

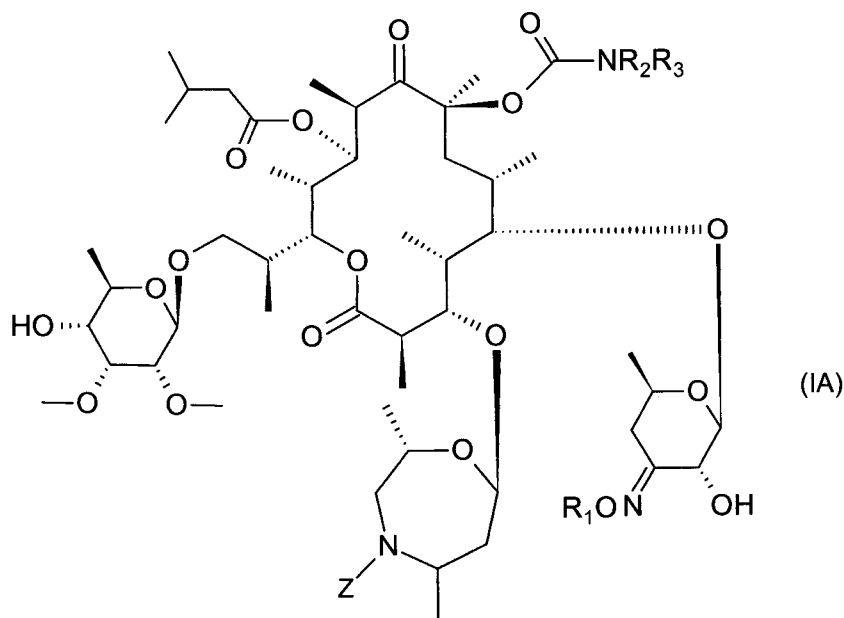
[19]	INTELLECTUAL PROPERTY PHILIPPINES		
[12]	INVENTION PUBLICATION		
[11]	Publication Number:	12015500527	Document Code: B1
[22]	Publication Date:	27/4/2015	
[21]	Application Number:	12015500527	Document Code: A
[22]	Date Filed:	11/3/2015	
[54]	Title:	MACROLIDE DERIVATIVES, PREPARATION AND THERAPEUTIC USE THEREOF	
[71]	Applicant(s):	SANOFI SA	
[72]	Inventor(s):	NICOLAS BAURIN YANNICK BENEDETTI EMMANUEL BOULEY JIDONG ZHANG	
[30]	Priority Data:	18/9/2012 FR20120058744	
[51]	International Class 8:	A61K 31/7048 20060101AFI20170615BHPH; A61P 31/04 20060101ALI20170615BHPH; A61P 31/06 20060101ALI20170615BHPH; A61P 31/08 20060101ALI20170615BHPH; C07H 15/26 20060101ALI20170615BHPH;	
[57]	Abstract:	The patent application relates to compounds of formula (I) below: formula (I) to a process for preparing them and to the therapeutic use thereof.	

- alkenyl represents a linear or branched hydrocarbon-based aliphatic group comprising at least one unsaturation in the form of a double bond, and comprising from 2 to 6 carbon atoms. Examples that may be mentioned include the vinyl and allyl groups.
- 5 • alkynyl represents a linear or branched hydrocarbon-based aliphatic group comprising at least one unsaturation in the form of a triple bond, and comprising from 2 to 6 carbon atoms. Examples that may be mentioned include the ethynyl and 2-propynyl groups.
- 10 • cycloalkyl represents a saturated cyclic aliphatic group comprising from 3 to 7 carbon atoms. Examples that may be mentioned include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups.
- halogen represents a fluorine, chlorine, bromine or iodine atom.
- fluoroalkyl represents an alkyl group comprising from 1 to 4 carbon atoms, in which one or more hydrogen atoms are replaced with a fluorine atom. Examples of fluoroalkyl groups that may be mentioned include trifluoromethyl, difluoromethyl, 3,3,3-15 trifluoropropyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, 2,2,3,3-tetrafluoropropyl, 1,1-difluoroethyl and 3,3,3-trifluoro-2-(trifluoromethyl)propyl.
- heterocycloalkyl represents a saturated or partially saturated, monocyclic or polycyclic, optionally substituted 3- to 9-membered ring including one or more heteroatoms such as nitrogen, oxygen or sulfur atoms. The sulfur atoms may be in the form of sulfoxide or sulfone. By way of example, a heterocycloalkyl may be a pyrrolidine, a morpholine, a piperazine, a diazetidine, a dihydropyrrolidine, a piperidine, an azepane, an imidazolidine, a thiomorpholine, a tetrahydropyran, a tetrahydrothiophene, a tetrahydrothiopyran, a diazepane or an azabicyclooctane, a tropane, a 3,6-20 diazabicyclo[3.1.0]hexane, a tetrahydrofuran, a 3,7-diazabicyclo[3.3.1]nonane or a tetrahydrothiophene 1,1-dioxide.
- 25 • aryl represents a monocyclic or polycyclic, optionally substituted aromatic system comprising from 6 to 14 carbon atoms. According to one embodiment of the invention, the aryl group comprises 6 to 10 carbon atoms. When the system is polycyclic, at least one of the rings is aromatic. Examples of aryl groups that may be mentioned include phenyl, naphthyl, indanyl, tetrahydronaphthyl, anthracenyl and azulenyl.
- 30 • heteroaryl represents a monocyclic or polycyclic, optionally substituted 5- to 14-membered aromatic system. According to one embodiment of the invention, the heteroaryl is 5- to 10-membered and comprises one or more heteroatoms such as nitrogen, oxygen or sulfur atoms. When the system is polycyclic, at least one of the35 rings is aromatic. Examples of monocyclic heteroaryls that may be mentioned include

thiazole, thiadiazole, thiophene, imidazole, triazole, tetrazole, pyridine, furan, oxazole, isoxazole, oxadiazole, pyrrole, pyrazole, pyrimidine, pyridazine and pyrazine. Examples of polycyclic heteroaryls that may be mentioned include indole, benzofuran, benzimidazole, benzothiophene, benzotriazole, benzothiazole, benzoxazole, quinoline, isoquinoline, indazole, quinazoline, phthalazine, quinoxaline, naphthyridine, 2,3-dihydro-1H-indole, 2,3-dihydrobenzofuran, tetrahydroquinoline, tetrahydroisoquinoline, tetrahydroisoquinazoline, furo[3,2-c]pyridine, 1H-pyrrolo[2,3-b]pyridine or tetrahydroquinazoline.

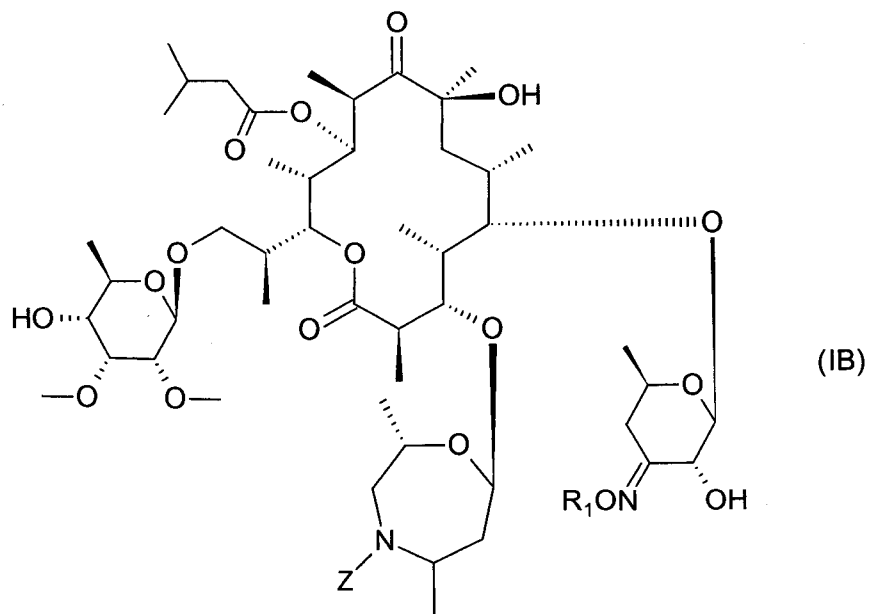
- alkoxy represents a group O-alkyl containing a saturated, linear or branched aliphatic chain comprising 1 to 4 carbon atoms. Examples of alkoxy groups that may be mentioned include methoxy and ethoxy.

According to the present invention, distinguished compounds are those of formula (I) in which Y represents a group $-(C=O)-NR_2R_3$, of formula:



in which R_1 , R_2 , R_3 and Z are as defined for the compounds of formula (I);
in the form of bases or of acid-addition salts.

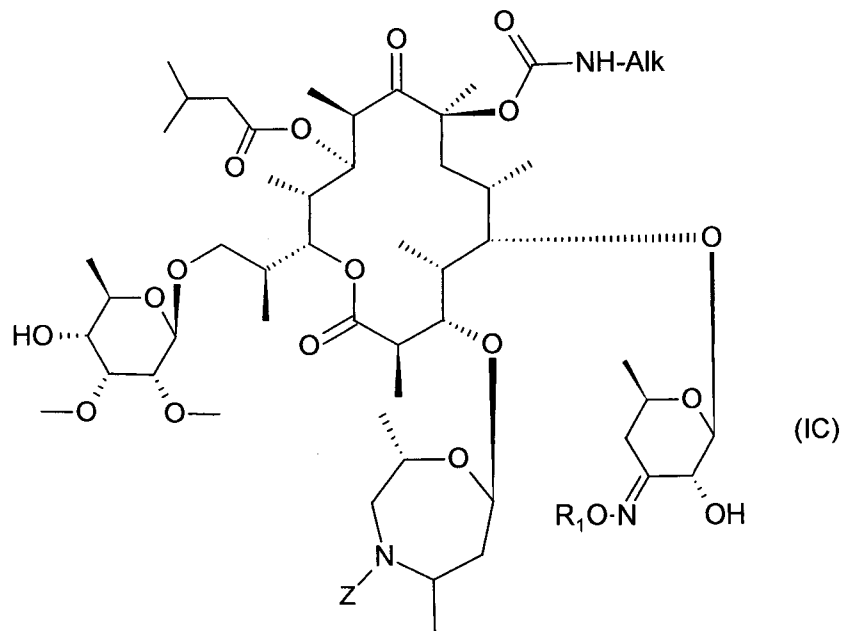
According to the present invention, distinguished compounds are also those of formula (I) in which Y represents a hydrogen atom, of formula:



in which R_1 and Z are as defined for a compound of formula (I);

in the form of bases or of acid-addition salts.

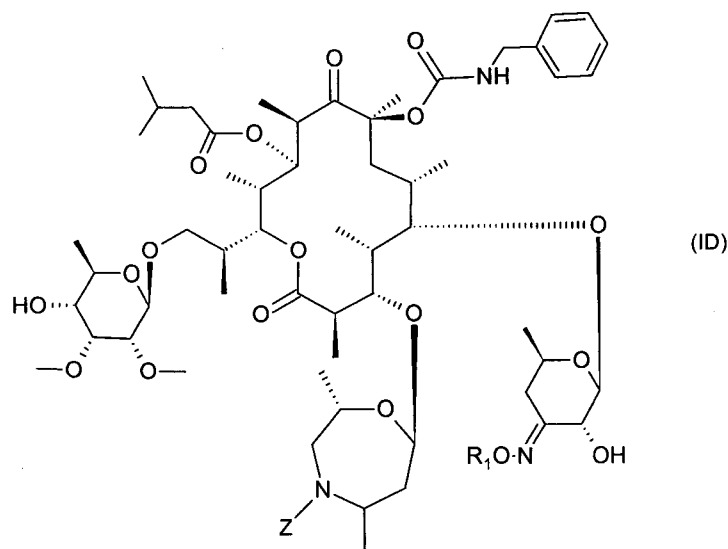
- 5 According to a first variant of formula (IA), R_2 represents a hydrogen atom and R_3 represents a linear C_{1-6} -alkyl (Alk), which is unsubstituted or substituted with a group as defined for the compounds of formula (I), the compounds then having the formula (IC) below:



- 10 in which R_1 and Z are as defined for the compounds of formula (I);

in the form of bases or of acid-addition salts.

Within the compounds of formula (IC), distinguished compounds are those of formula (ID) below in which Alk represents a methyl substituted with a phenyl group:

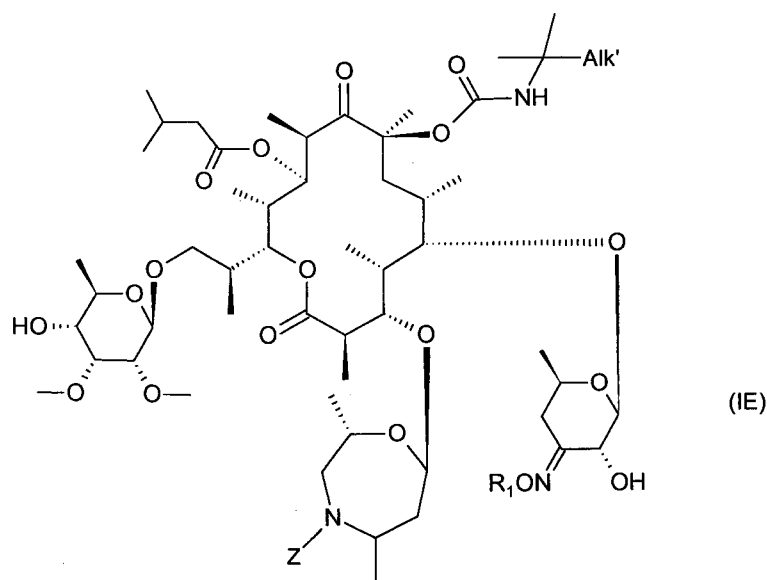


and R₁ and Z are as defined for a compound of formula (I);

5 in the form of bases or of acid-addition salts.

According to a second variant of formula (IA), distinguished compounds are those of formula (IE) in which R₂ represents a hydrogen atom and R₃ represents a branched C₁₋₆-alkyl (-C(CH₃)₂-Alk'), which is unsubstituted or substituted with a group as defined for the compounds of formula (I):

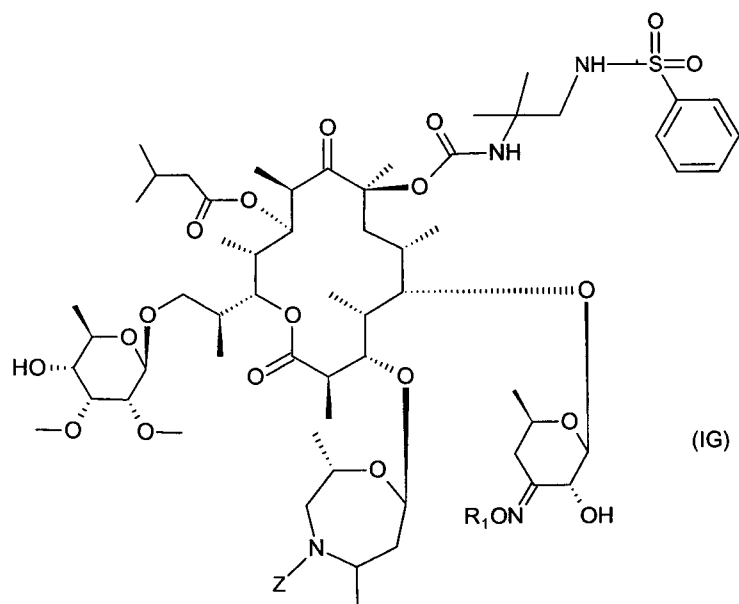
10



and R₁ and Z are as defined for the compounds of formula (I);

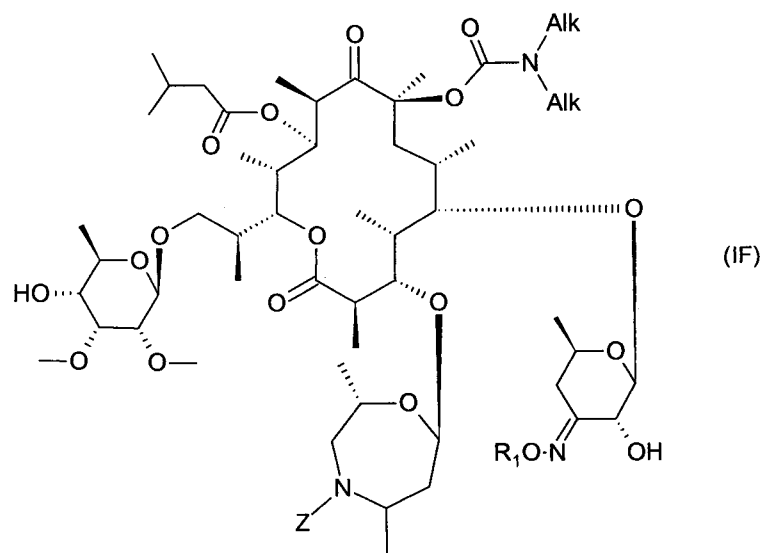
in the form of bases or of acid-addition salts.

Within the compounds of formula (IE), distinguished compounds are those of formula (IG) below in which Alk' represents a [(phenylsulfonyl)amino]methyl group:



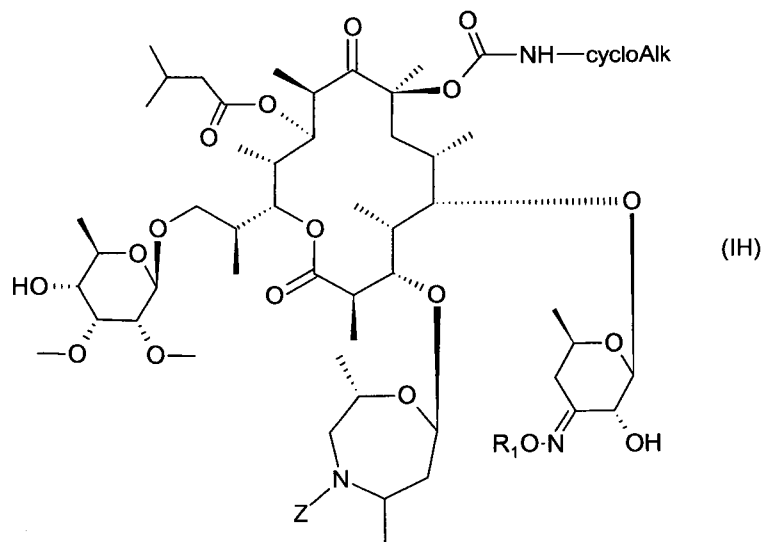
- 5 and R_1 and Z are as defined for the compounds of formula (I);
in the form of bases or of acid-addition salts.

According to a third variant of formula (IA), R_2 and R_3 represent an unsubstituted group $-C_{1-6}$ -alkyl (Alk), the compounds then having the formula (IF) below:



in which R_1 and Z are as defined for a compound of formula (I);
in the form of bases or of acid-addition salts.

According to a fourth variant of formula (IA), R_2 represents a hydrogen atom and R_3 represents an unsubstituted group $-C_{3-7}$ -cycloalkyl (cycloAlk), the compounds then having the formula (IH) below:

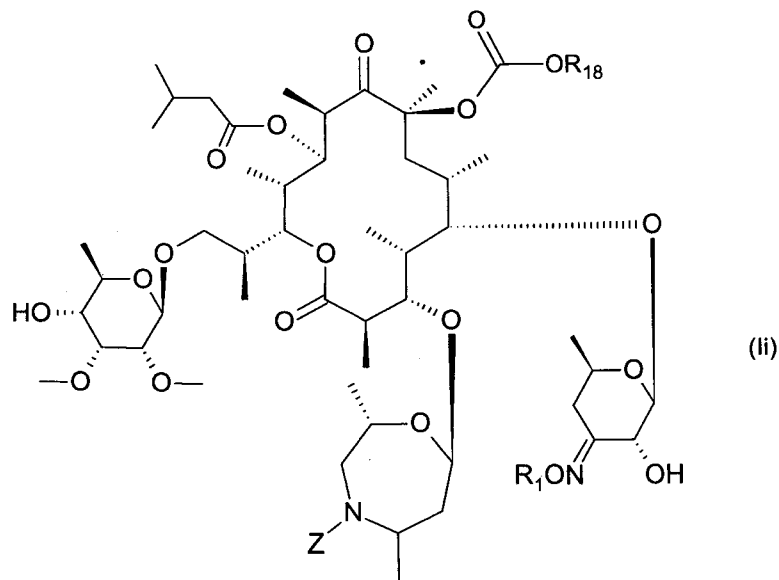


5

in which R_1 and Z are as defined for a compound of formula (I);
in the form of bases or of acid-addition salts.

10

According to the present invention, distinguished compounds are also those of formula (I) in which Y represents a group $-(C=O)-OR_{18}$, of formula:



in which R_1 , R_{18} and Z are as defined for a compound of formula (I);
in the form of bases or of acid-addition salts.

According to the present invention, distinguished compounds are those of formula (I) in which:

- Y represents a hydrogen atom, a group $-(C=O)-NR_2R_3$ or a group $-(C=O)-OMe$;
- Z represents:

- 5
 - a hydrogen atom,
 - a group $-C_{1-6}$ -alkyl, which is unsubstituted or substituted with one or more groups R_4 ,
 - a cyclopropyl group, a cyclobutyl group, a 3-(benzoylamino)cyclobutyl group, a 3-[(pyrazin-2-ylcarbonyl)amino]cyclobutyl group, a 3-[(methylsulfonyl)amino]cyclobutyl group, a 3-[(phenylsulfonyl)amino]cyclobutyl group, a cyclopentyl group, a cyclohexyl group,
 - 10
 - a tetrahydro-2H-pyranyl group,
 - a group $-NH-(C=O)-R_5$;
- R_1 represents a hydrogen atom, an ethyl group, a 2,2,2-trifluoroethyl group or a methyl group, which is unsubstituted or substituted with a 1,2,3-triazole group substituted with a 3-(3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-ylmethyl group;
- R_2 represents a hydrogen atom or a methyl group;
- R_3 represents:
 - 20
 - a cyclohexyl group, a 1-[(phenylsulfonyl)amino]methyl)cyclohexyl group or a 1-[(phenylsulfonyl)amino]methyl)cyclopentyl group,
 - a 5,6,7,8-tetrahydroquinolin-5-yl group,
 - or a linear or branched group C_{1-4} -alkyl, which is unsubstituted or substituted with a group chosen from:
 - 25
 - $-NH-R_6$,
 - $-NH-SO_2-R_7$,
 - $-NH-(C=O)-R_8$,
 - a 1-morpholin-4-ylcyclopentyl group,
 - a tetrahydro-2H-pyranyl group, a tetrahydrofuranlyl group or a morpholin-4-yl group,
 - 30
 - a phenyl group, which is unsubstituted or substituted with one or more groups chosen independently from a chlorine atom and a group $-CF_3$,

- a 1H-pyrrolo[2,3-b]pyridinyl group, a 4-methyl-5,6,7,8-tetrahydroquinazolin-2-yl group, a 6-methoxy-1H-benzimidazol-2-yl group, a pyridinyl group, which is unsubstituted or substituted with a group -CF₃ or with a morpholin-4-yl group,
- 5 • or alternatively with one or more methoxy groups;
- or alternatively R₂ and R₃, together with the nitrogen atom to which they are attached, constitute a -C₃₋₆-heterocycloalkyl group chosen from: azetidine, morpholine, 4-[5-(trifluoromethyl)pyridin-2-yl]piperazine;
- R₄ independently represents a group chosen from:
- 10 • a hydroxyl group,
- a deuterium,
- a fluorine atom,
- a cyclopropyl group,
- a phenyl group, which is unsubstituted or substituted with one or more groups
- 15 chosen independently from a fluorine atom, a methoxy group, a -CH₂OH group and a -CHO group,
- a pyridyl group,
- a morpholinyl group, a tetrahydro-2H-pyranyl group,
- a methoxy group,
- 20 • a group -(C=O)-NH-R₁₀,
- a group -NH-R₁₁,
- a group -NH-(C=O)-R₁₂,
- or a group -NH(SO₂)-R₁₃;
- R₅ represents a pyridyl group;
- 25 - R₆ represents a quinolyl group, the said quinolyl group being unsubstituted or substituted with a chlorine atom;
- R₇ represents a -CF₃ group, a phenyl, pyridyl, pyrazolyl, 1H-pyrrolo[2,3-b]pyridyl or indolyl group, the said phenyl, pyridyl, pyrazolyl, 1H-pyrrolo[2,3-b]pyridyl or indolyl groups being unsubstituted or substituted with one or more groups R₁;
- 30 - R₈ represents a pyrazinyl group, the said pyrazinyl group being unsubstituted or substituted with one or more groups R₂;

- R₁₀ represents a 1,8-naphthyridinyl group substituted with a methyl group;
- R₁₁ represents a tetrahydrothiophene-1,1-dioxide, quinolyl, pyridyl or benzyl group, the said quinolyl, pyridyl or benzyl groups being unsubstituted or substituted with a chlorine atom, a hydroxyl group, a nitro group or a methyl group;
- 5 - R₁₂ represents:
 - a tert-butoxy group,
 - a group -C₁₋₄-alkyl, which is unsubstituted or substituted with a group chosen from a group -NR₁₄R₁₅, pyridyl or pyrazolyl, the said pyridyl or pyrazolyl groups being unsubstituted or substituted with a methyl group,
 - 10 • a pyrazinyl or pyridyl, which is unsubstituted or substituted with one or more groups chosen from a hydroxyl group and a methyl group;
- R₁₃ represents:
 - a group -CF₃,
 - a phenyl group, which is unsubstituted or substituted with a nitro group,
 - 15 • or a pyridyl group, which is unsubstituted or substituted with a group -NR₁₆R₁₇;
- R₁₄, R₁₅, R₁₆ and R₁₇ each independently represent:
 - a hydrogen atom,
 - a methyl group or an isopropyl group;
- R_{1'} represents:
 - 20 • a fluorine atom, a chlorine atom,
 - a methoxy group,
 - a group -CF₃,
 - a group -OCF₃,
 - a nitro group,
 - 25 • a group -NH₂,
 - a group -NHCH₃;
- R_{2'} represents:
 - a hydroxyl group,
 - a methyl group;
- 30 in the form of bases or of acid-addition salts.

According to the present invention, distinguished compounds are those of formula (I) in which:

- Y represents a hydrogen atom or a group $-(C=O)-NR_2R_3$;
- Z represents:
 - 5 • a hydrogen atom,
 - a methyl group, an isopropyl group, a 2,2-dimethylpropyl group,
 - a group CD_3 ,
 - a 2-fluoroethyl group,
 - a cyclopropylmethyl group,
 - 10 • a 2-phenylethyl group,
 - a [(7-methyl-1,8-naphthyridin-2-yl)amino]-4-oxobutyl group,
 - a 2-[(2-nitrophenyl)sulfonyl]aminoethyl group,
 - a cyclopropyl group,
 - a tetrahydro-2H-pyran-2-yl group;
- R_1 represents a hydrogen atom, an ethyl group, a 2,2,2-trifluoroethyl group or a methyl group;
- R_2 represents a hydrogen atom or a methyl group;
- R_3 represents:
 - 20 • a methyl group,
 - a 2-[(2,6-difluorophenyl)sulfonyl]amino-1,1-dimethylethyl group,
 - a 1,1-dimethyl-2-[(4-(trifluoromethyl)phenyl)sulfonyl]aminoethyl group,
 - a 2-[(2-fluorophenyl)sulfonyl]amino-1,1-dimethylethyl group,
 - a 1,1-dimethyl-2-[(2-(trifluoromethoxy)phenyl)sulfonyl]aminoethyl group,
 - a 1,1-dimethyl-2-[(4-(trifluoromethoxy)phenyl)sulfonyl]aminoethyl group,
 - 25 • a 2-methyl-1-[(phenylsulfonyl)amino]propan-2-yl group,
 - a 2-methyl-1-[(5-nitro-1H-pyrazol-4-yl)sulfonyl]amino]propan-2-yl group,
 - a 2-methyl-1-[(trifluoromethyl)sulfonyl]amino]propan-2-yl group,
 - a 2-methyl-1-[(2-nitrophenyl)sulfonyl]amino]propan-2-yl group,
 - a 1-[(5-hydroxypyrazin-2-yl)carbonyl]amino-2-methylpropan-2-yl group,
 - 30 • a 1,1-dimethyl-2-morpholin-4-ylethyl group,
 - a benzyl group,
 - a 2-(4-pyridyl)ethyl group;

in the form of bases or of acid-addition salts.

Among the compounds according to the invention, mention may be made especially of the compounds below:

- 5 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-2-(1-
 {[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-
 yl]oxy}propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-
 2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-[[[(2S,5S,7R)-2,4,5-
 trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 10 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-2-
 (1{[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-
 yl]oxy}propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-
 2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-[[[(2S,5R,7R)-2,4,5-
 trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 15 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-[[[(2S,7R)-4-cyclopropyl-2,5-dimethyl-1,4-
 oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-
 methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-
 (methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-7-[[[(1-[[[(5-hydroxypyrazin-2-
 yl)carbonyl]amino]-2-methylpropan-2-yl)carbamoyl]oxy]-3,5,7,9,11,13-hexamethyl-
 6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 20 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2S,5R,7R)-
 2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-
 dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-
 hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-
 hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 25 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-
 dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-
 hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-
 hexamethyl-6,14-dioxo-7-[[[2-(pyridin-4-yl)ethyl]carbamoyl]oxy]-12-[[[(2S,5S,7R)-2,4,5-
 trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 30 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2S,7R)-4-
 cyclopropyl-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-
 3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-
 hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-
 hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;

- 5 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2S,7R)-2,5-dimethyl-4-(²H₃)methyl-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 10 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(dimethylcarbamoyl)oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-[[[(2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 15 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2S,7R)-2,5-dimethyl-4-(2-[[[(2-nitrophenyl)sulfonyl]amino]ethyl)-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 20 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2S,7R)-4-(2-fluoroethyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 25 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2S,7R)-2,5-dimethyl-4-{4-[[[(7-methyl-1,8-naphthyridin-2-yl)amino]-4-oxobutyl]-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 30 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2S,7R)-4-(2,2-dimethylpropyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-[[[(2S,7R)-2,5-dimethyl-4-(2-phenylethyl)-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-

methylnetetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methylnetetrahydro-2H-pyran-2-yl]oxy)-7-(((1-(((5-hydroxypyrazin-2-yl)carbonyl]amino)-2-methylpropan-2-yl)carbonyl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;

- 5 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methylnetetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methylnetetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-7-(((2-methyl-1-(((5-nitro-1H-pyrazol-4-yl)sulfonyl]amino}propan-2-yl)carbonyl]oxy)-6,14-dioxo-12-(((2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy}oxacyclotetradecan-4-yl 3-methylbutanoate;
- 10 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-hydroxy-2-(1-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methylnetetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methylnetetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-(((2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy}oxacyclotetradecan-4-yl 3-methylbutanoate;
- 15 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methylnetetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methylnetetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-7-(((2-methyl-1-(((trifluoromethyl)sulfonyl]amino}propan-2-yl)carbonyl]oxy)-6,14-dioxo-12-(((2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy}oxacyclotetradecan-4-yl 3-methylbutanoate;
- 20 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-(((2S,7R)-2,5-dimethyl-4-(2-phenylethyl)-1,4-oxazepan-7-yl]oxy)-7-hydroxy-2-(1-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methylnetetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methylnetetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 25 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methylnetetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methylnetetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-7-(((2-methyl-1-(((2-nitrophenyl)sulfonyl]amino}propan-2-yl)carbonyl]oxy)-6,14-dioxo-12-(((2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy}oxacyclotetradecan-4-yl 3-methylbutanoate;
- 30 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methylnetetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methylnetetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hydroxy-4-(methoxyimino)-6-methylnetetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-
- 35

hexamethyl-7-[[[2-methyl-1-[[[2-nitrophenyl)sulfonyl]amino]propan-2-yl]carbamoyl]oxy]-6,14-dioxo-12-[[[2S,5S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;

- 5 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-[[[2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-7-[[[2-methyl-1-[(phenylsulfonyl)amino]propan-2-yl]carbamoyl]oxy]-6,14-dioxo-12-[[[2S,5S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 10 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-[[[2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-7-[[[2-methyl-1-[(phenylsulfonyl)amino]propan-2-yl]carbamoyl]oxy]-6,14-dioxo-12-[[[2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 15 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[[[1,1-dimethyl-2-[(phenylsulfonyl)amino]ethyl]carbamoyl]oxy]-2-(2-[[[2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-[[[2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-12-[[[2S,7R)-4-isopropyl-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 20 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-[[[2S,5R,7R)-4-(cyclopropylmethyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-7-[[[1,1-dimethyl-2-[(phenylsulfonyl)amino]ethyl]carbamoyl]oxy]-2-(2-[[[2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-[[[2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 25 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-[[[2S,7R)-4-(cyclopropylmethyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-7-[[[1,1-dimethyl-2-[(phenylsulfonyl)amino]ethyl]carbamoyl]oxy]-2-(2-[[[2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-[[[2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 30 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-[[[2S,7R)-4-(cyclopropylmethyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-7-[[[1,1-dimethyl-2-[(phenylsulfonyl)amino]ethyl]carbamoyl]oxy]-2-(2-[[[2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-[[[2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 35 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[[[1,1-dimethyl-2-[(phenylsulfonyl)amino]ethyl]carbamoyl]oxy]-12-[[[2S,7R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1,4-

oxazepan-7-yl]oxy}-2-(2-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy)-1-methylethyl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;

- 5 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-(((2S,5S,7R)-4-(cyclopropylmethyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy)-7-(((1,1-dimethyl-2-((phenylsulfonyl)amino)ethyl) carbamoyl]oxy)-2-(2-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy)-1-methylethyl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 10 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-(((1,1-dimethyl-2-((phenylsulfonyl)amino)ethyl) carbamoyl]oxy)-12-(((2S,5R,7R)-4-(2,2-dimethylpropyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy)-2-(2-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy)-1-methylethyl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 15 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-(((1,1-dimethyl-2-((phenylsulfonyl)amino)ethyl) carbamoyl]oxy)-12-(((2S,7R)-4-(2,2-dimethylpropyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy)-2-(2-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy)-1-methylethyl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 20 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-(((1,1-dimethyl-2-((phenylsulfonyl)amino)ethyl) carbamoyl]oxy)-12-(((2S,7R)-4-(2,2-dimethylpropyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy)-2-(2-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy)-1-methylethyl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
- 25 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-(((1,1-dimethyl-2-morpholin-4-ylethyl) carbamoyl]oxy)-2-(2-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy)-1-methylethyl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-(((2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy)oxacyclotetradecan-4-yl 3-methylbutanoate;
- 30 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-(((2-(((2,6-difluorophenyl)sulfonyl)amino)-1,1-dimethylethyl) carbamoyl]oxy)-2-(2-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy)-1-methylethyl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-(((2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy)oxacyclotetradecan-4-yl 3-methylbutanoate;

- 5 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-([1,1-dimethyl-2-([4-(trifluoromethyl)phenyl]sulfonyl)amino)ethyl]carbamoyl]oxy)-2-(2-([[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-([[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-([[(2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 10 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-([2-([[(2-fluorophenyl)sulfonyl]amino)-1,1-dimethylethyl]carbamoyl]oxy)-2-(2-([[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-([[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-([[(2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 15 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-([1,1-dimethyl-2-([2-(trifluoromethoxy)phenyl]sulfonyl)amino)ethyl]carbamoyl]oxy)-2-(2-([[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-([[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-([[(2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 20 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-([1,1-dimethyl-2-([4-(trifluoromethoxy)phenyl]sulfonyl)amino)ethyl]carbamoyl]oxy)-2-(2-([[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-([[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-([[(2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 25 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-([1,1-dimethyl-2-([[(phenylsulfonyl)amino]ethyl]carbamoyl]oxy)-2-(2-([[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-10-([[(2S,3R,6R)-3-hydroxy-6-methyl-4-[(2,2,2-trifluoroethoxy)imino]tetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-([[(2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate;
- 30 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-([1,1-dimethyl-2-([[(phenylsulfonyl)amino]ethyl]carbamoyl]oxy)-10-([[(2S,3R,6R)-4-(ethoxyimino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-2-(2-([[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]-1-methylethyl)-3,5,7,9,11,13-hexamethyl-6,14-

dioxo-12-[[[(2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy}oxacyclotetradecan-4-yl
3-methylbutanoate;

in the form of bases or of acid-addition salts.

5 [PREPARATION]

[Nature of the strain]

10 The strain described in FR 2 126 108 deposited at the Northern Regional
Research Laboratory (NRRL) under the number NRRL 3892 may be used.

The strain named *Allokutzneria albata* deposited at the Deutsche Sammlung Von
Mikroorganismen und Zellkulturen GmbH (DSMZ) by the group Sanofi-Aventis (Sanofi
Aventis Deutschland GmbH, Industriepark Höchst H831, 65926 Frankfurt am Main) under
the identification reference ST108942 may also be used.

15

[Fermentation and purification to isolate sequanamycin of formula (A)]

20 The fermentation and purification process described in FR 2 126 108 makes it
possible to isolate sequanamycin of formula (A) from the strain *Allokutzneria albata*. This
may be performed by application of the protocol below. This protocol is given as a non-
limiting illustration: it may be adapted to other conditions.

Thus, the fermentation process described below was performed for 500 litres, but
may be adapted for smaller or larger proportions.

25 The preculture medium (named "medium 5294") used is typically the following:

Component	g/L
Glucose	4
Yeast extract	4
Malt extract	10
CaCO ₃	2

The pH of the medium before sterilization is 7.2.

The main culture medium (named "medium 5254-Seq01") used is typically the following:

Component	g/L
Glucose	15
Soybean meal	10
Corn maceration water	3
CaCO ₃	1
NaCl	5

The fermentation process is typically as follows:

5

1 vial from the Banque de Cellules de Travail (BCT)



Step 1: Preculture 1

500 µL of BCT were placed in a 300 ml conical flask comprising twice 100 ml of medium 5294. The mixture was stirred for 96 hours at 28°C.

10



Step 2: Preculture 2

25 ml of the culture medium from step 1 were placed in 4 times 500 ml of medium 5294 in a 2-litre conical flask, and the mixture was then stirred for 72 hours at 28°C.

15



Step 3: Preculture 3

1.5 L of the culture medium from step 2 were placed in 30 litres of medium 5294 in a 42-litre bioreactor, and the mixture was then stirred and aerated for 24 hours at 28°C, without monitoring the pH.

20



Step 4 (main culturing):

30 kg of the culture medium from step 3 were placed in 500 litres of medium 5294-Seq1 in an 800-litre bioreactor, and the mixture was then stirred and aerated for 96±5 hours at 28°C, without monitoring the pH.

25



Harvesting

The fermentation process described above was performed for 500 litres, but may be adapted for smaller or larger proportions. It was performed, for example, at a scale of 7000 litres as follows, using the same culture media:

5 Preculture 1 = 250 ml, inoculum: one vial of BCT.

Preculture 2 = 5 litres in flasks (2 × 2.5 litres), inoculum of 0.5% from preculture 1.

Preculture 3 = 400 litres of medium in a 600 litre bioreactor, seeding rate of 1.25% from preculture 2.

10 Main culture = 7000 litres of medium in a 10 000 litre bioreactor, seeding rate of 5.7% from preculture 3.

The fermentation process is followed by the purification process below (performed on the 500 litre fermentation broth described above).

15 Once the fermentation was complete, the fermentation broth was separated into culture supernatant and mycelium using a cylindrical seed grader. The separation led to about 440 litres of culture supernatant.

20 In separate batches, 100-120 litres of culture supernatant comprising, inter alia, the macrolide (sequanamycin (A)) were placed on a column filled with adsorption resin (glass column filled with styrene-divinylbenzene copolymer, inside diameter of 200, length of about 180 mm, flow rate of 250 ml/min). The resin was then washed with 30% 2-propanol.

The sequanamycin (A) was isolated by eluting the column with the following elution gradient: 30-70% B over 45 minutes, 70% B over 10 minutes, 100% B over 25 min; with A = H₂O, B = 2-propanol, modifier: 1 vol% NH₄Ac 50 g/L adjusted to pH 7).

25 The fractions comprising the sequanamycin (A) were combined and the 2-propanol was evaporated off. The pH of the solution obtained was adjusted to above 7.5 and the solution was then extracted twice with EtOAc. The organic phases were combined and the solvents were evaporated off. The oil obtained (about 10 g per 100 litres of culture supernatant) was purified on silica gel (column of 40 mm × 260 mm), the column being
30 eluted with an n-heptane to 30/70 n-heptane/EtOAc gradient over 45 minutes, followed by 30/70 n-heptane/EtOAc maintained for about 40 minutes (with a flow of 100 ml/minute). The monitoring of the purification may be performed by thin-layer chromatography, eluting with EtOAc and revealing the sequanamycins (in the form of blue spots) with a reagent such as vanillin.

According to the concentration of sequanamycin (A) in the individual 100 litre batches, about 2.5 to 3.5 g of sequanamycin (A) with a purity of 68-75% (determined by NMR) were obtained per batch.

5 If a higher purity is required, the sequanamycin (A) obtained may be repurified by reverse-phase chromatography on a WatersAtlantis machine with a 50×100 mm, 5 μ column. An elution gradient of H₂O (A) and acetonitrile (B) and 1 vol% NH₄Ac 50 g/L adjusted to pH 7 was used (40-60% B over 30 minutes, flow rate of 140 ml/min). The chromatography was monitored by a light-scattering electrical signal. The fractions
10 comprising the sequanamycin (A) were combined and lyophilized after having evaporated off the acetonitrile. The sequanamycin (A) yield after this final purification step was 57%, with an 85% pure compound according to the NMR analyses.

15 The compounds of formula (I) according to the invention are prepared from sequanamycin of formula (A).

[Processes for preparing the compounds of formula (I) from sequanamycin of formula (A)]

20 In the steps described below, the usual organic chemistry reactions may be followed, especially those described in "*Comprehensive Organic Transformations: A Guide to Functional Group Preparations*" by Richard C. Larock, published by John Wiley & Sons Inc.

25 In the text hereinbelow, the term "protecting group PG" means a group that can, firstly, protect a reactive function such as a hydroxyl or an amine during the synthesis and, secondly, regenerate the intact reactive function at the end of the synthesis. Examples of protecting groups and also protection and deprotection methods are given in *Protective Groups in Organic Synthesis*, Greene et al., 4th Edition (John Wiley & Sons, Inc., New
30 York), 2007.

 In the text hereinbelow, the term "leaving group LG" means a group that can be readily cleaved from a molecule by breaking a heterolytic bond, with loss of an electron pair. This group may thus be readily replaced with another group, for example during a substitution reaction. Such leaving groups are, for example, halogens or an activated hydroxyl group
35 such as a methanesulfonate, benzenesulfonate, p-toluenesulfonate, triflate, acetate, etc. Examples of leaving groups and also references for their preparation are given in

Macrolide derivatives, preparation thereof and therapeutic use thereof

The present invention relates to macrolide derivatives, and to the preparation and therapeutic use thereof. The compounds according to the present invention have substantial antimicrobial activity, mainly on gram-positive microorganisms, and also on mycobacteria, especially in the treatment of tuberculosis.

Due to the appearance of resistance, the development of novel antibacterial agents is necessary to make it possible to kill or to prevent the growth of mycobacteria, especially those which induce tuberculosis.

Tuberculosis is a disease which, at the present time, is still a worldwide health threat. Globally, a third of the human population is infected with *Mycobacterium tuberculosis*. Despite the fact that treatments exist and that the disease is curable, tuberculosis killed approximately 1.82 million people in 2008, and its global incidence increases by 1% per year, with an estimation in 2008 of 9.4 million annual new cases of declared disease. Added to this are the difficulties of correct prescription and of adherence to the treatment protocols, and also the emergence of multi-resistant strains of *M. tuberculosis*. Drug-drug interactions also interfere with the optimum treatment of AIDS and tuberculosis in the case of co-infected patients.

The common treatment protocols for combating sensitive strains of *M. tuberculosis* are mainly based on a combination of three or, more frequently, of four molecules: isoniazide (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB). These drugs constitute the "first-line" treatment.

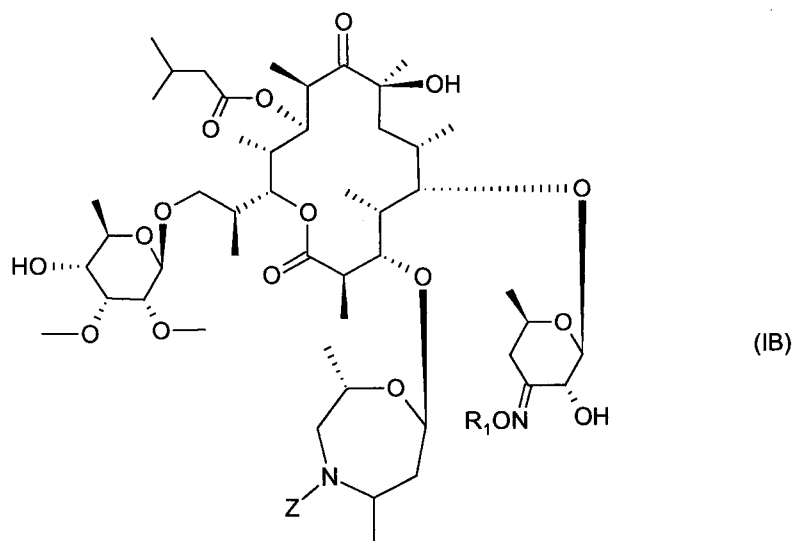
In recent decades, tuberculosis has become resistant to each of these molecules. Strains that are resistant at least to isoniazide and to rifampicin are referred to as "multi-resistant" (MDR-TB). Recently, novel strains have appeared which are resistant to a larger number of molecules: those that are resistant to isoniazide, to rifampicin, to fluoroquinolones and to at least one injectable second-line drug are defined as being "ultra-resistant" (XDR-TB).

According to an estimation made by the WHO in 2009, there were 0.5 million cases of MDR-TB in 2007. Other evaluations report a relative incidence of about 11% of multi-resistant strains among all new cases of tuberculosis.

Another therapeutic drawback in the treatment of tuberculosis is the interaction of rifampicin with treatments for combating HIV (human immunodeficiency virus), which represents an obstacle in the treatment of patients co-infected with tuberculosis and HIV. The current anti-HIV therapeutic recommendations favour, as a first-line treatment, an anti-retroviral triple therapy combining a protease inhibitor (PI) or a non-nucleoside

Advanced Organic Chemistry, M.B. Smith and J. March, 6th Edition, Wiley Interscience, 2007, pp. 496-501.

In accordance with the invention, the compounds of formula (I) in which Y represents a group $-(C=O)-NR_2R_3$ may be prepared according to the process characterized in that:
a compound of formula (I), in which Y represents a hydrogen atom below:

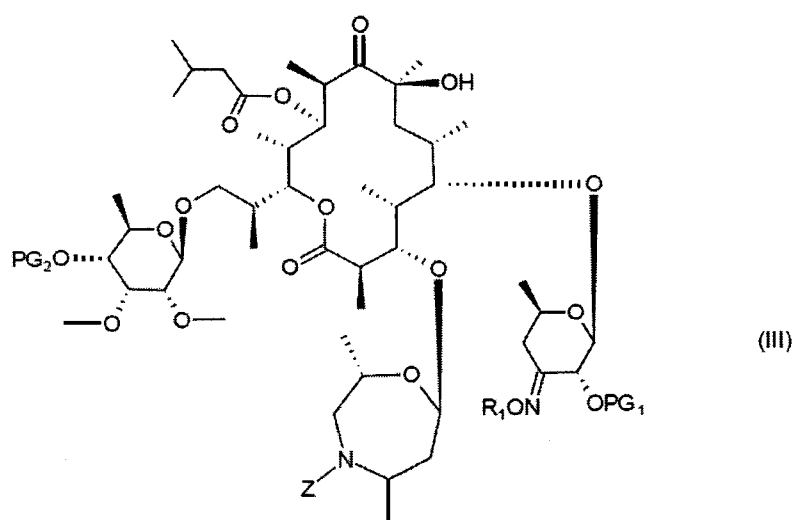


and R1 and Z are as defined for the compounds of formula (I), is reacted with a compound of formula (II) HNR_2R_3 in which R2 and R3 are as defined for the compounds of formula (I), in the presence of a carbonyl derivative and a base.

The introduction of a group Y representing a group $-(C=O)-NR_2R_3$ into the compounds of formula (IB) typically comprises the following four successive steps:

- a-1) protection of the hydroxyl functions of the compound of formula (IB),
- a-2) formation of a carbonyl intermediate from the hydroxyl function in position 7 of the macrocycle,
- a-3) reaction of the carbonyl intermediate with a compound of formula (II) HNR_2R_3 ,
- a-4) deprotection of the hydroxyl functions.

In step a-1), the hydroxyl functions of the compound of formula (IB) are protected to form a compound of formula (III) below, the hydroxyl function in position 7 of the macrocycle (onto which the group Y will be introduced) remaining free:

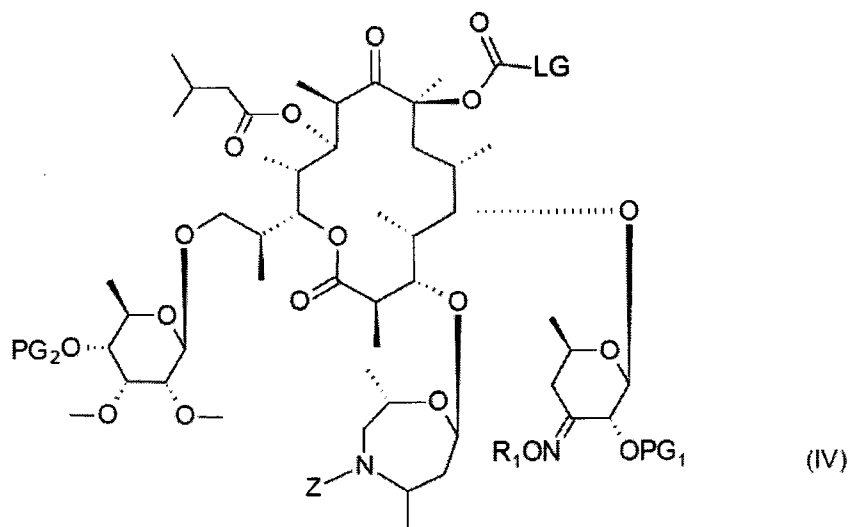


in which:

- R_1 and Z are as defined for the compounds of formula (I);
- PG_1 and PG_2 independently represent a hydroxyl-function protecting group.

5

In step a-2), the hydroxyl function in position 7 of the macrocycle of the compound of formula (III) is used to form a carbonyl intermediate of formula (IV) below:



in which:

10

- R_1 and Z are as defined for the compounds of formula (I);
- LG represents a leaving group;
- PG_1 and PG_2 independently represent a hydroxyl-function protecting group.

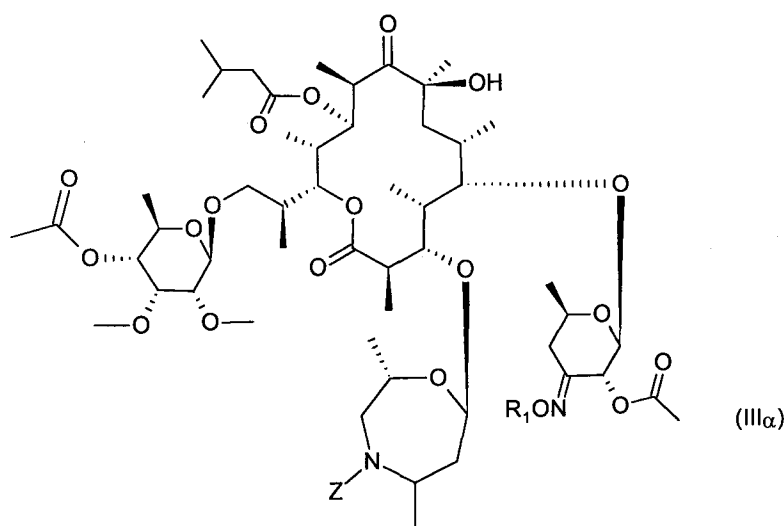
In step a-3), the carbonyl intermediate of formula (IV) is reacted with a compound of formula (II) HNR_2R_3 in which R_2 and R_3 are as defined for the compounds of formula (I).

Step a-3) is typically performed in a polar solvent, for instance dimethylformamide (DMF), generally for 10 to 48 hours and at room temperature.

In step a-4), the hydroxyl functions of the compound obtained in step a-3) are deprotected.

Step a-4) is typically performed according to the deprotection processes described in *Protective Groups in Organic Chemistry*, J.F.W. McOmie, Plenum Press, 1973 or in *Greene's Protective Groups in Organic Synthesis*, by Theodora W. Greene published by John Wiley & Sons Inc., 2006.

As regards step a-1), the hydroxyl functions of compound (IB) are protected, for example, with acetate functions. This protection reaction may be performed by placing the compound of formula (IB) in contact with acetic anhydride in the presence of a base, especially a nitrogenous base, for example pyridine, at room temperature, the hydroxyl function in position 7 of the macrocycle onto which the group Y will be introduced remaining free, to form a compound of formula (III α) below:

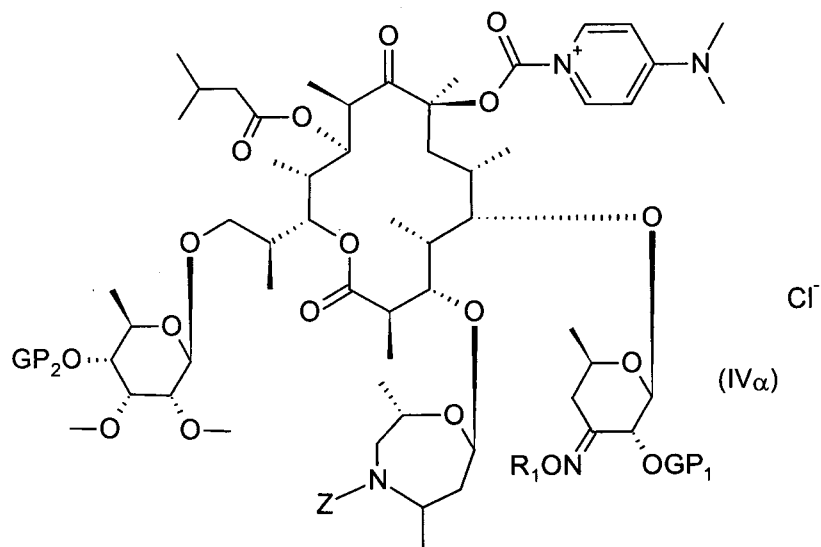


in which:

- R_1 and Z are as defined for the compounds of formula (I).

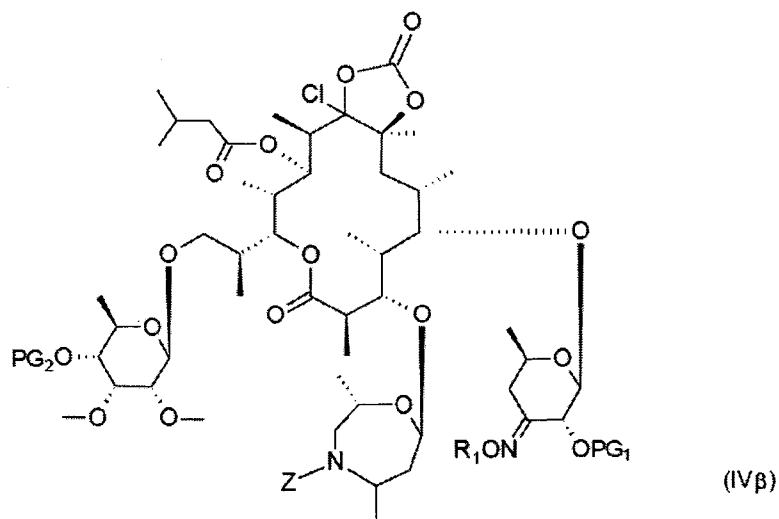
In a first embodiment of step a-2), a compound of formula (III) as defined above is reacted, for example, with 4-N,N-dimethylaminopyridine (DMAP) and trichloromethyl chloroformate, generally in the presence of a base, especially a nitrogenous base, for

example pyridine, in an apolar aprotic solvent, for example dichloromethane, at a temperature between -20°C and room temperature and for a time of between 5 and 30 hours, to form two carbonyl intermediates of formulae (IV α) and (IV β) below:



5 in which:

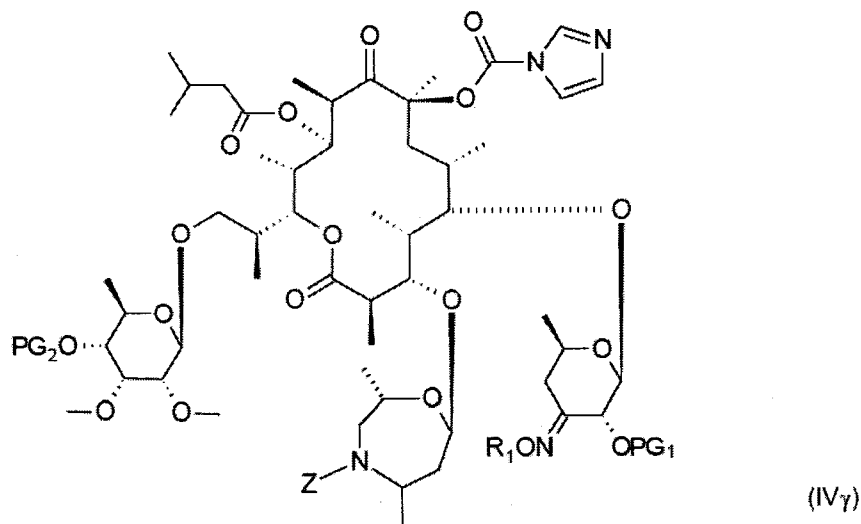
- R_1 and Z are as defined for the compounds of formula (I);
 - PG_1 and PG_2 independently represent a hydroxyl-function protecting group;
- or



10 in which:

- R_1 and Z are as defined for the compounds of formula (I);
- PG_1 and PG_2 independently represent a hydroxyl-function protecting group, for example an acetate function.

In a second embodiment of step a-2), a compound of formula (III) is reacted, for example, with imidazole and diphosgene to form a carbonyl intermediate of formula (IV γ) below:



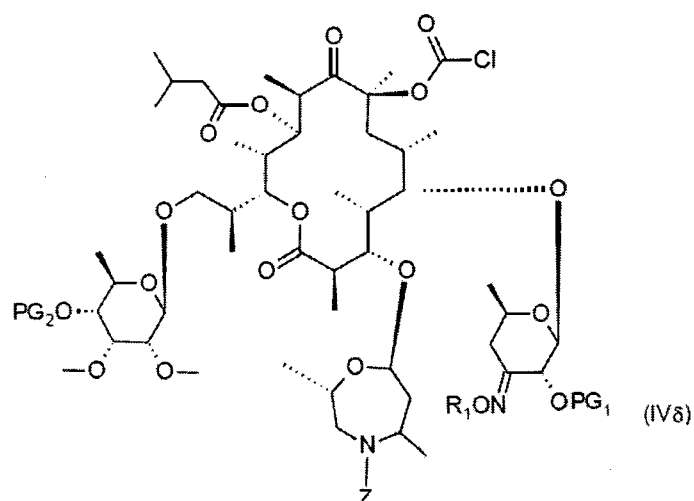
5

in which:

- R₁ and Z are as defined for the compounds of formula (I);
- PG₁ and PG₂ independently represent a hydroxyl-function protecting group, for example an acetate function.

10

In a third embodiment of step a-2), a compound of formula (III) is reacted, for example, with diphosgene to form a carbonyl intermediate of formula (IV δ) below:



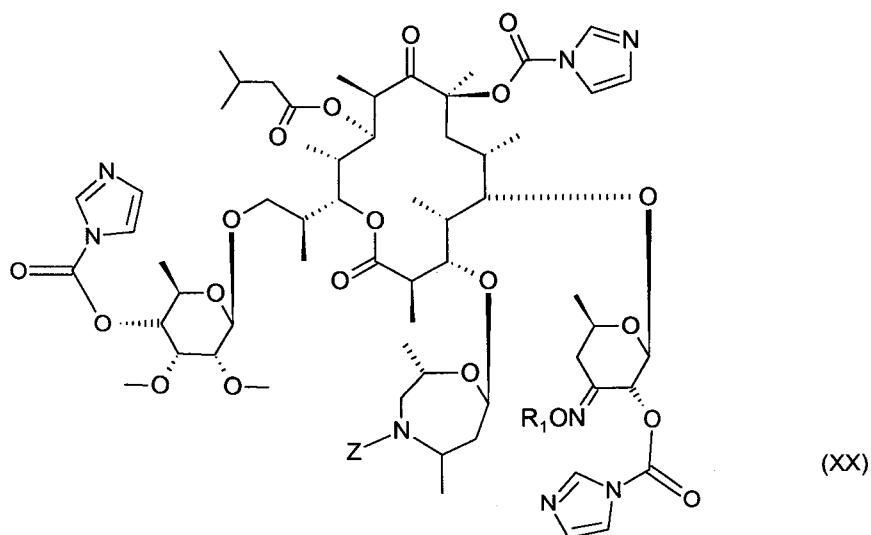
15

in which:

- R_1 and Z are as defined for the compounds of formula (I);
- PG_1 and PG_2 independently represent a hydroxyl-function protecting group, for example an acetate function.

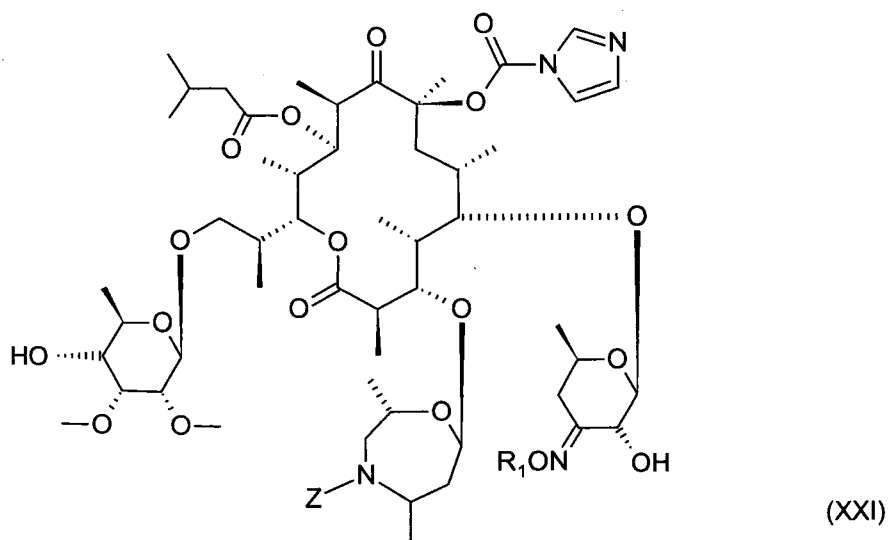
5 In particular, steps a-1), a-2), a-3) and a-4) may be performed simultaneously or in reverse order. Thus, for example:

a'-1) the hydroxyl functions of the compound of formula (IB) are protected, and a carbonyl intermediate is formed from the hydroxyl function in position 7 of the macrocycle by microwave heating of the compound of formula (IB) with, for example,
 10 N,N'-carbonyldiimidazole, in a solvent, for instance cyclohexane, and at a temperature of between 80°C and 100°C, to obtain a compound of formula:



in which Z and R_1 are as defined for a compound of formula (I);

a'-2) the hydroxyl functions are deprotected by placing the compound of formula
 15 (XX) in contact with an acid, for instance hydrochloric acid, in a solvent, for instance tetrahydrofuran, to obtain a compound of formula:



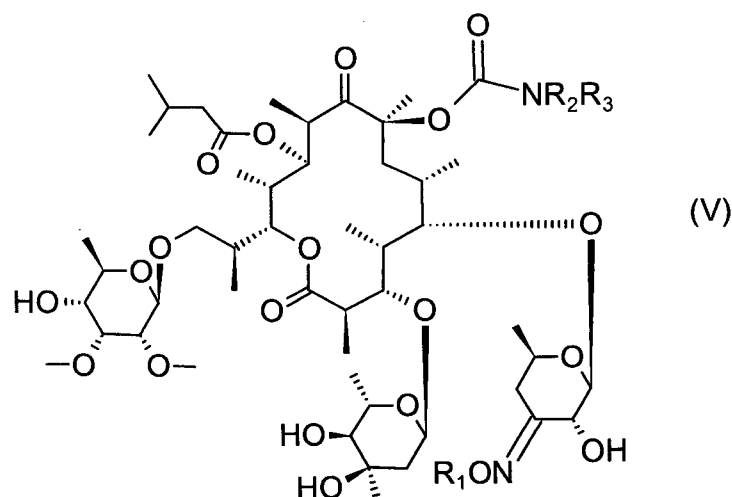
in which Z and R₁ are as defined for a compound of formula (I);

a'-3), the compound of formula (XXI) is reacted with a compound of formula (II) HNR₂R₃ in which R₂ and R₃ are as defined for the compounds of formula (I).

5 Step a'-3) is typically performed in a polar solvent, for instance dimethylformamide (DMF), in the presence of a base, for instance 1,8-diazabicyclo[5.4.0]undec-7-ene, generally for 10 to 48 hours and at room temperature.

10 In accordance with the invention, the compounds of formula (I) in which Y represents a group $-(C=O)-NR_2R_3$ may also be prepared according to the process characterized in that:

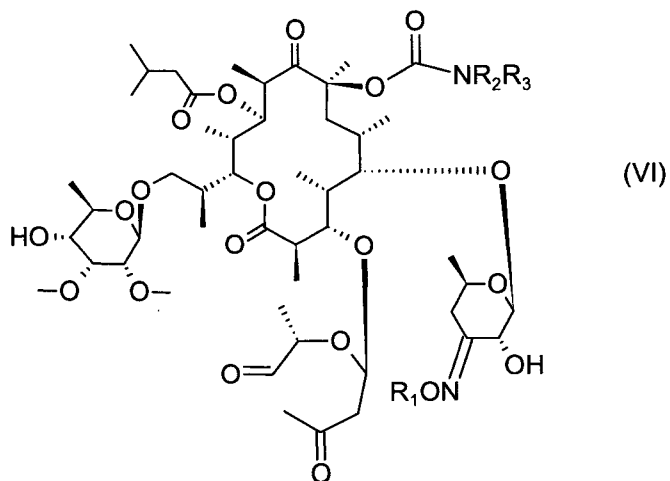
b-1) a compound of formula (V):



15 in which:

- R_1 , R_2 and R_3 are as defined for the compounds of formula (I);

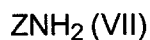
is reacted with an oxidizing agent to obtain a compound of formula (VI):



5 in which:

R_1 , R_2 and R_3 are as defined for the compounds of formula (I);

b-2) the compound of formula (VI) thus obtained is reacted with a compound of formula (VII):



10 in which Z is as defined for compound (I), in the presence of a reducing agent, to obtain the expected compound of formula (I).

In step b-1), the oxidation of the compound of formula (V) is performed via the action of an oxidizing agent, for instance sodium periodate, in a polar solvent, for instance MeOH, and at a temperature of between 0 and 10°C.

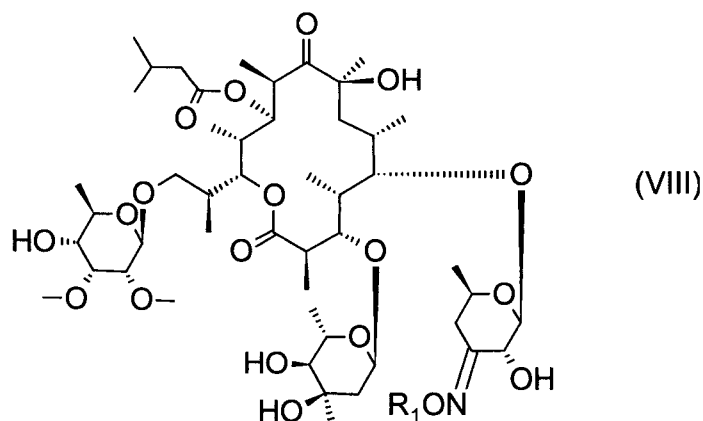
In step b-2), the reaction of the compound of formula (VI) with a compound of formula (VII) takes place in the presence of a reducing agent, for instance sodium cyanoborohydride, in a slightly acidic medium, in a solvent such as MeOH.

20

In accordance with the invention, the compounds of formula (I) in which Y represents a hydrogen atom may be prepared according to the process characterized in that:

25

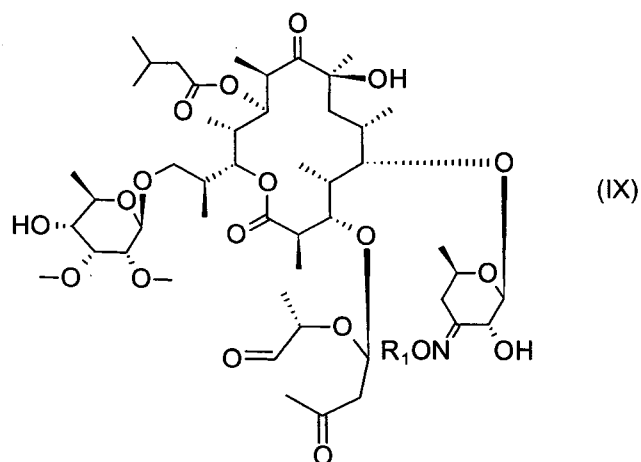
c-1) a compound of formula (VIII):



in which:

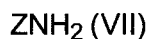
- R_1 is as defined for the compounds of formula (I);

5 is reacted with an oxidizing agent to obtain a compound of formula (IX):



in which R_1 is as defined for the compounds of formula (I);

10 c-2) the compound of formula (IX) thus obtained is reacted with a compound of formula (VII):



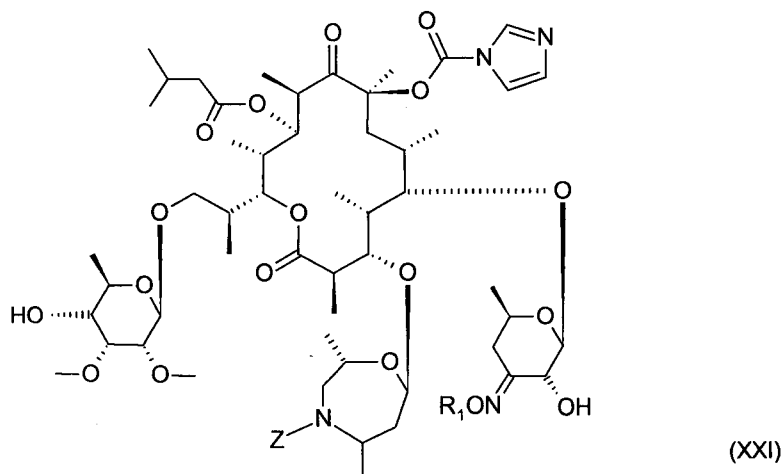
in which Z is as defined for compound (I), in the presence of a reducing agent, to obtain the expected compound of formula (I).

15

Steps c-1) and c-2) are performed under the same operating conditions as those described in steps b-1) and b-2) above.

In accordance with the invention, the compounds of formula (I) in which Y represents a group $-(C=O)-O-R_{18}$ may be prepared according to the process characterized in that:

a compound of formula (XXI):



in which Z and R_1 are as defined for a compound of formula (I), is reacted with an alcohol of formula $HO-R_{18}$ (XXII), in the presence of a base.

The reaction is performed in the presence of a mineral base, for instance potassium carbonate, at room temperature.

In particular, certain compounds of formula (I) may be prepared from other compounds of formula (I). Thus, for example, a compound of formula (I) in which $Z = Me$ may be prepared from a compound of formula (I) in which $Z = H$, by reaction with formaldehyde in the presence of formic acid and in a solvent, for instance chloroform.

The compounds of formula (I) thus obtained may be subsequently separated from the reaction medium and purified according to standard methods, for example by crystallization or chromatography.

The compounds of formula (I) thus obtained are isolated in the form of the free base or of a salt, according to the standard techniques.

The compounds of formula (II) are commercial, known or prepared according to methods known to those skilled in the art.

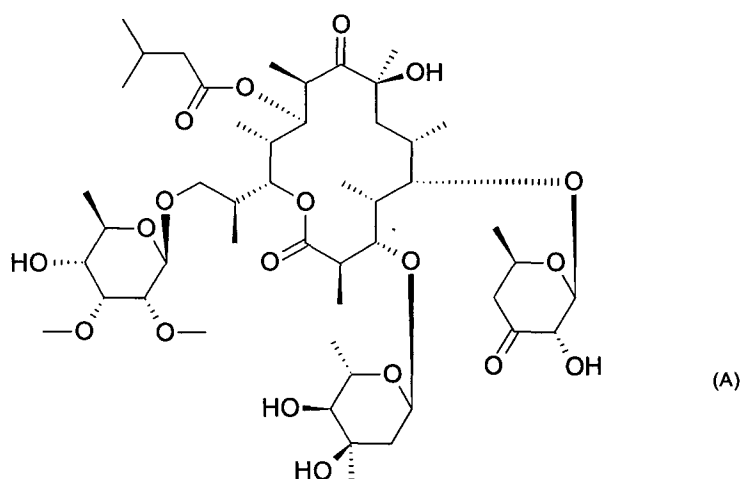
reverse transcriptase inhibitor (NNRTI) with two nucleoside reverse transcriptase inhibitors (NRTI). PI and NNRTI are metabolized by CYP3A4. Metabolic interactions between anti-retrovirals (ATRV) and certain combined drugs have been demonstrated. Thus, rifampicin, which is a powerful inducer of intestinal and hepatic CYP3A4, reduces the concentrations of ATRV.

There is an urgent need to develop improved therapies for combating tuberculosis. These novel anti-tuberculosis treatments should be capable of satisfying one or more of the following criteria:

- shorten the treatment time to improve the adherence to the treatment protocols and reduce the appearance of resistant bacteria,
- be well tolerated, acting via novel mechanisms of action and thus effective against multi-resistant and/or ultra-resistant strains,
- be active against tuberculosis,
- have a shortened latent tuberculosis (asymptomatic first infection) treatment time, so as to address the problem of the biological reservoir of *M. tuberculosis*.

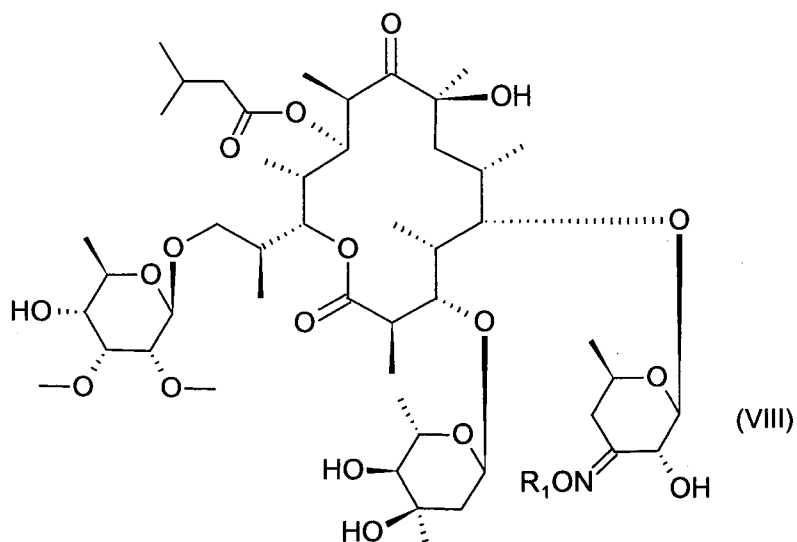
FR 2 126 108 and Arnoux et al. (Journal of the American Chemical Society 102(10), 1980, 3605) describe sequanamycin (A), having the following formula:

(3S,4S,5R,7S,9S,10S,11R,12S,13R)-12-[(4,5-dihydroxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy]-7-hydroxy-2-{1-[(5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy]propan-2-yl}-10-[(3-hydroxy-6-methyl-4-oxotetrahydro-2H-pyran-2-yl)oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl) 3-methylbutanoate.



This compound is described therein as an antimicrobial agent and especially enables the treatment of tuberculosis. However, this compound may show instability, in particular in acidic or basic aqueous medium, and/or may also show metabolic instability, which makes it difficult to use as a drug.

The compounds of formula (V) in which Y represents a group $-(C=O)NR_2R_3$ are prepared by reacting a compound of formula (VIII):



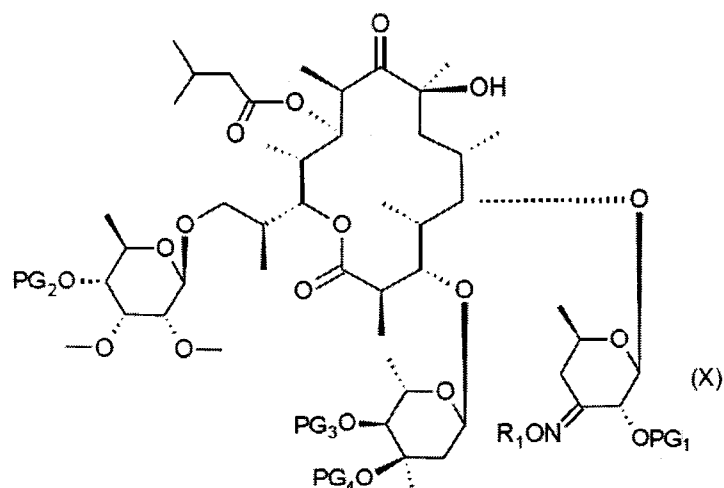
5 in which R_1 is as defined for the compounds of formula (I);

with a compound of formula (II) HNR_2R_3 in which R_2 and R_3 are as defined for the compounds of formula (I), in the presence of a carbonyl derivative, according to the four steps below:

- 10
- d-1) protection of the hydroxyl functions of the compound of formula (VIII),
 - d-2) formation of an activated intermediate by activation of the hydroxyl function in position 7 of the macrocycle,
 - d-3) reaction of the activated intermediate with a compound of formula (II) HNR_2R_3 ,
 - d-4) optional deprotection of the hydroxyl functions.

15

In step d-1), the hydroxyl functions of the compound of formula (VIII) are protected to form a compound of formula (X) below (the hydroxyl function in position 7 of the macrocycle onto which the group Y will be introduced remaining free):

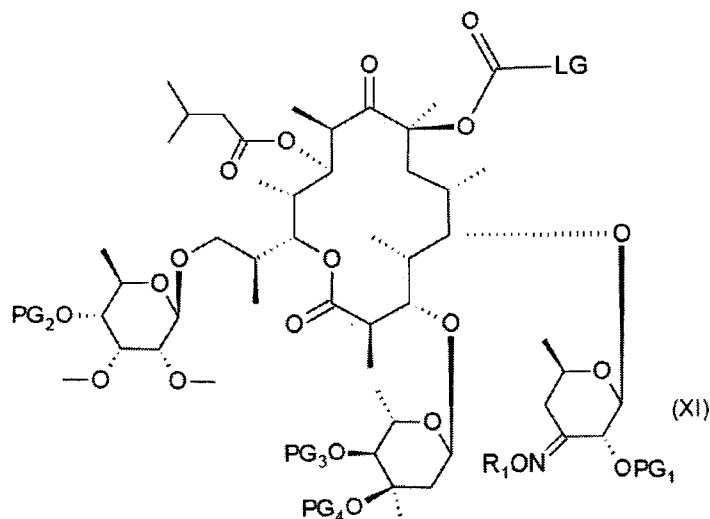


in which:

- R₁ is as defined for the compounds of formula (I);
- PG₁, PG₂, PG₃ and PG₄ independently represent a hydroxyl-function protecting group.

5

In step d-2), a carbonyl intermediate is formed from the hydroxyl function in position 7 of the macrocycle of the compound of formula (X), especially one or more of the carbonyl intermediates of formula (XI) below:



10

in which:

- R₁ is as defined for the compounds of formula (I);
- LG represents a leaving group;
- PG₁, PG₂, PG₃ and PG₄ independently represent a hydroxyl-function protecting group.

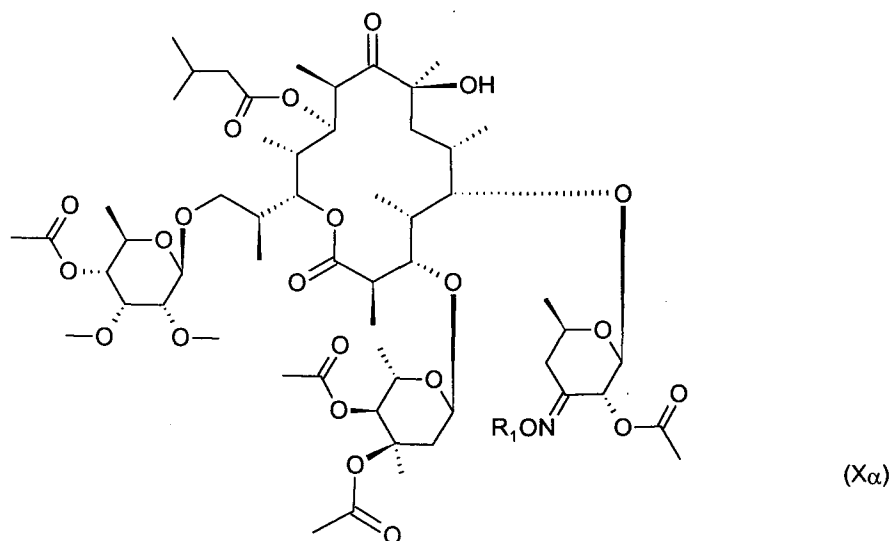
In step d-3), the carbonyl intermediate obtained in step d-2) is reacted with a compound of formula (II) HNR_2R_3 in which R_2 and R_3 are as defined for the compounds of formula (I).

Step d-3) is typically performed in a polar solvent, for instance dimethylformamide (DMF), generally for 10 to 48 hours and at room temperature.

In step d-4), the hydroxyl functions of the compound obtained in step d-3) are deprotected.

Step d-4) is typically performed according to the deprotection processes described in *Protective Groups in Organic Chemistry*, J.F.W. McOmie, Plenum Press, 1973 or in *Greene's Protective Groups in Organic Synthesis*, by Theodora W. Greene published by John Wiley & Sons Inc., 2006.

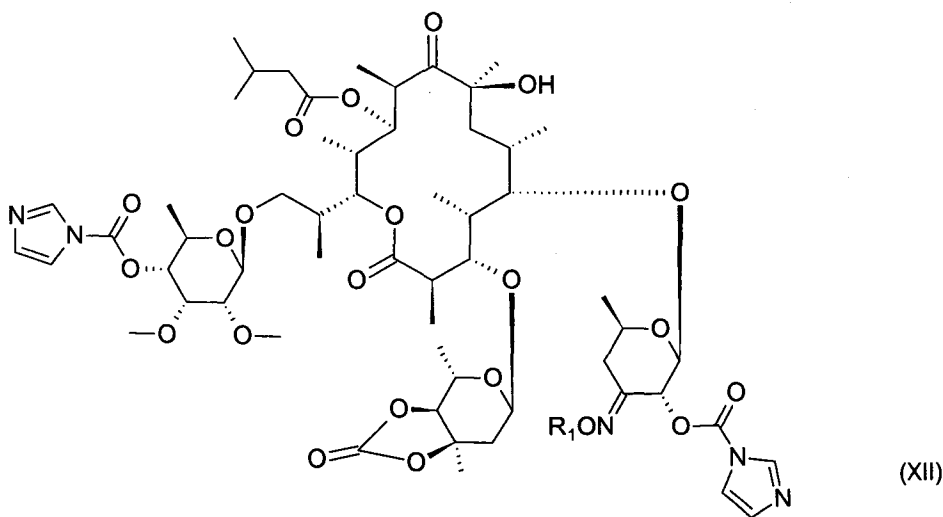
In a first embodiment of step d-1), the hydroxyl functions of compound (VIII) are protected, for example, with acetate functions. This protection reaction may be performed by placing the compound of formula (VIII) in contact with acetic anhydride in the presence of a base, especially a nitrogenous base, for example pyridine, at a temperature typically ranging from room temperature to 160°C , the hydroxyl function in position 7 of the macrocycle onto which the group Y will be introduced remaining free, to form a compound of formula (X_α) below:



in which R_1 is as defined for the compounds of formula (I).

In a second embodiment, step d-1) typically comprises the following three successive steps d-1-1), d-1-2) and d-1-3):

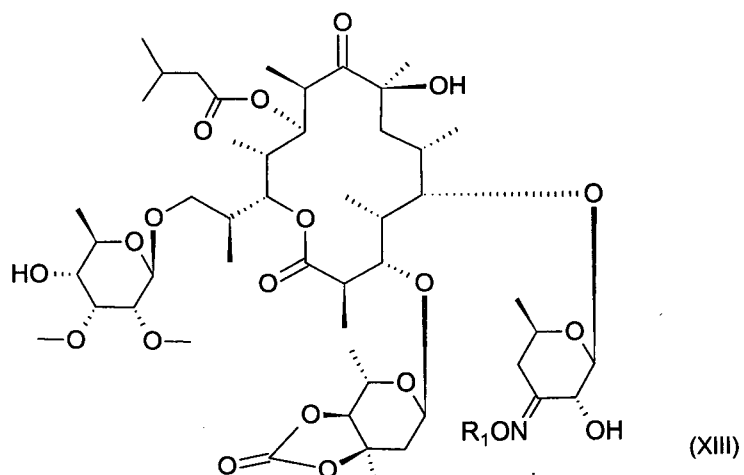
- step d-1-1) the hydroxyl functions of the compound of formula (VIII) are protected with acyl imidazole functions to form a compound of formula (XII) by placing compound (VIII) in contact with 1,1'-carbonyldiimidazole in an apolar aprotic solvent, for example toluene, for a time from 10 minutes to 3 hours and at a temperature between room temperature and 80°C:



in which R₁ is as defined for the compounds of formula (I).

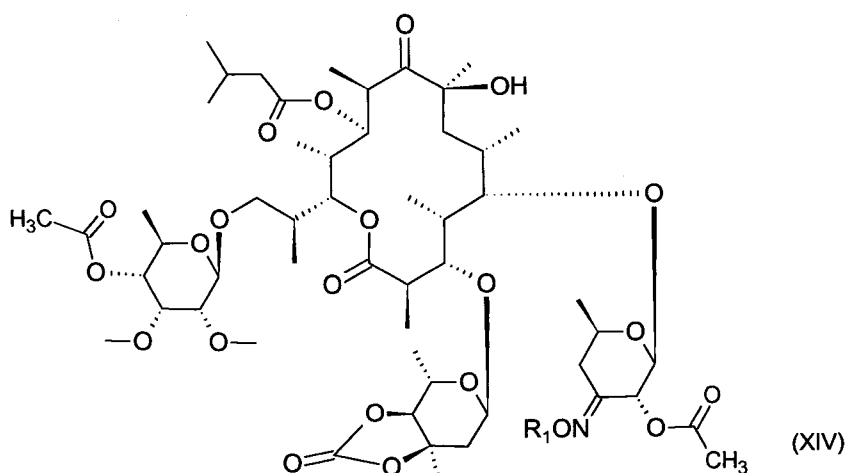
The tertiary alcohol of mycarose reacts with the acylimidazole of the secondary alcohol at α to form the carbonate.

- step d-1-2) the hydroxyl functions are deprotected by placing the compound of formula (XII) in contact with an acid, generally hydrochloric acid, in a polar aprotic solvent, for example tetrahydrofuran (THF), typically at room temperature and for a time from 2 to 24 hours, for example, to form the compound of formula (XIII) below:



in which R₁ is as defined for the compounds of formula (I).

- 5 - step d-1-3) the secondary hydroxyl functions of the compound of formula (XIII) are protected with acetate functions by placing the said compound in contact with acetic anhydride in the presence of a base, especially a nitrogenous base, for example pyridine, typically at room temperature and for a time from 5 to 48 hours, for example:



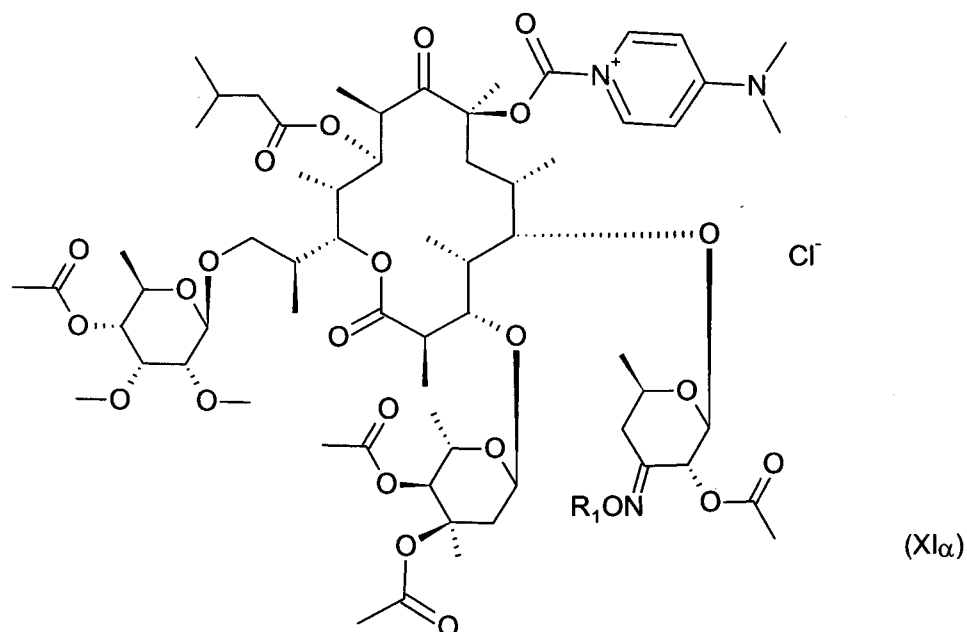
10

in which R₁ is as defined for the compounds of formula (I).

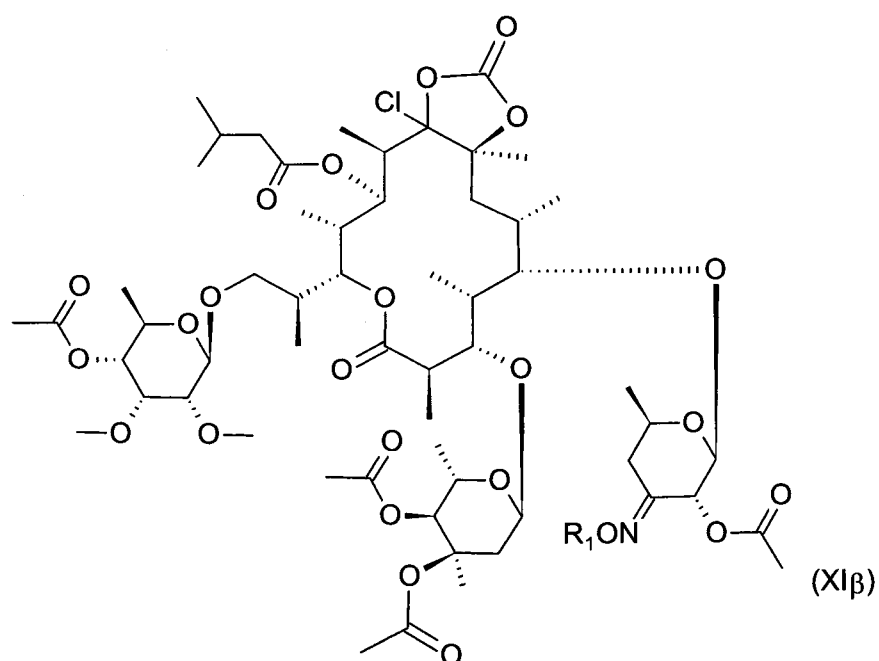
15

In a first embodiment of step d-2), a compound of formula (X_a) as defined above is reacted with 4-N,N-dimethylaminopyridine (DMAP) and trichloromethyl chloroformate, generally in the presence of a base, especially a nitrogenous base, for example pyridine, in an apolar aprotic solvent, for example dichloromethane, at a temperature between -20°C and 5°C for a time of between 30 minutes and 10 hours, and then at room

temperature for a time of between 5 and 30 hours, to form two carbonyl intermediates of formulae (XI α) and (XI β) below:



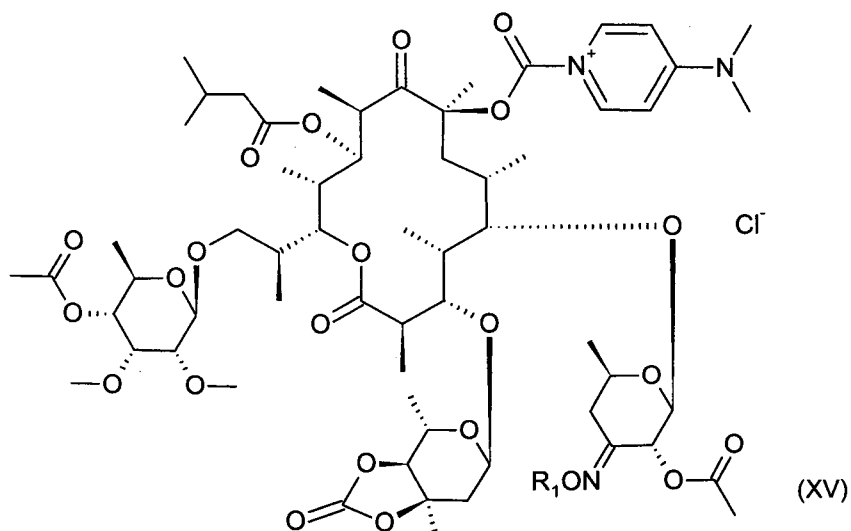
5 and



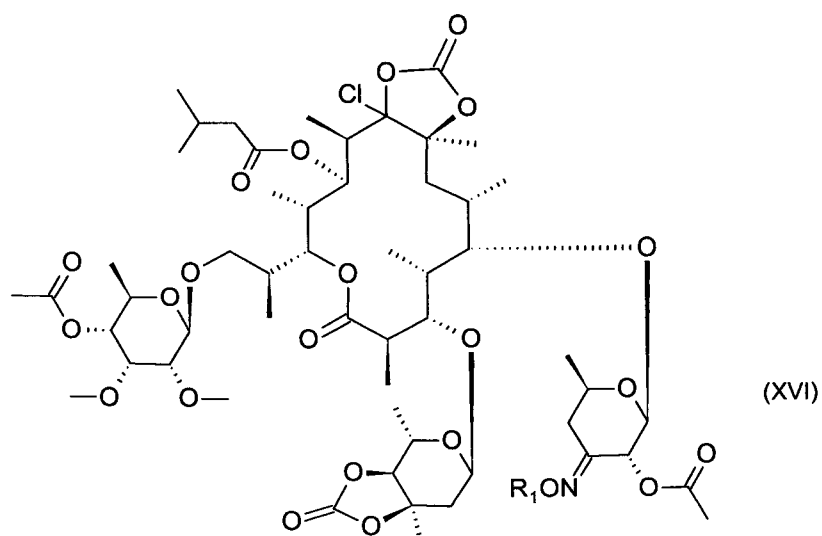
in which R₁ is as defined for the compounds of formula (I).

10

In a second embodiment of step d-2), the compound of formula (XIV) is reacted, for example, with DMAP and trichloromethyl chloroformate, generally in the presence of a base, especially a nitrogenous base, for example pyridine, to form two carbonyl intermediates of formulae (XV) and (XVI) below:



and

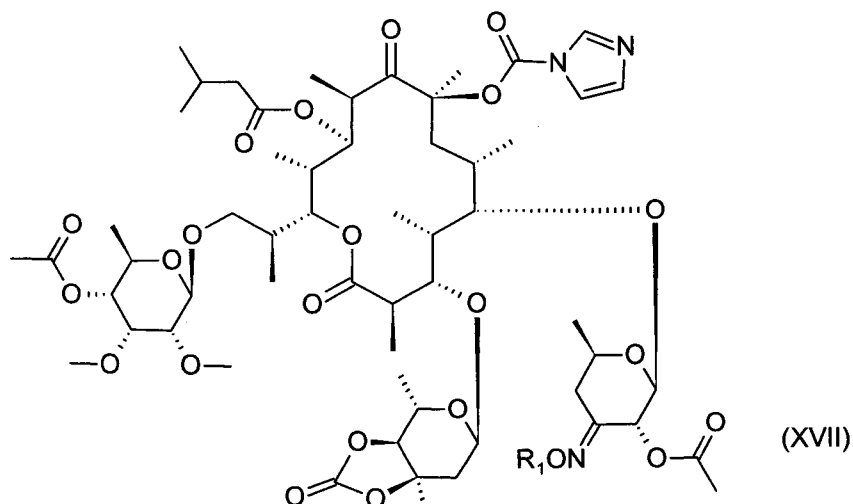


5

in which R_1 is as defined for the compounds of formula (I).

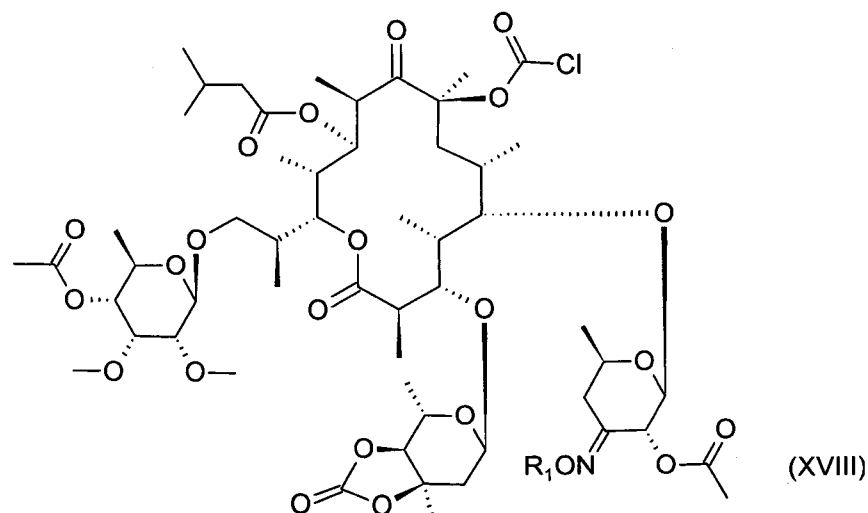
In a third embodiment of step d-2), a compound of formula (XIV) is reacted, for example, with 1,1-carbonyldiimidazole to form a carbonyl intermediate of formula (XVII) below:

10



in which R_1 is as defined for the compounds of formula (I).

5 In a fourth embodiment of step d-2), a compound of formula (XIV) is reacted, for example, with diphosgene to form a carbonyl intermediate of formula (XVIII) below:



in which R_1 is as defined for the compounds of formula (I).

10

The compounds of formula (VII) are commercially available, known or prepared according to methods known to those skilled in the art, and may be in salt form, such as the hydrochloride.

15

The compounds of formula (VIII) are prepared by reacting the sequanamycins (A) with a compound of formula (XIX) H_2NOR_1 in which R_1 is as defined for the compounds of

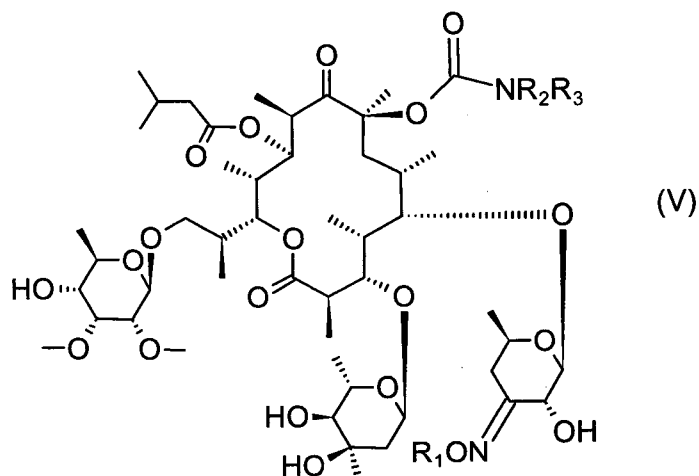
formula (I), in the presence of a base, for instance triethylamine, if necessary. The reaction is performed in a solvent, for instance methanol.

The compounds of formula (XIX) are commercially available, known or prepared according to methods known to those skilled in the art, and may be in salt form, such as the hydrochloride.

The compounds of formula (XXII) are commercially available, known or prepared according to methods known to those skilled in the art.

According to another of its aspects, a subject of the present invention is also the compounds of formulae (V) and (VIII). These compounds are useful as intermediates for synthesizing the compounds of formula (I).

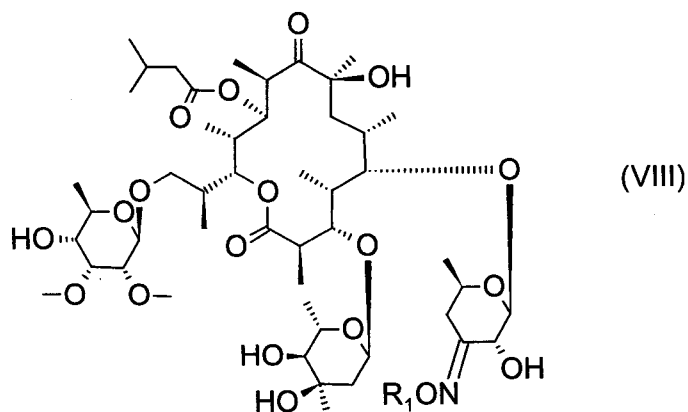
Thus, a subject of the invention is compounds of formula (V):



in which:

- R_1 , R_2 and R_3 are as defined for the compounds of formula (I).

A subject of the invention is also compounds of formula (VIII):



in which:

- R_1 is as defined for the compounds of formula (I).

[Examples of preparation of the compounds of formula (I) from sequanamycin of formula (A)]

5

The following Examples describe the preparation of certain compounds in accordance with the invention. These examples are not limiting and merely illustrate the present invention.

In the Preparations and in the Examples, the following abbreviations are used:

10

EtOAc: ethyl acetate

TLC: thin-layer chromatography

CHCl_3 : chloroform

DCM: dichloromethane

DMF: N,N-dimethylformamide

15

TEA: triethylamine

NaIO_4 : sodium metaperiodate, sodium periodate

K_2CO_3 : potassium carbonate

MeOH: methanol

MgSO_4 : magnesium sulfate

20

NaBH_3CN : sodium cyanoborohydride

NaCl : sodium chloride

NaHCO_3 : sodium bicarbonate

Na_2SO_4 : sodium sulfate

NH_4Cl : ammonium chloride

25

NH_4Ac : ammonium acetate

THF: tetrahydrofuran

RT: room temperature

MATERIALS AND METHODS

30

The progress of the synthetic reactions is monitored by TLC. The plates are made of glass and are coated with Merck 60 F₂₅₄ silica gel. After elution, the plates are observed under ultraviolet light at 254 nm and then revealed by spraying with a 5M sulfuric acid/water solution followed by heating.

35

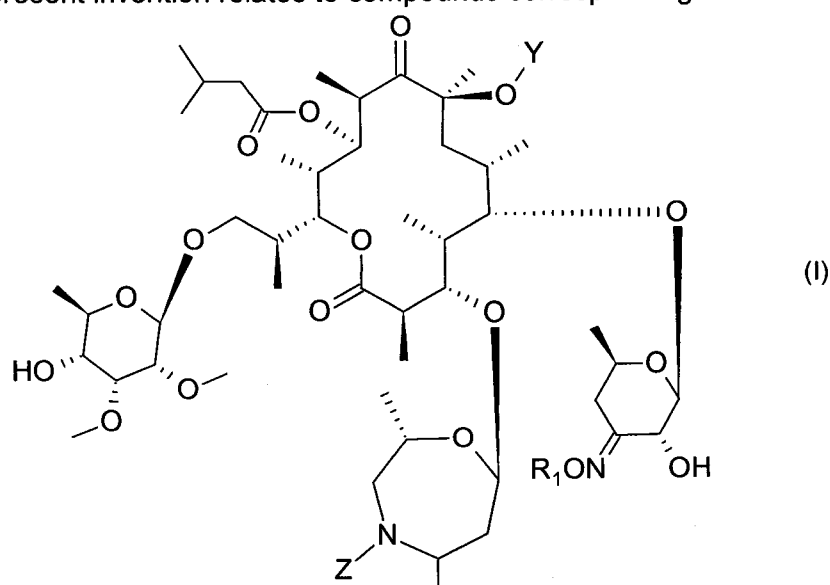
The microwave reactions were performed using a Biotage Initiator 8 EXP microwave machine.

It is therefore necessary to develop compounds with improved and/or more active pharmacokinetic properties, so as to enable their use as medicaments.

A subject of the present invention is in particular macrolide derivatives, which have bacteriostatic and/or bactericidal action, mainly on gram-positive microorganisms, and also on mycobacteria, especially against strains of sensitive *Mycobacterium* or *Corynebacterium* that are resistant to the first-line antibiotics, and the preparation and therapeutic uses thereof.

[COMPOUNDS]

The present invention relates to compounds corresponding to formula (I):



in which:

- Y represents a hydrogen atom, a group $-(C=O)-NR_2R_3$ or a group $-(C=O)-O-R_{18}$;
- Z represents:
 - a hydrogen atom,
 - a group $-C_{1-6}$ -alkyl, which is unsubstituted or substituted with one or more groups R_4 ,
 - a group $-C_{3-7}$ -cycloalkyl, which is unsubstituted or substituted with a group $-NH-(C=O)-R_{19}$ or with a group $-NH-SO_2-R_{20}$,
 - a group $-C_{3-6}$ -heterocycloalkyl,
 - a group $-NH-(C=O)-R_5$;

The products were purified, when necessary, on a Biotage SP-1 chromatograph or a Spot 2 chromatograph from Merck. The columns used are Merck 15-40 μm silica columns (2.5 g to 400 g).

5 Analyses

Mass Spectrometry (MS):

Method a:

- The spectra were acquired on a **Waters UPLC-SQD** machine;
- 10 • Ionization: electrospray in positive and/or negative mode (ES+/-);
- Chromatographic conditions:
 - Column: Acquity BEH C18 - 1.7 μm - 2.1 x 50 mm,
 - Solvents: A: H_2O (0.1% formic acid) B: CH_3CN (0.1% formic acid),
 - Column temperature: 50°C,
 - 15 • Flow rate: 1 ml/min,
 - Gradient (2 min): from 5% to 50% B over 0.8 min; 1.2 min: 100% B; 1.85 min: 100% B; 1.95: 5% B.

Method b:

- 20 • The spectra were acquired on a **Waters UPLC-SQD** machine;
- Ionization: electrospray in positive and/or negative mode (ES+/-);
- Chromatographic conditions:
 - Column: Acquity BEH C18 - 1.7 μm - 2.1 x 50 mm,
 - Solvents: A: H_2O (0.1% formic acid) B: CH_3CN (0.1% formic acid),
 - 25 • Column temperature: 50°C,
 - Flow rate: 0.8 ml/min,
 - Gradient (2.5 min): from 5% to 100% B over 1.8 min; 2.40 min: 100% B; 2.45 min: 100% B; from 100% to 5% B over 0.05 min.

30 Method c:

- The spectra were acquired on a **Waters ZQ** machine;
- Ionization: electrospray in positive and/or negative mode (ES+/-);
- Chromatographic conditions:
 - Column: XBridge C18- 2.5 μm - 3 x 50 mm,

- Solvents: A: H₂O (0.1% formic acid) B: CH₃CN (0.1% formic acid),
- Column temperature: 70°C,
- Flow rate: 0.9 ml/min,
- Gradient (7 min): from 5% to 100% B over 5.3 min; 5.5 min: 100% B; 6.3 min: 5% B.

5

Method d:

- The spectra were acquired on a **Waters UPLC-SQD** machine;
- Ionization: electrospray in positive and/or negative mode (ES+/-);
- Chromatographic conditions:
 - Column: Acquity BEH C18 - 1.7 µm - 2.1 x 50 mm,
 - Solvents: A: H₂O (0.1% formic acid) B: CH₃CN (0.1% formic acid),
 - Column temperature: 50°C,
 - Flow rate: 1 ml/min,
 - Gradient (5 min): from 5% to 100% B over 4.2 min; 4.6 min: 100% B; 4.8 min: 5% B.

10

15

Method e:

- The spectra were acquired on a **Waters ZQ** machine;
- Ionization: electrospray in positive and/or negative mode (ES+/-);
- Chromatographic conditions:
 - Xselect C18 column 3.5 µm - 3 x 50 mm,
 - Solvents: A: H₂O (0.1% formic acid) B: CH₃CN (0.1% formic acid),
 - Column temperature: 60°C,
 - Flow rate: 1 ml/min,
 - Gradient (7 min): from 10% to 100% B over 4.5 min; 4.85 min: 100% B; 6.5 min: 10% B.

20

25

Method f:

- The spectra were acquired on an **Agilent 6110** or **Shimadzu 2010** machine;
- Ionization: electrospray in positive and/or negative mode (ES+/-);
 - Xtimate C18 column 2.1 X 30 mm, 3 µm,
 - Solvents: A: H₂O (4L) + TFA (1.5 mL) B: CH₃CN (4L) + TFA (0.75 mL),
 - Column temperature: 50°C,

30

- Flow rate: 1.2 ml/min,
- Gradient (2 min): from 10% to 80% B over 0.9 min; 1.5 min: 80% B; 1.51 min: 10% B; 2 min: 10% B.

5 **Method g:**

- The spectra were acquired on a **Shimadzu 2010** machine;
- Ionization: electrospray in positive and/or negative mode (ES+/-);
 - Merck RP-18e 2 X 25 mm column,
 - Solvents: A: H₂O (4L) + TFA (1.5 mL) B: CH₃CN (4L) + TFA (0.75 mL),
- Column temperature: 50°C,
- Flow rate: 1.0 ml/min from 0 to 0.08 min; 1.5 ml from 0.08 to 1.50 min,
- Gradient (1.50 min): from 0 to 0.08 min 5% B; from 5% to 95% B from 0.08 to 0.7 min; 1.10 min: 95% B; 1.11: 5% B; 1.5 min: 5% B.

15 **Method h:**

- The spectra were acquired on an **Agilent 6110** or **Shimadzu 2010** machine;
- Ionization: electrospray in positive and/or negative mode (ES+/-);
 - Xtimate C18 column 2.1 X 30 mm, 3 µm,
 - Solvents: A: H₂O (4L) + TFA (1.5 mL) B: CH₃CN (4L) + TFA (0.75 mL),
- Column temperature: 50°C,
- Flow rate: 1.2 ml/min,
- Gradient (2 min): from 30% to 90% B over 0.9 min; 1.5 min: 90% B; 1.51 min: 30% B; 2 min: 30% B.

25 **Method i:**

- The spectra were acquired on an **Agilent 6110** machine;
- Ionization: electrospray in positive and/or negative mode (ES+/-);
 - Columns A: Durashell C18 2.1 X 30 mm, 3 µm; B: Xbrige RP18 2.1 X 50 mm, 5 µm,
- Solvents: A: H₂O (4L) + TFA (1.5 mL) B: CH₃CN (4L) + TFA (0.75 mL),
- Column temperature: 50°C,
- Flow rate: 1.2 ml/min,
- Gradient (2 min): from 10% to 80% B over 0.9 min; 1.5 min: 80% B; 1.51 min: 10% B; 2 min: 10% B.

1H Nuclear magnetic resonance (NMR)

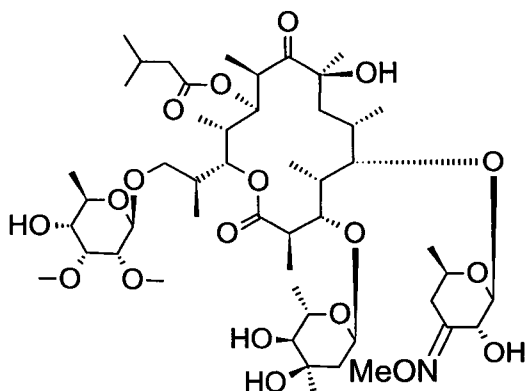
The ¹H NMR spectra were recorded on a Brüker Avance spectrometer (300 MHz, 400 MHz, 500 MHz or 600 MHz) in deuterated DMSO. The chemical shifts are expressed in units δ (ppm) using tetramethylsilane (TMS) as internal reference. For the interpretation of the spectra, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, dd = doubled doublet, ddd = doublet of doubled doublets, m = multiplet, ax. = axial, equat. = equatorial.

PREPARATION

Preparation of the intermediates for the examples described below:

Preparation 1:

(2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-[[[(2R,4R,5S,6S)-4,5-dihydroxy-4,6-dimethyltetrahydro-2H-pyran-2-yl]oxy]-7-hydroxy-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate.



12 g of sequanamycin (A) are placed in 175 ml of MeOH with stirring, and 5.3 ml of TEA, and 3 g of methylhydroxylamine hydrochloride are then added, in this order. The stirring is continued at RT for 20 hours and the MeOH is then evaporated off under vacuum. The crude reaction product is taken up in 150 ml of DCM and washed with 100 ml of water and then with 100 ml of saturated aqueous NaCl solution. The aqueous phases are extracted with 150 ml of DCM. The organic phases are combined, dried over MgSO₄, filtered and concentrated under vacuum. 12.7 g of the product obtained are suspended in 70 ml of a petroleum ether (40-60°C)/isopropanol mixture (2/1). The mixture is heated to 70°C, the insoluble matter is filtered off while hot and the product is then left

to precipitate out at RT over 20 hours. It is filtered off by suction and rinsed with 20 ml of a petroleum ether (40-60°C)/isopropanol mixture (2/1). The precipitate is dried under vacuum at 35°C to give 10.62 g of expected product.

5

MS: method c

Retention time Tr (min) = 4.87; [M+Na]⁺: m/z 1014; [M-H+HCO₂H]⁻: m/z 1036.

10

15

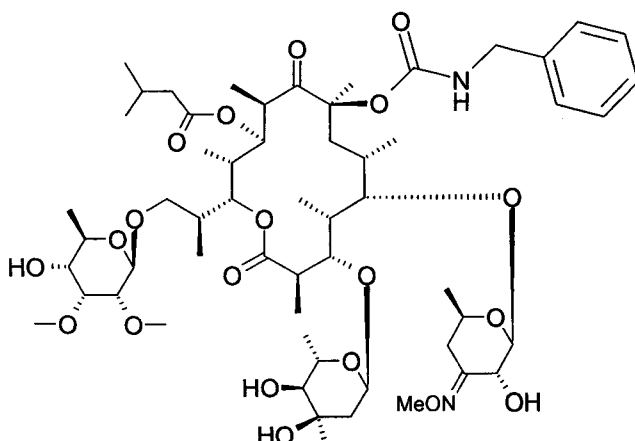
¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 0.81 (d, J=6.8 Hz, 3 H); 0.93 to 1.01 (m, 15 H); 1.07 (d, J=7.0 Hz, 3 H); 1.09 to 1.13 (m, 9 H); 1.17 (d, J=6.0 Hz, 3 H); 1.18 (d, J=6.0 Hz, 3 H); 1.24 (s, 3H); 1.44 (dd, J=10.8 and 14.4 Hz, 1 H); 1.68 to 1.76 (m, 2 H); 1.81 (d, J=14.4 Hz, 1 H); 1.88 (dd, J=11.5 and 15.9 Hz, 1 H); 1.96 to 2.06 (m, 3 H); 2.07 to 2.20 (m, 4 H); 2.73 (quint, J=7.0 Hz, 1 H); 2.81 (t, J=9.0 Hz, 1H); 2.89 to 2.97 (m, 2 H); 3.03 (ddd, J=2.5 and 7.3 and 9.5 Hz, 1 H); 3.18 (q, J=6.8 Hz, 1 H); 3.34 to 3.36 (m, 2 H); 3.37 (s, 3 H); 3.45 (s, 3 H); 3.52 (dq, J=6.2 and 9.4 Hz, 1 H); 3.60 (s, 1 H); 3.62 to 3.65 (m, 1 H); 3.66 (t, J=2.5 Hz, 1 H); 3.71 to 3.77 (m, 1 H); 3.78 (m, 1 H); 3.80 (s, 3 H); 3.81 to 3.84 (m, 1 H); 3.87 (m, 1 H); 4.39 to 4.46 (m, 3 H); 4.50 (s, 1 H); 4.72 (d, J = 8.3 Hz, 1 H); 4.78 (d, J=8.3 Hz, 1 H); 4.84 (d, J=7.3 Hz, 1 H); 4.87 (d, J=3.8 Hz, 1 H); 5.19 (d, J=4.4 Hz, 1 H).

Preparation 2: benzyl carbamate

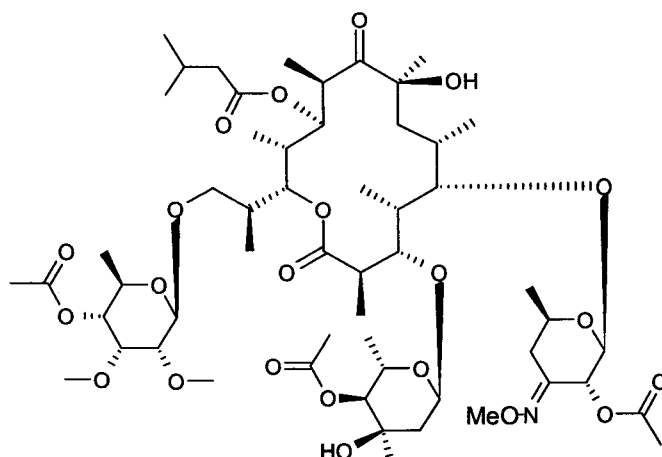
20

25

(2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2R,4R,5S,6S)-4,5-dihydroxy-4,6-dimethyltetrahydro-2H-pyran-2-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate.



Preparation 2.1:



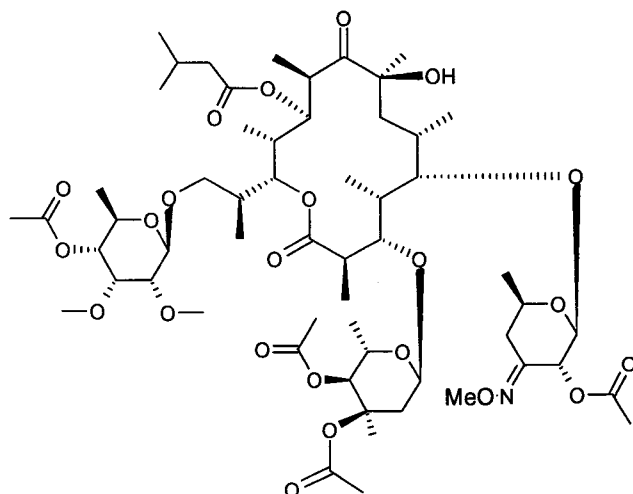
8.6 g of the compound obtained in Preparation 1 are placed in 86 ml of pyridine, and 8.27 ml of acetic anhydride are added. The mixture is stirred for 24 hours at room temperature, and the pyridine is then concentrated under vacuum. 150 ml of DCM are added and the resulting mixture is washed with 120 ml of 1N HCl solution and then with 100 ml of saturated aqueous NaCl solution. The aqueous phases are extracted with 150 ml of DCM. The organic phases are combined, dried over Na₂SO₄, filtered and then evaporated to dryness. 9.75 g of the expected product are obtained.

MS: method a

Retention time Tr (min) = 1.27; [M+Na]⁺: m/z 1140.

¹H NMR spectrum (400 MHz, in ppm, DMSO-d₆): 0.81 (d, J=6.8 Hz, 3 H); 0.91 to 1.01 (m, 15 H); 1.02 (s, 3 H); 1.03 to 1.12 (m, 12 H); 1.21 (d, J=6.1 Hz, 3 H); 1.24 (s, 3 H); 1.50 (dd, J=10.5 and 14.5 Hz, 1H); 1.72 to 1.94 (m, 6 H); 1.96 to 2.10 (m, 8 H); 2.12 to 2.18 (m, 3 H); 2.22 (s, 3 H); 2.77 (m, 1 H); 3.02 (dd, J=2.7 and 8.1 Hz, 1 H); 3.08 (m, 1 H); 3.16 (q, J=7.1 Hz, 1 H); 3.36 (m, 1 H); 3.39 (s, 3 H); 3.41 (s, 3H); 3.45 (m, 1 H); 3.63 to 3.72 (m, 2 H); 3.76 (broad s, 4 H); 3.80 (m, 1 H); 3.85 (t, J=2.7 Hz, 1 H); 4.11 (m, 1 H); 4.17 (s, 1 H); 4.35 (dd, J=2.7 and 10.3 Hz, 1 H); 4.42 (m, 2 H); 4.52 (d, J=8.1 Hz, 1 H); 4.63 (d, J=7.3 Hz, 1 H); 4.69 (d, J=9.0 Hz, 1 H); 4.75 (d, J=9.0 Hz, 1 H); 4.93 (d, J = 4.0 Hz, 1 H); 5.00 (d, J=7.3 Hz, 1 H).

Preparation 2.2:



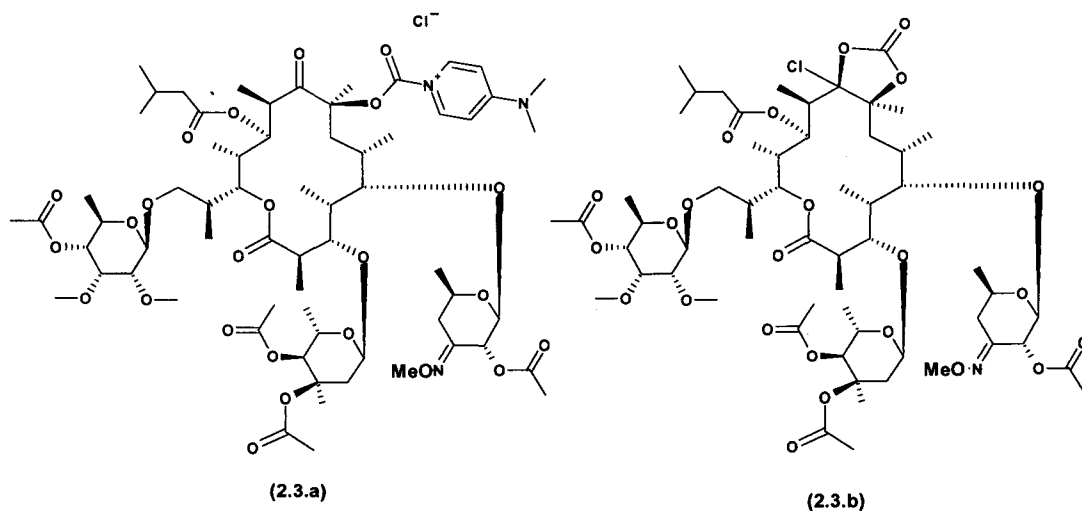
1 g of the compound obtained in Preparation 2.1 are placed in 20 ml of pyridine in a microwave reactor, and 1 ml of acetic anhydride and 50 mg of 4-dimethylaminopyridine are added. The solution is heated for 2 hours at 155°C by microwave. The reaction medium is poured into 50 ml of DCM and washed with 30 ml of 1N HCl solution and then with 30 ml of water. The aqueous phases are extracted with twice 50 ml of DCM. The organic phases are combined, dried over Na₂SO₄, filtered and then evaporated to dryness under vacuum. The residue, 1.1 g of a brown foam, is purified by chromatography on a Merck cartridge (50 g of 15-40 µm silica), eluting with a 40/60 EtOAc/heptane mixture. 0.69 g of the expected compound is obtained.

MS: method a

Retention time Tr (min) = 1.29; [M+Na]⁺: m/z 1182.

¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 0.81 (d, J=6.9 Hz, 3 H); 0.91 to 1.02 (m, 18 H); 1.06 (m, 6 H); 1.10 (d, J=6.9 Hz, 3 H); 1.19 to 1.26 (m, 6 H); 1.35 (s, 3 H); 1.44 (dd, J=10.5 and 14.5 Hz, 1H); 1.79 (m, 1 H); 1.84 to 2.09 (m, 15 H); 2.11 to 2.18 (m, 6 H); 2.73 (m, 1 H); 3.02 (dd, J=2.7 and 7.8 Hz, 1 H); 3.06 to 3.20 (m, 3 H); 3.35 to 3.42 (m, 8 H); 3.60 to 3.69 (m, 2 H); 3.77 (broad s, 4 H); 3.80 (m, 1 H); 3.85 (t, J=2.7 Hz, 1 H); 4.16 (m, 1 H); 4.36 (dd, J=2.7 and 9.9 Hz, 1 H); 4.48 to 4.53 (m, 3 H); 4.59 (d, J = 7.1 Hz, 1 H); 4.73 to 4.80 (m, 2 H); 4.87 (d, J=4.3 Hz, 1 H); 5.00 (d, J=7.1 Hz, 1 H).

Preparation 2.3:



3.5 g of the compound obtained in Preparation 2.2 dissolved in 140 ml of DCM and 3.6 ml of pyridine are placed under argon with stirring. The yellow solution obtained is cooled to -10°C , followed by rapid addition of trichloromethyl chloroformate (diphosgene), and stirring is continued at -10°C for 3 hours. 0.368 g of 4-dimethylaminopyridine dissolved in 10 ml of DCM is then added. The reaction medium is maintained at -5°C for a further 30 minutes and is then allowed to warm to room temperature, and stirring is continued for 20 hours. The solvent is evaporated off and 150 ml of EtOAc are added to the crude reaction product. The mixture is stirred for 15 minutes at room temperature and the precipitate formed is then filtered off. It is rinsed with 70 ml of EtOAc and the filtrate is evaporated to dryness under vacuum. 3.92 g of a mixture of the expected compounds (structures **2.3.a** and **2.3.b**) are obtained. The mixture is used as obtained for the following stage.

Preparation 2.4:

a) Condensation of the amine (benzylamine)

1.5 g of the compound obtained in Preparation 2.3 are placed in 30 ml of DMF in a 100 ml round-bottomed flask, and 0.61 ml of benzylamine are then added. The mixture is stirred for 24 hours at room temperature, followed by addition of 100 g of ice and 100 ml of water. The precipitate formed is filtered off by suction and washed with a minimum amount of water. After drying in an oven under vacuum at 35°C , 1.18 g of the expected compound are obtained.

b) Deprotection

1.18 g of the compound obtained in the preceding step are placed in 20 ml of MeOH, and 0.63 g of K_2CO_3 is added. The heterogeneous medium is stirred at room

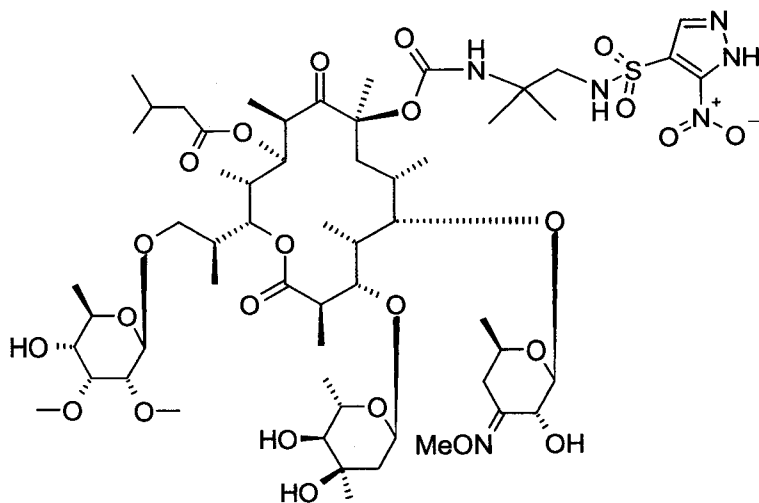
temperature for 3 hours and then filtered through a No. 4 sinter funnel. The filtrate is taken up in 100 ml of EtOAc and washed with saturated aqueous NaCl solution. The organic phase is dried over MgSO_4 , filtered and then evaporated to dryness. 1.05 g of crude compound are obtained, which product is purified by chromatography on a Merck column (30 g of 15-40 μm silica) with a 30/70 to 60/40 EtOAc/heptane elution gradient. 0.466 g of the expected product is obtained.

MS: method c

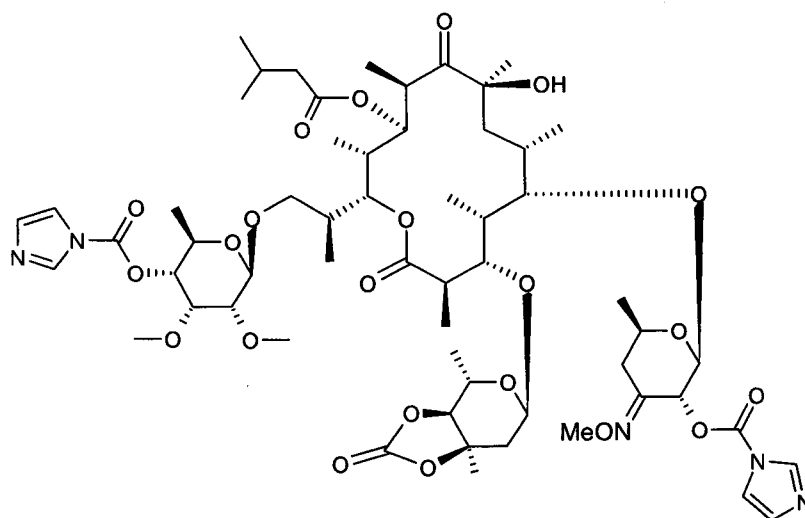
Retention time T_r (min) = 5.21; $[\text{M}+\text{H}]^+$: m/z 1125; base peak: m/z 981 $[\text{M}-\text{H}+\text{HCO}_2\text{H}]^-$: m/z 1169.

^1H NMR spectrum (500 MHz, in ppm, $\text{DMSO}-d_6$): 0.80 (d, $J=6.8$ Hz, 3 H); 0.92 (d, $J=6.8$ Hz, 3 H); 0.96 to 1.02 (m, 9 H); 1.05 (m, 6 H); 1.08 to 1.15 (m, 9 H); 1.18 (m, 6 H); 1.67 to 2.18 (m, 10 H); 1.73 (s, 3 H); 2.18 (d, $J=6.8$ Hz, 2 H); 2.59 to 2.67 (m, 1 H); 2.80 (t, $J=8.8$ Hz, 1 H); 2.92 (dd, $J=2.7$ and 8.1 Hz, 1 H); 2.94 to 3.06 (m, 3 H); 3.27 to 3.35 (partially masked m, 1 H); 3.38 (s, 3 H); 3.41 (d, $J=9.8$ Hz, 1 H); 3.45 (s, 3 H); 3.49 to 3.56 (m, 1 H); 3.60 to 3.72 (m, 4 H); 3.80 (s, 3 H); 3.82 (m, 1 H); 3.87 (broad d, $J=5.4$ Hz, 1 H); 4.01 to 4.17 (m, 3 H); 4.34 to 4.39 (m, 2 H); 4.45 (d, $J=7.8$ Hz, 1 H); 4.50 to 4.57 (m, 2 H); 4.85 (d, $J=7.3$ Hz, 1 H); 4.93 (d, $J=2.4$ Hz, 1 H); 5.13 (broad s, 1 H); 7.18 to 7.36 (m, 6 H).

Preparation 3:



Preparation 3.1:



11.1 g of the compound prepared in Preparation 1 are placed in 220 ml of toluene.
 9.07 g of 1,1'-carbonyldiimidazole are added and the reaction medium is then heated at
 60°C for 45 minutes. It is allowed to cool to room temperature and the precipitate is
 filtered off and washed with toluene. The toluene phase is washed with 100 ml of water
 and then dried over MgSO₄. After filtration, the solvent is evaporated off to dryness and
 14.26 g of the expected product are recovered.

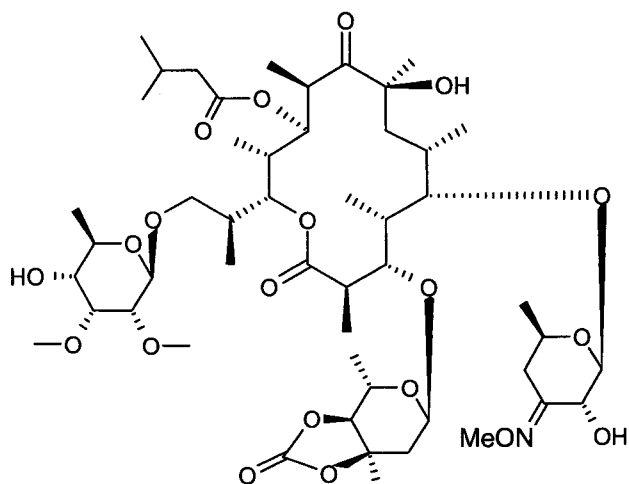
MS: method a

Retention time Tr (min) = 1.22; [M+H]⁺: m/z 1206; [M-H+HCOOH]⁻: m/z 1250.

¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 0.80 (d, J=6.8 Hz, 3 H);
 0.83 (d, J=7.3 Hz, 3 H); 0.90 (d, J=6.8 Hz, 3 H); 0.98 (dt, J=3.2 and 6.4 Hz, 9 H); 1.03 (d,
 J = 7.3 Hz, 3 H); 1.13 (d, J=6.8 Hz, 3 H); 1.16 (d, J=6.4 Hz, 3 H); 1.24 (t, J=2.9 Hz, 6 H);
 1.29 (d, J=5.9 Hz, 3 H); 1.53 (m, 4 H); 1.78 (m, 1 H); 1.84 to 1.91 (m, 1 H); 1.98 (m, 1 H);
 2.02 to 2.11 (m, 3 H); 2.16 (m, 3 H); 2.21 (m, 1 H); 2.34 (dd, J=5.9 and 14.2 Hz, 1 H);
 2.73 (dq, J=7.2 and 7.3 Hz, 1 H); 3.08 to 3.17 (m, 3 H); 3.38 (m, 1 H); 3.41 (s, 3 H);
 3.44 (s, 3 H); 3.56 (d, J=5.9 Hz, 1 H); 3.66 to 3.74 (m, 5 H); 3.78 (ddd, J=2.9 and 6.0 and
 11.6 Hz, 1 H); 3.96 (m, 1 H); 4.07 to 4.20 (m, 3 H); 4.39 (s, 1 H); 4.58 (m, 2 H); 4.63 (d,
 J=9.3 Hz, 1 H); 4.76 (d, J=9.8 Hz, 1 H); 4.91 (s, 2 H); 5.22 (d, J=6.8 Hz, 1 H); 7.12 (d,
 J=10.3 Hz, 2 H); 7.61 (d, J=1.5 Hz, 2 H); 8.29 (d, J=8.8 Hz, 2 H).

- R₁ represents a hydrogen atom, a group -C₂₋₆-alkenyl, a group -C₂₋₆-alkynyl or a group -C₁₋₆-alkyl which is unsubstituted or substituted with a group -C₁₋₄-fluoroalkyl or with a heteroaryl group which is unsubstituted or substituted with a group 3-(3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-ylmethyl;
- 5 - R₂ represents a hydrogen atom or a group -C₁₋₆-alkyl;
- R₃ represents:
 - a group -C₃₋₇-cycloalkyl, which is unsubstituted or substituted with a group -C₁₋₃-alkyl substituted with a group -NH-SO₂-R₂₁,
 - a heteroaryl group,
 - 10 • a linear or branched group -C₁₋₆-alkyl, which is unsubstituted or substituted with a group chosen from:
 - a group -NH-R₆,
 - a group -NH-SO₂-R₇,
 - a group -NH-(C=O)-R₈,
 - 15 • a group -C₃₋₇-cycloalkyl, which is unsubstituted or substituted with a group -C₃₋₆-heterocycloalkyl,
 - a group -C₃₋₆-heterocycloalkyl,
 - an aryl group, which is unsubstituted or substituted with one or more groups chosen independently from a halogen atom and a group -C₁₋₄-fluoroalkyl,
 - 20 • a heteroaryl group, which is unsubstituted or substituted with a group -C₁₋₃-alkyl, a group -C₁₋₄-alkoxy, a group -C₁₋₄-fluoroalkyl or a group -C₃₋₆-heterocycloalkyl,
 - or alternatively with one or more groups -C₁₋₄-alkoxy;
- 25 - or alternatively R₂ and R₃, together with the nitrogen atom to which they are attached, constitute a group -C₃₋₆-heterocycloalkyl chosen from: aziridine, azetidine, pyrrolidine, piperidine, morpholine, thiomorpholine or piperazine; the said heterocycloalkyl group being unsubstituted or substituted with a heteroaryl group, the said heteroaryl group being unsubstituted or substituted with a group
- 30 -C₁₋₄-fluoroalkyl;

Preparation 3.2:



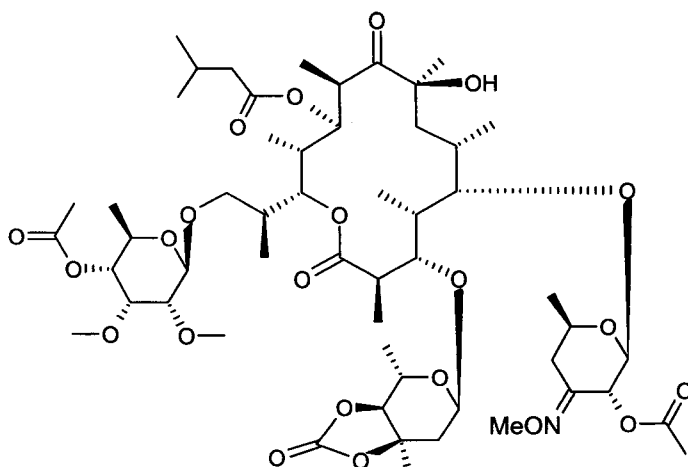
14.01 g of the compound obtained in Preparation 3.1 are placed in 140 ml of THF, 34.8 ml of 1N HCl solution are added and stirring is continued for 24 hours at room temperature. The reaction medium is poured into 200 ml of DCM and washed with 100 ml of water and then with 100 ml of saturated aqueous sodium bicarbonate solution. The aqueous phases are extracted with 200 ml of DCM, and the organic phases are combined, dried over Na₂SO₄, filtered and then evaporated to dryness under vacuum. 11.48 g of the expected product are obtained.

MS: method a

Retention time Tr (min) = 1.19; [M+Na]⁺: m/z 1040; [M-H + HCOOH]⁻: m/z 1062.

¹H NMR spectrum (400 MHz, in ppm, DMSO-d₆): 0.80 (d, J = 6.8 Hz, 3 H); 0.95 (m, 15 H); 1.03 to 1.17 (m, 12 H); 1.23 (s, 3 H); 1.30 (d, J = 5.9 Hz, 3 H); 1.45 (m, 1 H); 1.52 (s, 3 H); 1.78 to 1.89 (m, 2 H); 1.90 to 2.24 (m, 8 H); 2.37 (dd, J = 5.1 and 13.9 Hz, 1 H); 2.79 (m, 2 H); 2.91 (m, 1 H); 3.03 (ddd, J = 2.7 and 6.8 and 9.5 Hz, 1 H); 3.13 (q, J = 6.7 Hz, 1 H); 3.32 (masked m, 1 H); 3.37 (s, 3 H); 3.45 (s, 3 H); 3.52 (m, 2 H); 3.63 to 3.72 (m, 3 H); 3.80 (s, 3 H); 3.92 (t, J = 3.9 Hz, 1 H); 4.00 (ddd, J = 3.2 and 6.1 and 11.7 Hz, 1 H); 4.08 (m, 1 H); 4.15 (m, 1 H); 4.34 (s, 1 H); 4.45 (d, J = 8.1 Hz, 1 H); 4.63 (d, J = 9.8 Hz, 1 H); 4.68 (d, J = 4.2 Hz, 1 H); 4.76 (d, J = 9.5 Hz, 1 H); 4.83 (d, J = 7.1 Hz, 1 H); 4.98 (dd, J = 5.1 and 9.0 Hz, 1 H); 5.43 (d, J = 3.9 Hz, 1 H).

Preparation 3.3:

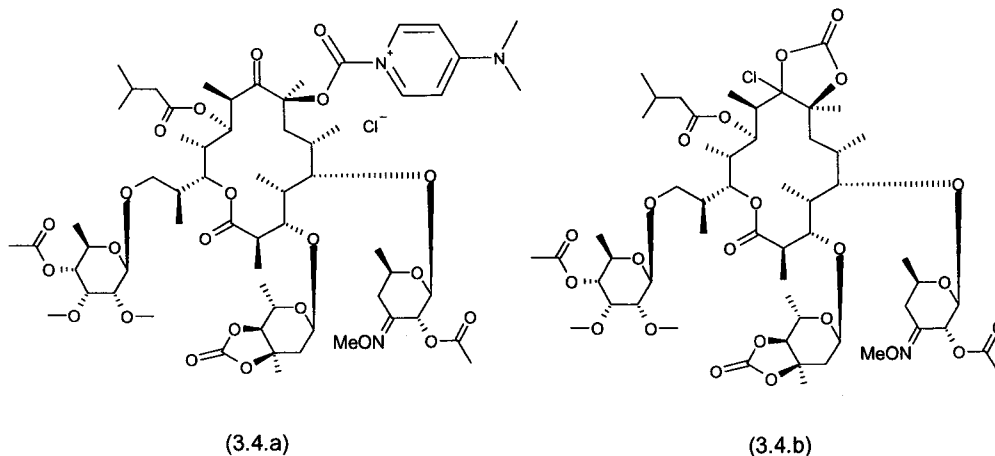


11.4 g of the compound obtained in Preparation 3.2 are placed in 114 ml of pyridine, and 7.4 ml of acetic anhydride are then added. The reaction medium is stirred at room temperature for 24 hours. The pyridine is evaporated off under vacuum and 200 ml of DCM are added to the crude reaction mixture. The resulting mixture is washed with 150 ml of 1N HCl solution and then with 150 ml of water. The aqueous phases are extracted with twice 200 ml of DCM, and the organic phases are combined, dried over Na_2SO_4 , filtered and then evaporated to dryness under vacuum. 12.2 g of compound are obtained, which product is purified by chromatography on a Merck column (400 g of 15-40 μm silica), eluting with a 45/55 EtOAc/heptane mixture. 8.6 g of the expected product are recovered.

MS: method aRetention time T_r (min) = 1.29;[$\text{M}+\text{H}$] $^+$: m/z 1102; [$\text{M}-\text{H}+\text{HCOOH}$] $^-$: m/z 1146.

^1H NMR spectrum (400 MHz, in ppm, $\text{DMSO}-d_6$): 0.81 (d, $J=7.3$ Hz, 3 H); 0.95 (m, 15 H); 1.06 (m, 6 H); 1.11 (d, $J=6.6$ Hz, 3 H); 1.20 (d, $J=6.1$ Hz, 3 H); 1.24 (s, 3 H); 1.29 (d, $J=3.9$ Hz, 3 H); 1.41 to 1.54 (m, 4H); 1.77 to 1.91 (m, 2 H); 1.96 to 2.09 (m, 10 H); 2.11 to 2.23 (m, 4 H); 2.36 (m, 1 H); 2.79 (m, 1 H); 3.02 (m, 2 H); 3.13 (m, 1 H); 3.35 (m, 1 H); 3.38 (s, 3 H); 3.41 (s, 3 H); 3.52 (d, $J=7.1$ Hz, 1 H); 3.64 to 3.73 (m, 2 H); 3.74 to 3.83 (m, 5 H); 3.86 (broad s, 1 H); 4.06 to 4.14 (m, 2 H); 4.33 to 4.40 (m, 2 H); 4.52 (d, $J=8.1$ Hz, 1 H); 4.65 (d, $J=9.8$ Hz, 1 H); 4.76 (m, 2 H); 4.97 (dd, $J=5.3$ and 8.9 Hz, 1 H); 5.02 (d, $J=6.1$ Hz, 1 H).

Preparation 3.4:

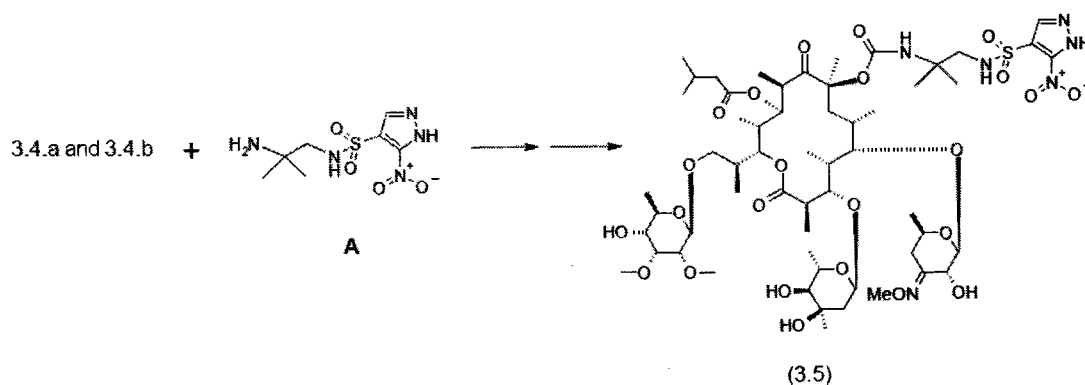


4 g of the compound obtained in Preparation 3.3 are placed, under argon, in 190 ml of DCM, and 4.12 ml of pyridine are added. The solution is cooled to -20°C , followed by addition, in a single portion, of 0.8 ml diphosgene, and stirring is continued at -20°C for 3 hours. 0.443 g of 4-dimethylaminopyridine is added, while still at -20°C , the mixture is then allowed to warm to room temperature and stirring is continued for 20 hours. The DCM is evaporated off under vacuum and the crude reaction product is taken up in 150 ml of EtOAc and stirred for 1 hour at room temperature. The precipitate formed is filtered off and rinsed with 80 ml of EtOAc. The filtrate is evaporated to dryness under vacuum, 4.7 g of the expected compounds (structures 3.4.a and 3.4.b) are obtained as a mixture, and the mixture is used as obtained for the following stage.

MS: method a

Retention time 3.4.a: Tr (min) = 1.1 $[\text{M}+\text{H}]^{+}$: 1251; 3.4.b: Tr (min) = 1.3 $[\text{M}+\text{Na}]^{+}$: 1187.

Preparation 3.5:



a) Condensation of the amine A.

0.64 g of the mixture of compounds obtained in Preparation 3.4 is dissolved in 16 ml of DMF, followed by addition of 401 mg of N-(2-amino-2-methylpropyl)-5-nitro-1H-pyrazole-4-sulfonamide dihydrochloride (prepared according to the process described in international patent application WO 2009/29439 A1) and 374 μ l of TEA. The mixture is stirred for 4 days at room temperature, and 75 ml of EtOAc are then added. The mixture is washed with 50 ml of water and then with 50 ml of saturated aqueous NaCl solution. The organic phase is dried over MgSO_4 , filtered and concentrated under reduced pressure. 0.7 g of compound is obtained, which product is purified by chromatography on a silica column (Merck, 30 g of 15-40 μ m silica), eluting with a 60/40 heptane/EtOAc mixture.

147 mg of the expected compound are obtained.

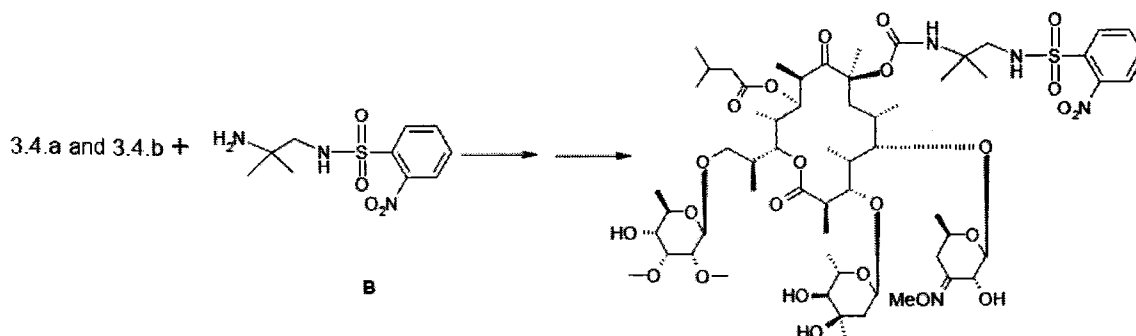
b) Deprotection

140 mg of the compound obtained in the preceding step are placed in 3 ml of MeOH. 70 mg of K_2CO_3 are added to the solution obtained. The mixture is stirred for 24 hours at room temperature. 15 ml of EtOAc are then added. The mixture is washed with 10 ml of water and then with 10 ml of saturated aqueous NaCl solution. The organic phase is dried over MgSO_4 , filtered and then evaporated to dryness under vacuum. 0.114 g of the expected product is obtained.

MS: method b

ES^+ : m/z 1137 (base peak)

^1H NMR spectrum (500 MHz, in ppm, DMSO-d_6): 0.79 (d, $J=6.8$ Hz, 3 H); 0.93 (m, 9 H); 1.01 (d, $J=6.8$ Hz, 3 H); 1.10 (m, 18 H); 1.17 (m, 9 H); 1.64 (s, 3 H); 1.80 (m, 5 H); 1.99 (m, 4 H); 2.13 (m, 3 H); 2.65 (m, 1 H); 2.82 (m, 2 H); 2.96 (m, 5 H); 3.30 (masked m, 1 H); 3.37 (s, 3 H); 3.40 (d, $J=9.8$ Hz, 1 H); 3.46 (s, 3H); 3.51 (m, 1 H); 3.60 (m, 2 H); 3.67 (m, 2 H); 3.78 (m, 1 H); 3.80 (s, 3 H); 3.85 (m, 1 H); 4.08 (broad s, 1H); 4.36 (m, 2 H); 4.44 (d, $J=8.3$ Hz, 1 H); 4.56 (m, 2 H); 4.80 (d, $J=6.4$ Hz, 1 H); 4.99 (broad d, $J=2.0$ Hz, 1H); 5.09 (d, $J=3.9$ Hz, 1 H); 6.33 (s, 1 H); 6.86 (m, 1 H); 8.07 (broad s, 1 H); 14.52 (m, 1 H).

Preparation 4:

a) Condensation of the amine B

0.64 g of the mixture of compounds obtained in Preparation 3.4 is placed in 15 ml of DMF. 462 mg of N-(2-amino-2-propylmethyl)-2-nitrobenzenesulfonamide hydrochloride (prepared according to the process described in Tetrahedron Letters, 2009, vol. 50, 28, pp. 4050 – 4053) and then 249 μ l of TEA are added to the solution obtained. The mixture is stirred for 3 days at room temperature, and 75 ml of EtOAc are then added. The mixture is washed with 50 ml of water and then with 50 ml of saturated aqueous NaCl solution. The organic phase is dried over MgSO_4 , filtered and concentrated under reduced pressure. 0.57 g of compound is obtained, which product is purified by chromatography on silica (30 g of 15-40 μ m silica), eluting with a 55/45 heptane/EtOAc mixture.

0.25 g of the expected compound is obtained.

b) Deprotection

0.24 g of the compound obtained in the preceding step is placed in 4 ml of MeOH. 119 mg of potassium carbonate are added to the solution obtained. The suspension is stirred at room temperature for 24 hours. 20 ml of EtOAc are added and the mixture is washed with 10 ml of water and then with 20 ml of saturated aqueous NaCl solution. The organic phase is dried over MgSO_4 , filtered and concentrated under reduced pressure. 0.197 g of the expected product is obtained.

MS: method b

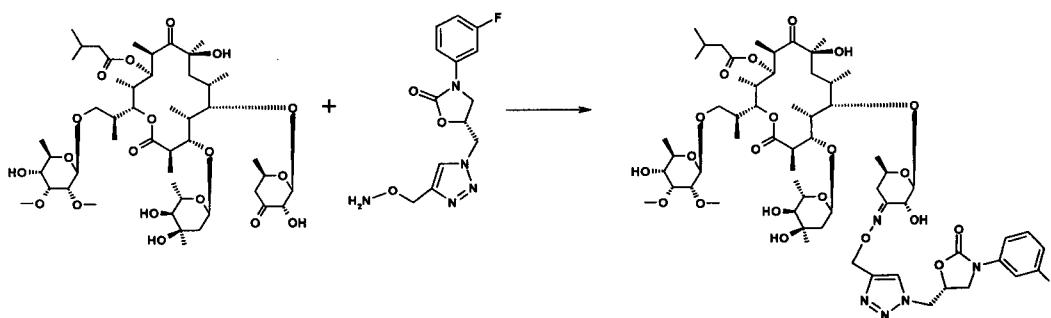
ES^+ : m/z 1147 (base peak)

^1H NMR spectrum (500 MHz, in ppm, DMSO-d_6): 0.79 (d, $J=6.8$ Hz, 3 H); 0.90 to 0.95 (m, 9 H); 1.01 (d, $J=6.8$ Hz, 3 H); 1.04 to 1.14 (m, 18 H); 1.15 to 1.20 (m, 9 H); 1.64 (s, 3 H); 1.67 to 1.88 (m, 5 H); 1.92 to 2.05 (m, 4 H); 2.09 to 2.18 (m, 3 H); 2.65 (m, 1 H); 2.81 (t, $J=9.0$ Hz, 1 H); 2.89 to 3.12 (m, 6 H); 3.31 (partially masked m, 1 H); 3.37 (s, 3 H); 3.40 (d, $J=9.5$ Hz, 1 H); 3.45 (s, 3 H); 3.51 (m, 1 H); 3.59 to 3.63 (m, 2 H); 3.65 to

3.71 (m, 2 H); 3.78 (m, 1 H); 3.80 (s, 3 H); 3.85 (dd, $J=4.7$ and 6.5 Hz, 1 H); 4.07 (broad s, 1 H); 4.36 (d, $J=6.5$ Hz, 1 H); 4.38 (d, $J=8.9$ Hz, 1 H); 4.43 (d, $J=7.9$ Hz, 1 H); 4.52 to 4.61 (m, 2 H); 4.83 (d, $J=7.1$ Hz, 1 H); 4.99 (broad d, $J=2.9$ Hz, 1 H); 5.11 (broad d, $J=4.7$ Hz, 1 H); 6.32 (broad s, 1 H); 7.77 to 8.05 (m, 5 H).

5

Preparation 5:



400 mg of sequanamycin (A), 180 mg of (R)-5-((4-((aminooxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)-3-(3-fluorophenyl)oxazolidin-2-one (prepared according to the process described in Journal of Carbohydrate Chemistry, 2006, vol. 25, pp. 407 – 425) and 10 ml of MeOH are added. The solution obtained is stirred for 5 hours at room temperature. 20 ml of DCM are added. The mixture is washed with 20 ml of 1 M HCl and then with 20 ml of water. The organic phase is dried over MgSO_4 , filtered through a sinter funnel and then evaporated to dryness. The product is purified by chromatography on a column of silica (Merck, 15–40 μm , 20 g), eluting with a 95/5 DCM/MeOH mixture. 205 mg of the expected compound are recovered.

MS: method b

ES⁻: $[\text{M}-\text{H}+\text{HCO}_2\text{H}]^-$: m/z 1296.

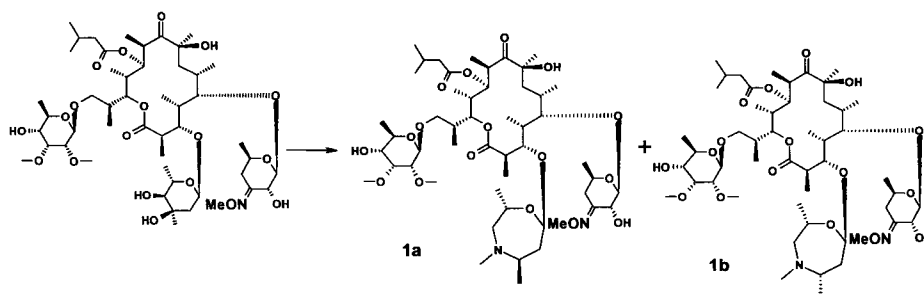
¹H NMR spectrum (400 MHz, in ppm, DMSO- d_6): 0.81 (d, $J=6.8$ Hz, 3 H); 0.96 (d, $J=6.4$ Hz, 9 H); 1.00 (m, 6 H); 1.07 (d, $J=7.3$ Hz, 3 H); 1.08 to 1.13 (m, 9 H); 1.17 (m, 6 H); 1.24 (s, 3 H); 1.46 (m, 1 H); 1.69 to 1.75 (m, 2 H); 1.79 to 1.91 (m, 2 H); 1.95 to 2.20 (m, 7 H); 2.73 (m, 1 H); 2.81 (m, 1 H); 2.89 to 2.97 (m, 2 H); 3.03 (m, 1 H); 3.19 (broad q, $J=6.8$ Hz, 1 H); 3.27 to 3.38 (partially masked m, 2 H); 3.37 (s, 3 H); 3.45 (s, 3 H); 3.52 (m, 1 H); 3.60 (broad s, 1 H); 3.62 to 3.68 (m, 2 H); 3.72 (m, 1 H); 3.76 to 3.85 (m, 2 H); 3.86 to 3.94 (m, 2 H); 4.26 (t, $J=9.3$ Hz, 1 H); 4.38 to 4.46 (m, 3 H); 4.50 (s, 1 H); 4.72 (d, $J=8.3$ Hz, 1 H); 4.78 (d, $J=8.6$ Hz, 1 H); 4.82 (m, 3 H); 4.89 (broad d, $J=3.8$ Hz, 1 H); 5.10 (s, 2 H); 5.12 to 5.20 (m, 2 H); 6.97 (dt, $J=2.2$ and 8.4 Hz, 1 H); 7.27 (broad d, $J=8.4$ Hz, 1 H); 7.37 to 7.51 (m, 2 H); 8.22 (s, 1 H).

30

EXAMPLE 1: Compound 1

Compound 1-a: (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-hydroxy-2-(1-
 5 {[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-
 yl]oxy}propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-
 pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-[[[(2S,5R,7R)-2,4,5-trimethyl-1,4-
 oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate.

Compound 1-b: (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-hydroxy-2-(1-
 10 {[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-
 yl]oxy}propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-
 pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-[[[(2S,5S,7R)-2,4,5-trimethyl-1,4-
 oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate.



3 g of the compound of Preparation 1 are placed in 68 ml of MeOH. The reaction medium is cooled in an ice bath to a temperature of +4°C, followed by dropwise addition of a solution of 3.23 g of sodium periodate in 68 ml of water. The mixture is stirred for 6 hours at room temperature.

The medium is saturated with NaCl and filtered, and the filtrate is extracted with DCM (3×200 ml). The organic phases are combined, washed with saturated aqueous NaCl solution, dried over MgSO₄, filtered and finally concentrated under reduced pressure. The oily residue obtained is dissolved, under argon, in 680 ml of MeOH. The pH is adjusted to 7 by addition of acetic acid, followed by addition of 2 M methylamine dissolved in 12.1 ml of THF. The pH is maintained at 7 with acetic acid. After stirring for 30 minutes at room temperature, 0.95 g of NaBH₃CN is added in a single portion, and the mixture is stirred for a further 16 hours at room temperature. The reaction medium is filtered and rinsed with MeOH. The filtrate is concentrated under reduced pressure and then taken up in 600 ml of DCM. The resulting mixture is washed with saturated aqueous NaCl solution (3 × 60 ml). The organic phase is dried over MgSO₄, filtered and then evaporated to dryness under vacuum. 3.5 g of product are purified by chromatography on

a Merck cartridge (150 g of 15-40 μ m silica) with a 100/0 to 90/10 DCM/MeOH elution gradient. 530 mg of diastereoisomer **1-a**, 380 mg of diastereoisomer **1-b** and 661 mg of a mixture of the two isomers are obtained.

5 **Compound 1-a:**

MS: method b

Retention time Tr (min) = 1.26; [M+H]⁺: m/z 989; [M-H+HCO₂H]⁻: m/z 1033 (base peak).

10 **¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆):** 0.79 (d, J=6.8 Hz, 3 H);
0.89 to 1.01 (m, 15 H); 1.03 (d, J=6.8 Hz, 3 H); 1.05 to 1.10 (m, 9 H); 1.11 (d, J=6.1 Hz,
3 H); 1.13 (d, J=6.1 Hz, 3 H); 1.24 (s, 3H); 1.48 (dd, J=11.4 and 14.7 Hz, 1 H); 1.70 to
2.08 (m, 8 H); 2.10 to 2.22 (m, 3 H); 2.18 (broad s, 3 H); 2.36 (m, 1 H); 2.57 (m, 1 H);
2.70 (d, J=13.6 Hz, 1 H); 2.75 (m, 1 H); 2.83 (dd, J=2.9 and 16.6 Hz, 1 H); 2.92 (dd,
J=2.7 and 8.0 Hz, 1 H); 3.03 (m, 1 H); 3.12 (q, J=6.8 Hz, 1 H); 3.30 (partially masked m,
15 1H); 3.38 (s, 3 H); 3.45 (s, 3 H); 3.52 (m, 1 H); 3.58 to 3.72 (m, 4 H); 3.80 (s, 3 H);
3.89 (m, 2 H); 4.26 (m, 1 H); 4.31 (s, 1 H); 4.45 (d, J=8.0 Hz, 1 H); 4.65 (broad d,
J=9.8 Hz, 1 H); 4.70 (d, J=4.6 Hz, 1 H); 4.74 (d, J=9.6 Hz, 1 H); 4.86 (d, J=7.1 Hz, 1 H);
4.93 (dd, J=3.1 and 9.5 Hz, 1 H); 5.33 (d, J=4.6 Hz, 1 H).

20 **Compound 1-b:**

MS: method b

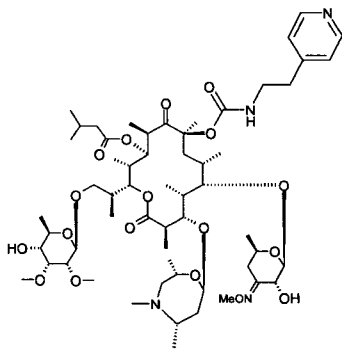
Retention time Tr (min) = 1.26; [M-H+HCO₂H]⁻: m/z 1033 (base peak).

25 **¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆):** 0.82 (d, J=6.8 Hz, 3 H);
0.91 to 1.32 (m, 36 H); 1.44 to 1.51 (m, 1 H); 1.80 to 1.87 (m, 1 H); 1.96 to 2.37 (m, 10 H);
2.76 to 2.80 (m, 2 H); 2.77 (s, 3 H); 2.85 (dd, J=3.1 and 16.8 Hz, 1 H); 2.93 (dd, J=2.7 and
8.0 Hz, 1 H); 3.00 to 3.07 (m, 2 H); 3.12 to 3.18 (m, 1 H); 3.28 (d, J=13.7 Hz, 1 H); 3.31 to
3.36 (m, 1 H); 3.40 (s, 3 H); 3.48 (s, 3 H); 3.51 to 3.58 (m, 2 H); 3.64 to 3.70 (m, 2H);
3.82 (s, 3 H); 3.86 to 3.90 (m, 1 H); 3.94 to 4.02 (m, 2 H); 4.31 to 4.37 (m, 1 H); 4.47 (d,
J=7.9 Hz, 1 H); 4.66 to 4.77 (m, 3 H); 5.12 (dd, J=5.8 and 8.9 Hz, 1 H).

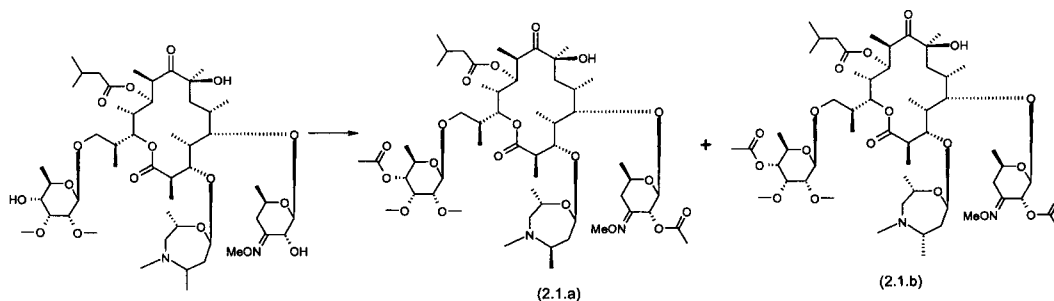
30

EXAMPLE 2: Compound 2

(2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-([(2R,3R,4R,5R,6R)-5-hydroxy-3,4-
dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy)propan-2-yl)-10-([(2S,3R,6R)-3-hydroxy-
4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy)-3,5,7,9,11,13-hexamethyl-6,14-
35 dioxo-7-([(2-(pyridin-4-yl)ethyl]carbamoyl)oxy)-12-([(2S,5S,7R)-2,4,5-trimethyl-1,4-
oxazepan-7-yl]oxy)oxacyclotetradecan-4-yl 3-methylbutanoate;



Step 2.1:



660 mg of the mixture of diastereoisomers prepared in Example 1 are placed in 14.7 ml of pyridine. 631 μ l of acetic anhydride are added. After stirring for 24 hours at room temperature, 189 μ l of acetic anhydride are added and stirring is continued at room temperature for 24 hours. The solution is concentrated under vacuum and the residue is taken up in 200 ml of DCM. The resulting mixture is washed with 1N HCl solution (3 $\times$ 5 ml) and then with saturated aqueous sodium bicarbonate solution (2 $\times$ 5 ml) and finally with saturated aqueous NaCl solution (3 $\times$ 5 ml). The organic phase is dried over MgSO_4 , filtered and then evaporated to dryness under vacuum. 756 mg of crude product are obtained, which product is purified by chromatography on a Merck cartridge (15-40 μ m silica) with a 100/0 to 95/5 DCM/MeOH elution gradient. 287 mg of diastereoisomer **2.1.a** and 266 mg of diastereoisomer **2.1.b** are obtained.

Compound 2.1.a:

MS: method b

Retention time T_r (min) = 1.46; $[M+H]^+$: 1073

^1H NMR spectrum (500 MHz, in ppm, DMSO-d_6): 0.79 (s, 3 H); 0.91 (m, 6 H); 0.97 (m, 9 H); 1.02 (d, $J=6.6$ Hz, 3 H); 1.07 (m, 12 H); 1.19 (d, $J=6.1$ Hz, 3 H); 1.24 (s, 3 H); 1.49 (dd, $J=11.7$ and 14.5 Hz, 1 H); 1.82 (m, 4 H); 1.98 (m, 4 H); 2.05 (s, 3 H); 2.08 (s, 3 H); 2.16 (m, 3 H); 2.20 (s, 3 H); 2.44 (dd, $J=9.9$ and 14.4 Hz, 1 H); 2.64 (m, 1 H); 2.74 (m, 2 H); 3.03 (m, 2 H); 3.12 (q, $J=6.7$ Hz, 1 H); 3.35 (dd, $J=4.9$ and 10.1 Hz, 1 H); 3.39 (s, 3 H); 3.41 (s, 3 H); 3.55 (d, $J=8.0$ Hz, 1 H); 3.67 (m, 2 H); 3.79 (m, 2 H); 3.78 (s, 3 H); 3.86 (t, $J=2.7$ Hz, 1 H); 4.14 (m, 1 H); 4.31 (s, 1 H); 4.37 (dd, $J=2.5$ and

9.9 Hz, 1 H); 4.52 (d, $J=8.0$ Hz, 1H); 4.65 (d, $J=9.8$ Hz, 1 H); 4.76 (d, $J=9.5$ Hz, 1 H); 4.79 (d, $J=6.8$ Hz, 1 H); 4.88 (dd, $J=3.4$ and 8.6 Hz, 1H); 5.01 (d, $J=6.8$ Hz, 1 H).

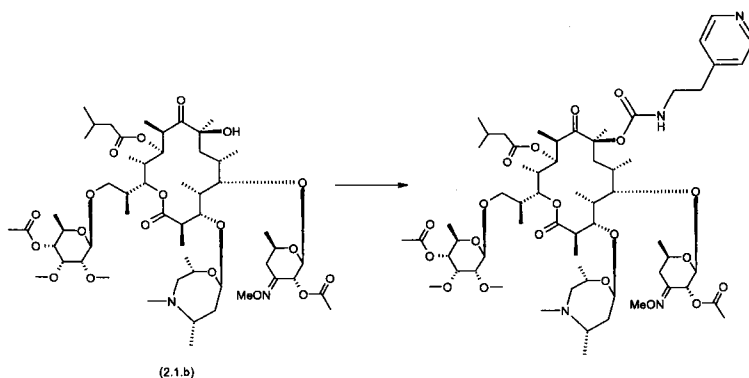
Compound 2.1.b:

MS: method b

Retention time T_r (min) = 1.46; $[M+H]^+$: 1073

^1H NMR spectrum (500 MHz, in ppm, in DMSO- d_6 + TFA + AcOD) : 0.82 (d, $J=6.8$ Hz, 3 H); 0.95 (m, 15 H); 1.06 (m, 9 H); 1.20 (m, 6 H); 1.25 (s, 3 H); 1.30 (d, $J=6.9$ Hz, 3 H); 1.48 (m, 1 H); 1.84 (m, 1 H); 1.94 to 2.36 (m, 10 H); 2.08 (s, 6 H); 2.75 (m, 1 H); 2.76 (s, 3 H); 3.06 (m, 3 H); 3.15 (q, $J=6.5$ Hz, 1 H); 3.20 (d, $J=13.7$ Hz, 1 H); 3.37 (dd, $J=4.7$ and 9.7 Hz, 1 H); 3.40 (s, 3 H); 3.43 (s, 3 H); 3.54 (m, 1 H); 3.60 (m, 1 H); 3.68 to 3.77 (m, 2 H); 3.81 (m, 1 H); 3.79 (s, 3 H); 3.87 (t, $J=2.4$ Hz, 1 H); 3.91 (m, 1 H); 4.26 (m, 1 H); 4.38 (dd, $J=2.4$ and 9.9 Hz, 1 H); 4.54 (d, $J=8.0$ Hz, 1 H); 4.67 (d, $J=9.5$ Hz, 1 H); 4.72 (m, 2 H); 5.04 (d, $J=6.6$ Hz, 1 H); 5.09 (dd, $J=5.1$ and 8.9 Hz, 1 H).

Step 2.2:



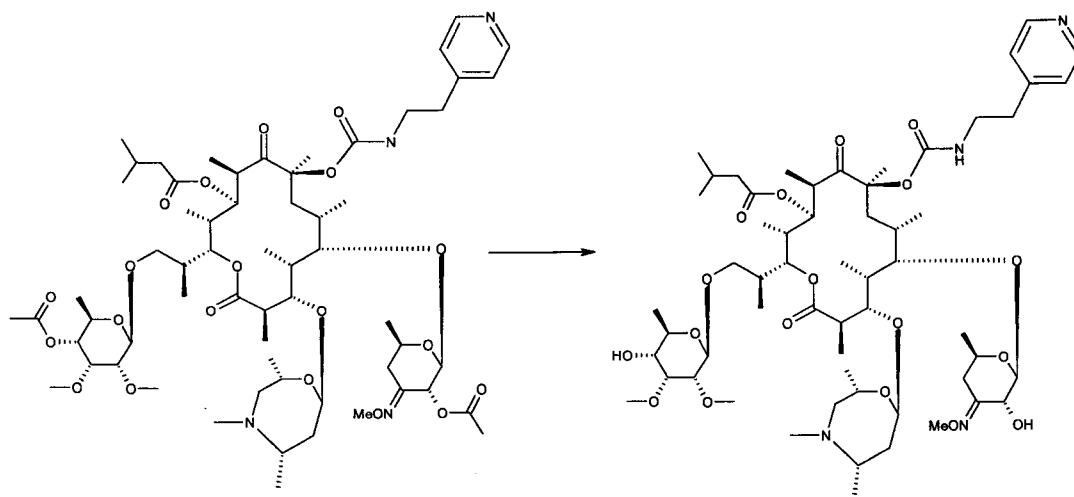
50 mg of diastereoisomer **2.1.b** of the preceding step are placed, under argon, in 2 ml of DCM and 65 μ l of pyridine. The colourless solution is cooled to -10°C . 10 μ l of trichloromethyl chloroformate are then added, stirring is continued at -10°C for 3 hours, and 5.7 mg (46.67 μ mol) of 4-dimethylaminopyridine are then added. The mixture is allowed to warm to room temperature, and stirring is then continued for 20 hours. The resulting mixture is concentrated under vacuum, the residue is taken up in 5 ml of EtOAc and the insoluble matter is filtered off and rinsed with 2 ml of EtOAc. The filtrate is concentrated under vacuum. 55 mg of the compound obtained are dissolved in 2 ml of DMF. 53.4 mg of 4-(2-aminoethyl)pyridine are then added and the mixture is stirred for 48 hours at room temperature. The medium is poured onto an ice/water mixture. The resulting mixture is filtered by suction and the precipitate formed is then dried under vacuum. 34 mg of the expected product are obtained.

- R₄ independently represents a group chosen from:
 - a hydroxyl group,
 - a deuterium,
 - a halogen atom,
 - 5 • a group -C₃₋₇-cycloalkyl,
 - an aryl group, which is unsubstituted or substituted with one or more groups -R₉,
 - a heteroaryl group,
 - a group -C₃₋₆-heterocycloalkyl,
 - 10 • a group -C₁₋₄-alkoxy,
 - a group -(C=O)-NH-R₁₀,
 - a group -NH-R₁₁,
 - a group -NH-(C=O)-R₁₂,
 - or a group -NH(SO₂)-R₁₃;
- 15 - R₅ represents a heteroaryl group;
- R₆ represents a heteroaryl group, which is unsubstituted or substituted with one or more halogen atoms;
- R₇ represents a group -C₁₋₄-fluoroalkyl, an aryl group or a heteroaryl group, the said aryl and heteroaryl groups being unsubstituted or substituted with one or
- 20 more groups R₁;
- R₈ represents a heteroaryl group, which is unsubstituted or substituted with one or more groups R₂;
- R₉ represents a halogen atom, a group -C₁₋₄-alkoxy, a formyl group (CHO) or a group -C₁₋₄-alkyl, which is unsubstituted or substituted with a hydroxyl group;
- 25 - R₁₀ represents a heteroaryl group, which is unsubstituted or substituted with a group -C₁₋₃-alkyl;
- R₁₁ represents:
 - a group -C₃₋₁₀-heterocycloalkyl, which is unsubstituted or substituted with one or more oxide groups,

MS: method b

Retention time Tr (min) = 1.16 ES+: $[M+2H]^{2+}$ m/z 611 (base peak); ES-: $[M-H+HCO_2H]^-$: m/z 1265 (base peak)

5 **^1H NMR spectrum (500 MHz, in ppm, DMSO- d_6):** 0.79 (d, $J=6.9$ Hz, 3 H); 0.89 to 1.11 (m, 30 H); 1.17 (m, 3 H); 1.64 to 2.18 (m, 12 H); 1.67 (s, 3 H); 2.07 (s, 3 H); 2.08 (s, 3 H); 2.27 (s, 3 H); 2.44 (d, $J=13.2$ Hz, 1 H); 2.55 (masked m, 1 H); 2.70 (m, 3 H); 2.85 (m, 1 H); 3.02 (m, 5 H); 3.35 (masked m, 1 H); 3.38 (s, 3H); 3.41 (s, 3 H); 3.67 (m, 3 H);
 10 3.80 (m, 2 H); 3.78 (s, 3 H); 3.86 (s, 1 H); 4.14 (m, 1 H); 4.37 (dd, $J=2.2$ and 9.9 Hz, 1 H); 4.52 (d, $J=8.0$ Hz, 1 H); 4.57 (d, $J=9.6$ Hz, 1 H); 4.64 (d, $J=9.3$ Hz, 1 H); 4.75 (d, $J=6.6$ Hz, 1H); 4.96 (m, 1 H); 5.01 (d, $J=6.6$ Hz, 1 H); 6.89 (broad t, $J=5.4$ Hz, 1 H); 7.18 to 7.23 (m, 2 H); 8.43 (d, $J=5.5$ Hz, 2 H)

Step 2.3:

15

32.5 mg of the product prepared in the preceding step are placed in 2 ml of MeOH with 11 mg of K_2CO_3 . After stirring for 1 hour 30 minutes at room temperature, 20 ml of EtOAc are added to the reaction medium. The resulting mixture is washed with 20 ml of saturated aqueous NaCl solution. After separation of the phases by settling, the organic phase is dried over $MgSO_4$, filtered and then evaporated to dryness under vacuum. 24 mg of the expected compound are obtained.

20

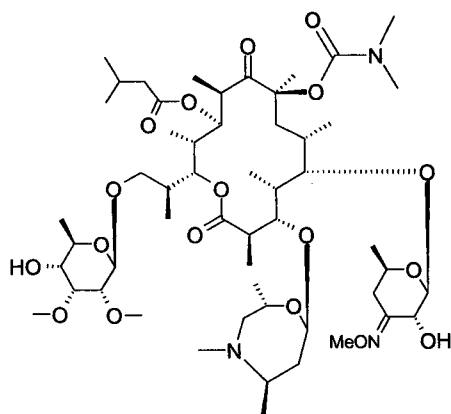
MS: method b

25 Retention time Tr (min) = 0.97; $[M+2H]^{2+}$: 569 (base peak); $[M-H+HCO_2H]^-$: m/z 1181.

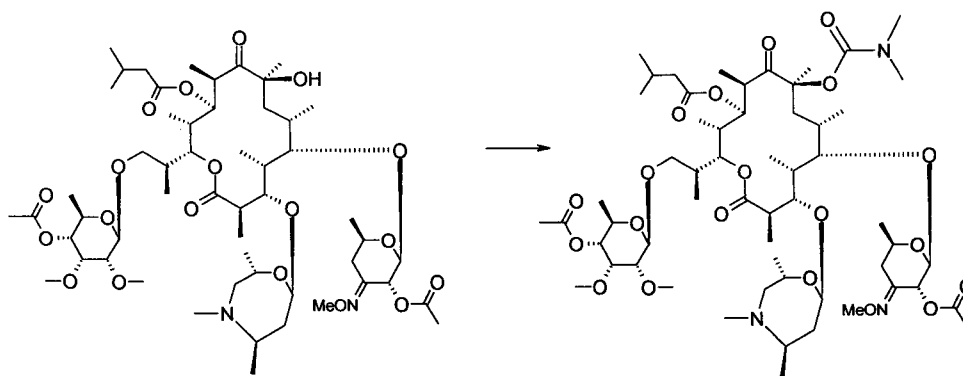
¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 0.78 (d, J=6.9 Hz, 3 H); 0.96 to 1.15 (m, 33 H); 1.64 to 1.87 (m, 6 H); 1.92 to 2.19 (m, 9 H); 2.25 (s, 3 H); 2.42 (d, J=13.4 Hz, 1 H); 2.55 (masked m, 1 H); 2.70 (m, 3 H); 2.85 (m, 2 H); 2.92 (dd, J=2.3 and 8.1 Hz, 1 H); 3.01 (m, 2 H); 3.12 (m, 2 H); 3.30 (masked m, 1 H); 3.37 (s, 3 H); 3.45 (s, 3 H); 3.52 (m, 1 H); 3.61 (m, 2 H); 3.68 (broad s, 1 H); 3.80 (m, 4 H); 3.97 (m, 2 H); 4.28 (m, 1 H); 4.44 (d, J=8.0 Hz, 1 H); 4.53 to 4.65 (m, 2 H); 4.69 (d, J=4.7 Hz, 1 H); 4.86 (d, J=7.1 Hz, 1 H); 4.99 (m, 1 H); 5.38 (d, J=4.7 Hz, 1 H); 6.89 (m, 1 H); 7.23 (d, J=5.2 Hz, 2 H); 8.43 (d, J=5.5 Hz, 2 H).

EXAMPLE 3: Compound 3

(2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(dimethylcarbamoyl)oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-[[[(2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy}oxacyclotetradecan-4-yl 3-methylbutanoate.



Step 3.1:



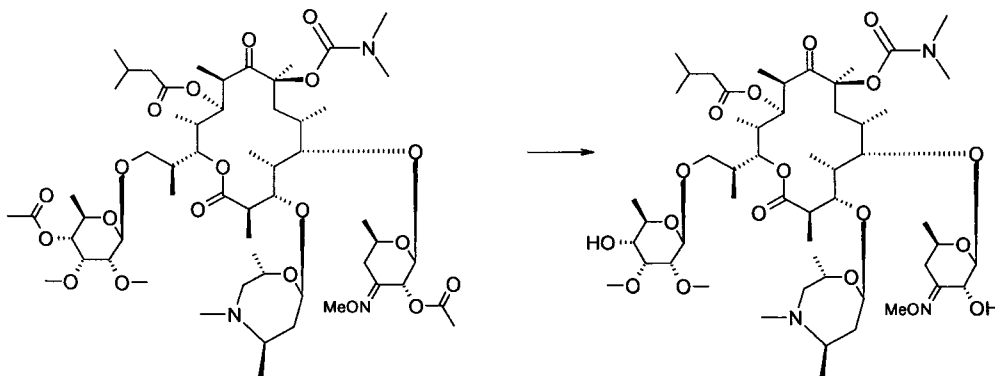
150 mg of compound **2.1.a** obtained in step 2.1 of Example 2 are placed in 9 ml of DCM and 210 μ l of pyridine in a 30 ml round-bottomed flask, under argon. The colourless solution is cooled to -10°C . 30 μ l of trichloromethyl chloroformate are then added and stirring is continued for 3 hours at -10°C , followed by addition of 17 mg of 4-dimethylaminopyridine dissolved in 2 ml of DCM. The mixture is allowed to warm to room temperature, and stirring is continued for 20 hours. The resulting mixture is concentrated under vacuum, the residue is taken up in 4 ml of DMF, and dimethylamine hydrochloride (173 mg) dissolved in DMF (2 ml) and TEA (0.3 ml) is then added. The reaction medium is stirred for 3 hours at room temperature. The resulting mixture is poured into an ice/water mixture, and the precipitate formed is filtered off by suction. 146 mg of product are recovered, which product is purified by chromatography on a Merck cartridge (5 g of 15-40 μ m silica), eluting with a 95/5 DCM/MeOH mixture. 93 mg of the expected compound is obtained.

MS: method b

Retention time T_r (min) = 1.33; $[M+H]^+$: 1144

^1H NMR spectrum (500 MHz, in ppm, $\text{DMSO}-d_6$): 0.79 (d, $J=6.9$ Hz, 3 H); 0.92 (m, 6 H); 0.96 (d, $J=6.6$ Hz, 6 H); 1.05 (m, 18 H); 1.17 to 1.19 (m, 3 H); 1.69 to 2.03 (m, 9 H); 1.71 (s, 3 H); 2.05 (s, 3 H); 2.08 (s, 3H); 2.13 (m, 3 H); 2.21 (s, 3 H); 2.44 to 2.49 (masked m, 1 H); 2.72 (m, 6 H); 2.84 (broad s, 3 H); 3.03 (m, 3H); 3.33 (masked, 1 H); 3.39 (s, 3 H); 3.42 (s, 3 H); 3.65 (m, 3 H); 3.77 (s, 3 H); 3.80 (m, 1 H); 3.86 (t, $J=2.6$ Hz, 1 H); 3.89 (d, $J=4.3$ Hz, 1 H); 4.10 (m, 1 H); 4.37 (dd, $J=2.5$ and 9.9 Hz, 1 H); 4.52 (d, $J=8.0$ Hz, 1H); 4.59 (d, $J=10.1$ Hz, 1 H); 4.69 (d, $J=9.6$ Hz, 1 H); 4.73 (d, $J=7.3$ Hz, 1H); 4.83 (dd, $J=3.8$ and 7.9 Hz, 1H); 5.00 (d, $J=7.3$ Hz, 1 H).

Step 3.2:



90 mg of the product obtained in the preceding step are placed in 5.5 ml of MeOH, and 32.6 mg of K_2CO_3 . After stirring for 1 hour 30 minutes at room temperature, 50 ml of

EtOAc are added to the reaction medium. The resulting mixture is washed with 20 ml of saturated aqueous NaCl solution. After separation of the phases by settling, the organic phase is dried over MgSO₄, filtered and then evaporated to dryness under vacuum. 50 mg of the expected compound is obtained.

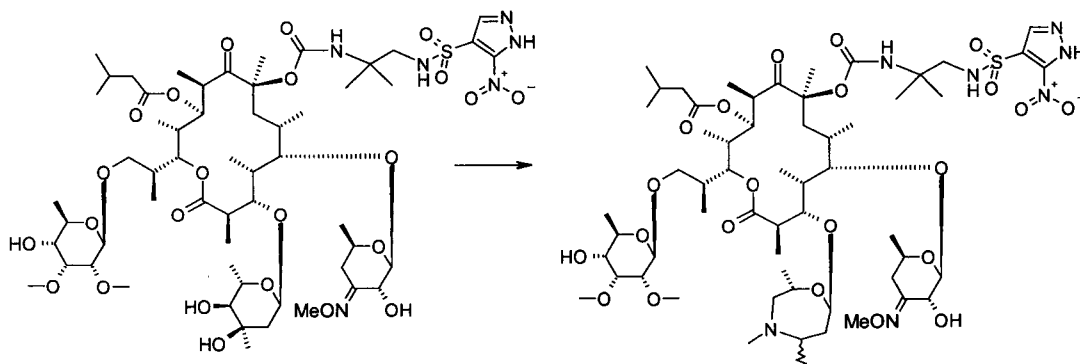
MS: method b

Retention time Tr (min) = 1.12; [M+H]⁺: 1060.

¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 0.78 (d, J=6.9 Hz, 3 H); 0.92 (m, 6 H); 0.96 (d, J=6.6 Hz, 6 H); 1.01 to 1.14 (m, 21 H); 1.70 to 2.06 (m, 9 H); 1.71 (s, 3 H); 2.09 to 2.17 (m, 3 H); 2.19 (s, 3 H); 2.38 (dd, J=9.4 and 14.0 Hz, 1 H); 2.59 (m, 1 H); 2.79 (m, 9 H); 2.92 (dd, J=2.6 and 8.0 Hz, 1 H); 3.02 (m, 2 H); 3.30 (masked m, 1 H); 3.38 (s, 3 H); 3.46 (s, 3 H); 3.51 (m, 1 H); 3.63 (dd, J=4.4 and 9.6 Hz, 1 H); 3.67 (broad s, 1 H); 3.71 (d, J=6.9 Hz, 1 H); 3.77 (d, J=5.4 Hz, 1 H); 3.83 (m, 4 H); 3.89 (t, J=4.9 Hz, 1 H); 4.21 (m, 1 H); 4.45 (d, J=7.9 Hz, 1 H); 4.62 (m, 3 H); 4.88 (m, 2 H); 5.24 (d, J=4.6 Hz, 1 H).

EXAMPLE 4: Compound 4

(2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl)oxy)-3,5,7,9,11,13-hexamethyl-7-(((2-methyl-1-(((5-nitro-1H-pyrazol-4-yl)sulfonyl)amino)propan-2-yl)carbamoyl)oxy)-6,14-dioxo-12-(((2S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl)oxy)oxacyclotetradecan-4-yl 3-methylbutanoate.



102 mg of the product obtained in Preparation 3 are placed in 2 ml of MeOH. The solution is cooled to 0°C, and a solution of 86 mg of sodium metaperiodate in water (2 ml) is added. The reaction mixture is stirred magnetically at room temperature for 5 hours. 15 ml of DCM are added and the mixture is washed with 10 ml of water and then with 10 ml of saturated aqueous NaCl solution. The organic phase is dried over MgSO₄, filtered

and concentrated under reduced pressure. 86 mg of product obtained are dissolved in MeOH (10 ml), the solution is cooled to 0°C and methylamine (84 µl of a 2M solution in THF) and then acetic acid (9.7 µl) are added. After stirring for 10 minutes at 0°C, 13.34 mg of NaBH₃CN are added. The reaction medium is stirred for 1 hour at 0°C and is then allowed to warm to room temperature, and stirring is continued for 20 hours. 20 ml of DCM are added and the mixture is washed with 15 ml of saturated aqueous NaHCO₃ solution and then with 15 ml of saturated aqueous NaCl solution. The organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure. 0.12 g of product obtained is purified by preparative LC/MS, eluting with a 15/85 to 95/5 gradient of acetonitrile/water containing 0.1% TFA. The fractions of mass 1278 to 1281 are recovered. The recovered phases are brought to pH 8 with saturated aqueous NaHCO₃ solution and then extracted with 50 ml of EtOAc. The organic phase is dried over MgSO₄, filtered and then evaporated to dryness under vacuum. 38 mg of the expected product are obtained.

MS: method b

Retention time Tr (min) = 1.06; [M+Na]⁺: 1278

¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 70/30 mixture of the diastereoisomers, 0.78 (d, J=6.8 Hz, 3 H); 0.91 (d, J=6.8 Hz, 3 H); 0.95 (m, 9 H); 1.02 to 1.16 (m, 27 H); 1.68 (broad s, 3 H); 1.71 to 1.90 (m, 4 H); 1.93 to 2.21 (m, 8 H); 2.36 (broad s, 2.1 H); 2.46 (broad s, 0.9 H); 2.61 (m, 1 H); 2.69 to 3.06 (m, 9 H); 3.30 (masked m, 1 H); 3.38 (s, 3 H); 3.46 (s, 3 H); 3.49 to 3.64 (m, 2.3 H); 3.67 (t, J=2.6 Hz, 1 H); 3.72 (m, 1 H); 3.78 to 3.91 (m, 2.7 H); 3.80 (s, 3 H); 4.30 (m, 1 H); 4.45 (d, J=7.9 Hz, 1 H); 4.57 to 4.67 (m, 3 H); 4.83 (d, J=6.8 Hz, 1 H); 4.96 (dd, J=3.0 and 9.2 Hz, 0.7 H); 5.04 (dd, J=4.8 and 8.6 Hz, 0.3 H); 5.26 (broad s, 0.7 H); 5.36 (broad s, 0.3 H); 6.32 (broad s, 1 H); 6.70 m, 1 H); 7.89 to 7.93 (m, 1 H).

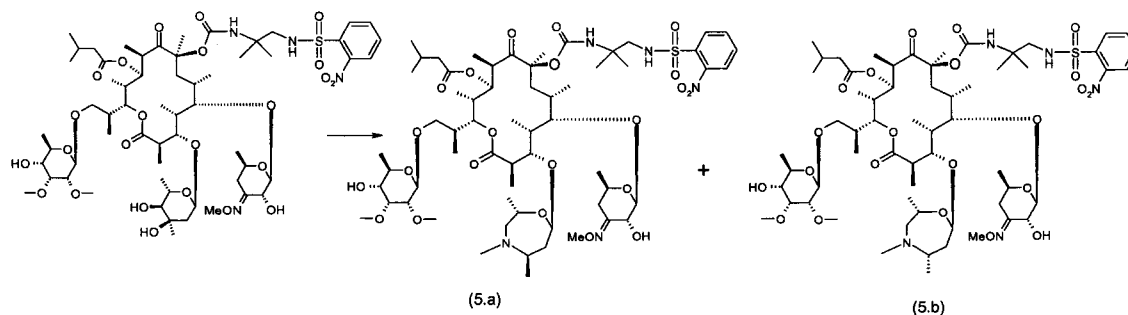
EXAMPLE 5: Compound 5

Compound 5-a: (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-
 {[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy}propan-2-yl)-10-
 {[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyl-7-
 {[(2-methyl-1-
 {[(2-nitrophenyl)sulfonyl]amino}propan-2-yl)carbamoyl]oxy}-6,14-dioxo-12-
 {[(2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy}oxacyclotetradecan-4-yl 3-methylbutanoate.

Compound 5-b: (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-(1-
 {[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-

yl]oxy}propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-7-[[[(2-methyl-1-[[[(2-nitrophenyl)sulfonyl]amino}propan-2-yl)carbonyl]oxy]-6,14-dioxo-12-[[[(2S,5S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy}oxacyclotetradecan-4-yl 3-methylbutanoate.

5



A solution of 99 mg of the product obtained in Preparation 4 in 2 ml of MeOH is cooled to 0°C. A solution of 83 mg of NaIO₄ in 2 ml of water is then added dropwise. After 15 minutes at 0°C, the mixture is allowed to warm to room temperature, and stirring is continued for 3 hours. The reaction medium is poured into 20 ml of DCM. The resulting mixture is washed with 10 ml of water, the phases are separated by settling and then washed again with 10 ml of saturated aqueous NaCl solution. The organic phase is dried over MgSO₄, filtered and then evaporated to dryness. 110 µl of a 2M solution of methylamine in THF, 13.9 µl of AcOH and finally 16.67 mg of NaBH₃CN are added, in this order, to a solution of 95 mg of the compound thus obtained in 8 ml of MeOH. The mixture is stirred for 20 hours at room temperature. 20 ml of DCM are added and the resulting mixture is washed with saturated aqueous NaHCO₃ solution and then with aqueous NaCl solution. The aqueous phases are extracted with DCM. The organic phases are combined, dried over MgSO₄, filtered and then evaporated to dryness. The 85 mg of product obtained are combined with another batch of 68 mg prepared in a preceding reaction under the conditions described above. This mixture is purified by chromatography on silica (10 g of 15-40 µm silica) with a 94.5/5.5 DCM/MeOH elution solvent. 49 mg of diastereoisomer **5-a** and 30 mg of isomer **5-b** are obtained.

Compound 5-a:

MS: method b

Retention time Tr (min) = 1.16; [M+H]⁺: 1288

¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 0.78 (d, J=6.8 Hz, 3 H); 0.90 (d, J=6.8 Hz, 3 H); 0.92 to 0.97 (m, 9 H); 1.00 to 1.17 (m, 27 H); 1.62 to 1.70 (m, 4 H); 1.71 to 1.85 (m, 4 H); 1.89 to 2.08 (m, 4 H); 2.13 (s, 3 H); 2.19 (s, 3 H); 2.39 (dd, J=9.7 and 14.2 Hz, 1 H); 2.59 (m, 1 H); 2.74 (m, 2 H); 2.83 to 3.11 (m, 6 H); 3.28 (masked

m, 1 H); 3.38 (s, 3 H); 3.46 (s, 3 H); 3.52 (quint, J=6.2 Hz, 1 H); 3.62 (dd, J=4.4 and 9.8 Hz, 1 H); 3.68 (m, 2 H); 3.76 (d, J=4.5 Hz, 1 H); 3.82 (m, 5 H); 4.26 (quint, J=7.2 Hz, 1 H); 4.45 (d, J=7.9 Hz, 1 H); 4.59 (d, J=9.9 Hz, 1 H); 4.68 (m, 2 H); 4.83 (d, J=7.1 Hz, 1 H); 4.91 (dd, J=2.8 and 9.2 Hz, 1 H); 5.23 (d, J=4.4 Hz, 1 H); 6.28 (s, 1 H); 7.91 (m, 5 H).

5

Compound 5-b:

MS: method b

Retention time Tr (min) = 1.16; [M+H]⁺: 1288

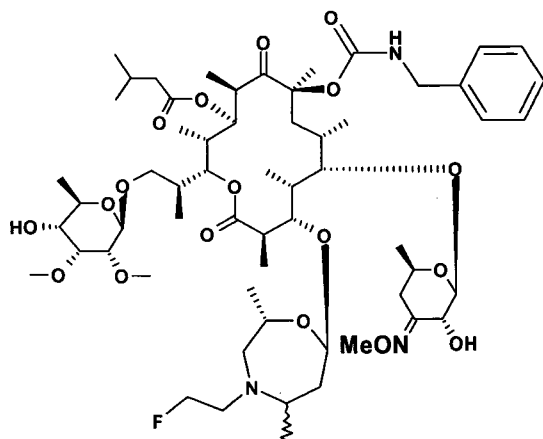
¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 0.78 (d, J=6.8 Hz, 3 H);
 10 0.90 (d, J=7.0 Hz, 3 H); 0.95 (d, J=6.7 Hz, 9 H); 1.00 (d, J=6.7 Hz, 3 H); 1.05 (m, 9 H);
 1.09 (d, J=6.2 Hz, 3 H); 1.13 (m, 9 H); 1.24 (s, 3 H); 1.66 (s, 3 H); 1.78 (m, 4 H); 1.99 (m,
 4 H); 2.13 (m, 4 H); 2.25 (s, 3 H); 2.42 (d, J=13.0 Hz, 1 H); 2.53 (m, 1 H); 2.74 (quint,
 J=7.3 Hz, 1 H); 2.87 (m, 4 H); 2.98 (q, J=6.4 Hz, 1 H); 3.07 (m, 2 H); 3.32 (masked m,
 1 H); 3.37 (s, 3 H); 3.46 (s, 3 H); 3.52 (m, 1 H); 3.62 (m, 2 H); 3.67 (t, J=2.5 Hz, 1 H);
 15 3.80 (m, 4 H); 3.88 (m, 2 H); 4.29 (quint, J=7.8 Hz, 1 H); 4.44 (d, J=7.9 Hz, 1 H); 4.58 (d,
 J=9.3 Hz, 1 H); 4.63 (d, J=9.4 Hz, 1 H); 4.72 (d, J=4.5 Hz, 1 H); 4.83 (d, J=7.2 Hz, 1 H);
 5.00 (dd, J=4.5 and 9.1 Hz, 1 H); 5.35 (d, J=4.5 Hz, 1 H); 6.27 (broad s, 1 H); 7.74 to
 8.05 (m, 5 H).

20

EXAMPLE 6: Compound 6

(2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[(benzylcarbamoyl)oxy]-12-[[[(2S,7R)-4-(2-fluoroethyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate.

25



0.5 g of the compound obtained in Preparation 2 is placed in 10 ml of MeOH.

The solution obtained is cooled to 0°C. A solution of 0.475 mg of sodium metaperiodate in 10 ml of water is then rapidly added dropwise. After 15 minutes at 0°C, the mixture is allowed to warm to room temperature, and stirring is continued for 5 hours. The medium is saturated with NaCl (~3 g) and taken up in DCM (40 ml). The precipitate is filtered off and washed with saturated aqueous NaCl solution. The aqueous phase is extracted with DCM. The organic phases are combined, dried over MgSO₄, filtered and then evaporated to dryness under vacuum. 443 mg of the expected product are obtained.

100 mg of this compound are dissolved in 2.2 ml of MeOH, followed by addition, in the following order, of 25 µl of TEA, 22 mg of 2-fluoroethylamine hydrochloride, 12.7 µl of acetic acid and finally 16.8 mg of NaBH₃CN. The medium is stirred for 20 hours at room temperature. 20 ml of DCM are added and the resulting mixture is washed with saturated aqueous sodium bicarbonate solution and then with aqueous NaCl solution. The aqueous phases are extracted with DCM. The organic phases are combined, dried over Na₂SO₄, filtered and then evaporated to dryness. 92 g of the product obtained are purified by chromatography on silica (5 g of 15-40 µm silica) with a 97/3 DCM/MeOH eluent mixture. The expected product is obtained in the form of a mixture of diastereoisomers.

MS: method b

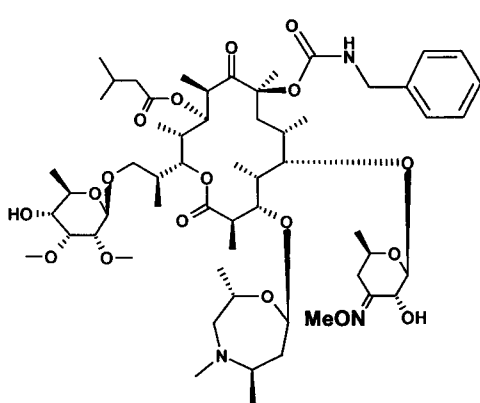
Retention time Tr (min) = 1.28; [M-H+HCO₂H]⁻: m/z 1198.

¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆): 70/30 mixture of the diastereoisomers 0.78 (d, J=6.8 Hz, 3 H); 0.91 (d, J=6.9 Hz, 3 H); 0.94 (d, J=7.3 Hz, 3 H); 0.98 (dd, J=1.6 and 6.6 Hz, 6 H); 1.01 to 1.16 (m, 21 H); 1.60 to 2.22 (m, 15 H); 2.52 (masked m, 1 H); 2.59 (d, J=5.0 Hz, 1 H); 2.68 to 3.08 (m, 9 H); 3.28 (masked m, 1 H); 3.38 (s, 3 H); 3.46 (s, 3 H); 3.52 (m, 1 H); 3.64 (m, 2 H); 3.72 to 3.93 (m, 7 H); 4.10 (d, J=6.0 Hz, 2 H); 4.24 (m, 1 H); 4.41 (m, 3 H); 4.56 to 4.72 (m, 3 H); 4.83 (d, J=7.1 Hz, 1 H); 4.88 (m, 0.7 H); 4.99 (dd, J=4.0 and 9.1 Hz, 0.3 H); 5.13 (d, J=4.6 Hz, 0.7 H); 5.31 (d, J=4.6 Hz, 0.3 H); 7.28 (m, 5 H).

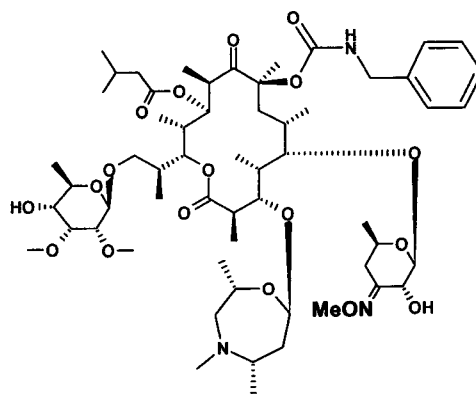
EXAMPLE 7: Compound 7

Compound 7-a: (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[[[(benzylcarbamoyl)oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxo-12-[[[(2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-methylbutanoate.

Compound 7-b: (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-
 [(benzylcarbonyl)oxy]-2-(1-[[[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-
 methyltetrahydro-2H-pyran-2-yl]oxy]propan-2-yl]-10-[[[(2S,3R,6R)-3-hydroxy-4-
 (methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-
 dioxo-12-[[[(2S,5S,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl]oxy]oxacyclotetradecan-4-yl 3-
 methylbutanoate.



(7.a)



(7.b)

0.68 g of the compound obtained in Preparation 2 is placed in THF (7 ml). The solution obtained is cooled to 0°C. A solution of sodium metaperiodate in 7ml of water is then rapidly added. After 15 minutes at 0°C, the mixture is allowed to warm to room temperature, and stirring is continued for 6 hours. The precipitate formed is filtered off and rinsed with 7 ml of THF. A 2N solution of methylamine in 1.21 ml of THF and then 139.04 µl of acetic acid are added. After stirring for 5 minutes at room temperature, 199.63 mg of NaBH₃CN are added. The suspension obtained is stirred at room temperature for 20 hours. The precipitate formed is filtered off and rinsed with 50 ml of DCM. The filtrate is washed with 30 ml of saturated aqueous NaHCO₃ solution and then with 30 ml of saturated aqueous NaCl solution. The aqueous phases are extracted with 50 ml of DCM. The organic phases are combined, dried over MgSO₄, filtered and then evaporated to dryness under vacuum. The product obtained is purified by chromatography on a Merck cartridge (50 g of 15-40 µm silica), eluting with a 94/6 CHCl₃/MeOH mixture. 320 mg of the expected compound **7-a**, 77 mg of the other diastereoisomer **7-b** and 147 mg of a mixture of diastereoisomers are obtained.

Compound 7-a:

MS: method b

Retention time Tr (min) = 1.31; [M-H+HCO₂H]: m/z 1166 (base peak).

¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆ + CD₃COOD): 0.81 (d, J=6.9 Hz, 3 H); 0.93 (d, J=6.8 Hz, 3 H); 0.95 to 1.02 (m, 9 H); 1.05 to 1.17 (m, 15 H); 1.24 (d, J=6.0 Hz, 3 H); 1.30 (d, J=6.6 Hz, 3 H); 1.74 (m, 7 H); 2.04 (m, 3 H); 2.18 (m, 5 H); 2.78 (s, 3 H); 2.79 (m, 1 H); 2.89 (d, J=14.8 Hz, 1 H); 2.93 (dd, J=2.5 and 8.0 Hz, 1 H); 3.03 (m, 2 H); 3.13 (m, 1 H); 3.35 (m, 2 H); 3.40 (s, 3 H); 3.45 (m, 1 H); 3.48 (s, 3 H); 3.51 (m, 2 H); 3.68 (m, 2 H); 3.82 (s, 3 H); 3.87 (m, 2 H); 3.94 (d, J=4.9 Hz, 1 H); 4.13 (d, J=5.7 Hz, 2 H); 4.45 (m, 2 H); 4.62 (m, 3 H); 5.12 (dd, J=4.5 and 8.4 Hz, 1 H); 7.28 (m, 6 H).

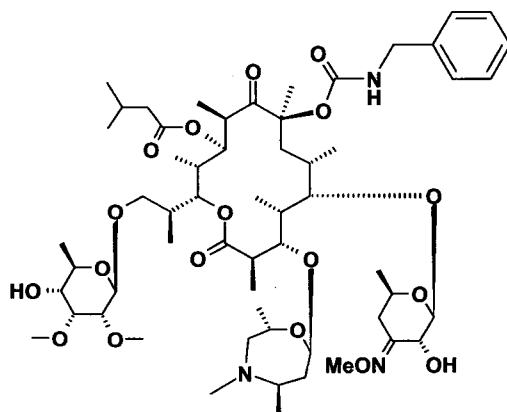
Compound 7-b:

MS: method b

Retention time Tr (min) = 1.32; [M-H+HCO₂H]⁺: m/z 1166 (base peak).

¹H NMR spectrum (500 MHz, in ppm, DMSO-d₆ + CD₃COOD): 0.82 (d, J=6.9 Hz, 3 H); 0.94 (d, J=6.8 Hz, 3 H); 1.02 (m, 9 H); 1.08 (m, 6 H); 1.14 (m, 9 H); 1.22 (d, J=6.1 Hz, 3 H); 1.34 (d, J=6.8 Hz, 3 H); 1.75 (s, 3 H); 1.82 (m, 3 H); 1.90 to 1.95 (masked m, 1 H); 1.99 (m, 2 H); 2.09 (m, 1 H); 2.19 (m, 3 H); 2.35 (m, 2 H); 2.69 (m, 1 H); 2.79 (s, 3 H); 2.96 (m, 2 H); 3.04 (m, 2 H); 3.15 (dd, J=9.6 and 13.6 Hz, 1 H); 3.23 (d, J=13.6 Hz, 1 H); 3.32 (dd, J=4.8 and 9.7 Hz, 1 H); 3.40 (s, 3 H); 3.48 (s, 3 H); 3.53 (m, 2 H); 3.66 (m, 2 H); 3.70 (t, J=1.0 Hz, 1 H); 3.80 (m, 4 H); 3.94 (d, J=5.2 Hz, 1 H); 4.06 (broad s, 1 H); 4.14 (m, 2 H); 4.38 (m, 1 H); 4.47 (d, J=7.9 Hz, 1 H); 4.56 (m, 3 H); 5.15 (m, 1 H); 7.21 to 7.33 (m, 6 H).

Alternative for the preparation of compound 7-a



(7.a)

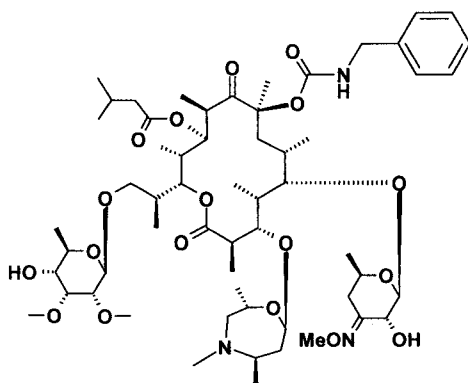
0.2 ml of CHCl₃, 12 mg of compound **8-a** of Example 8, 108 µl of 0.1 M formic acid and 3 µl of formaldehyde are added together with stirring, under argon, and the mixture is heated for 30 minutes at 50°C. The reaction medium is neutralized with saturated

- a heteroaryl group or an aryl-C₁₋₄-alkyl group, the said heteroaryl or aryl groups being unsubstituted or substituted with one or more groups independently chosen from a halogen atom, a hydroxyl group, a nitro group and a group -C₁₋₃-alkyl;
- 5 - R₁₂ represents:
- a group -C₁₋₄-alkoxy,
 - a group -C₁₋₄-alkyl, which is unsubstituted or substituted with a group -NR₁₄R₁₅ or with a heteroaryl group, the said heteroaryl group being unsubstituted or substituted with a group -C₁₋₃-alkyl,
- 10 • a heteroaryl group, which is unsubstituted or substituted with one or more groups chosen from a hydroxyl group and a group -C₁₋₃-alkyl;
- R₁₃ represents:
- a group -C₁₋₄-alkyl,
 - a group -C₁₋₄-fluoroalkyl,
- 15 • an aryl group, which is unsubstituted or substituted with a nitro group,
- or a heteroaryl group, which is unsubstituted or substituted with a group -NR₁₆R₁₇;
- R₁₄, R₁₅, R₁₆ and R₁₇ each independently represent:
- a hydrogen atom,
- 20 • or a group -C₁₋₄-alkyl;
- R₁₈ represents a group -C₁₋₄-alkyl or a benzyl group;
- R₁₉ represents an aryl group or a heteroaryl group;
- R₂₀ represents a group -C₁₋₄-alkyl or an aryl group;
- R₂₁ represents an aryl group;
- 25 - R_{1'} represents:
- a halogen atom,
 - a group -C₁₋₄-alkoxy,
 - a group -C₁₋₄-fluoroalkyl,
 - a group -OCF₃,

aqueous sodium bicarbonate solution and extracted with DCM. The organic phase is dried over MgSO_4 , filtered and then evaporated to dryness under vacuum. The residue obtained is purified by chromatography on silica (2.5 g of 15-40 μm SiOH) with a 95/5 to 90/10 $\text{CHCl}_3/\text{MeOH}$ elution gradient. 6.2 mg of the expected product are obtained.

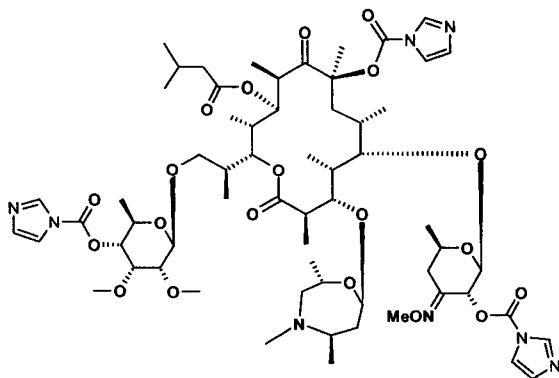
5

Other alternative for the preparation of compound 7-a



(7.a)

Step 1



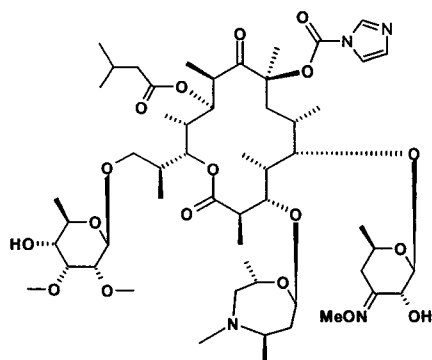
10 1.35 g of compound **1-a** of Example 1 and 1.11 g of N,N'-carbonyldiimidazole are placed in 8 ml of cyclohexane. The mixture is heated at 100°C for 35 minutes by microwave. The heterogeneous medium is taken up in 60 ml of DCM and washed with 40 ml of water and then with 40 ml of saturated NaCl solution. The aqueous phases are re-extracted with 60 ml of DCM. The organic phases are combined, dried over MgSO_4 ,
15 filtered and then evaporated to dryness under vacuum. 1.7 g of the expected compound is obtained.

MS: method e

Retention time Tr (min) = 3.67; $[\text{M}+\text{H}]^+$: 1271

20

Step 2

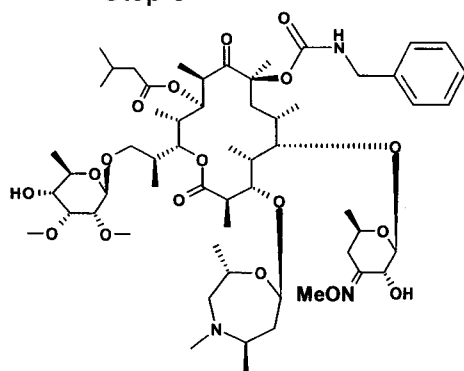


1.7 g of the compound prepared in step 1 are placed in 17 ml of THF. 6.84 ml of 1 M HCl are added. The mixture is stirred for 3 hours at room temperature. 50 ml of DCM are added and the resulting mixture is washed with saturated NaHCO₃ solution (20 ml) and then with saturated NaCl solution (20 ml). The aqueous phases are re-extracted with 50 ml of DCM. The organic phases are combined, dried over MgSO₄, filtered and then evaporated to dryness under vacuum. 1.48 g of the expected product are recovered.

MS: method e

Retention time Tr (min) = 3.41; [M+H]⁺: 1083

Step 3



(7.a)

1 g of the product prepared above is placed in DMF (10 ml). Benzylamine (305.54 μ l) and 1,8-diazabicyclo[5.4.0]undec-7-ene (168.87 μ l) are added. The mixture is stirred at room temperature for 24 hours. The resulting mixture is extracted with 60 ml of EtOAc and washed with 30 ml of water and then with 30 ml of saturated NaCl solution. The aqueous phases are re-extracted with 60 ml of EtOAc. The organic phases are combined, dried over MgSO_4 , filtered and then evaporated to dryness under vacuum. 1.1 g of a yellow oil are obtained. The product is purified by chromatography on a Merck

cartridge (50 g of 15-40 μm SiOH), eluting with a 98/2 EtOAc/TEA mixture. 400 mg of the expected compound is obtained.

EXAMPLE 8: Compound 8

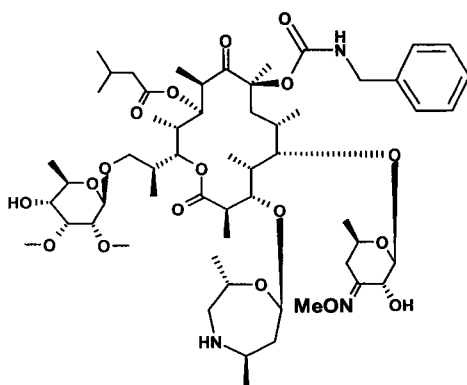
5

Compound 8-a: (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-

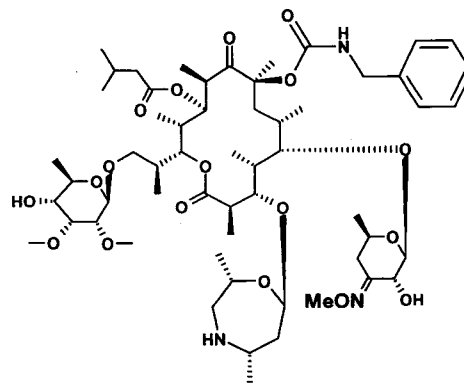
[(benzylcarbamoyl)oxy]-12-[[[(2S,5R,7R)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-2-(1-
 {[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-
 yl]oxy}propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-
 pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-
 10 methylbutanoate.

Compound 8-b: (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-

[(benzylcarbamoyl)oxy]-12-[[[(2S,5S,7R)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy]-2-(1-
 {[(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-
 yl]oxy}propan-2-yl)-10-[[[(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-
 15 pyran-2-yl]oxy]-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-
 methylbutanoate.

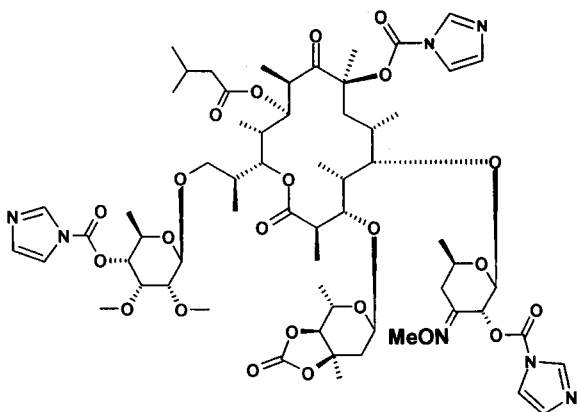


(8.a)



(8.b)

Step 8.1:

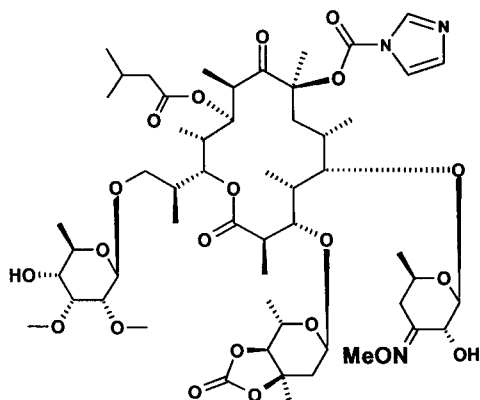


1 ml of toluene, 0.2 g of the product obtained in Preparation 1 and 196 mg of N,N'-carbonyldiimidazole are placed under argon. The reaction medium is heated for 3 hours at 80°C and then concentrated under vacuum. DCM is added and the resulting mixture is then washed with saturated aqueous NaCl solution. The organic phase is dried over
 5 MgSO₄, filtered and then evaporated to dryness under vacuum. The residue is purified by chromatography (10 g of 15-40 µm silica) with a 98/2 to 95/5 DCM/MeOH elution gradient. 112 mg of the expected compound is obtained.

MS: method b

10 Retention time Tr (min) = 1.63; [M+H]⁺: 1300

Step 8.2:

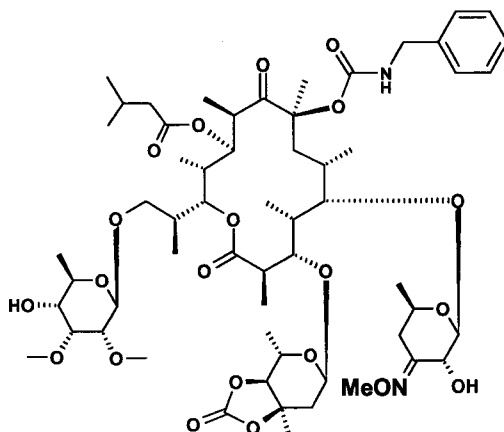


3 ml of THF, 240 mg of the macrolide prepared in step 8.1 and 369 µl of 1 M HCl
 15 are stirred together under argon. The pale yellow homogeneous medium is stirred overnight at room temperature. A further 369 µl of 1 M HCl are added and stirring is continued for 24 hours. The reaction medium is neutralized with saturated aqueous sodium bicarbonate solution. The resulting mixture is extracted with EtOAc. The organic phase is dried over MgSO₄, filtered and then evaporated to dryness under vacuum.
 20 181 mg of the residue obtained are purified by chromatography (10 g of 15-40 µm silica) with a 50/50 to 70/30 EtOAc/heptane elution gradient. 87 mg of the expected compound is obtained.

MS: method b

25 Retention time Tr (min) = 1.56; [M-H+HCO₂H]: m/z 1156 (base peak).

Step 8.3:



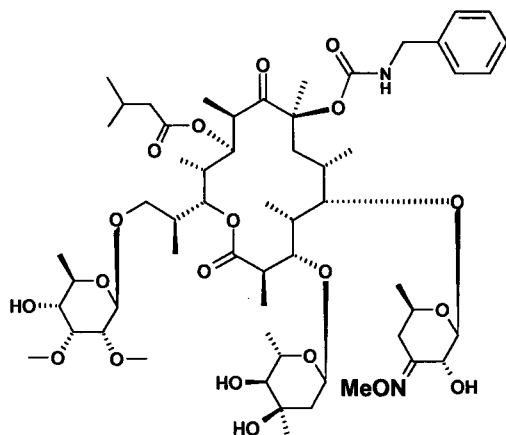
10 ml of DMF, 1 g of the compound obtained in step 8.2, 188 μ l of 1,8-diazabicyclo
 5 [5.4.0]undec-7-ene and 138 μ l of benzylamine are stirred together under argon. The
 homogeneous medium is stirred overnight at room temperature. 20 g of ice are added to
 the reaction medium and the resulting mixture is then extracted with 3 $\times$ 20 ml of EtOAc.
 The organic phases are combined and washed with 20 ml of saturated aqueous NaCl
 solution, and the organic phase is dried over MgSO_4 , filtered and then evaporated to
 10 dryness under vacuum. 975 mg of residue are purified by chromatography (50 g of 15-
 40 μ m silica), eluting with a 7/3 EtOAc/heptane mixture. 490 mg of the expected
 compound is obtained.

MS: method b

15 Retention time T_r (min) = 1.68; $[\text{M}-\text{H}+\text{HCO}_2\text{H}]^-$: m/z 1195 (base peak).

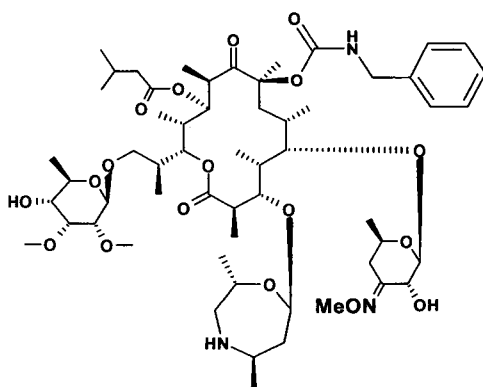
^1H NMR spectrum (500 MHz, in ppm, $\text{DMSO}-d_6$): 0.79 (d, $J=6.9$ Hz, 3 H);
 0.88 to 1.01 (m, 12 H); 1.05 (m, 6 H); 1.11 (m, 6 H); 1.14 (d, $J=6.0$ Hz, 3 H); 1.30 (d,
 $J=5.5$ Hz, 3 H); 1.52 (s, 3 H); 1.67 to 1.86 (m, 4 H); 1.71 (s, 3 H); 1.94 to 2.10 (m, 4 H);
 2.15 (m, 4 H); 2.36 (dd, $J=5.1$ and 13.6 Hz, 1 H); 2.77 (m, 2 H); 2.92 (dd, $J=2.5$ and
 20 8.0 Hz, 1 H); 3.01 (m, 2 H); 3.27 to 3.32 (masked m, 1 H); 3.37 (s, 3 H); 3.45 (s, 3 H);
 3.52 (m, 2 H); 3.61 to 3.68 (m, 2 H); 3.80 (s, 3 H); 3.84 (d, $J=6.9$ Hz, 1 H); 3.95 (m, 2 H);
 4.13 (m, 3 H); 4.45 (d, $J=8.0$ Hz, 1 H); 4.55 (d, $J=9.9$ Hz, 1 H); 4.65 (m, 2 H); 4.87 (d,
 $J=7.1$ Hz, 1 H); 4.99 (dd, $J=5.4$ and 8.4 Hz, 1H); 5.43 (m, 1 H); 7.26 (m, 5 H); 7.38 (broad
 t, $J=6.0$ Hz, 1 H).

Step 8.4:

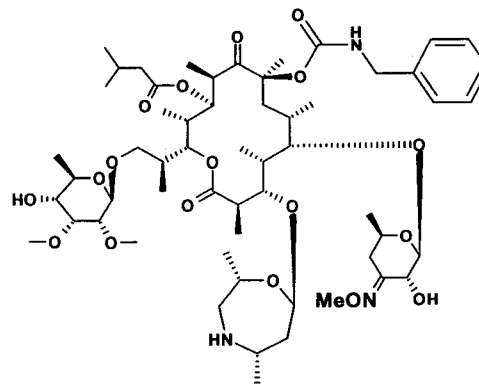


55 ml of MeOH, 300 mg of the macrolide prepared in the preceding step and 108 mg of K_2CO_3 are stirred together under argon. The reaction medium is stirred for 24 hours at room temperature, followed by addition of a further 72 mg of K_2CO_3 . The reaction medium is stirred for a further 24 hours, and 30 ml of saturated aqueous NaCl solution are then added. The resulting mixture is extracted with EtOAc (3×100 ml). The organic phase is separated out after settling of the phases, dried over $MgSO_4$, filtered and then evaporated to dryness. 300 mg of the residue obtained are purified by chromatography (30 g of 15-40 μm silica), eluting with a 7/3 EtOAc/heptane mixture. 265 mg of the expected product are obtained.

Step 8.5:



(8.a)



(8.b)

3.5 ml of THF and 340 mg of the compound obtained in the preceding step are stirred together under argon. The solution obtained is cooled to $0^\circ C$, followed by dropwise addition of an aqueous solution of 325 mg of sodium metaperiodate in 3.5 ml of water. Stirring is continued at $0^\circ C$ for 10 minutes, and the mixture is then allowed to warm to

room temperature. After stirring for 5 hours 30 minutes, the precipitate formed is filtered off and rinsed with 4 ml of THF. 64.8 mg of NH_4Cl are added to the filtrate obtained, followed, after stirring for 5 minutes at room temperature, by 95 mg of NaBH_3CN . The reaction medium is stirred at room temperature for 20 hours. The precipitate formed is filtered off and rinsed with DCM. The filtrate is washed with saturated sodium bicarbonate solution and then with aqueous NaCl solution. The aqueous phases are extracted with DCM. The organic phases are combined, dried over MgSO_4 , filtered and then evaporated to dryness under vacuum. The 278 mg of residue are purified by chromatography on silica (20 g of 15-40 μ SiOH) with a 98/2 to 95/5 $\text{CHCl}_3/\text{MeOH}$ elution gradient. 120 mg of diastereoisomer **8-a** and 14 mg of diastereoisomer **8-b** are obtained.

Compound 8-a:

MS: method b

Retention time T_r (min) = 1.3; $[\text{M-H}+\text{HCO}_2\text{H}]^+$: m/z 1152 (base peak).

^1H NMR spectrum (500 MHz, in ppm, DMSO-d_6): 0.78 (d, $J=6.6$ Hz, 3 H); 0.91 (d, $J=6.9$ Hz, 3 H); 0.95 (d, $J=7.1$ Hz, 3 H); 0.99 (d, $J=6.6$ Hz, 6 H); 1.03 to 1.12 (m, 21 H); 1.75 (m, 8 H); 1.99 (m, 4 H); 2.15 (m, 3 H); 2.50 (masked m, 1 H); 2.68 to 2.94 (m, 5 H); 3.01 (m, 2 H); 3.29 (masked m, 1 H); 3.38 (s, 3 H); 3.45 (s, 3 H); 3.52 (m, 1 H); 3.61 to 3.90 (m, 6 H); 3.80 (s, 3 H); 4.10 (m, 3 H); 4.45 (d, $J=7.7$ Hz, 1 H); 4.62 (m, 3 H); 4.86 (d, $J=7.1$ Hz, 1 H); 4.95 (m, 1 H); 5.26 (d, $J=4.4$ Hz, 2 H); 7.20 to 7.32 (m, 5 H); 7.36 (t, $J=6.0$ Hz, 1 H).

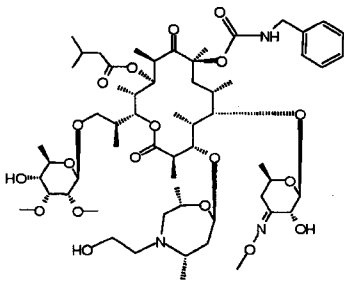
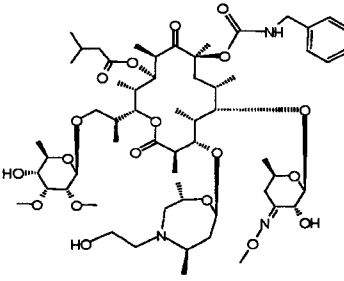
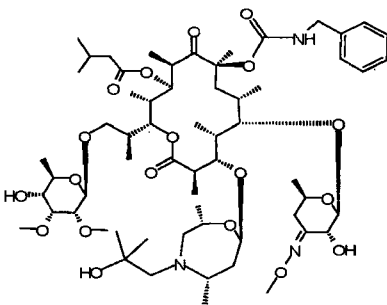
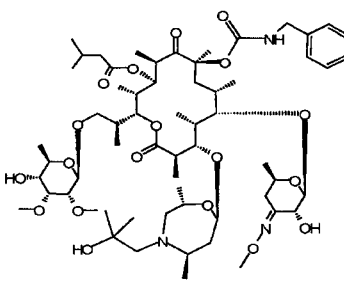
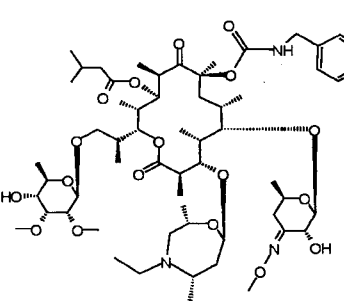
Compound 8-b:

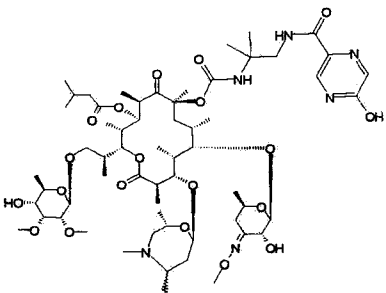
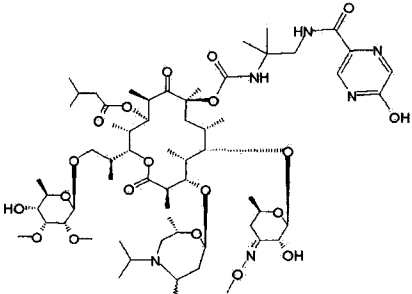
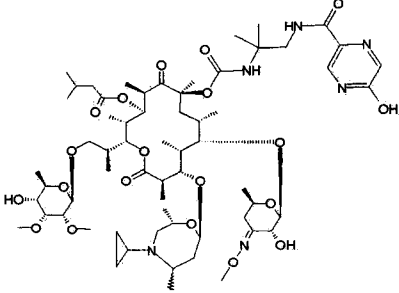
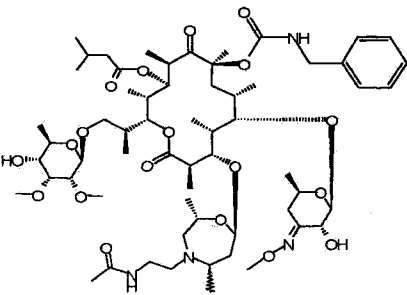
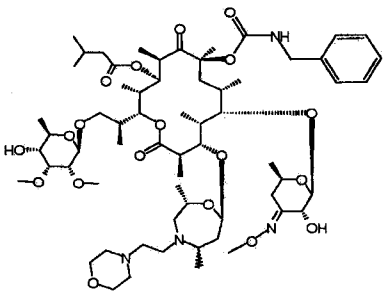
MS: method b

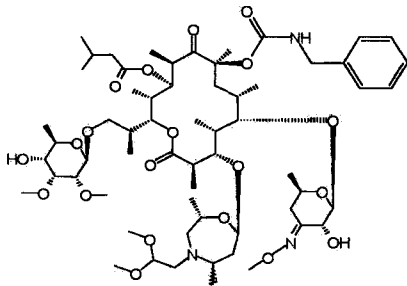
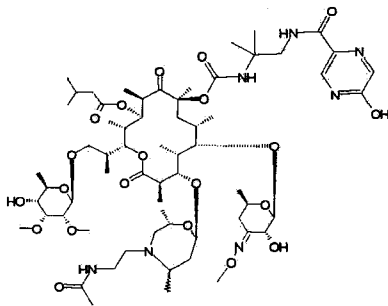
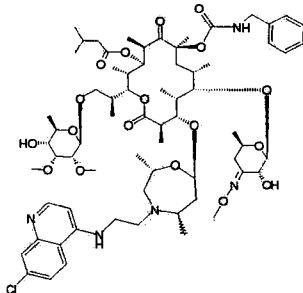
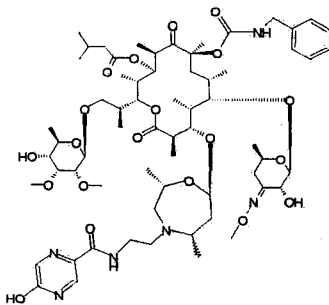
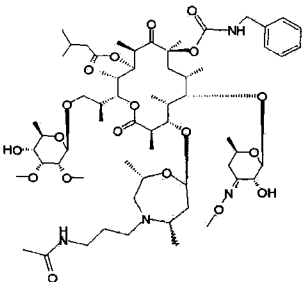
Retention time T_r (min) = 1.12; $[\text{M-H}+\text{HCO}_2\text{H}]^+$: m/z 1152 (base peak).

^1H NMR spectrum (500 MHz, in ppm, DMSO-d_6): 0.78 (d, $J=6.9$ Hz, 3 H); 0.91 (d, $J=6.6$ Hz, 3 H); 0.98 (m, 9 H); 1.03 to 1.16 (m, 21 H); 1.69 to 2.20 (m, 12 H); 1.72 (s, 3 H); 2.71 (m, 3 H); 2.92 (m, 2 H); 3.01 (m, 3 H); 3.10 (m, 1 H); 3.34 (masked m, 1 H); 3.38 (s, 3 H); 3.45 (s, 3 H); 3.52 (m, 1 H); 3.63 (dd, $J=4.5$ and 9.7 Hz, 1 H); 3.67 (broad s, 1 H); 3.71 to 3.81 (m, 3 H); 3.79 (s, 3 H); 3.87 (t, $J=4.7$ Hz, 1 H); 4.09 (m, 3 H); 4.45 (d, $J=8.0$ Hz, 1 H); 4.60 (m, 3 H); 4.83 (d, $J=6.9$ Hz, 1 H); 5.01 (m, 1 H); 5.14 (d, $J=3.6$ Hz, 1 H); 7.20 to 7.35 (m, 6 H).

Table 1: Structures and analyses of compounds prepared according to one of the processes described in Examples 1 to 8 above and 9 to 11 below.

Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
9		a	1,02	[M-H+HCO ₂ H] ⁻ : m/z 1196 (base peak)
10		a	1,01	[M-H+HCO ₂ H] ⁻ : m/z 1196 (base peak)
11		a	1,04	[M-H+HCO ₂ H] ⁻ : m/z 1224 (base peak)
12		a	1,03	[M-H+HCO ₂ H] ⁻ : m/z 1224 (base peak)
13		b	1,04	[M-H+HCO ₂ H] ⁻ : m/z 1180 (base peak)

Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
14		b	1,19	[M+H] ⁺ : 1225
15		b	1,2 1,25	[M+H] ⁺ : 1253, mixture of isomers
16		b	1,2	[M+H] ⁺ : 1251
17		b	1,31	[M-H+HCO ₂ H] ⁻ : m/z 1237 (base peak)
18		b	1,32	[M+H] ⁺ : 1221

Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
19		b	1,36	[M-H+HCO ₂ H]- : m/z 1240 (base peak)
20		b	1,16	[M+H] ⁺ : 1296
21		b	1,17- 1,19	m/z 306 (base peak) – mixture of isomers
22		b	1,26	[M+H] ⁺ : 1273
23		b	1,29	m/z 1251 (base peak) – mixture of isomers

- a nitro group,
- a group -NH_2 ,
- a group -NHCH_3 ;

- R_2' represents:

- a hydroxyl group,
- a group $\text{-C}_{1-6}\text{-alkyl}$.

The compounds of general formula (I) may comprise one or more asymmetric carbons. They may therefore exist in the form of enantiomers or diastereoisomers. These enantiomers, diastereoisomers, and also mixtures thereof, including racemic mixtures, form part of the invention.

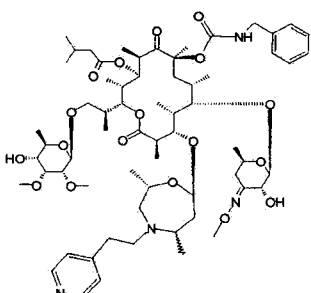
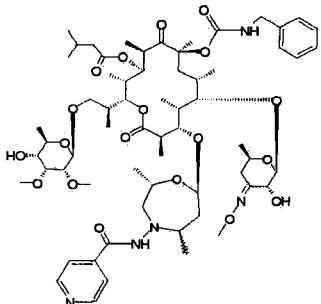
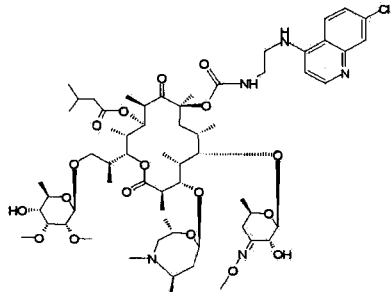
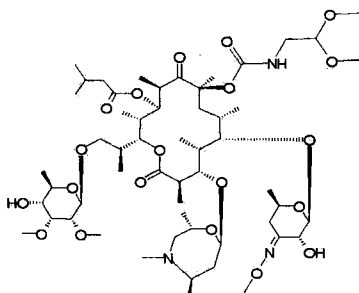
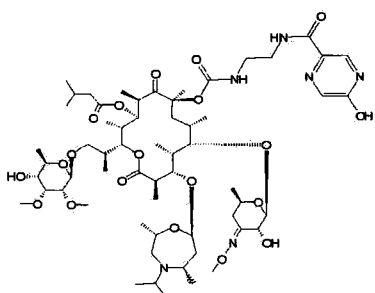
The compounds of formula (I) may exist in the form of bases or acid-addition salts. Such addition salts form part of the invention.

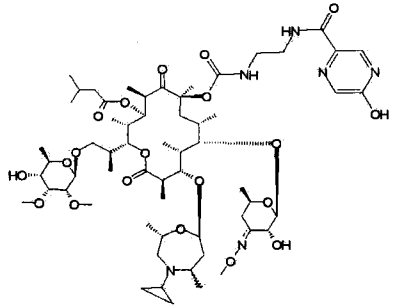
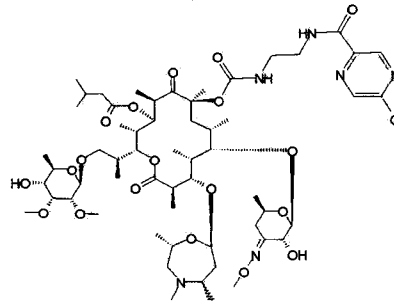
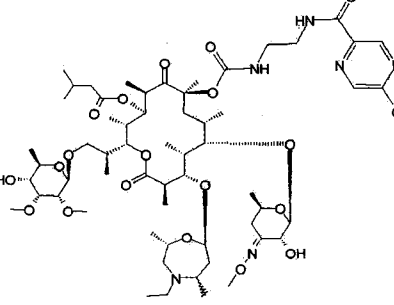
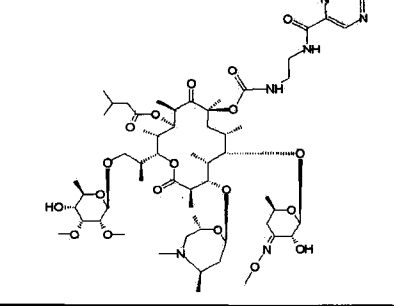
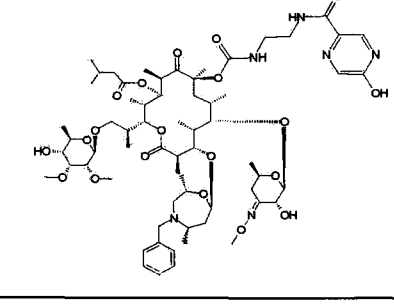
These salts are advantageously prepared with pharmaceutically acceptable acids, but salts of other acids, for example for purifying or isolating the compounds of general formula (I), also form part of the invention.

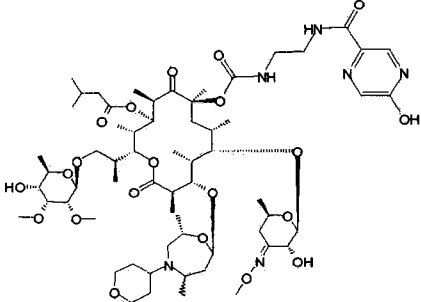
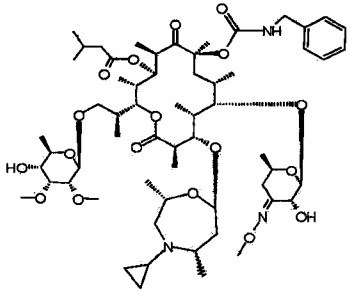
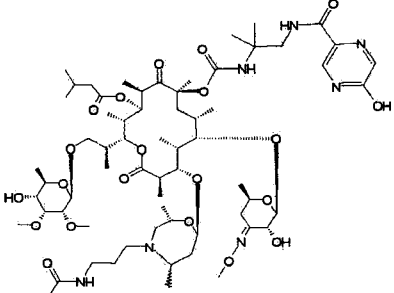
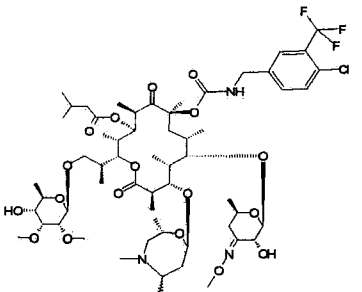
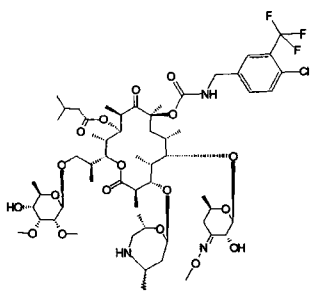
The compounds of formula (I) according to the present invention also comprise those in which one or more hydrogen, carbon or halogen atoms, especially chlorine or fluorine atoms, have been replaced with their radioactive isotopes, for example deuterium or tritium to replace hydrogen or carbon-14 to replace carbon-12. Such labelled compounds are useful in research, metabolism or pharmacokinetic studies, and also in biological and pharmacological tests as tools.

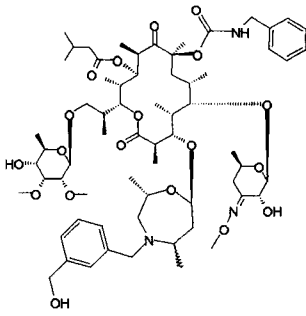
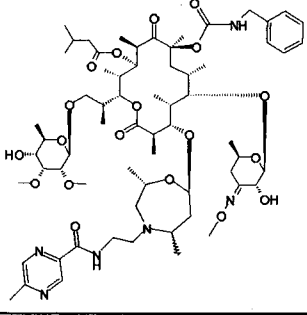
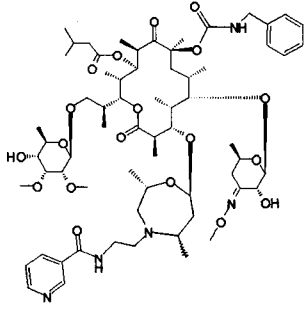
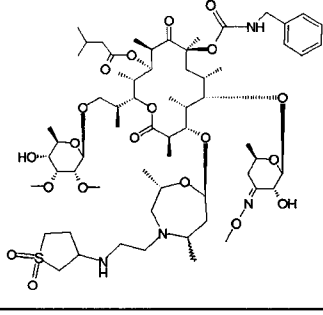
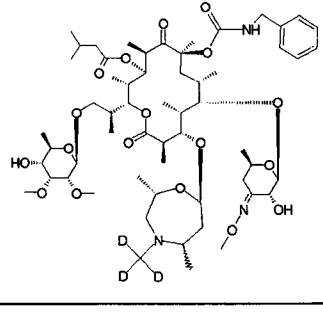
In the context of the present invention:

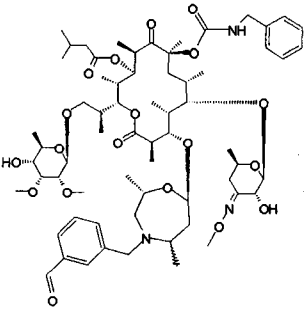
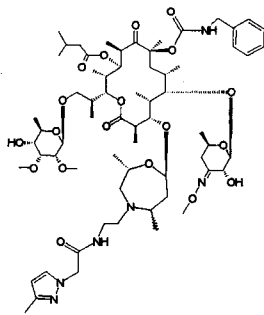
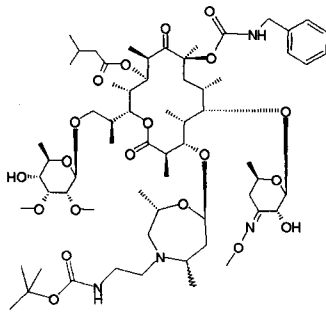
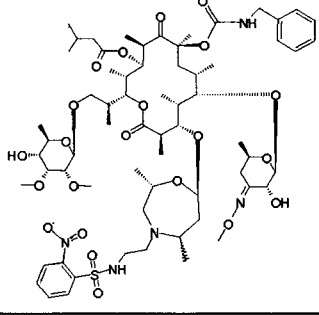
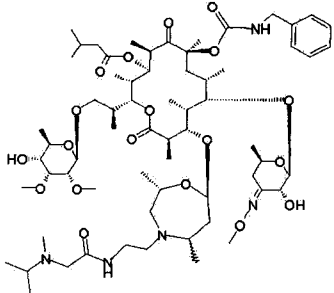
- alkyl represents a saturated, linear or branched aliphatic group; for example, a group $\text{C}_{1-3}\text{-alkyl}$ represents a linear or branched carbon-based chain of 1 to 3 carbon atoms, especially a methyl, ethyl, propyl or isopropyl. Similarly, a group $\text{C}_{1-4}\text{-alkyl}$ represents a linear or branched carbon-based chain of 1 to 4 carbon atoms, especially a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl or *tert*-butyl. Similarly, a group $\text{C}_{1-6}\text{-alkyl}$ represents a linear or branched carbon-based chain of 1 to 6 carbon atoms, especially a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, neopentyl, *tert*-pentyl, hexyl or isohexyl.

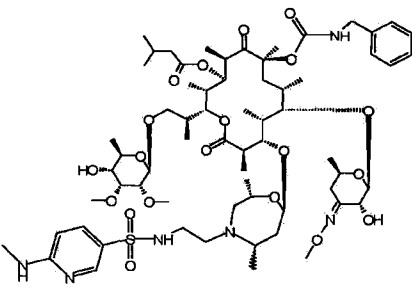
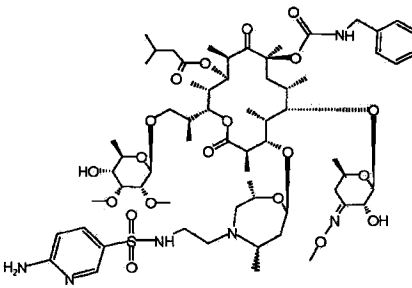
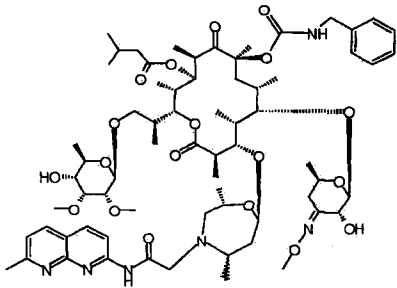
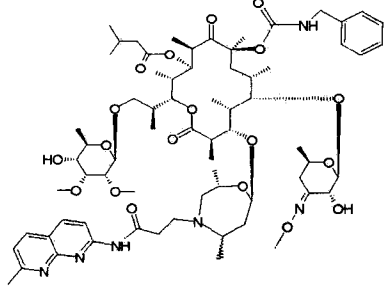
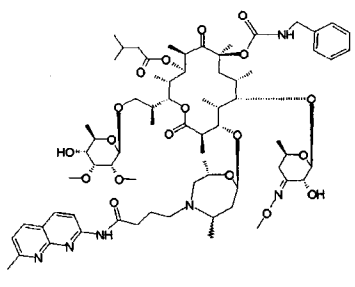
Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
24		b	1,2	m/z : 207 (base peak) ; [M-H+HCO ₂ H]- : m/z 1257
25		b	1,53	[M-H+HCO ₂ H]- : m/z 1272 (base peak)
26		b	1,04	[M+2H] ²⁺ : 619 (base peak) ; [M-H+HCO ₂ H]- : m/z 1280
27		b	1,21	[M-H+HCO ₂ H]- : m/z 1164 (base peak)
28		b	1,1	[M+H] ⁺ : 1225

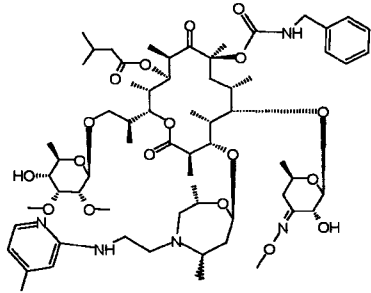
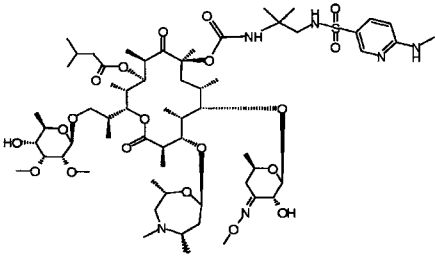
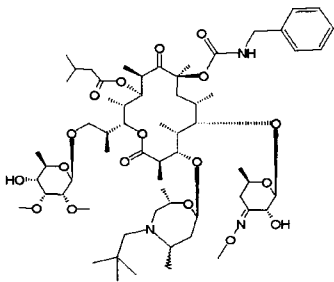
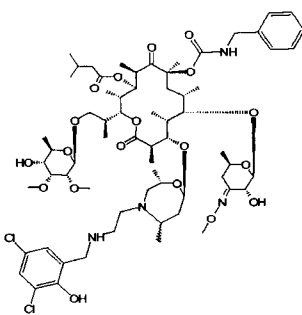
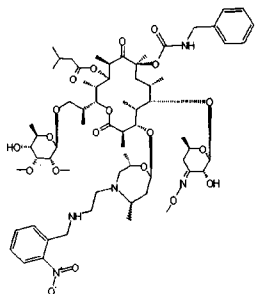
Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
29		b	1,1 - 1,21	[M+H] ⁺ : 1223 mixture of isomers
30		b	1,09	[M+H] ⁺ : 1197
31		b	1,11	[M+H] ⁺ : 1211
32		b	1,17	[M-H+HCO ₂ H] ⁻ : m/z 1240
33		b	1,18	[M+H] ⁺ : 1273

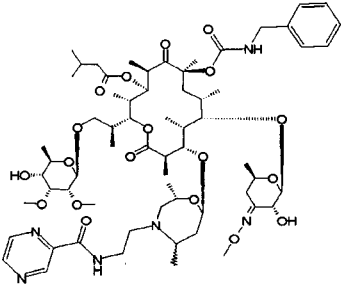
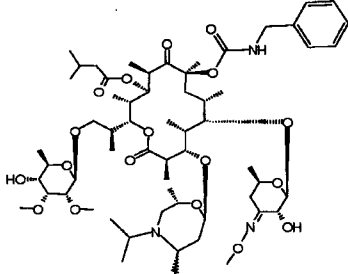
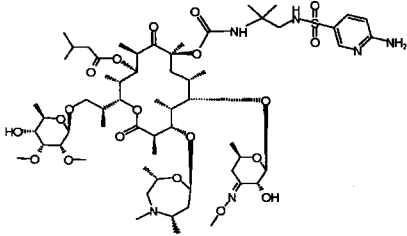
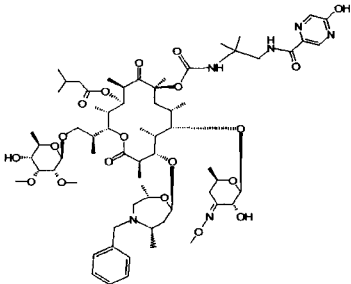
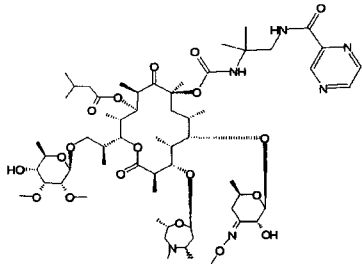
Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
34		b	1,1	$[M+H]^+ : 1267$
35		b	1,35	$[M-H+HCO_2H]^- : m/z 1192$
36		b	1,16- 1,17	$[M+H]^+ : 1311$ mixture of isomers
37		b	1,38	$[M-H+HCO_2H]^- : m/z 1268$ (base peak)
38		b	1,35	$[M-H+HCO_2H]^- : m/z 1254$ (base peak)

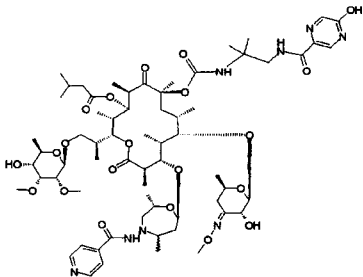
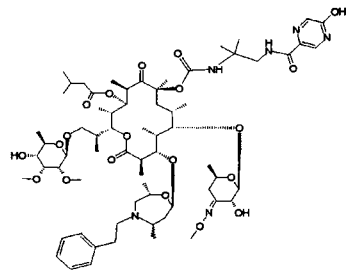
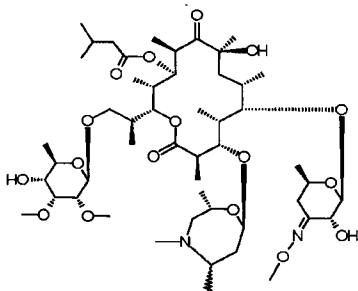
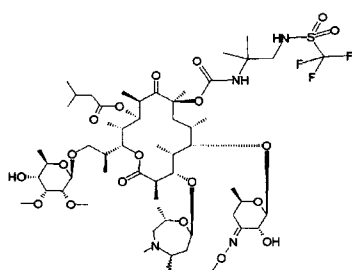
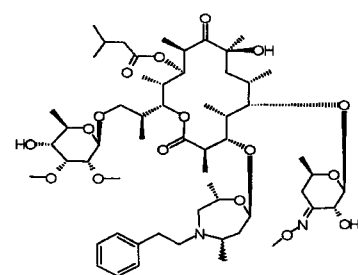
Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
39		b	1,3	[M-H+HCO ₂ H] ⁻ : m/z 1272 (base peak)
40		b	1,33 (d)	m/z : 265 (base peak) ; [M-H+HCO ₂ H] ⁻ : m/z 1315 – mixture of isomers
41		b	1,29 (d)	m/z : 250 (base peak) ; [M-H+HCO ₂ H] ⁻ : m/z 1300 – mixture of isomers
42		b	1,25	m/z : 263 (base peak) ; [M-H+HCO ₂ H] ⁻ : m/z 1313
43		b	1,24	[M-H+HCO ₂ H] ⁻ : m/z 1169 (base peak)

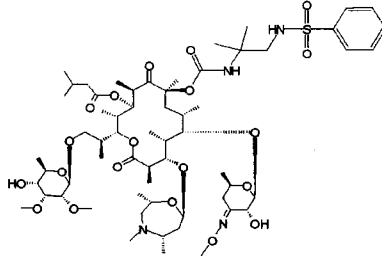
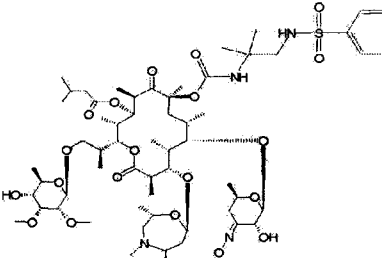
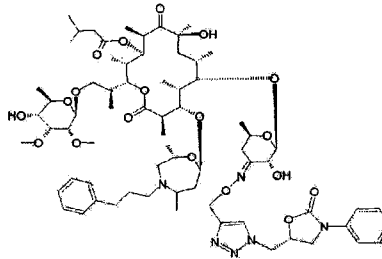
Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
44		b	1,30-1,32	[M+H] ⁺ : 1226 mixture of isomers
45		b	1,23	m/z : 267 (base peak) ; [M-H+HCO ₂ H] ⁻ : m/z 1317
46		b	1,29	[M-H+HCO ₂ H] ⁻ : m/z 1295 (base peak)
47		b	1,33	m/z : 330 (base peak)
48		b	0,99	m/z : 258 (base peak) ; [M-H+HCO ₂ H] ⁻ : m/z 1308

Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
49		b	1,28	[M-H+HCO ₂ H] ⁻ : m/z 1365
50		b	1,15 (d)	[M-H+HCO ₂ H] ⁻ : m/z 1351 – mixture of isomers
51		b	1,25- 1,29	m/z : 327 (base peak) ; m/z : 301 (base peak)
52		b	1,14	m/z : 315 (base peak)
53		b	1,12	m/z : 315 (base peak)

Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
54		d	2,20- 2,22	[M-H+HCO ₂ H] ⁻ : m/z 1286 (base peak) – mixture of isomers
55		b	1,06	[M+2H] ²⁺ : 637 (base peak)
56		d	2,36- 2,39	[M-H+HCO ₂ H] ⁻ : m/z 1222 (base peak) – mixture of isomers
57		b	2,38- 2,41	m/z : 345 (base peak) – mixture of isomers
58		b	1,21- 1,23	m/z 306 (base peak) ; [M-H+HCO ₂ H] ⁻ : m/z 1330 – mixture of isomers

Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
59		b	1,16	[M-H+HCO ₂ H]- : m/z 1301 (base peak)
60		b	1,18	[M-H+HCO ₂ H]- : m/z 1194 (base peak)
61		b	1	[M+2H] ²⁺ : 630 (base peak)
62		b	1,12	[M+H] ⁺ : 1301
63		b	1,08	m/z : 1035 (base peak)

Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
64		b	1,33- 1,34	[M+2H] ²⁺ : 666 - m/z :248 (base peak) – mixture of isomers
65		b	1,13	[M+H] ⁺ : 1315
66		b	1,16	[M-H+HCO ₂ H] ⁻ : m/z 1033 (base peak)
67		b	1,19	[M+H] ⁺ : 1235
68		b	1,19- 1,20	[M-H+HCO ₂ H] ⁻ : m/z 1123 (base peak) – mixture of isomers

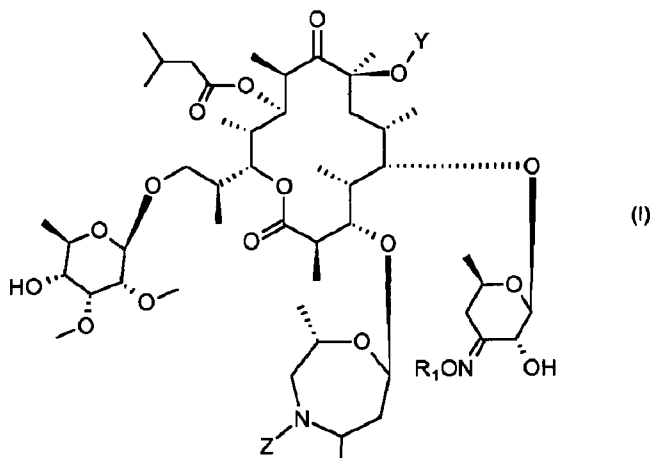
Compound	CHEMISTRY	LCSM		
		Méth	Tr	MS
69		a	1,15	[M+H] ⁺ : 1243
70		a	1,15	[M+H] ⁺ : 1243
71		a	1,23- 1,24	[M+H] ⁺ : 1354 mixture of isomers

EXAMPLE 9: Compound 70

5 (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-2-((S)-1-(((2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)propan-2-yl)-10-(((2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl)oxy)-3,5,7,9,11,13-hexamethyl-7-(((2-methyl-1-((phenylsulfonamido)propan-2-yl)carbamoyl)oxy)-6,14-dioxo-12-(((2S,5R,7R)-2,4,5-trimethyl-1,4-oxazepan-7-yl)oxy)oxacyclotetradecan-4-yl 3-methylbutanoate.

CLAIMS

1. Compound of formula (I):



in which:

- 5 - Y represents a hydrogen atom, a group $-(C=O)-NR_2R_3$ or a group $-(C=O)-O-R_{18}$;
 - Z represents:

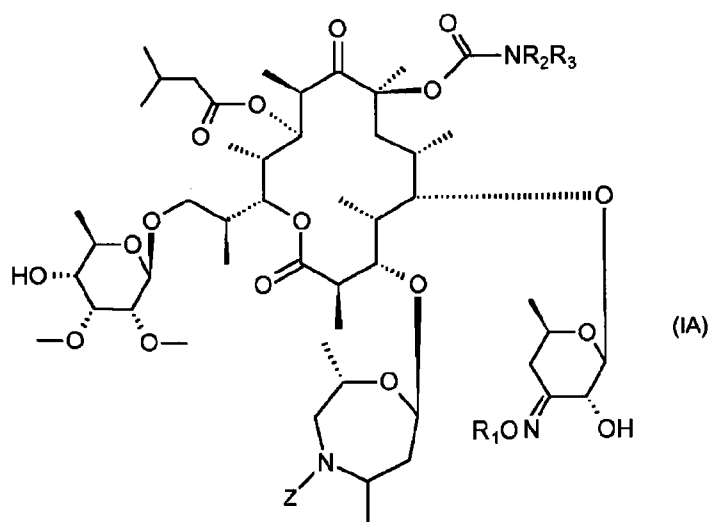
- 10 • a hydrogen atom,
 • a group $-C_{1-6}$ -alkyl, which is unsubstituted or substituted with one or more groups R_4 ,
 • a group $-C_{3-7}$ -cycloalkyl, which is unsubstituted or substituted with a group $-NH-(C=O)-R_{19}$ or with a group $-NH-SO_2-R_{20}$,
 • a group $-C_{3-6}$ -heterocycloalkyl,
 • a group $-NH-(C=O)-R_5$;

- 15 - R_1 represents a hydrogen atom, a group $-C_{2-6}$ -alkenyl, a group $-C_{2-6}$ -alkynyl or a group $-C_{1-6}$ -alkyl which is unsubstituted or substituted with a group $-C_{1-4}$ -fluoroalkyl or with a heteroaryl group which is unsubstituted substituted
 with a group 3-(3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-ylmethyl;

20 - R_2 represents a hydrogen atom or a group $-C_{1-6}$ -alkyl;

 - R_3 represents:

- 25 • a group $-C_{3-7}$ -cycloalkyl, which is unsubstituted or substituted with a group $-C_{1-3}$ -alkyl substituted with a group $-NH-SO_2-R_{21}$,
 • a heteroaryl group,

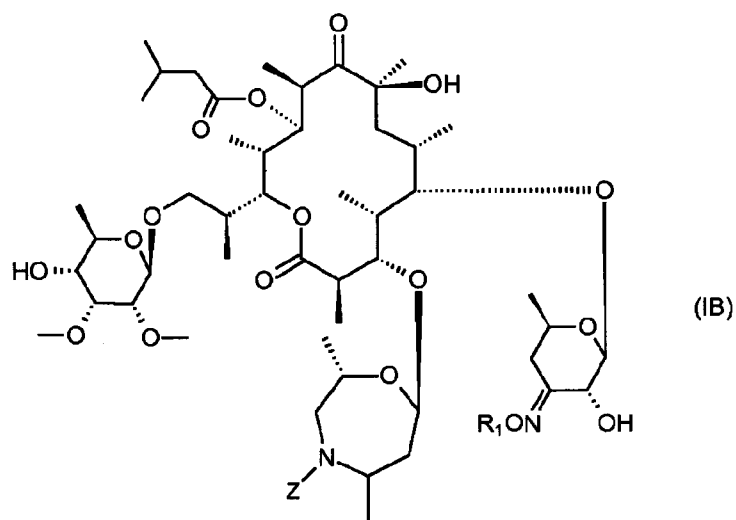


in which:

- R_1 , R_2 , R_3 and Z are as defined in Claim 1.

5

2. Compound according to Claim 1, of formula (IB):



in which:

10

- R_1 and Z are as defined in Claim 1.

15

- pyran-2-yl]oxy}-1-methylethyl)-10-{{{(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[[{1,1-dimethyl-
 5 2-[(phenylsulfonyl)amino]ethyl}carbamoyl]oxy]-12-{{{(2S,7R)-2,5-dimethyl-4-(tetrahydro-2H-pyran-4-yl)-1,4-oxazepan-7-yl]oxy}-2-(2-
 {{{(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy}-1-methylethyl)-10-{{{(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-3,5,7,9,11,13-
 10 hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-12-{{{(2S,5S,7R)-4-(cyclopropylmethyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy}-7-[[{1,1-dimethyl-2-[(phenylsulfonyl)amino]ethyl}carbamoyl]oxy]-2-(2-
 {{{(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy}-1-methylethyl)-10-{{{(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-3,5,7,9,11,13-
 15 hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[[{1,1-dimethyl-2-[(phenylsulfonyl)amino]ethyl}carbamoyl]oxy]-12-{{{(2S,5R,7R)-4-(2,2-dimethylpropyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy}-2-(2-
 20 {{{(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy}-1-methylethyl)-10-{{{(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[[{1,1-dimethyl-2-[(phenylsulfonyl)amino]ethyl}carbamoyl]oxy]-12-{{{(2S,7R)-4-(2,2-dimethylpropyl)-2,5-dimethyl-1,4-oxazepan-7-yl]oxy}-2-(2-
 25 {{{(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy}-1-methylethyl)-10-{{{(2S,3R,6R)-3-hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-3,5,7,9,11,13-hexamethyl-6,14-dioxooxacyclotetradecan-4-yl 3-methylbutanoate;
 • (2R,3S,4R,5R,7S,9S,10S,11R,12S,13R)-7-[[{1,1-dimethyl-2-morpholin-4-ylethyl}carbamoyl]oxy]-2-(2-{{{(2R,3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl]oxy}-1-methylethyl)-10-{{{(2S,3R,6R)-3-
 30 hydroxy-4-(methoxyimino)-6-methyltetrahydro-2H-pyran-2-yl]oxy}-
 35