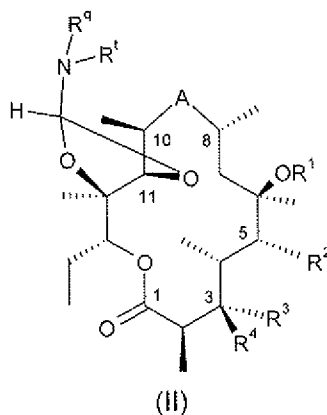
R¹² is 5-6 membered unsubstituted heteroaromatic ring;

or a salt thereof.

- 5 In one aspect, the present invention comprises a compound of Formula (I) selected from:
 (E)-2',4''-O-diacetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A,
 (E)-4''-O-acetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A,
- 10 (E)-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A,
 (E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A,
 (E)-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A,
- 15 (E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-3'-N-(methoxy)acetyl-6-O-methyl-9a-aza-9a-homoerythromycin A,
 (E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-3'-N-(4-pyridinylthio)acetyl-9a-aza-9a-homoerythromycin A,
 (E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-3'-N-(2-pyrazinyl)carbonyl-9a-aza-9a-homoerythromycin A,
- 20 (E)-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-3'-N-(methoxy)acetyl-6-O-methyl-9a-aza-9a-homoerythromycin A,
 (E)-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-3'-N-(4-pyridinylthio)acetyl-9a-aza-9a-homoerythromycin A,
- 25 (E)-2',4''-O-diacetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 (E)-4''-O-acetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 (E)-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
- 30 (E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 (E)-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 (E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(methoxy)acetyl-9a-methyl-9a-aza-9a-homoerythromycin A,
- 35 (E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(4-methoxy-4-oxobutanoyl)-9a-methyl-9a-aza-9a-homoerythromycin A,
 (E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(N,N-dimethylglycyl)-9a-methyl-9a-aza-9a-homoerythromycin A,
- 40 (E)-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(methoxy)acetyl-9a-methyl-9a-aza-9a-homoerythromycin A,
 (E)-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(N,N-dimethylglycyl)-9a-

- methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-*N*-(4-methoxy-4-oxobutanoyl)-9a-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-(2-hydroxyethyl)-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-(3-hydroxypropyl)-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-{[(2*R*)-5-oxotetrahydro-2-furanyl]methyl}-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-{[(2*S*)-5-oxotetrahydro-2-furanyl]methyl}-9a-aza-9a-homoerythromycin A,
 (*E*)-4''-*O*-acetyl-2'-*O*-(2-cyanoethyl)-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, or
 (*E*)-3-*O*-decladinosyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A;
 or a salt thereof.

In one aspect the present invention also relates to 11,12-(*N,N*-di-substituted-formamide) acetal intermediates of Formula (II) useful for the preparation of compounds of Formula (I)

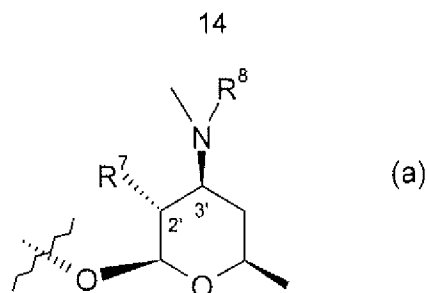


wherein,

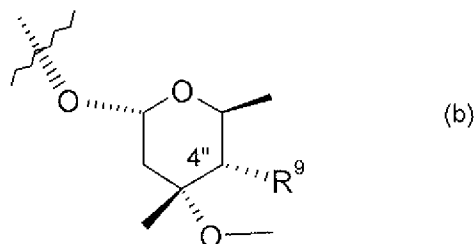
- A is a bivalent radical $-C(O)-$, $-N(R^5)CH_2-$, $-CH_2N(R^5)-$, $-C(=NOR^6)-$, $-CH(OH)-$, $-NHC(O)-$ or $-C(O)NH$;

R^1 is hydrogen or CH_3 ;

- R^2 is a β -D-desosaminyl group of Formula (a),



R³ is an α -L-cladinosyl group of Formula (b)



5 R⁴ is hydrogen;

R⁵ is hydrogen or -C₁₋₄alkyl;

10 R⁶ is hydrogen or -C₁₋₄alkyl, wherein -C₁₋₄alkyl may be optionally interrupted by one or two oxygen atoms, and/or is unsubstituted or substituted by one or two substituents independently selected from -C₁₋₄alkoxy or -C₃₋₇cycloalkyl, with the proviso that when the -C₁₋₄alkyl is interrupted by two oxygen atoms, the two oxygen atoms are not adjacent one another;

15 R⁷ is hydroxyl, hydroxyl protecting group or -O-(CH₂)₂CN;

R⁸ is CH₃;

R⁹ is hydroxyl or hydroxyl protecting group;

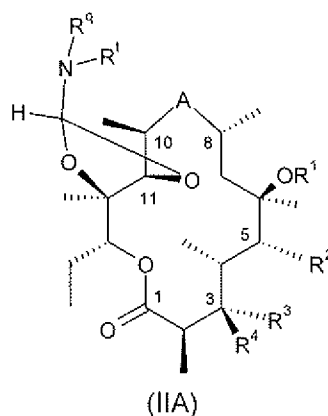
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R^q and R^t independently are -C₁₋₄alkyl or -C₁₋₄alkyl substituted by phenyl,

or a salt thereof.

25 In a further aspect of the invention, there is provided 11,12-(*N,N*-disubstituted-formamide) acetal intermediate of Formula (II) useful for the preparation of compounds of Formula (I) represented by Formula (IIA):

15



wherein,

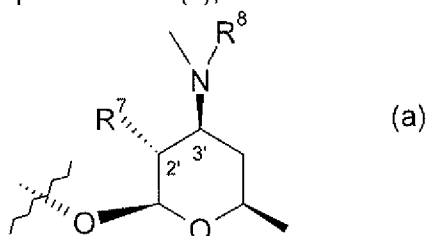
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R^1 is

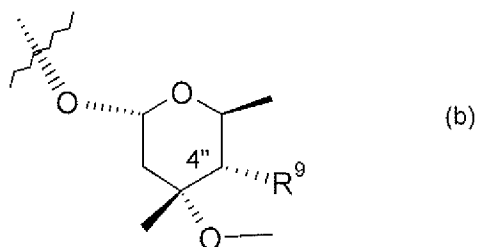
- a) CH_3 and A is a bivalent radical $-C(O)-$, $-N(R^5)CH_2-$, $-CH_2N(R^5)-$, $-C(=NOR^6)-$, $-CH(OH)-$, $-NHC(O)-$ or $-C(O)NH-$; or
- b) hydrogen and A is a bivalent radical $-C(O)-$, $-C(=NOR^6)-$, $-CH(OH)-$, $-NHC(O)-$ or $-C(O)NH-$;

10

R^2 is a β -D-desosaminyl group of Formula (a),



15 R^3 is an α -L-cladinosyl group of Formula (b)



R^4 is hydrogen;

R^5 is hydrogen or $-C_{1-4}$ alkyl;

20

R^6 is hydrogen or $-C_{1-4}$ alkyl, wherein $-C_{1-4}$ alkyl may be optionally interrupted by one or two oxygen atoms, and/or is unsubstituted or substituted by one or two substituents independently selected from $-C_{1-4}$ alkoxy or $-C_{3-7}$ cycloalkyl, with the proviso that when the -

C₁₋₄alkyl is interrupted by two oxygen atoms, the two oxygen atoms are not adjacent one another;

R⁷ is hydroxyl, hydroxyl protecting group or -O-(CH₂)₂CN;

R⁸ is CH₃;

R⁹ is hydroxyl or hydroxyl protecting group;

R^q and R^t independently are -C₁₋₄alkyl or -C₁₋₄alkyl substituted by phenyl, or a salt thereof.

In one aspect the present invention relates to 11,12-(N,N-disubstituted-formamide) acetal intermediates of Formula (II), wherein, R^q and R^t independently are -C₁₋₄alkyl. In a further aspect of the invention R^q and R^t independently are methyl.

In one aspect the present invention relates to 11,12-(N,N-disubstituted-formamide) acetal intermediates of Formula (II), wherein A is a bivalent radical -NHC(O)- and R^t is CH₃.

Compounds of the present invention inhibit infiltration of neutrophils into inflamed lung tissue (as demonstrated hereinafter). Therefore these compounds may have utility in acute and chronic treatment of inflammatory pathologies, especially of those pathologies associated with extensive neutrophil infiltration into the lung tissue, for example chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diffuse panbronchiolitis (DPB), bronchiolitis obliterans (BOS), bronchitis, bronchiectasis, adult respiratory distress syndrome (ARDS, known also as acute respiratory distress syndrome or respiratory distress syndrome, RDS), severe or steroid-resistant asthma (Simpson JL et al. (2008) *Am J Respir Crit Care Med*, 177: 148-155), and emphysema or into the respiratory tract, for example chronic rhinosinusitis (with or without nasal polyposis) (Wallwork B et al. (2006) *Laryngoscope*, 116: 189-193). In addition, compounds of the present invention may be used for the treatment of other diseases associated with altered cellular functionality of neutrophils, for example rheumatoid arthritis (Kitsis E and, Weissmann G, *Clin Orthop Relat Res.* (1991), 265: 63-72), gouty arthritis, inflammatory bowel diseases (such as ulcerative colitis and Chron's disease), glomerulonephritis (Heinzelmann M et al., *Am J Kidney Dis.* (1999), 34(2): 384-399), damage from ischemic reperfusion (Kaminski KA et al., *Int J Cardiol.* (2002), 86(1): 41-59), atherosclerosis (Henriksen PA and Sallénave JM. *Int J Biochem Cell* (2008), 40: 1095-1100), dermatoses such as psoriasis (Terui T et al., *Exp Dermatol.* (2000), 9(1): 1-10) and vasculitis, systemic lupus erythematoses (SLE), systemic inflammatory response syndrome (SIRS), sepsis, ischemia-reperfusion injury, rosacea, periodontitis, gingival hyperplasia and prostatitis syndrome.

The induction of lung neutrophil infiltration in rodents by the local application of bacterial lipopolysaccharide (LPS) is widely used as a test model for neutrophilic infiltration of human lungs during pulmonary inflammatory disease. We have observed a correlation between the inhibitory activity of compounds on cell infiltration into broncho-alveolar lung fluid (BALF) of mice treated intranasally with LPS and their inhibition of interleukin-6 (IL-6) production by LPS-stimulated mouse splenocytes *in vitro* (Figure 1). Therefore, inhibition of IL-6 production in LPS-stimulated murine spleen cells may be a suitable *in-vitro* model (biomarker) for the *in-vivo* activity of compounds in treating inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils.

"Treating" or "treatment" of neutrophil dominated inflammatory diseases, especially those resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils means the alleviation of the symptoms and/or retardation of progression of the disease, and may include the suppression of symptom recurrence in an asymptomatic patient.

Inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils include chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diffuse panbronchiolitis (DPB), bronchiolitis obliterans (BOS), bronchitis, bronchiectasis, adult respiratory distress syndrome (ARDS), severe or steroid-resistant asthma, emphysema, chronic rhinosinusitis (with or without nasal polyposis), rheumatoid arthritis, gouty arthritis, inflammatory bowel disease (ulcerative colitis and Chron's disease), glomerulonephritis, damage from ischemic reperfusion, atherosclerosis, dermatoses such as psoriasis and vasculitis, systemic lupus erythematosus (SLE), systemic inflammatory response syndrome (SIRS), sepsis, ischemia-reperfusion injury, rosacea, periodontitis, gingival hyperplasia and prostatitis syndrome.

In one aspect, the present invention provides a method of treating chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diffuse panbronchiolitis (DPB), bronchiolitis obliterans (BOS), bronchitis, bronchiectasis, adult respiratory distress syndrome (ARDS), severe or steroid-resistant asthma, emphysema, chronic rhinosinusitis (with or without nasal polyposis), rheumatoid arthritis, gouty arthritis, inflammatory bowel disease (ulcerative colitis and Chron's disease), glomerulonephritis, damage from ischemic reperfusion, atherosclerosis, dermatoses such as psoriasis and vasculitis, systemic lupus erythematosus (SLE), systemic inflammatory response syndrome (SIRS), sepsis, ischemia-reperfusion injury, rosacea, periodontitis, gingival hyperplasia and prostatitis syndrome in a subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

5 In one aspect, the present invention provides a method of treating chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, bronchitis, bronchiectasis, adult respiratory distress syndrome, severe or steroid-resistant asthma, emphysema and chronic rhinosinusitis (with or without nasal polyposis) in a subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

10 In one aspect, the present invention provides a method of treating chronic obstructive pulmonary disease in a subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 In a further aspect, the present invention provides a method of treating bronchiolitis obliterans in a subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

20 In a further aspect, the present invention provides a method of treating severe or steroid-resistant asthma in a subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

25 In a further aspect, the present invention provides a method of treating cystic fibrosis in a subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

30 In one aspect, the present invention provides a method of treating chronic rhinosinusitis (with or without nasal polyposis) in a subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

35 In one aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in medical therapy.

40 In one aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diffuse panbronchiolitis (DPB), bronchiolitis obliterans (BOS), bronchitis, bronchiectasis, adult respiratory distress syndrome (ARDS), severe or steroid-resistant asthma, emphysema, chronic rhinosinusitis (with or without nasal polyposis), rheumatoid arthritis, gouty arthritis, inflammatory bowel

disease (ulcerative colitis and Chron's disease), glomerulonephritis, damage from ischemic reperfusion, atherosclerosis, dermatoses such as psoriasis and vasculitis, systemic lupus erythematosus (SLE), systemic inflammatory response syndrome (SIRS), sepsis, ischemia-reperfusion injury, rosacea, periodontitis, gingival hyperplasia and prostatitis syndrome.

In another aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, bronchitis, bronchiectasis, adult respiratory distress syndrome, severe or steroid-resistant asthma, emphysema and chronic rhinosinusitis (with or without nasal polyposis).

In a further aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic obstructive pulmonary disease.

In a further aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of bronchiolitis obliterans.

In a further aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of severe or steroid-resistant asthma.

In a further aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of cystic fibrosis.

In a further aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic rhinosinusitis (with or without nasal polyposis).

In a further aspect, the present invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diffuse panbronchiolitis (DPB), bronchiolitis obliterans (BOS), bronchitis, bronchiectasis, adult respiratory distress syndrome (ARDS), severe or steroid-resistant asthma, emphysema, chronic rhinosinusitis (with or without nasal polyposis), rheumatoid arthritis, gouty arthritis, inflammatory bowel disease (ulcerative colitis and Chron's disease), glomerulonephritis, damage from ischemic reperfusion, atherosclerosis, dermatoses such as psoriasis and vasculitis, systemic lupus erythematosus (SLE), systemic inflammatory response syndrome (SIRS), sepsis, ischemia-reperfusion injury, rosacea, periodontitis, gingival hyperplasia and prostatitis syndrome.

In a further aspect of the invention, the present invention provides the use of a compound of Formula (I) or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, bronchitis, bronchiectasis, adult respiratory distress syndrome, severe or steroid-resistant asthma, emphysema and chronic rhinosinusitis (with or without nasal polyposis).

In a further aspect, the present invention provides the use of a compound of Formula (I) or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease.

In a further aspect, the present invention provides the use of a compound of Formula (I) or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of bronchiolitis obliterans.

In a further aspect, the present invention provides the use of a compound of Formula (I) or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of severe or steroid-resistant asthma.

In a further aspect, the present invention provides the use of a compound of Formula (I) or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cystic fibrosis.

In a further aspect, the present invention provides the use of a compound of Formula (I) or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of chronic rhinosinusitis (with or without nasal polyposis).

The benefit to a subject to be treated is either statistically significant or at least perceptible to the subject or to the physician.

"Subject" refers to an animal, in particular a mammal and more particularly to a human or a domestic animal or an animal serving as a model for a disease (e.g., mouse, monkey, etc.). In one aspect, the subject is a human.

A "therapeutically effective amount" means the amount of a compound that, when administered to a subject for treating a neutrophil dominated inflammatory disease resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated and will ultimately be at the discretion of the attendant physician.

Pharmaceutical Compositions

While it is possible that, for use in the methods of the invention, a compound of Formula (I) or a pharmaceutically acceptable salt thereof may be administered as the bulk substance, it is preferable to present the active ingredient in a pharmaceutical formulation, for example, wherein the agent is in admixture with at least one pharmaceutically acceptable carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

- Accordingly, the present invention provides a pharmaceutical composition comprising a) a compound of Formula (I) or a pharmaceutically acceptable salt thereof and b) one or more pharmaceutically acceptable carriers.

The term "carrier" refers to a diluent, excipient, and/or vehicle with which an active compound is administered. The pharmaceutical compositions of the invention may contain combinations of more than one carrier. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th Edition. The choice of pharmaceutical carrier can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as, in addition to, the carrier any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilizing agent(s).

The phrase "pharmaceutically acceptable", as used herein, refers to salts, molecular entities and other ingredients of compositions that are generally physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., human). Suitably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, and more particularly in humans.

A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the present application includes both one and more than one such excipient.

The present invention is further related to a pharmaceutical composition for the treatment

of a neutrophil dominated inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

- 5 The present invention is further related to a pharmaceutical composition for the treatment of chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), diffuse panbronchiolitis (DPB), bronchiolitis obliterans (BOS), bronchitis, bronchiectasis, adult respiratory distress syndrome (ARDS), severe or steroid-resistant asthma, emphysema, chronic rhinosinusitis (with or without nasal polyposis), rheumatoid arthritis, gouty arthritis, inflammatory bowel disease (ulcerative colitis and Chron's disease), glomerulonephritis, damage from ischemic reperfusion, atherosclerosis, dermatoses such as psoriasis and vasculitis, systemic lupus erythematosus (SLE), systemic inflammatory response syndrome (SIRS), sepsis, ischemia-reperfusion injury, rosacea, periodontitis, gingival hyperplasia and prostatitis syndrome comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

- The present invention is further related to a pharmaceutical composition for the treatment of chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, bronchitis, bronchiectasis, adult respiratory distress syndrome, severe or steroid-resistant asthma, emphysema and chronic rhinosinusitis (with or without nasal polyposis), comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

- The present invention is even further related to a pharmaceutical composition comprising a) 10 to 2000 mg of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and b) 0.1 to 2 g of one or more pharmaceutically acceptable excipients.

- It will be appreciated that pharmaceutical compositions for use in accordance with the present invention may be in the form of oral, parenteral, transdermal, inhalation, sublingual, topical, implant, nasal, or enterally administered (or other mucosally administered) suspensions, solutions, capsules or tablets, which may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

- In one aspect, the pharmaceutical composition is formulated for oral administration.

The compounds of the invention can be administered for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

- In one aspect, oral compositions are slow, delayed or positioned release (e.g., enteric especially colonic release) tablets or capsules. This release profile can be achieved, for example, by use of a coating resistant to conditions within the stomach but releasing the

contents in the colon or other portion of the GI tract wherein a lesion or inflammation site has been identified. Or a delayed release can be achieved by a coating that is simply slow to disintegrate. Or the two (delayed and positioned release) profiles can be combined in a single formulation by choice of one or more appropriate coatings and other excipients.

5 Such formulations constitute a further feature of the present invention.

Suitable compositions for delayed or positioned release and/or enteric coated oral formulations include tablet formulations film coated with materials that are water resistant, pH sensitive, digested or emulsified by intestinal juices or sloughed off at a slow but regular rate when moistened. Suitable coating materials include, but are not limited to, hydroxypropyl methylcellulose, ethyl cellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polymers of metacrylic acid and its esters, and combinations thereof. Plasticizers such as, but not limited to polyethylene glycol, dibutylphthalate, triacetin and castor oil may be used. A pigment may also be used to color the film. Suppositories are prepared by using carriers like cocoa butter, suppository bases such as Suppocire C, and Suppocire NA50 (supplied by Gattefossé Deutschland GmbH, D-Weil am Rhein, Germany) and other Suppocire type excipients obtained by interesterification of hydrogenated palm oil and palm kernel oil (C₈-C₁₈ triglycerides), esterification of glycerol and specific fatty acids, or polyglycosylated glycerides, and whitesol (hydrogenated plant oils derivatives with additives). Enemas are formulated by using the appropriate active compound according to the present invention and solvents or excipients for suspensions. Suspensions are produced by using micronized compounds, and appropriate vehicle containing suspension stabilizing agents, thickeners and emulsifiers like carboxymethylcellulose and salts thereof, polyacrylic acid and salts thereof, carboxyvinyl polymers and salts thereof, alginic acid and salts thereof, propylene glycol alginate, chitosan, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, methylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone, N-vinylacetamide polymer, polyvinyl methacrylate, polyethylene glycol, pluronic, gelatin, methyl vinyl ether-maleic anhydride copolymer, soluble starch, pullulan and a copolymer of methyl acrylate and 2-ethylhexyl acrylate lecithin, lecithin derivatives, propylene glycol fatty acid esters, glycerin fatty acid esters, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyethylene glycol fatty acid esters, polyoxyethylene hydrated castor oil, polyoxyethylene alkyl ethers, and pluronic and appropriate buffer system in pH range of 6.5 to 8. The use of preservatives, masking agents is suitable. The average diameter of micronized particles can be between 1 and 20 micrometers, or can be less than 1 micrometer. Compounds can also be incorporated in the formulation by using their water-soluble salt forms.

Alternatively, materials may be incorporated into the matrix of the tablet e.g. hydroxypropyl methylcellulose, ethyl cellulose or polymers of acrylic and metacrylic acid esters. These latter materials may also be applied to tablets by compression coating.

Pharmaceutical compositions can be prepared by mixing a therapeutically effective amount of the active substance with a pharmaceutically acceptable carrier that can have different forms, depending on the way of administration. Pharmaceutical compositions can be prepared by using conventional pharmaceutical excipients and methods of preparation.

- 5 The forms for oral administration can be capsules, powders or tablets where usual solid vehicles including lactose, starch, glucose, methylcellulose, magnesium stearate, di-calcium phosphate, mannitol may be added, as well as usual liquid oral excipients including, but not limited to, ethanol, glycerol, and water. All excipients may be mixed with disintegrating agents, solvents, granulating agents, moisturizers and binders. When a
- 10 solid carrier is used for preparation of oral compositions (e.g., starch, sugar, kaolin, binders disintegrating agents) preparation can be in the form of powder, capsules containing granules or coated particles, tablets, hard gelatin capsules, or granules without limitation, and the amount of the solid carrier can vary (between 1 mg to 1g). Tablets and capsules are the preferred oral composition forms.

- 15 Pharmaceutical compositions containing the compounds of the present invention may be in any form suitable for the intended method of administration, including, for example, a solution, a suspension, or an emulsion. Liquid carriers are typically used in preparing solutions, suspensions, and emulsions. Liquid carriers contemplated for use in the
- 20 practice of the present invention include, for example, water, saline, pharmaceutically acceptable organic solvent(s), pharmaceutically acceptable oils or fats, and the like, as well as mixtures of two or more thereof. The liquid carrier may contain other suitable pharmaceutically acceptable additives such as solubilizers, emulsifiers, nutrients, buffers, preservatives, suspending agents, thickening agents, viscosity regulators, stabilizers, and
- 25 the like. Suitable organic solvents include, for example, monohydric alcohols, such as ethanol, and polyhydric alcohols, such as glycols. Suitable oils include, for example, soybean oil, coconut oil, olive oil, safflower oil, cottonseed oil, and the like. For parenteral administration, the carrier can also be an oily ester such as ethyl oleate, isopropyl myristate, and the like. Compositions of the present invention may also be in the form of
- 30 microparticles, microcapsules, liposomal encapsulates, and the like, as well as combinations of any two or more thereof.

- Examples of pharmaceutically acceptable disintegrants for oral compositions useful in the present invention include, but are not limited to, starch, pre-gelatinized starch, sodium
- 35 starch glycolate, sodium carboxymethylcellulose, croscarmellose sodium, microcrystalline cellulose, alginates, resins, surfactants, effervescent compositions, aqueous aluminum silicates and crosslinked polyvinylpyrrolidone.

- Examples of pharmaceutically acceptable binders for oral compositions useful herein
- 40 include, but are not limited to, acacia; cellulose derivatives, such as methylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose or hydroxyethylcellulose; gelatin, glucose, dextrose, xylitol, polymethacrylates,

polyvinylpyrrolidone, sorbitol, starch, pre-gelatinized starch, tragacanth, xanthane resin, alginates, magnesium–aluminum silicate, polyethylene glycol or bentonite.

5 Examples of pharmaceutically acceptable fillers for oral compositions include, but are not limited to, lactose, anhydrolactose, lactose monohydrate, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (particularly microcrystalline cellulose), dihydro- or anhydro-calcium phosphate, calcium carbonate and calcium sulfate.

10 Examples of pharmaceutically acceptable lubricants useful in the compositions of the invention include, but are not limited to, magnesium stearate, talc, polyethylene glycol, polymers of ethylene oxide, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, and colloidal silicon dioxide.

15 Examples of suitable pharmaceutically acceptable flavourings for the oral compositions include, but are not limited to, synthetic aromas and natural aromatic oils such as extracts of oils, flowers, fruits (e.g., banana, apple, sour cherry, peach) and combinations thereof, and similar aromas. Their use depends on many factors, the most important being the organoleptic acceptability for the population that will be taking the pharmaceutical compositions.

20 Examples of suitable pharmaceutically acceptable dyes for the oral compositions include, but are not limited to, synthetic and natural dyes such as titanium dioxide, beta-carotene and extracts of grapefruit peel.

25 Suitable examples of pharmaceutically acceptable sweeteners for the oral compositions include, but are not limited to, aspartame, saccharin, saccharin sodium, sodium cyclamate, xylitol, mannitol, sorbitol, lactose and sucrose.

30 Suitable examples of pharmaceutically acceptable buffers include, but are not limited to, citric acid, sodium citrate, sodium bicarbonate, dibasic sodium phosphate, magnesium oxide, calcium carbonate and magnesium hydroxide.

35 Suitable examples of pharmaceutically acceptable surfactants include, but are not limited to, sodium lauryl sulfate and polysorbates.

Suitable examples of pharmaceutically acceptable preservatives include, but are not limited to, various antibacterial and antifungal agents such as solvents, for example ethanol, propylene glycol, benzyl alcohol, chlorobutanol, quaternary ammonium salts, and parabens (such as methyl paraben, ethyl paraben, propyl paraben, etc.).

40 Suitable examples of pharmaceutically acceptable stabilizers and antioxidants include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), thiourea, tocopherol and butyl

hydroxyanisole.

The compounds of the invention may also, for example, be formulated as suppositories *e.g.*, containing conventional suppository bases for use in human or veterinary medicine
5 or as pessaries *e.g.*, containing conventional pessary bases.

The compounds according to the invention may be formulated for topical administration, for use in human and veterinary medicine, in the form of ointments, creams, gels, hydrogels, lotions, solutions, shampoos, powders (including spray or dusting powders),
10 pessaries, tampons, sprays, dips, aerosols, drops (*e.g.*, eye ear or nose drops) or pour-ons.

For application topically to the skin, the compound of the present invention can be formulated as a suitable ointment containing the active compound suspended or dissolved
15 in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. Such compositions may also contain other pharmaceutically acceptable excipients, such as
20 polymers, oils, liquid carriers, surfactants, buffers, preservatives, stabilizers, antioxidants, moisturizers, emollients, colorants, and flavourings.

Examples of pharmaceutically acceptable polymers suitable for such topical compositions include, but are not limited to, acrylic polymers; cellulose derivatives, such as
25 carboxymethylcellulose sodium, methylcellulose or hydroxypropylcellulose; natural polymers, such as alginates, tragacanth, pectin, xanthan and cytosan.

As indicated, the compound of the present invention can be administered intranasally or by inhalation and is conveniently delivered in the form of a dry powder inhaler or an
30 aerosol spray presentation from a pressurized container, pump, spray or nebulizer with the use of a suitable propellant, *e.g.*, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134AT) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA), or a mixture thereof. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container, pump, spray
35 or nebulizer may contain a solution or suspension of the active compound, *e.g.*, using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, *e.g.*, sorbitan trioleate.

Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound and a suitable
40 powder base such as lactose or starch.

For topical administration by inhalation the compound according to the invention may be delivered for use in human or veterinary medicine via a nebulizer.

5 If the compound of the present invention is administered parenterally, then examples of such administration include one or more of: intravenously, intraarterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously administering the agent, and/or by using infusion techniques.

10 For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by
15 standard pharmaceutical techniques well-known to those skilled in the art.

The compounds according to the invention may be formulated for use in human or veterinary medicine by injection (e.g. by intravenous bolus injection or infusion or via intramuscular, subcutaneous or intrathecal routes) and may be presented in unit dose
20 form, in ampoules, or other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, solubilising and/or dispersing agents. Alternatively the active ingredient may be in sterile powder form for
25 reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The pharmaceutical compositions of the invention may contain from 0.01 to 99% weight per volume of the active material. For topical administration, for example, the composition will generally contain from 0.01-10%, more preferably 0.01-1% of the active compound.
30

A therapeutically effective amount of the compound of the present invention can be determined by methods known in the art. The therapeutically effective quantities will depend on the age and on the general physiological condition of the subject, the route of administration and the pharmaceutical formulation used. The therapeutic doses will
35 generally be between about 10 and 2000 mg/day and suitably between about 30 and 1500 mg/day. Other ranges may be used, including, for example, 50-500 mg/day, 50-300 mg/day, 100-200 mg/day. The daily dose as employed for acute human treatment will range from 0.01 to 2 mg/kg body weight, suitably 2 to 20 mg/kg body weight, or suitably 5 to 10 mg/kg body weight, which may be administered in one to four daily doses, for
40 example, depending on the route of administration and the condition of the subject. When the composition comprises dosage units, each unit will contain 10 mg to 2 g of active ingredient, suitably 200 mg to 1 g of active ingredient.

Administration may be once a day, twice a day, or more often, and may be decreased during a maintenance phase of the disease or disorder, e.g. once every second or third day instead of every day or twice a day. The dose and the administration frequency will
5 depend on the clinical signs with the reduction or absence of at least one or more, preferably more than one, clinical signs of the acute phase known to the person skilled in the art. In one aspect of the present invention, administration is once daily oral dosing.

10 In one aspect, the present invention provides a combination comprising a) a compound of Formula (I) or a pharmaceutically acceptable salt thereof and b) one or more further therapeutically active agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a
15 combination as defined above together with one or more pharmaceutically acceptable carriers thereof represent a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate
20 doses of known therapeutic agents will be readily appreciated by those skilled in the art.

Methods of preparation:

Compounds of Formula (I) and salts thereof may be prepared by the general methods
25 outlined hereinafter or any method known in the art, said methods constituting a further aspect of the invention. In the following description, the groups A, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² have the meaning defined for the compounds of Formula (I) unless otherwise stated.

30 It will be appreciated by those skilled in the art that it may be desirable to use protected derivatives of intermediates used in the preparation of the compounds of Formula (I). Protection and deprotection of functional groups may be performed by methods known in the art. Hydroxyl, amino or keto groups may be protected with any hydroxyl, amino or keto protecting group (for example, as described in Green and Wuts. *Protective Groups in*
35 *Organic Synthesis*. John Wiley and Sons, New York, 1999). The protecting groups may be removed by conventional techniques. For example, acyl groups (such as alkanoyl, alkoxycarbonyl and aryloyl groups) may be removed by solvolysis (e.g., by hydrolysis under acidic or basic conditions). Benzyl group may be cleaved by hydrogenolysis in the presence of a catalyst such as palladium-on-carbon. Hydroximino group may be
40 converted to keto group by reaction with Na₂S₂O₅ as described in WO2006/087644. 1,2 diol groups may be protected as acetal by reaction with dimethyl acetal of N,N-dimethylacetamide (DMADMA) or dimethyl acetal of N,N-dimethylformamide (DMFDMA)

which may be removed by hydrogenolysis or methanolysis at reflux (*Tetrahedron Lett.* **12** (1971), 813-816, *Collection Czech. Chem. Commun.* **32** (1967), 3159).

- 5 The synthesis of the compounds of Formula (I) may be completed, if appropriate, by removing any protecting groups which are present in the penultimate intermediate using standard techniques which are well-known to those skilled in the art. The compounds of Formula (I) may be purified by conventional methods known in the art. For example, the compounds may be purified using standard techniques such as silica gel chromatography, HPLC on silica gel, HPLC using an aqueous solution of an acid such as formic acid or
- 10 trifluoroacetic acid, or an ammonium salt of carbonic acid, such as ammonium bicarbonate with an organic co-solvent such as acetonitrile or methanol, and the like. Alternatively, compounds of Formula (I) may be purified by differential partition between aqueous and organic solvents and/or crystallisation.
- 15 Compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is hydrogen, methyl or $-C(=O)-R^{10}$, R^7 and R^9 are hydroxyl, may be prepared from compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is hydrogen, methyl or $-C(=O)-R^{10}$, R^7 is hydroxyl and R^9 is hydroxyl protecting group (suitably acetyl), by using suitable base, for example K_2CO_3 or $LiOH$ in a suitable solvent,
- 20 such as methanol or mixture of methanol and water.

The reaction may be carried out for example using excess of a suitable base, such as K_2CO_3 , suitably 5-10 equivalents of base, in a suitable solvent, such as methanol or a mixture of methanol and water at room temperature.

- 25 Alternatively, compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is $-C(=O)-R^{10}$, R^7 and R^9 are hydroxyl, may be prepared by reaction of compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is hydrogen, R^7 and R^9 are hydroxyl with suitable acid of Formula (III)



- in the presence of carbodiimides such as polymer-supported carbodiimide (PS CDI), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), dicyclohexylcarbodiimide (DCC) or 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) in the presence of hydroxybenzotriazole monohydrate (HOBt) in a suitable inert organic solvent such as a halohydrocarbon (e.g.
- 35 dichloromethane), N,N-dimethylformamide or mixture thereof optionally in the presence of a tertiary organic base such as triethylamine or dimethylaminopyridine or in the presence of an inorganic base (eg. sodium hydroxide) and at a temperature in the range 0° to $120^\circ C$.

- 40 Compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is $-C_{1-6}$ alkyl, R^7 and R^9 are hydroxyl, may be prepared by N-alkylation of compounds of Formula (I) wherein R^8 is hydrogen using suitable halo derivative of Formula (IV)

Hal-C₁₋₆alkyl (IV)

wherein Hal is chloro, bromo or iodo (suitably iodo).

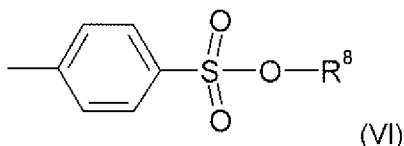
- 5 The N-alkylation is suitably carried out in a presence of an organic base (suitably N,N-diisopropylethylamine) in an inert organic solvent such as lower alcohol (suitably methanol) or acetonitrile.

- 10 Alternatively, compounds of Formula (I) wherein R³ is an α-L-cladinosyl group of Formula (b), R⁸ is -C₁₋₆alkyl, R⁷ and R⁹ are hydroxyl, may be prepared by reductive amination of compounds of Formula (I) wherein R⁸ is hydrogen, using suitable aldehyde of Formula (V)

J-C(O)H (V)

wherein J represents the group R⁸ but comprises one carbon atom less than the R⁸ group (for example if R⁸ is n-butyl, then J is n-propyl).

- 15 The reductive amination reaction is suitably carried out in a solvent such as methanol, dichloromethane, chloroform, N,N-dimethylformamide or a mixture thereof, in the presence of a suitable reducing agent, for example sodium triacetoxyborohydride or sodium cyanoborohydride.
- 20 Specifically, compounds of Formula (I), wherein R³ is an α-L-cladinosyl group of Formula (b), R⁸ is methyl, R⁷ and R⁹ are hydroxyl, may be prepared from compounds of Formula (I) wherein R⁸ is hydrogen, by the Eschweiler-Clarke procedure using formaldehyde and formic acid.
- 25 Specifically, compounds of Formula (I) wherein R³ is an α-L-cladinosyl group of Formula (b), R⁸ is -C₁₋₆alkyl substituted at the terminal carbon atom by a -(5-oxotetrahydro-2-furanyl) group, R⁷ and R⁹ are hydroxyl, may be prepared by N-alkylation of compounds of Formula (I) wherein R⁸ is hydrogen, using a suitable tosylate derivative of Formula (VI),
- 30 wherein R⁸ is -C₁₋₆alkyl substituted at the terminal carbon atom by a -(5-oxotetrahydro-2-furanyl) group.



in the presence of tertiary organic base such as diisopropylethylamine (DIPEA), triethylamine (TEA), or mixture thereof.

- 35 The reaction is suitably carried out in a lower alcohol solvent such as methanol, in a presence of a base such as diisopropylethylamine (DIPEA) at room or elevated temperature (suitably at about 50 °C).

Compounds of Formula (I) wherein R³ is an α-L-cladinosyl group of Formula (b), R⁸ is -

$C(=O)-R^{10}$, R^7 is hydroxyl and R^9 is hydroxyl protecting group (suitably acetyl), may be prepared by reaction of compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is hydrogen, R^7 is hydroxyl and R^9 is hydroxyl protecting group (suitably acetyl) with suitable acid of Formula (III)



in the presence of carbodiimides such as polymer-supported carbodiimide (PS CDI), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), dicyclohexylcarbodiimide (DCC) or 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) in the presence of hydroxybenzotriazole monohydrate (HOBt) in a suitable inert organic solvent such as a halohydrocarbon (e.g. dichloromethane), N,N-dimethylformamide or mixture thereof optionally in the presence of a tertiary organic base such as triethylamine or dimethylaminopyridine or in the presence of an inorganic base (eg. sodium hydroxide) and at a temperature in the range 0° to 120°C.

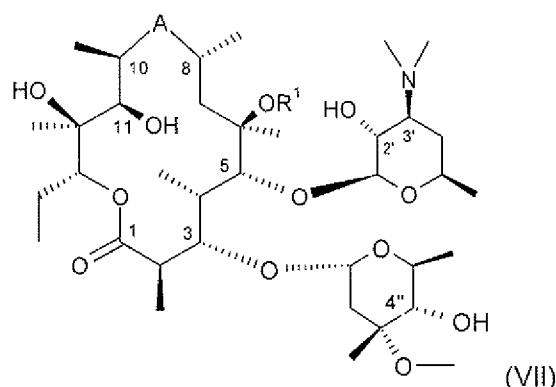
15 Compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is hydrogen, R^7 is hydroxyl, and R^9 is hydroxyl or hydroxyl protecting group (suitably acetyl), may be prepared by reaction of compounds of Formula (I), wherein R^8 is C_{1-6} alkyl (suitably methyl), R^3 is an α -L-cladinosyl group of Formula (b), R^7 is hydroxyl and R^9 is hydroxyl or hydroxyl protecting group (suitably acetyl), by conventional techniques for mono-demethylation of the 3'-NMe₂ group, for example by reaction with azodicarboxylic acid esters, suitably DEAD in DMF (E. E. Smisman, et al. *J. Org. Chem.* 38 (1973) 1652-1657), or with iodine under UV radiation (preferably with 500 W halogen lamp), in the presence of sodium acetate (US 3,725,385 and WO2004/013153), or by reaction of compound of Formula (I) with N-iodosuccinimide in acetonitrile at room temperature (*J. Org. Chem.* 65 (2000) 3875-3876), or with iodine in presence of morpholine or with benzylchloroformate, followed by elimination of benzyloxycarbonyl groups at position 2' and 3' as described in US 5,250,518.

30 Compounds of Formula (I) wherein R^3 is hydroxyl may be prepared by acid hydrolysis of compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b) using diluted hydrochloric acid at a temperature within the range of 20° to 40°C.

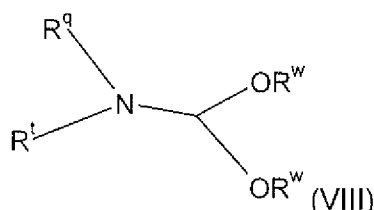
35 Compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is methyl, R^7 is hydroxyl and R^9 is hydroxyl protecting group (suitably acetyl), may be prepared by selective solvolysis of C/2'-hydroxyl protecting group from compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is methyl, R^7 and R^9 are hydroxyl protecting group (suitably acetyl) according to the methods known in the art, such as *J. Med. Chem.* (1972) 15, 631-634 and *J. Antibiotics* (1987) 40, 1006-1015.

40 The reaction may be carried out for example using methanol at a temperature in the range from room temperature to 60 °C.

- Alternatively compounds Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is methyl, R^7 is hydroxyl and R^9 is hydroxyl protecting group (suitably acetyl), may be prepared by reaction of compounds of Formula (II) wherein R^7 and R^9 are hydroxyl with the appropriate carboxylic acid anhydride (suitably acetanhydride) in a suitable inert organic solvent such as toluene or halohydrocarbon (e.g. dichloromethane), in the presence of tertiary organic base such as triethylamine (TEA), diisopropylethylamine (DIPEA) or mixture thereof, and catalytic amount of dimethylaminopyridine (DMAP) at a temperature in the range from room to reflux, followed by solvolysis with methanol.
- 10 The reaction may be carried out for example using excess of carboxylic acid anhydride (suitably acetanhydride), suitably 5 to 10 equivalents, in a suitable solvent, such as toluene, at reflux temperature in the presence of triethylamine and dimethylaminopyridine, followed by treatment with methanol.
- 15 Compounds of Formula (I) wherein R^3 is an α -L-cladinosyl group of Formula (b), R^8 is methyl, R^7 is hydroxyl protecting group (suitably acetyl) or $-O-(CH_2)_2CN$ and R^9 is hydroxyl protecting group (suitably acetyl), may be prepared by decarboxylation reaction of compounds of Formula (II), wherein R^7 is hydroxyl protecting group (suitably acetyl) or $-O-(CH_2)_2CN$, and R^9 is hydroxyl protecting group (suitably acetyl) with the appropriate carboxylic acid halide (suitably benzoyl chloride) or with the appropriate carboxylic acid anhydride (suitably acetanhydride) in a suitable inert organic solvent such as halohydrocarbon (e.g. dichloromethane) or toluene, in the presence of tertiary organic base such as triethylamine (TEA), diisopropylethylamine (DIPEA) or mixture thereof, and catalytic amount of dimethylaminopyridine (DMAP) at a temperature in the range from room to reflux.
- 20
- 25
- The reaction may be carried out for example using excess of carboxylic acid halide (suitably benzoyl chloride) suitably 5 to 10 equivalents, in a suitable solvent, such as a halohydrocarbon (e.g. dichloromethane) at room temperature in the presence of a suitable base, such as triethylamine.
- 30
- Compounds of Formula (II), wherein R^7 is hydroxyl protecting group (suitably acetyl) or $-O-(CH_2)_2CN$, and R^9 is hydroxyl protecting group (suitably acetyl), may be prepared from compounds of Formula (II) wherein R^7 is hydroxyl or $-O-(CH_2)_2CN$, and R^9 is hydroxyl, by reaction with $(C_{1-4}alkylCO)_2O$ carboxylic acid anhydride (suitably acetanhydride) in a suitable aprotic solvent such as halohydrocarbon (e.g. dichloromethane) or *N,N*-dimethylformamide and in the presence of organic base such as dimethylamino pyridine, triethylamine, mixture thereof or pyridine, and at a temperature range from 0° C to room temperature.
- 35
- 40
- Compounds of Formula (II) wherein R^7 and R^9 are hydroxyl may be prepared by reaction of compounds of Formula (VII).



with the *N,N*-substituted formamide acetal of formula (VIII)



wherein R^1 and R^2 independently are $-C_{1-4}$ alkyl (suitably methyl) or $-C_{1-4}$ alkyl substituted by phenyl and R^3 is $-C_{1-4}$ alkyl (suitably methyl), in a suitable inert organic solvent such as halohydrocarbon (e.g. chloroform or DCM), *N,N*-dimethylformamide (DMF) or toluene at a temperature in the range from room to reflux.

The reaction may be carried out for example using excess of *N,N*-substituted formamide acetal (suitably *N,N*-dimethylformamide dimethylacetal (DMF-DMA)) suitably 2 to 6 equivalents, in a halohydrocarbon (e.g. chloroform) or in DMF at 60-70 °C.

Compounds of Formula (VII) are known compounds or may be prepared by processes known in the art.

Compounds of Formula (VII) wherein A represents $-C(O)-$ and R^1 is methyl, may be prepared according to *J. Antibiotics* (1984) 37, 187-189.

Compounds of Formula (VII) wherein A represents $-C(=NOR^6)-$ and R^1 is hydrogen or methyl, may be prepared according to US patent 3,478,014 or *J. Antibiotics* (1991), 44, 313-330.

Compounds of Formula (VII) wherein A represents $-CH(OH)-$ may be prepared from compounds of Formula (VII) where A is $-C(O)-$ using a suitable reducing agent, for instance a hydride (sodium borohydride lithium borohydride, sodium cyano borohydride or lithium aluminium hydride) according to *J. Antibiotics* (1990) 1334-1336.

Compounds of Formula (VII) wherein A represents $-N(R^5)CH_2-$ or $-NCH_2(R^5)-$ may be obtained by reduction of the corresponding 9a- or 8a-imino ether followed by reductive N-alkylation according to the procedure described in *J. Chem. Soc. Perkin Trans* (1986) 1881-1890, *J. Chem Res. S* (1988) 152-153; (M) (1988) 1239-1261, EP0508725 and EP0507595.

Compounds of Formula (VII) wherein A is $-NHC(O)-$ or $-C(O)NH-$ and R^1 is methyl are known compounds or they may be prepared from the corresponding 6-O-methyl erythromycin A oxime by Beckman rearrangement according to the procedure described in WO9951616.

Compounds of Formula (VII) wherein A is $-C(O)NH-$ and R^1 is hydrogen are known compounds or they may be prepared from the corresponding erythromycin A (9Z)-oxime by Beckman rearrangement according to the procedure described in *Bioorg. Med. Chem. Lett.* (1993) 3, 1287-1292.

Compounds of Formulae III, IV, V, VI and VIII are commercially available or may be readily prepared by methods well known in the art.

Pharmaceutically acceptable acid addition salts, which also represent an object of the present invention, may be obtained by reaction of a compound of Formula (I) with an at least equimolar amount of the corresponding inorganic or organic acid such as hydrochloric acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, propionic acid, benzoic acid, benzenesulfonic acid, methane sulfonic acid, laurylsulfonic acid, stearic acid, palmitic acid, succinic acid, ethylsuccinic acid, lactobionic acid, oxalic acid, salicylic acid and similar acid, in a solvent inert to the reaction. Addition salts are isolated by evaporating the solvent or, alternatively, by filtration after a spontaneous precipitation or a precipitation by the addition of a non-polar cosolvent.

Biological Assays

The potential for a compound of the present invention to have an advantageous profile for providing therapeutic benefit in the treatment of neutrophil dominated inflammatory diseases resulting from neutrophilic infiltration and/or diseases associated with altered cellular functionality of neutrophils may be demonstrated, for example, using the following assays.

In the assays used and described herein, the compounds of the present invention were not necessarily from the same batch described in the experimental section. A test compound from one batch may have been combined with other batch(es) for the assay(s).

A compound analysed using biological assays defined herein is considered to be active if it exhibits at least one of the following results:

- a) 40% or more, suitably 50% or more, inhibition in the *in vitro* Inhibition of IL-6 production in LPS-stimulated murine spleenocytes assay; and/or
- b) 30% or more, suitably 50% or more, inhibition in the *in vivo* Lung neutrophilia induced by bacterial lipopolysaccharide in mice assay.

5

The following abbreviations are used in the text: DMSO for dimethyl sulfoxide, PBS for phosphate buffered saline, DMEM for Dulbecco's modified Eagle medium, FBS for fetal bovine serum, LPS for bacterial lipopolysaccharide, and BALF for bronchoalveolar lavage fluid.

10

In vitro screening protocol

Compound preparation

Test and reference substances used in an *in vitro* assay are dissolved in dimethyl sulfoxide (DMSO) (Sigma Chemical Co., USA) at a concentration of 50 mM and are further diluted to final concentrations of 50 μ M, 25 μ M, 12.5 μ M, 6.3 μ M and 3.1 μ M in Dulbecco's modified Eagle medium (DMEM) (Gibco, USA) supplemented with 1% heat inactivated fetal bovine serum (FBS) (BioWest, Ringmer, United Kingdom).

15

Inhibition of IL-6 production in LPS-stimulated murine spleenocytes *in vitro*

After cervical dislocation, mouse spleens are removed using sterile dissection tools. Spleens are transferred to a pre-wetted cell strainer in a 50 mL sterile conical tube and cell suspension was made by gentle puddle. Cells are centrifuged (20 min, 300xg) and resuspended in 2 mL of sterile phosphate buffered saline (PBS) (Sigma Chemical Co., USA). Red blood cells are lysed by addition of 3 mL of sterile water and occasionally gentle shaking for 1 minute. Afterwards, the tube is filled to 40 mL with DMEM medium and centrifuged (20 min, 300xg). Cells are resuspended in DMEM supplemented with 1% FBS and seeded in a 24-well plate, 1×10^6 cells per mL medium.

25

Cells are pre-incubated with the test compounds for 3 h at 37°C, in an atmosphere of 5% CO₂ and 90% humidity. Afterwards, cells are stimulated with 1 μ g/mL lipopolysaccharide (LPS, *E. coli* 0111:B4, Sigma Chemical Co., USA) and incubated overnight. Concentration of IL-6 is determined in cell supernatants by sandwich ELISA using capture and detection antibodies (R&D Systems, USA) according to the manufacturer's recommendations.

30

Inhibition (as percentage) is calculated using the following formula:

% inhibition = $[1 - (\text{concentration of IL-6 in sample} - \text{concentration of IL-6 in negative control}) / (\text{concentration of IL-6 in positive control} - \text{concentration of IL-6 in negative control})] \times 100$.

35

The positive control refers to LPS-stimulated samples that were not preincubated with the compounds.

The negative control refers to unstimulated and untreated samples.

40

In vivo screening protocol

Lung neutrophilia induced by bacterial lipopolysaccharide (LPS) in mice

For intraperitoneal administration (i.p.) compounds are dissolved in a final concentration of 10mg/mL. The required amount of compound is first dissolved in dimethylsulfoxide (DMSO, Sigma) and then diluted with 0.5% (w/v) methyl-cellulose so that the final DMSO concentration was 5% (v/v). The obtained solution is applied in a dose volume of 0.1mL per 10g of animal. Therefore, the compound dose is 100mg/kg.

- Male BALB/c mice (Charles River, Germany), with an average weight of ~25g are randomly grouped (n=8 in testing group, 10 in positive control and 6-8 in negative control). Mice received intraperitoneally (i.p.) a single dose of 100 mg/kg of test compound. Two hours after administration, 0.4 µg of LPS (from *Escherichia coli* serotype 0111:B4, Sigma), dissolved in sterile saline (0.9% NaCl) in a volume of 50 µL, is intranasally administered to all experimental groups except the negative control group, which received the same volume of vehicle (saline). Animals are sacrificed approximately 24 hours after application of LPS in order to obtain bronchoalveolar lavage fluid (BALF), which is used to determine absolute number of cells and the percentage of neutrophils. Results are expressed as percentage decrease in total cell number and number of neutrophils in BALF of treated animals compared to positive control (LPS challenged, but untreated animals), as revealed by cytopspine evaluation. In some experiments neutrophil levels in BALF are assessed by measurement of concentration of a neutrophil-specific enzyme myeloperoxidase (MPO). Results are then expressed as percentage of decrease in myeloperoxidase (MPO) concentration measured in BALF lysates of treated animals compared to positive control (Mouse MPO ELISA Kit, Hycult biotechnology, Netherlands). For this purpose, BALF is sonicated after addition of 1.5% Triton-X-100 (Pharmacia Biotech) in Milli-Q water and frozen at -80°C until analysed.

Examples

- The following abbreviations are used in the text: DMF-DMA for *N,N*-dimethylformamide dimethylacetal, DCM for dichloromethane, DMAP for dimethylaminopyridine, TEA or Et₃N for triethylamine, DEA or Et₂N for diethylamine, MeOH for methanol, DMF for *N,N*-dimethylformamide, Ac₂O for acetic anhydride, EtOAc for ethyl acetate, DEAD for diethyl azodicarboxylate, DIPEA for diisopropylethylamine, HOBt for 1-hydroxybenzotriazole hydrate, PS-CDI for polymer-supported carbodiimide, PS-trisamine for polymer-supported trisamine, DMSO for dimethyl sulfoxide, and THF for tetrahydrofuran.

- The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and

modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

- 5 Where reactions are described as having been carried out in a similar manner to earlier, more completely described reactions, the general reaction conditions used were essentially the same. Work up conditions used were of the types standard in the art, but may have been adapted from one reaction to another. The starting material may not necessarily have been prepared from the batch referred to. Compounds synthesised may
- 10 have various purities, determined unless otherwise stated as area percentage by LC-MS, ranging from for example 73% to 99.6%. However, calculations of number of moles and yield are generally not adjusted for this. In the procedures that follow, reference to the product of an Intermediate or Example by number is typically provided. This is provided merely for assistance to the skilled chemist to identify the starting material used. The
- 15 starting material may not necessarily have been prepared from the batch referred to.

The compounds of Formula (I) and derivatives thereof may be purified by conventional methods known in the art. For example, the compounds may be purified by reverse phase preparative HPLC, such as reverse phase mass directed automatic preparative

20 HPLC using an aqueous solution of an acid, such as formic acid (HCOOH) or an ammonium salt of carbonic acid, such as ammonium bicarbonate (NH_4HCO_3), with an organic co-solvent such as acetonitrile. Alternatively, said compounds may be purified by crystallisation, chromatography and/or differential partition between aqueous and organic solvents.

25 Reverse phase mass directed automatic preparative HPLC refers to the use of Waters Mass Directed AutoPurification System using XBridge MS C18 column (19 x 100 mm, 5 μm) and isocrat technique, using mixture of eluents 10mM NH_4HCO_3 /pH 10 and CH_3CN .

30 Unless otherwise stated, column chromatography was conducted on silica gel.

9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin A, may be prepared by the procedure as described in *J. Chem. Res. (S)* 1988, page 152. 6-O-Methyl-9a-aza-9a-homoerythromycin A may be prepared according to procedure of WO99/51616, example

35 2, page 15. 2'-O-(2-Cyanoethyl-4"-O-acetyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A 11,12-(*N,N*-dimethylformamide) acetal may be prepared by the procedure as described in WO2009/016142, Intermediate 1, Procedure B, Step 4, compound 11b.

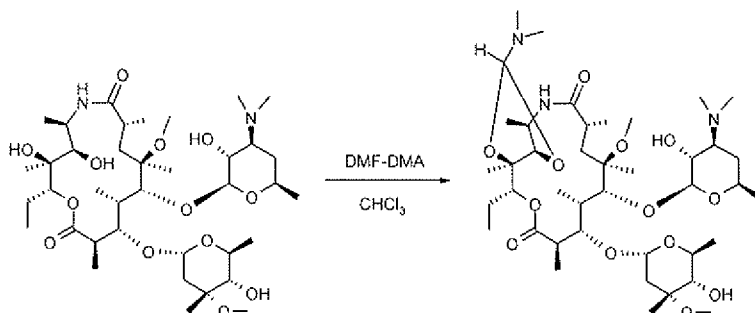
40

INTERMEDIATES

Intermediate 1

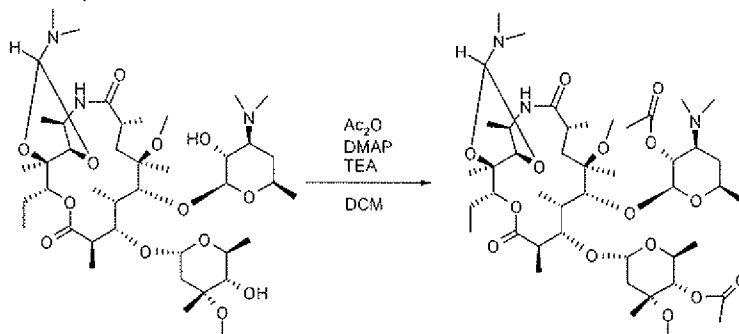
6-O-Methyl-9a-aza-9a-homoerythromycin A 11,12-(*N,N*-dimethylformamide) acetal

5



To a solution of **6-O-methyl-9a-aza-9a-homoerythromycin A** (10 g, 13.1 mmol, calculated based on 100% purity of starting macrolide) in chloroform (50 mL), DMF-DMA (5.74 mL, 40.6 mmol) was added, the reaction mixture was warmed at 60 °C and stirred for 12 hours. Then, additional amount of DMF-DMA (0.5 mL, 3.5 mmol) was added and stirring continued at 60 °C for 8 hours. After that, additional amount of reagent DMF-DMA (0.5 mL, 3.5 mmol) was added and stirring continued at 60 °C for a further 20 hours. The solvent was evaporated to afford crude **title product** (11.20 g, purity: 73 %) as a yellow foam which was used in the next step without further purification; MS (ES⁺, *m/z*): 818.42 [M]⁺.

Intermediate 2

2',4''-O-Diacetyl-6-O-methyl-9a-aza-9a-homoerythromycin A 11,12-(*N,N*-dimethylformamide) acetal

20

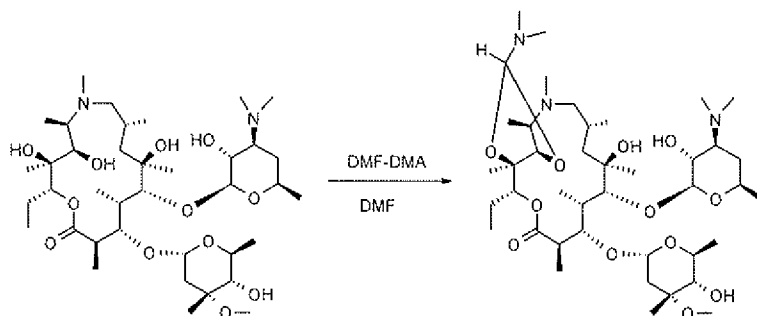
To a solution of DMAP (0.12 g, 1.00 mmol) in DCM (150 mL) cooled at 0 °C, TEA (4.76 mL, 34.0 mmol) and Ac₂O (2.08 mL, 22.01 mmol), followed by **Intermediate 1** (11.20 g, 10.00 mmol, calculated based on 73% purity of Intermediate 1) solution in DCM (60 mL) were added. Reaction mixture was stirred at 0 °C for 1 hour, and at room temperature for 15 hours. Then, additional amount of TEA (1.0 mL, 7.1 mmol) and Ac₂O (0.5 mL, 5.3 mmol) were added and stirring continued for 20 hours. Reaction mixture was washed with saturated aqueous NaHCO₃ solution (2 × 200 mL) and with brine (200 mL). The organic layer was dried over anhydrous Na₂SO₄ and evaporated to afford **Intermediate 2** (11.25

25

g, purity: 79 %) which was used in the next step without further purification; MS (ES^+ , m/z): 902.56 $[M]^+$.

Intermediate 3

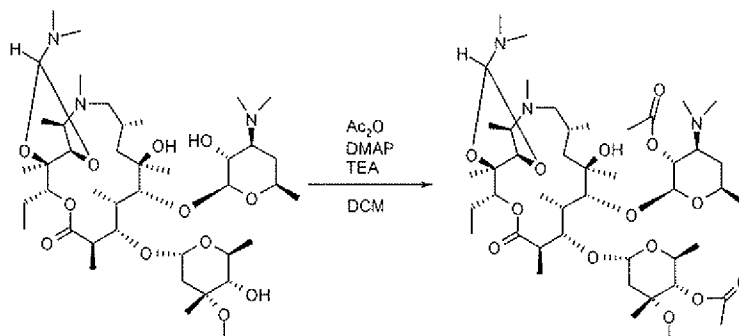
5 9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A 11,12-(*N,N*-dimethylformamide) acetal



To a solution of **9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A** (100 g, 132 mmol, calculated based on 99% purity of starting macrolide) in DMF (150 mL), DMF-DMA (84 mL, 595 mmol) was added and the reaction mixture stirred at 70 °C for 20 hours. To the reaction mixture water (1000 mL) was added and product extracted by DCM (400 mL, 2 x 200 mL). Combined organic layers were washed with water (4 x 300 mL), dried over anhydrous Na_2SO_4 , filtered, evaporated and dried in a vacuum oven at 50 °C over night to afford crude **title product** (101 g, purity: 87 %) which was used in the next step without further purification; MS (ES^+ , m/z): 804.40 $[M]^+$.

Intermediate 4

20 2',4''-O-Diacetyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A 11,12-(*N,N*-dimethylformamide) acetal

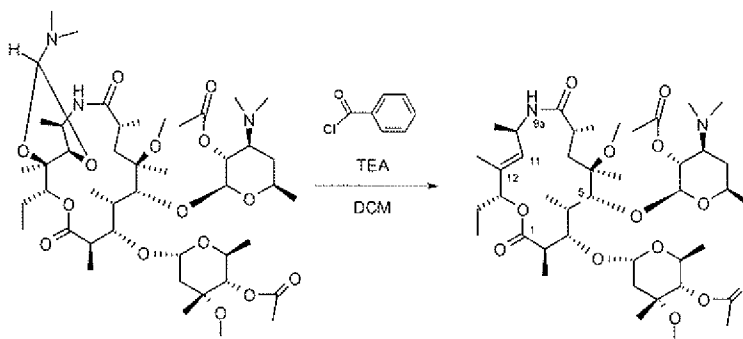


To a solution of **Intermediate 3** (101 g, 109 mmol, calculated based on 87% purity of Intermediate 3) in DCM (500 mL), TEA (94 mL, 678 mmol) and DMAP (1.335 g, 10.9 mmol) were added, and the reaction mixture was cooled to 0 °C. Ac_2O (56.7 mL, 601 mmol) was added dropwise and stirring continued at 0 °C for 5 hours. Temperature was allowed to reach room temperature and reaction mixture stirred further 12 hours. Reaction mixture was washed with saturated aqueous NH_4CO_3 solution (4 x 300 mL) and with water

(500 mL). Organic layer was dried over anhydrous Na_2SO_4 , filtered, evaporated and dried in a vacuum oven at 50 °C over night to afford **Intermediate 4** (103.25 g, purity: 82.5 %) which was used in the next step without further purification; MS (ES^+ , m/z): 888.40 $[\text{M}]^+$.

5 Example 1

(E)-2',4''-O-Diacetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A



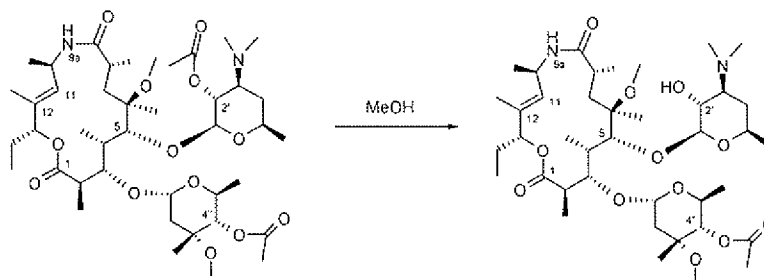
- 10 A solution of TEA (3.48 mL, 24.99 mmol) and benzoyl chloride (2.64 mL, 22.71 mmol) in DCM (150 mL) was stirred for 10 minutes. Then solution of **Intermediate 2** (5.2 g, 4.54 mmol, calculated based on 79% purity of Intermediate 2) in DCM (100 mL) was added dropwise over 2 hours and stirring continued for 4 hours. Reaction mixture was quenched with saturated aqueous NaHCO_3 solution (200 mL). Organic layer was washed with
- 15 saturated aqueous NaHCO_3 solution (250 mL), dried over anhydrous Na_2SO_4 , filtered and evaporated to afford crude **title product** (6.42 g) which was purified by column chromatography (using solvent system 0-100% (DCM/MeOH/ NH_4OH = 90/5/0.5) in DCM) to afford two fractions of crude title product: fraction A (1.982 g, purity 80%), which was used in next step without further purification and fraction B (596.9 mg, purity 85%), which
- 20 was further purified by precipitation from acetonitrile to afford **title product** (126.6 mg, purity 96.36%); MS (ES^+ , m/z): 813.71 $[\text{MH}]^+$.

- ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm: 0.78 (m, 3H), 0.79 (m, 3H), 0.93 (d, 3H), 1.06 (m, 3H), 1.06 (m, 3H), 1.08 (m, 3H), 1.14 (m, 3H), 1.16 (m, 3H), 1.18 (m, 1H), 1.22 (m, 1H), 1.24 (s, 3H), 1.41 (m, 1H), 1.50 (s, 3H), 1.54 (m, 1H), 1.65 (m, 1H), 1.72 (m, 1H), 1.75 (m,
- 25 1H), 1.78 (m, 1H), 1.93 (s, 3H), 2.07 (s, 3H), 2.17 (s, 6H), 2.23 (m, 1H), 2.40 (d, 1H), 2.62 (m, 1H), 2.74 (m, 1H), 3.20 (s, 3H), 3.26 (s, 3H), 3.67 (m, 1H), 3.68 (m, 1H), 3.78 (m, 1H), 4.26 (m, 1H), 4.44 (m, 1H), 4.54 (m, 1H), 4.57 (m, 1H), 4.70 (d, 1H), 4.91 (m, 2H), 5.38 (d, 1H), 6.55 (d, 1H).

30 Example 2

(E)-4''-O-Acetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A

Method A:

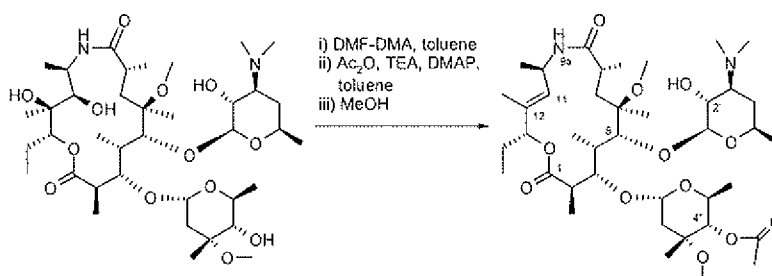


A solution of **(E)-2',4''-O-diacetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A, Example 1** (1.98 g, 1.95 mmol, calculated based on 80% purity of Example 1) in MeOH (40 mL) was stirred at 60 °C for 15 hours. Solvent was evaporated, the crude product dissolved in DCM (3 mL), and precipitated by addition of diisopropylether (200 mL) to afford after filtration **title product** (1.01 g, purity: 94 %); MS (ES⁺, *m/z*): 771.70 [MH]⁺.

¹H NMR (500 MHz, CDCl₃) δ ppm: 0.86 (t, 3H), 1.05 (d, 3H), 1.13 (m, 3H), 1.14 (m, 3H), 1.17 (m, 3H), 1.18 (m, 3H), 1.20 (m, 3H), 1.24 (d, 3H), 1.30 (m, 1H), 1.35 (s, 3H), 1.53 (s, 3H), 1.59 (m, 2H), 1.60 (m, 1H), 1.68 (m, 1H), 1.70 (m, 1H), 1.75 (m, 1H), 1.92 (m, 1H), 2.12 (s, 3H), 2.33 (m, 1H), 2.32 (s, 6H), 2.44 (m, 1H), 2.56 (m, 1H), 2.92 (m, 1H), 3.20 (dd, 1H), 3.32 (s, 3H), 3.37 (s, 3H), 3.78 (dd, 1H), 3.84 (m, 1H), 3.86 (d, 1H), 4.39 (m, 1H), 4.62 (m, 1H), 4.68 (m, 1H), 4.69 (m, 1H), 4.94 (t, 1H), 5.03 (d, 1H), 5.58 (d, 1H), 6.44 (d, 1H).

Mother liquor was evaporated, obtained residue dissolved in DCM (2 mL) and precipitated by addition of diisopropylether (150 mL), which after filtration gave additional amount of **title product** (157.8 mg, purity: 92 %).

Method B:

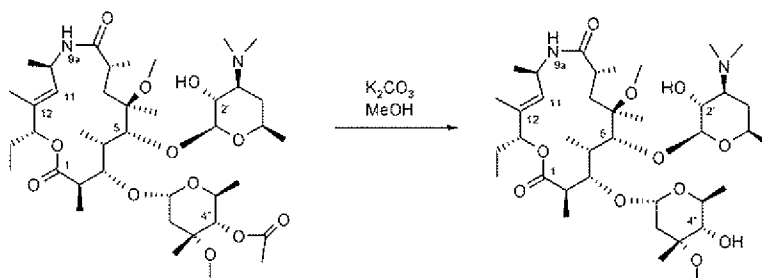


To a solution of **6-O-methyl-9a-aza-9a-homoerythromycin A** (7.63 g, 10 mmol) in toluene (40 mL), DMF-DMA (5.36 mL, 40.0 mmol) was added, reaction mixture heated to reflux temperature and stirred overnight. Volatiles were removed under reduced pressure. The residue was dissolved in toluene (40 mL), then Ac₂O (5.66 mL, 60.0 mmol) and TEA (8.36 mL, 60.0 mmol), followed by DMAP (0.122 g, 1.0 mmol) were added, and the reaction mixture was stirred at reflux temperature overnight. To the reaction mixture EtOAc (40 mL) and water (40 mL) were added and pH was adjusted to 4. Layers were separated and the organic one was washed with water (2 × 20 mL). The combined

aqueous layers were extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, solvent was removed under reduced pressure, to the obtained brown sticky residue MeOH (20 mL) was added and mixture stirred at 40 °C overnight. Solvent was removed under reduced pressure and brown residue purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/1.5) to afford **title product** in three fractions: fraction A (1.08 g, purity: 78 %), fraction B (2.76 g, purity: 93 %) and fraction C (0.62 g, purity: 87 %), all of which, according to LC-MS profile, conform to the reference.

Example 3

(E)-11,12-Didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A

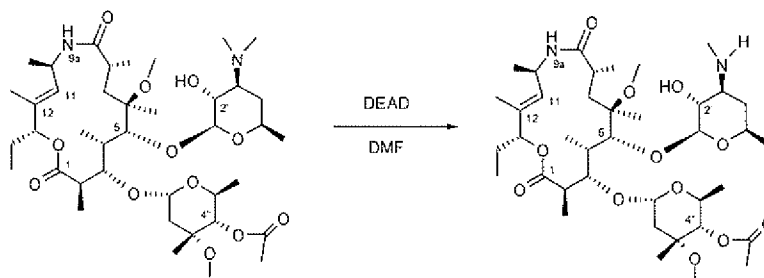


To a solution of (*E*)-4''-O-acetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A, Example 2 (457.3 mg, 0.49 mmol, calculated based on 87% purity of Example 2) in MeOH (10 mL), potassium carbonate (676 mg, 4.89 mmol) was added, and the reaction mixture shaken at room temperature for 60 hours. Solvent was evaporated, the obtained residue dissolved in DCM (50 mL) and washed with brine (2 × 50 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and evaporated to yield crude product (313.4 mg), which was purified by precipitation using DCM (1 mL) and diisopropylether (50 mL), giving still crude product (156.8 mg), which was further purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/0.5), to afford title product (85.1 mg) which was precipitated from DCM and diisopropylether and dried to afford **title product** (53 mg, purity: 95 %); MS (ES⁺, *m/z*): 729.35 [M]⁺.

¹H NMR (500 MHz, CDCl₃) δ ppm: 0.86 (t, 3H), 1.05 (d, 3H), 1.13 (d, 3H), 1.19 (d, 3H), 1.22 (m, 3H), 1.24 (m, 3H), 1.27 (s, 3H), 1.30 (m, 1H), 1.34 (d, 3H), 1.36 (s, 3H), 1.53 (s, 3H), 1.59 (m, 2H), 1.60 (m, 1H), 1.68 (m, 1H), 1.70 (m, 1H), 1.75 (m, 1H), 1.90 (m, 1H), 2.22 (m, 1H), 2.31 (s, 6H), 2.37 (d, 1H), 2.45 (m, 1H), 2.91 (m, 1H), 3.07 (m, 1H), 3.21 (dd, 1H), 3.34 (s, 3H), 3.37 (s, 3H), 3.54 (m, 1H), 3.77 (m, 1H), 3.77 (m, 1H), 3.89 (d, 1H), 4.08 (m, 1H), 4.54 (d, 1H), 4.63 (m, 1H), 4.94 (t, 1H), 4.98 (d, 1H), 5.58 (d, 1H), 6.45 (d, 1H).

Example 4

(E)-4''-O-Acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A

**Method A:**

To a solution of (*E*)-4''-O-acetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin **A, Example 2** (436.7 mg, 0.53 mmol, calculated based on 93% purity of Example 2) in DMF (20 mL), DEAD (0.083 mL, 0.53 mmol) was added and reaction mixture stirred at room temperature for 3 hours. After solvent was evaporated, yellow residue was dissolved in MeOH (15 mL), saturated aqueous NH₄Cl (4 mL) was added and mixture refluxed for 2 hours. Reaction mixture was cooled to room temperature, concentrated under reduced pressure, water (50 mL) and DCM (50 mL) were added and pH adjusted to 9.5 (1 M NaOH). Layers were separated and aqueous one extracted with DCM (3 × 15 mL). Combined organic layers were washed with brine (2 × 50 mL), dried over anhydrous Na₂SO₄, filtered and evaporated to afford crude product (885.8 mg), which was purified by column chromatography (using solvent system (0 - 100% (DCM/MeOH/NH₄OH = 90/9/1.5) in DCM) to afford **title product** in three fractions: fraction A (52.4 mg), fraction B (154.8 mg, purity determined by TLC: 80 %) and fraction C (153.4 mg, purity determined by TLC: 75 %).

Fraction A (52.4 mg) was further purified by precipitation from DCM (0.5 mL) and diisopropylether (50 mL) to afford **title product** (40.8 mg, purity: 91 %); MS (ES⁺, *m/z*): 757.35 [M]⁺.

¹³C NMR (125 MHz, CDCl₃) δ ppm: 9.81, 9.95, 10.50, 16.44, 17.95, 18.38, 18.92, 20.83, 21.00, 21.52, 22.00, 24.22, 32.97, 33.04, 35.29, 36.70, 37.31, 39.95, 41.28, 44.12, 49.21, 51.36, 59.56, 63.29, 66.93, 72.47, 75.13, 78.24, 78.39, 79.11, 79.67, 81.62, 96.48, 100.50, 134.72, 135.83, 170.45, 174.20, 176.02.

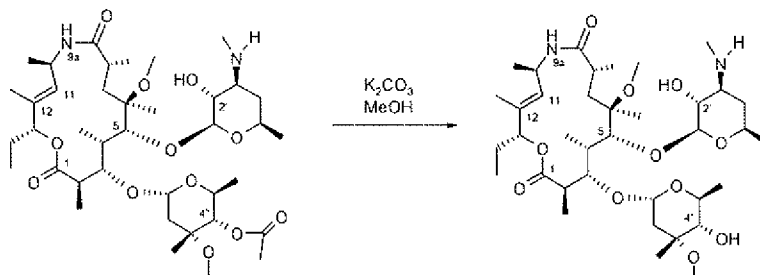
Method B:

To a solution of (*E*)-4''-O-acetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin **A, Example 2** (2.74 g, 3.25 mmol, calculated based on 93% purity of Example 2) in DMF (125 mL), DEAD (0.849 mL, 4.88 mmol) was added and reaction mixture stirred at room temperature for 3 hours. After solvent was evaporated, yellow residue was dissolved in MeOH (75 mL), saturated aqueous NH₄Cl (25 mL) was added and mixture refluxed for 2 hours. Reaction mixture was cooled to room temperature, concentrated under reduced pressure, water (100 mL) and DCM (100 mL) were added and pH adjusted to 9.5 using 1 M NaOH. Layers were separated and aqueous one extracted with DCM (3 × 55 mL). Combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na₂SO₄, filtered and evaporated to afford crude product (3.48 g), which was purified by precipitation from DCM/diisopropylether to afford **title**

product (2.164 g, purity: 91.5 %).

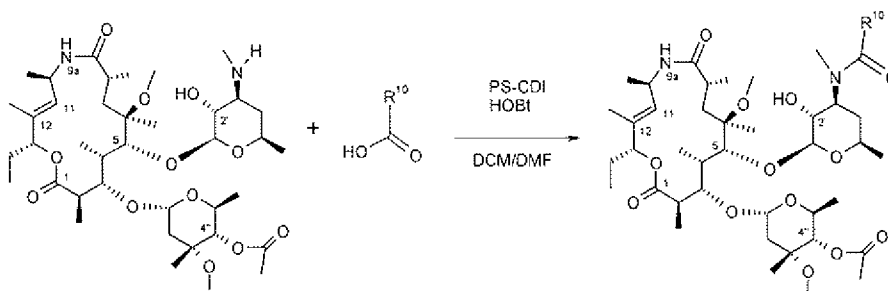
Example 5

5 (E)-3'-N-Demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A



To a solution of **(E)-4'-O-acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A, Example 4** (154.8 mg, 0.16 mmol, calculated based on 80% purity of Example 4, in MeOH (15 mL), potassium carbonate (226 mg, 1.64 mmol) was added, and the reaction mixture stirred at room temperature for 10 days. TLC showed that conversion is not completed therefore reaction mixture was heated to 80 °C and stirred for 2 hours. Solvent was evaporated, the obtained residue dissolved in DCM (20 mL) and washed with saturated aqueous NaHCO₃ solution (2 × 20 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and evaporated to yield crude product (51.4 mg), which was purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/0.5), to afford crude product (36.9 mg, purity: 82%), which was further purified by precipitation using DCM and diisopropylether to afford **title product** (14.7 mg, purity: 94 %); MS (ES⁺, *m/z*): 715.99 [MH]⁺.
¹³C NMR (150 MHz, CDCl₃) δ ppm: 9.86, 9.90, 10.62, 16.42, 18.07, 18.68, 18.97, 21.15, 21.49, 22.09, 24.34, 32.26, 33.18, 35.34, 36.81, 37.00, 40.00, 41.40, 44.25, 49.31, 51.35, 60.16, 66.74, 67.86, 72.95, 73.00, 77.48, 79.66, 79.76, 79.96, 81.71, 96.64, 101.42, 134.76, 134.96, 174.00, 176.09.

25 EXAMPLES 6-8



General procedure for Examples 6-8:

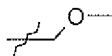
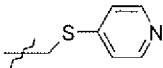
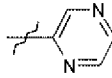
Dry PS-Carbodiimide resin (PS-CDI, loading: 1.25 mmol/g, 1 equivalent) was added to a dry reaction vessel. The corresponding acid (1-1.06 equivalent) and HOBt (0.7

equivalent), dissolved in a dry mixture of DCM (2 mL) and DMF (0.3 mL), were added to the resin. The mixture was stirred at room temperature for 5 minutes upon which **(E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-**

homoerythromycin A, Example 4 dissolved in dry DCM (2 mL) was added. The reaction mixture was heated by microwave irradiation at 75 °C for 7 to 10 minutes.

HOBt was scavenged using PS-trisamine (loading: 4.11 mmol/g, 5 equivalent according to HOBt) for 3 hours at room temperature. The resin was removed from the reaction mixture by filtration and washed with DCM (2 x 5 mL). Evaporation of the solvent under reduced pressure afforded corresponding compound of examples 6 to 8 as crude product.

Table 1.:

Example	R ¹⁰	Example 4 (mg/mmol)	R ¹⁰ COOH (mmol)	PS-CDI (mg/mmol)	HOBt (mmol)	Reaction time (minutes)
6		400 mg/ 0.48 ^a mmol	Methoxyacetic acid 0.51	387 mg/ 0.48 mmol	0.34	7
7		400 mg/ 0.48 ^a mmol	(4- pyridinylthio)acetic acid 0.48	387 mg/ 0.48 mmol	0.34	10
8		400 mg/ 0.48 ^a mmol	2- Pyrazinecarboxylic acid 0.48	387 mg/ 0.48 mmol	0.34	10

a = molar quantity was calculated based on 91.5% purity of Example 4

Example 6

(E)-4''-O-Acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-3'-N-(methoxy)acetyl-6-O-methyl -9a-aza-9a-homoerythromycin A

Crude product (526 mg) obtained according the above general procedure was further purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/1.5) to afford **title product** as two fractions: fraction A (45 mg, purity: 90 %) and fraction B (158 mg, purity: 95 %). Due to restrained rotation around amide bond, there are two rotamers present in ratio **A : B** = 1 : 1.

Example 6, fraction A

MS (ES⁺, *m/z*): 829.53 [M]⁺.

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 9.75, 10.15, 10.76, 10.79, 16.04, 18.57, 18.62, 19.42, 19.43, 19.51, 19.52, 20.85, 20.92, 21.10, 21.64, 21.70, 24.28, 26.63, 27.00, 33.34,

33.41, 34.93, 34.97, 35.15, 35.62, 38.09, 40.00, 41.36, 44.15, 44.22, 49.28, 49.35, 51.28, 51.37, 57.57, 58.50, 58.55, 62.96, 63.07, 66.49, 66.58, 69.92, 70.07, 71.05, 71.61, 72.59, 72.62, 78.19, 78.27, 78.99, 79.14, 79.19, 81.36, 96.11, 96.21, 101.89, 134.35, 134.69, 134.84, 169.29, 169.35, 170.50, 170.65, 174.68, 174.74, 175.46.

5

Example 7**(E)-4''-O-Acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-3'-N-(4-pyridinylthio)acetyl-9a-aza-9a-homoerythromycin A**

Crude product (818.8 mg) obtained according the above general procedure was further purified by column chromatography (using solvent system: EtOAc/n-hexane/DEA = 1/1/0.2) to afford **title product** as two fractions: fraction A (75.9 mg, purity: 97 %) and fraction B (250 mg, purity: 80 %). Due to restrained rotation around amide bond, there are two rotamers present in ratio A : B = 1.5 : 1.

Example 7, fraction A

15 MS (ES⁺, m/z): 908.37 [M]⁺.

¹³C NMR (125 MHz, CDCl₃-d) δ ppm: 9.80, 10.05, 10.09, 10.49, 16.46, 17.97, 18.01, 18.39, 18.89, 19.01, 20.80, 20.85, 20.97, 21.29, 21.99, 22.43, 24.22, 29.87, 32.97, 34.18, 34.65, 35.12, 35.36, 36.55, 36.66, 40.00, 41.30, 44.05, 44.10, 49.20, 49.26, 51.39, 51.43, 54.00, 58.01, 63.22, 63.35, 66.53, 66.67, 71.40, 71.67, 72.42, 72.75, 78.27, 78.36, 78.62, 20 78.86, 79.01, 79.49, 81.59, 81.66, 96.39, 96.53, 100.83, 100.95, 120.60, 120.86, 134.64, 135.89, 148.00, 149.27, 167.85, 168.03, 170.09, 170.50, 174.02, 174.16, 175.82, 175.94.

Example 8**(E)-4''-O-Acetyl-3'-N-demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-3'-N-(2-pyrazinyl)carbonyl-9a-aza-9a-homoerythromycin A**

Crude product (669 mg) obtained according the above general procedure was further purified by column chromatography (using solvent system: (DCM/MeOH/NH₄OH = 90/9/1.5)/DCM = 7/5) to afford **title product** as two fractions: fraction A (56.9 mg, purity: 90 %) and fraction B (269 mg, purity: 85 %). Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 1 : 1.

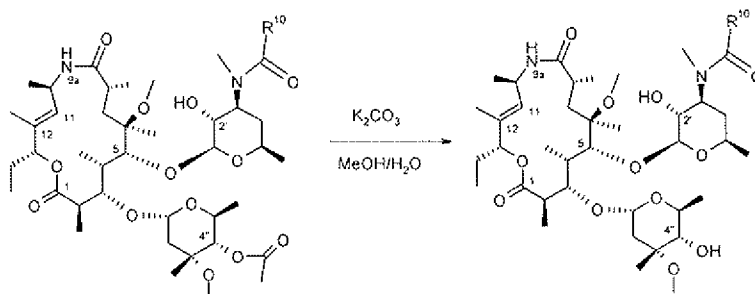
Example 8, fraction A

30 MS (ES⁺, m/z): 863.44 [M]⁺.

¹³C NMR (126 MHz, CDCl₃-d) δ ppm: 9.81, 9.94, 10.10, 10.48, 10.51, 16.44, 17.98, 18.92, 18.96, 20.74, 20.74, 20.88, 20.94, 20.94, 21.02, 21.02, 21.35, 21.99, 24.22, 27.32, 35 31.29, 32.99, 35.00, 35.20, 35.28, 36.48, 36.60, 39.88, 39.95, 41.30, 44.04, 48.33, 49.24, 51.32, 51.42, 54.16, 58.66, 63.19, 63.26, 66.31, 66.74, 71.26, 71.54, 72.40, 72.49, 78.20, 78.41, 78.71, 78.81, 78.91, 79.50, 79.55, 81.59, 81.64, 96.23, 96.54, 100.78, 100.97, 134.64, 134.68, 135.83, 135.92, 141.90, 142.60, 144.69, 145.10, 145.25, 145.21, 150.00, 150.29, 167.57, 167.72, 170.10, 170.53, 174.06, 174.19, 175.85, 175.95.

40

EXAMPLES 9 AND 10



General procedure for Examples 9 and 10:

- 5 4"-O-Acetyl-compound was dissolved in methanol (15 mL), then K_2CO_3 (10 equivalents) dissolved in water (2 mL) was added. The mixture was stirred at room temperature for 24 hours and evaporated to dryness. The residue was portioned between DCM (60 mL) and water (60 mL), pH adjusted to 2, and the crude product isolated from the organic layer at pH 2, after drying over anhydrous K_2CO_3 , filtration and evaporation and then purified
- 10 either by precipitation or by column chromatography to give desired product.

Table 2.:

Example	R^{10}	Starting 4"-O-acetyl compound	Amount of starting compound (mg/mmol)	K_2CO_3 (mg/mmol)	Reaction time (hours)
9		Example 6	158 mg/ 0.19 ^a mmol	263 mg/ 1.91 mmol	24
10		Example 7	250 mg/ 0.22 ^b mmol	304 mg/ 2.20 mmol	24

a = molar quantity was calculated based on 95% purity of starting 4"-O-acetyl compound

b = molar quantity was calculated based on 80% purity of starting 4"-O-acetyl compound

15

Example 9

(E)-3'-N-Demethyl-11,12-didehydro-11,12-dideoxy-3'-N-(methoxy)acetyl-6-O-methyl-9a-aza-9a-homoerythromycin A

- Crude product (128.1 mg) obtained according the above general procedure was isolated at pH 2 and further purified by precipitation from DCM/diisopropylether to afford **title product** (90.1 mg, purity: 92 %) as a white solid; MS (ES^+ , m/z): 809.40 [$M+Na$] $^+$.
- 20

Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 1 : 1.

- ^{13}C NMR (125 MHz, $DMSO-d_6$) δ ppm: 9.80, 10.15, 10.78, 16.12, 19.22, 19.36, 19.48, 21.21, 21.25, 21.55, 21.61, 21.76, 24.28, 26.56, 28.10, 33.38, 35.22, 35.40, 36.52, 37.88, 38.01, 40.00, 41.35, 44.25, 49.14, 49.22, 51.26, 51.31, 57.19, 58.49, 58.62, 65.58, 65.69, 66.57, 66.64, 69.98, 70.09, 70.98, 71.09, 73.01, 77.48, 78.20, 78.91, 79.20, 79.27, 81.25,
- 25

96.22, 96.34, 101.90, 134.33, 134.81, 134.94, 169.18, 169.40, 174.68, 175.47.

Example 10

(E)-3'-N-Demethyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-3'-N-(4-pyridinylthio)acetyl-9a-aza-9a-homoerythromycin A

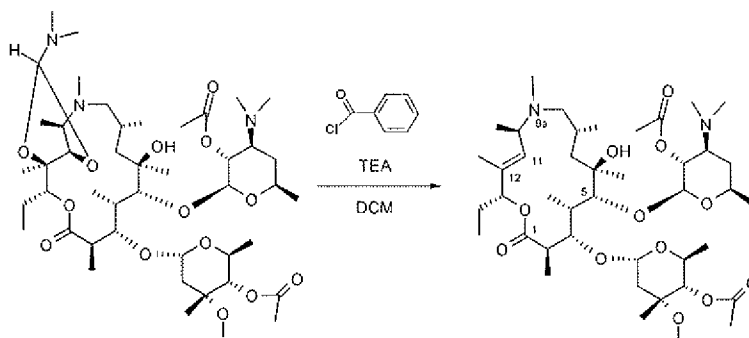
Crude product (258.6 mg) obtained according the above general procedure was isolated at pH 2 and further purified by column chromatography (using system: n-hexane/EtOAc/DEA = 1/1/0.2), which after drying at 50 °C for 24 hours afforded **title product** (200.9 mg, purity: 92 %); MS (ES⁺, *m/z*): 866.41 [M]⁺.

Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 1 : 1.

¹³C NMR (125 MHz, CDCl₃-*d*) δ ppm: 9.80, 9.80, 10.52, 16.32, 17.96, 18.44, 18.52, 18.87, 18.93, 20.94, 20.99, 21.28, 21.44, 21.99, 24.25, 27.45, 29.89, 33.02, 34.03, 34.59, 35.23, 35.33, 35.34, 36.27, 36.50, 36.59, 39.94, 40.01, 41.30, 44.09, 49.15, 49.23, 51.21, 54.21, 58.46, 66.91, 67.07, 67.68, 67.93, 70.99, 71.41, 72.86, 73.04, 77.10, 79.55, 80.01, 80.12, 80.34, 80.42, 81.55, 81.63, 96.54, 96.63, 102.25, 102.42, 120.64, 120.92, 134.53, 135.84, 135.91, 147.90, 149.21, 167.83, 167.95, 174.07, 174.17, 175.83, 175.92.

Example 11

(E)-2',4''-O-Diacetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A



A solution of TEA (73.5 mL, 528 mmol) and benzoyl chloride (55.7 mL, 480 mmol) in DCM (1500 mL) was stirred for 10 minutes. Then solution of **Intermediate 4** (103.25 g, 96 mmol, calculated based on 82.5% purity of Intermediate 4) in DCM (500 mL) was added dropwise over 2 hours and stirring continued for 4 hours. Reaction mixture was quenched with saturated aqueous NaHCO₃ solution (1000 mL). Organic layer was washed with saturated aqueous NaHCO₃ solution (1000 mL), dried over anhydrous Na₂SO₄, filtered and evaporated to afford crude product. Crude product was dissolved in DCM (200 mL), water (500 mL) was added and pH adjusted to 3 (using 6 M HCl). Organic layer was discharged and to the aqueous one DCM (400 mL) was added and pH adjusted to 8.4 (using 20% NaOH), dried over anhydrous K₂CO₃, filtered, evaporated and dried at 50 °C for 17 hours to afford **title product** (67.53 g, purity: 94 %). The water layer, pH 8.4 was re-extracted by DCM (2 x 200 mL), which after drying over over anhydrous K₂CO₃,

filtration, evaporation and drying at 50 °C for 17 hours afforded additional amount of **title product** (0.41 g, purity: 97 %), which was characterized as follows:

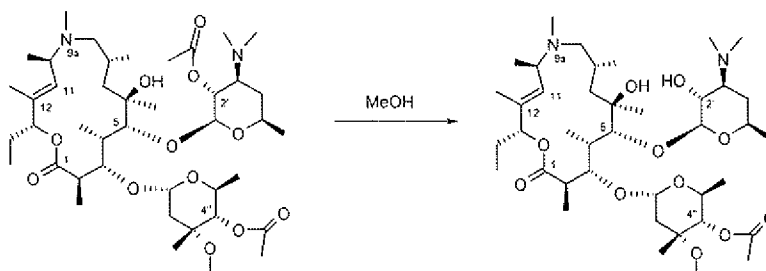
MS (ES⁺, *m/z*): 799.48 [M]⁺

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm: 0.78 (t, 3H), 0.83 (d, 3 H), 0.88 (d, 3H), 0.97 (d, 3H), 1.03 (m, 3H), 1.04 (s, 3H), 1.08 (d, 3H), 1.09 (s, 3H), 1.12 (m, 1H), 1.15 (d, 3H), 1.25 (m, 1H), 1.52 (s, 3H), 1.63 (m, 2H), 1.72 (m, 1H), 1.73 (m, 1H), 1.76 (m, 1H), 1.88 (m, 1H), 1.89 (m, 1H), 1.96 (s, 3H), 2.04 (m, 1H), 2.06 (s, 3H), 2.11 (s, 3H), 2.18 (s, 2x3H), 2.26 (m, 1H), 2.37 (d, 1H), 2.66 (m, 1H), 2.81 (m, 1H), 3.05 (m, 1H), 3.28 (s, 3H), 3.48 (d, 1H), 3.77 (m, 1H), 4.16 (dd, 1H), 4.29 (m, 1H), 4.55 (d, 1H), 4.61 (m, 1H), 4.67 (m, 1H), 4.68 (m, 1H), 4.99 (t, 1H), 5.17 (bs, 1H), 5.40 (d, 1H).

Example 12

(*E*)-4''-O-Acetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A

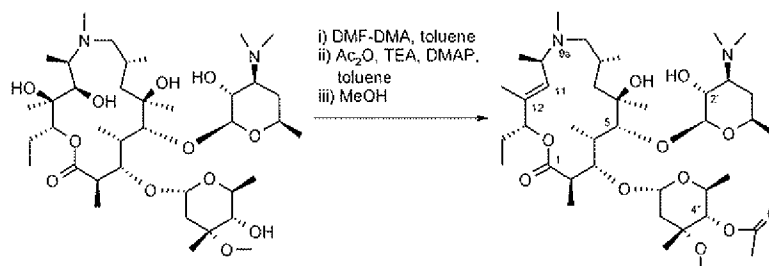
Method A:



A solution of (*E*)-2',4''-O-diacetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, Example 11 (1.5 g, 1.52 mmol, calculated based on 81% purity of Example 11) in MeOH (20 mL) was shaken at 60 °C for 15 hours. Solvent was evaporated, the residue dissolved in DCM (100 mL), and washed with acidic water (pH 3, 100 mL). To the water layer DCM (100 mL) was added and pH adjusted to 9 (using 5 M NaOH). Organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to give crude product (1.8 g). Crude product was dissolved in DCM (60 mL), water added (70 mL) and pH adjusted to 2 (using 2 M HCl). Organic layer was discharged and to the water one DCM (60 mL) was added, and pH adjusted to 5.5 (using 2 M NaOH). Organic layer at pH 5.5 was dried over anhydrous Na₂SO₄, filtered, and evaporated to afford **title product** (479.2 mg, purity: 98%); MS (ES⁺, *m/z*): 758.2 [MH]⁺.

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 8.99, 9.85, 13.12, 14.06, 17.96, 18.11, 20.98, 21.02, 21.72, 21.79, 24.63, 26.07, 27.28, 30.67, 34.80, 38.09, 40.80, 41.09, 43.01, 43.28, 49.35, 57.71, 62.84, 64.85, 65.03, 67.44, 70.58, 72.85, 73.49, 77.64, 77.71, 78.36, 83.13, 95.46, 102.03, 130.45, 130.48, 170.61, 174.83.

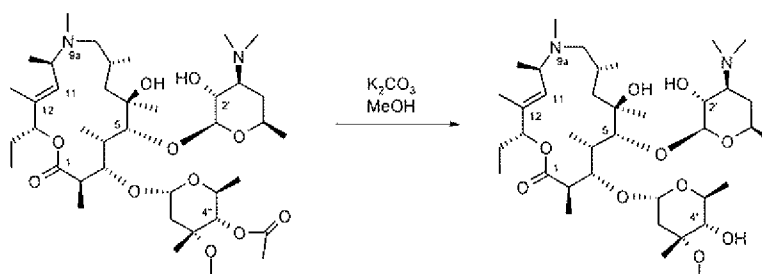
To the water layer at pH 5.5, DCM (60 mL) was added and pH adjusted to 9.5. Organic layer at pH 9.5 was dried over anhydrous Na₂SO₄, filtered, and evaporated to afford additional amount of **title product** (985.0 mg, purity 87%).

Method B:

- 5 To a solution of **9-deoxy-9a-methyl-9a-aza-9a-homoerythromycin A** (7.49 g, 10 mmol) in toluene (40 mL), *N,N*-dimethylformamide dimethylacetal (5.36 mL, 40.0 mmol) was added, reaction mixture heated to reflux temperature and stirred for 4 hours. Volatiles were removed under reduced pressure. The residue was dissolved in toluene (40 mL), then Ac₂O (5.66 mL, 60.0 mmol) and TEA (8.36 mL, 60.0 mmol), followed by DMAP
- 10 (0.122 g, 1.0 mmol) were added, and the reaction mixture was stirred at reflux temperature overnight. Reaction mixture was allowed to cool to ambient temperature, EtOAc (40 mL) and water (40 mL) were added and pH was adjusted to 3. Layers were separated and the organic one was washed with water (2 × 40 mL). The combined aqueous layers were extracted with EtOAc (2 × 20 mL). Aqueous layer was then
- 15 submitted to the acid-base extraction at pH 4, 5, 6, 7 and 9, using at each pH level EtOAc for extraction (3 × 40 mL). Organic layers at pH 6 and 7 were combined, dried over anhydrous Na₂SO₄, filtrated and evaporated to give crude product (7 g) as beige foam. Crude product was dissolved in MeOH (70 mL) and stirred at room temperature over the weekend, evaporated and the obtained residue purified by column chromatography (using
- 20 solvent system: DCM/MeOH/NH₄OH = 90/6/0.5) to afford **title product** as two fractions: fraction A (1.06 g, purity: 83 %) and fraction B (0.9 g, purity: 91 %), both of which, according to LC-MS profile, conform to the reference.

Example 13

- 25 **(E)-11,12-Didehydro-9-deoxy-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A**



- To a solution of **(E)-4''-O-acetyl-11,12-didehydro-9-deoxy-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A**, Example 12 (300.0 mg, 0.396 mmol) in MeOH (10
- 30

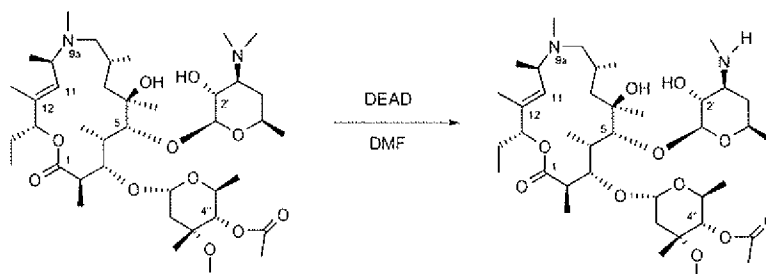
mL), potassium carbonate (548 mg, 3.96 mmol) was added, and the reaction mixture shaken at room temperature for 48 hours. Solvent was evaporated, the obtained residue dissolved in DCM (40 mL), water was added (40 mL) and pH adjusted to 3 (using 3M HCl). To the water layer DCM (40 mL) was added and pH adjusted to 9 (using 2N NaOH). Organic layer at pH 9 was dried over anhydrous Na₂SO₄, filtrated and evaporated to give crude product (324.4 mg), which was first precipitated from DCM/diisopropylether (1 mL/50 mL) and then purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/0.5) to afford **title product** (229.5 mg), which was further purified by precipitation from DCM/diisopropylether to afford **title product** (57.3 mg, purity: 99%); MS (ES⁺, *m/z*): 715.25 [M]⁺.

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm: 0.79 (t, 3H), 0.84 (d, 3H), 0.97 (d, 3H), 1.02 (d, 3H), 1.06 (m, 3H), 1.08 (m, 3H), 1.08 (m, 1H), 1.14 (s, 3H), 1.15 (m, 3H), 1.16 (s, 3H), 1.27 (m, 1H), 1.49 (m, 1H), 1.53 (s, 3H), 1.61 (m, 1H), 1.64 (m, 2H), 1.65 (m, 1H), 1.85 (m, 1H), 1.93 (m, 1H), 1.98 (m, 1H), 2.12 (s, 3H), 2.21 (m, 1H), 2.26 (s, 2 × 3H), 2.28 (m, 1H), 2.45 (m, 1H), 2.75 (m, 1H), 2.90 (dd, 1H), 3.07 (m, 1H), 3.08 (m, 1H), 3.22 (s, 3H), 3.54 (d, 1H), 3.69 (m, 1H), 4.06 (m, 1H), 4.17 (dd, 1H), 4.27 (d, 1H), 4.44 (d, 1H), 4.61 (d, 1H), 4.95 (t, 1H), 5.16 (bs, 1H), 5.44 (d, 1H).

An additional amount of title product (149.9 mg) was obtained by evaporation of mother liquor.

Example 14

(E)-4''-O-Acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A



Method A

To a solution of **(E)-4''-O-acetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, Example 12**, (520 mg, 0.58 mmol, calculated based on 85% purity of Example 12) in DMF (25 mL), DEAD (0.14 mL, 0.88 mmol) was added and reaction mixture stirred at room temperature over night. Then additional amount of DEAD (30 μL, 0.19 mmol) was added and reaction mixture stirred over night. Solvent was evaporated, residue dissolved in MeOH (15 mL), saturated aqueous NH₄Cl (5 mL) was added and mixture refluxed for 2 hours. Reaction mixture was cooled to room temperature, solvent evaporated, residue dissolved in DCM (30 mL), water (30 mL) added and pH adjusted to 2.5 (using 2M HCl). Organic layer was discharged and to the water

layer DCM (40 mL) was added, pH adjusted to 7 (using 2M NaOH). Water layer was discharged and organic layer dried over anhydrous Na₂SO₄, filtered and evaporated to afford crude product (365 mg), which was purified by column chromatography (using solvent system (DCM/MeOH/NH₄OH = 90/9/1.5) to afford **title product** in three fractions:

- 5 fraction A (103.9 mg, purity: 96%), fraction B (67.4 mg, purity: 90%), and fraction C (67.6 mg, purity: 97%). Fraction A was characterized as follows:

MS (ES⁺, *m/z*): 744.10 [MH]⁺

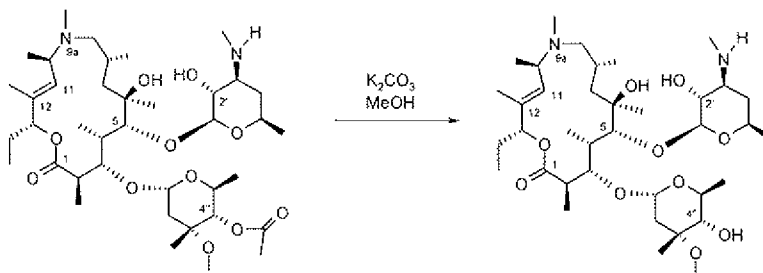
- ¹³C NMR (75 MHz, DMSO-*d*₆) δ ppm: 9.08, 9.97, 13.29, 14.07, 18.05, 18.33, 21.09, 21.13, 21.76, 21.87, 24.77, 25.98, 27.44, 32.98, 34.89, 37.23, 38.31, 41.38, 43.19, 43.32, 49.42, 10 57.83, 60.58, 62.98, 64.97, 67.30, 72.96, 73.53, 73.59, 77.65, 77.77, 78.48, 83.24, 95.47, 101.64, 130.54, 130.66, 170.73, 175.00.

Method B

- To a solution of (*E*)-4''-O-acetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-15 9a-aza-9a-homoerythromycin A, Example 12, (7.7 g, 10.17 mmol, calculated based on 88% purity of Example 12) in DMF (250 mL), DEAD (2.416 mL, 15.26 mmol) was added and reaction mixture stirred at room temperature for 6 hours. Solvent was evaporated, residue dissolved in MeOH (150 mL), saturated aqueous NH₄Cl (70 mL) was added and mixture refluxed for 2 hours. Reaction mixture was cooled to room temperature, solvent 20 evaporated, residue dissolved in DCM (70 mL), water (70 mL) added and pH adjusted to 2.5 (using 2M HCl). Organic layer was discharged and to the water layer DCM (80 mL) was added, pH adjusted to 7 (using 2M NaOH). Water layer was discharged and organic layer dried over anhydrous Na₂SO₄, filtered and evaporated to afford crude product (10.51 g), which was purified by silica gel column chromatography (using solvent system 25 (DCM/MeOH/NH₄OH = 90/9/1.5) to afford **title product** in six fractions: fraction A (0.27 g, purity: 92%), fraction B (0.31 g, purity: 93%), fraction C (1.15 g, purity: 96%), fraction D (0.96 g, purity 98.2%), fraction E (1.04 g, purity 98.5%) and fraction F (0.63 g, purity 89%).

Example 15

- 30 (*E*)-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A



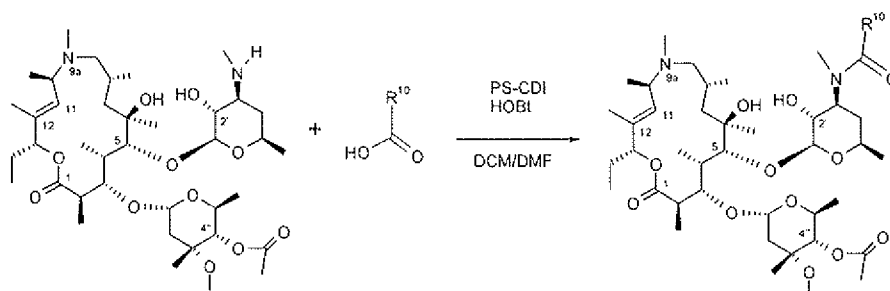
- To a solution of (*E*)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12- 35 dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, Example 14 (184.0 mg, 0.22 mmol, calculated based on 90% purity of Example 14) in MeOH (15 mL), potassium

carbonate (308 mg, 2.23 mmol) was added, and the reaction mixture stirred at room temperature for 40 hours. Solvent was evaporated, the obtained residue dissolved in DCM (60 mL), water added (60 mL), pH adjusted to 2 (using 2M HCl), and organic layer discharged. To the water layer DCM (60 mL) was added, pH adjusted to 7 (using 2M NaOH), layers separated, the organic layer dried over anhydrous Na₂SO₄, filtered, and evaporated to afford **title product** (76.4 mg, purity: 95 %); MS (ES⁺, *m/z*): 702.10 [MH]⁺.

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 9.08, 9.97, 12.97, 14.22, 17.94, 18.60, 21.33, 21.64, 21.67, 24.61, 25.95, 27.24, 33.52, 35.18, 37.76, 37.90, 41.27, 43.13, 43.51, 49.14, 57.63, 60.72, 64.97, 65.33, 67.38, 73.15, 73.59, 74.01, 77.73, 77.95, 78.04, 83.36, 95.72, 101.81, 130.52, 130.91, 174.96.

An additional amount of title product was obtained after adding fresh DCM (60 mL) to the water layer, re-adjusting pH to 7 (using 2M NaOH). The organic layer was dried over anhydrous Na₂SO₄, filtered, and evaporated to afford **title product** (20.5 mg, purity: 94 %).

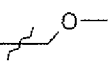
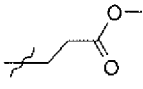
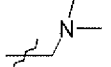
EXAMPLES 16-18



General procedure for Examples 16-18:

Dry PS-Carbodiimide resin (PS-CDI, loading: 1.25 mmol/g, 1 equivalent) was added to a dry reaction vessel. The corresponding acid (1-1.05 equivalent) and HOBT (0.7 equivalent), dissolved in a dry mixture of DCM (2 to 5 mL) and DMF (0.3 mL), were added to the resin. The mixture was stirred at room temperature for 5 minutes upon which **(E)-4''-O-acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, Example 14**, dissolved in dry DCM (2 to 3 mL) was added. The reaction mixture was heated by microwave irradiation at 75 °C for 7 minutes. HOBT was scavenged using PS-trisamine (loading: 4.11 mmol/g, 5 equivalent according to HOBT) for 3 hours at room temperature. The resin was removed from the reaction mixture by filtration and washed with DCM (2 x 5 mL). Evaporation of the solvent under reduced pressure afforded corresponding compound of examples **16 to 18** as a crude product.

Table 3.:

Example	R ¹⁰	Example 14 (mg/mmol)	R ¹⁰ COOH (mmol)	PS-CDI (mg/mmol)	HOBt (mmol)	DCM (mL) in a) For DCM/DMF mixture b) For dissolving Example 14
16		400 mg/ 0.50 ^a mmol	Methoxyacetic acid 0.52 mmol	518 mg/ 0.65 mmol	0.35	a) 2 mL b) 2 mL
17		400 mg/ 0.52 ^b mmol	4-(Methyloxy)-4-oxobutanoic acid 0.52 mmol	538 mg/ 0.67 mmol	0.36	a) 5 mL b) 3 mL
18		400 mg/ 0.52 ^b mmol	N,N-Dimethylglycine 0.52 mmol	538 mg/ 0.67 mmol	0.36	a) 5 mL b) 3 mL

a = molar quantity was calculated based on 92.5% purity of starting Example 14

b = molar quantity was calculated based on 96% purity of starting Example 14

5 Example 16

(E)-4'-O-Acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(methoxy)acetyl-9a-methyl-9a-aza-9a-homoerythromycin A

Crude product (397.8 mg) obtained according the above general procedure was further purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/1.5) to afford **title product** as two fractions: fraction A (92.2 mg, purity: 93 %) and fraction B (186.7 mg, purity: 80 %). Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 1 : 1. Fraction A was characterized as follows:

MS (ES⁺, *m/z*): 815.72 [M]⁺

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 8.93, 8.96, 9.56, 10.00, 13.17, 13.95, 17.88, 17.97, 18.19, 18.26, 20.93, 21.07, 21.48, 21.57, 21.64, 24.63, 25.87, 26.67, 27.33, 29.02, 34.65, 35.61, 36.57, 38.13, 38.24, 41.22, 43.01, 43.13, 43.14, 43.25, 49.30, 49.33, 57.65, 57.72, 58.53, 58.54, 62.93, 64.75, 64.86, 67.07, 67.15, 69.61, 69.83, 71.05, 71.54, 72.89, 73.44, 77.50, 77.62, 78.33, 78.40, 81.41, 83.68, 95.31, 102.09, 130.39, 130.44, 169.39, 170.54, 170.68, 174.85, 174.91.

Example 17**(E)-4''-O-Acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(4-methoxy-4-oxobutanoyl)-9a-methyl-9a-aza-9a-homoerythromycin A**

Crude product (646 mg) obtained according the above general procedure was further purified by precipitation using DCM/n-hexane to afford title **title product** (300.4 mg, purity: 91 %), which was characterized as follows:

Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 1 : 1.

MS (ES⁺, *m/z*): 857.50 [M]⁺

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 8.93, 8.97, 9.92, 10.01, 13.16, 13.96, 17.90, 17.99, 18.18, 18.25, 20.94, 20.99, 21.08, 21.50, 21.57, 21.64, 24.63, 25.72, 26.79, 27.31, 28.16, 28.70, 29.12, 29.41, 34.67, 34.82, 35.82, 36.50, 38.24, 41.20, 42.98, 43.12, 43.24, 49.28, 49.33, 51.58, 54.50, 57.73, 57.98, 62.89, 64.86, 67.13, 69.89, 69.99, 72.88, 72.94, 73.47, 77.51, 77.67, 78.40, 83.38, 83.59, 95.35, 102.15, 130.48, 131.00, 170.60, 170.69, 171.23, 171.46, 173.44, 174.85, 174.91.

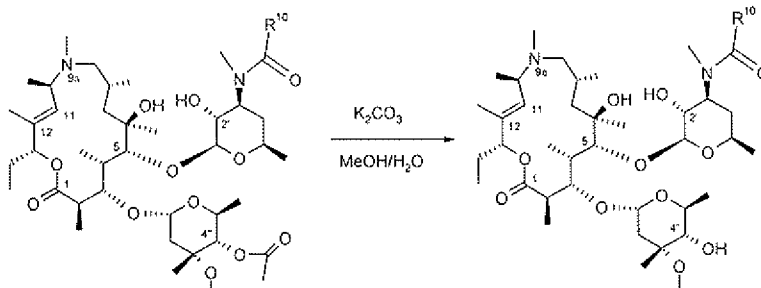
Evaporation of mother liquor gave additional amount of title product (131.9 mg, purity 75%).

Example 18**(E)-4''-O-Acetyl-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(N,N-dimethylglycyl)-9a-methyl-9a-aza-9a-homoerythromycin A**

Crude product (611.9 mg) obtained according the above general procedure was further purified by column chromatography (using solvent system: EtOAc/n-hexane/DEA = 1/1/0.1) to afford **title product** (338.8 mg, purity: 97 %); MS (ES⁺, *m/z*): 828.56 [M]⁺.

Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 2 : 1.

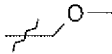
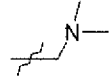
¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm : 8.93, 8.96, 9.91, 9.95, 13.17, 13.98, 17.85, 17.96, 18.20, 18.30, 20.81, 20.84, 20.96, 21.08, 21.47, 21.59, 21.64, 24.63, 25.78, 26.79, 27.29, 27.34, 29.00, 34.58, 34.83, 35.68, 36.78, 38.11, 38.26, 41.43, 43.12, 43.27, 45.31, 45.48, 49.30, 49.33, 53.00, 57.62, 57.72, 58.45, 62.71, 62.88, 62.98, 63.13, 64.70, 64.87, 67.09, 67.15, 69.76, 69.89, 72.86, 72.89, 73.44, 73.47, 77.53, 77.70, 78.30, 78.41, 83.35, 83.80, 95.25, 95.35, 102.20, 102.26, 130.44, 130.58, 169.85, 170.26, 170.44, 170.68, 174.86, 174.92.

EXAMPLES 19 AND 20

General procedure for Examples 19 and 20:

- 4"-O-Acetyl-compound was dissolved in methanol (15 mL), then K₂CO₃ (10 equivalents) dissolved in water (2 mL) was added. The mixture was stirred at room temperature for 24 hours and evaporated to dryness. The residue was partitioned between DCM (60 mL) and water (60 mL), and purified by acid-base extraction at pH 1.5 and 8. The crude product isolated from the organic layer at pH 8 was dried over anhydrous K₂CO₃, filtrated, evaporated and purified either by precipitation or by column chromatography to give desired product.

10 **Table 4.:**

Example	R ¹⁰	Starting 4"-O-acetyl compound	Amount of starting compound (mg/mmol)	K ₂ CO ₃ (mg/mmol)	Reaction time (hours)
19		Example 16	220 mg/ 0.23 ^a mmol	313 mg/ 2.27 mmol	24
20		Example 18	285 mg/ 0.33 ^b mmol	46.1 mg/ 0.33 mmol	24

a = molar quantity was calculated based on 84% purity of starting 4"-O-acetyl compound

b = molar quantity was calculated based on 97% purity of starting 4"-O-acetyl compound

Example 19

- 15 **(E)-3'-N-Demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(methoxy)acetyl-9a-methyl-9a-aza-9a-homoerythromycin A**

- Crude product (108.5 mg) obtained according the above general procedure was isolated at pH 8 and further purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/0.5), followed by reverse phase preparative HPLC (using mixture of eluents 40 % 10mM NH₄HCO₃/pH 10 and 60 % CH₃CN) to afford **title product** (39.8 mg, purity: 98 %); MS (ES⁺, *m/z*): 773.50 [M]⁺.

Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 1 : 1.

- 25 ¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 9.06, 9.99, 12.97, 14.26, 18.00, 18.62, 21.31, 21.35, 21.38, 21.43, 21.65, 24.59, 25.87, 26.60, 27.22, 28.10, 35.10, 35.24, 35.61, 37.88, 41.00, 43.02, 43.46, 49.15, 54.95, 57.34, 57.64, 58.50, 58.62, 64.76, 64.86, 65.34, 65.42, 67.11, 67.23, 69.72, 69.88, 70.96, 71.10, 73.19, 73.60, 77.68, 77.73, 78.06, 83.00, 95.61, 102.17, 102.31, 130.40, 130.41, 169.27, 169.46, 174.93.

- 30 **Example 20**

(E)-3'-N-Demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-N-(N,N-dimethylglycyl)-9a-methyl-9a-aza-9a-homoerythromycin A

Crude product (271.8 mg) obtained according the above general procedure was isolated at pH 8 and further purified by column chromatography (using solvent system: EtOAc/n-

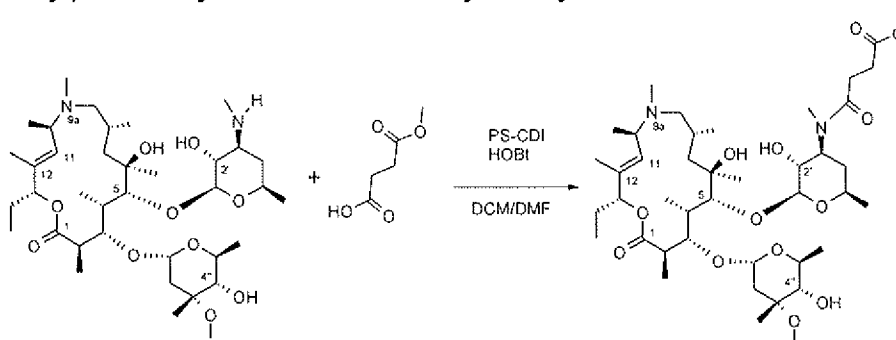
hexane/DEA = 1/1/0.1), followed by precipitation from DCM and n-hexane to afford **title product** (200.8 mg, purity: 99 %), MS (ES⁺, *m/z*): 786.59 [M]⁺.

Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 2 : 1.

- 5 ¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 9.06, 9.96, 10.01, 13.00, 14.26, 17.91, 18.03, 18.64, 21.22, 21.35, 21.43, 21.70, 24.60, 25.93, 26.06, 26.77, 27.22, 29.00, 35.07, 35.23, 35.40, 36.90, 37.87, 37.93, 41.17, 43.03, 43.51, 45.37, 45.48, 49.14, 49.28, 54.10, 57.61, 58.14, 62.48, 62.73, 64.80, 64.86, 65.33, 65.38, 67.15, 67.24, 69.85, 69.99, 73.16, 73.20, 73.57, 77.61, 77.72, 78.03, 83.52, 95.59, 102.34, 102.38, 130.55, 130.74, 169.75, 170.20,
10 174.90, 174.95.

Example 21

(*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-*N*-(4-methoxy-4-oxobutanoyl)-9a-methyl-9a-aza-9a-homoerythromycin A



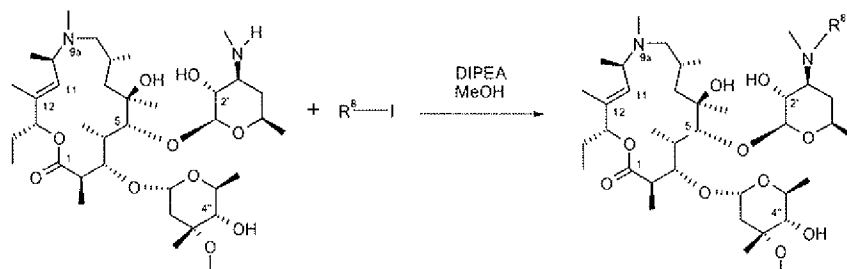
- 15 Dry PS-Carbodiimide resin (PS-CDI, 401 mg, 0.50 mmol, loading: 1.25 mmol/g, 1 equivalent) was added to a dry reaction vessel. The 4-(methoxy)butanoic acid (50.9 mg, 0.39 mmol) and HOBt (41.3 mg, 0.27 mmol, 0.7 equivalent) dissolved in a dry mixture of DCM (5 mL) and DMF (0.3 mL), were added to the resin. The mixture was
20 stirred at room temperature for 5 minutes upon which **(*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, Example 15** (300 mg, 0.385 mmol, calculated based on 90% purity of Example 15) dissolved in dry DCM (3 mL) was added. The reaction mixture was heated by microwave irradiation at 75 °C for 7 minutes.
- 25 HOBt was scavenged using PS-trisamine (328 mg, 1.35 mmol, loading: 4.11 mmol/g, 5 equivalent according to HOBt) for 3 hours at room temperature. The resin was removed from the reaction mixture by filtration and washed with DCM (2 x 5 mL). Evaporation of the solvent under reduced pressure afforded a crude product (508.8 mg), which was purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/0.5), to
30 afford **title product** (248.1 mg, purity: 94 %); MS (ES⁺, *m/z*): 815.58 [M]⁺.
- Due to restrained rotation around amide bond, there are two rotamers present in ratio **A** : **B** = 1.2 : 1.

¹³C NMR (150 MHz, DMSO-*d*₆) δ ppm: 8.58, 9.50, 9.63, 12.50, 12.55, 13.74, 17.43, 17.56, 18.16, 18.20, 20.88, 20.96, 21.19, 24.13, 25.37, 26.30, 26.77, 27.71, 28.29, 28.50, 28.72,

28.98, 34.61, 34.77, 35.35, 36.09, 37.45, 40.72, 42.56, 42.98, 48.62, 48.72, 51.09, 54.00, 57.15, 57.18, 57.37, 64.41, 64.50, 64.88, 64.96, 66.68, 66.77, 69.51, 69.58, 72.72, 73.06, 73.11, 77.26, 77.41, 77.53, 83.02, 83.33, 95.11, 95.25, 101.71, 101.83, 130.03, 130.07, 130.32, 130.40, 170.85, 170.88, 172.96, 174.45.

5

EXAMPLES 22-23



General procedure for Examples 22-23:

10 To a solution of (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, Example 15 in MeOH (10 mL), DIPEA and corresponding R⁸-iodo reagent were added and the reaction mixture was stirred at the elevated temperature for 20 to 40 hours. Evaporation of the solvent under reduced pressure afforded corresponding compound of examples 22 to 23 as a crude product.

15

Table 5.:

Example	R ⁸	Example 15 (mg/mmol)	R ⁸ -I (mmol)	DIPEA (mL/mmol)	temperature	Reaction time
22		300mg/ 0.39 ^a mmol	2-iodoethanol (2.36 mmol)	0.69 mL/ 3.94 mmol	reflux	20 hours
23		300mg/ 0.39 ^a mmol	3-iodopropanol (2.36 mmol)	0.69 mL/ 3.94 mmol	reflux	40 hours

a = molar quantity was calculated based on 92% purity of starting Example 15

Example 22

20 (*E*)-3'-*N*-Demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-(2-hydroxyethyl)-9a-aza-9a-homoerythromycin A

Crude product (858.3 mg) obtained according the above general procedure was purified by column chromatography (using solvent system: DCM/MeOH/NH₄OH = 90/9/1.5) to afford **title product** as two fractions: fraction A (133.5 mg, purity: 98 %) and fraction B (163.4 mg, purity: 94 %). Fraction A was characterized as follows:

25

MS (ES⁺, *m/z*): 745.00 [M]⁺

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 9.09, 9.93, 12.89, 14.29, 17.80, 18.57, 21.35,

21.64, 21.71, 24.58, 25.95, 27.20, 30.96, 35.17, 37.20, 37.78, 41.13, 43.05, 43.52, 49.12, 56.07, 57.60, 59.13, 64.90, 64.95, 65.34, 67.78, 70.84, 73.17, 73.57, 77.73, 78.17, 78.17, 83.64, 95.80, 102.36, 130.52, 131.00, 174.88.

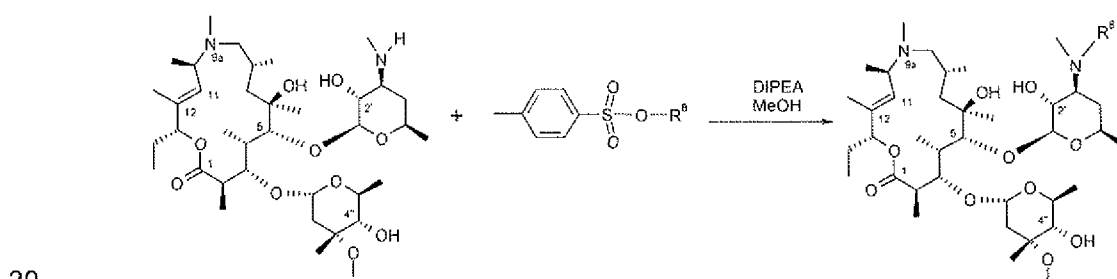
5 Example 23

(*E*)-3'-*N*-Demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-(3-hydroxypropyl)-9a-aza-9a-homoerythromycin A

Crude product (909 mg) obtained according the above general procedure was purified by column chromatography (first using solvent system: DCM/MeOH/NH₄OH = 90/9/1.5, then using solvent system: DCM/MeOH/NH₄OH = 90/9/0.5), followed by reverse phase preparative HPLC (using mixture of eluents 30 % 10mM NH₄HCO₃/pH 10 and 70 % CH₃CN) to afford **title product** (95.0 mg, purity:99.6 %); MS (ES⁺, *m/z*): 759.53 [M]⁺.

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 9.10, 9.96, 12.89, 14.32, 17.79, 18.59, 21.35, 21.65, 21.71, 24.58, 25.99, 27.20, 31.00, 31.14, 35.17, 37.08, 37.77, 41.09, 43.03, 43.54, 49.12, 50.96, 57.62, 59.62, 64.50, 64.94, 65.33, 67.76, 70.72, 73.17, 73.57, 77.72, 78.12, 78.13, 83.58, 95.79, 102.38, 130.05, 130.10, 174.89.

EXAMPLES 24-25

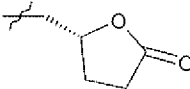
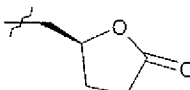


General procedure for Examples 24-25:

To the solution of (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, **Example 15** in MeOH (10 mL), DIPEA and corresponding R⁸-tosylate reagent were added and the reaction mixture was stirred at room or elevated temperature for 5 to 7 days. Evaporation of the solvent under reduced pressure afforded corresponding compound of examples **24** to **25** as a crude product.

Table 6.:

Example	R ⁸	Example 15 (mg/mmol)	R ⁸ -tosylate (mg/mmol)	DIPEA (mL/mmol)	temperature	Reaction time
---------	----------------	----------------------	------------------------------------	-----------------	-------------	---------------

24		150 mg/ 0.20 ^a mmol	(R)-(-)-dihydro- 5-(p- tolylsulfonyloxy- methyl)-2(3H)- furanone (106 mg/ 0.39 mmol)	0.21mL/ 1.18 mmol	room temper ature	7 days
25		150 mg/ 0.20 ^a mmol	(S)-(+)-dihydro- 5-(p- tolylsulfonyloxy- methyl)-2(3H)- furanone, (106 mg/ 0.39 mmol)	0.21mL/ 1.18 mmol	50 °C	5 days

a = molar quantity was calculated based on 98% purity of starting Example 15

Example 24

5 (E)-3'-N-Demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-N-{[(2R)-5-oxotetrahydro-2-furanyl]methyl}-9a-aza-9a-homoerythromycin A

Crude product (280 mg) obtained according the above general procedure was purified by column chromatography (first using solvent system: DCM/MeOH/NH₄OH = 90/9/0.5 and then using solvent system: (DCM/MeOH/NH₄OH = 90/9/1.5)/DCM = 7/3) to afford **title product** (52.0 mg, purity: 90 %); MS (ES⁺, *m/z*): 799.54 [M]⁺.

¹³C NMR (125 MHz, DMSO-*d*₆) δ ppm: 9.08, 10.01, 12.92, 14.26, 17.85, 18.56, 21.36, 21.65, 21.66, 24.58, 25.71, 25.95, 27.21, 28.26, 32.75, 35.16, 37.81, 38.24, 41.19, 43.09, 43.54, 49.13, 57.60, 58.40, 64.93, 65.35, 65.41, 67.63, 71.00, 73.15, 73.58, 77.73, 78.11, 78.12, 80.02, 83.64, 95.77, 102.43, 130.53, 130.97, 174.92, 177.65.

15 Example 25

20 (E)-3'-N-Demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-N-{[(2S)-5-oxotetrahydro-2-furanyl]methyl}-9a-aza-9a-homoerythromycin A

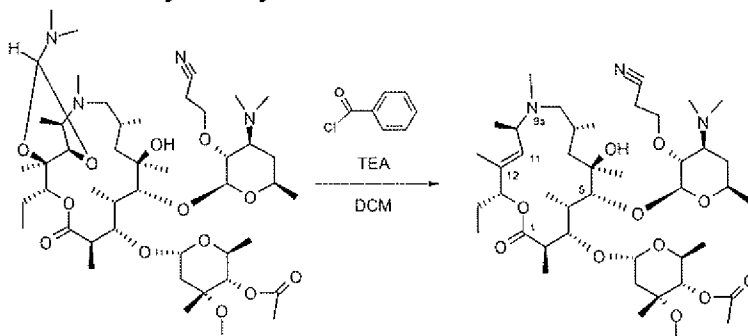
Crude product (230 mg) obtained according the above general procedure was purified by column chromatography (first using solvent system: (EtOAc/n-hexane/DEA = 1/1/0.2)/n-hexane = 7/3, and then using solvent system: DCM/MeOH/NH₄OH = 90/9/1.5), followed by reverse phase preparative HPLC (using mixture of eluents 50 % 10mM NH₄HCO₃/pH 10 and 50 % CH₃CN) to afford **title product** (27.2 mg, purity:90 %); MS (ES⁺, *m/z*): 799.50 [M]⁺.

^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ ppm: 8.65, 9.52, 12.44, 13.89, 17.34, 18.11, 20.90, 21.19, 21.19, 24.00, 25.00, 25.04, 26.00, 27.96, 33.80, 35.00, 37.24, 37.74, 40.65, 42.00, 43.00, 48.69, 57.17, 57.80, 64.43, 64.85, 64.85, 67.23, 70.63, 72.69, 73.14, 77.27, 77.71, 77.71, 78.92, 83.19, 95.35, 101.91, 130.54, 130.98, 174.48, 177.23.

5

Example 26

(E)-4''-O-Acetyl-2'-O-(2-cyanoethyl)-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A

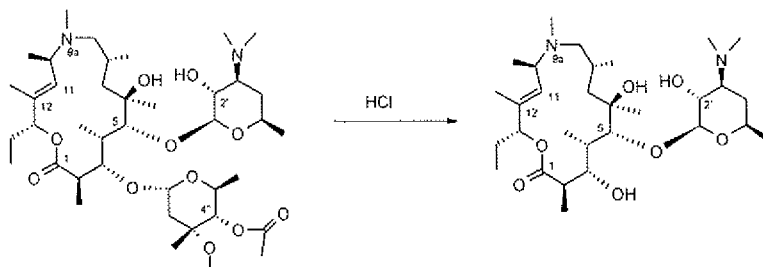


- 10 A solution of TEA (4.26 mL, 30.6 mmol) and benzoyl chloride (3.23 mL, 27.8 mmol) in DCM (120 mL) was stirred for 10 minutes. Then solution of **2'-O-(2-cyanoethyl-4''-O-acetyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A 11,12-(N,N-dimethylformamide) acetal** (5.0 g, 5.56 mmol, may be prepared by the procedure as described in WO2009/016142, Intermediate 1, Procedure B, Step 4, compound 11b) in
- 15 DCM (80 mL) was added dropwise over 2 hours and stirring continued for 4 hours. Reaction mixture was washed with saturated aqueous NaHCO_3 solution (2 x 800 mL), dried over anhydrous Na_2SO_4 , filtered and evaporated to afford crude oily title product (8.4 g). Crude product was dissolved in DCM (100 mL), water (100 mL) was added and pH adjusted to 3 (using 6 M HCl). The organic layer was discharged and to the aqueous one
- 20 DCM (100 mL) was added and pH adjusted to 9.0 (using 20% NaOH). Organic layer at pH 9.0 was separated, dried over anhydrous Na_2SO_4 , filtered and evaporated to afford crude product (1.7 g), which was purified by column chromatography (using solvent system: EtOAc/n-hexane/DEA = 10/10/2) to afford **title product** (0.71 g, purity: 94 %); MS (ES^+ , m/z): 810.82 [M] $^+$.
- 25 ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ ppm: 8.98, 9.54, 13.20, 13.65, 17.82, 18.32, 18.92, 20.99, 21.02, 21.48, 21.64, 24.68, 25.67, 27.35, 32.07, 34.71, 38.28, 41.32, 41.67, 43.22, 43.29, 49.31, 57.69, 62.85, 64.32, 64.73, 66.84, 67.55, 72.90, 73.40, 77.19, 77.41, 78.33, 80.10, 83.27, 95.22, 101.56, 119.47, 130.39, 130.65, 170.60, 175.03.

30

Example 27

(E)-3-O-Decladinosyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A



(E)-4''-O-Acetyl-11,12-didehydro-9-deoxy-11,12-dideoxy-9a-methyl-9a-aza-9a-

homoerythromycin A, Example 12 (300 mg, 0.340 mmol, calculated based on 81% purity of starting macrolide) was dissolved in hydrochloric acid (5 mL, 15.00 mmol, 3 M) and stirred at room temperature for 2 hours. Then water (20 mL) was added, and reaction mixture extracted with EtOAc (25 mL). EtOAc layer was discharged, to the water layer DCM (25 mL) was added, pH adjusted to 8.0 and water layer washed once more with DCM (25 mL). Combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to afford crude product (192.3 mg), which was purified by column chromatography (using solvent system EtOAc/*n*-hexane/DEA = 1/1/0.2) to afford **title product** (115.2 mg, purity: 99 %); MS (ES⁺, *m/z*): 557.33 [M]⁺.

¹³C NMR (150 MHz, DMSO-*d*₆) δ ppm: 8.61, 9.23, 11.49, 15.22, 15.50, 21.16, 21.77, 24.16, 26.58, 26.86, 30.56, 35.71, 36.13, 40.43, 41.16, 43.17, 57.16, 64.67, 64.92, 68.16, 70.42, 72.93, 76.42, 79.55, 87.02, 102.81, 130.69, 131.28, 173.76.

In Vitro Assay

The *in vitro* potency of the compounds of the invention was measured using the methodology described in the *in vitro* protocol for *Inhibition of IL-6 production in LPS-stimulated murine splenocytes in vitro*.

Tested compounds of Formula (I) exhibited 40% or more inhibition of interleukin-6 (IL-6) production in LPS-stimulated splenocytes treated by the compound at 50μM or/and 25μM concentration. Suitably compounds of Formula (I) exhibit 50% or more inhibition of interleukin-6 (IL-6) production in LPS-stimulated splenocytes treated by the compound at 50μM or/and 25μM concentration.

Activity data is an average calculated from 1, 2, 3, 4, 6 or 7 independent experiments in which each compound is tested in duplicate.

Compounds of examples 1-5, 7-15, 17-18, and 20-27 exhibited more than 40% inhibition of interleukin-6 (IL-6) production in LPS-stimulated splenocytes treated by the compound at 50μM or/and 25μM concentration.

For example compound of example 3 showed 45.5% and compound of example 15 showed 94.6% inhibition of interleukin-6 (IL-6) production in LPS-stimulated splenocytes treated by the compound at 50μM concentration. Compound of example 3 showed 59.5% and compound of example 15 showed 86.6% inhibition of interleukin-6 (IL-6) production in

LPS-stimulated splenocytes treated by the compound at 25 μ M concentration.

Compounds of examples 6, 16 and 19 exhibited less than 40% and more than 20% inhibition of interleukin-6 (IL-6) production in LPS-stimulated splenocytes treated by the
5 compound at 50 μ M concentration.

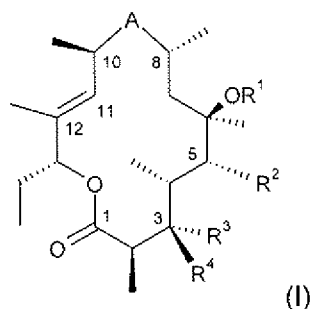
In Vivo Assay

The *in vivo* potency of representative compounds of the invention was measured using the methodology described in the *in vivo* protocol for *Lung neutrophilia induced by*
10 *bacterial lipopolysaccharide in mice*.

The compound of example 20 showed more than 50% inhibition of total cell number and more than 15% decrease in myeloperoxidase concentration in BALF of treated animals which received intraperitoneally (i.p.) a single dose of 100 mg/kg of test compound tested
15 in *Lung neutrophilia induced by bacterial lipopolysaccharide in mice*.

CLAIMS

1 A compound of Formula (I):

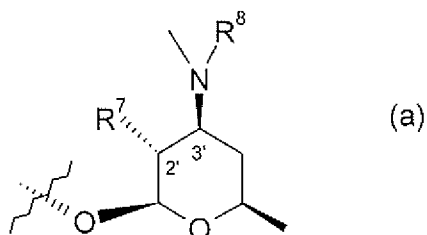


5

wherein,

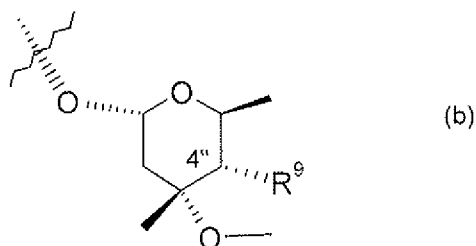
R^1 is hydrogen or CH_3 ;

10 R^2 is a β -D-desosaminyl group of Formula (a);



R^3 is:

15 i) an α -L-cladinosyl group of Formula (b)



and A is a bivalent radical $-C(O)-$, $-N(R^5)CH_2-$, $-CH_2N(R^5)-$, $-C(=NOR^6)-$, $-CH(OH)-$, $-NHC(O)-$ or $-C(O)NH-$, or

20 ii) hydroxyl and A is a bivalent radical $-N(R^5)CH_2-$, $-CH_2N(R^5)-$, $-NHC(O)-$ or $-C(O)NH-$;

R^4 is hydrogen;

25 R^5 is hydrogen or $-C_{1-4}alkyl$;

- R^6 is hydrogen or $-C_{1-4}$ alkyl, wherein $-C_{1-4}$ alkyl may be optionally interrupted by one or two oxygen atoms, and/or is unsubstituted or substituted by one or two substituents independently selected from $-C_{1-4}$ alkoxy or $-C_{3-7}$ cycloalkyl, with the proviso that when the $-C_{1-4}$ alkyl is interrupted by two oxygen atoms, the two oxygen atoms are not adjacent one another;

R^7 is hydroxyl, hydroxyl protecting group or $-O-(CH_2)_2CN$;

- R^8 is independently selected from:

- ai) hydrogen,
- bi) $-C_{1-6}$ alkyl, unsubstituted or substituted at the terminal carbon atom by a substituent selected from the group consisting of:
 - (aii) hydroxyl,
 - (bii) $-(5\text{-oxotetrahydro-2-furanyl})$,
 - (cii) $-C_{1-3}$ alkoxy, and
 - (dii) $-C(O)C_{1-3}$ alkyl, or
- ci) $-C(=O)-R^{10}$;

- R^9 is hydroxyl or hydroxyl protecting group;

R^{10} is independently selected from:

- (aiii) $-C_{1-4}$ alkyl, unsubstituted or substituted at the terminal carbon atom by a substituent selected from the group consisting of hydroxyl, $-C_{1-4}$ alkoxy, $-C(O)OC_{1-4}$ alkyl, $-N(R^5)(R^{11})$ and $-S-R^{12}$,
- (biii) a 5-6 membered heteroaromatic ring, unsubstituted or substituted by one or two substituents independently selected from the group consisting of halo, hydroxyl, $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-CF_3$, $-OCF_3$ and $-NH_2$,
- (ciii) phenyl, unsubstituted or substituted by one or two substituents independently selected from the group consisting of halo, hydroxyl, $-C_{1-3}$ alkyl, $-C_{1-3}$ alkoxy, $-CF_3$, $-OCF_3$ and $-NH_2$,
- (diii) a 4-6-membered heterocyclic ring, unsubstituted or substituted by one or two $-C_{1-3}$ alkyl, or
- (eiii) $-C_{3-7}$ cycloalkyl, unsubstituted or substituted by one or two substituents independently selected from the group consisting of hydroxy, $-C_{1-3}$ alkoxy and $-C(O)OC_{1-3}$ alkyl;

R^{11} is $-C_{1-4}$ alkyl;

R^{12} is a 5-6 membered heteroaromatic ring, unsubstituted or substituted by one or two substituents independently selected from the group consisting of halo, hydroxyl, $-C_{1-3}$ alkyl,

-C₁₋₃alkoxy, -CF₃, -OCF₃ and -NH₂;

or a salt thereof.

5 2. A compound or a salt thereof as claimed in claim 1, wherein A is a bivalent radical -N(R⁵)CH₂-, -CH₂N(R⁵)-, -NHC(O)- or -C(O)NH-.

3. A compound or a salt thereof as claimed in claim 1, wherein A is a bivalent radical -N(R⁵)CH₂-, or -NHC(O)-.

10

4. A compound or a salt thereof as claimed in any of claims 1 to 3, wherein R⁵ is methyl.

15 5. A compound or a salt thereof as claimed in any of claims 1 to 4, wherein R¹ is hydrogen.

6. A compound or a salt thereof as claimed in any of claims 1 to 4, wherein R¹ is methyl.

20 7. A compound or a salt thereof as claimed in any of claims 1 to 6, wherein R³ is α-L-cladinosyl group of Formula (b).

8. A compound or a salt thereof as claimed in any of claims 1 to 7, wherein R⁷ and R⁹ are hydroxyl.

25

9. A compound or a salt thereof as claimed in any of claims 1 to 7, wherein R⁷ and R⁹ are hydroxyl protecting group.

30 10. A compound or a salt thereof as claimed in any of claims 1 to 9, wherein R⁸ is -C₁₋₄alkyl.

11. A compound or a salt thereof as claimed in any of claims 1 to 9, wherein R⁸ is -C(=O)-R¹⁰.

35 12. A compound or a salt thereof as claimed in any of claims 1 to 9, wherein R⁸ is hydrogen.

13. A compound of Formula (I) as claimed in claim 1, selected from:

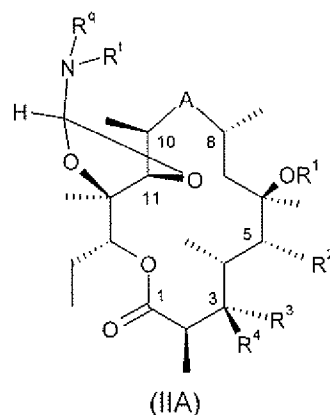
40 (E)-2',4"-O-diacetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A,
(E)-4"-O-acetyl-11,12-didehydro-11,12-dideoxy-6-O-methyl-9a-aza-9a-homoerythromycin A,

- (*E*)-11,12-didehydro-11,12-dideoxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-4''-*O*-acetyl-3'-*N*-demethyl-11,12-didehydro-11,12-dideoxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-11,12-dideoxy-6-*O*-methyl-9a-aza-9a-homoerythromycin A,
 5 (*E*)-4''-*O*-acetyl-3'-*N*-demethyl-11,12-didehydro-11,12-dideoxy-3'-*N*-(methoxy)acetyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-4''-*O*-acetyl-3'-*N*-demethyl-11,12-didehydro-11,12-dideoxy-6-*O*-methyl-3'-*N*-(4-pyridinylthio)acetyl-9a-aza-9a-homoerythromycin A,
 10 (*E*)-4''-*O*-acetyl-3'-*N*-demethyl-11,12-didehydro-11,12-dideoxy-6-*O*-methyl-3'-*N*-(2-pyrazinyl)carbonyl-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-11,12-dideoxy-3'-*N*-(methoxy)acetyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-11,12-dideoxy-6-*O*-methyl-3'-*N*-(4-pyridinylthio)acetyl-9a-aza-9a-homoerythromycin A,
 15 (*E*)-2',4''-*O*-diacetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-4''-*O*-acetyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 20 (*E*)-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-4''-*O*-acetyl-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A,
 25 (*E*)-4''-*O*-acetyl-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-*N*-(methoxy)acetyl-9a-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-4''-*O*-acetyl-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-*N*-(4-methoxy-4-oxobutanoyl)-9a-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-4''-*O*-acetyl-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-*N*-(*N,N*-dimethylglycyl)-9a-methyl-9a-aza-9a-homoerythromycin A,
 30 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-*N*-(methoxy)acetyl-9a-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-*N*-(*N,N*-dimethylglycyl)-9a-methyl-9a-aza-9a-homoerythromycin A,
 35 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-3'-*N*-(4-methoxy-4-oxobutanoyl)-9a-methyl-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-(2-hydroxyethyl)-9a-aza-9a-homoerythromycin A,
 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-(3-hydroxypropyl)-9a-aza-9a-homoerythromycin A,
 40 (*E*)-3'-*N*-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-*N*-{[(2*R*)-5-oxotetrahydro-2-furanyl]methyl}-9a-aza-9a-homoerythromycin A,

- (E)-3'-N-demethyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-3'-N-[(2S)-5-oxotetrahydro-2-furanyl]methyl}-9a-aza-9a-homoerythromycin A,
(E)-4''-O-acetyl-2'-O-(2-cyanoethyl)-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A, or
- 5 (E)-3-O-decladinosyl-11,12-didehydro-9-deoxo-11,12-dideoxy-9a-methyl-9a-aza-9a-homoerythromycin A;
or a salt thereof.
14. A compound of Formula (I) or a salt thereof as claimed in any of claims 1 to 13,
10 wherein the salt is a pharmaceutically acceptable salt.
15. A method for the treatment of chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, bronchitis, bronchiectasis, adult respiratory distress syndrome, severe or steroid-resistant asthma, emphysema, chronic
15 rhinosinusitis, rheumatoid arthritis, gouty arthritis, inflammatory bowel disease, glomerulonephritis, damage from ischemic reperfusion, atherosclerosis, dermatoses such as psoriasis and vasculitis, systemic lupus erythematosus, systemic inflammatory response syndrome, sepsis, ischemia-reperfusion injury, rosacea, periodontitis, gingival hyperplasia or prostatitis syndrome in a subject in need of such treatment comprising
20 administering to the subject a therapeutically effective amount of a compound of Formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof.
16. The method of claim 15, wherein disease is selected from chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans,
25 bronchitis, bronchiectasis, adult respiratory distress syndrome, severe or steroid-resistant asthma, emphysema or chronic rhinosinusitis.
17. A pharmaceutical composition comprising a) a compound of Formula (I) as claimed in any of claims 1 to 13, or a pharmaceutically acceptable salt thereof and b) one
30 or more pharmaceutically acceptable carriers.
18. A compound of Formula (I) as claimed in claim 1, for use in medical therapy.
19. Use of a compound of Formula (I) as claimed in claim 1 in the manufacture of a
35 medicament for the treatment of chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, bronchitis, bronchiectasis, adult respiratory distress syndrome, severe or steroid-resistant asthma, emphysema, chronic rhinosinusitis, rheumatoid arthritis, gouty arthritis, inflammatory bowel disease, glomerulonephritis damage from ischemic reperfusion, atherosclerosis, dermatoses such
40 as psoriasis and vasculitis, systemic lupus erythematosus, systemic inflammatory response syndrome, sepsis, ischemia-reperfusion injury, rosacea, periodontitis, gingival hyperplasia or prostatitis syndrome.

20. Use as claimed in claim 19, wherein the disease is selected from chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, bronchitis, bronchiectasis, adult respiratory distress syndrome, severe or steroid-resistant asthma, emphysema or chronic rhinosinusitis.

21. A compound of Formula (IIA)

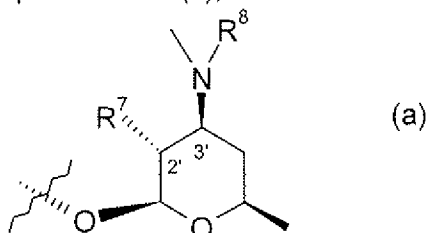


wherein,

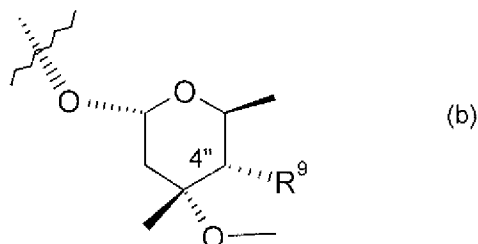
R^1 is

- a) CH_3 and A is a bivalent radical $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^5)\text{CH}_2-$, $-\text{CH}_2\text{N}(\text{R}^5)-$, $-\text{C}(=\text{NOR}^6)-$, $-\text{CH}(\text{OH})-$, $-\text{NHC}(\text{O})-$ or $-\text{C}(\text{O})\text{NH}-$; or
 b) hydrogen and A is a bivalent radical $-\text{C}(\text{O})-$, $-\text{C}(=\text{NOR}^6)-$, $-\text{CH}(\text{OH})-$, $-\text{NHC}(\text{O})-$ or $-\text{C}(\text{O})\text{NH}-$;

R^2 is a β -D-desosaminyl group of Formula (a),



R^3 is an α -L-cladinosyl group of Formula (b)



R⁴ is hydrogen;

R⁵ is hydrogen or -C₁₋₄alkyl;

- 5 R⁶ is hydrogen or -C₁₋₄alkyl, wherein -C₁₋₄alkyl may be optionally interrupted by one or two oxygen atoms, and/or is unsubstituted or substituted by one or two substituents independently selected from -C₁₋₄alkoxy or -C₃₋₇cycloalkyl, with the proviso that when the -C₁₋₄alkyl is interrupted by two oxygen atoms, the two oxygen atoms are not adjacent one another;

10

R⁷ is hydroxyl, hydroxyl protecting group or -O-(CH₂)₂CN;

R⁸ is CH₃;

- 15 R⁹ is hydroxyl or hydroxyl protecting group;

R^a and Rⁱ independently are -C₁₋₄alkyl or -C₁₋₄alkyl substituted by phenyl,

or a salt thereof.

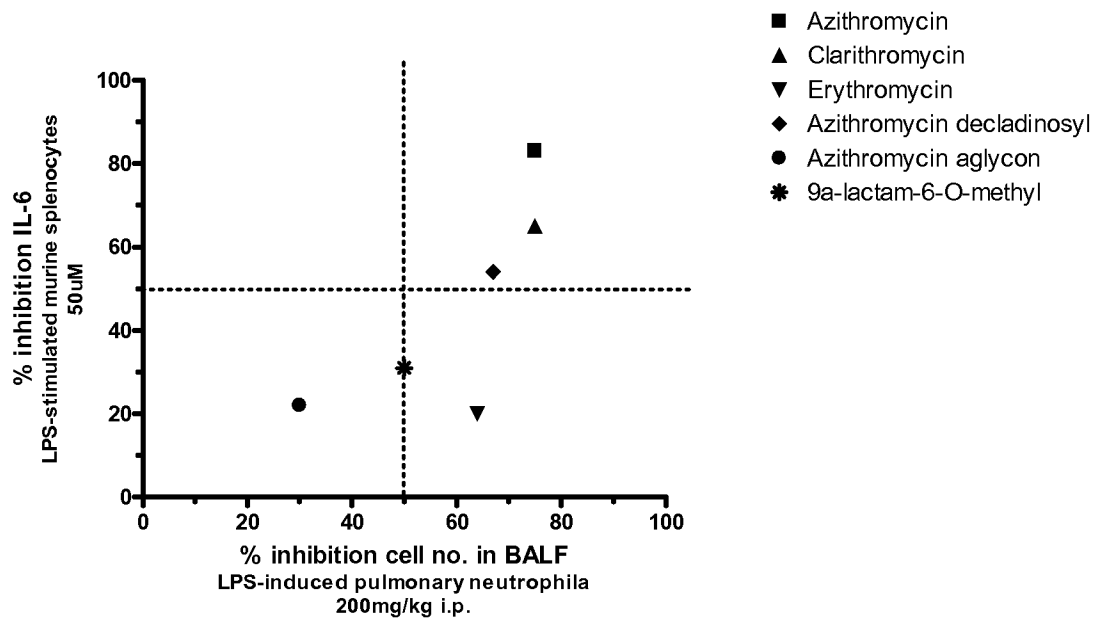
20

22. A combination comprising a) a compound of Formula (I) as claimed in any of claims 1 to 13, or a pharmaceutically acceptable salt thereof and b) one or more further therapeutically active agents.

25

Figure 1

Correlation of inhibition of IL-6 production *in vitro* and inhibition of cell infiltration into BALF *in vivo*.



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/056401

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07H17/08 A61K31/7048 A61P11/00
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)

C07H A61K A61P

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 practical, search terms used)

EPO-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	WO 2009/130189 A1 (GLAXOSMITHKLINE ZAGREB [HR]; BUKVIC-KRAJACIC MIRJANA [HR]; HUTINEC ANT) 29 October 2009 (2009-10-29) -----	1-22
A,P	WO 2010/086350 A1 (GLAXOSMITHKLINE ZAGREB [HR]; ALIHODZIC SULEJMAN [HR]; HUTINEC ANTUN [H]) 5 August 2010 (2010-08-05) -----	1-22
A,P	WO 2010/086349 A1 (GLAXOSMITHKLINE ZAGREB [HR]; GLAXO GROUP LTD [GB]; DAY CAROLINE JANE []) 5 August 2010 (2010-08-05) -----	1-22



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search

30 May 2011

Date of mailing of the international search report

08/06/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Klein, Didier

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/056401

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009130189 A1	29-10-2009	EP 2271656 A1 US 2011039795 A1	12-01-2011 17-02-2011

WO 2010086350 A1	05-08-2010	NONE	

WO 2010086349 A1	05-08-2010	AR 075340 A1 US 2010197623 A1 UY 32408 A	23-03-2011 05-08-2010 30-07-2010
