Sugimoto et al. J. Bioorg. Med. Chem. 20 (2012) p. 5787-5801 shows similar C/12-C/13 substituted antibacterial analogues of 6-O-methyl erythromycin A (clarithromycin) and of 9-amino-erythromycin A where conversion of the 9-keto to the 9-OH and protection of the 9-OH in case of clarithromycin or protection of the 9-amino in the case of 9-amino-erythromycin A is required before ring opening with $Pb(OAc)_4$ is performed.

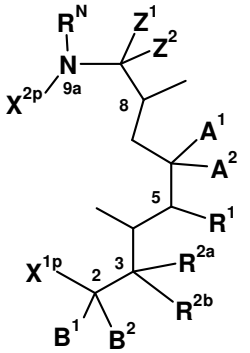
However, prior art documents do not disclose synthetic processes which allow single step ring opening of a wide variety of semisynthetic 9a-aza-9a-homoerythromycin macrolides, and immediate use of thus obtained seco macrolide compounds as intermediates whereby the previously introduced eastern portion substitution pattern has been preserved. Moreover, prior art documents do not disclose processes that allow for keeping beneficial substituents, linkers and other modifications previously introduced into the semisynthetic 9a-aza-9a-homoerythromycin macrolide by which the western portion can be subsequently substantially diversified using simple and robust process resulting in new macrolide based macrocycles having from 11 to multi-number ring members depending on the nature of the fragment inserted to the west side of the seco macrolide and therefore providing a powerful tool in development of novel macrolide based macrocycles.

The present invention therefore provides novel seco (opened ring) macrolide compounds which are useful as intermediates for preparation of macrolide based macrocycles and the process for preparation thereof. The seco (opened ring) macrolide compounds of the invention may already have diverse substituents introduced in eastern portion of molecule allowing western portion to be further diversified resulting in macrolide based macrocycles having from 11 to multi-number ring members which can be used as therapeutic agents.

SUMMARY

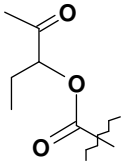
The present disclosure is based on the identification that seco (opened ring) macrolide compounds of the disclosure may be useful as intermediates for preparation of macrolide based macrocycles. Therefore, the present disclosure relates to seco (opened ring) macrolide compounds, to the process for preparation thereof, to their use as intermediates for preparation of macrolide based macrocycles, to macrolide based macrocycles obtained from said seco macrolide compounds, to the process for preparation of macrolide based macrocycles, to the pharmaceutical compositions comprising macrolide based macrocycles, and to the use of macrolide based macrocycles as therapeutic agents.

In one aspect, the present disclosure refers to a process for preparation of seco (opened ring) macrolide compound of Formula (I), or a salt or solvate thereof,



(I)

wherein,

X^{1p} is  , -C(=O)OH, –C(=O)NH_2, -C(=S)NH_2, -C(=O)NHNH_2, -CH_2NH_2, -CH_2OH, -C(=O)H, -CN or –NH_2;

X^{2p} is hydrogen,–$CH(CH_3)$C(=O)H, -C(=S)NH_2 or -C(=O)NH_2;

Z^1 and Z^2

(i) are both hydrogen, or

(ii) together with carbon atom to which they are attached form a keto group provided R^N is hydrogen and A^1 is $OC_{1\text{-}6}$alkyl,

A^1 is OH, $OC_{1\text{-}6}$alkyl, $OC_{2\text{-}6}$alkenyl, $OC_{2\text{-}6}$alkynyl, OR^p, or A^1 together with R^{2b} forms cyclic hemiketal or ether;

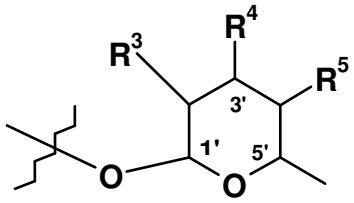
A^2 is CH_3 or H;

B^1 and B^2 are independently H, $C_{1\text{-}6}$alkyl or halogen, or

B^2 together with R^{2a} forms a double bond;

R^1 is S^1, OH, $OC_{1\text{-}6}$alkyl or OR^p;

S^1 is sugar group of formula **(b1)**:



(b1)

wherein,

R^3 is OH, H, OR^p, –O-L^1-G or -OC(=O)G, provided when R^3 is –O-L^1-G or -OC(=O)G group then R^4 is $–N(CH_3)_2$ and R^5 is H, wherein

L^1 $-(CH_2)_{a1}$-U^1-$(CH_2)_{b1}$-;

U^1 is $–N(R^6)$-, -NHC(=O)- or –C(=O)NH-;

R^6 is H or $C_{1\text{-}3}$alkyl;

a^1 is an integer from 2 to 6;

b^1 is an integer from 0 to 6;

G is selected from:

(i) G^1, wherein G^1 is C_{1-8}alkyl, wherein alkyl may be optionally interrupted by 1 to 3 bivalent radical groups selected from –O-, -S- and –N(R^{g1})-, where R^{g1} is H or C_{1-6}alkyl, and where alkyl may be optionally substituted by one or more groups independently selected from halogen, OH, keto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, -C(=O)OC_{1-6}alkyl, -C_{1-6}alkyl-OH, NH_2, *N*-(C_{1-6}-alkyl)amino, *N,N*-di(C_{1-6}alkyl)amino; aryl or heteroaryl wherein said aryl and heteroaryl may be mono or biyclic and independently each may be optionally substituted by one or more groups independently selected from halogen, CN, OH, NO_2, OC_{1-6}alkyl, NH_2, *N*-(C_{1-6}-alkyl)amino, *N,N*-di(C_{1-6}alkyl)amino, -C(=O)C_{1-6}alkyl, -OC(=O)C_{1-6}alkyl, -C(=O)OH, -C(=O)OC_{1-6}alkyl, -C(=O)NHC_{1-6}alkyl and -NHC(=O)C_{1-6}alkyl;

(ii) G^2, wherein G^2 is 3-7 membered cycloalkyl which may be optionally substituted by one or more groups independently selected from OH, halogen, CN, NH_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, haloC_{1-6}alkyloxy, -C_{1-6}alkyl-OH, -C(=O)C_{1-6}alkyl, -C(=O)OC_{1-6}alkyl, -C(=O)OH, -C(=O)NH_2, -C_{0-6}alkyl-aryl or C_{0-6}alkyl-heteroaryl wherein aryl and heteroaryl independently from each other may be optionally substituted by one or more groups independently selected from halogen, CN, OH, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, haloC_{1-6}alkyloxy, -C_{1-6}alkyl-OH, NH_2, *N*-(C_{1-6}-alkyl)amino, *N,N*-di(C_{1-6}alkyl)amino, -C(=O)C_{1-6}alkyl, -OC(=O)C_{1-6}alkyl, -C(=O)OH, -C(=O)OC_{1-6}alkyl, -C(=O)NHC_{1-6}alkyl and -NHC(=O)C_{1-6}alkyl;

(iii) G^3, wherein G^3 is 3-7 membered heterocycloalkyl containing one or two heteroatoms independently selected from N, O and S, where heterocycloalkyl may be optionally substituted by one or more groups independently selected from OH, halogen, CN, NH_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, haloC_{1-6}alkyloxy, -C_{1-6}alkyl-OH, -C(=O)C_{1-6}alkyl, -C(=O)OC_{1-6}alkyl, -C(=O)OH and -C(=O)NH_2;

(iv) G^4, wherein G^4 is aryl wherein aryl may be optionally substituted by one or more groups independently selected from halogen, CN, OH, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, haloC_{1-6}alkyloxy,

-C_{1-6}alkyl-OH, NH_2, *N*-(C_{1-6}-alkyl)amino, *N,N*-di(C_{1-6}alkyl)amino, -C(=O)C_{1-6}alkyl, -O(C=O)C_{1-6}alkyl, -C(=O)OH, -C(=O)OC_{1-6}alkyl, -C(=O)NHC_{1-6}alkyl and -NHC(=O)C_{1-6}alkyl;

(v) G^5, wherein G^5 is heteroaryl wherein heteroaryl may be optionally substituted by one or more groups independently selected from halogen, CN, OH, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, haloC_{1-6}alkyloxy, -C_{1-6}alkyl-OH, NH_2, *N*-(C_{1-6}-alkyl)amino, *N,N*-di(C_{1-6}alkyl)amino, -C(=O)C_{1-6}alkyl, -O(C=O)C_{1-6}alkyl, -C(=O)OH, -C(=O)OC_{1-6}alkyl, -C(=O)NHC_{1-6}alkyl and -NHC(=O)C_{1-6}alkyl;

R^4 is –N(R^7)R^8, wherein

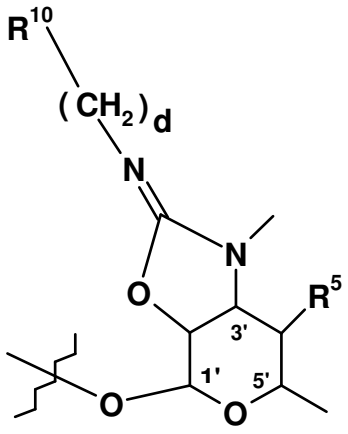
R^7 is CH_3,

R^8 is C_{1-6}alkyl, H, -C(=O)R^9 or R^p wherein R^9 is C_{1-6}alkyl or H;

R^5 is hydrogen;

or both R^4 and R^5 are hydrogen or together form a bond;

or S^1 is sugar group of formula **(b2)**:



(b2)

wherein:

R^5 is H;

d is an integer from zero to 3;

R^{10} is C_{1-4}alkyl;

R^{2a} is:

(i) S^2;

(ii) -OH;

(iii) -OC_{1-6}alkyl,

(iv) H;

(v) together with R^{2b} forms a keto group (=O);

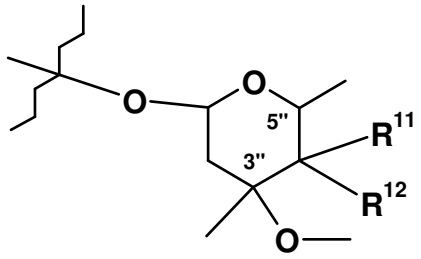
(vi) together with B^2 forms a double bond;

(vii) $-OC(=O)Y^1$, wherein Y^1 is G^1, G^2, G^3, G^4, G^5 or H; or

(viii) $-OR^p$;

R^{2b} is H, together with R^{2a} forms a keto group, together with A^1 forms cyclic hemiketal and R^{2a} is OH, or together with A^1 forms cyclic ether group and R^{2a} is H;

S^2 is sugar group of formula **(d)**



(d)

wherein,

R^{11} is:

(i) H;

(ii) together with R^{12} and carbon atom to which they are attached forms a keto or epoxy group;

(iii) one of R^{11} and R^{12} is OH and the other is $–CH_2N(R^{13})R^{14}$, wherein one of R^{13} and R^{14} is C_{1-6}alkyl and the other is H, G^1, G^2, G^3, G^4, G^5 or R^p, or wherein R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form a non-aromatic heterocyclic ring containing between 2 and 6 carbon atoms which is:

a. saturated or unsaturated and contains zero or 1 additional heteroatom selected from O, S and N; and/or

b. unsubstituted or substituted by from 1 to 2 groups selected from C_{1-5}alkanoyl; C_{1-6}alkyl wherein alkyl is uninterrupted or is interrupted by 1-3 bivalent radical groups selected from-O-, -S- and and $–N(R^{18})-$, and/or wherein C_{1-6}alkyl is unsubstituted or substituted by from 1 to 2 groups selected from OH, NH_2, a non-aromatic heterocyclic ring containing between 2 and 6 carbon atoms which is unsubstituted or is substituted by a group selected from C_{1-4}alkyl, halogen, NH_2, OH, SH, C_{1-6}alkoxy and C_{1-4}hydroxyalkyl, and C_{3-7}cycloalkyl which is unsubstituted or is substituted by a group selected from C_{1-4}alkyl,

halogen, NH_2, OH, SH, C_{1-6}alkoxy, C_{1-4}hydroxyalkyl; and C_{1-4}dialkylamino;

R^{12} is:

(i) OH,

(ii) together with R^{11} and carbon atom to which they are attached forms a keto or epoxy group;

(iii) -OC(=O)Y^3, wherein Y^3 is H, G^1, G^2, G^3, G^4, or G^5; or

(iv) OR^p;

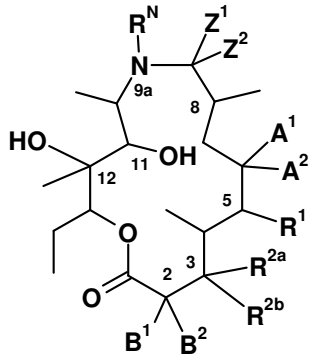
R^N is hydrogen, G^1 (preferably CH^3), G^2, G^3, G^4, G^5, R^p, or R^{15} wherein R^{15} is –C_{1-4}alkyl-G, -C(=O)G, -C(=O)NH-C_{0-4}alkyl-G, wherein G is G^1, G^2, G^3, G^4 or G^5;

R^p is a protective group;

or a salt or solvate thereof;

wherein said process comprises the following steps:

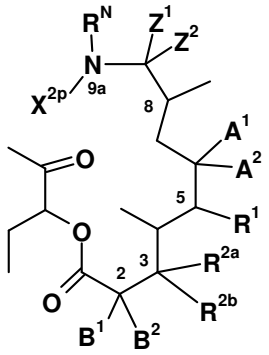
(a) reacting a 9a-aza-9a-homoerythromycin compound of formula **(II)**



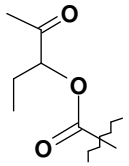
(II)

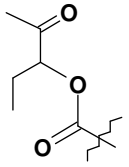
wherein,

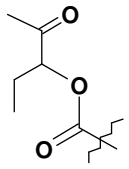
Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above, with a suitable oxidative cleavage reactant (suitably lead tetracaetate or periodic acid salts such as sodium periodate) in a suitable solvent or mixture of solvents to give:

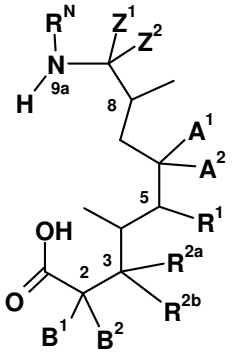


(I-A)

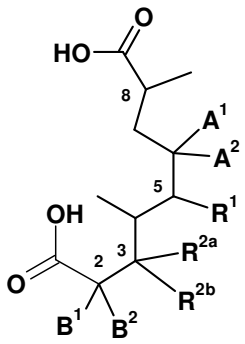
(i) a seco macrolide compound of formula (**I-A**), which is subset of formula (I), wherein X^{1p} is , X^{2p} is hydrogen, Z^1 and Z^2 are both hydrogen, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) when starting from compound of formula (II), wherein Z^1 and Z^2 are both hydrogen, or

(ii) a seco macrolide compound of formula (**I-A**), which is subset of formula (I) wherein X^{1p} is , X^{2p} is $-CH(CH_3)C(=O)H$, Z^1 and Z^2 together with carbon atom to which they are attached form a keto group, R^N is hydrogen, A^1 is $-OC_{1\text{-}6}$alkyl, A^2, R^1, R^{2a}, R^{2b}, B^1 and B^2, are as defined for formula (I) when starting from compound of formula (II) wherein Z^1 and Z^2 together with carbon atom to which they are attached form a keto group;

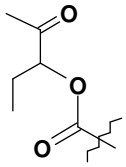
(b) hydrolyzing a compound of formula (I-A) wherein X^{1p} is  obtained in step (a) to give compound of formula (**I-B**), which is subset of formula (I) wherein X^{1p} is $-C(=O)OH$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; and optionally subjecting a compound of formula (I-B) wherein X^{1p} is $-C(=O)OH$, X^{2p} is hydrogen, R^N is hydrogen and Z^1 and Z^2 together with carbon atom to which they are attached form a keto group to a further hydrolyzing conditions to give di-carboxylic acid of formula (XC), wherein A^1, A^2, B^1, B^2, R^1, R^{2a} and R^{2b} are as defined for formula (I); or

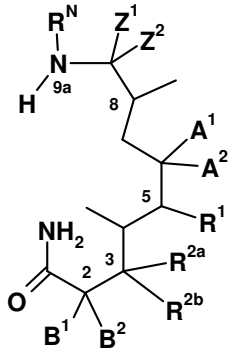


(I-B)



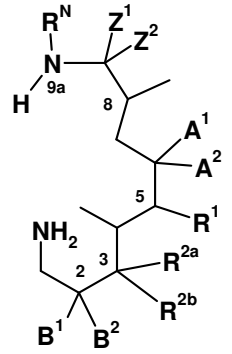
(XC)

(c) reacting a compound of formula (IA) wherein X^{1p} is , X^{2p} is hydrogen obtained in step (a) or compound of formula (I-B) wherein X^{1p} is –C(=O)OH and X^{2p} is hydrogen obtained in step (b) with ammonium salt in the presence of base and coupling agent or with ammonia in organic solvents, or with ammonia hydroxide to give a compound of formula (**I-C**), which is subset of formula (I) wherein X^{1p} is $–C(=O)NH_2$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or

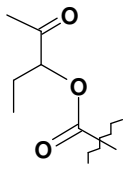


(I-C)

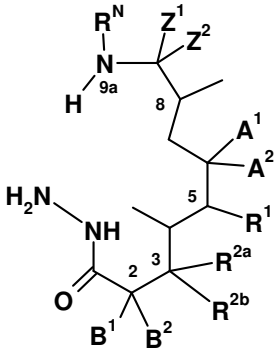
(d) reducing amide compound of formula (I-B) wherein X^{1p} is $–C(=O)NH_2$, and X^{2p} is hydrogen obtained in step (c) using sutable reducing agent (for example $LiAlH_4$, $NaBH_4$, $LiEt_3BH$, or borane-THF) to compound of formula (**I-D**), which is subset of formula (I) wherein X^{1p} is $–CH_2NH_2$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



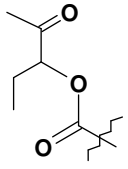
(I-D)



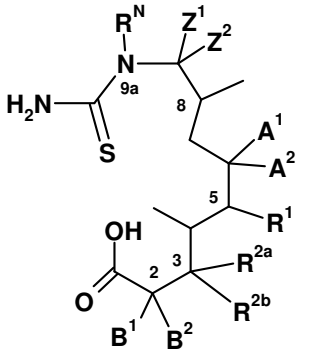
(e) reacting a compound of formula (I-A) obtained in step (a) wherein X^{1p} is with hydrazine hydrate in a suitable solvent to give compound of formula (**I-E**), which is subset of formula (I) wherein X^{1p} is –C(=O)-NH-NH_2 group, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



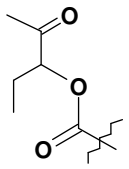
(I-E)



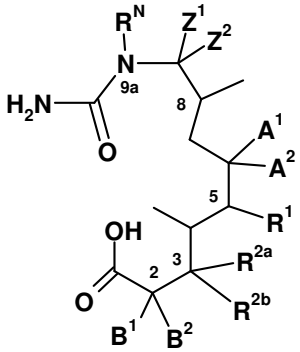
(f) reacting a compound of formula (I-A) obtained in step (a) wherein X^{1p} is or a compound of formula (I-B) obtained in step (b) wherein X^{1p} is –C(=O)OH with thiocarbonyldiimidazole followed by the amonolysis reaction conditions (provided when starting from compound of formula (I-A) then C/1-keto ester hydrolysis step (b) is usually performed prior amonolysis), or in alternative with thiocyanates or isothiocyanates to give compound of formula (**I-FA**), which is subset of formula (I) wherein X^{1p} is –C(=O)OH group, X^{2p} is –C(=S)NH_2 group, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



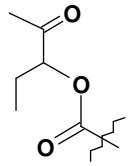
(I-FA)

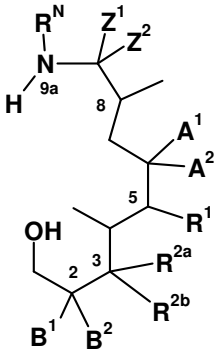


(g) reacting a compound of formula (I-A) obtained in step (a) wherein X^{1p} is or a compound of formula (I-B) obtained in step (b) wherein X^{1p} is –C(=O)OH with carbonyldiimidazole followed by the amonolysis reaction conditions (provided when starting from compound of formula (I-A) then C/1-keto ester hydrolysis step (b) is usually performed prior amonolysis), or in alternative with alkali metal cyanates or isocyanates to give compound of formula (**I-FB**), which is subset of formula (I) wherein X^{1p} is –C(=O)OH group, X^{2p} is –C(=O)NH_2 group, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



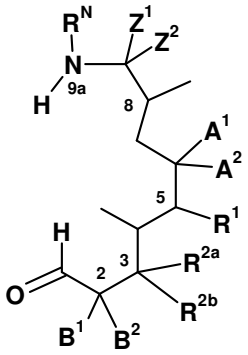
(I-FB)

(h) subjecting a compound of formula (I-A) obtained in step (a) wherein X^{1p} is  or a compound of formula (I-B) obtained in step (b) wherein X^{1p} is –C(=O)OH to the standard carboxylic acid reduction conditions to give compound of formula (**I-KA-a**), which is subset of formula (I) wherein X^{1p} is –CH_2OH group, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



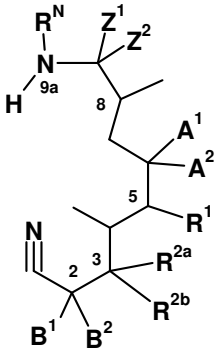
(I-KA-a)

(i) reacting a compound of formula (I-KA-a) obtained in step (h) wherein X^{1p} is $–CH_2OH$ group and X^{2p} is hydrogen with the standard oxidizing reagents to give compound of formula (**I-KA**), which is subset of formula (I) wherein X^{1p} is –C(=O)H group, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



(I-KA)

(j) subjecting compound of formula (I-C) obtained in step (c) where X^{1p} is $–C(=O)NH_2$ group and X^{2p} is hydrogen to dehydration reaction (for example thionyl chloride, phosphorus pentoxide, thionyl chloride, phosphorus pentoxide, phosphorus oxychloride, titanium tetrachloride, pivaloyl chloride, ethyl dichlorophosphate, trichloroacetyl chloride, silanes/TBAF) to give compound of formula (**I-MN**), which is subset of formula (I) wherein X^{1p} is –CN, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



(I-MN)

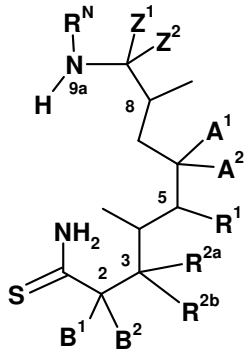
(k) reacting

a. a compound of formula (I-C) obtained in step (c) where X^{1p} $–C(=O)NH_2$, and X^{2p} is hydrogen with Lawesson's or Bellau's reagents or with P_4S_{10} alone or in combination with hexamethyldisiloxane, or in alternative

b. a compound of formula (I-MN) obtained in step (j) where X^{1p} –CN, and X^{2p} is hydrogen using alkali metal hydrogen sulfide or ammonium sulfide under high pressure, phosphorus decasulfide, thioacids, thioacetic acid in

combination with Lewis acid or benzylamine or calcium hydride, thioacetamide, DowexSH, *O*-dialkyldithiophosphates,12 diphenylphosphinodithioacids, sodium trimethylsilanethiolate, sodium hydrosulfide hydrate and diethyl amine hydrochloride, sodium hydrosulfide hydrate and magnesium chloride hexahydrate, and $(P_4S_{11})Na_2$

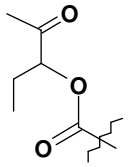
to give compound of formula (**I-M**), which is subset of formula (I) wherein X^{1p} is $–C(=S)NH_2$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



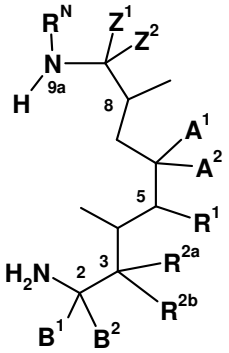
(I-M)

(l) subjecting

a. a compound of formula (I-B) obtained in step (b) where X^{1p} $–C(=O)OH$, and X^{2p} is hydrogento the modified Curtius rearrangement followed by mild acidic hydrolysis or hydrogenation of the carbamate group, or

b. a compound of formula (I-A) obtained in step (a) where X^{1p} is  and X^{2p} is hydrogento the modified Lossen rearrangement followed by mild acidic hydrolysis or hydrogenation of the carbamate group,

to give compound of formula (**I-RE**), which is subset of formula (I) wherein X^{1p} is $–NH_2$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; and



(I-RE)

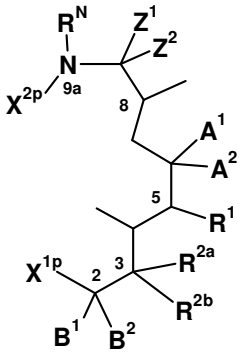
(m) if required after any of previous steps (a) – (l), subjecting the resulting compound to one or more of the following operations:

(i) removal of the protecting group R^p,

(ii) removal of S^2 sugar group and/or S^1 sugar group,

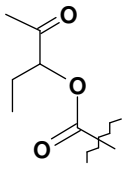
(iii) conversion of the resulting compound of formula (I) into a salt or solvate thereof.

In the first example, the present disclosure relates to seco (opened ring) macrolide compound of Formula (I)



(I)

wherein,

X^{1p} is  , -C(=O)OH, –C(=O)NH_2, -C(=S)NH_2, -C(=O)$NHNH_2$, -CH_2NH_2, -CH_2OH, -C(=O)H, -CN or –NH_2;

X^{2p} is hydrogen, –$CH(CH_3)C(=O)H$, -C(=S)NH_2 or -C(=O)NH_2;

Z^1 and Z^2 are

(i) both hydrogen, or

(ii) together with carbon atom to which they are attached form a keto group provided R^N is hydrogen and A^1 is $OC_{1\text{-}6}$alkyl,

A^1 is OH, $OC_{1\text{-}6}$alkyl, $OC_{2\text{-}6}$alkenyl, $OC_{2\text{-}6}$alkynyl, OR^p, or A^1 together with R^{2b} forms cyclic hemiketal or ether;

A^2 is CH_3 or H;

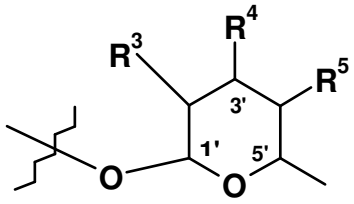
B^1 and B^2 are independently H, $C_{1\text{-}6}$alkyl or halogen, or

B^2 together with R^{2a} forms a double bond;

R^1 is S^1, OH, $OC_{1\text{-}6}$alkyl or OR^p;

wherein,

S^1 is sugar group of formula **(b1)**:



(b1)

wherein,

R^3 is OH, H, OR^p, –O-L^1-G or -OC(=O)G, provided when R^3 is –O-L^1-G or -OC(=O)G group then R^4 is $–N(CH_3)_2$ and R^5 is H, wherein

unsubstituted or is substituted by a group selected from C_{1-4}alkyl, halogen, NH_2, OH, SH, C_{1-6}alkoxy, C_{1-4}hydroxyalkyl; and C_{1-4}dialkylamino;

R^{12} is:

(i) OH;

(ii) together with R^{11} and carbon atom to which they are attached forms a keto or epoxy group;

(iii) -OC(=O)Y^3, wherein Y^3 is H, G^1, G^2, G^3, G^4, or G^5; or

(iv) OR^p;

R^N is hydrogen, G^1 (preferably CH^3), G^2, G^3, G^4, G^5, R^p, or R^{15} wherein R^{15} is –C_{1-4}alkyl-G, -C(=O)G, -C(=O)NH-C_{0-4}alkyl-G, wherein G is G^1, G^2, G^3, G^4 or G^5;

R^p is a protective group;

or a salt or solvate thereof.

In another example, the disclosure relates to the use of seco (opened ring) macrolide compound of Formula (I) as intermediate for preparation of macrolide based macrocycles of formula (III). In particular, the disclosure relates to seco (opened ring) macrolide compound of Formula (I) for use as intermediate for preparation of macrolide based macrocycles of formula (III).

In a further example, the disclosure relates to the process for preparation of seco (opened ring) macrolide compound of Formula (I). In particular, the disclosure relates to the process of preparation of seco (opened ring) macrolide compound of Formula (I) wherein in the first step (a) the macrolide ring of compound of Formula (II) is cleaved using suitable oxidative cleavage reactant (suitably lead tetracaetate or periodic acid salts such as sodium periodate) in a suitable solvent or mixture of solvents, said initial step (a) being optionally followed by steps selected form (b) to (m).

In another example, the disclosure relates to the macrolide compound of Formula (II-X), which is subset of Formula (II). In particular, the disclosure relates to compound of formula (II-X) for use as intermediate for preparation of compound of formula (I).

In another example, the disclosure relates to macrolide based macrocyle compound of Formula (III).

In a further example, the disclosure relates to the process for preparation of macrolide based macrocyle compound of Formula (III). In particular, the disclosure relates to the process for preparation of macrolide based macrocyle compound of Formula (III) from seco (opened ring) macrolide compound of Formula (I).

In another example, the disclosure relates to the pharmaceutical compositions comprising a macrolide based macrocyle compound of Formula (III).

In a further example, the present disclosure also relates to pharmaceutical compositions comprising a macrolide based macrocyle compound of Formula (III) and a pharmaceutical carrier, excipient or diluent.

In another example, the disclosure relates to a macrolide based macrocyle compound of Formula (III) for use in therapy.

In a further example, the disclosure relates to a macrolide based macrocyle compound of Formula (III) for use in the prophylaxis and/or treatment of conditions involving inflammation or immune responses and/or autoimmune diseases.

In another example, the disclosure relates to the use of a macrolide based macrocyle compound of Formula (III) in the manufacture of a medicament for the prophylaxis and/or treatment of conditions involving inflammation or immune responses and/or autoimmune diseases.

In further example, the disclosure relates to methods of prophylaxis and/or treatment of conditions involving inflammation or immune responses and/or autoimmune diseases by administering of an effective amount of a macrolide based macrocyle compound of compound of the disclosure or one or more pharmaceutical compositions of the disclosure.

In another example of the disclosure, this disclosure provides a methods of prophylaxis and/or treatment of a subject, in particular humans, susceptible to or afflicted with a condition selected from among those listed herein, and particularly conditions involving inflammation or immune responses and/or autoimmune diseases, which methods comprise the administration of an effective amount of a macrolide based macrocyle compound of Formula (III) or one or more pharmaceutical compositions of the disclosure.

Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

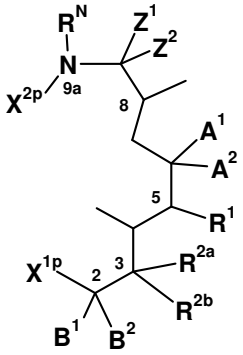
It will be understood that the present invention covers all combinations of aspects, suitable, convenient and preferred groups described herein.

When describing the invention, which may include processes, compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. Unless otherwise stated, the term "substituted" is to

CLAIMS

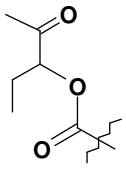
WE CLAIM:

1. A process for preparation of seco (opened ring) macrolide compound of Formula (I), or a salt or solvate thereof,



(I)

wherein,

X^{1p} is , -C(=O)OH, –C(=O)NH_2, -C(=S)NH_2, -C(=O)$NHNH_2$, -CH_2NH_2, -CH_2OH, -C(=O)H, -CN or –NH_2;

X^{2p} is hydrogen,–$CH(CH_3)C(=O)H$, -C(=S)NH_2 or -C(=O)NH_2;

Z^1 and Z^2

(i) are both hydrogen, or

(ii) together with carbon atom to which they are attached form a keto group provided R^N is hydrogen and A^1 is $OC_{1\text{-}6}$alkyl,

A^1 is OH, $OC_{1\text{-}6}$alkyl, $OC_{2\text{-}6}$alkenyl, $OC_{2\text{-}6}$alkynyl, OR^p, or A^1 together with R^{2b} forms cyclic hemiketal or ether;

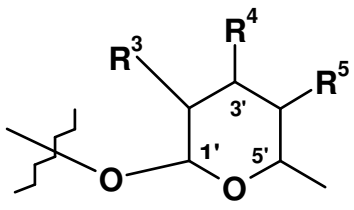
A^2 is CH_3 or H;

B^1 and B^2 are independently H, $C_{1\text{-}6}$alkyl or halogen, or

B^2 together with R^{2a} forms a double bond;

R^1 is S^1, OH, $OC_{1\text{-}6}$alkyl or OR^p;

S^1 is sugar group of formula **(b1)**:



(b1)

wherein,

R^3 is OH, H, OR^p, $–O\text{-}L^1\text{-}G$ or $\text{-}OC(=O)G$, provided when R^3 is $–O\text{-}L^1\text{-}G$ or $\text{-}OC(=O)G$ group then R^4 is $–N(CH_3)_2$ and R^5 is H, wherein

L^1 $\text{-}(CH_2)_{a1}\text{-}U^1\text{-}(CH_2)_{b1}\text{-}$;

U^1 is $–N(R^6)\text{-}$, -NHC(=O)- or –C(=O)NH-;

R^6 is H or $C_{1\text{-}3}$alkyl;

a^1 is an integer from 2 to 6;

b^1 is an integer from 0 to 6;

G is selected from:

(i) G^1, wherein G^1 is $C_{1\text{-}8}$alkyl, wherein alkyl may be optionally interrupted by 1 to 3 bivalent radical groups selected from –O-, -S- and $–N(R^{g1})\text{-}$, where R^{g1} is H or $C_{1\text{-}6}$alkyl, and where alkyl may be optionally substituted by one or more groups independently selected from halogen, OH, keto, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $OC_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, $\text{-}C(=O)OC_{1\text{-}6}$alkyl, $\text{-}C_{1\text{-}6}$alkyl-OH, NH_2, *N*-($C_{1\text{-}6}$-alkyl)amino, *N,N*-di($C_{1\text{-}6}$alkyl)amino; aryl or heteroaryl wherein said aryl and heteroaryl may be mono or biyclic and independently each may be optionally substituted by one or more groups independently selected from halogen, CN, OH, NO_2, $OC_{1\text{-}6}$alkyl, NH_2, *N*-($C_{1\text{-}6}$-alkyl)amino, *N,N*-di($C_{1\text{-}6}$alkyl)amino, $\text{-}C(=O)C_{1\text{-}6}$alkyl, $\text{-}OC(=O)C_{1\text{-}6}$alkyl, -C(=O)OH, $\text{-}C(=O)OC_{1\text{-}6}$alkyl, $\text{-}C(=O)NHC_{1\text{-}6}$alkyl and $\text{-}NHC(=O)C_{1\text{-}6}$alkyl;

(ii) G^2, wherein G^2 is 3-7 membered cycloalkyl which may be optionally substituted by one or more groups independently selected from OH, halogen, CN, NH_2, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, $\text{-}OC_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, $\text{-}C_{1\text{-}6}$alkyl-OH, $\text{-}C(=O)C_{1\text{-}6}$alkyl, $\text{-}C(=O)OC_{1\text{-}6}$alkyl, -C(=O)OH, $\text{-}C(=O)NH_2$, $\text{-}C_{0\text{-}6}$alkyl-aryl or $C_{0\text{-}6}$alkyl-heteroaryl wherein aryl and heteroaryl independently from each other may be optionally substituted by one or more groups independently selected from halogen, CN, OH, NO_2, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, $\text{-}OC_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, $\text{-}C_{1\text{-}6}$alkyl-OH, NH_2, *N*-($C_{1\text{-}6}$-alkyl)amino, *N,N*-di($C_{1\text{-}6}$alkyl)amino, $\text{-}C(=O)C_{1\text{-}6}$alkyl, $\text{-}OC(=O)C_{1\text{-}6}$alkyl, -C(=O)OH, $\text{-}C(=O)OC_{1\text{-}6}$alkyl, $\text{-}C(=O)NHC_{1\text{-}6}$alkyl and $\text{-}NHC(=O)C_{1\text{-}6}$alkyl;

(iii) G^3, wherein G^3 is 3-7 membered heterocycloalkyl containing one or two heteroatoms independently selected from N, O and S, where heterocycloalkyl may be optionally substituted by one or more groups independently selected from OH, halogen, CN, NH_2, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl,

C_{2-6}alkynyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, haloC_{1-6}alkyloxy, -C_{1-6}alkyl-OH, -C(=O)C_{1-6}alkyl, -C(=O)OC_{1-6}alkyl, -C(=O)OH and -C(=O)NH_2;

(iv) G^4, wherein G^4 is aryl wherein aryl may be optionally substituted by one or more groups independently selected from halogen, CN, OH, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, haloC_{1-6}alkyloxy, -C_{1-6}alkyl-OH, NH_2, *N*-(C_{1-6}-alkyl)amino, *N,N*-di(C_{1-6}alkyl)amino, -C(=O)C_{1-6}alkyl, -O(C=O)C_{1-6}alkyl, -C(=O)OH, -C(=O)OC_{1-6}alkyl, -C(=O)NHC_{1-6}alkyl and -NHC(=O)C_{1-6}alkyl;

(v) G^5, wherein G^5 is heteroaryl wherein heteroaryl may be optionally substituted by one or more groups independently selected from halogen, CN, OH, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, -OC_{1-6}alkyl, haloC_{1-6}alkyloxy, -C_{1-6}alkyl-OH, NH_2, *N*-(C_{1-6}-alkyl)amino, *N,N*-di(C_{1-6}alkyl)amino, -C(=O)C_{1-6}alkyl, -O(C=O)C_{1-6}alkyl, -C(=O)OH, -C(=O)OC_{1-6}alkyl, -C(=O)NHC_{1-6}alkyl and -NHC(=O)C_{1-6}alkyl;

R^4 is $-N(R^7)R^8$, wherein

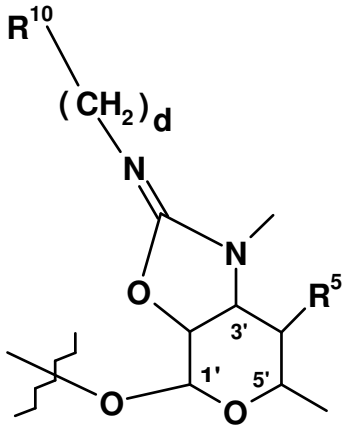
R^7 is CH_3,

R^8 is C_{1-6}alkyl, H, -C(=O)R^9 or R^p wherein R^9 is C_{1-6}alkyl or H;

R^5 is hydrogen;

or both R^4 and R^5 are hydrogen or together form a bond;

or S^1 is sugar group of formula **(b2)**:



(b2)

wherein:

R^5 is H;

d is an integer from zero to 3;

R^{10} is C_{1-4}alkyl;

R^{2a} is:

(i) S^2;

(ii) -OH;

(iii) $-OC_{1-6}$alkyl,

(iv) H;

(v) together with R^{2b} forms a keto group (=O);

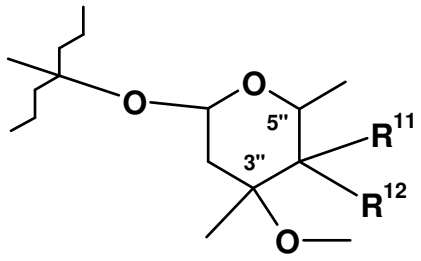
(vi) together with B^2 forms a double bond;

(vii) $-OC(=O)Y^1$, wherein Y^1 is G^1, G^2, G^3, G^4, G^5 or H; or

(viii) $-OR^p$;

R^{2b} is H, together with R^{2a} forms a keto group, together with A^1 forms cyclic hemiketal and R^{2a} is OH, or together with A^1 forms cyclic ether group and R^{2a} is H;

S^2 is sugar group of formula **(d)**



(d)

wherein,

R^{11} is:

(i) H;

(ii) together with R^{12} and carbon atom to which they are attached forms a keto or epoxy group;

(iii) one of R^{11} and R^{12} is OH and the other is $-CH_2N(R^{13})R^{14}$, wherein one of R^{13} and R^{14} is C_{1-6}alkyl and the other is H, G^1, G^2, G^3, G^4, G^5 or R^p, or wherein R^{13} and R^{14} taken together with the nitrogen atom to which they are attached form a non-aromatic heterocyclic ring containing between 2 and 6 carbon atoms which is:

a. saturated or unsaturated and contains zero or 1 additional heteroatom selected from O, S and N; and/or

b. unsubstituted or substituted by from 1 to 2 groups selected from C_{1-5}alkanoyl; C_{1-6}alkyl wherein alkyl is uninterrupted or is interrupted by 1-3 bivalent radical groups selected from-O-, -S- and and $-N(R^{18})-$, and/or wherein C_{1-6}alkyl is unsubstituted or substituted by from 1 to 2 groups selected from OH, NH_2, a non-aromatic heterocyclic ring

containing between 2 and 6 carbon atoms which is unsubstituted or is substituted by a group selected from C_{1-4}alkyl, halogen, NH_2, OH, SH, C_{1-6}alkoxy and C_{1-4}hydroxyalkyl, and C_{3-7}cycloalkyl which is unsubstituted or is substituted by a group selected from C_{1-4}alkyl, halogen, NH_2, OH, SH, C_{1-6}alkoxy, C_{1-4}hydroxyalkyl; and C_{1-4}dialkylamino;

R^{12} is:

(i) OH,

(ii) together with R^{11} and carbon atom to which they are attached forms a keto or epoxy group;

(iii) $-OC(=O)Y^3$, wherein Y^3 is H, G^1, G^2, G^3, G^4, or G^5; or

(iv) OR^p;

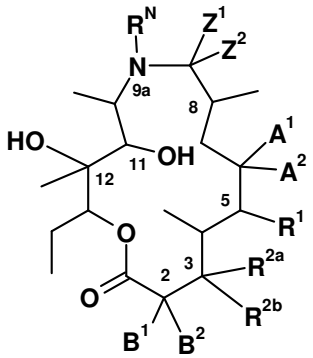
R^N is hydrogen, G^1 (preferably CH^3), G^2, G^3, G^4, G^5, R^p, or R^{15} wherein R^{15} is $-C_{1-4}$alkyl-G, -C(=O)G, -C(=O)NH-C_{0-4}alkyl-G, wherein G is G^1, G^2, G^3, G^4 or G^5;

R^p is a protective group;

or a salt or solvate thereof;

wherein said process comprises the following steps:

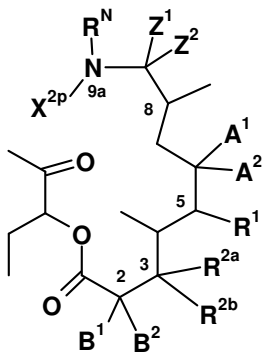
(a) reacting a 9a-aza-9a-homoerythromycin compound of formula **(II)**



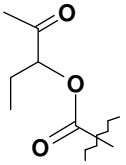
(II)

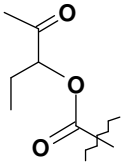
wherein,

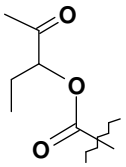
Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above, with a suitable oxidative cleavage reactant (suitably lead tetracaetate or periodic acid salts such as sodium periodate) in a suitable solvent or mixture of solvents to give:

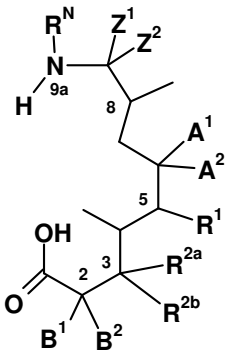


(I-A)

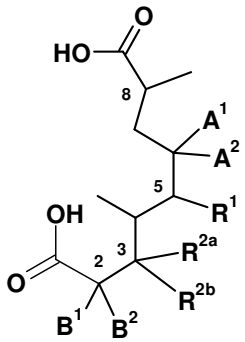
(i) a seco macrolide compound of formula (**I-A**), which is subset of formula (I), wherein X^{1p} is , X^{2p} is hydrogen, Z^1 and Z^2 are both hydrogen, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) when starting from compound of formula (II), wherein Z^1 and Z^2 are both hydrogen, or

(ii) a seco macrolide compound of formula (**I-A**), which is subset of formula (I) wherein X^{1p} is , X^{2p} is $–CH(CH_3)C(=O)H$, Z^1 and Z^2 together with carbon atom to which they are attached form a keto group, R^N is hydrogen, A^1 is $-OC_{1\text{-}6}$alkyl, A^2, R^1, R^{2a}, R^{2b}, B^1 and B^2, are as defined for formula (I) when starting from compound of formula (II) wherein Z^1 and Z^2 together with carbon atom to which they are attached form a keto group;

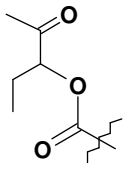
(b) hydrolyzing a compound of formula (I-A) wherein X^{1p} is  obtained in step (a) to give compound of formula (**I-B**), which is subset of formula (I) wherein X^{1p} is $–C(=O)OH$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; and optionally subjecting a compound of formula (I-B) wherein X^{1p} is $–C(=O)OH$, X^{2p} is hydrogen, R^N is hydrogen and Z^1 and Z^2 together with carbon atom to which they are attached form a keto group to a further hydrolyzing conditions to give di-carboxylic acid of formula (XC), wherein A^1, A^2, B^1, B^2, R^1, R^{2a} and R^{2b} are as defined for formula (I); or

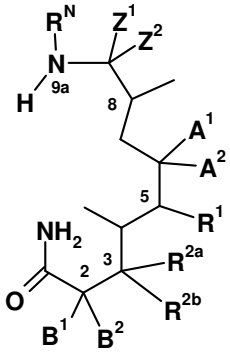


(I-B)



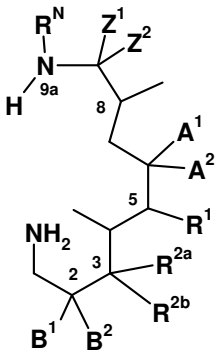
(XC)

(c) reacting a compound of formula (IA) wherein X^{1p} is , X^{2p} is hydrogen obtained in step (a) or compound of formula (I-B) wherein X^{1p} is –C(=O)OH and X^{2p} is hydrogen obtained in step (b) with ammonium salt in the presence of base and coupling agent or with ammonia in organic solvents, or with ammonia hydroxide to give a compound of formula (**I-C**), which is subset of formula (I) wherein X^{1p} is $–C(=O)NH_2$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or

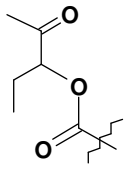


(I-C)

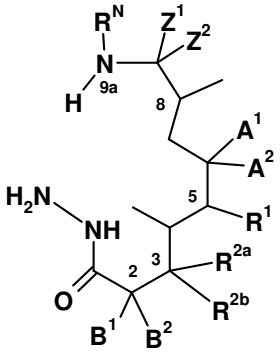
(d) reducing amide compound of formula (I-B) wherein X^{1p} is $–C(=O)NH_2$, and X^{2p} is hydrogen obtained in step (c) using sutable reducing agent (for example $LiAlH_4$, $NaBH_4$, $LiEt_3BH$, or borane-THF) to compound of formula (**I-D**), which is subset of formula (I) wherein X^{1p} is $–CH_2NH_2$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



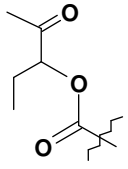
(I-D)



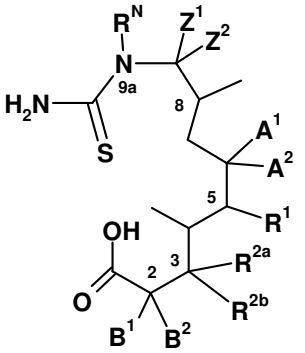
(e) reacting a compound of formula (I-A) obtained in step (a) wherein X^{1p} is with hydrazine hydrate in a suitable solvent to give compound of formula (**I-E**), which is subset of formula (I) wherein X^{1p} is –C(=O)-NH-NH_2 group, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



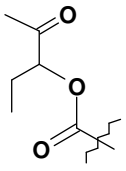
(I-E)

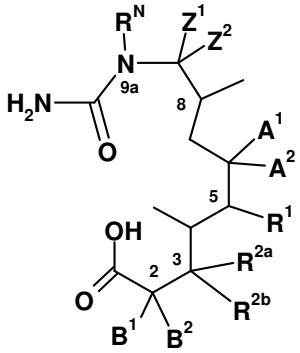


(f) reacting a compound of formula (I-A) obtained in step (a) wherein X^{1p} is or a compound of formula (I-B) obtained in step (b) wherein X^{1p} is –C(=O)OH with thiocarbonyldiimidazole followed by the amonolysis reaction conditions (provided when starting from compound of formula (I-A) then C/1-keto ester hydrolysis step (b) is usually performed prior amonolysis), or in alternative with thiocyanates or isothiocyanates to give compound of formula (**I-FA**), which is subset of formula (I) wherein X^{1p} is –C(=O)OH group, X^{2p} is –C(=S)NH_2 group, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or

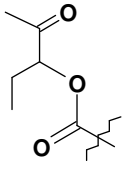


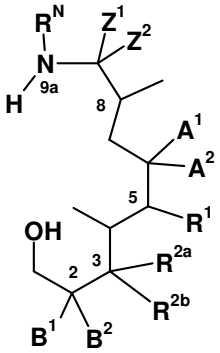
(I-FA)

(g) reacting a compound of formula (I-A) obtained in step (a) wherein X^{1p} is  or a compound of formula (I-B) obtained in step (b) wherein X^{1p} is –C(=O)OH with carbonyldiimidazole followed by the amonolysis reaction conditions (provided when starting from compound of formula (I-A) then C/1-keto ester hydrolysis step (b) is usually performed prior amonolysis), or in alternative with alkali metal cyanates or isocyanates to give compound of formula (**I-FB**), which is subset of formula (I) wherein X^{1p} is –C(=O)OH group, X^{2p} is –C(=O)NH_2 group, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



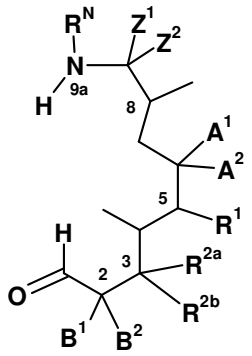
(I-FB)

(h) subjecting a compound of formula (I-A) obtained in step (a) wherein X^{1p} is  or a compound of formula (I-B) obtained in step (b) wherein X^{1p} is –C(=O)OH to the standard carboxylic acid reduction conditions to give compound of formula (**I-KA-a**), which is subset of formula (I) wherein X^{1p} is $–CH_2OH$ group, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



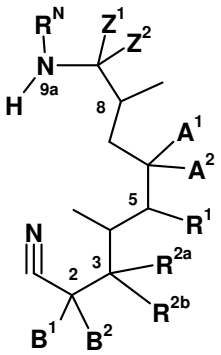
(I-KA-a)

(i) reacting a compound of formula (I-KA-a) obtained in step (h) wherein X^{1p} is $–CH_2OH$ group and X^{2p} is hydrogen with the standard oxidizing reagents to give compound of formula (**I-KA**), which is subset of formula (I) wherein X^{1p} is –C(=O)H group, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



(I-KA)

(j) subjecting compound of formula (I-C) obtained in step (c) where X^{1p} is $–C(=O)NH_2$ group and X^{2p} is hydrogen to dehydration reaction (for example thionyl chloride, phosphorus pentoxide, thionyl chloride, phosphorus pentoxide, phosphorus oxychloride, titanium tetrachloride, pivaloyl chloride, ethyl dichlorophosphate, trichloroacetyl chloride, silanes/TBAF) to give compound of formula (**I-MN**), which is subset of formula (I) wherein X^{1p} is –CN, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



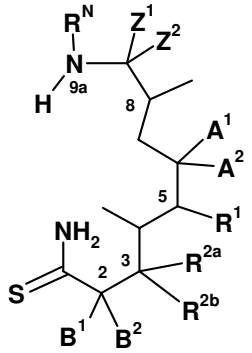
(I-MN)

(k) reacting

a. a compound of formula (I-C) obtained in step (c) where X^{1p} –C(=O)NH_2, and X^{2p} is hydrogen with Lawesson's or Bellau's reagents or with P_4S_{10} alone or in combination with hexamethyldisiloxane, or in alternative

b. a compound of formula (I-MN) obtained in step (j) where X^{1p} –CN, and X^{2p} is hydrogen using alkali metal hydrogen sulfide or ammonium sulfide under high pressure, phosphorus decasulfide, thioacids, thioacetic acid in combination with Lewis acid or benzylamine or calcium hydride, thioacetamide, DowexSH, *O*-dialkyldithiophosphates,12 diphenylphosphinodithioacids, sodium trimethylsilanethiolate, sodium hydrosulfide hydrate and diethyl amine hydrochloride, sodium hydrosulfide hydrate and magnesium chloride hexahydrate, and $(P_4S_{11})Na_2$

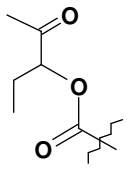
to give compound of formula (**I-M**), which is subset of formula (I) wherein X^{1p} is –C(=S)NH_2, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; or



(I-M)

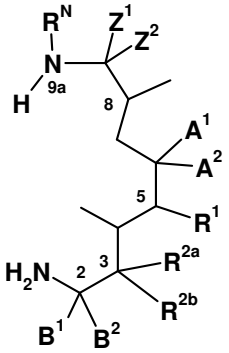
(l) subjecting

a. a compound of formula (I-B) obtained in step (b) where X^{1p} –C(=O)OH, and X^{2p} is hydrogento the modified Curtius rearrangement followed by mild acidic hydrolysis or hydrogenation of the carbamate group, or



b. a compound of formula (I-A) obtained in step (a) where X^{1p} is and X^{2p} is hydrogento the modified Lossen rearrangement followed by mild acidic hydrolysis or hydrogenation of the carbamate group,

to give compound of formula (**I-RE**), which is subset of formula (I) wherein X^{1p} is $-NH_2$, X^{2p} is hydrogen, Z^1, Z^2, A^1, A^2, R^1, R^{2a}, R^{2b}, B^1, B^2 and R^N are as defined for formula (I) above; and



(I-RE)

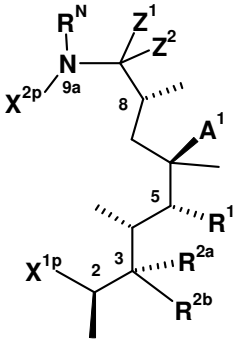
(m) if required after any of previous steps (a) – (l), subjecting the resulting compound to one or more of the following operations:

(i) removal of the protecting group R^p,

(ii) removal of S^2 sugar group and/or S^1 sugar group,

(iii) conversion of the resulting compound of formula (I) into a salt or solvate thereof.

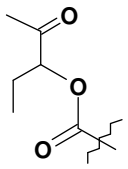
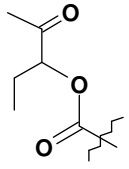
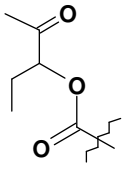
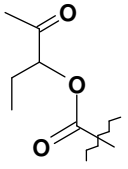
2. The process according to claim 1, wherein compound of formula (I) is represented by formula (I-ii)



(I-ii)

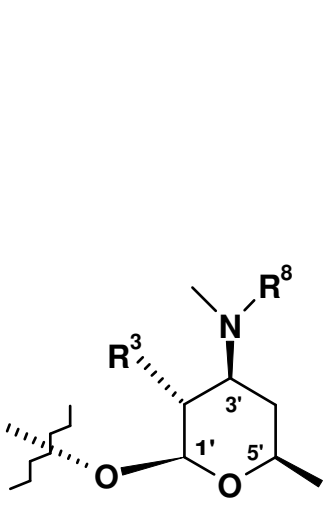
wherein

X^{1p}, X^{2p}, R^N, Z^1, Z^2, A^1, R^1, R^{2a} and R^{2b} are as defined above in claim 1.

3. The process according to claim 1, wherein X^{1p} is  or -C(=O)OH.
4. The process according to claims 1 to 3, wherein X^{2p} is hydrogen.
5. The process according to claim 1 or 2, wherein
   (a) X^{2p} is hydrogen, X^{1p} is , -C(=O)OH, –C(=O)NH_2, -C(=S)NH_2, -C(=O)$NHNH_2$, -CH_2NH_2, -CH_2OH, -C(=O)H, -CN or –NH_2;
   (b) X^{2p} is -C(=S)NH_2 or -C(=O)NH_2, X^{1p} is -C(=O)OH; or
   (c) X^{2p} is –$CH(CH_3)$C(=O)H and X^{1p} is .
6. The process according to claim 1 or 2, wherein
   (a) X^{2p} is hydrogen, X^{1p} is –C(=O)NH_2, -C(=S)NH_2, -C(=O)$NHNH_2$, -CH_2NH_2, -CH_2OH, -C(=O)H, -CN or –NH_2; or
   (b) X^{2p} is -C(=S)NH_2 or -C(=O)NH_2, X^{1p} is -C(=O)OH; or
   (c) X^{2p} is –$CH(CH_3)$C(=O)H and X^{1p} is .
7. The process according to any of claims 1 to 6, wherein Z^1 and Z^2 are both hydrogen.

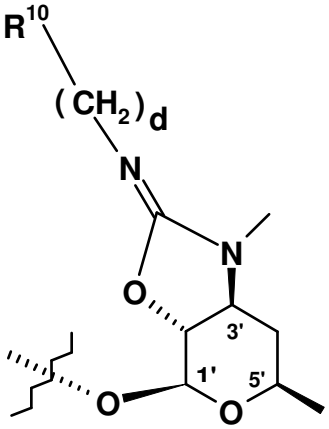
8. The process according to any of claims 1-7, wherein R^N is $C_{1\text{-}6}$alkyl (preferably CH_3) or hydrogen.
9. The process according to any of claims 1-8, wherein A^1 is OH or -$OC_{1\text{-}6}$alkyl (preferably OCH_3).
10. The process according to any of claims 1-9, wherein R^1 is S^1 or OH.
11. The process according to claims 1-10, wherein R^{2a} is S^2, OH or –OC(=O)Y^1, wherein S^2 and Y^1 are as defined in claim 1 above.
12. The process according to claims 1-11, wherein R^{2b} is H.
13. The compound according to claims 1-12, wherein B^1 and B^2 independently are H or $C_{1\text{-}6}$alkyl (suitably H or CH_3).

14. The process according to claims 1-13, wherein S^1 is sugar group of formula



(b1-ii)

or

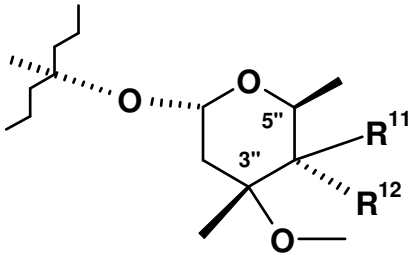


(b2-ii)

wherein R^3, R^8, d, and R^{10} are as defined in claim 1 above.

15. The process according to claim 14, wherein R^3 is OH, H or –O-L^1-G group, R^{10} is C_{1-6}alkyl, and L^1, G and d are as defined in claim 1 above.

16. The process according to claims 1-15, wherein S^2 is sugar group of formula



(d-i)

, and wherein R^{11} and R^{12} are as defined in claim 1 above.

17. The process according to claim 16, wherein

(i) R^{11} is H and R^{12} is OH; or

(ii) one of R^{11} and R^{12} is OH and the other is $–CH_2N(R^{13})R^{14}$, wherein R^{13} and R^{14} are as defined in claim 1 above.

18. The process according to claim 17, wherein

(i) one of R^{13} and R^{14} is C_{1-6}alkyl (suitably methyl or ethyl) and the other is H or C_{1-6}alkyl (suitably methyl or ethyl); or

(ii) R^{13} and R^{14} together with nitrogen to which they are attached form a heterocyclic ring (suitably morpholinyl).