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(54) Titre : MACROLIDES ET LEURS PROCEDES DE PREPARATION ET D'UTILISATION
(54) Title: MACROLIDES AND METHODS OF THEIR PREPARATION AND USE

(57) Abrégé/Abstract:
Provided herein are methods of preparing macrolides by the coupling of an eastern and western half, followed by macrocyclization, to provide macrolides, including both known and novel macrolides. Intermediates in the synthesis of macrolides including the eastern and western halves are also provided. Pharmaceutical compositions and methods of treating infectious diseases and inflammatory conditions using the inventive macrolides are also provided. A general diastereoselective aldol methodology used in the synthesis of the western half is further provided.

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Certificat de correction

Certificate of Correction

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Les corrections suivantes sont faites en raison de l'article 109 des *Règles sur les brevets* et le brevet doit être lu tel que corrigé.

The following corrections are made pursuant to section 109 of the *Patent Rules* and the patent should read as corrected.

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The attached pages 1 to 504 should be read in place of pages 1 to 504 in the description.

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(74) Agent: **BAKER, C., Hunter**; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-2206 (US).

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(54) Title: MACROLIDES AND METHODS OF THEIR PREPARATION AND USE

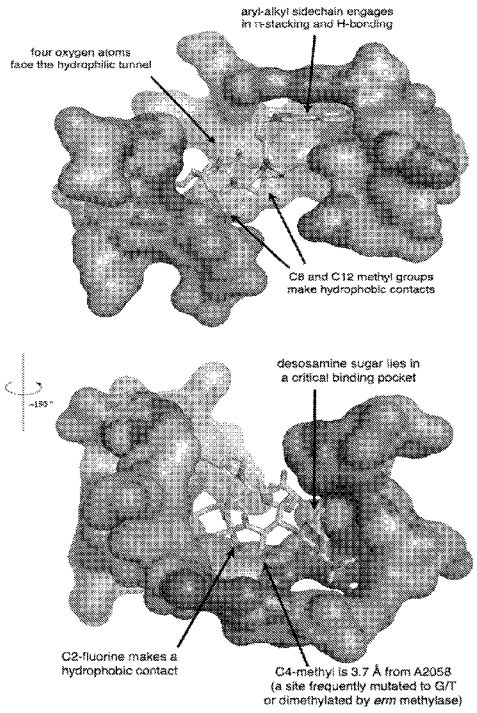

Figure 2

(57) Abstract: Provided herein are methods of preparing macrolides by the coupling of an eastern and western half, followed by macrocyclization, to provide macrolides, including both known and novel macrolides. Intermediates in the synthesis of macrolides including the eastern and western halves are also provided. Pharmaceutical compositions and methods of treating infectious diseases and inflammatory conditions using the inventive macrolides are also provided. A general diastereoselective aldol methodology used in the synthesis of the western half is further provided.

WO 2014/165792 A3

WO 2014/165792 A3

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CECI EST LE TOME __1___ DE __2 __

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

MACROLIDES AND METHODS OF THEIR PREPARATION AND USE

[0001]

BACKGROUND OF THE INVENTION

[0002] Emerging resistance to existing antibiotics is rapidly developing as a crisis of global proportions, especially for *Staphylococcus aureus, Streptococcus pyogenes*, and *Streptococcus pneumonia* infections. Pathogenic bacteria can transmit genes coding for antibiotic resistance both vertically (to their progeny) and horizontally (to neighboring bacteria of different lineages), and as a result antibiotic resistance can evolve quickly, particularly in nosocomial (hospital) settings. See, *e.g.*, Wright, *Chem. Commun.* (2011) 47:4055–4061. This year, >99,000 people will die in the U.S. from healthcare-associated infections, more than all casualties from car accidents, HIV, and breast cancer combined, creating an estimated burden of up to $45 billion in U.S. healthcare costs. See, *e.g.*, Klevens *et al.*, *Public Health Rep* (2007) *122*:160–166. The current crisis is exacerbated by the fact that most major pharmaceutical companies have essentially abandoned research in the development of new antibiotics. See, *e.g.*, Projan *Curr. Opin. Microbiol.* (2003) *6*: 427–430. The current rate of introduction of new antibiotics does not adequately address growing resistance, and with the ease of international travel and increasing population densities, the need for innovation in the field has never been higher.

[0003] The macrolides are one of the few major clinically important classes of antibiotics for which the only practical access has been through semi–synthesis, or chemical manipulation of structurally complex fermentation products, in routes as long as 16 steps. See, *e.g.*, Paterson, *Tetrahedron* (1985) *41*:3569–3624; Omura, Ed., *Macrolide Antibiotics: Chemistry, Biology, and Practice, Second Edition*; Academic Press, 2002. The macrolide class of antibiotics has proven safe and effective in the battle against pathogenic bacteria since the discovery of erythromycin over 60 years ago. See, *e.g.,* Wu *et al.*, *Curr. Med. Chem.* (2001) *8*, 1727–1758. Erythromycin displays a spectrum of antibacterial activity against Gram– positive bacteria similar to that of penicillin but has a lesser propensity to induce allergic interactions, and has been routinely prescribed for upper and lower respiratory tract infections and urogenital infections. See, *e.g.*, Washington *et al.*, *Mayo. Clin. Proc.* (1985) *60*:189–203; Washington *et al.*, *Mayo. Clin. Proc.* (1985) *60*:271–278. However, erythromycin is known to undergo acid–promoted internal ketalization (cyclization of the C6 and C12 hydroxyl groups onto the C9 ketone) in the gut, which leads to adverse gastrointestinal events. See, *e.g.*, Kurath *et al.*, *Experientia* (1971) *27*:362. Second–generation macrolide antibiotics

Date Reçue/Date Received 2020-06-25

clarithromycin and azithromycin addressed issues of acid instability and were prepared semi–synthetically in 4–6 steps from erythromycin, which is readily available through large-scale fermentation. See, *e.g.*, Ma *et al.*, *Curr. Med. Chem.* (2011) *18*:1993–2015; Wu *et al.*, *Curr. Pharm. Des.* (2000) *6*:181–223; Ma *et al.*, *Mini–Rev. Med. Chem.* (2010) *10*:272–286; Asaka *et al.*, *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)* (2003) *3*:961–989; Morimoto *et al.*, *J. Antibiot.* (1990) *43*:286–294; Morimoto *et al.*, *J. Antibiot.* (1984) *37*:187–189; Watanabe *et al.*, *J. Antibiot.* (1993) *46*: 1163–1167; Watanabe *et al.*, *J. Antibiot.* (1993) *46*:647–660; Bright *et al.*, *J. Antibiot.* (1988) *41*: 1029–1047; Djokic *et al.*, *J. Antibiot.* (1987) *40*:1006–1015; Mutak *et al.*, *J. Antibiot.* (2007) *60*: 85–122; and Retsema *et al.*, *Antimicrob. Agents Chemother.* (1987) *31*:1939–1947. Azithromycin has been shown to exhibit markedly improved efficacy against Gram–negative organisms, and has a longer half–life and higher tissue distribution than the other macrolide antibiotics, thought to correlate with its 15– membered ring containing a tertiary amine. See, *e.g.*, Ferwerda *et al.*, *J. Antimicrob. Chemother.* (2001) *47*:441–446; Girard *et al.*, *Antimicrob. Agents Chemother.* (1987) *31*:1948–1954. The natural product tylosin, a 16–membered macrolide used in veterinary medicine, has been shown by X–ray crystallography to occupy the same binding pocket as erythromycin and azithromycin, suggesting that there is a high tolerance for variability in ring size and composition of the macrocycle.

[0004] The three primary causes of resistance to macrolides in bacterial organisms are ribosome methylation encoded by *erm* genes, mutations in ribosomal RNA or peptides, and cell efflux mediated by *mef* and *msr* genes. See, *e.g.*, Leclercq *et al.*, *Antimicrob. Agents Chemother.* (1991) *35*:1273–1276; Leclercq *et al.*, *Antimicrob. Agents Chemother.* (1991) *35*:1267–1272; Weisblum, *Antimicrob. Agents Chemother.* (1995) *39*:577–585; Vester *et al.*, *Antimicrob. Agents Chemother.* (2001) *45*:1–12; Prunier *et al.*, *Antimicrob. Agents Chemother.* (2002) *46*:3054–3056; Li *et al.*, *J. Antimicrob. Chemother.* (2011) *66*:1983–1986; Sutcliffe *et al.*, *Antimicrob. Agents Chemother.* (1996) *40*:1817–1824; Wondrack *et al.*, *Antimicrob. Agents Chemother.* (1996) *40*: 992–998. Ketolides such as telithromycin and solithromycin defeat the efflux mechanism of resistance by replacement of the C3 cladinose sugar with a carbonyl group (hence the name "ketolides"), and are thought to exhibit greatly increased binding by virtue of favorable interactions between the novel aryl–alkyl sidechain and the ribosome. See, *e.g.*, Ma *et al.*, *Curr. Med. Chem.* (2011) *18*:1993–2015; Ma *et al.*, *Mini–Rev. Med. Chem.* (2010) *10*:272–286. Despite greatly improved ribosomal binding, ketolides such as telithromycin and solithromycin have not addressed several of the newest

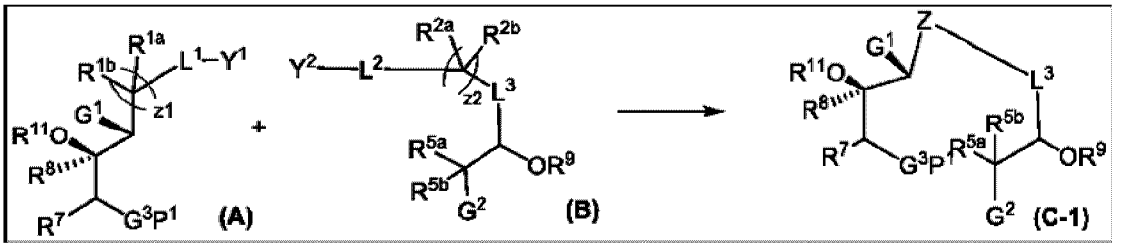
Date Reçue/Date Received 2020-06-25

forms of macrolide resistanc that have evolved in nosocomial settings, especially ribosome methylation and RNA point mutations.

SUMMARY OF THE INVENTION

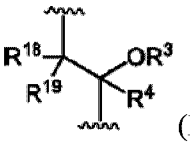
[0005] Described herein are methods and intermediates for making macrolides, such as known macrolides, as well as new and improved macrolides, in a practical manner via a fully synthetic route. This practical synthetic methodology includes the coupling of two components, the western half (**A**), and the eastern half (**B**), as depicted in Scheme 1, to provide a compound of Formula (**C–1**):

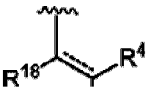
Scheme 1.

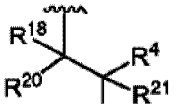


or salt thereof, wherein G^1, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{5a}, R^{5b}, R^7, R^8, R^9, R^{11}, z1, and z2 are as defined herein;

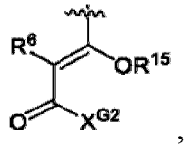
L_3 is a group of formula:


(**L^3-i**),


(**L^3-ii**),


or (**L^3-iii**);

wherein , R^3, R^4, R^{18}, R^{19}, R^{20}, and R^{21} are as defined herein; G_2 is a group of formula: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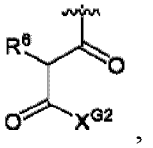
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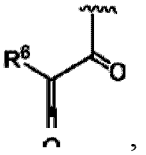
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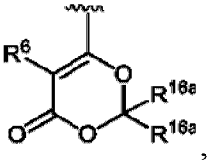
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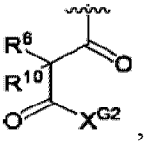
or


,

wherein R^6, R^{10}, R^{15}, R^{16a}, and X^{G2} are as defined herein;

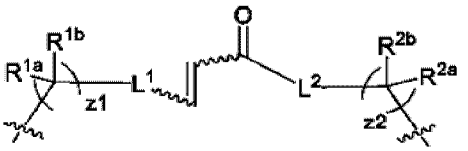
Date Reçue/Date Received 2020-06-25

P_1 is hydrogen, silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group;

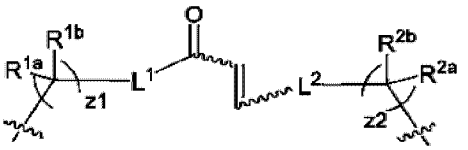
G_3 is –O–, –S–, or $–N(R^{G1})–$, wherein R^{G1} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group; and

one of Y^1 and Y^2 is $–Z^4H$ or $–CH_2NO_2$, and the other of Y^1 and Y^2 is a leaving group (LG), $–C(=O)R^{Z3}$, $–C(=O)OR^{Z3}$, –C(=O)LG, $–C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3})$, or $–C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3})$, wherein Z^4 is –O–, –S–, or $–NR^{Z2}–$, and wherein the leaving group (LG), R^{Z3}, R^{Z4}, R^{P1}, R^{P2}, and R^{P3} are as defined herein, to provide various linkages of formula Z, as defined herein.

[0006] For example, in certain embodiments, when Y^1 is $–C(=O)R^{Z3}$ and R^{Z3} is hydrogen (*aka* wherein Y^1 is –CHO) and Y^2 is $–C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3})$ or $–C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3})$, coupling of the eastern and western halves *via* a Wittig or Horner-Emmons reaction forms the moiety –CH=CH-C(=O)–, and provides a compound of Formula (**C-1**), wherein Z is an a,J3-unsaturated ketone of formula:



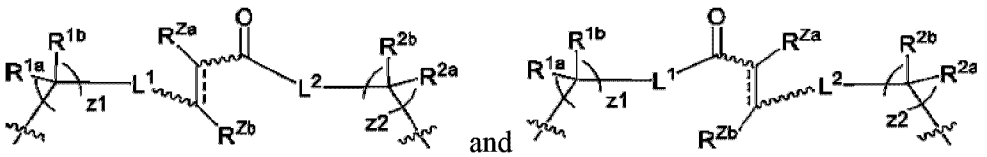
[0007] In certain embodiments, when Y^2 is $–C(=O)R^{Z3}$ and R^{Z3} is hydrogen (*aka* wherein Y_1 is –CHO) and Y^1 is $–C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3})$ or $–C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3})$, coupling of the eastern and western halves *via* a Wittig reaction or Horner-Emmons reaction forms a moiety -C(=O)–CH=CH-, and provides a compound of Formula (**C-1**), wherein Z is an a,J3 -unsaturated ketone of formula:



[0008] Optional synthetic modification of the moieties –CH=CH-C(=O)– and -C(=O)–CH=CH- is further contemplated herein. For example, the double bond may be reduced to a single bond, and optionally the carbon alpha to the ketone may be substituted by a non-hydrogen group R^{Za}. A nucleophile may react with the double bond via 1,4-addition of a non-hydrogen group R^{Zb} optionally followed by alpha substitution via a non-hydrogen group R^{Za}.

Date Reçue/Date Received 2020-06-25

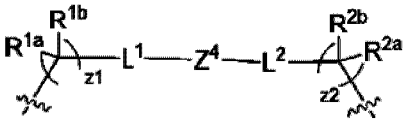
Various synthetic modifications of the □□□ -unsaturated ketone formula contemplated herein are thus encompassed by the formulae:



and

wherein represents a single or double bond, and R^{Za} and R^{Zb} are each independently hydrogen or a non-hydrogen group, as defined herein.

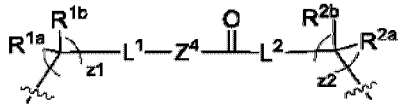
[0009] In certain embodiments, when Y^1 is $–Z^4H$ and Y^2 is a leaving group (LG), or when Y_2 is $–Z^4H$ and Y^1 is a leaving group (LG), coupling of the eastern and western halves by nucleophilic displacement, optionally in the presence of a base, provides a compound of Formula (**C-1**), wherein Z is an ether, thioether, or amine of formula:



,

wherein Z^4 is –O–, –S–, or $–NR^{Z2}–$, and wherein R^{Z2} is hydrogen or a non-hydrogen group.

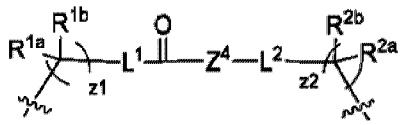
[0010] In certain embodiments, when Y^1 is $–Z^4H$, and Y^2 is $–C(=O)OR^{Z3}$ or –C(=O)LG, coupling of the eastern and western halves by 1,2-nucleophilic addition , optionally in the presence of a base, provides a compound of Formula (**C-1**), wherein Z is an ester, thioester, or amide of formula:



,

wherein Z^4 is –O–, –S–, or $–NR^{Z2}–$, and wherein R^{Z2} is hydrogen or a non-hydrogen group.

[0011] Alternatively, in certain embodiments, when Y^2 is $–Z^4H$, and Y^1 is $–C(=O)OR^{Z3}$ or –C(=O)LG, coupling of the eastern and western halves by 1,2-nucleophilic addition, optionally in the presence of a base, provides a compound of Formula (**C-1**), wherein Z is an ester, thioester, or amide of formula:



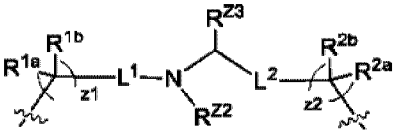
,

wherein Z^4 is –O–, –S–, or $–NR^{Z2}–$, and wherein R^{Z2} is hydrogen or a non-hydrogen group.

[0012] In certain embodiments, wherein Y^1 is $–NH_2$ or $–NHR^{Z2}$, and Y^2 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves by reductive amination, optionally followed by

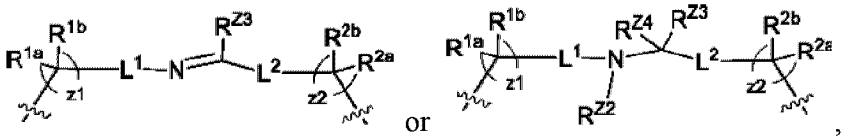
Date Reçue/Date Received 2020-06-25

protection of the amine group by a non-hydrogen R^{Z2}, provides a compound of Formula (**C-1**), wherein Z is an amine of formula:



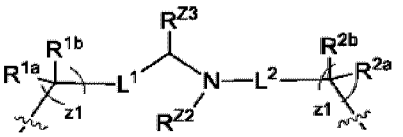
wherein R^{Z2} is hydrogen or a non-hydrogen group.

[0013] In certain embodiments, wherein Y^1 is $–NH_2$, and Y^2 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves by imine formation, optionally followed by addition of a group R_{Z4} to the imine double bond, and optionally followed by protection of the amine group by a non-hydrogen R^{Z2}, provides a compound of Formula (**C-1**), wherein Z is an imine or amine of formula:



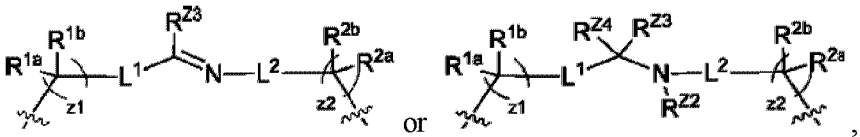
wherein R^{Z2} is hydrogen or a non-hydrogen group.

[0014] Alternatively, in certain embodiments, wherein Y^2 is $–NH_2$ or $–NHR^{Z2}$ and Y^1 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves by reductive amination, optionally followed by protection of the amine group by a non-hydrogen R^{Z2}, provides a compound of Formula (**C-1**), wherein Z is an amine of formula:



wherein R^{Z2} is hydrogen or a non-hydrogen group.

[0015] In certain embodiments, wherein Y^2 is $–NH_2$, and Y^1 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves by imine formation, optionally followed by addition of a group R_{Z4} to the imine double bond, optionally followed by protection of the amine group by a non-hydrogen R^{Z2}, provides a compound of Formula (**C-1**), wherein Z is an imine or amine of formula:

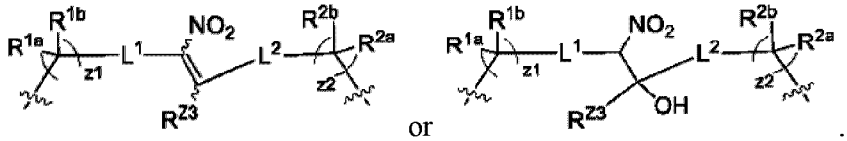


wherein R^{Z2} is hydrogen or a non-hydrogen group.

Date Reçue/Date Received 2020-06-25

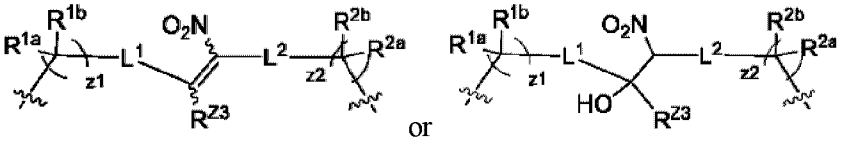
[0016] Further contemplated are nitro-aldol reaction coupling products, and oxidized, reduced, and/or addition products formed therefrom.

[0017] For example, in certain embodiments, wherein Y^1 is $–CH_2NO_2$, and Y^2 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves provides a compound of Formula (**C-1**), wherein Z is a group of formula:



or

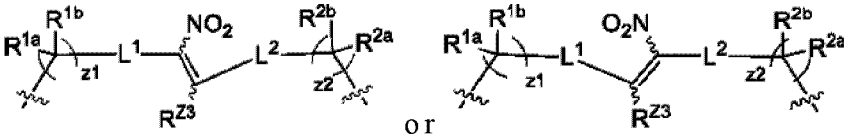
[0018] Alternatively, in certain embodiments, wherein Y^2 is $–CH_2NO_2$, and Y^1 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves provides a compound of Formula (**C-1**), wherein Z is a group of formula:



or

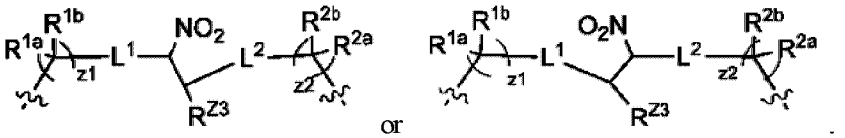
[0019] With the nitro-aldol coupling product in hand, the nitro ($-NO_2$) moiety may be manipulated at any stage in the synthesis, *e.g.,* after coupling but before macrocylization, or after the macrolide has been formed.

[0020] For example, reduction of the double bond of the nitro-aldol product of formula:



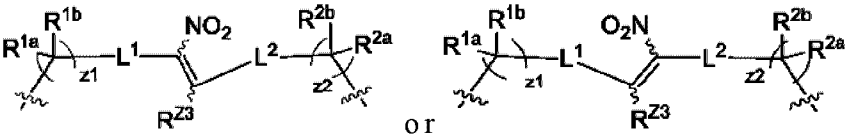
or

provides a Z group of formula:



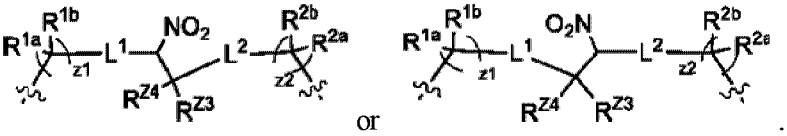
or

[0021] Addition of a group R^{Z4} to the nitro-aldol product of formula:



or

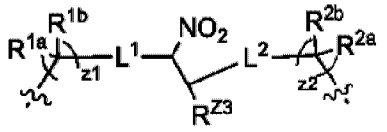
provides a Z group of formula:



or

Date Reçue/Date Received 2020-06-25

[0022] Reduction of the nitro group as provided in formulae: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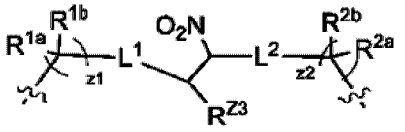
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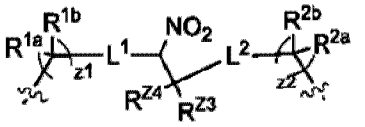
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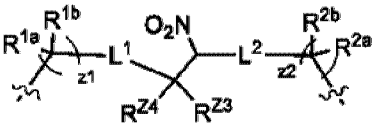
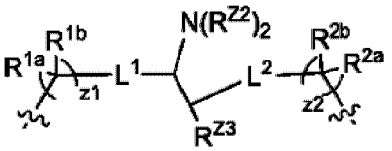

,

to the free amine, which may be optionally mono- or bis-protected, provides a Z group of formula: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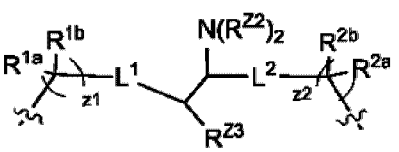
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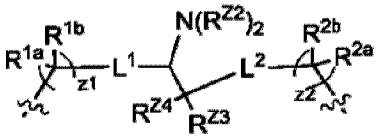
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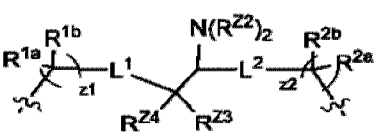
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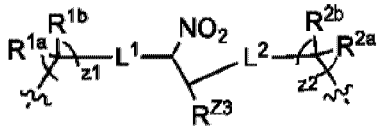
[0023] Oxidation of the nitro group as provided in formula: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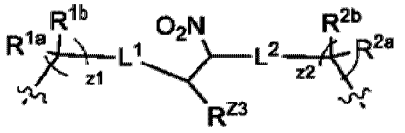
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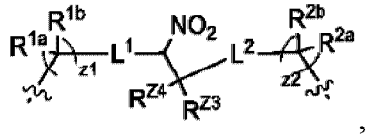
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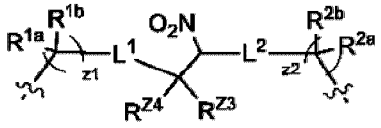
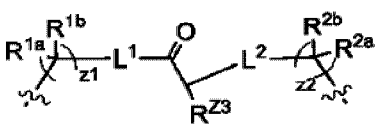


provides the keto (oxo) product of formula: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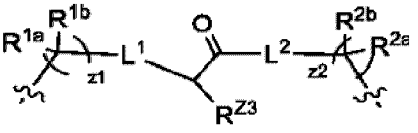
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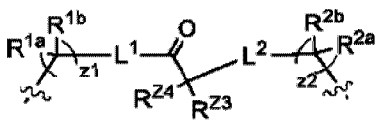
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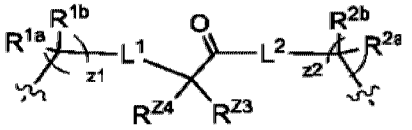
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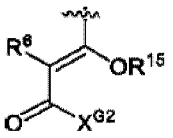
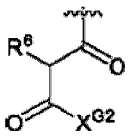
[0024] Alternative methods of preparing the above depicted keto (oxo) products are further contemplated herein.

Date Reçue/Date Received 2020-06-25

[0025] Furthermore, various macrolides may be accessed from the coupled product of Formula (**C-1**), depending upon the nature of the group G^2, upon macrocyclization, *e.g.* via thermally induced macrocylization. For example, as depicted in Scheme 2, when G^2 is a group of formula:





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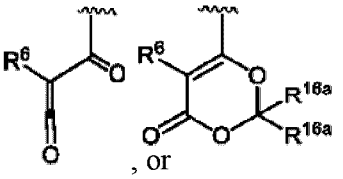
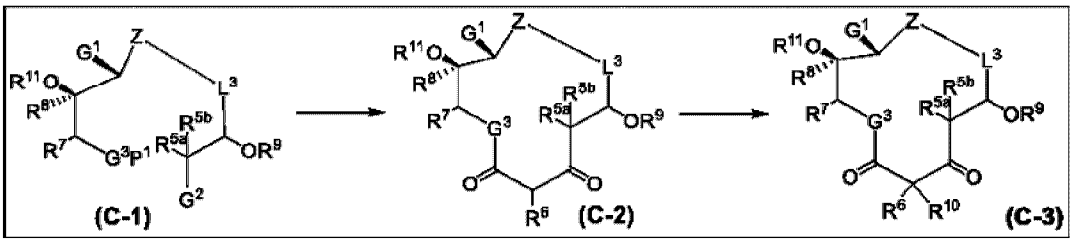


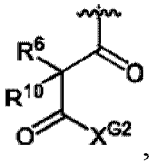
, or

P_1 is hydrogen, and R^6 is a hydrogen or non-hydrogen group, macrocyclization of the compound of Formula (**C-1**) provides a macrolide of Formula (**C-2**). Enolization of the macrolide of Formula (**C-2**) in the presence of a base, followed by addition of a non-hydrogen group R^{10}, provides a macrolide of Formula (**C-3**).

Scheme 2.



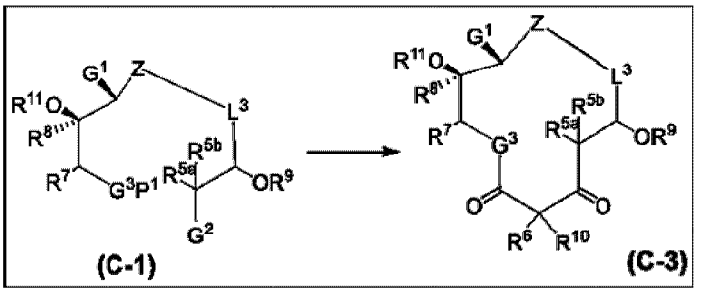
[0026] Alternatively, as depicted in Scheme 3, when G^2 is a group of formula:



,

wherein P^1 is hydrogen, and each of R^6 and R^{10} is independently a hydrogen or non-hydrogen group, macrocyclization of the compound of Formula (**C-1**) provides a macrolide of Formula (**C-3**).

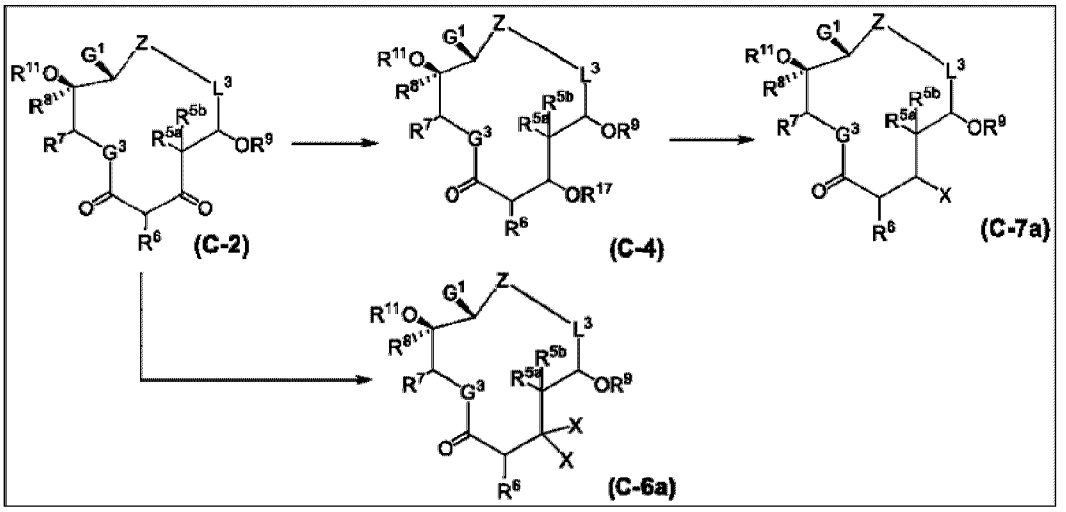
Scheme 3.



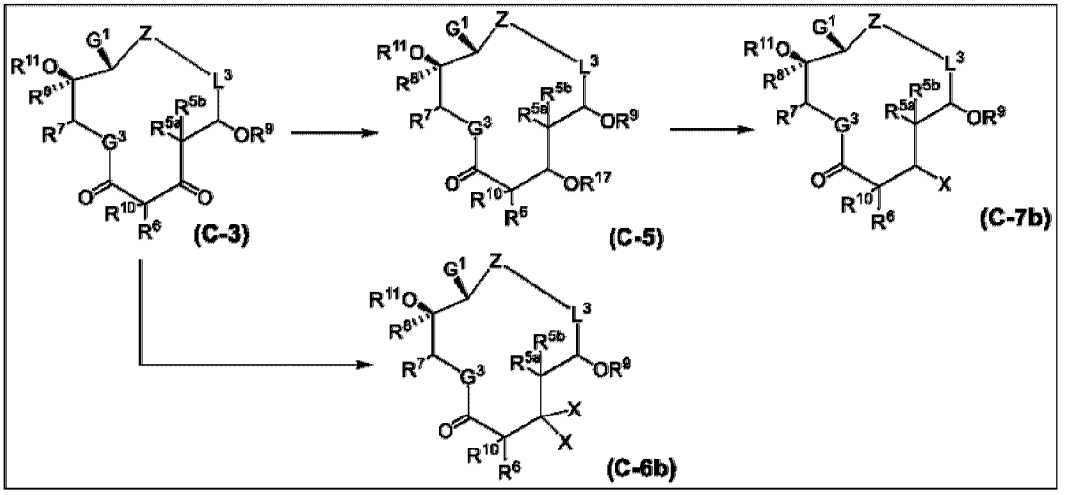
[0027] Additional functionalization of the macrolide is contemplated herein. For example, as depicted in Schemes 4 and 5, reduction of the C3 ketone of macrolides (**C-2**) and (**C-3**) to a

Date Reçue/Date Received 2020-06-25

hydroxyl group, optionally followed by protection, provides macrolides (**C-4**) and (**C-5**), respectively, wherein R^{17} is as defined herein. Dihalogenation of the C3 ketone of macrolides (**C-2**) and (**C-3**), or monohalogenation of macrolides (**C-4**) and (**C-5**), providing the products, (**C6a/b**) and (**C7a/b**), is further contemplated herein, wherein X is halogen, *e.g.*, fluoro. *Scheme 4.*

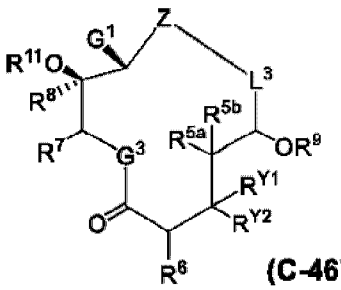


Scheme 5.

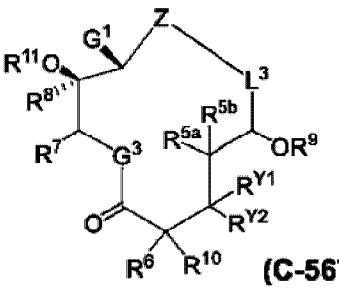


[0028] Formula (**C-467**) and subgenera thereof as described herein are intended to encompass compounds of Formula (**C-2**), (**C-4**), (**C6a**), and (**C7a**) and subgenera thereof, wherein R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is halogen. Likewise, Formula (**C-567**) and subgenera thereof are intended to encompass compounds of Formula (**C-3**), (**C-5**), (**C6b**), and (**C7b**), wherein R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is halogen, or R^{Y1} and R^{Y2} are joined to form an oxo (=O) group.

Date Reçue/Date Received 2020-06-25



(C-467)



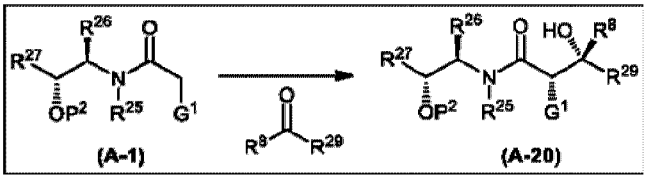
(C-567)

[0029] Additional functionalization of the coupled product (**C-1**) and the macrolides (**C-2**), (**C-3**), (**C-4**), (**C-5**), (**C-6**), and (**C-7**), for example, by addition and synthetic manipulation of a tethered moiety on the eastern or western portion of the molecule, and construction of the eastern and western halves, is also described herein.

[0030] Is is generally understood that the synthetic methodology as described herein is both useful in the synthesis of known macrolides, such as those depicted in Figure 1, and in the synthesis and development of new macrolides as described herein. New macrolides synthesized using the inventive methodology, and pharmaceutical compositions thereof, are contemplated to be useful in the treatment of various conditions such as, for example, the treatment of infectious diseases, such as bacterial and parasitic infections, and the treatment of inflammatory conditions.

[0031] An additional aspect of the present invention is further described herein. In the construction of the western half (**A**), it was discovered that pseudoephanamine glycinamide undergoes highly selective addition to aldehydes and ketones to generate products with high diastereoselectivity in a single step. See, *e.g.,* Scheme 7. Such a reaction is considered broadly applicable using other chiral auxiliaries, such as pseudoephedrine glycinamide, in combination with a wide range of aldehydes and ketones.

Scheme 7.



[0032] The details of certain embodiments of the invention are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the invention will be apparent from the Definitions, Examples, and Figures.

Date Reçue/Date Received 2020-06-25

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] *Figure 1* depicts exemplary 14–, 15–, and 16–membered macrolide antibiotics used in the United States.

[0034] *Figure 2* depicts the crystal structure of solithromycin bound to *E. coli*. Residues in a 12–Å sphere generated using MacPyMol from PDB #3ORB. See, *e.g.*, Llano–Sotelo *Antimicrob. Agents Chemother.* (2010) *54*:4961–4970.

[0035] *Figure 3* depicts the Zimmerman Traxler and Felkin-Ahn model of an aldol reaction between pseudoephanamine glycinamide and a ketone.

DEFINITIONS

Chemical definitions

[0036] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0037] Compounds and macrolides described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds and macrolides described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds and

Date Reçue/Date Received 2020-06-25

macrolides as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0038] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "$C_{1–6}$ alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, $C_{1–6}$, $C_{1–5}$, $C_{1–4}$, $C_{1–3}$, $C_{1–2}$, $C_{2–6}$, $C_{2–5}$, $C_{2–4}$, $C_{2–3}$, $C_{3–6}$, $C_{3–5}$, $C_{3–4}$, $C_{4–6}$, $C_{4–5}$, and $C_{5–6}$ alkyl.

[0039] As used herein, "alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("$C_{1–10}$ alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("$C_{1–9}$ alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("$C_{1–8}$ alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("$C_{1–7}$ alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("$C_{1–6}$ alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("$C_{1–5}$ alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("$C_{1–4}$ alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("$C_{1–3}$ alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("$C_{1–2}$ alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("$C_{2–6}$ alkyl"). Examples of $C_{1–6}$ alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents. In certain embodiments, the alkyl group is an unsubstituted $C_{1–10}$ alkyl (*e.g.,* –CH_3). In certain embodiments, the alkyl group is a substituted $C_{1–10}$ alkyl. **[0040]** As used herein, "haloalkyl" is a substituted alkyl group as defined herein wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.,* fluoro, bromo, chloro, or iodo. "Perhaloalkyl" is a subset of haloalkyl, and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.,* fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("$C_{1–8}$ haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("$C_{1–6}$ haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("$C_{1–4}$ haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("$C_{1–3}$ haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("$C_{1–2}$ haloalkyl"). In some embodiments, all of the haloalkyl hydrogen atoms are replaced with

Date Reçue/Date Received 2020-06-25

fluoro to provide a perfluoroalkyl group. In some embodiments, all of the haloalkyl hydrogen atoms are replaced with chloro to provide a "perchloroalkyl" group. Examples of haloalkyl groups include $-CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like. **[0041]** As used herein, "heteroalkyl" refers to an alkyl group as defined herein which further includes at least one heteroatom (*e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-10} alkyl. **[0042]** As used herein, "alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon–carbon double bonds (*e.g.,* 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9

Date Reçue/Date Received 2020-06-25

carbon atoms ("$C_{2–9}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("$C_{2–8}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("$C_{2–7}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("$C_{2–6}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("$C_{2–5}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("$C_{2–4}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("$C_{2–3}$ alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of $C_{2–4}$ alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of $C_{2–6}$ alkenyl groups include the aforementioned $C_{2–4}$ alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted $C_{2–10}$ alkenyl. In certain embodiments, the alkenyl group is a substituted $C_{2–10}$ alkenyl.

[0043] As used herein, "heteroalkenyl" refers to an alkenyl group as defined herein which further includes at least one heteroatom (*e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–10}$ alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–9}$ alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–8}$ alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–7}$ alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–6}$ alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("hetero$C_{2–5}$ alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1or 2 heteroatoms

Date Reçue/Date Received 2020-06-25

within the parent chain ("heteroC_{2-4} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

[0044] As used herein, "alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon–carbon triple bonds (*e.g.,* 1, 2, 3, or 4 triple bonds) ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{2-10} alkynyl.

[0045] As used herein, "heteroalkynyl" refers to an alkynyl group as defined herein which further includes at least one heteroatom (*e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or

Date Reçue/Date Received 2020-06-25

more heteroatoms within the parent chain ("heteroC_{2-10} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

[0046] As used herein, "carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 9 ring carbon atoms ("C_{3-9} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5),

Date Reçue/Date Received 2020-06-25

cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (*e.g.,* containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon–carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl.

[0047] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 9 ring carbon atoms ("C_{3-9} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 7 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise

Date Reçue/Date Received 2020-06-25

specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl.

[0048] As used herein, "heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 14–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.,* a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon–carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl.

[0049] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from

Date Reçue/Date Received 2020-06-25

nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0050] Exemplary 3–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5– membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5–membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6–membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro–1,8–naphthyridinyl, octahydropyrrolo[3,2–b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H–benzo[e][1,4]diazepinyl, 1,4,5,7–tetrahydropyrano[3,4–b]pyrrolyl, 5,6–dihydro–4H–furo[3,2–b]pyrrolyl, 6,7–dihydro–5H–furo[3,2–b]pyranyl, 5,7–dihydro–4H–thieno[2,3–c]pyranyl, 2,3–dihydro–1H–pyrrolo[2,3–b]pyridinyl, 2,3–dihydrofuro[2,3–b]pyridinyl, 4,5,6,7–tetrahydro–1H–pyrrolo-[2,3–b]pyridinyl, 4,5,6,7–tetrahydrofuro[3,2–c]pyridinyl, 4,5,6,7–tetrahydrothieno[3,2–b]pyridinyl, 1,2,3,4–tetrahydro–1,6–naphthyridinyl, and the like.

[0051] As used herein, "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 □ electrons shared in a cyclic

Date Reçue/Date Received 2020-06-25

array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("$C_{6–14}$ aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted $C_{6–14}$ aryl. In certain embodiments, the aryl group is a substituted $C_{6–14}$ aryl.

[0052] "Aralkyl" is a subset of "alkyl" and refers to an alkyl group, as defined herein, substituted by an aryl group, as defined herein, wherein the point of attachment is on the alkyl moiety. An exemplary aralkyl group is $–CH_2$-phenyl (benzyl, Bz), wherein the phenyl moiety may be substituted or unsubstituted.

[0053] As used herein, "heteroaryl" refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.,* bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 □ electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl,

Date Reçue/Date Received 2020-06-25

and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl).

[0054] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5–14 membered heteroaryl.

[0055] Exemplary 5–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing 1 heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6– bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl,

Date Reçue/Date Received 2020-06-25

benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl and phenazinyl.

[0056] "Heteroaralkyl" is a subset of "alkyl" and refers to an alkyl group, as defined herein, substituted by a heteroaryl group, as defined herein, wherein the point of attachment is on the alkyl moiety.

[0057] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (*e.g.,* aryl or heteroaryl moieties) as herein defined.

[0058] As used herein, the term "saturated" refers to a ring moiety that does not contain a double or triple bond, *i.e.*, the ring contains all single bonds.

[0059] Affixing the suffix "–ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0060] As understood from the above, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are, in certain embodiments, optionally substituted. Optionally substituted refers to a group which may be substituted or unsubstituted (*e.g.,* "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.,* a substituent which upon substitution results in a stable compound, *e.g.,* a compound which does not

Date Reçue/Date Received 2020-06-25

spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0061] Exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_2$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)_2R^{aa}$, $-OP(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, $-OP(=O)_2N(R^{bb})_2$, $-P(=O)(NR^{bb})_2$, $-OP(=O)(NR^{bb})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(NR^{bb})_2$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-14} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group $=O$, $=S$, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R_{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl,

Date Reçue/Date Received 2020-06-25

carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3^+X^–$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)_2R^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, hetero$C_{1–6}$ alkyl, hetero$C_{2–6}$ alkenyl, hetero$C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R_{gg} groups, or two geminal R_{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, hetero$C_{1–6}$ alkyl, hetero$C_{2–6}$alkenyl, hetero$C_{2–6}$ alkynyl, $C_{3–10}$

Date Reçue/Date Received 2020-06-25

carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, –OC_{1-6} alkyl, –ON(C_{1-6} alkyl)$_2$, –N(C_{1-6} alkyl)$_2$, –N(C_{1-6} alkyl)$_3^+X^-$, –NH(C_{1-6} alkyl)$_2^+X^-$, –NH_2(C_{1-6} alkyl) $^+X^-$, $–NH_3^+X^-$, –N(OC_{1-6} alkyl)(C_{1-6} alkyl), –N(OH)(C_{1-6} alkyl), –NH(OH), –SH, –SC_{1-6} alkyl, –SS(C_{1-6} alkyl), –C(=O)(C_{1-6} alkyl), $–CO_2H$, $–CO_2$(C_{1-6} alkyl), –OC(=O)(C_{1-6} alkyl), –OCO_2(C_{1-6} alkyl), –C(=O)NII$_2$, –C(=O)N(C_{1-6} alkyl)$_2$, –OC(=O)NH(C_{1-6} alkyl), –NHC(=O)(C_{1-6} alkyl), –N(C_{1-6} alkyl)C(=O)(C_{1-6} alkyl), –NHCO_2(C_{1-6} alkyl), –NHC(=O)N(C_{1-6} alkyl)$_2$, –NHC(=O)NH(C_{1-6} alkyl), $–NHC(=O)NH_2$, –C(=NH)O(C_{1-6} alkyl),–OC(=NH)(C_{1-6} alkyl), –OC(=NH)OC_{1-6} alkyl, –C(=NH)N(C_{1-6} alkyl)$_2$, –C(=NH)NH(C_{1-6} alkyl), $–C(=NH)NH_2$, –OC(=NH)N(C_{1-6} alkyl)$_2$, –OC(NH)NH(C_{1-6} alkyl), $–OC(NH)NH_2$, –NHC(NH)N(C_{1-6} alkyl)$_2$, $–NHC(=NH)NH_2$, –NHSO_2(C_{1-6} alkyl), –SO_2N(C_{1-6} alkyl)$_2$, –SO_2NH(C_{1-6} alkyl), $–SO_2NH_2$,–SO_2C_{1-6} alkyl, –SO_2OC_{1-6} alkyl, –OSO_2C_{1-6} alkyl, –SOC_{1-6} alkyl, –Si(C_{1-6} alkyl)$_3$, –OSi(C_{1-6} alkyl)$_3$, –C(=S)N(C_{1-6} alkyl)$_2$, -C(=S)NH(C_{1-6} alkyl), $-C(=S)NH_2$, –C(=O)S(C_{1-6} alkyl), –C(=S)SC_{1-6} alkyl, –SC(=S)SC_{1-6} alkyl, –P(=O)$_2$(C_{1-6} alkyl), –P(=O)(C_{1-6} alkyl)$_2$, –OP(=O)(C_{1-6} alkyl)$_2$, – OP(=O)(OC_{1-6} alkyl)$_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6}alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion.

[0062] In certain embodiments, the carbon substituents are selected from the group consisting of halogen, –CN, $–NO_2$, –OH, –OR^{aa}, –N(R^{bb})$_2$, –SH, –SR^{aa}, –C(=O)R^{aa}, $–CO_2H$, –CHO, –CO_2R^{aa}, –OC(=O)R^{aa}, –C(=O)N(R^{bb})$_2$, –OC(=O)N(R^{bb})$_2$, –NR^{bb}C(=O)R^{aa}, –SO_2N(R^{bb})$_2$, –SO_2R^{aa}, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3–6 membered heterocyclyl, C_6 aryl, and 5–6 membered heteroaryl, wherein each alkyl, alkenyl,

Date Reçue/Date Received 2020-06-25

alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups.

[0063] As used herein, the term "halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0064] As used herein, a "counterion" is a negatively charged group associated with a positively charged quarternary amine in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.,* F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (*e.g.,* methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), and carboxylate ions (*e.g.,* acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0065] As used herein, the term "hydroxyl" or "hydroxy" refers to the group –OH. The term "substituted hydroxyl" or "substituted hydroxy," by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $–OR^{aa}$, $–ON(R^{bb})_2$, $–OC(=O)SR^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–OC(=O)N(R^{bb})_2$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})N(R^{bb})_2$, $–OS(=O)R^{aa}$, $–OSO_2R^{aa}$, $–OSi(R^{aa})_3$, $–OP(R^{cc})_2$, $–OP(R^{cc})_3$, $–OP(=O)_2R^{aa}$, $–OP(=O)(R^{aa})_2$, $–OP(=O)(OR^{cc})_2$, $–OP(=O)_2N(R^{bb})_2$, and $–OP(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[0066] As used herein, the term "thiol" or "thio" refers to the group –SH. The term "substituted thiol" or "substituted thio," by extension, refers to a thiol group wherein the sulfur atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $–SR^{aa}$, $–S=SR^{cc}$, $–SC(=S)SR^{aa}$, $–SC(=O)SR^{aa}$, $–SC(=O)OR^{aa}$, and $–SC(=O)R^{aa}$, wherein R^{aa} and R^{cc} are as defined herein.

[0067] As used herein, the term, "amino" refers to the group $–NH_2$. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino, as defined herein. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group.

[0068] As used herein, the term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $–NH(R^{bb})$, $–NHC(=O)R^{aa}$, $–NHCO_2R^{aa}$, $–NHC(=O)N(R^{bb})_2$, $–NHC(=NR^{bb})N(R^{bb})_2$, $–NHSO_2R^{aa}$, –

Date Reçue/Date Received 2020-06-25

$NHP(=O)(OR^{cc})_2$, and $–NHP(=O)(NR^{bb})_2$, wherein R_{aa}, R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $–NH(R^{bb})$ is not hydrogen.

[0069] As used herein, the term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from $–N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–NR^{bb}CO_2R^{aa}$, $–NR^{bb}C(=O)N(R^{bb})_2$, $–NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $–NR^{bb}SO_2R^{aa}$, $–NR^{bb}P(=O)(OR^{cc})_2$, and $–NR^{bb}P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen. **[0070]** As used herein, the term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from $–N(R^{bb})_3$ and $–N(R^{bb})_3{}^+X^-$, wherein R^{bb} and X^- are as defined herein.

[0071] As used herein, the term "alkoxyalkyl" refers to an alkyl group as defined herein substituted by a group of formula $–OR^{aa}$ wherein R^{aa} is as defined herein, wherein the point of attachment is on the alkyl group.

[0072] As used herein, the term "aminoalkyl" refers to an alkyl group as defined herein substituted by an amino or substituted amino group, as defined herein, wherein the point of attachment is on the alkyl group.

[0073] As used herein, the term "sulfonyl" refers to a group selected from $–SO_2N(R^{bb})_2$, $–SO_2R^{aa}$, and $–SO_2OR^{aa}$, wherein R^{aa} and R^{bb} are as defined herein.

[0074] As used herein, the term "sulfinyl" refers to the group $–S(=O)R^{aa}$, wherein R^{aa} is as defined herein.

[0075] As used herein, the term "carbonyl" refers a group wherein the carbon directly attached to the parent molecule is sp^2 hybridized, and is substituted with an oxygen, nitrogen or sulfur atom, *e.g.*, a group selected from ketones ($–C(=O)R^{aa}$), carboxylic acids ($–CO_2H$), aldehydes (–CHO), esters ($–CO_2R_{aa}$, $–C(=O)SR^{aa}$, $–C(=S)SR^{aa}$), amides ($–C(=O)N(R^{bb})_2$, $–C(=O)NR^{bb}SO_2R^{aa}$, $–C(=S)N(R^{bb})_2$), and imines ($–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$), $–C(=NR^{bb})N(R^{bb})_2$), wherein R^{aa} and R^{bb} are as defined herein.

[0076] As used herein, the term "silyl" refers to the group $–Si(R^{aa})_3$, wherein R^{aa} is as defined herein.

[0077] As used herein, the term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

[0078] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom

Date Reçue/Date Received 2020-06-25

substituents include, but are not limited to, hydrogen, –OH, –OR^{aa}, –$N(R^{cc})_2$, –CN, –$C(=O)R^{aa}$, –$C(=O)N(R^{cc})_2$, –CO_2R^{aa}, –SO_2R^{aa}, –$C(=NR^{bb})R^{aa}$, –$C(=NR^{cc})OR^{aa}$, –$C(=NR^{cc})N(R^{cc})_2$, –$SO_2N(R^{cc})_2$, –SO_2R^{cc}, –SO_2OR^{cc}, –SOR^{aa}, –$C(=S)N(R^{cc})_2$, –$C(=O)SR^{cc}$, –$C(=S)SR^{cc}$, –$P(=O)_2R^{aa}$, –$P(=O)(R^{aa})_2$, –$P(=O)_2N(R^{cc})_2$, –$P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0079] In certain embodiments, the substituent present on the nitrogen atom is an nitrogen protecting group (also referred to herein as an "amino protecting group"). Nitrogen protecting groups include, but are not limited to, –OH, –OR^{aa}, –$N(R^{cc})_2$, –$C(=O)R^{aa}$, –$C(=O)N(R^{cc})_2$, –CO_2R^{aa}, –SO_2R^{aa}, –$C(=NR^{cc})R^{aa}$, –$C(=NR^{cc})OR^{aa}$, –$C(=NR^{cc})N(R^{cc})_2$, –$SO_2N(R^{cc})_2$, –SO_2R^{cc}, –SO_2OR^{cc}, –SOR^{aa}, –$C(=S)N(R^{cc})_2$, –$C(=O)SR^{cc}$, –$C(=S)SR^{cc}$, $C_{1–10}$ alkyl (*e.g.,* aralkyl, heteroaralkyl), $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

[0080] For example, nitrogen protecting groups such as amide groups *(e.g.,* –$C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxyacylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 3–(*o*–nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2–methyl–2–(*o*–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*–acetylmethionine derivative, *o*–nitrobenzamide and *o*–(benzoyloxymethyl)benzamide.

Date Reçue/Date Received 2020-06-25

[0081] Nitrogen protecting groups such as carbamate groups (*e.g.*, –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–*t*–butylphenyl)–1–methylethyl carbamate (*t*–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(*N,N*–dicyclohexylcarboxamido)ethyl carbamate, *t*–butyl carbamate (BOC), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, *N*–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–methoxybenzyl carbamate (Moz), *p*–nitobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), *m*–nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, *o*–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(*o*–nitrophenyl)methyl carbamate, *t*–amyl carbamate, *S*–benzyl thiocarbamate, *p*–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*–decyloxybenzyl carbamate, 2,2–dimethoxyacylvinyl carbamate, *o*–(*N,N*–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(*N,N*–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*–(*p'*–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(*p*–phenylazophenyl)ethyl

Date Reçue/Date Received 2020-06-25

carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, *p*–(phenylazo)benzyl carbamate, 2,4,6–tri–*t*–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, and 2,4,6–trimethylbenzyl carbamate.

[0082] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, *p*–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0083] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl–(10)–acyl derivative, *N'*–*p*–toluenesulfonylaminoacyl derivative, *N'*–phenylaminothioacyl derivative, *N*–benzoylphenylalanyl derivative, *N*–acetylmethionine derivative, 4,5–diphenyl–3–oxazolin–2–one, *N*–phthalimide, *N*–dithiasuccinimide (Dts), *N*–2,3–diphenylmaleimide, *N*–2,5–dimethylpyrrole, *N*–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl– 1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, *N*–methylamine, *N*–allylamine, *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentaacylchromium– or tungsten)acyl]amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp),

Date Reçue/Date Received 2020-06-25

dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3–nitropyridinesulfenamide (Npys).

[0084] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an "hydroxyl protecting group"). Oxygen protecting groups include, but are not limited to, $–R^{aa}$, $–N(R^{bb})_2$, $–C(=O)SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–S(=O)R^{aa}$, $–SO_2R^{aa}$, $–Si(R^{aa})_3$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)(OR^{cc})_2$, $–P(=O)_2N(R^{bb})_2$, and $–P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

[0085] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, *t*–butyl, allyl, *p*–chlorophenyl, *p*–methoxyphenyl, 2,4–dinitrophenyl, benzyl (Bn), *p*–methoxybenzyl, 3,4–dimethoxybenzyl, *o*–nitrobenzyl, *p*–nitrobenzyl, *p*–halobenzyl, 2,6–dichlorobenzyl, *p*–cyanobenzyl, *p*–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl *N*–oxido, diphenylmethyl, *p,p'*–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, *p*–methoxyphenyldiphenylmethyl, di(*p*–methoxyphenyl)phenylmethyl, tri(*p*–methoxyphenyl)methyl, 4–(4'–

Date Reçue/Date Received 2020-06-25

bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4′,4″–tris(levulinoyloxyphenyl)methyl, 4,4′,4″–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4′,4″–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1′–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodithiolan–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*–butyldimethylsilyl (TBDMS), *t*–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–*p*–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, *p*– phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *t*–butyl carbonate (BOC), *p*–nitrophenyl carbonate, benzyl carbonate, *p*–methoxybenzyl carbonate, 3,4–dimethoxybenzyl carbonate, *o*–nitrobenzyl carbonate, *p*–nitrobenzyl carbonate, *S*–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, *o*–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)–2–methyl–2–butenoate, *o*–(methoxyacyl)benzoate, α–naphthoate, nitrate, alkyl *N,N,N',N'*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0086] In certain embodiments, the substituent present on an sulfur atom is a sulfur protecting group (also referred to as a "thiol protecting group"). Sulfur protecting groups include, but are not limited to, $–R^{aa}$, $–N(R^{bb})_2$, $–C(=O)SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–S(=O)R^{aa}$, $–SO_2R^{aa}$, $–Si(R_{aa})_3$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)(OR^{cc})_2$, $–P(=O)_2N(R^{bb})_2$, and –

Date Reçue/Date Received 2020-06-25

$P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

[0087] As used herein, a "leaving group" (LG) is an art–understood term referring to a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. See, for example, Smith, March *Advanced Organic Chemistry* 6th ed. (501–502). Exemplary leaving groups include, but are not limited to, halo (*e.g.*, chloro, bromo, iodo), $-OR^{aa}$ (when attached to a carbonyl group, wherein R^{aa} is as defined herein), $-O(C=O)R^{LG}$, or $-O(SO)_2R^{LG}$ (*e.g.*, tosyl, mesyl, besyl), wherein R^{LG} is optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

[0088] As used herein, use of the phrase "at least one instance" refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

[0089] A "non-hydrogen group" refers to any group that is defined for a particular variable that is not hydrogen.

[0090] A "carbohydrate group" or a "carbohydrate" refers to a monosaccharide or a polysaccharide (*e.g.*, a disaccharide or oligosaccharide). Exemplary monosaccharides include, but are not limited to, natural sugars, such as allose, altrose, glucose, mannose, gulose, idose, galactose, talose, ribose, arabinose, xylose, and lyxose. Disaccharides are two joined monosaccharides. Exemplary disaccharides include, but are not limited to, sucrose, maltose, cellobiose, and lactose. Typically, an oligosaccharide includes between three and ten monosaccharide units (*e.g.*, raffinose, stachyose). The carbohydrate group may be a natural sugar or a modified sugar. Exemplary modified sugars include, but are not limited to, sugars where the hydroxyl group is replaced with an amino group and/or alkyl group (*e.g.,* such as desosamine), 2′-deoxyribose wherein a hydroxyl group is removed, 2′-fluororibose wherein a hydroxyl group is replace with a fluorine, or N-acetylglucosamine, or a nitrogen-containing form of glucose (*e.g.*, 2′-fluororibose, deoxyribose, and hexose), and the like. Various carbohydrates are further described below and herein. Carbohydrates may exist in many different forms, for example, conformers, cyclic forms, acyclic forms, stereoisomers, tautomers, anomers, and isomers.

[0091] These and other exemplary substituents are described in more detail in the Detailed Description and Examples. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Date Reçue/Date Received 2020-06-25

Other definitions

[0092] As used herein, the term "salt" refers to any and all salts, and encompasses pharmaceutically acceptable salts.

[0093] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the macrolides of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate. **[0094]** A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)) and/or other non–human animals, for example mammals [*e.g.*, primates (*e.g.,* cynomolgus monkeys,

Date Reçue/Date Received 2020-06-25

rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs], birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys), reptiles, amphibians, and fish. In certain embodiments, the non–human animal is a mammal. The non–human animal may be a male or female and at any stage of development. A non–human animal may be a transgenic animal.

[0095] "Disease," "disorder," and "condition" are used interchangeably herein.

[0096] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified infectious disease or inflammatory condition, which reduces the severity of the infectious disease or inflammatory condition, or retards or slows the progression of the infectious disease or inflammatory condition ("therapeutic treatment"), and also contemplates an action that occurs before a subject begins to suffer from the specified infectious disease or inflammatory condition ("prophylactic treatment").

[0097] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, health, and condition of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0098] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of an infectious disease or inflammatory condition, or to delay or minimize one or more symptoms associated with the infectious disease or inflammatory condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the infectious disease or inflammatory condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of infectious disease or inflammatory condition, or enhances the therapeutic efficacy of another therapeutic agent.

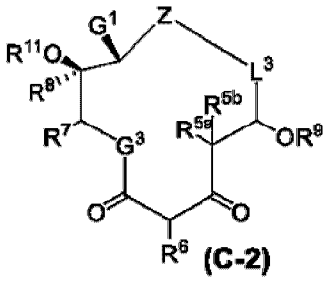
[0099] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to prevent an infectious disease or inflammatory condition, or one or more symptoms associated with the infectious disease or inflammatory condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which

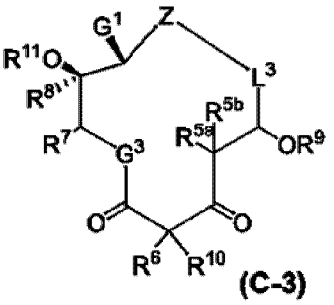
Date Reçue/Date Received 2020-06-25

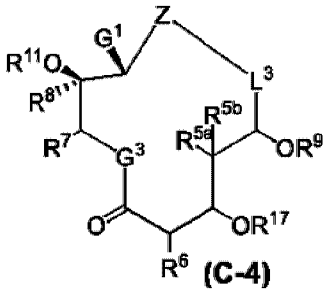
provides a prophylactic benefit in the prevention of the infectious disease or inflammatory condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

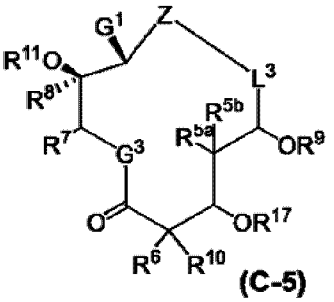
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

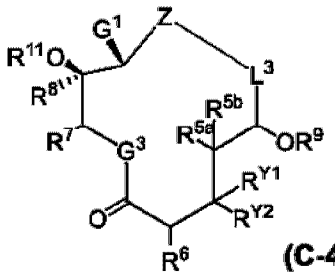
[00100] As generally understood from the present disclosure, the present invention is, in part, directed to macrolides of the formulae below, constructed from the coupling of an eastern half and western half, followed by macrocyclization and further synthetic manipulation:

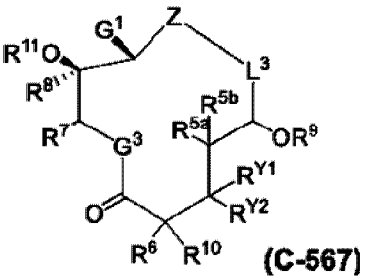

(C-2)


(C-3)


(C-4)


(C-5)


(C-467)


(C-567)

and salts thereof;

wherein:

Z is:

[1] an ether, thioether, or amine of formula:

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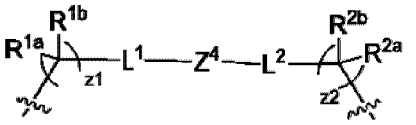
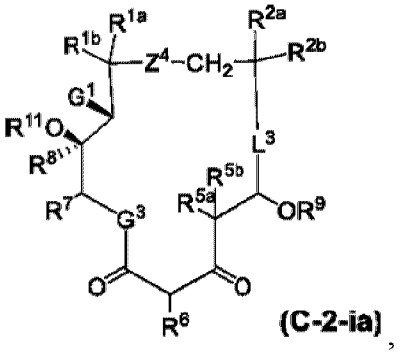
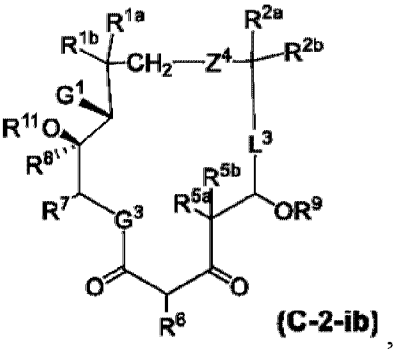


wherein L^1 and L^2 are each independently a bond or $–CH_2–$; z1 and z2 are each independently 0, 1, or 2 and Z^4 is –O–, –S–, or $–NR^{Z2}–$, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:



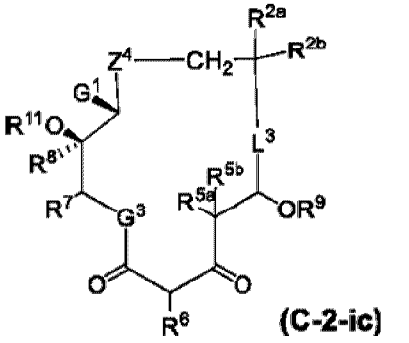
(C-2-ia),

15-membered ring system



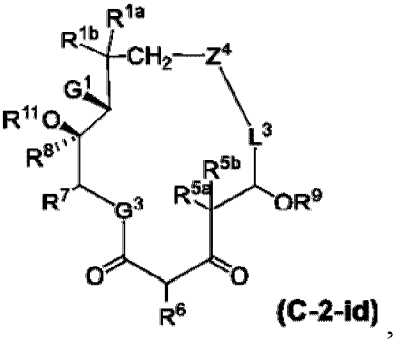
(C-2-ib),

15-membered ring system



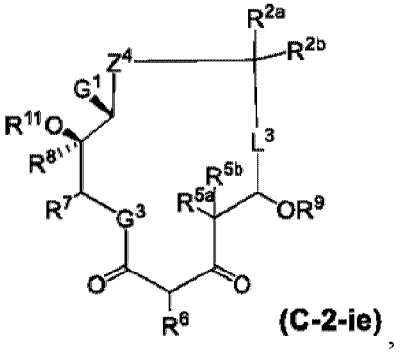
(C-2-ic),

14-membered ring system



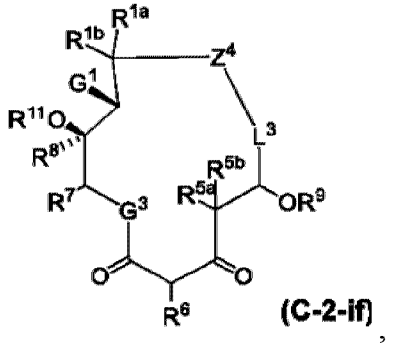
(C-2-id),

14-membered ring system



(C-2-ie),

13-membered ring system



(C-2-if),

13-membered ring system

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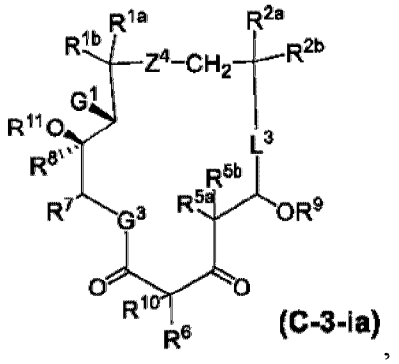
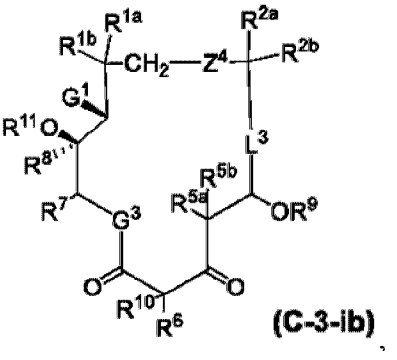


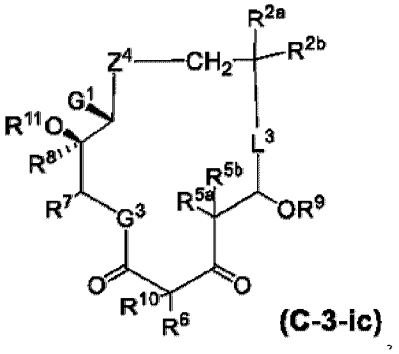
(C-3-ia)

15-membered ring system



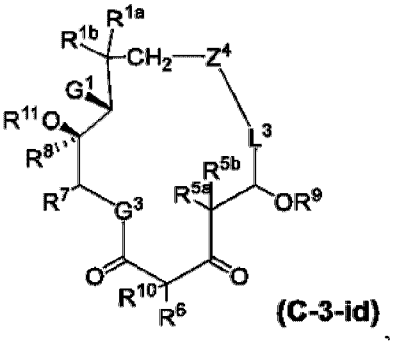
(C-3-ib)

15-membered ring system



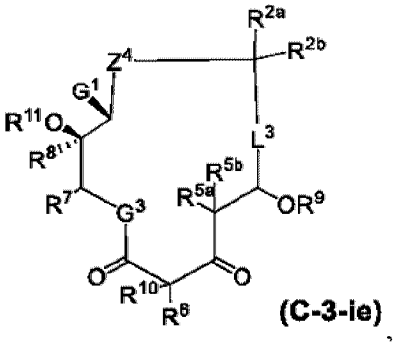
(C-3-ic)

14-membered ring system



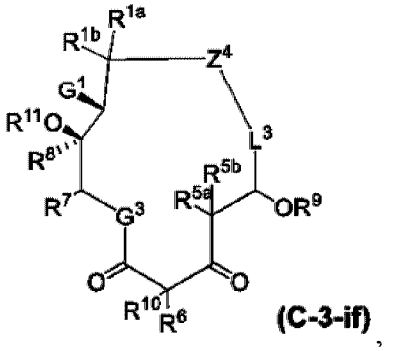
(C-3-id)

14-membered ring system



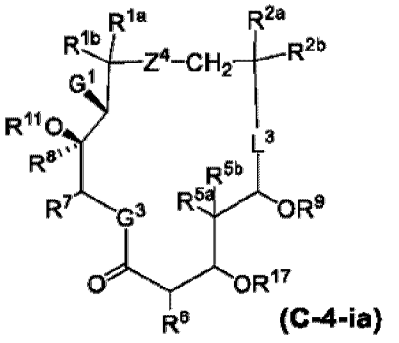
(C-3-ie)

13-membered ring system



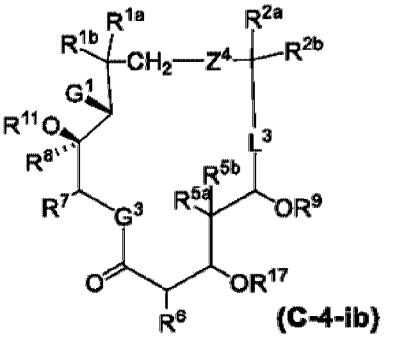
(C-3-if)

13-membered ring system



(C-4-ia)

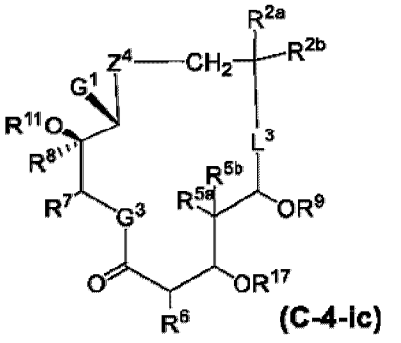
15-membered ring system



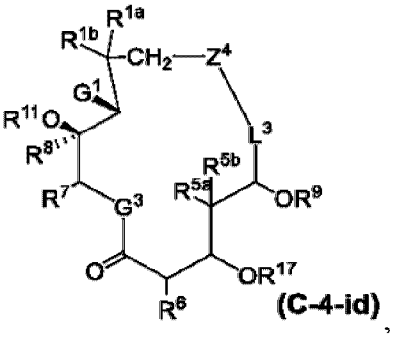
(C-4-ib)

15-membered ring system

Date Reçue/Date Received 2020-06-25



14-membered ring system



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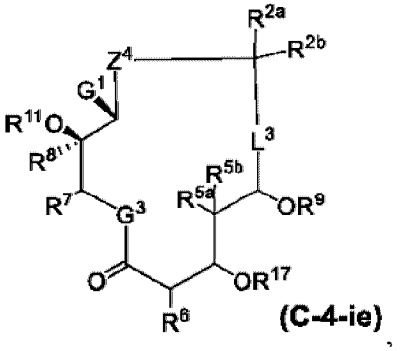

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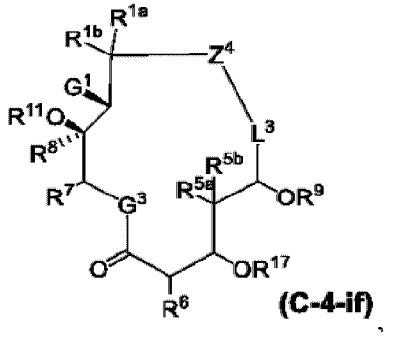

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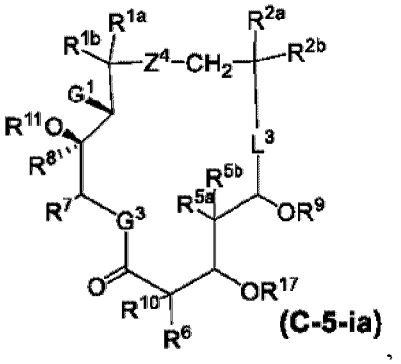

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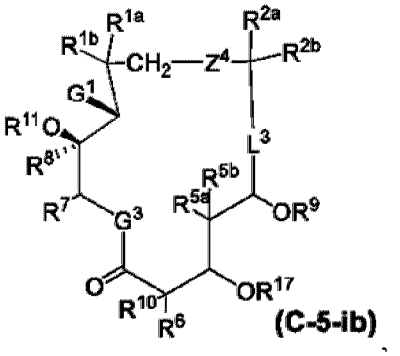

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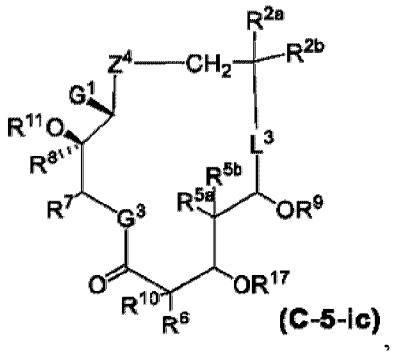

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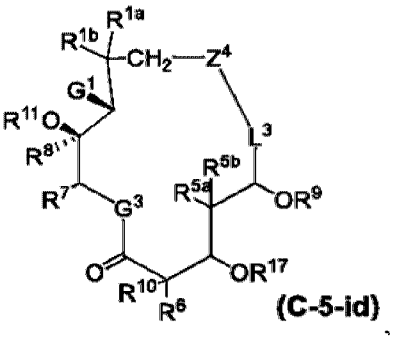

14-membered ring system

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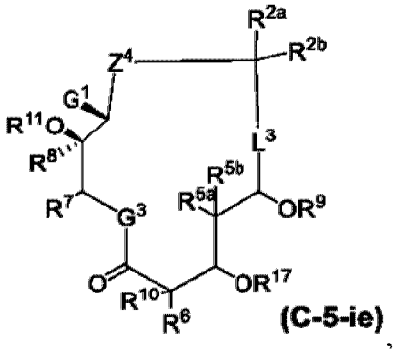

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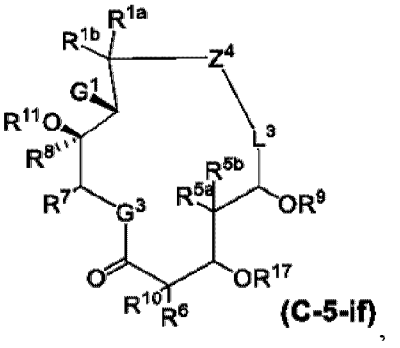

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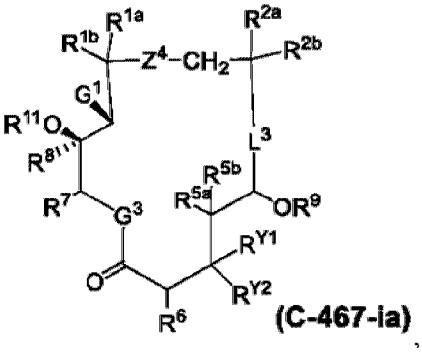

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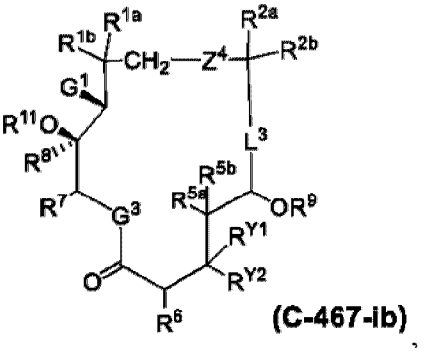

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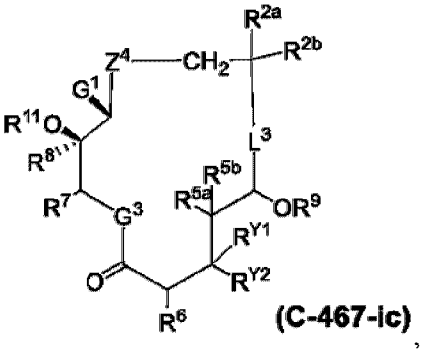

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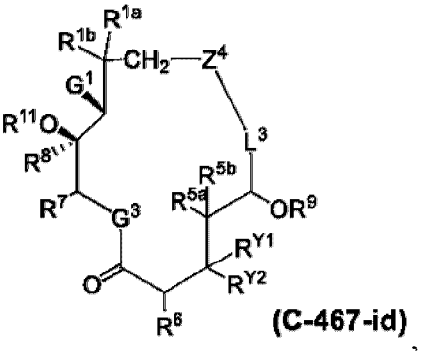

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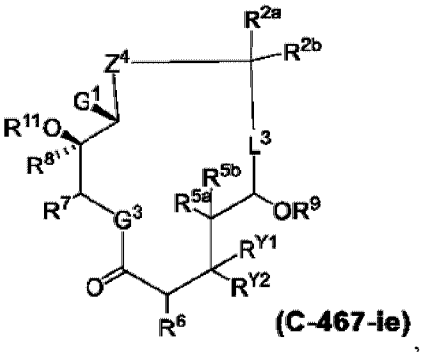
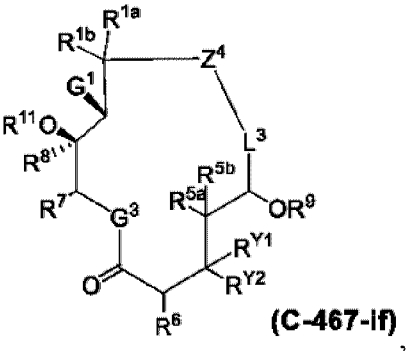


13-membered ring system



13-membered ring system

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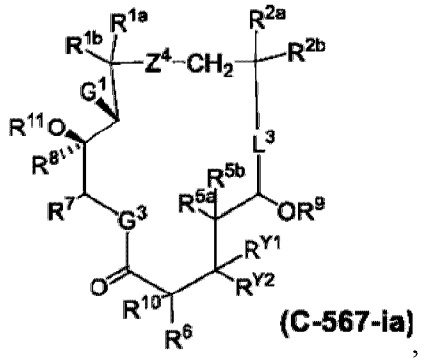

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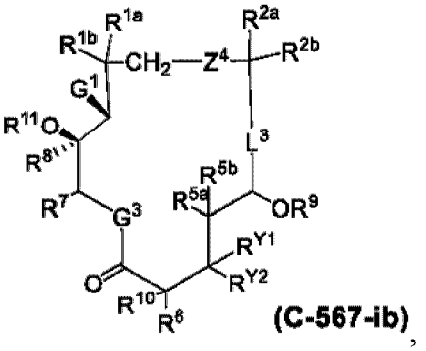
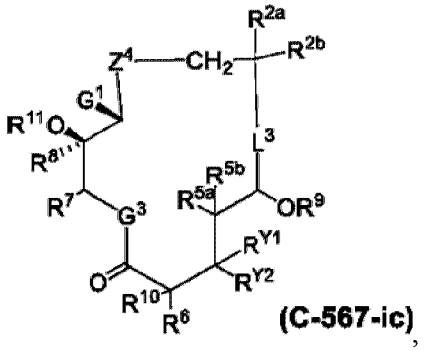
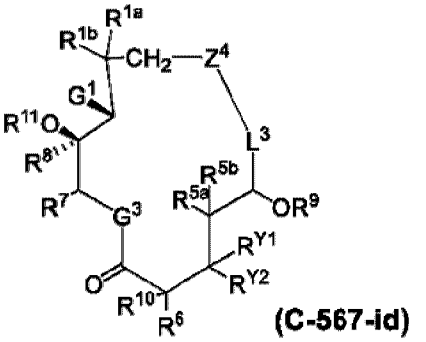


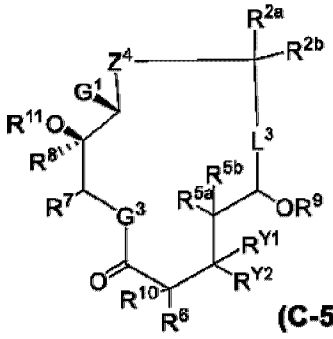
15-membered ring system



14-membered ring system

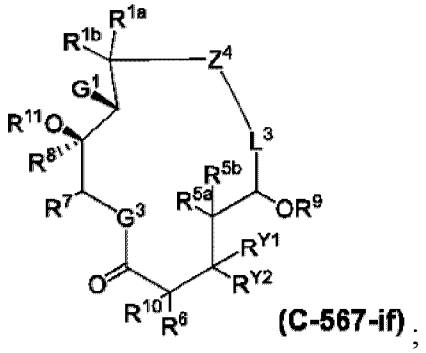


14-membered ring system



, or

13-membered ring system

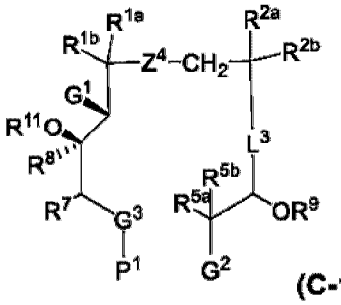


;

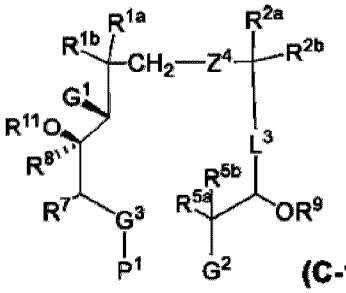
13-membered ring system

wherein the macrolide is prepared by macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor of one of the formulae below, optionally followed by further synthetic manipulation, as described herein:

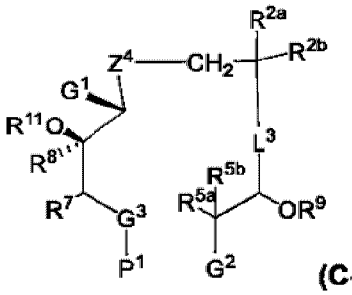
Date Reçue/Date Received 2020-06-25



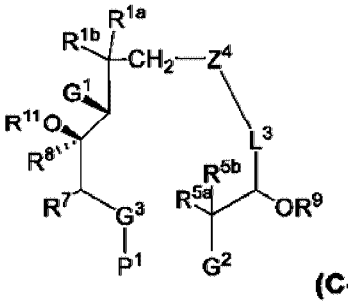
(C-1-ia),



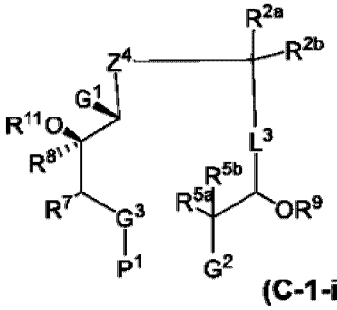
(C-1-ib),



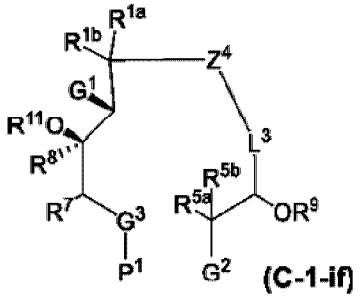
(C-1-ic),



(C-1-id),

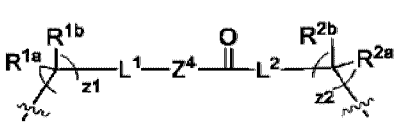


(C-1-ie), or

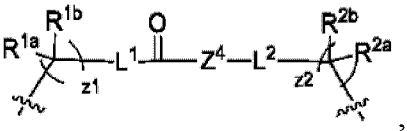


(C-1-if);

[2] an ester, thioester, or amide of formula:



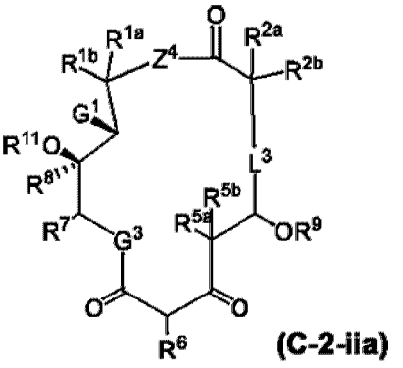
or



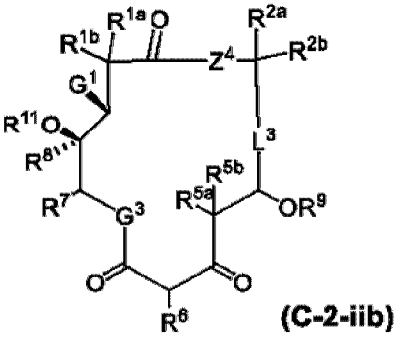
,

wherein L^1 and L^2 are each independently a bond or $–CH_2–$; z1 and z2 are each independently 0, 1, or 2, and Z^4 is –O–, –S–, or $–NR^{Z2}–$, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:

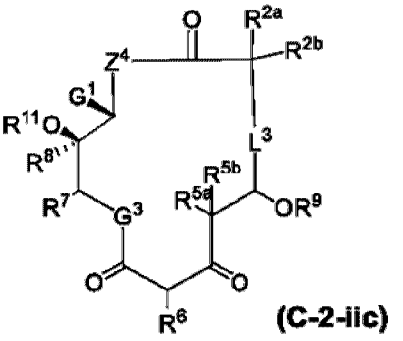
Date Reçue/Date Received 2020-06-25



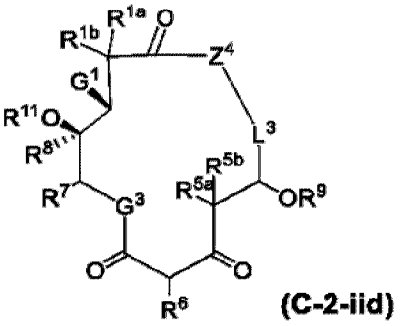
15-membered ring system



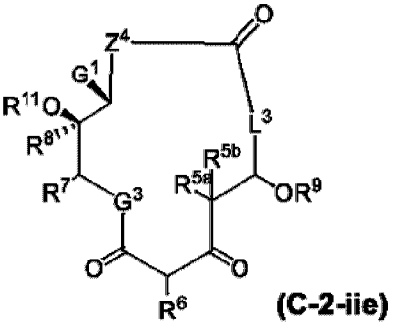
15-membered ring system



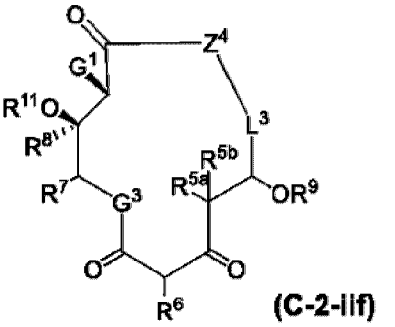
14-membered ring system



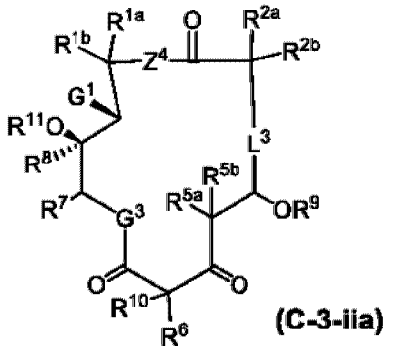
14-membered ring system



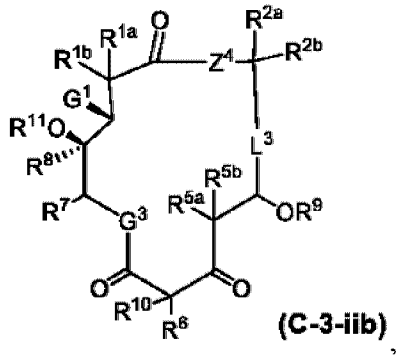
13-membered ring system



13-membered ring system

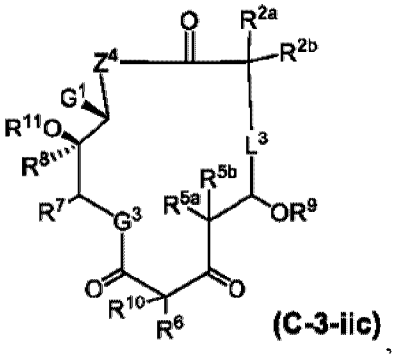


15-membered ring system

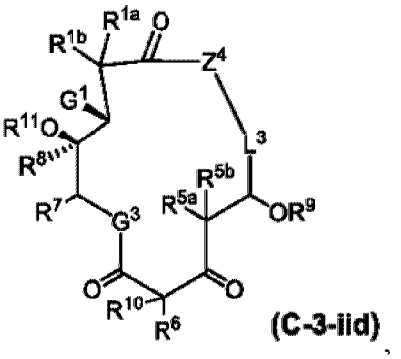


15-membered ring system

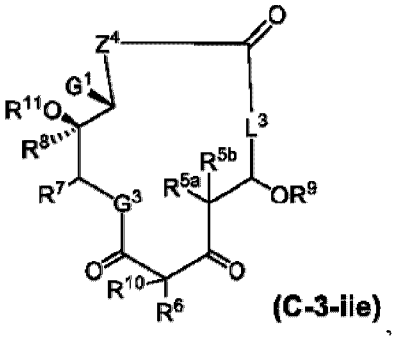
Date Reçue/Date Received 2020-06-25



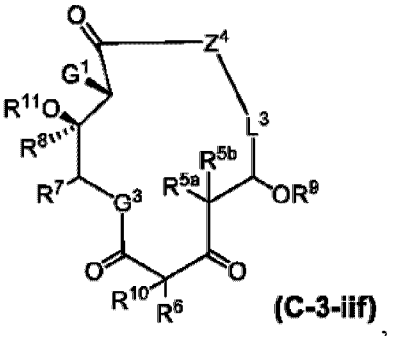
14-membered ring system



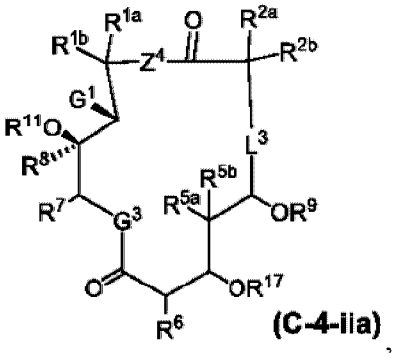
14-membered ring system



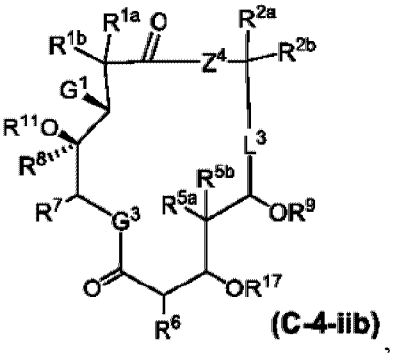
13-membered ring system



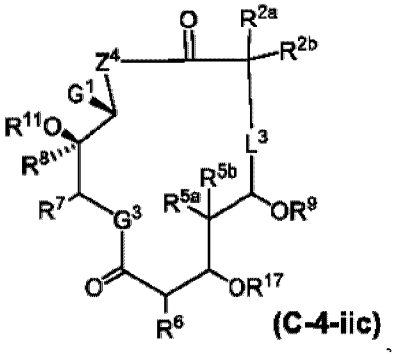
13-membered ring system



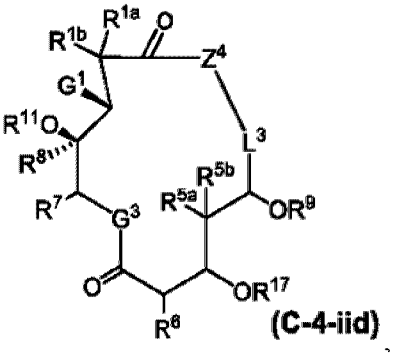
15-membered ring system



15-membered ring system

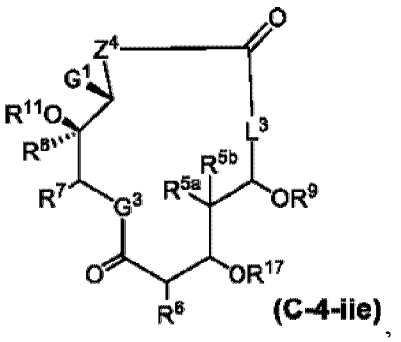


14-membered ring system

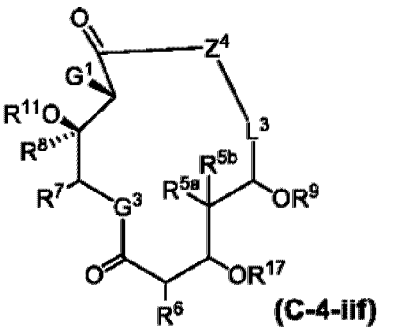


14-membered ring system

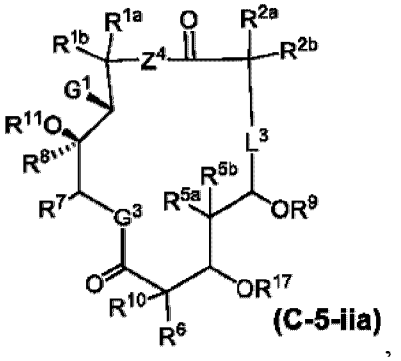
Date Reçue/Date Received 2020-06-25



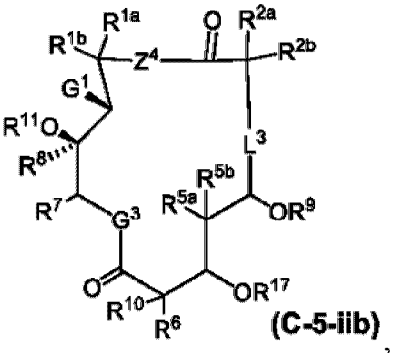
13-membered ring system



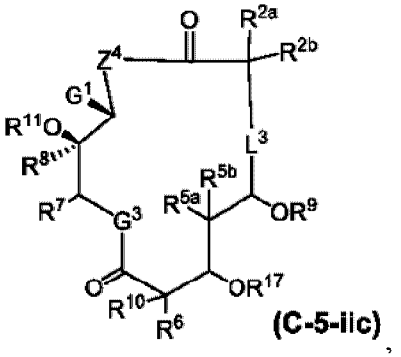
13-membered ring system



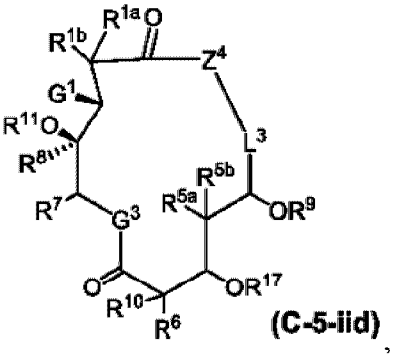
15-membered ring system



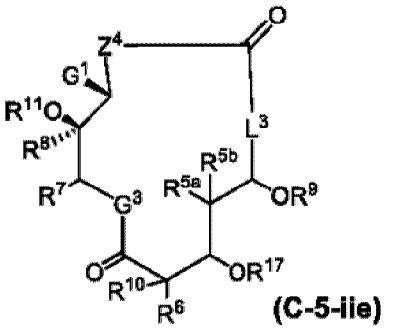
15-membered ring system



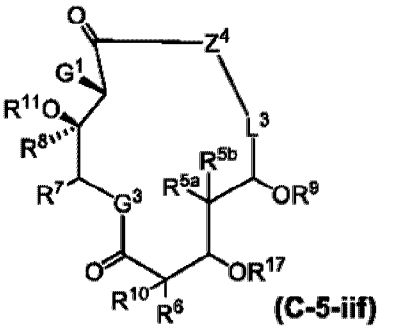
14-membered ring system



14-membered ring system

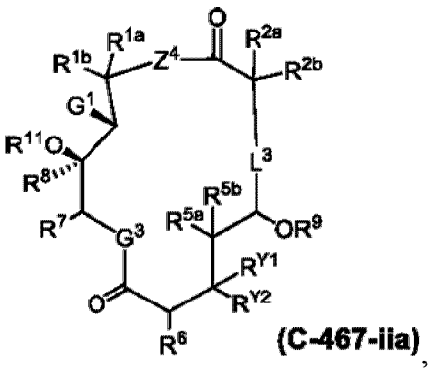


13-membered ring system



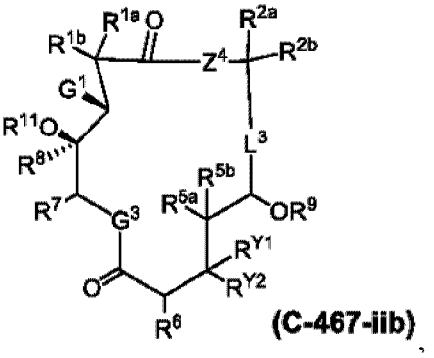
13-membered ring system

Date Reçue/Date Received 2020-06-25



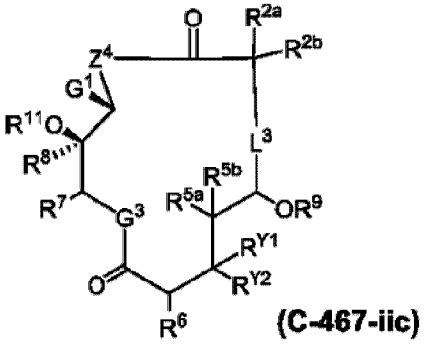
(C-467-iia)

15-membered ring system



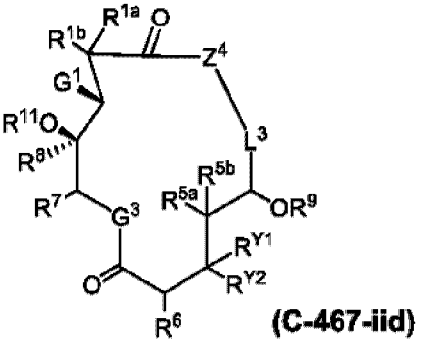
(C-467-iib)

15-membered ring system



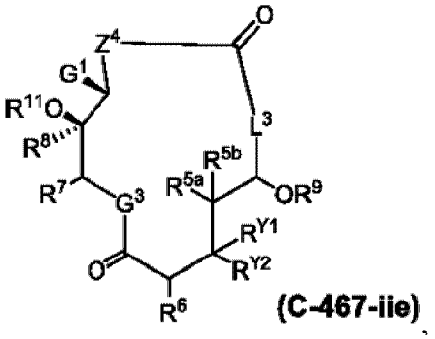
(C-467-iic)

14-membered ring system



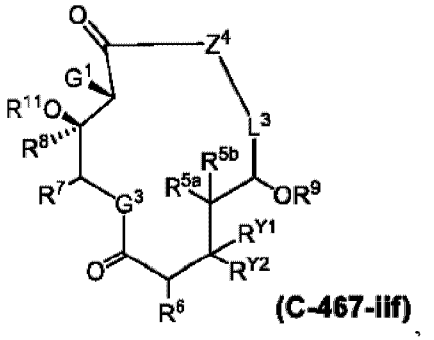
(C-467-iid)

14-membered ring system



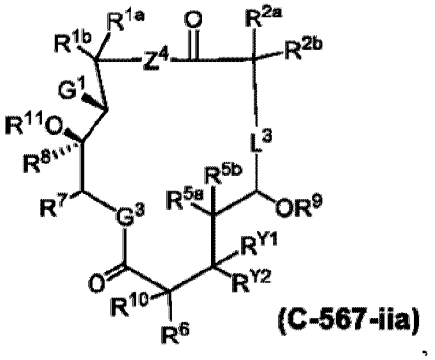
(C-467-iie)

13-membered ring system



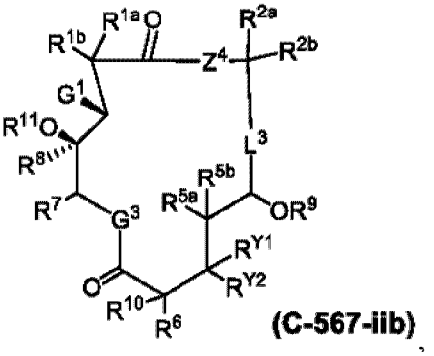
(C-467-iif)

13-membered ring system



(C-567-iia)

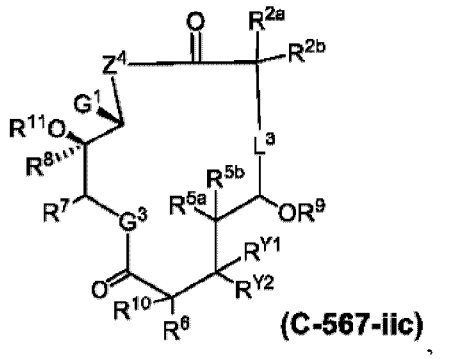
15-membered ring system



(C-567-iib)

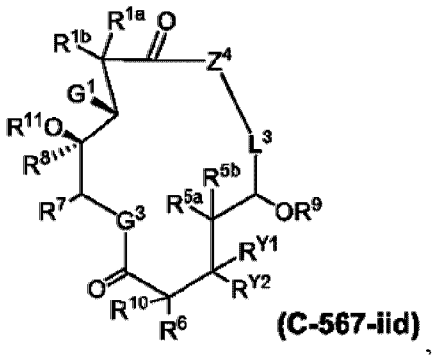
15-membered ring system

Date Reçue/Date Received 2020-06-25



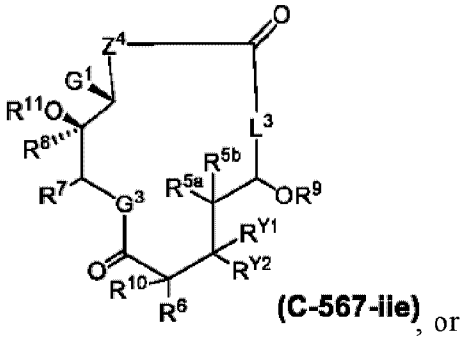
(C-567-iic),

14-membered ring system



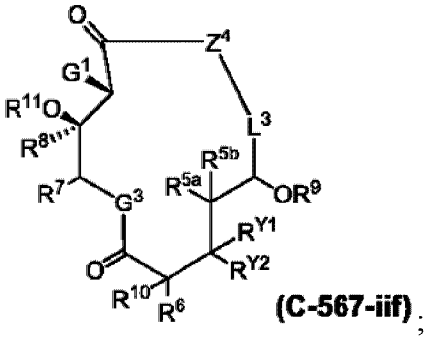
(C-567-iid),

14-membered ring system



(C-567-iie), or

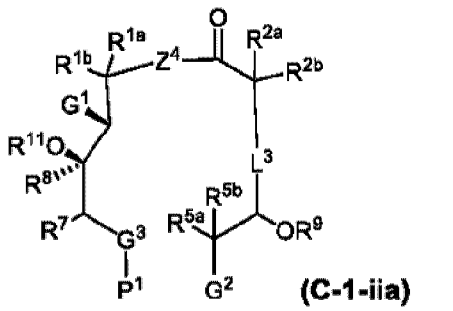
13-membered ring system



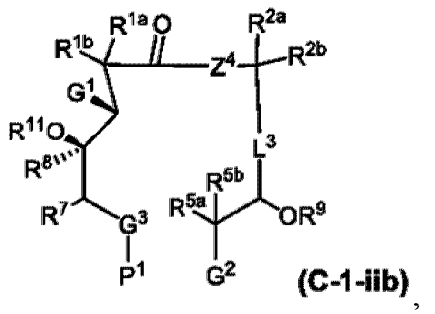
(C-567-iif),

13-membered ring system

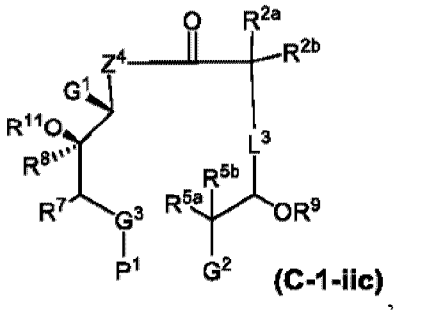
wherein in certain embodiments the macrolide is prepared from macrocyclization (*e.g.,* thermally induced) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



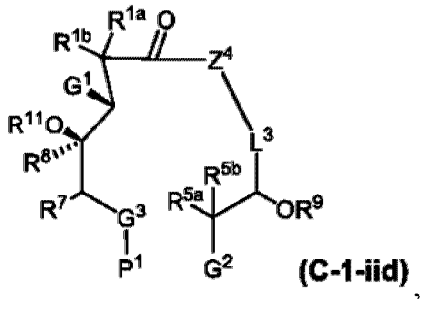
(C-1-iia),



(C-1-iib),

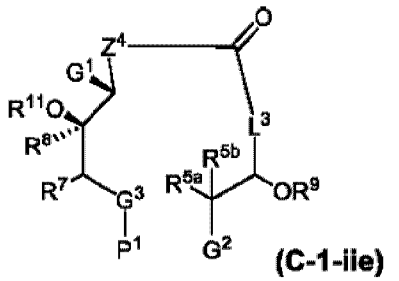


(C-1-iic),

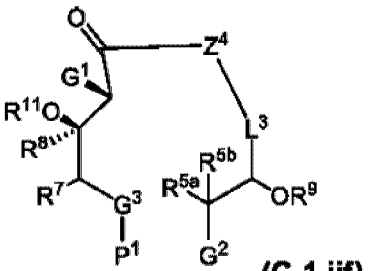


(C-1-iid),

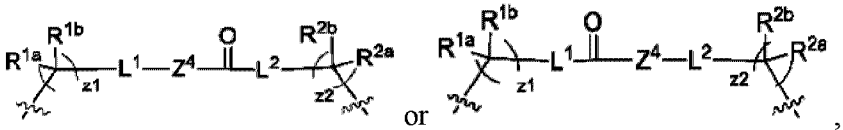
Date Reçue/Date Received 2020-06-25


(C-1-iie)

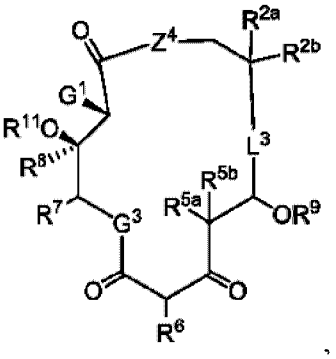
, or


(C-1-iif)

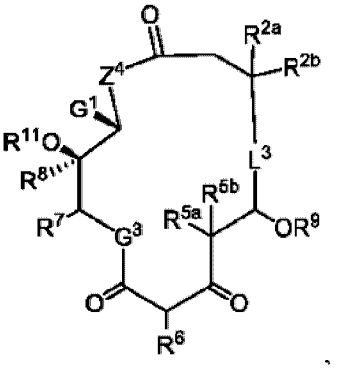
[3] an ester, thioester, or amide of formula:



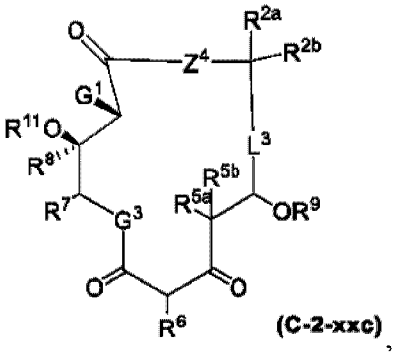
wherein L^1 and L^2 are each independently a bond or $–CH_2–$; z1 and z2 are each independently 0, 1, or 2, and Z^4 is –O–, –S–, or $–NR^{Z2}–$, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:



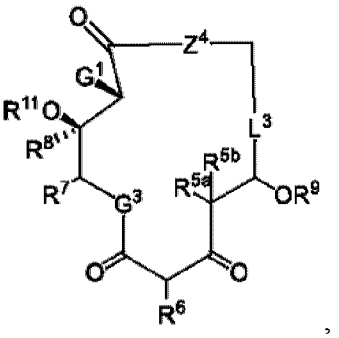
15-membered ring system



15-membered ring system

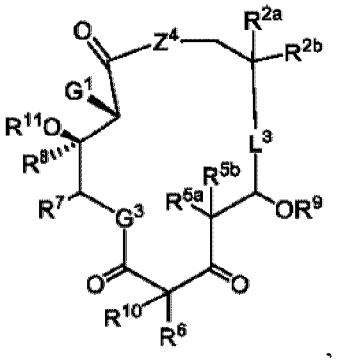

(C-2-xxc)

14-membered ring system

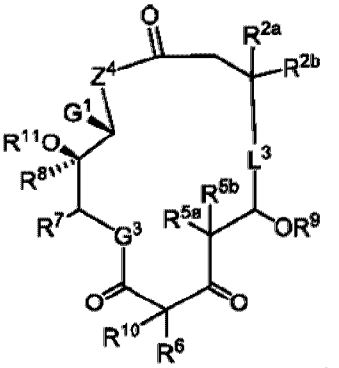


14-membered ring system

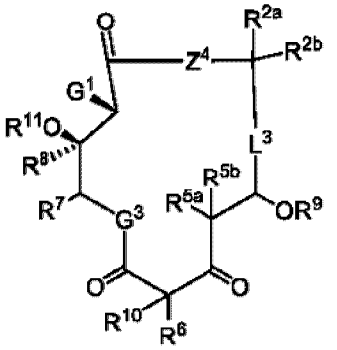
Date Reçue/Date Received 2020-06-25



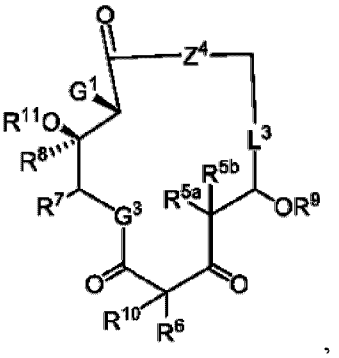
15-membered ring system



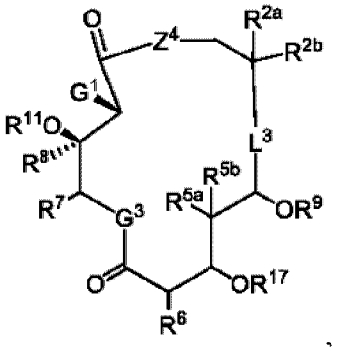
15-membered ring system



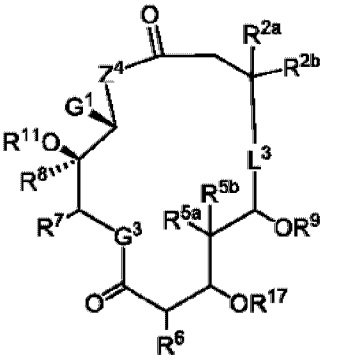
14-membered ring system



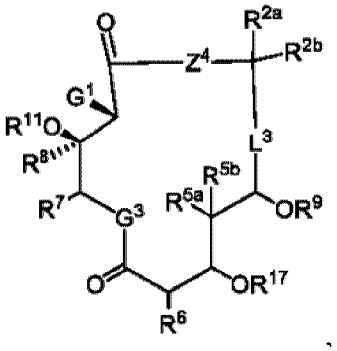
14-membered ring system



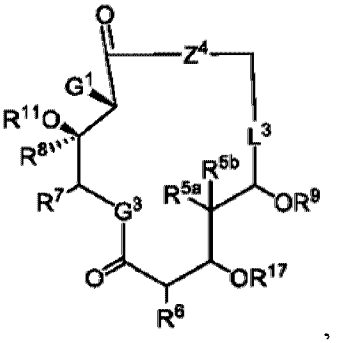
15-membered ring system



15-membered ring system

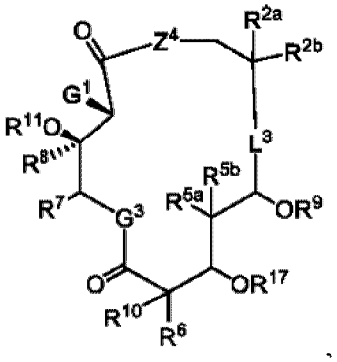


14-membered ring system

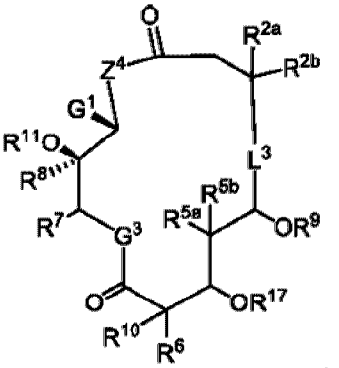


14-membered ring system

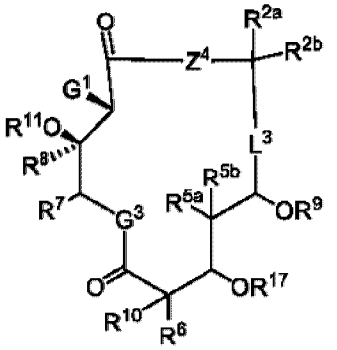
Date Reçue/Date Received 2020-06-25



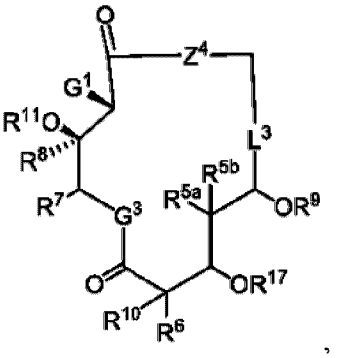
15-membered ring system



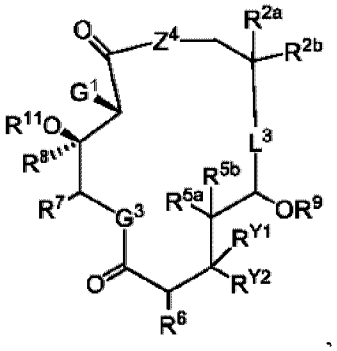
15-membered ring system



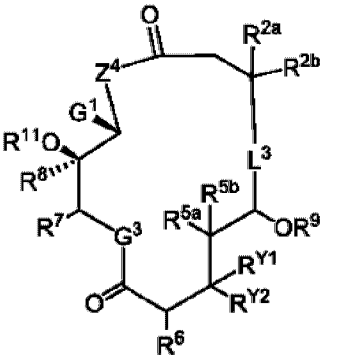
14-membered ring system



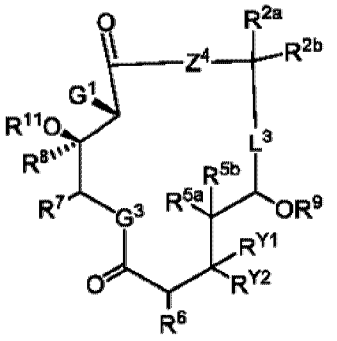
14-membered ring system



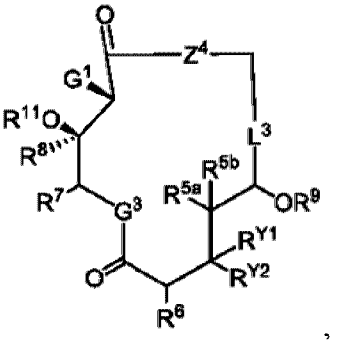
15-membered ring system



15-membered ring system

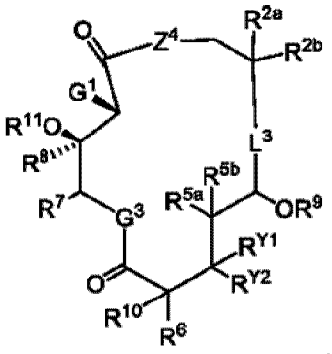


14-membered ring system

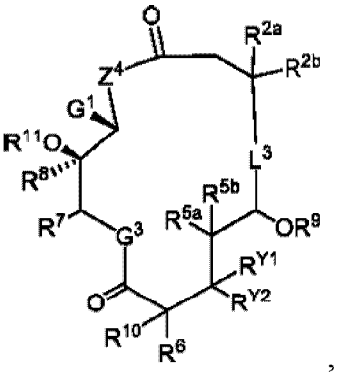


14-membered ring system

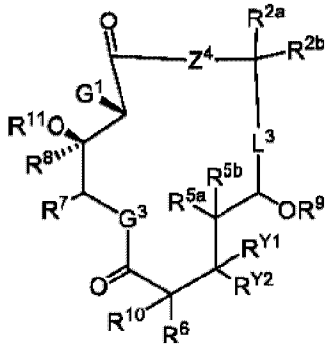
Date Reçue/Date Received 2020-06-25



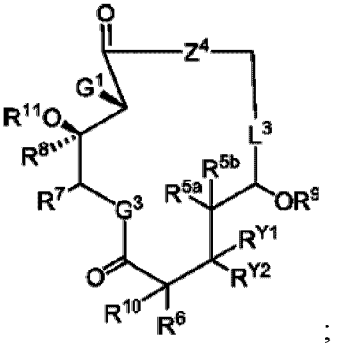
15-membered ring system



15-membered ring system

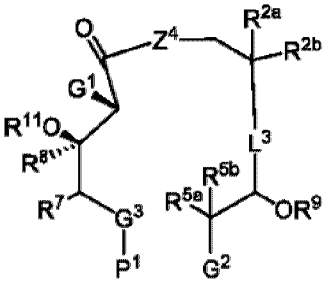


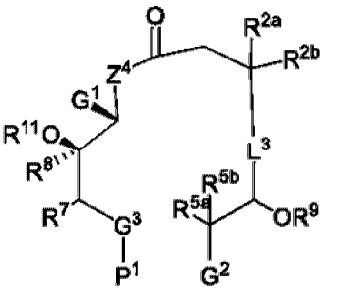
14-membered ring system



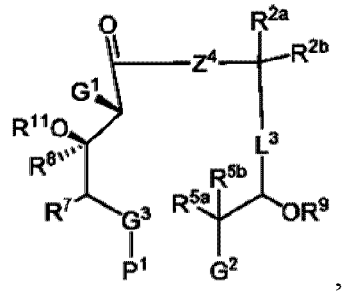
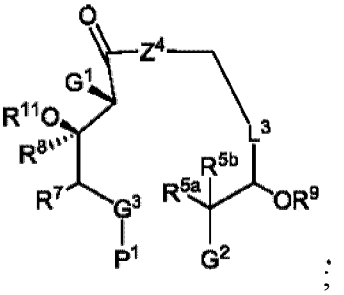
14-membered ring system

wherein in certain embodiments the macrolide is prepared from macrocyclization (*e.g.*, thermally induced) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:

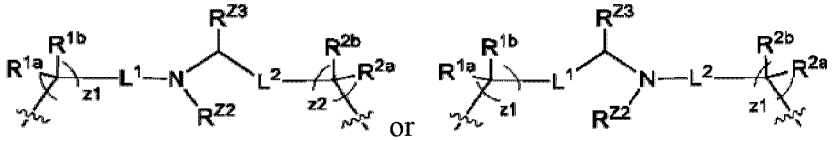




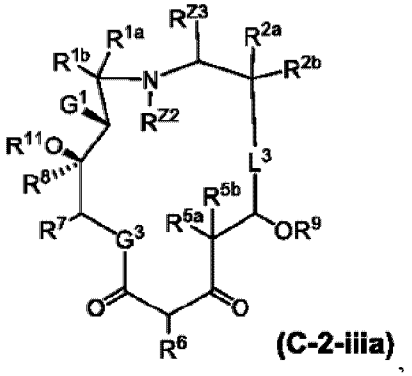
Date Reçue/Date Received 2020-06-25


, or

;

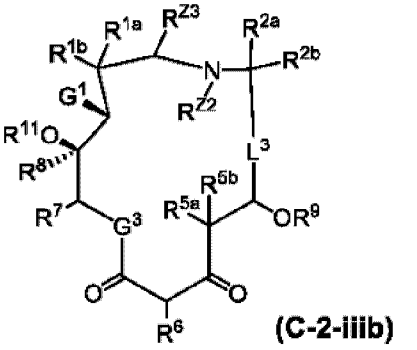
[4] an amine of formula:



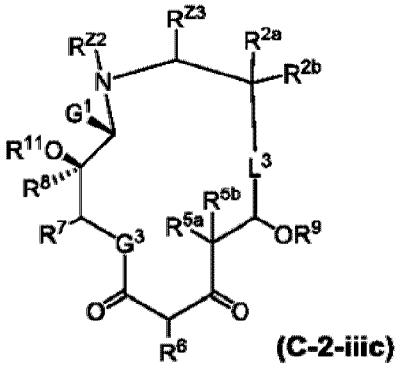
wherein L^1 and L^2 are each independently a bond or $–CH_2–$; z1 and z2 are 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:


(C-2-iiia),

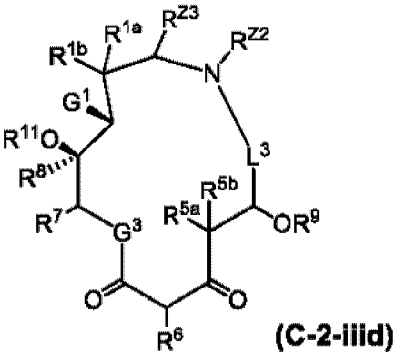
15-membered ring system


(C-2-iiib),

15-membered ring system

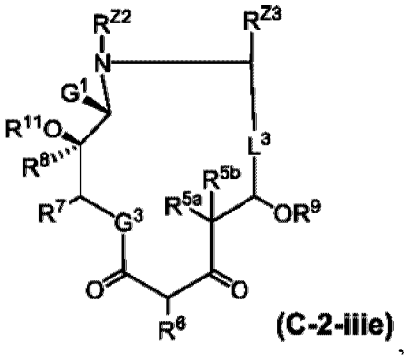

(C-2-iiic),

14-membered ring system


(C-2-iiid),

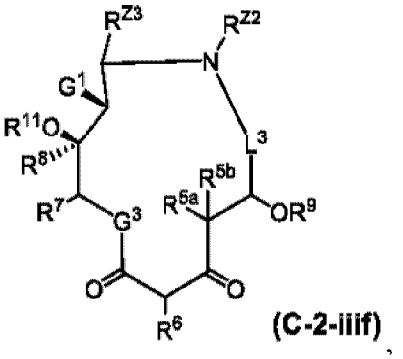
14-membered ring system

Date Reçue/Date Received 2020-06-25



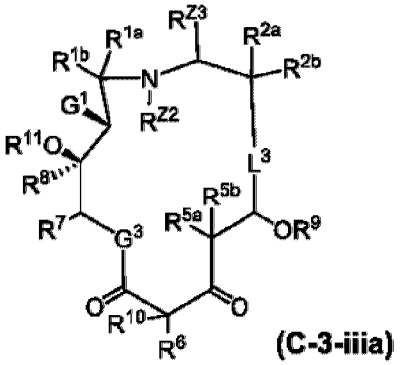
(C-2-iiie)

13-membered ring system



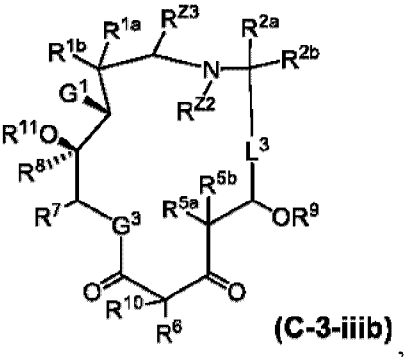
(C-2-iiif)

13-membered ring system



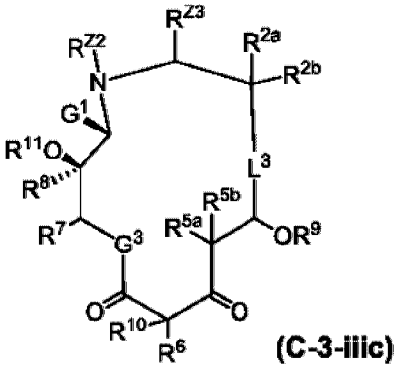
(C-3-iiia)

15-membered ring system



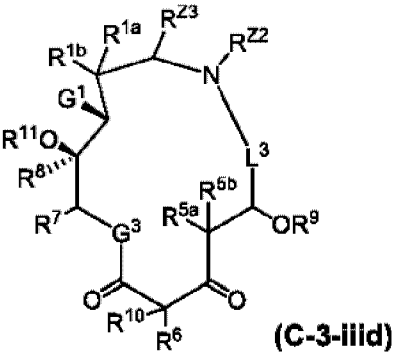
(C-3-iiib)

15-membered ring system



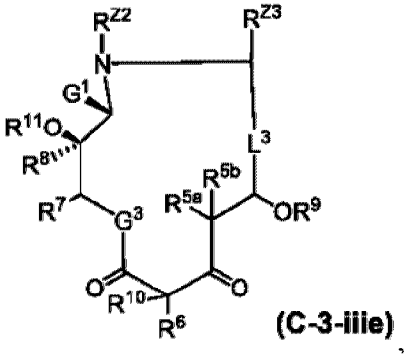
(C-3-iiic)

14-membered ring system



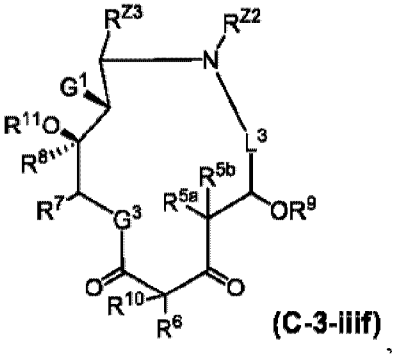
(C-3-iiid)

14-membered ring system



(C-3-iiie)

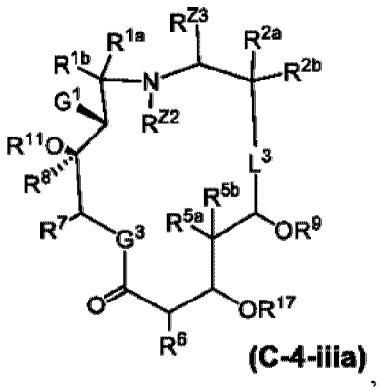
13-membered ring system



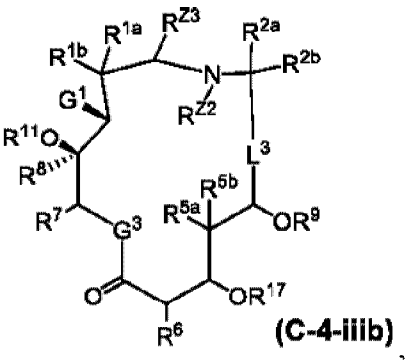
(C-3-iiif)

13-membered ring system

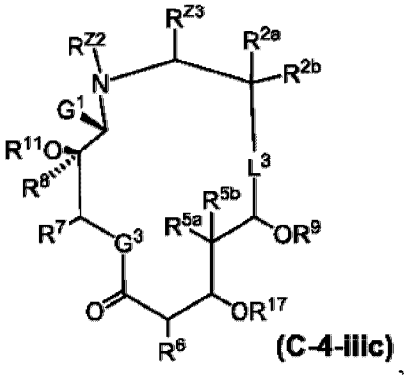
Date Reçue/Date Received 2020-06-25



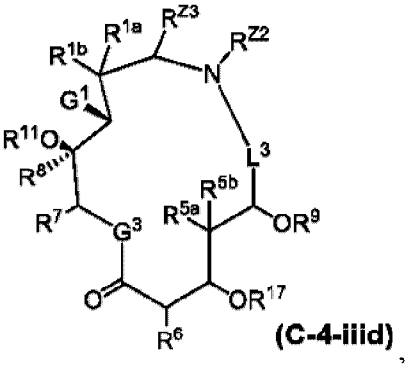
15-membered ring system



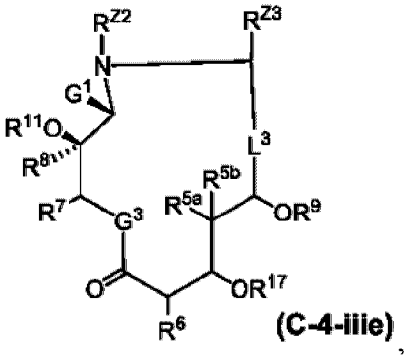
15-membered ring system



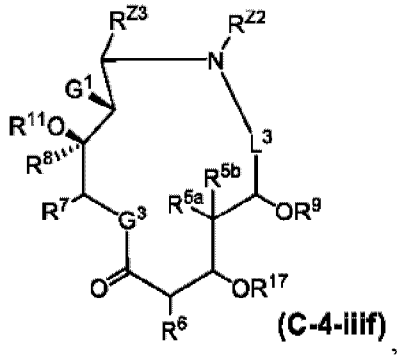
14-membered ring system



14-membered ring system

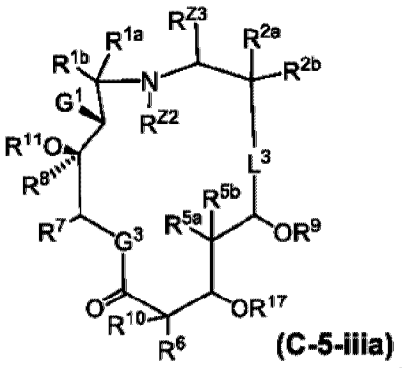


13-membered ring system



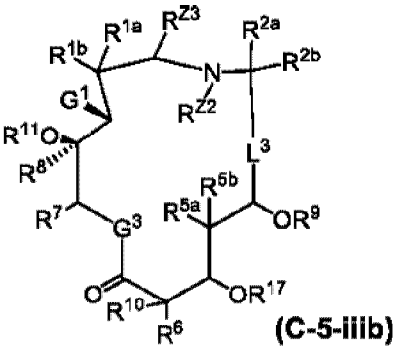
13-membered ring system

Date Reçue/Date Received 2020-06-25



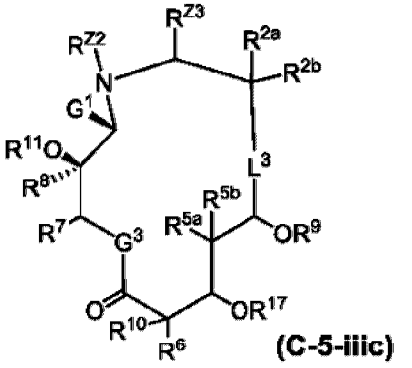
(C-5-iiia)

15-membered ring system



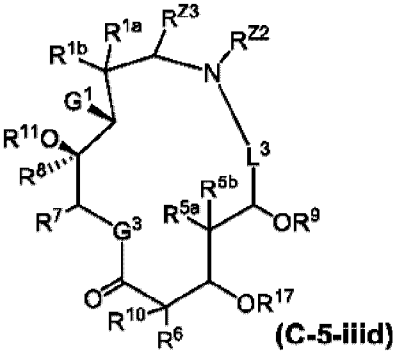
(C-5-iiib)

15-membered ring system



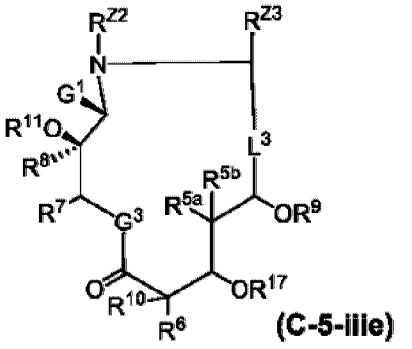
(C-5-iiic)

14-membered ring system



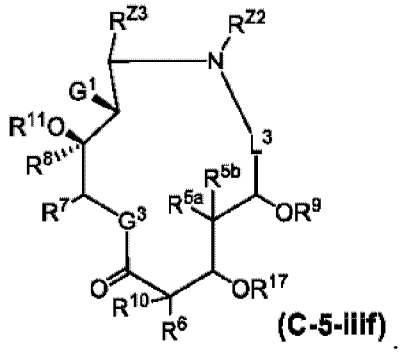
(C-5-iiid)

14-membered ring system



(C-5-iiie)

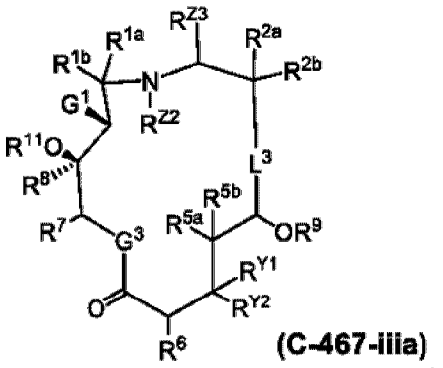
13-membered ring system



(C-5-iiif)

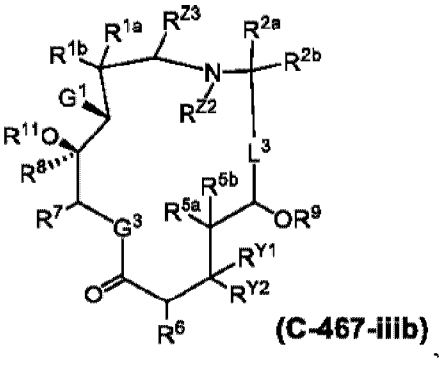
13-membered ring system

Date Reçue/Date Received 2020-06-25



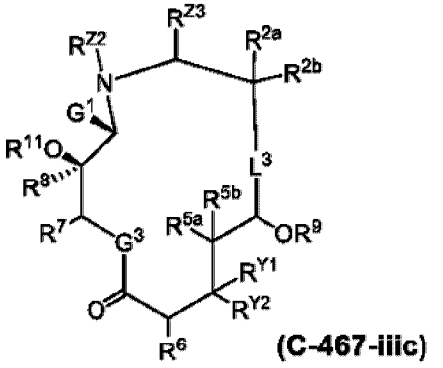
(C-467-iiia)

15-membered ring system



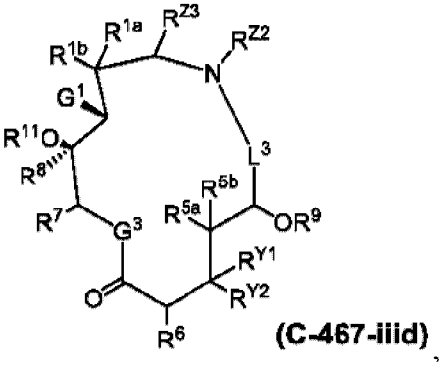
(C-467-iiib)

15-membered ring system



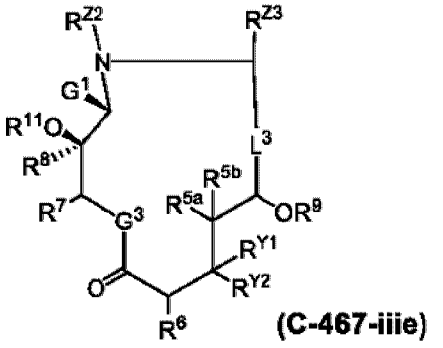
(C-467-iiic)

14-membered ring system



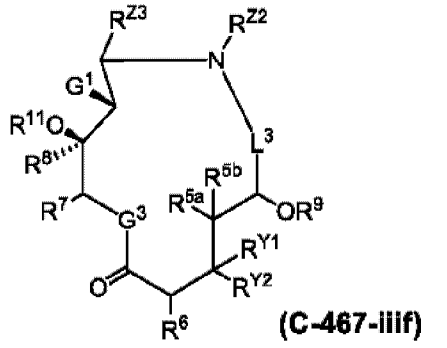
(C-467-iiid)

14-membered ring system



(C-467-iiie)

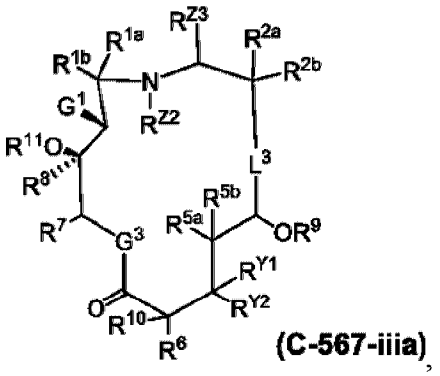
13-membered ring system



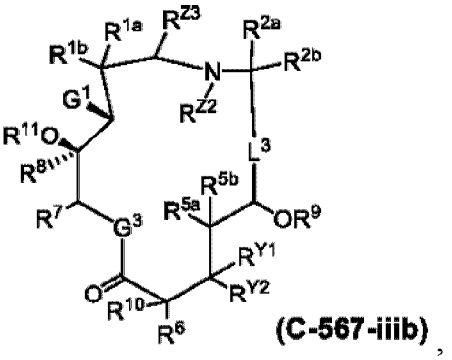
(C-467-iiif)

13-membered ring system

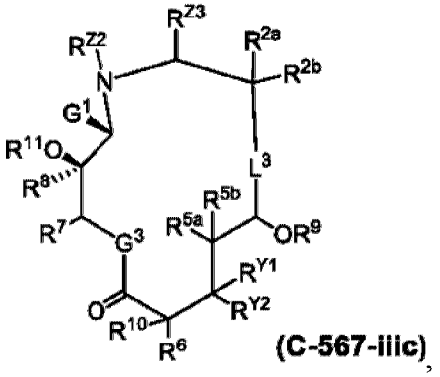
Date Reçue/Date Received 2020-06-25



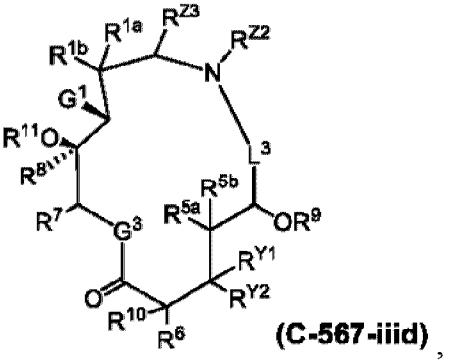
15-membered ring system



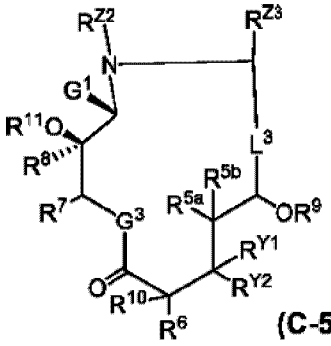
15-membered ring system



14-membered ring system

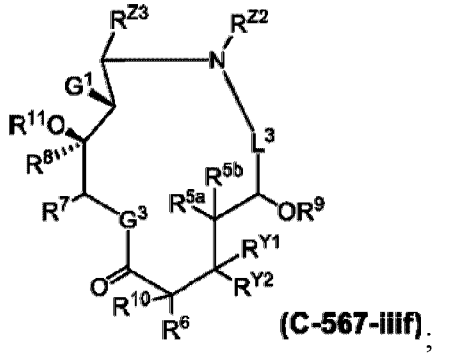


14-membered ring system



, or

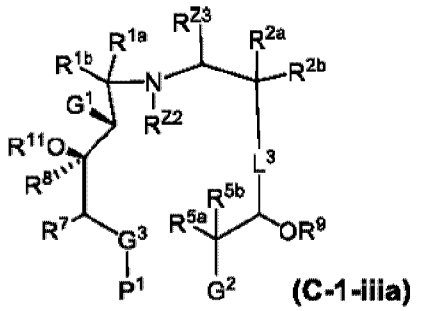
13-membered ring system



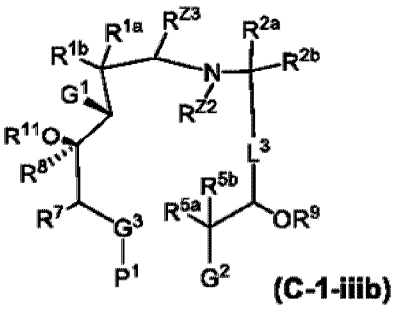
13-membered ring system

wherein the macrolide is prepared from macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor of the below formula, optionally followed by further synthetic manipulation, as described herein:

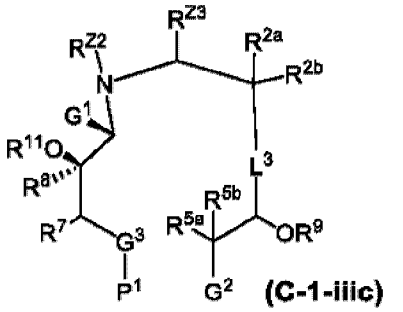
Date Reçue/Date Received 2020-06-25



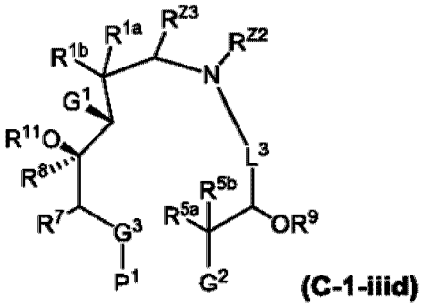
(C-1-iiia),



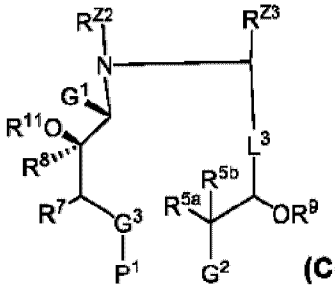
(C-1-iiib).



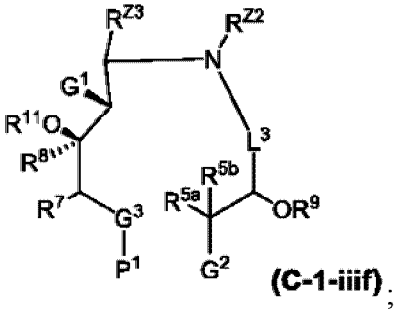
(C-1-iiic),



(C-1-iiid).

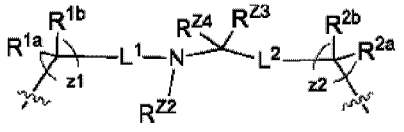


(C-1-iiie), or

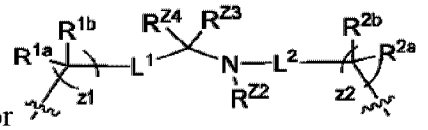


(C-1-iiif);

[5] an amine of Formula:



or



wherein L^1 and L^2 are each independently a bond or $-CH_2-$; z1 and z2 are each independently 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:

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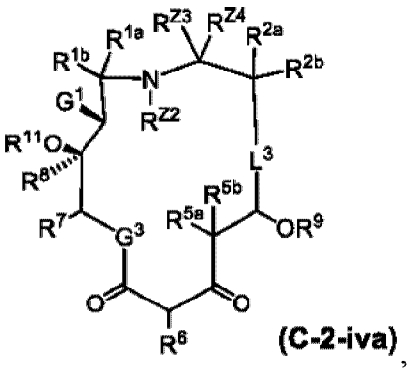
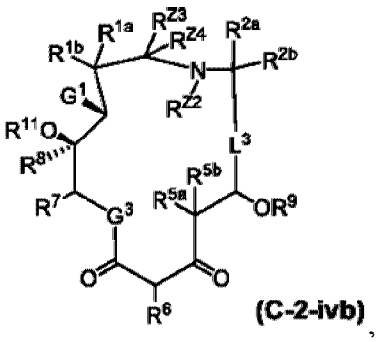


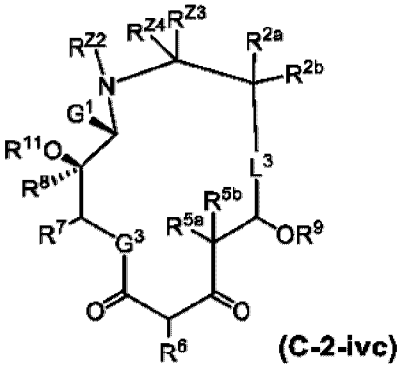
(C-2-iva),

15-membered ring system



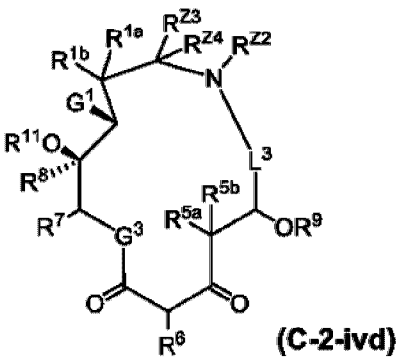
(C-2-ivb),

15-membered ring system



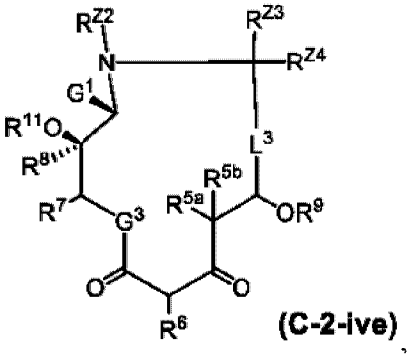
(C-2-ivc),

14-membered ring system



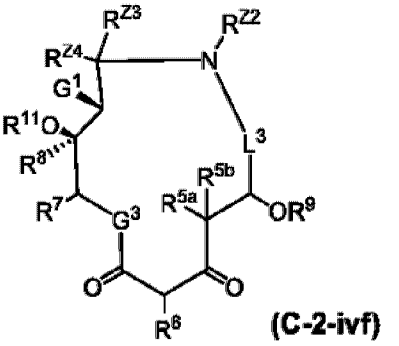
(C-2-ivd),

14-membered ring system



(C-2-ive),

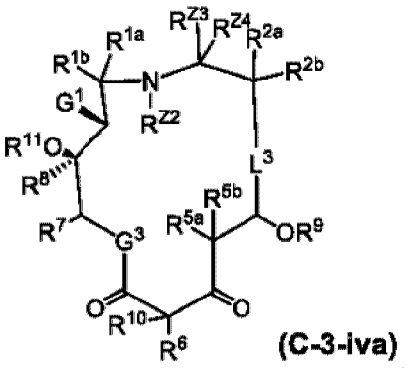
13-membered ring system



(C-2-ivf),

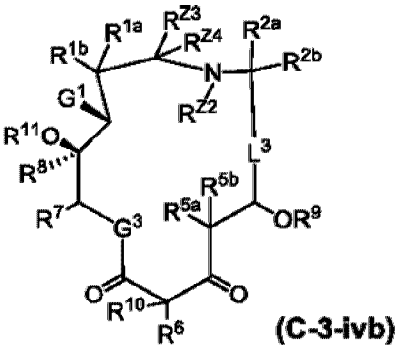
13-membered ring system

Date Reçue/Date Received 2020-06-25



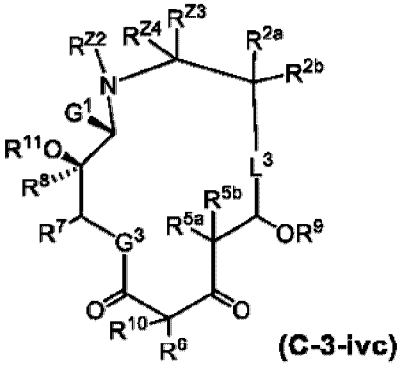
(C-3-iva)

15-membered ring system



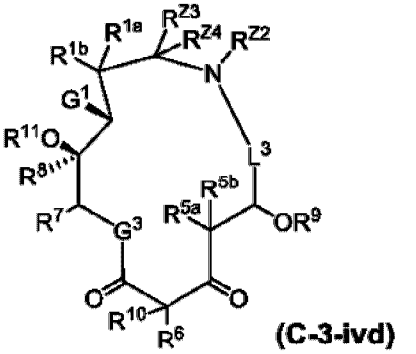
(C-3-ivb)

15-membered ring system



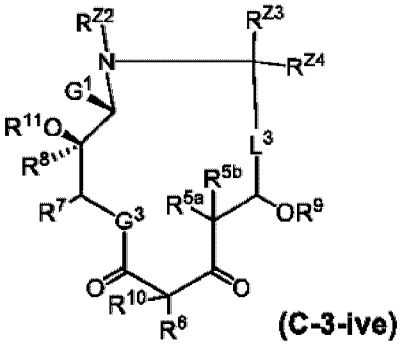
(C-3-ivc)

14-membered ring system



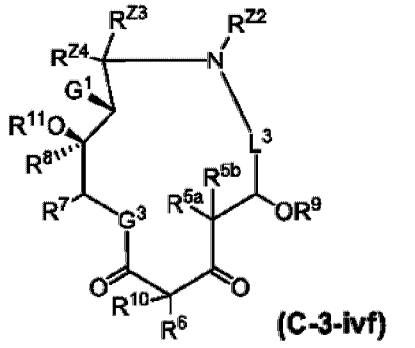
(C-3-ivd)

14-membered ring system



(C-3-ive)

13-membered ring system



(C-3-ivf)

13-membered ring system

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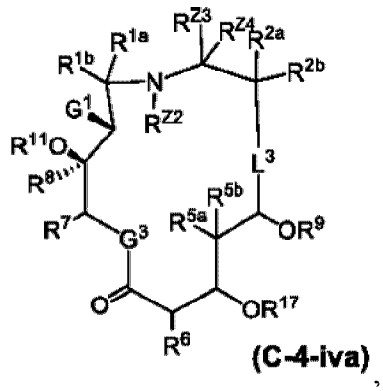
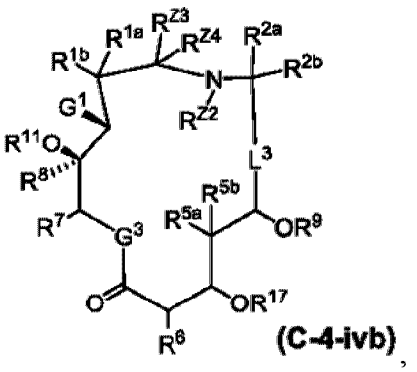


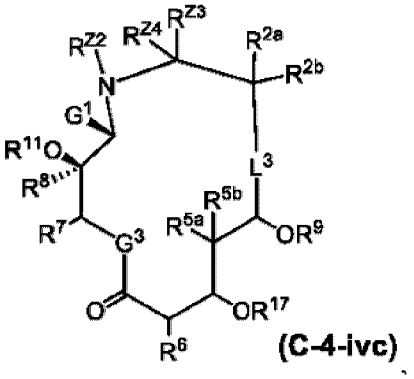
(C-4-iva),

15-membered ring system



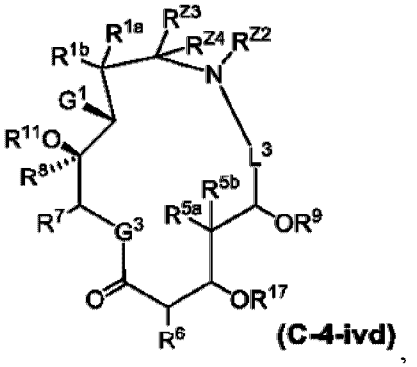
(C-4-ivb),

15-membered ring system



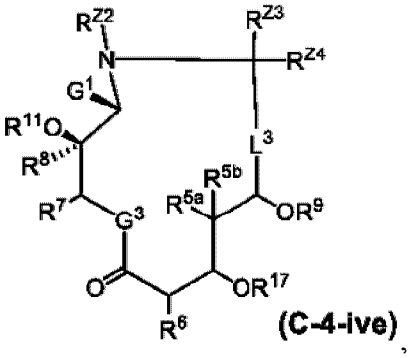
(C-4-ivc),

14-membered ring system



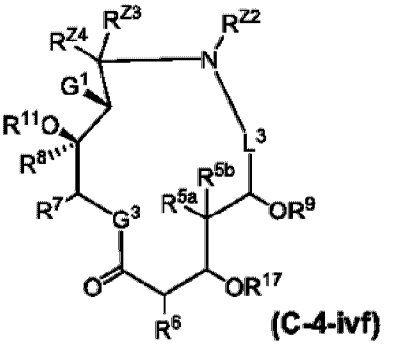
(C-4-ivd),

14-membered ring system



(C-4-ive),

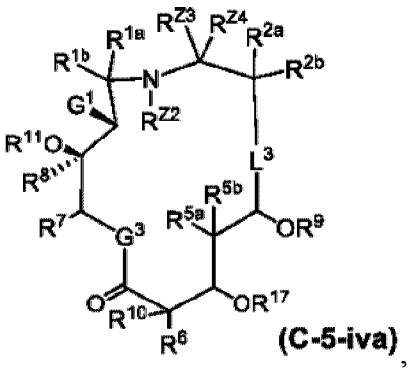
13-membered ring system



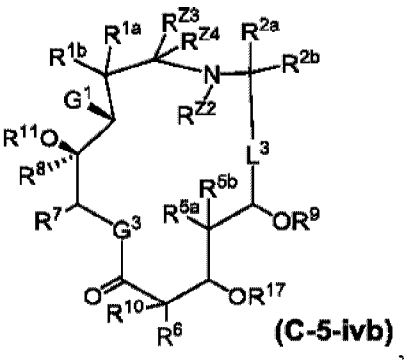
(C-4-ivf),

13-membered ring system

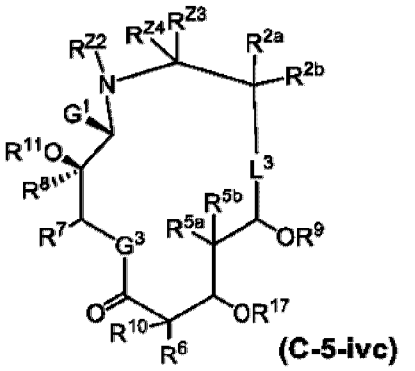
Date Reçue/Date Received 2020-06-25



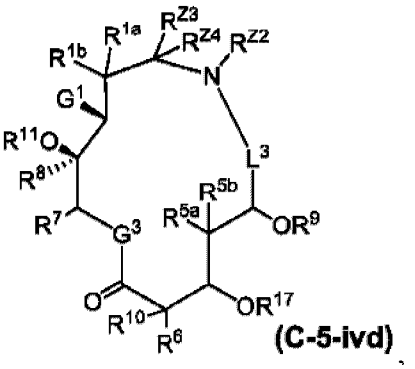
15-membered ring system



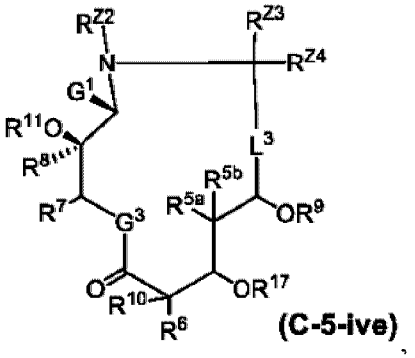
15-membered ring system



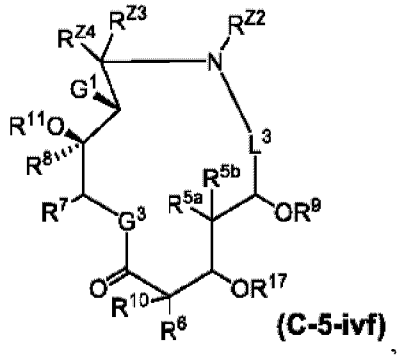
14-membered ring system



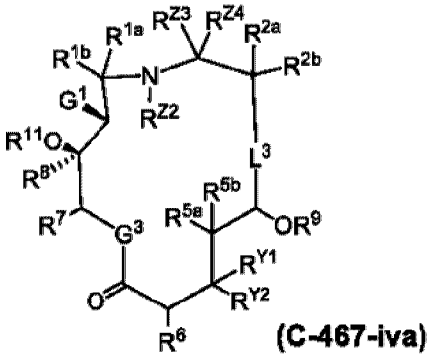
14-membered ring system



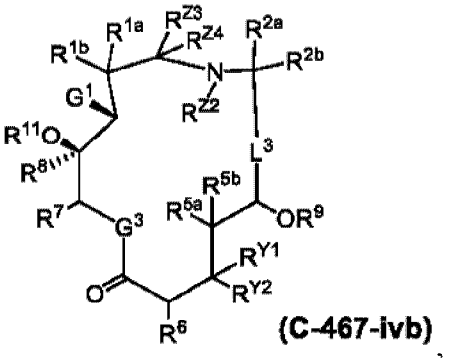
13-membered ring system



13-membered ring system

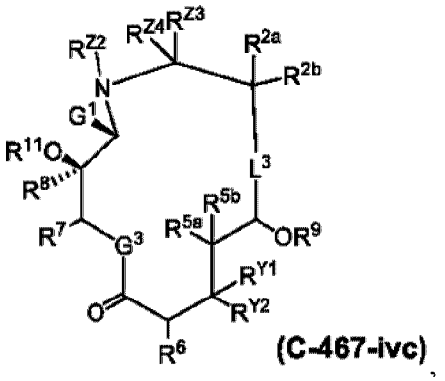


15-membered ring system



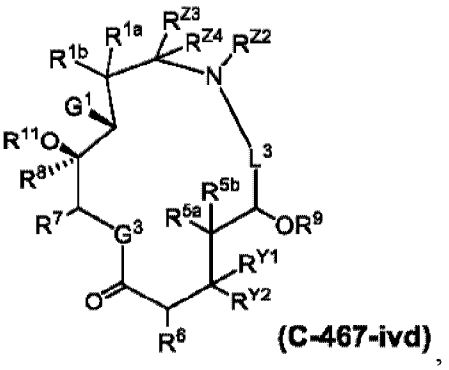
15-membered ring system

Date Reçue/Date Received 2020-06-25



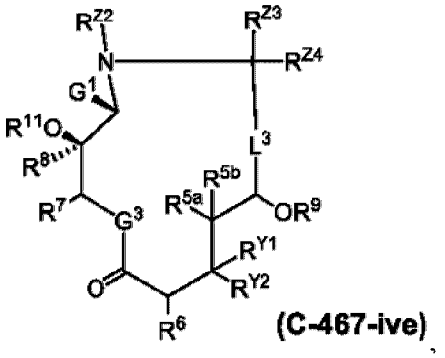
(C-467-ivc)

14-membered ring system



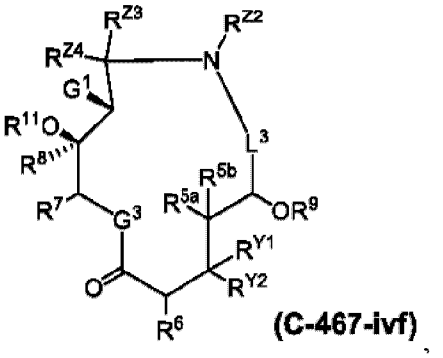
(C-467-ivd)

14-membered ring system



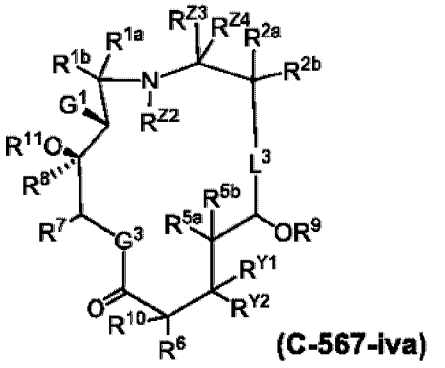
(C-467-ive)

13-membered ring system



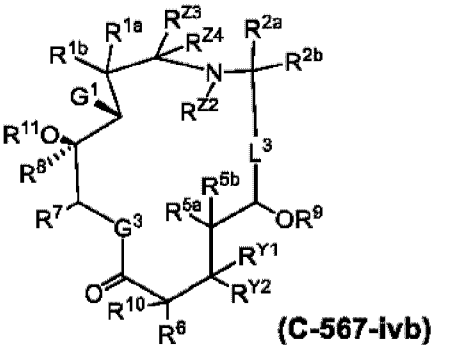
(C-467-ivf)

13-membered ring system



(C-567-iva)

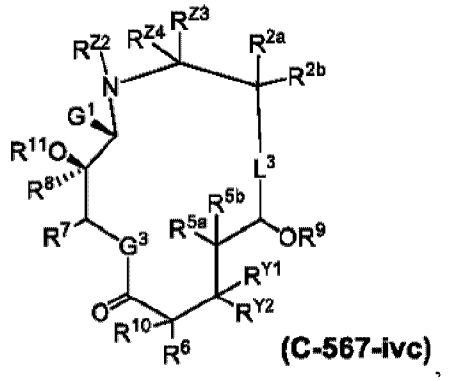
15-membered ring system



(C-567-ivb)

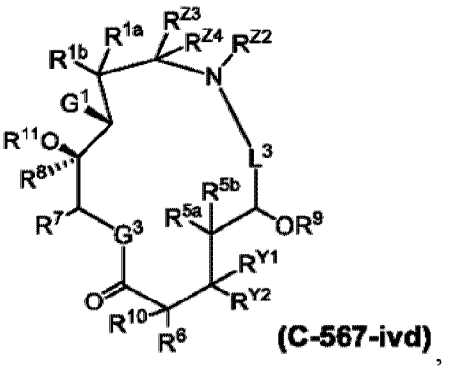
15-membered ring system

Date Reçue/Date Received 2020-06-25



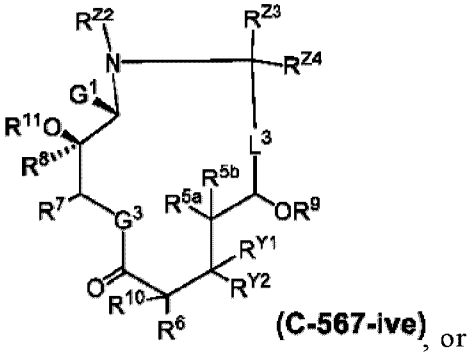
(C-567-ivc),

14-membered ring system



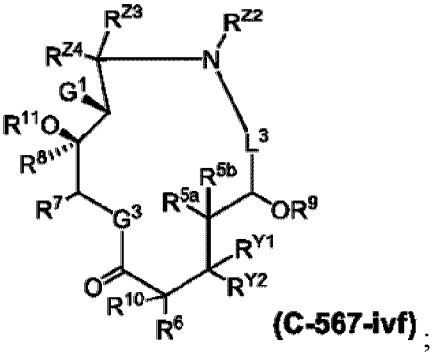
(C-567-ivd),

14-membered ring system



(C-567-ive), or

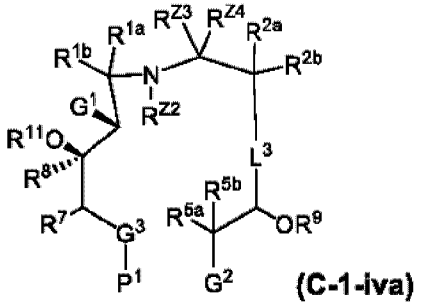
13-membered ring system



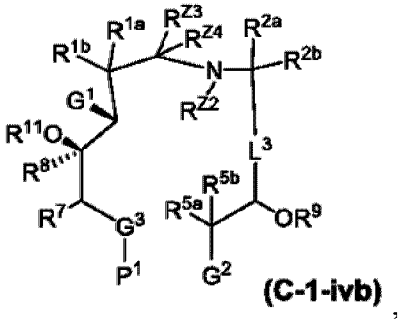
(C-567-ivf);

13-membered ring system

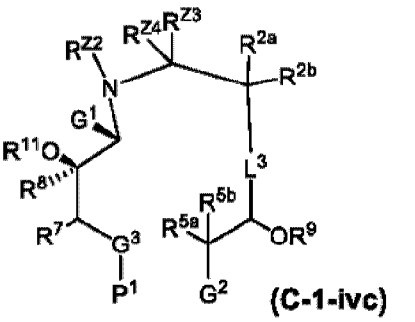
wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



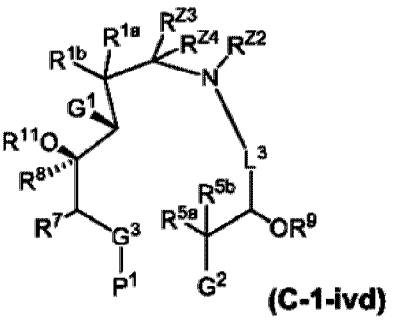
(C-1-iva),



(C-1-ivb),

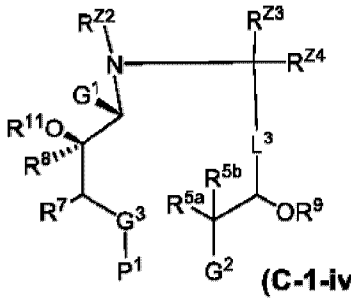


(C-1-ivc),

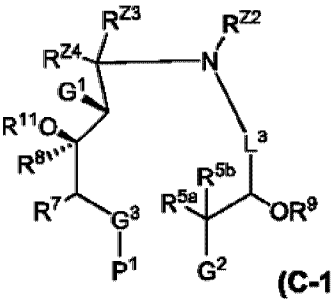


(C-1-ivd)

Date Reçue/Date Received 2020-06-25

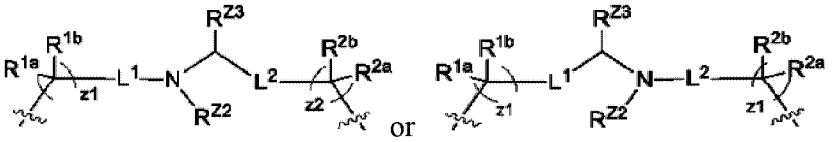


(C-1-ive), or

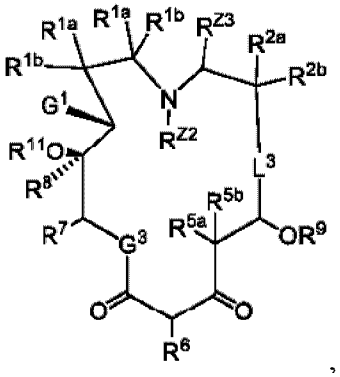


(C-1-ivf);

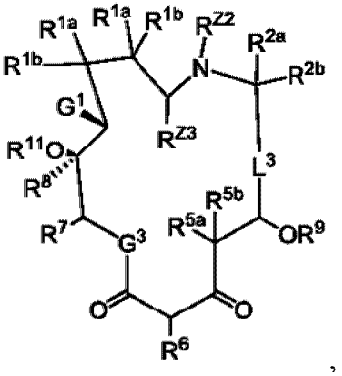
[6] an amine of formula:



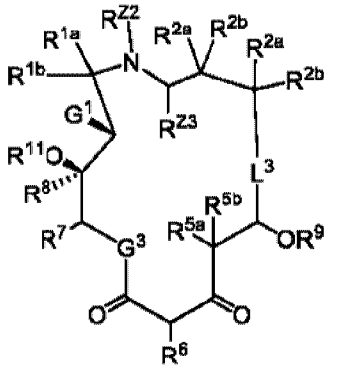
wherein L^1 and L^2 are each independently a bond and z1 and z2 are 1 or 2, *e.g.,* to provide a ring system of formula:



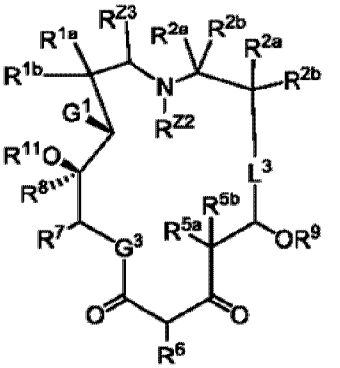
16-membered ring system



16-membered ring system

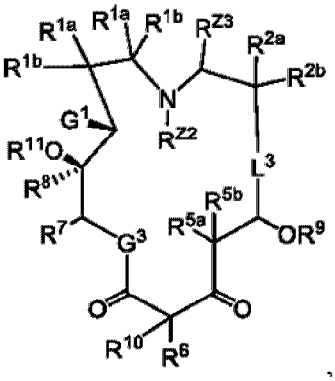


16-membered ring system

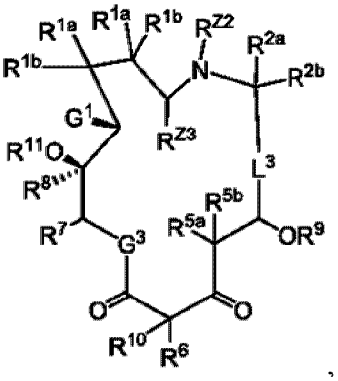


16-membered ring system

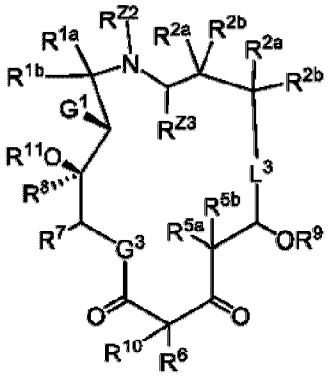
Date Reçue/Date Received 2020-06-25



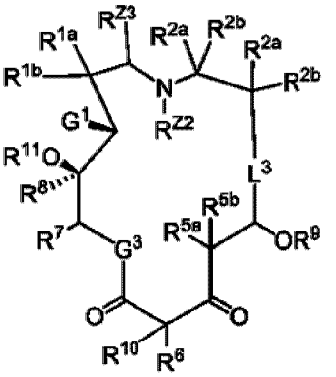
16-membered ring system



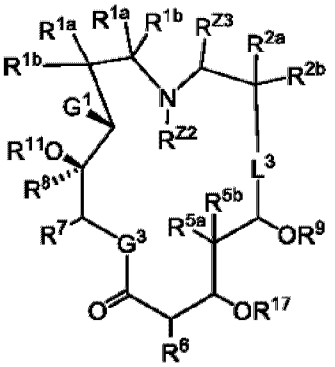
16-membered ring system



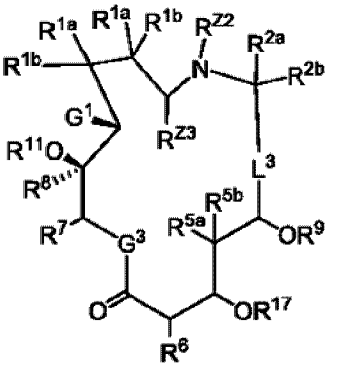
16-membered ring system



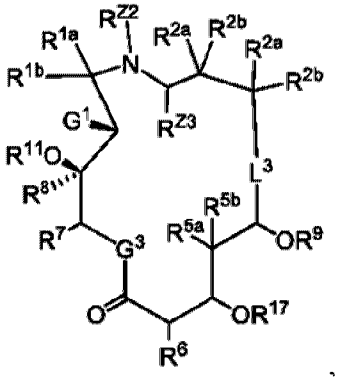
16-membered ring system

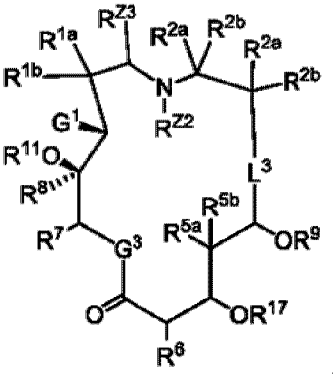


16-membered ring system



16-membered ring system





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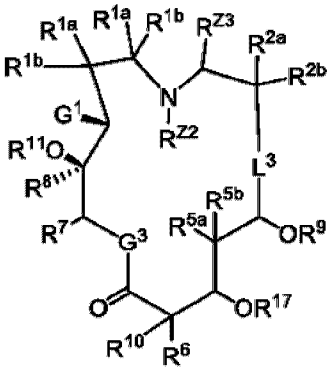
16-membered ring system



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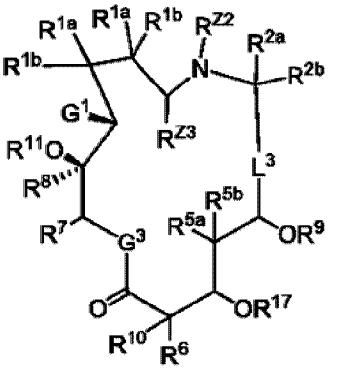

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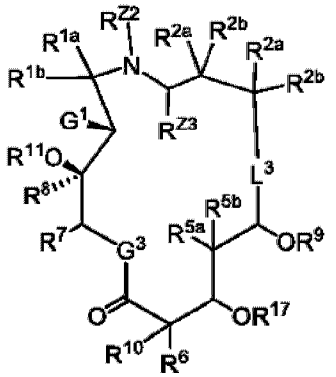

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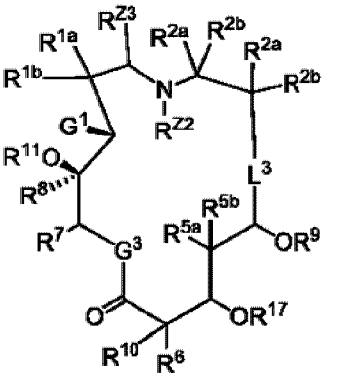

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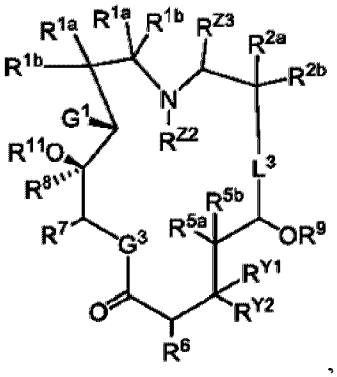
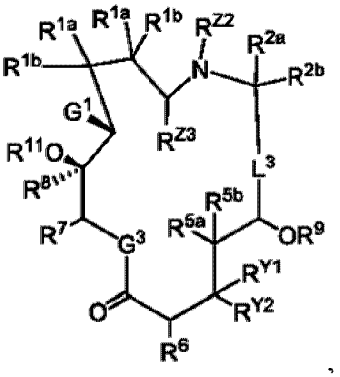


16-membered ring system



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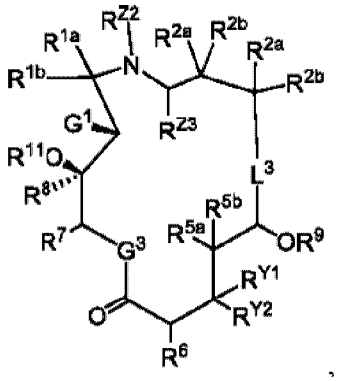
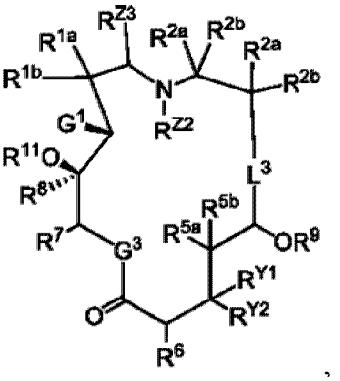


16-membered ring system



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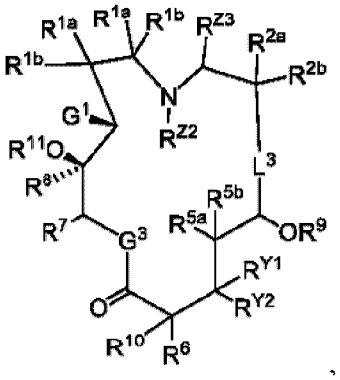

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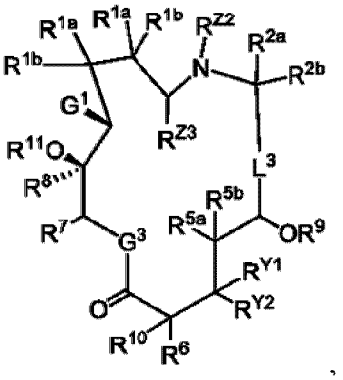

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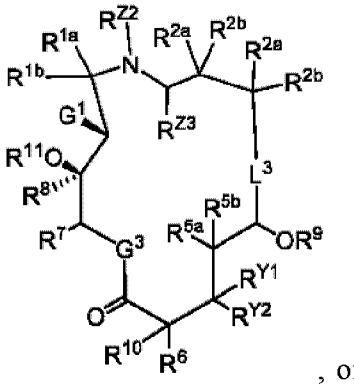
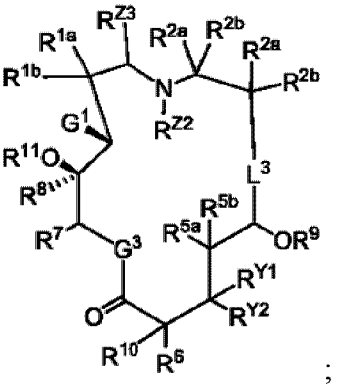


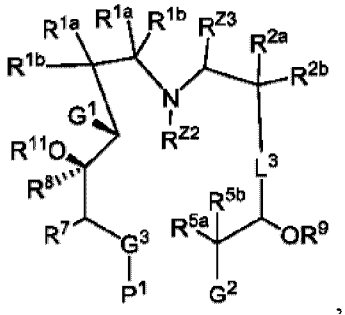
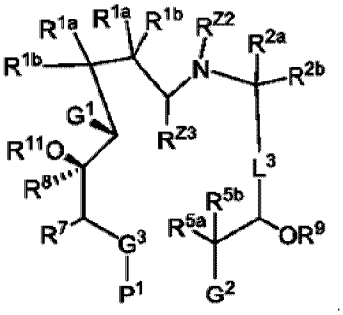
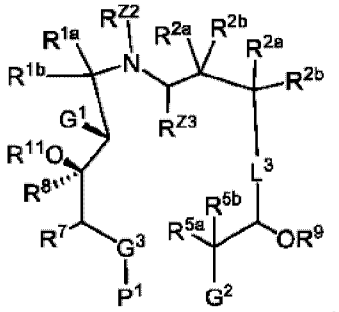
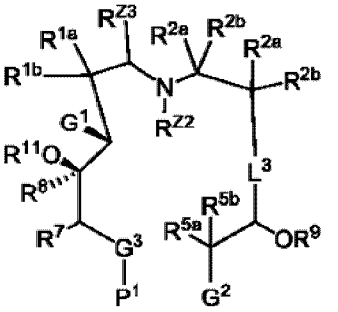
16-membered ring system



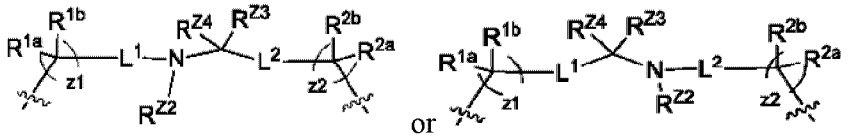
16-membered ring system

wherein the macrolide is prepared from macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor of the below formula, optionally followed by further synthetic manipulation, as described herein:

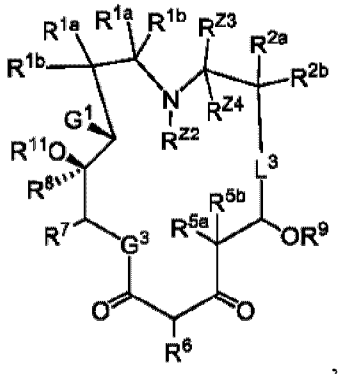
Date Reçue/Date Received 2020-06-25

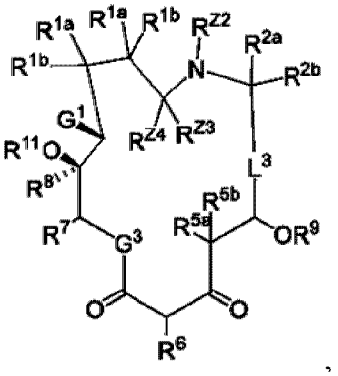
[7] an amine of formula:



wherein L^1 and L^2 are each independently a bond and z1 and z2 are each independently 1 or 2 to provide a ring system of formula:

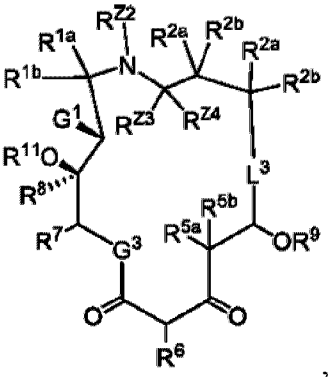


16-membered ring system

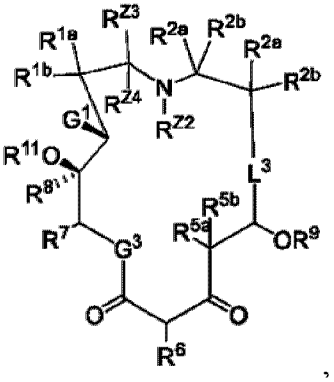


16-membered ring system

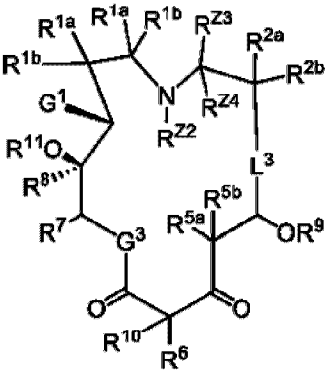
Date Reçue/Date Received 2020-06-25



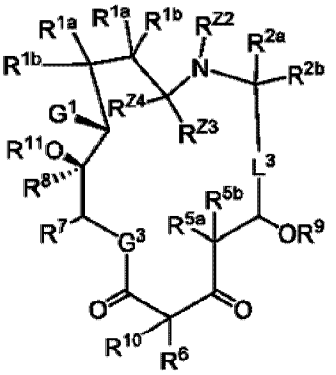
16-membered ring system



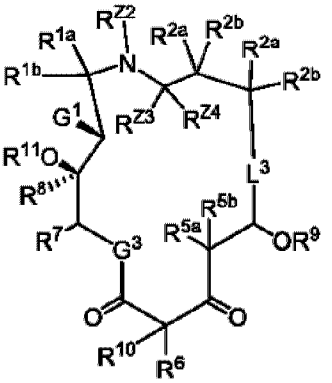
16-membered ring system



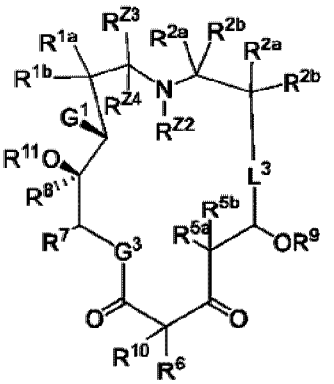
16-membered ring system



16-membered ring system



16-membered ring system



16-membered ring system

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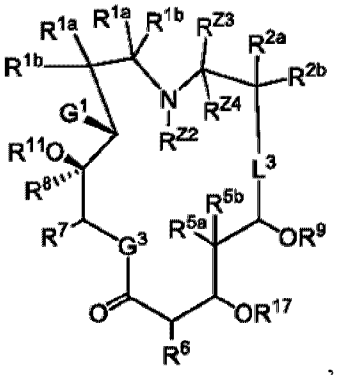
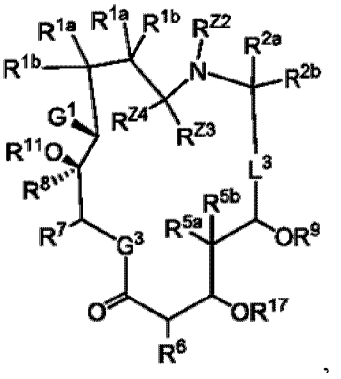
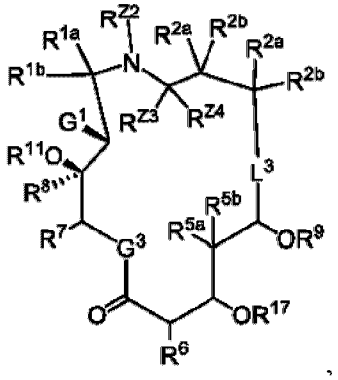


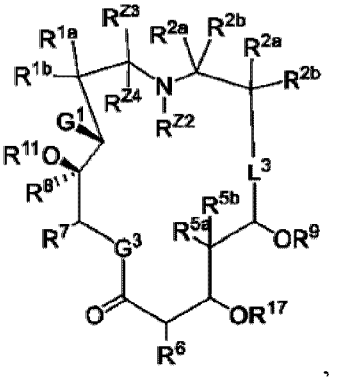
16-membered ring system



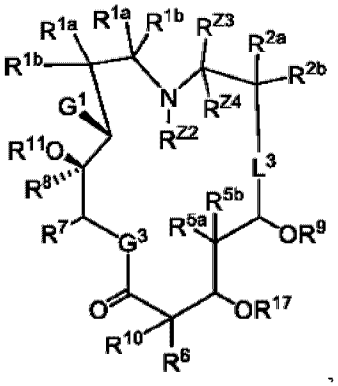
16-membered ring system



16-membered ring system



16-membered ring system



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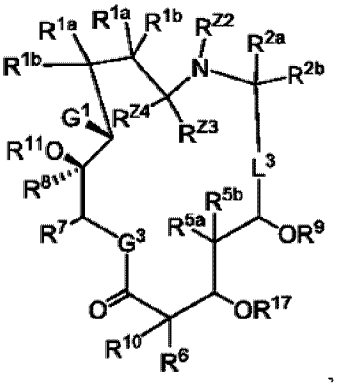

16-membered ring system

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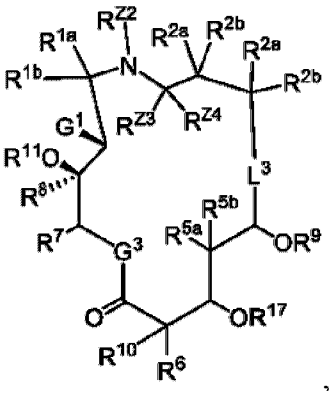

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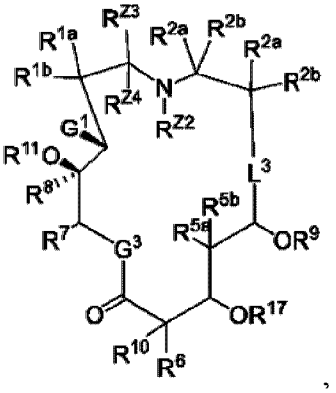

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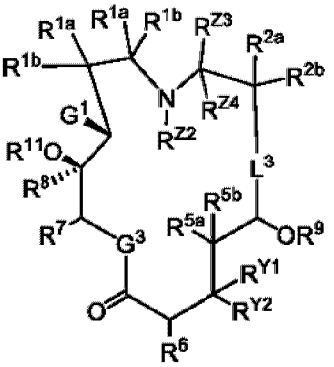

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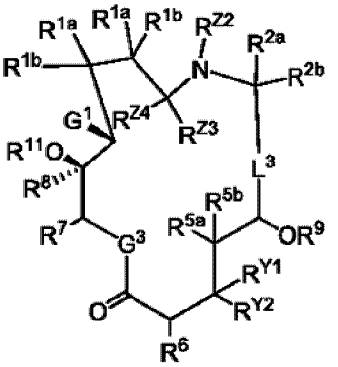
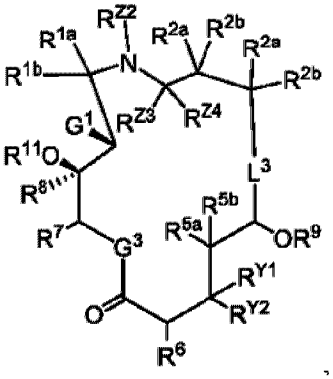
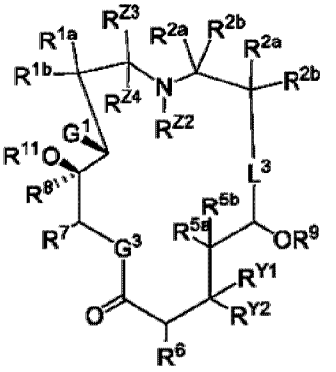


16-membered ring system

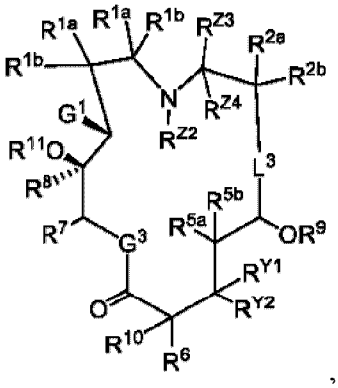


16-membered ring system

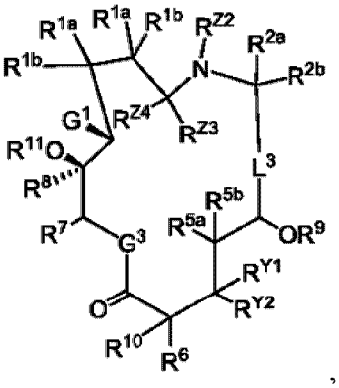


16-membered ring system

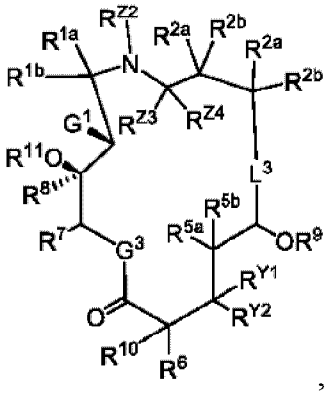
Date Reçue/Date Received 2020-06-25



16-membered ring system

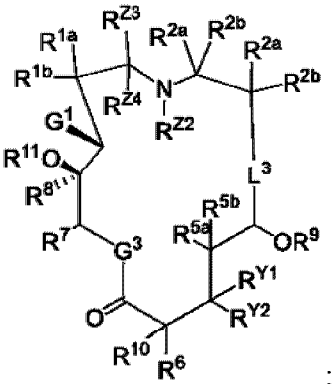


16-membered ring system



, or

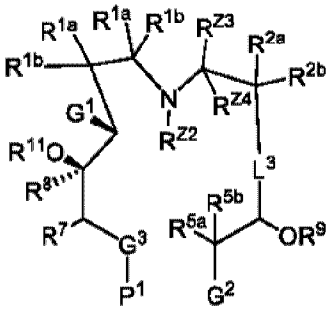
16-membered ring system



;

16-membered ring system

wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



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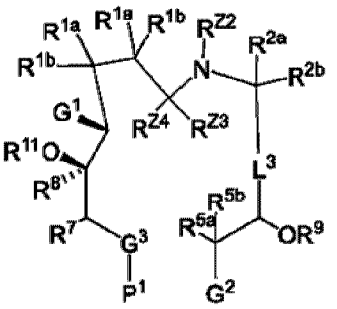

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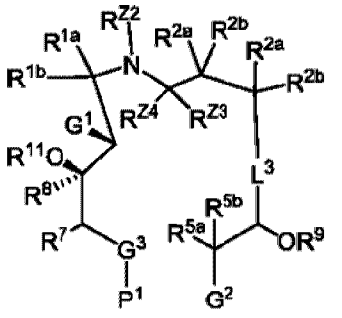
Date Reçue/Date Received 2020-06-25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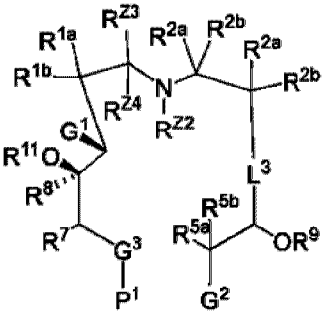
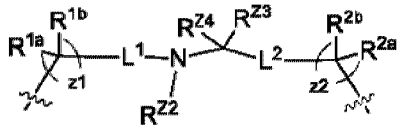


[8] an amine of Formula: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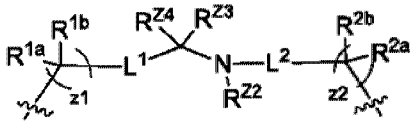
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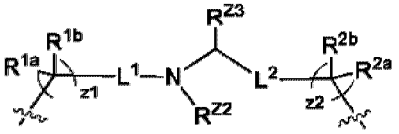
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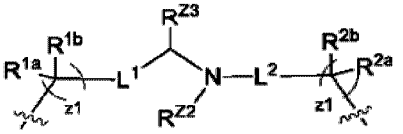
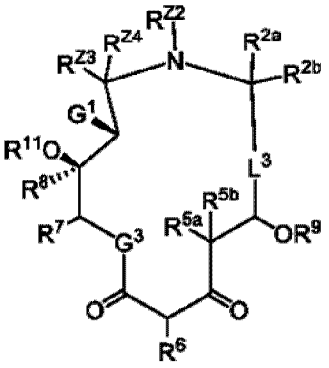
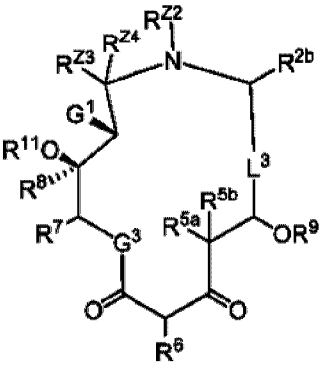
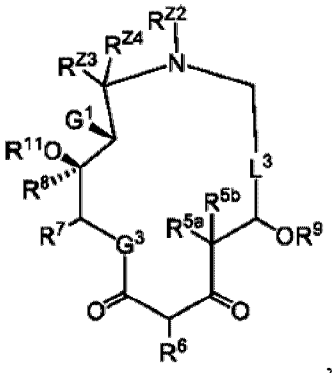


wherein L^1 and L^2 are each independently a bond or $-CH_2-$; $z1$ and $z2$ are each independently 0, 1, or 2, *e.g.,* to provide a ring system of any one of formula:


,
14-membered ring system


,
14-membered ring system

Date Reçue/Date Received 2020-06-25



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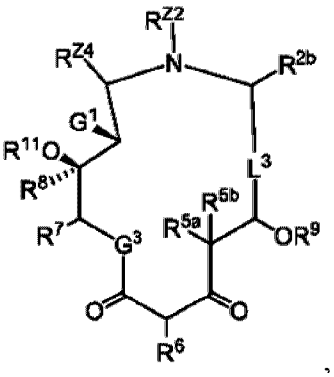

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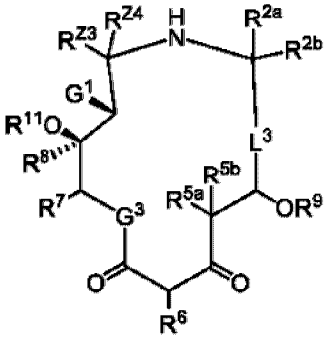

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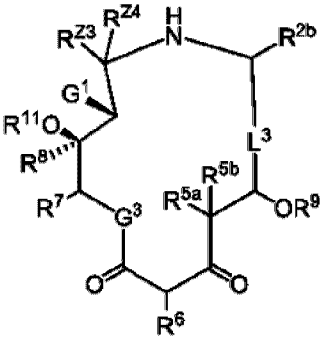

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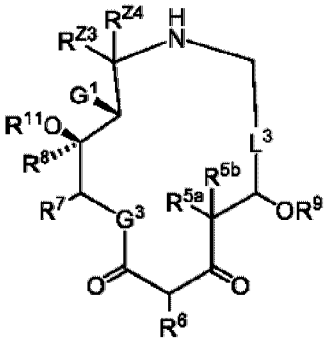

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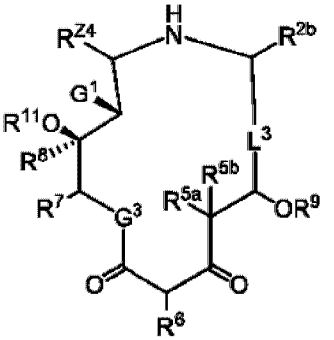

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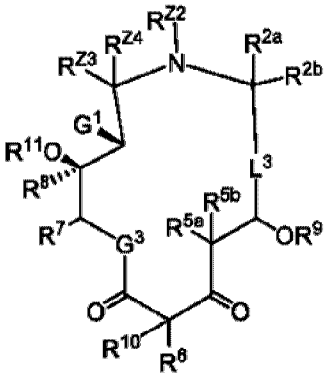

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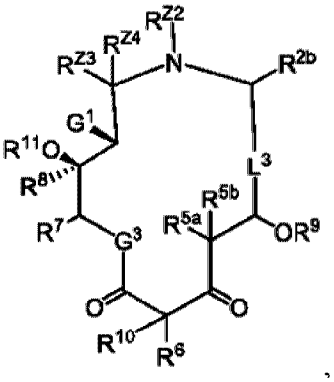

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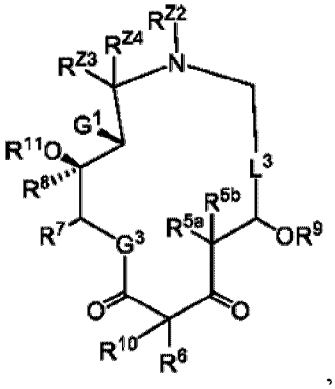

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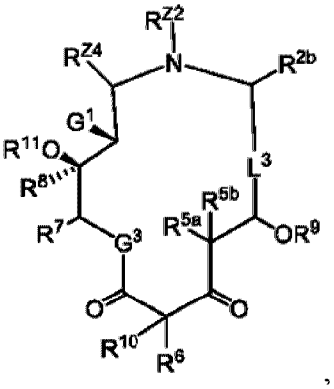

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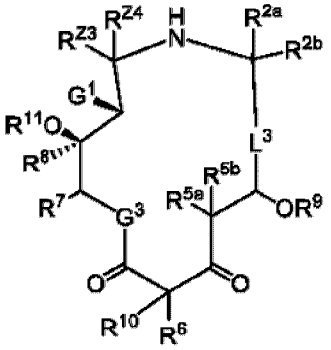

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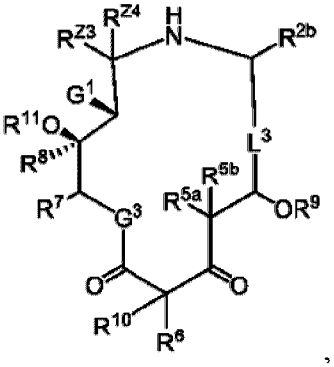

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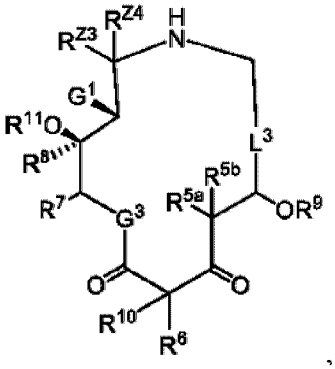

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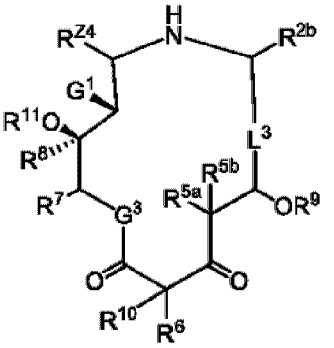

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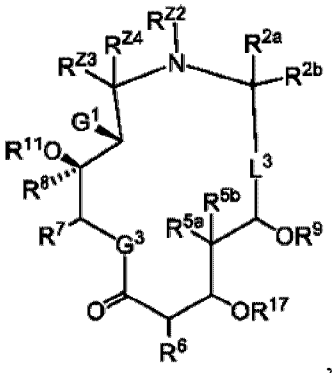

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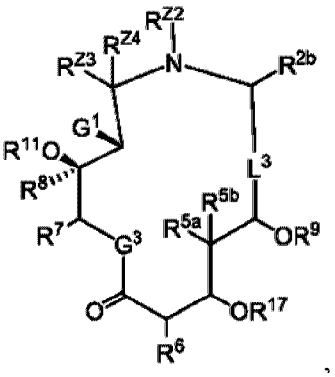

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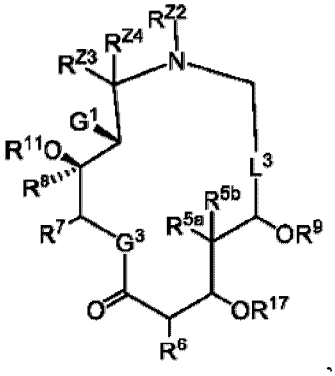

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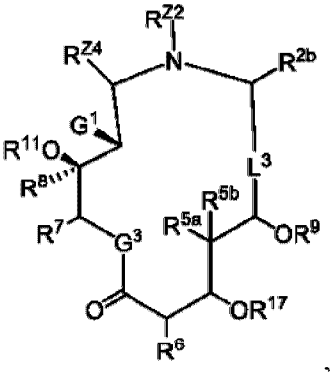

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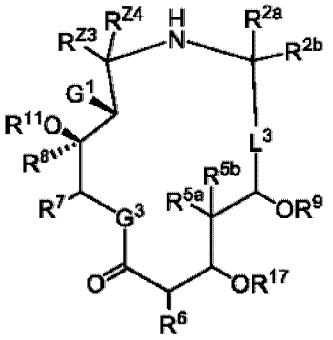

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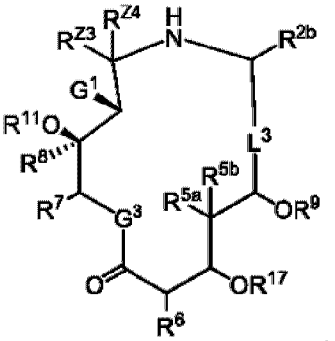

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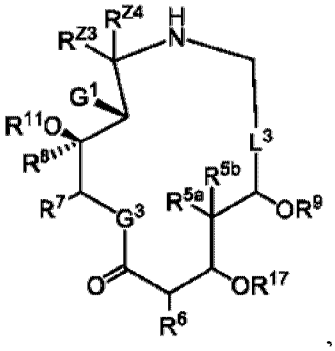

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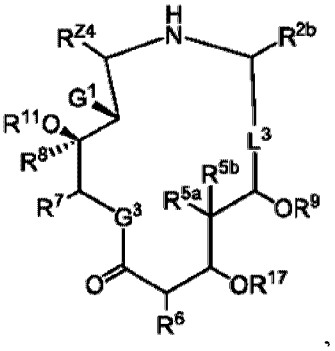

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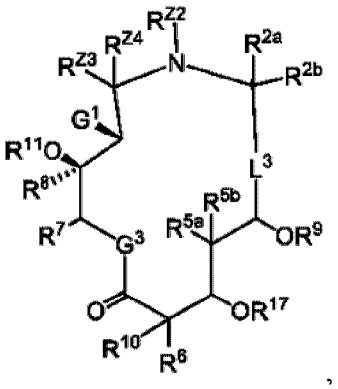

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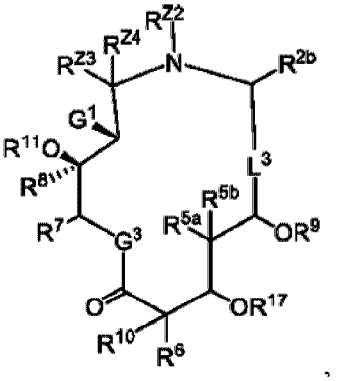

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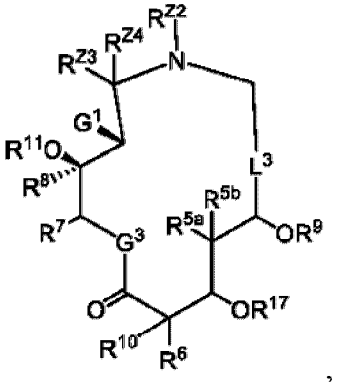

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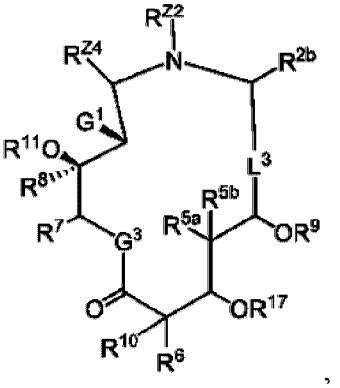

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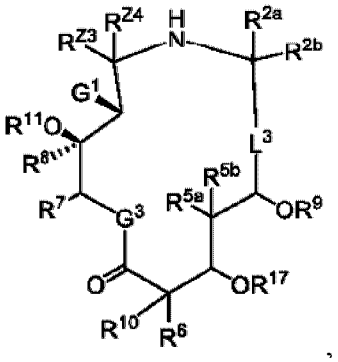

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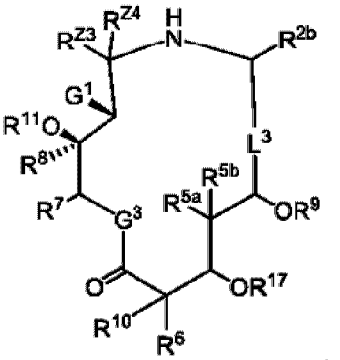

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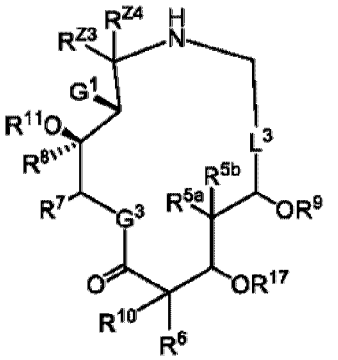

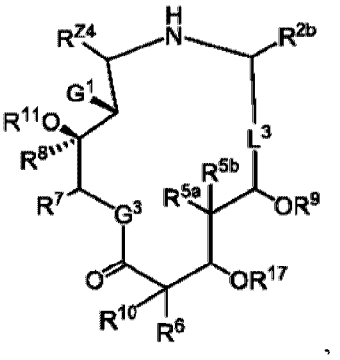

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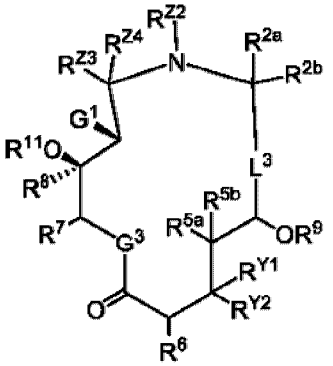

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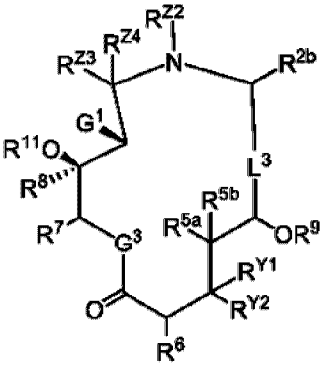

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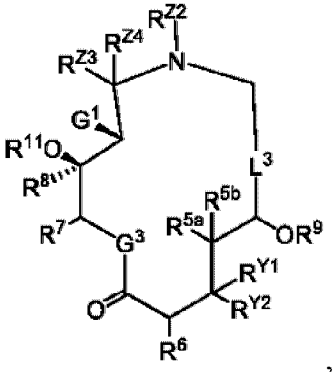

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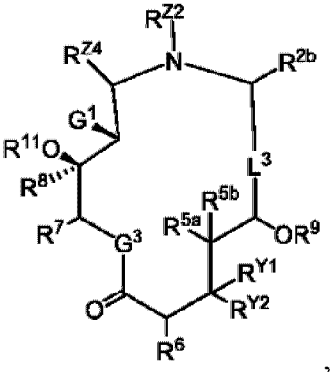

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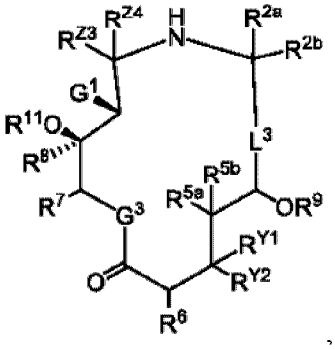

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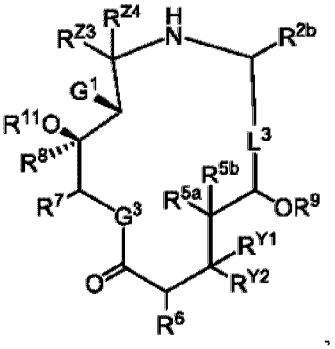

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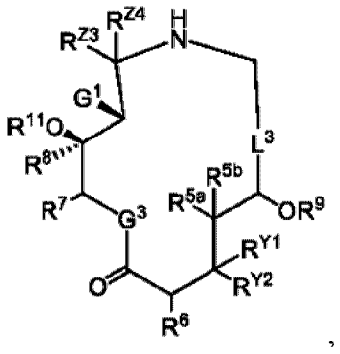

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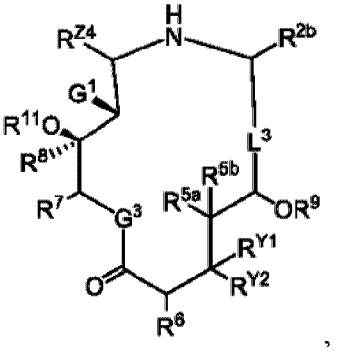

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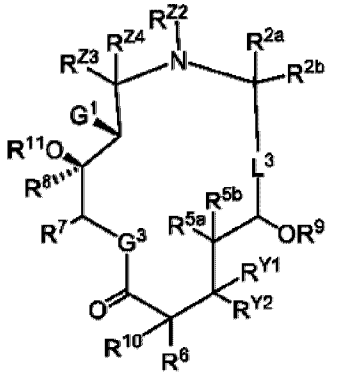

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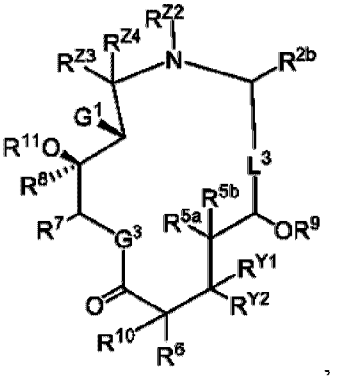

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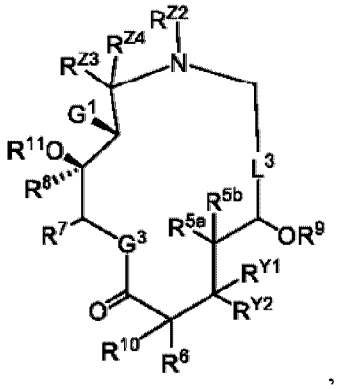

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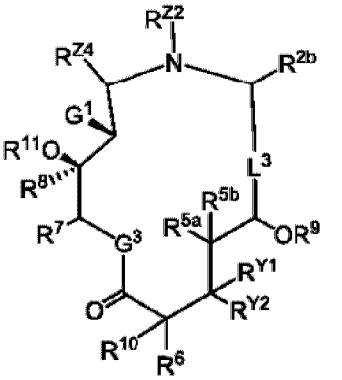

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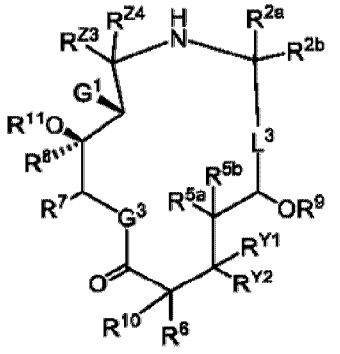

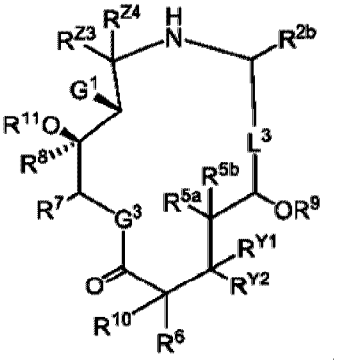

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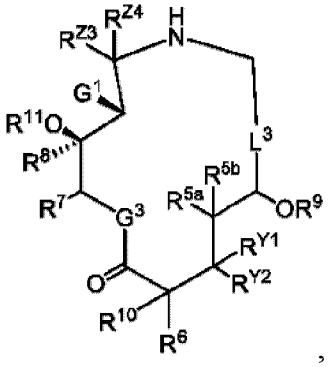

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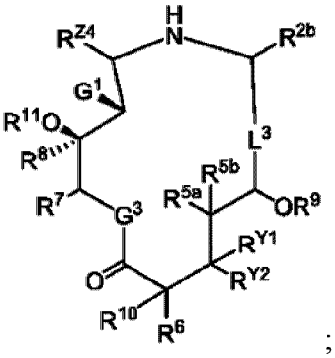
14-membered ring system



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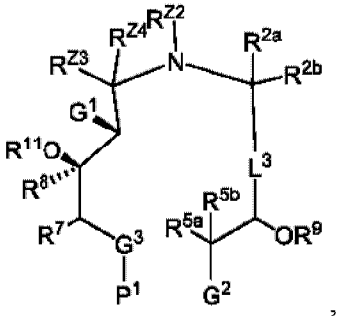
14-membered ring system

14-membered ring system

wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



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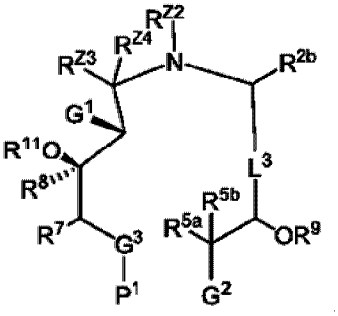

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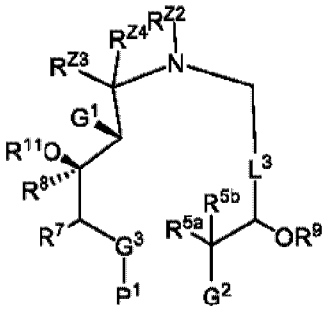

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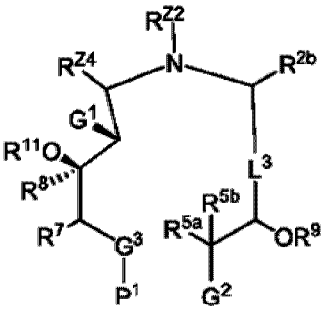

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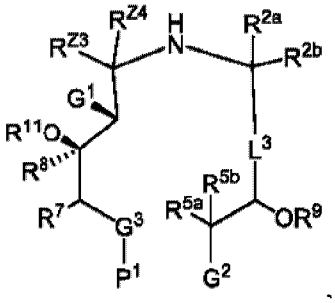

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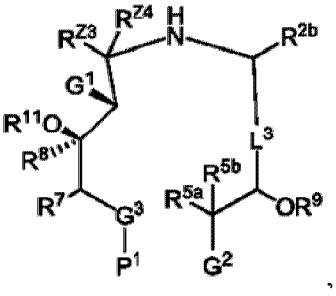

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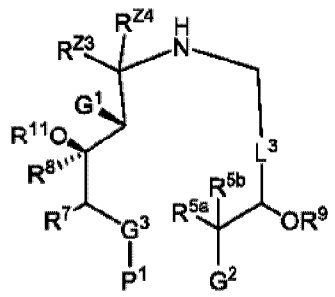
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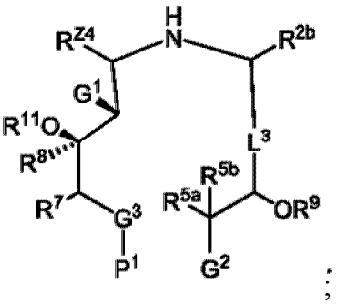
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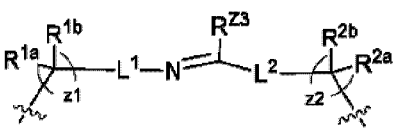
[9] an imine of formula: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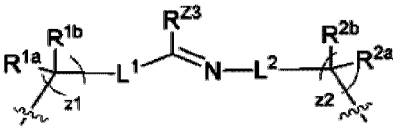
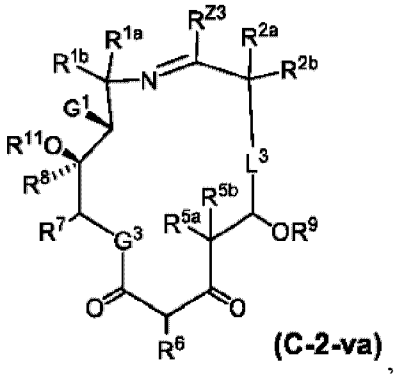
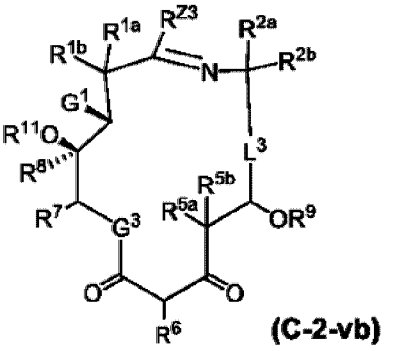


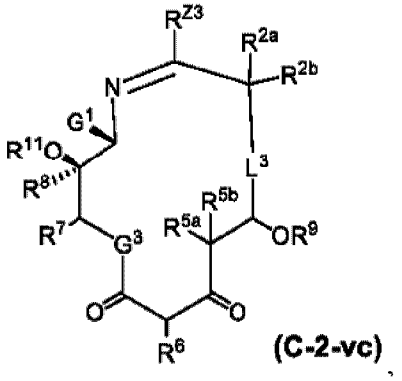
wherein L^1 and L^2 are each independently a bond or $–CH_2–$; z1 and z2 are each independently 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:


(C-2-va),

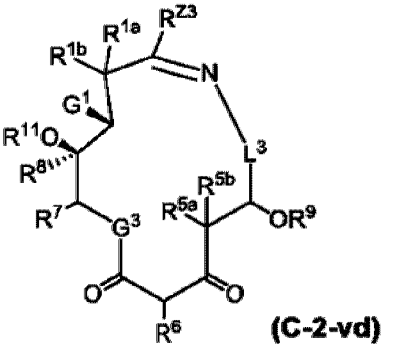
15-membered ring system


(C-2-vb),

15-membered ring system

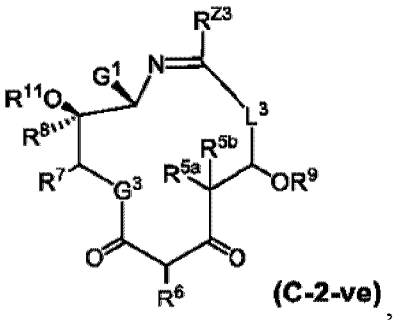

(C-2-vc),

14-membered ring system


(C-2-vd),

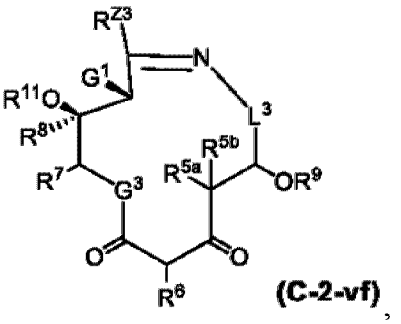
14-membered ring system

Date Reçue/Date Received 2020-06-25



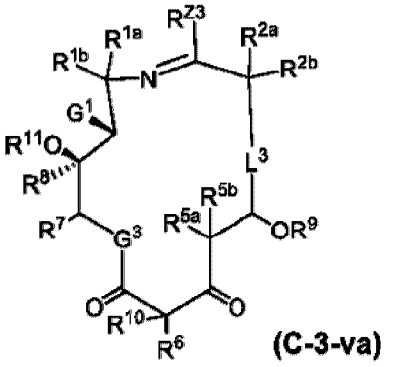
(C-2-ve),

13-membered ring system



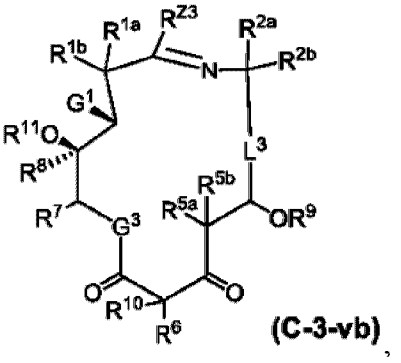
(C-2-vf),

13-membered ring system



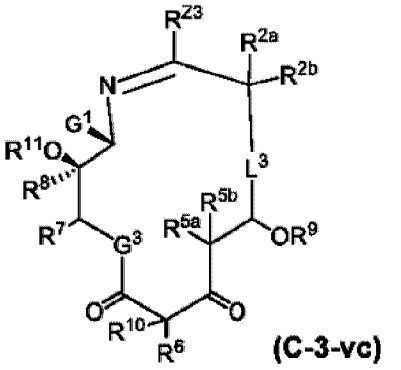
(C-3-va),

15-membered ring system



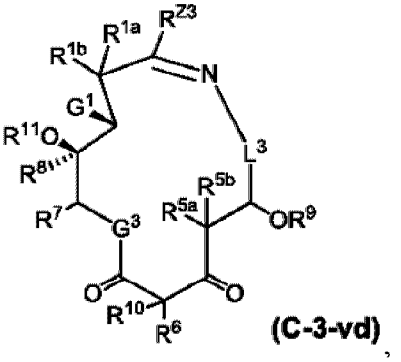
(C-3-vb),

15-membered ring system



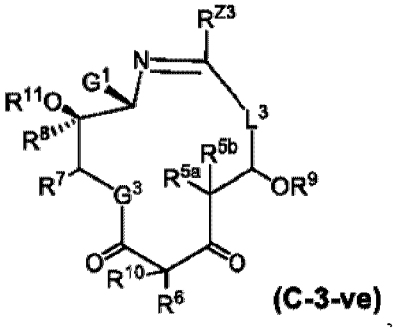
(C-3-vc),

14-membered ring system



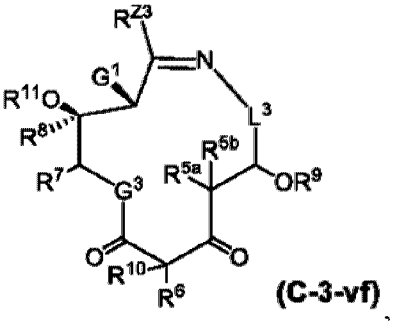
(C-3-vd),

14-membered ring system



(C-3-ve),

13-membered ring system



(C-3-vf),

13-membered ring system

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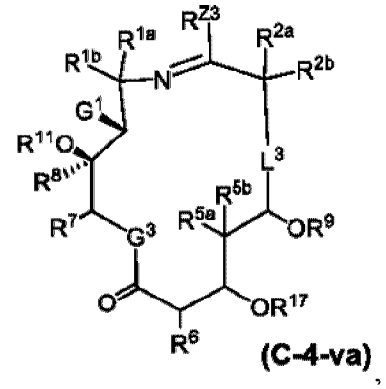
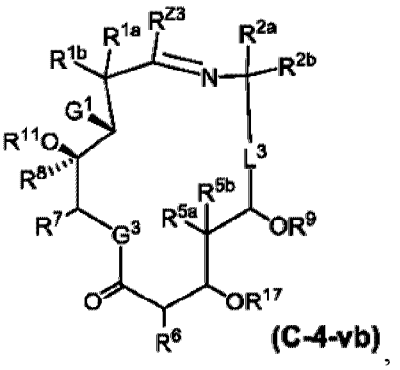
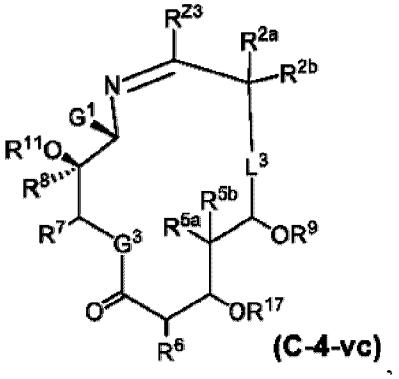


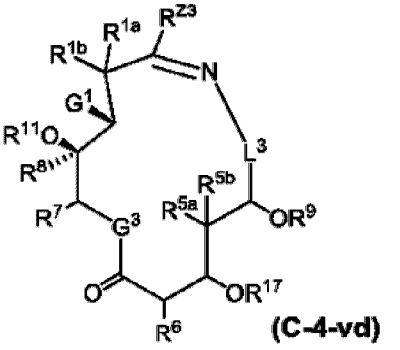
15-membered ring system



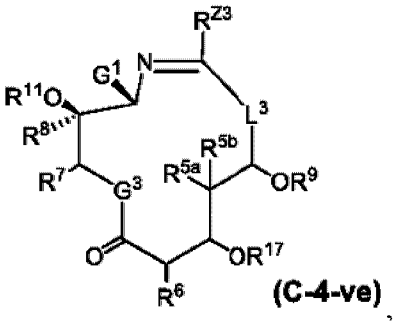
15-membered ring system



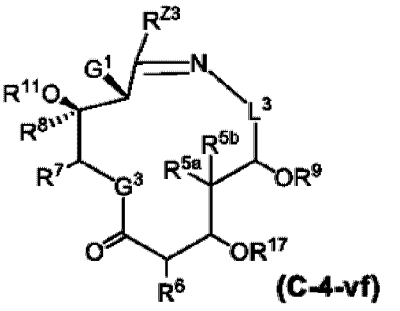
14-membered ring system



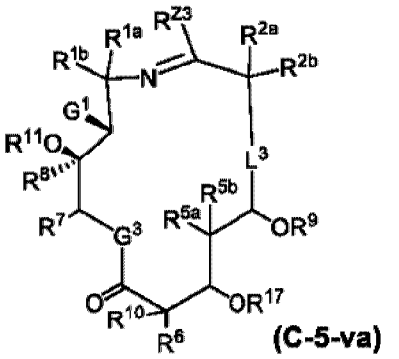
14-membered ring system



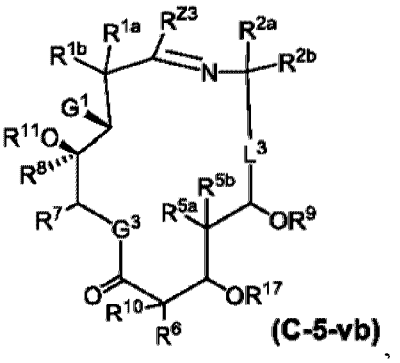
13-membered ring system



13-membered ring system



15-membered ring system



15-membered ring system

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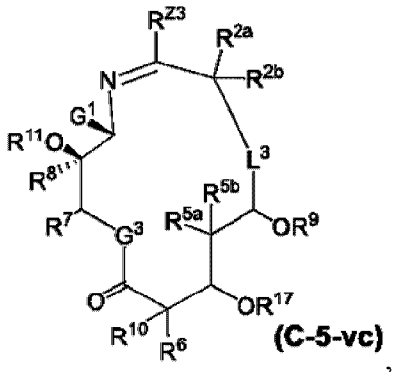
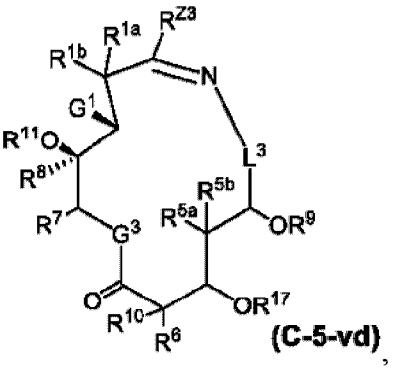
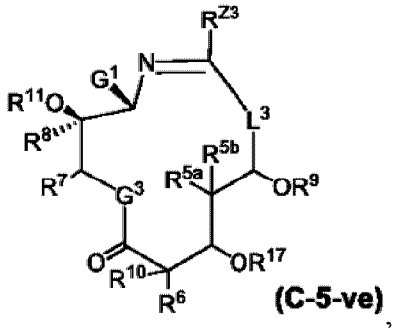


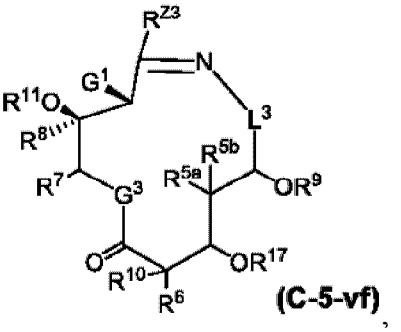
14-membered ring system



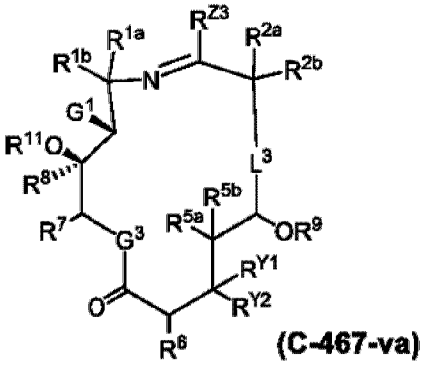
14-membered ring system



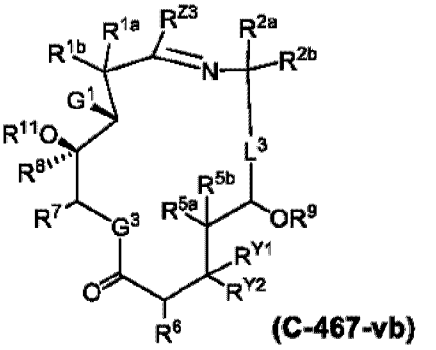
13-membered ring system



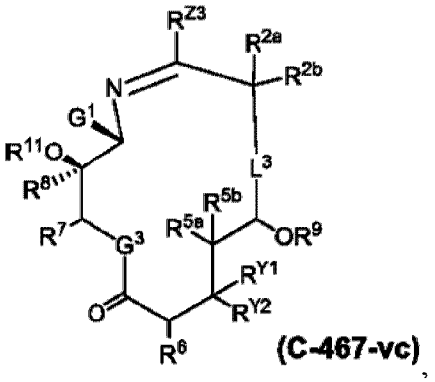
13-membered ring system



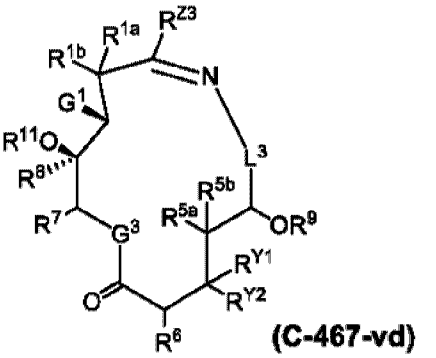
15-membered ring system



15-membered ring system



14-membered ring system



14-membered ring system

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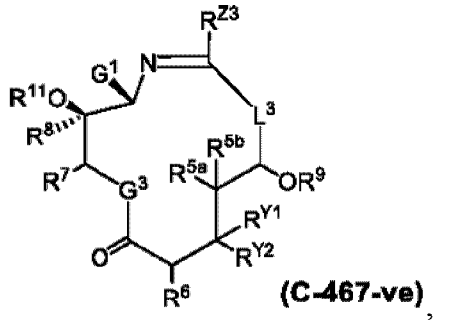
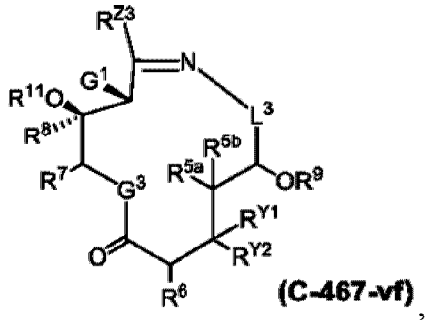
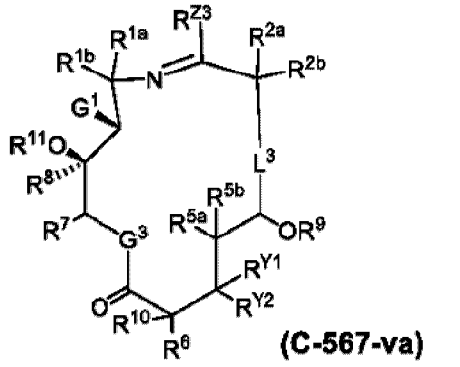


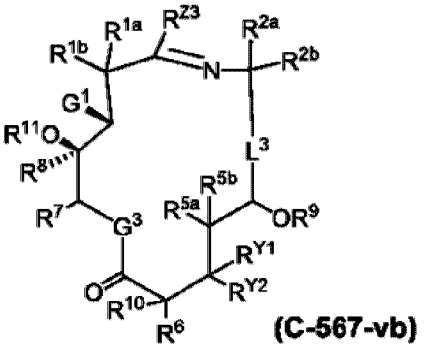
13-membered ring system



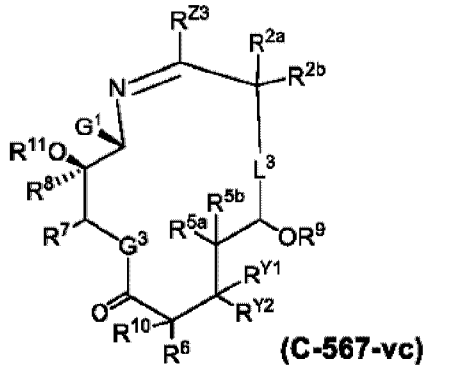
13-membered ring system



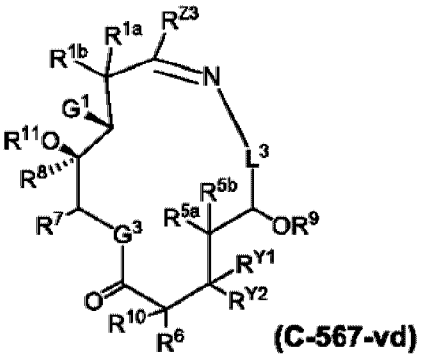
15-membered ring system



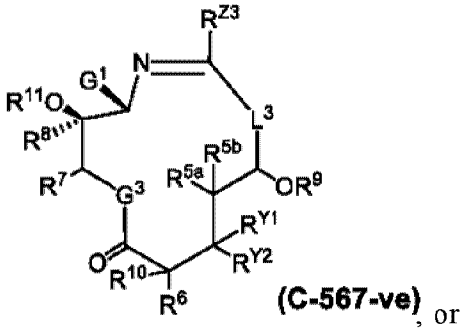
15-membered ring system



14-membered ring system

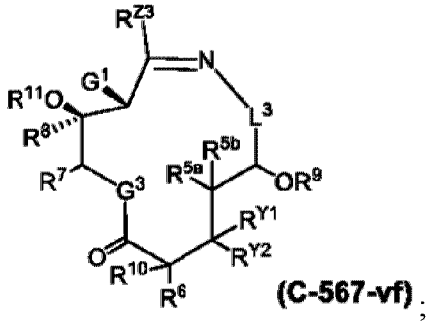


14-membered ring system



, or

13-membered ring system

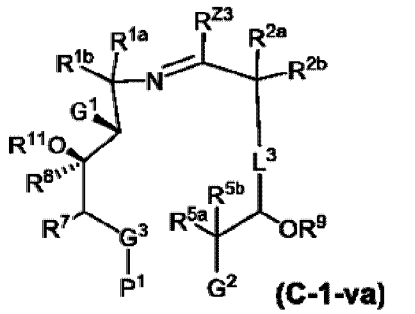


;

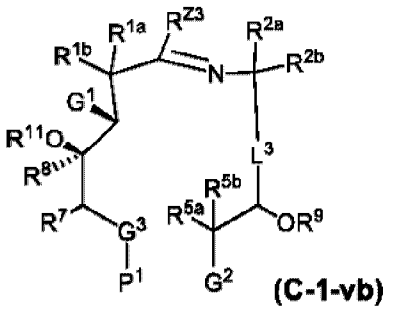
13-membered ring system

Date Reçue/Date Received 2020-06-25

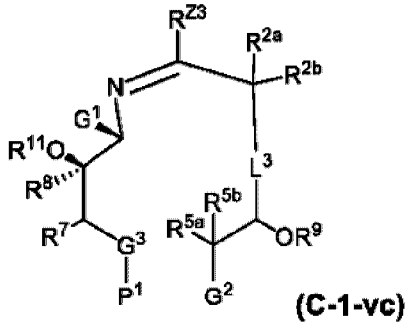
wherein in certain embodiments the macrolide is prepared from macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



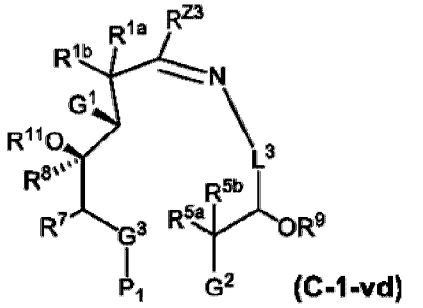
(C-1-va),



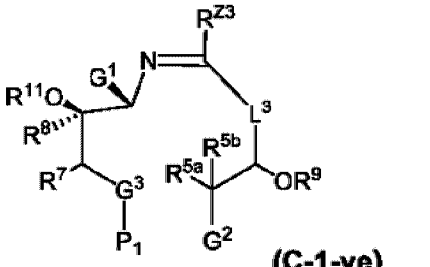
(C-1-vb),



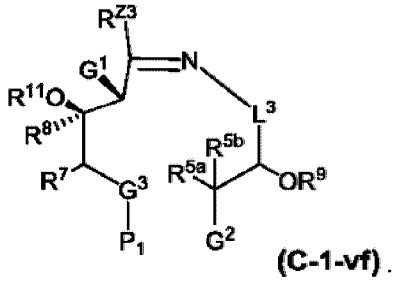
(C-1-vc),



(C-1-vd),

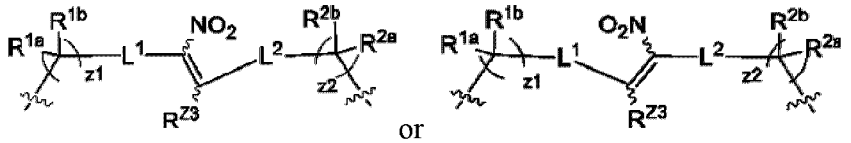


(C-1-ve), or



(C-1-vf);

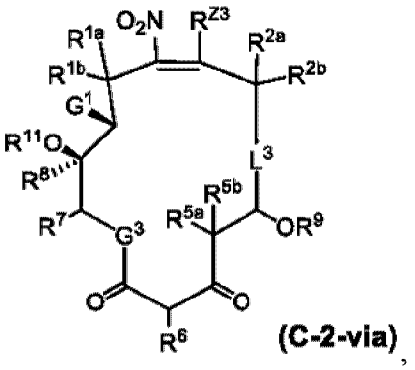
[10] an nitro alkene of formula:



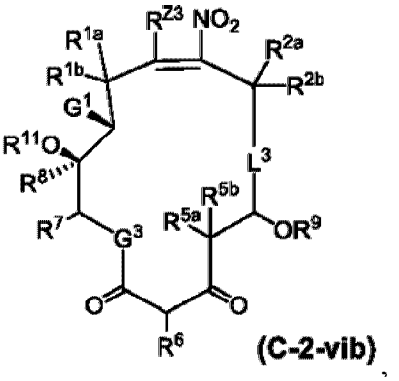
or

wherein L^1 and L^2 are each independently a bond or $–CH_2–$; z1 and z2 are 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:

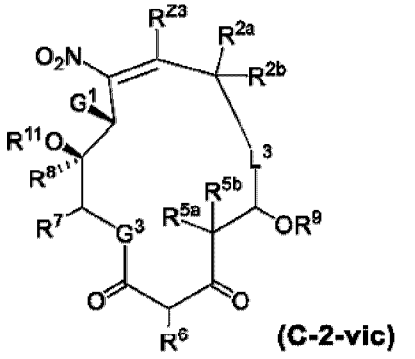
Date Reçue/Date Received 2020-06-25



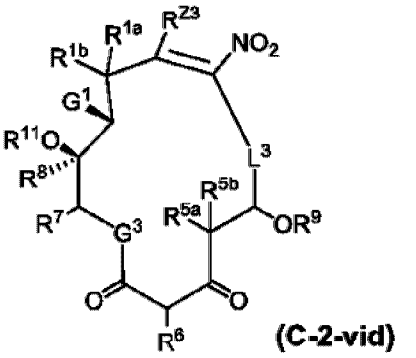
15-membered ring system



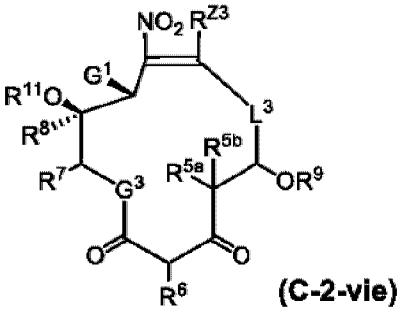
15-membered ring system



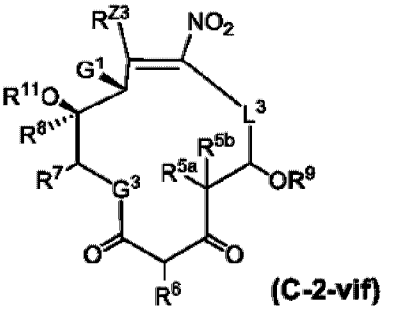
14-membered ring system



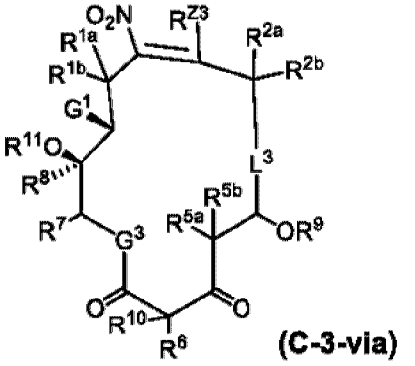
14-membered ring system



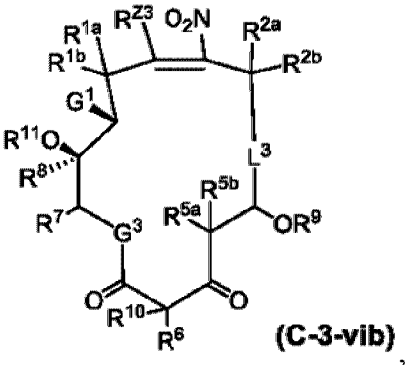
13-membered ring system



13-membered ring system

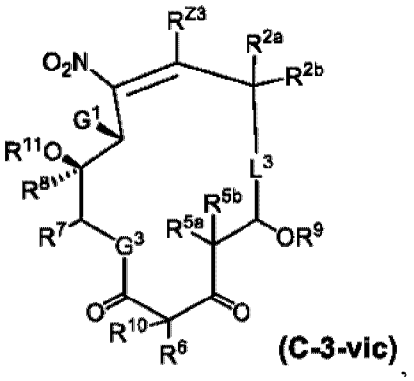


15-membered ring system

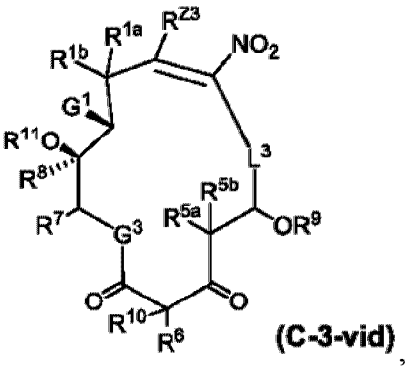


15-membered ring system

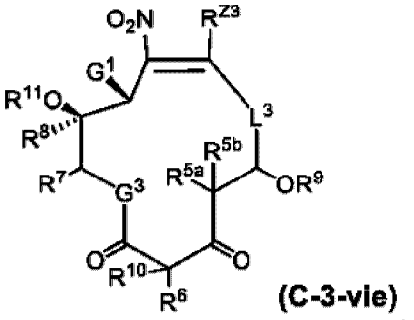
Date Reçue/Date Received 2020-06-25



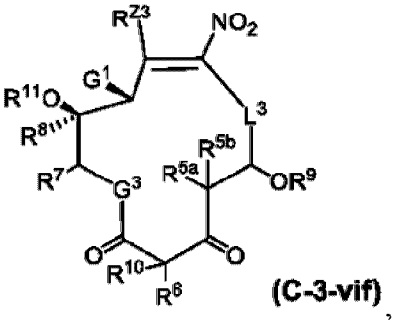
14-membered ring system



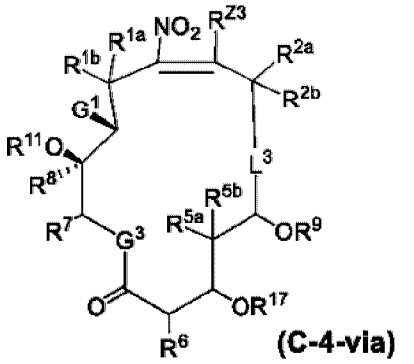
14-membered ring system



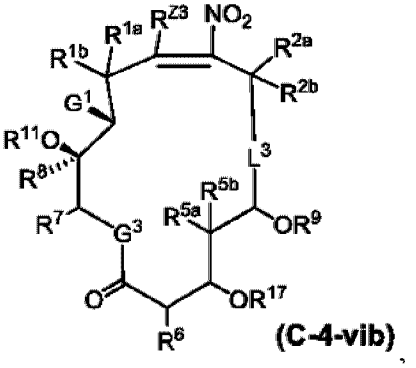
13-membered ring system



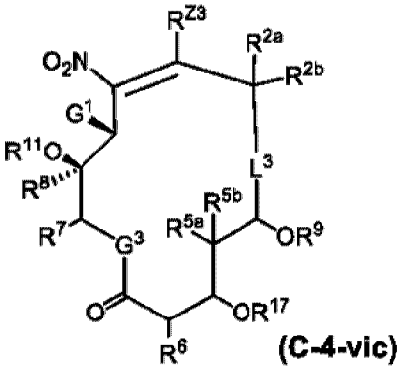
13-membered ring system



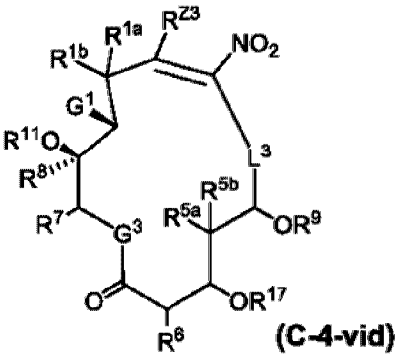
15-membered ring system



15-membered ring system

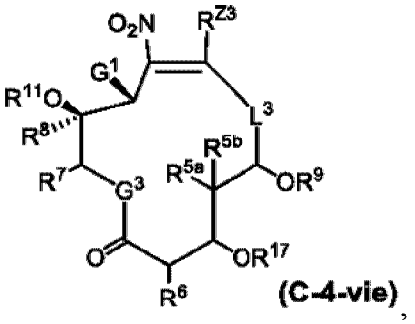


14-membered ring system

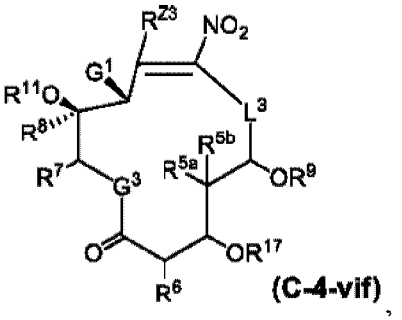


14-membered ring system

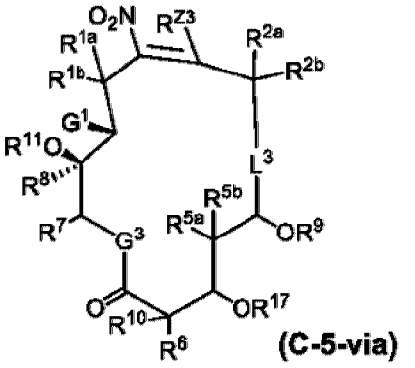
Date Reçue/Date Received 2020-06-25



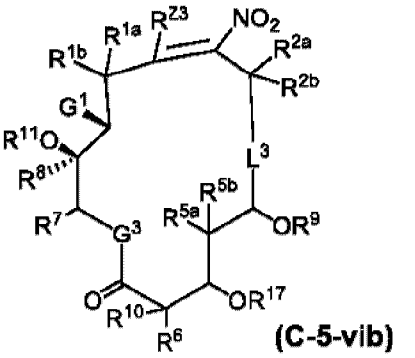
13-membered ring system



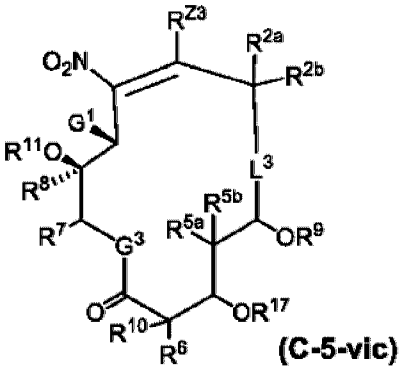
13-membered ring system



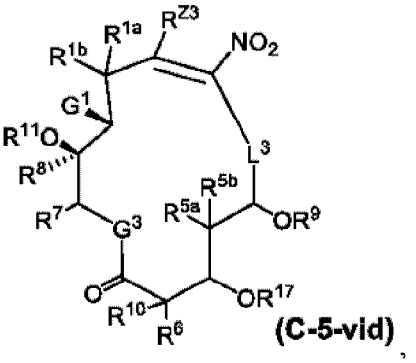
15-membered ring system



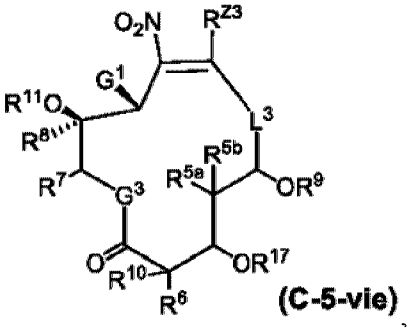
15-membered ring system



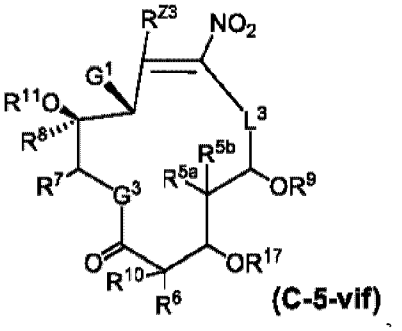
14-membered ring system



14-membered ring system

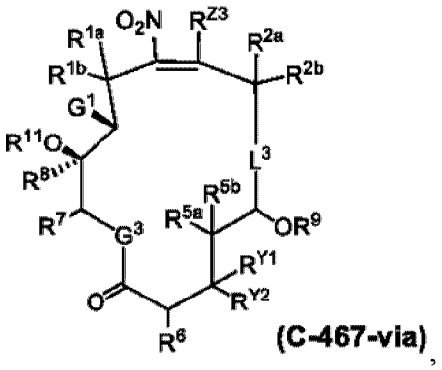


13-membered ring system



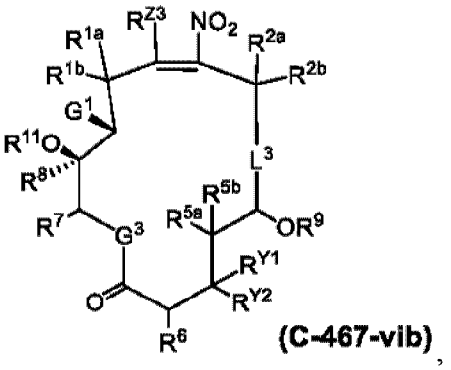
13-membered ring system

Date Reçue/Date Received 2020-06-25



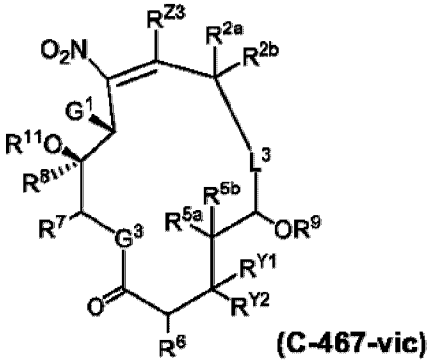
(C-467-via),

15-membered ring system



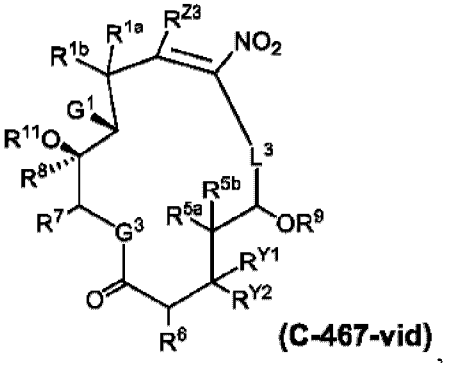
(C-467-vib),

15-membered ring system



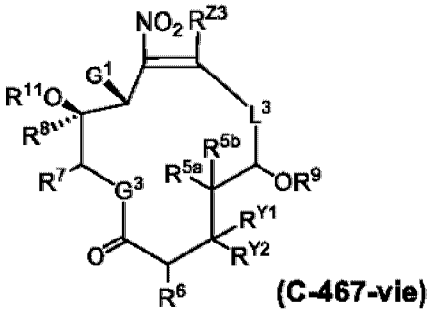
(C-467-vic),

14-membered ring system



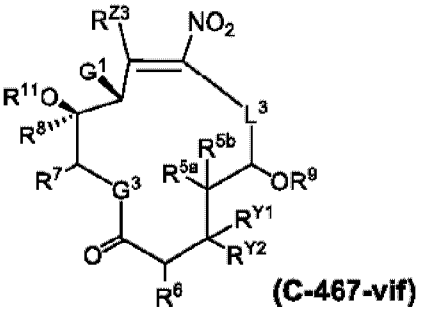
(C-467-vid),

14-membered ring system



(C-467-vie),

13-membered ring system



(C-467-vif),

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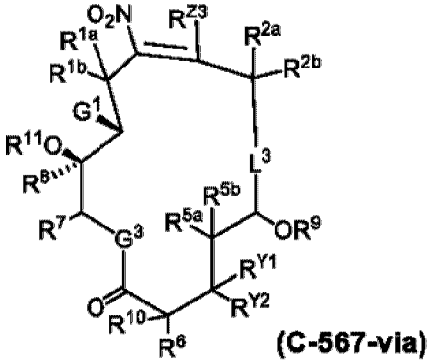
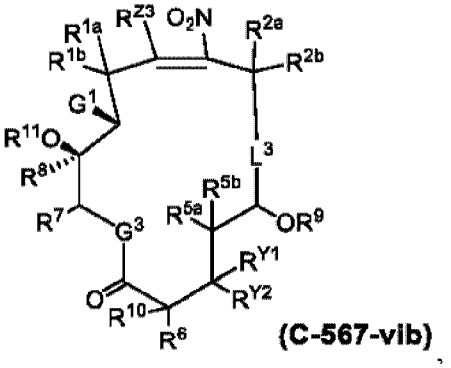


(C-567-via),

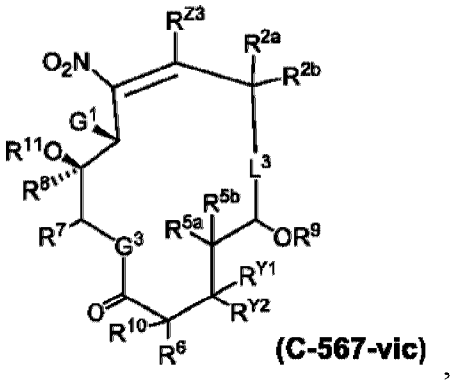
15-membered ring system



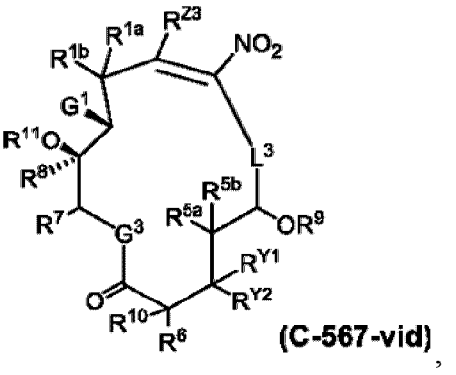
(C-567-vib),

15-membered ring system

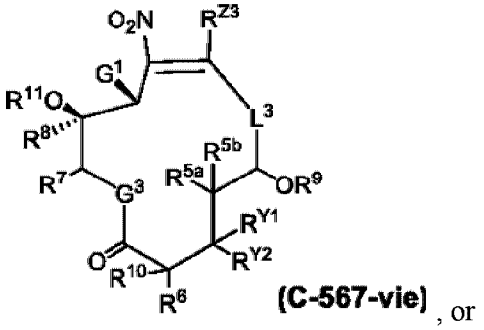
Date Reçue/Date Received 2020-06-25



14-membered ring system

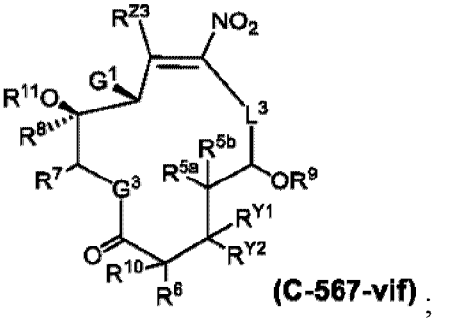


14-membered ring system



, or

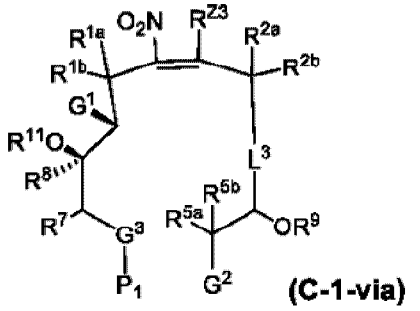
13-membered ring system

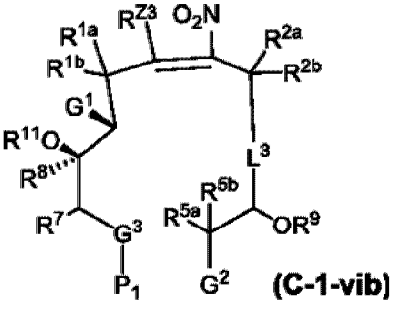


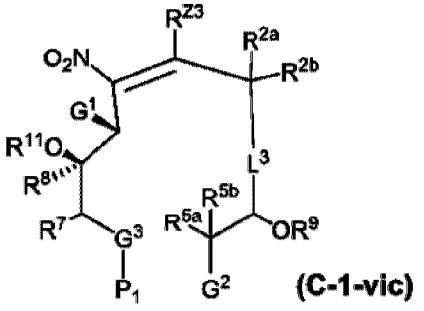
;

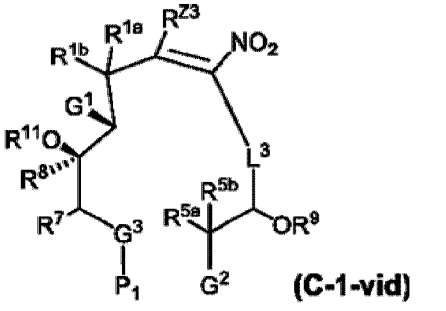
13-membered ring system

wherein in certain embodiments the macrolide is prepared from macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor of one of the formulae, optionally followed by further synthetic manipulation, as described herein:









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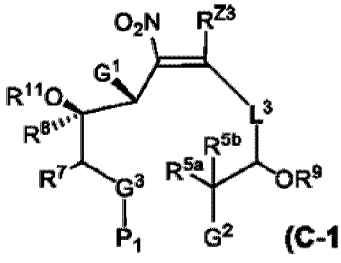
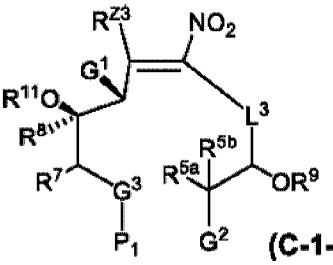
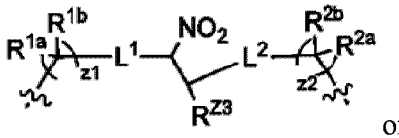


(C-1-vie), or

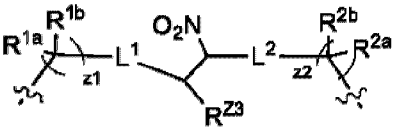


(C-1-vif);

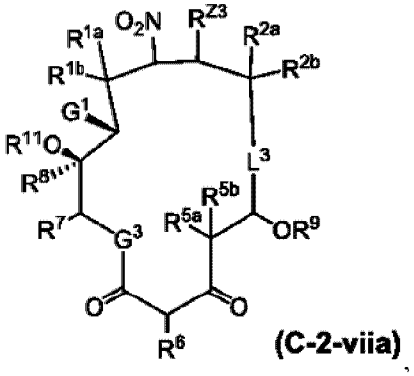
[11] an nitro compound of formula:



or

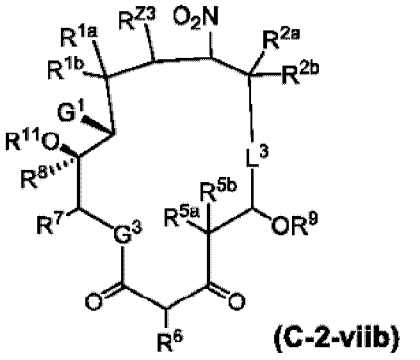


wherein L^1 and L^2 are each independently a bond or $-CH_2-$; z1 and z2 are 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:



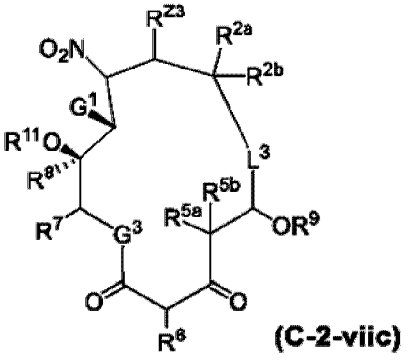
(C-2-viia),

15-membered ring system



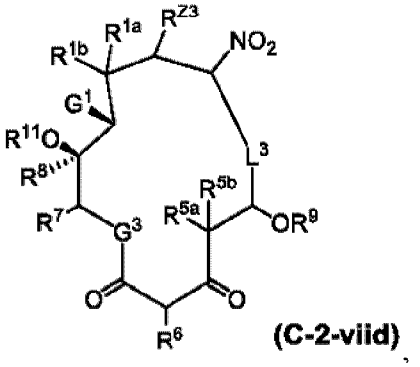
(C-2-viib),

15-membered ring system



(C-2-viic),

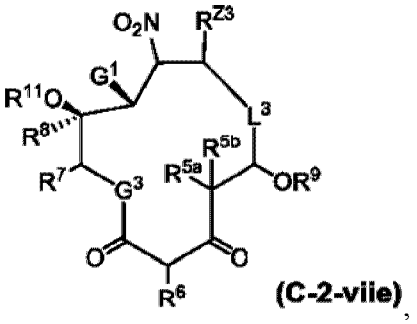
14-membered ring system



(C-2-viid),

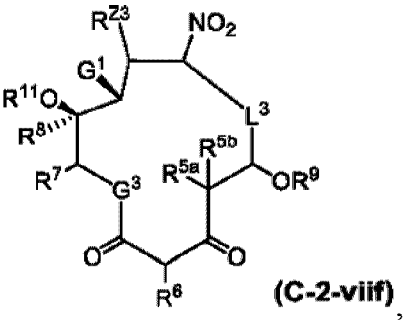
14-membered ring system

Date Reçue/Date Received 2020-06-25



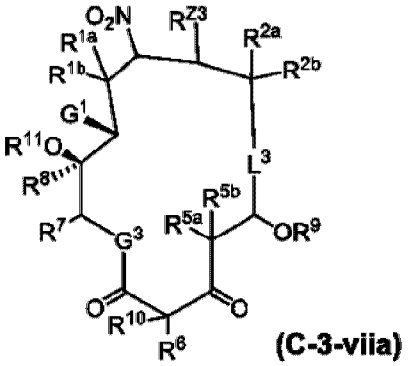
(C-2-viie),

13-membered ring system



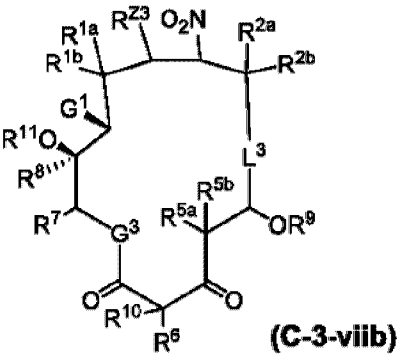
(C-2-viif),

13-membered ring system



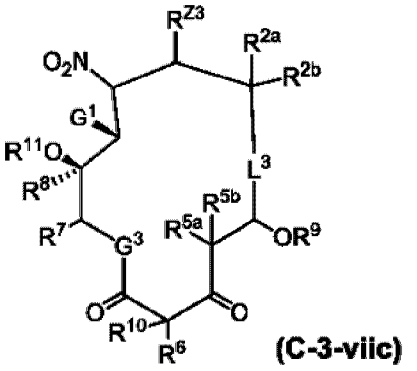
(C-3-viia),

15-membered ring system



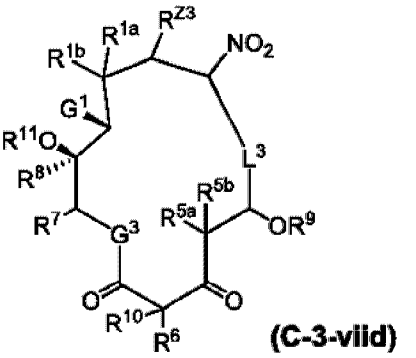
(C-3-viib),

15-membered ring system



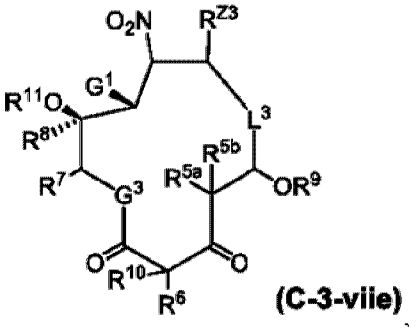
(C-3-viic),

14-membered ring system



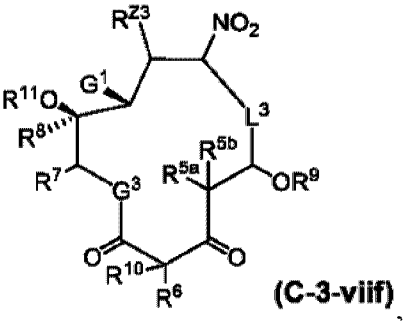
(C-3-viid),

14-membered ring system



(C-3-viie),

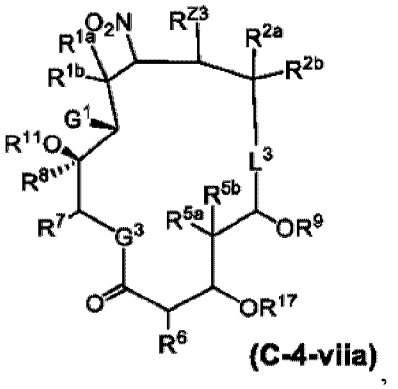
13-membered ring system



(C-3-viif),

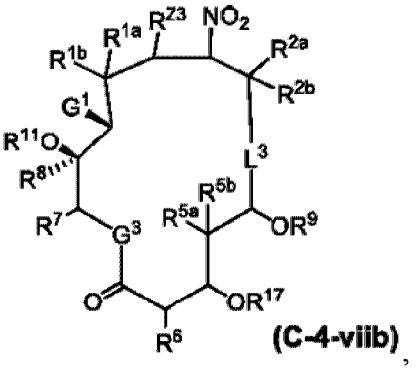
13-membered ring system

Date Reçue/Date Received 2020-06-25



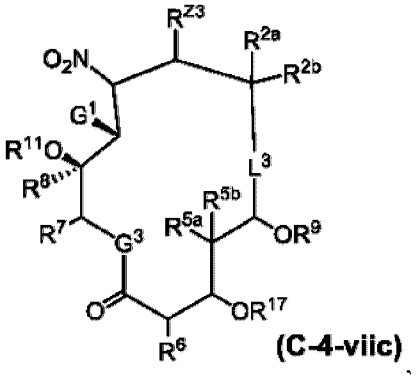
(C-4-viia),

15-membered ring system



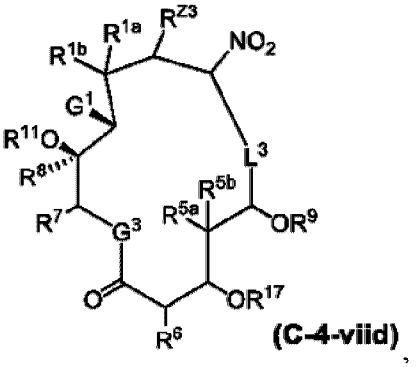
(C-4-viib),

15-membered ring system



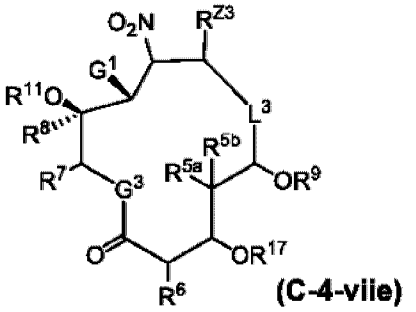
(C-4-viic),

14-membered ring system



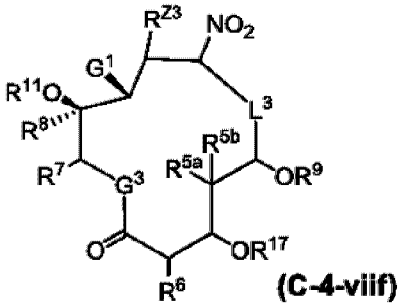
(C-4-viid),

14-membered ring system



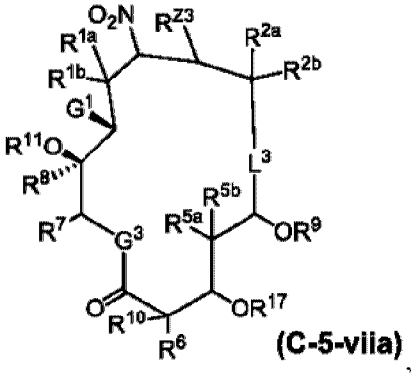
(C-4-viie),

13-membered ring system



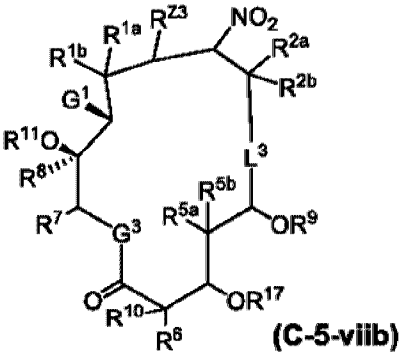
(C-4-viif),

13-membered ring system



(C-5-viia),

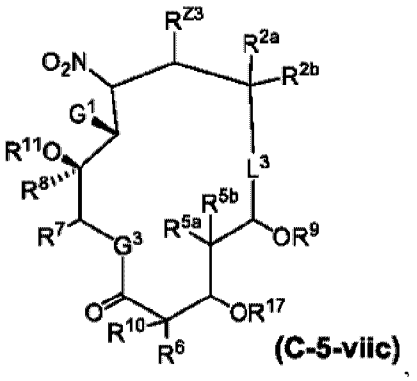
15-membered ring system



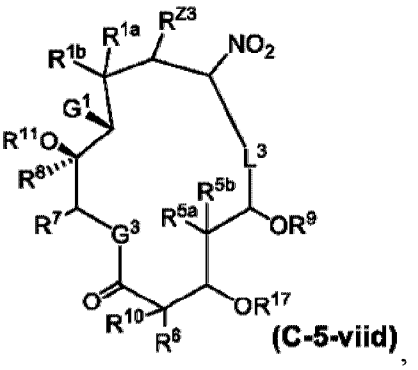
(C-5-viib),

15-membered ring system

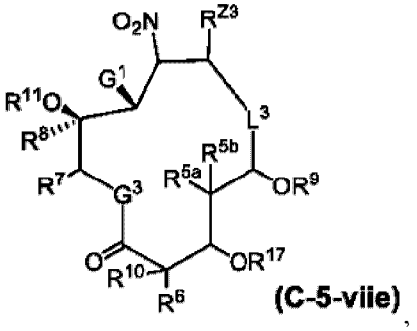
Date Reçue/Date Received 2020-06-25



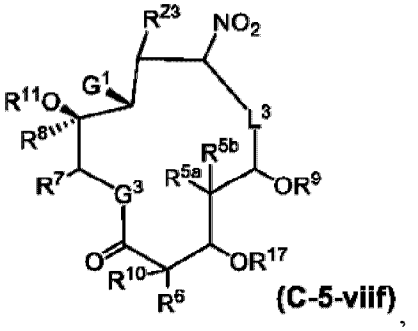
14-membered ring system



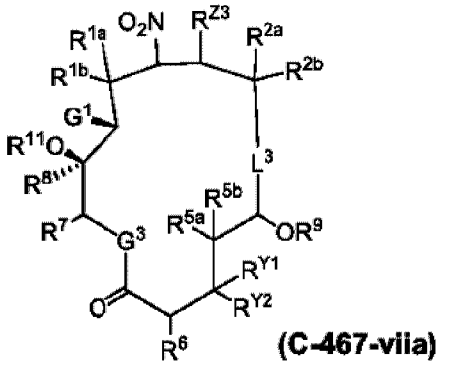
14-membered ring system



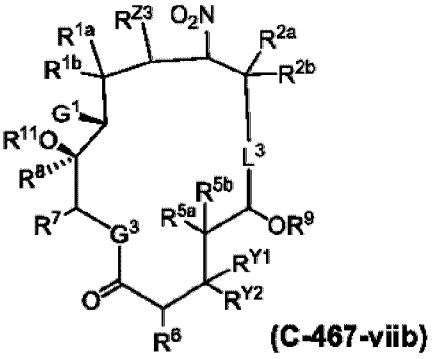
13-membered ring system



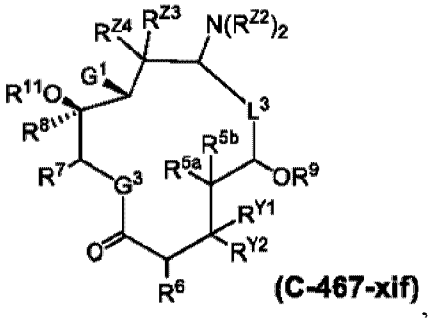
13-membered ring system



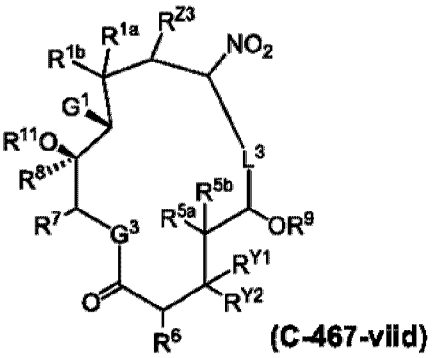
15-membered ring system



15-membered ring system

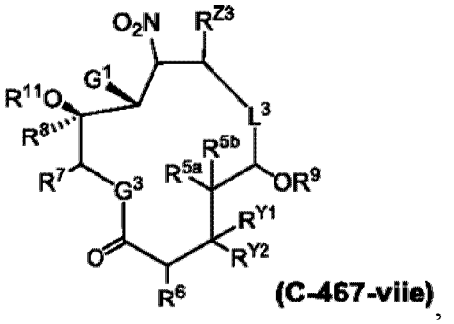


14-membered ring system

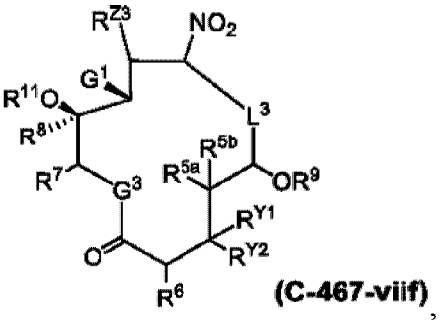


14-membered ring system

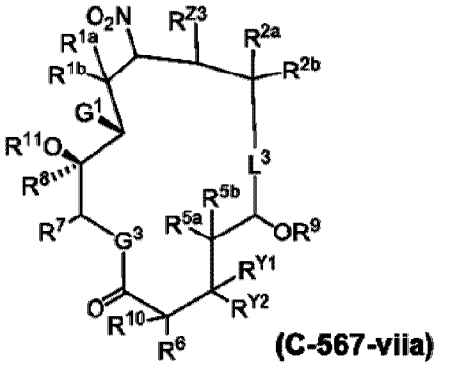
Date Reçue/Date Received 2020-06-25



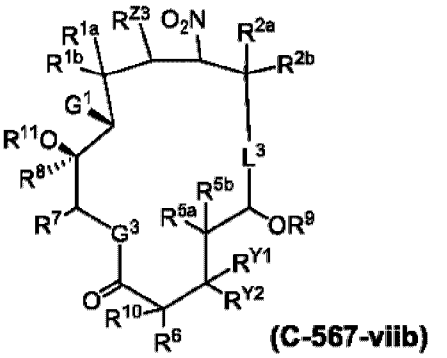
13-membered ring system



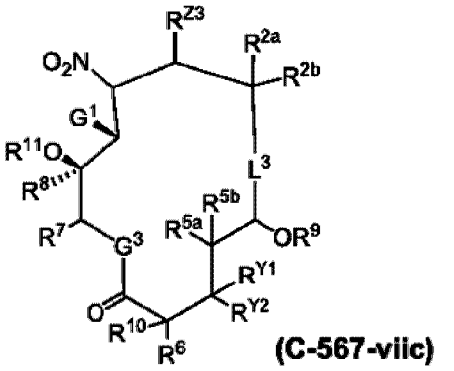
13-membered ring system



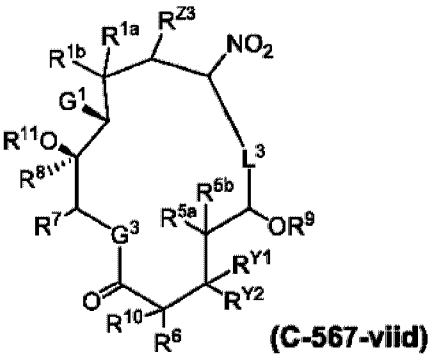
15-membered ring system



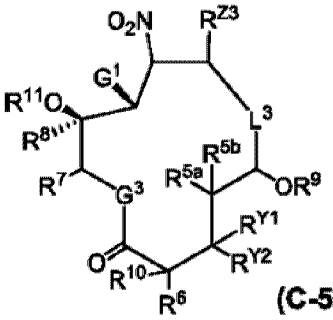
15-membered ring system



14-membered ring system

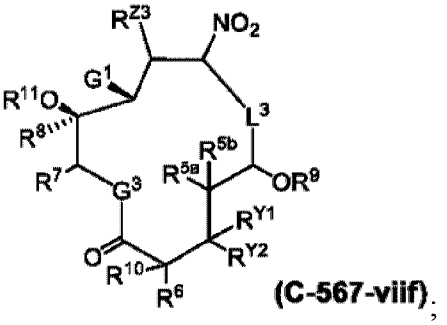


14-membered ring system



, or

13-membered ring system

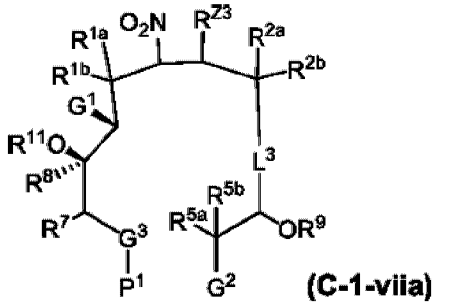


;

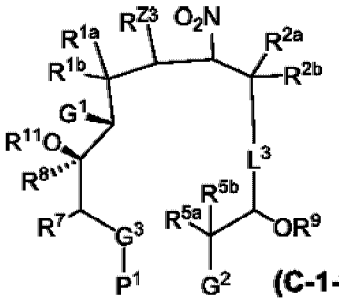
13-membered ring system

Date Reçue/Date Received 2020-06-25

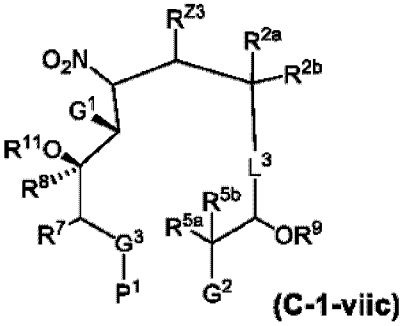
wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



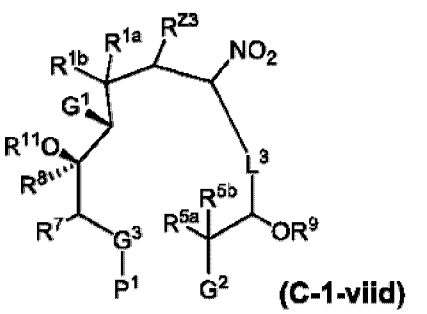
(C-1-viia),



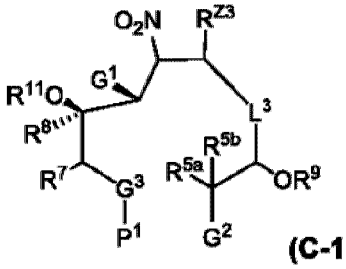
(C-1-viib),



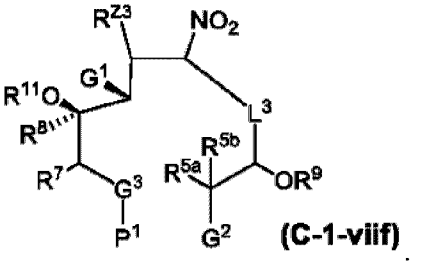
(C-1-viic),



(C-1-viid),

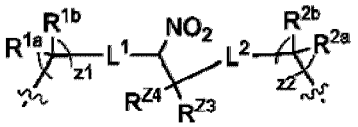


(C-1-viie), or

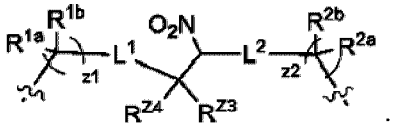


(C-1-viif);

[12] an nitro compound of Formula:



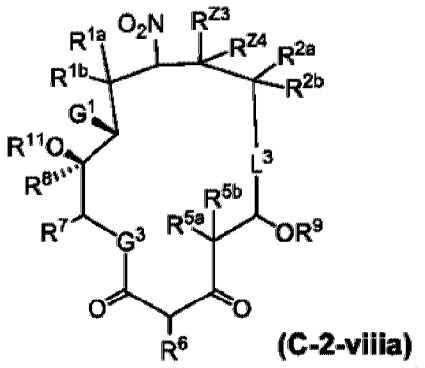
or



;

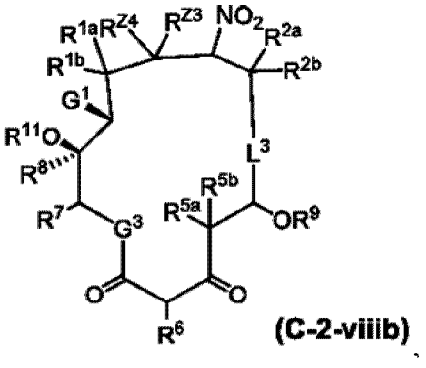
wherein L^1 and L^2 are each independently a bond or –CH_2–; z1 and z2 are 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:

Date Reçue/Date Received 2020-06-25



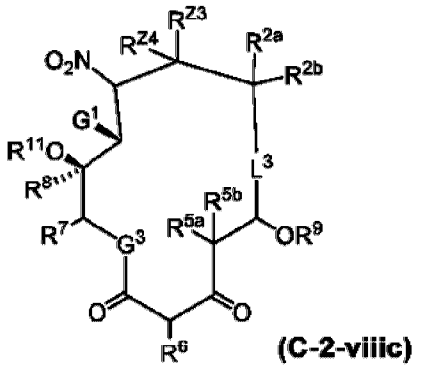
(C-2-viiia)

15-membered ring system



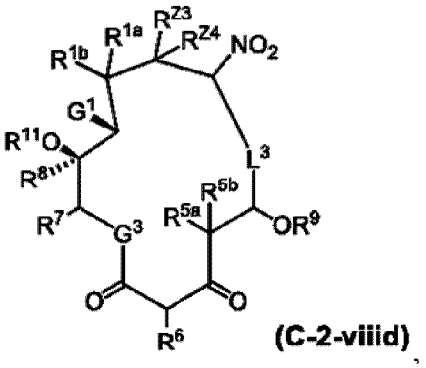
(C-2-viiib)

15-membered ring system



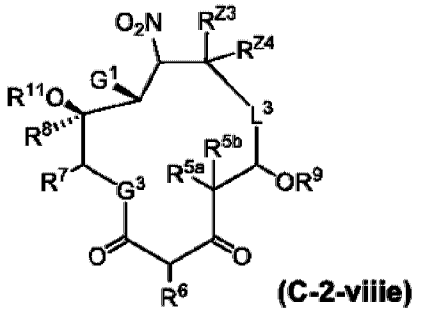
(C-2-viiic)

14-membered ring system



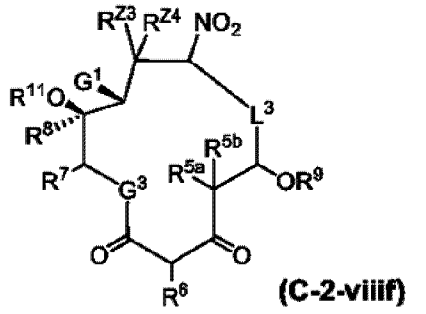
(C-2-viiid)

14-membered ring system



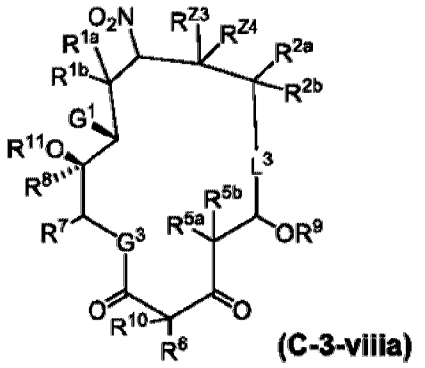
(C-2-viiie)

13-membered ring system



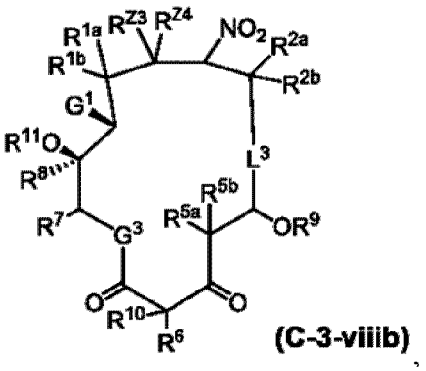
(C-2-viiif)

13-membered ring system



(C-3-viiia)

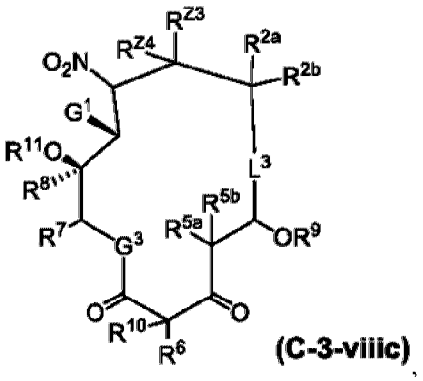
15-membered ring system



(C-3-viiib)

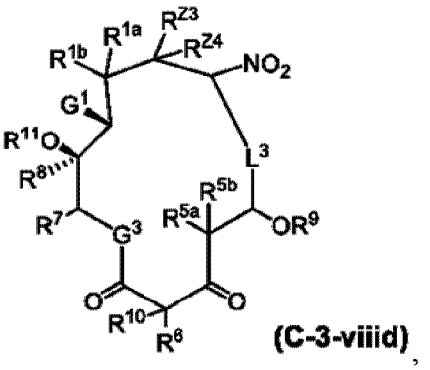
15-membered ring system

Date Reçue/Date Received 2020-06-25



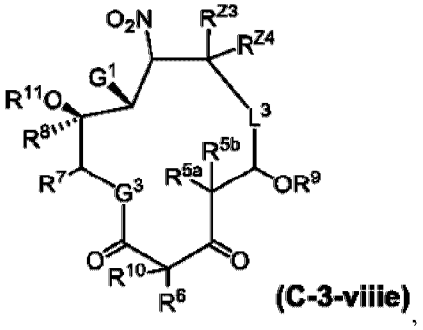
(C-3-viiic)

14-membered ring system



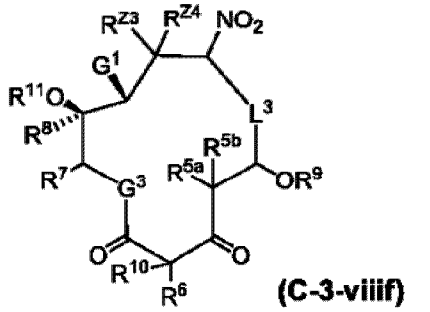
(C-3-viiid)

14-membered ring system



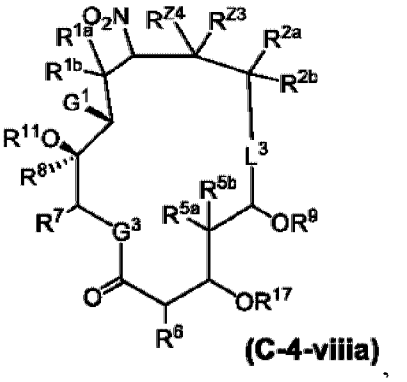
(C-3-viiie)

13-membered ring system



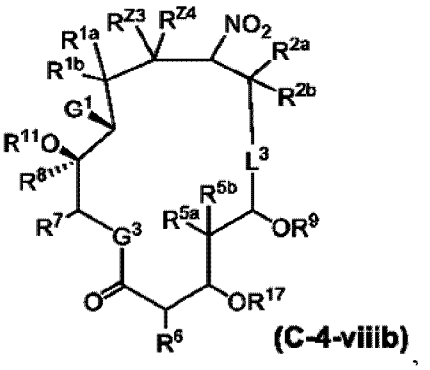
(C-3-viiif)

13-membered ring system



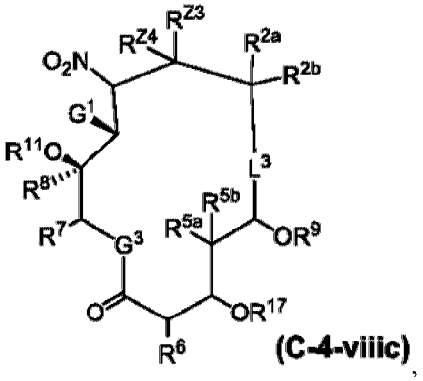
(C-4-viiia)

15-membered ring system



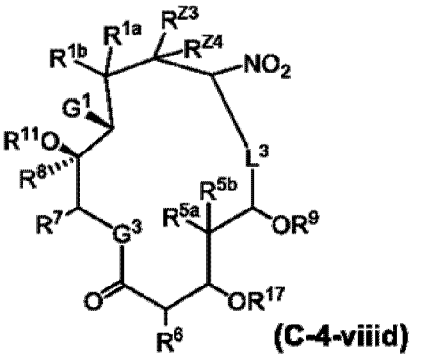
(C-4-viiib)

15-membered ring system



(C-4-viiic)

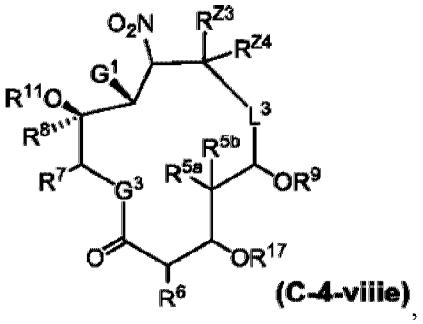
14-membered ring system



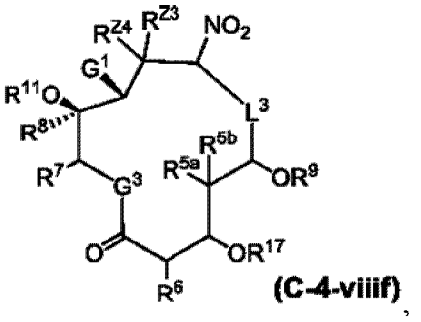
(C-4-viiid)

14-membered ring system

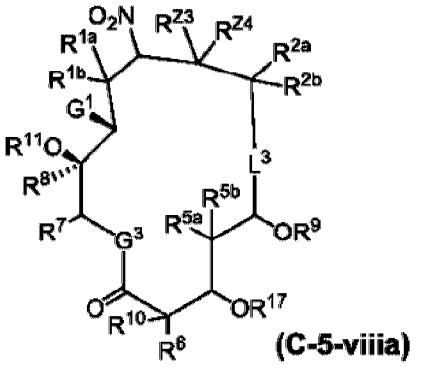
Date Reçue/Date Received 2020-06-25



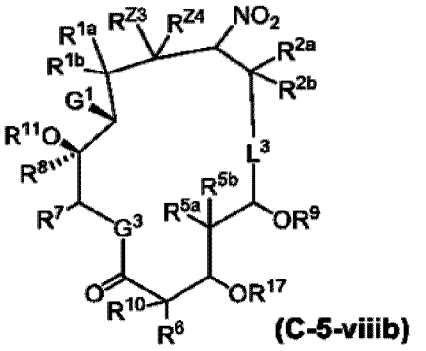
13-membered ring system



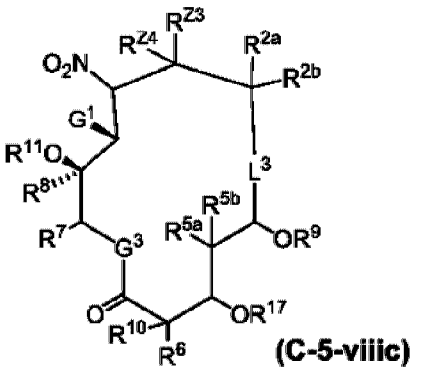
13-membered ring system



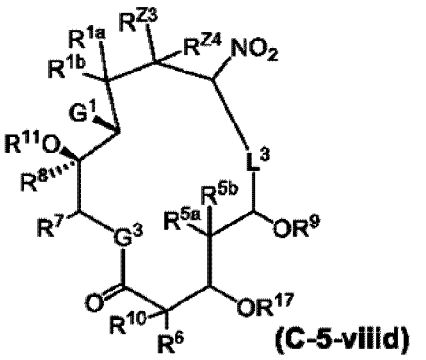
15-membered ring system



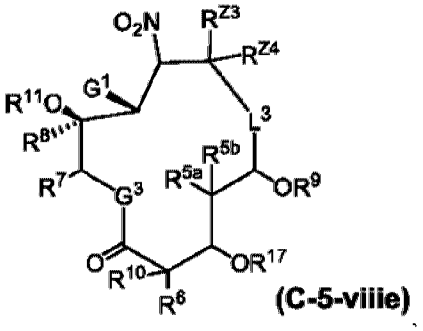
15-membered ring system



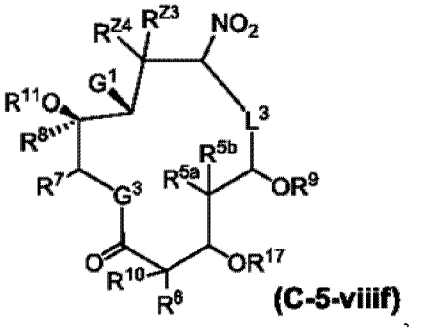
14-membered ring system



14-membered ring system

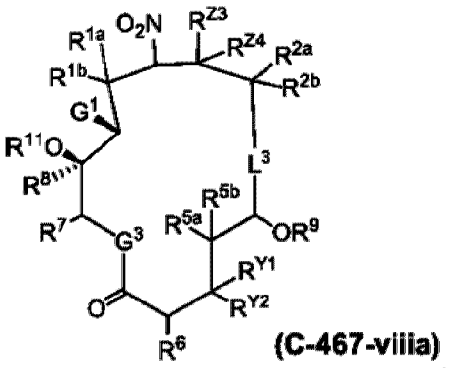


13-membered ring system



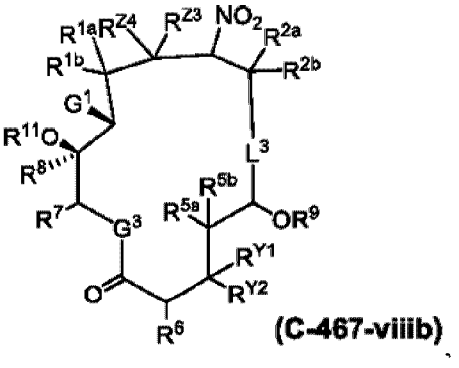
13-membered ring system

Date Reçue/Date Received 2020-06-25



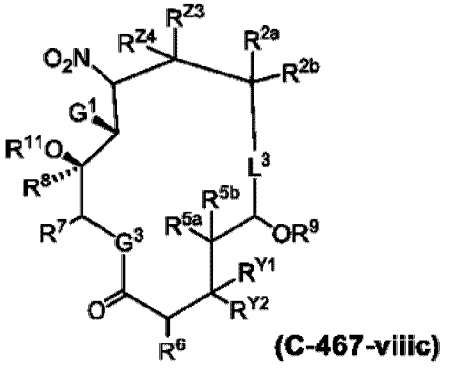
(C-467-viiia)

15-membered ring system



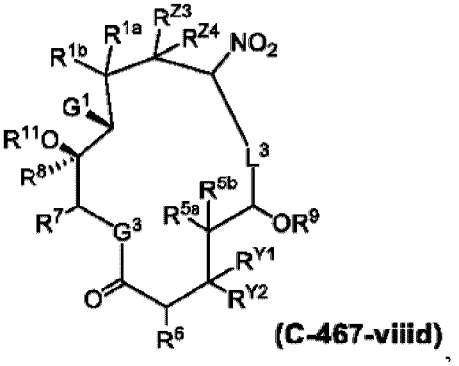
(C-467-viiib)

15-membered ring system



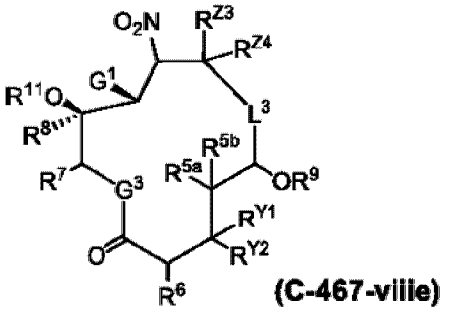
(C-467-viiic)

14-membered ring system



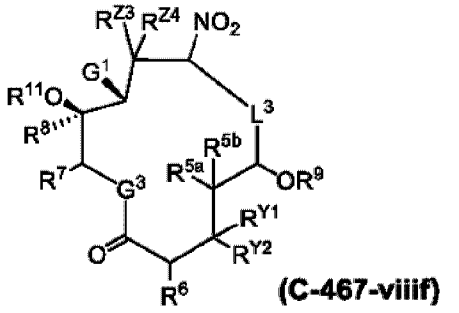
(C-467-viiid)

14-membered ring system



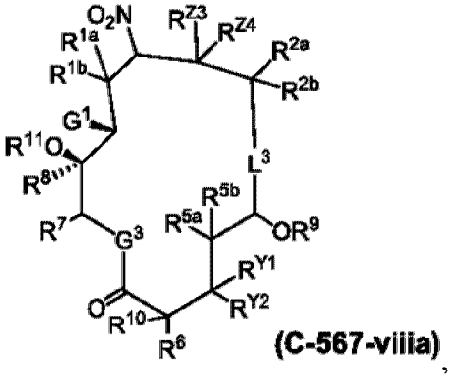
(C-467-viiie)

13-membered ring system



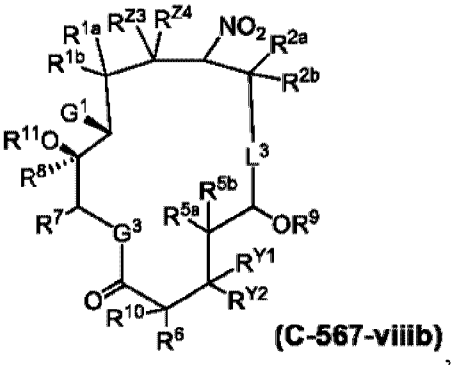
(C-467-viiif)

13-membered ring system



(C-567-viiia)

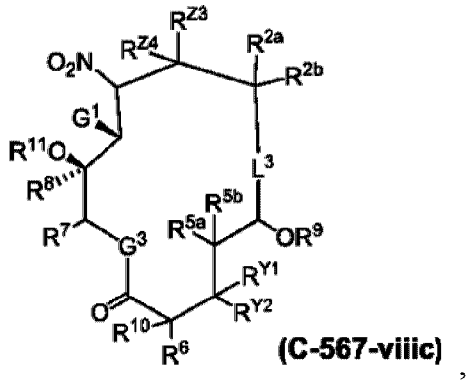
15-membered ring system



(C-567-viiib)

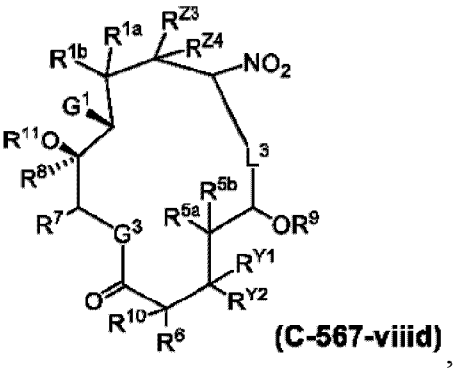
15-membered ring system

Date Reçue/Date Received 2020-06-25



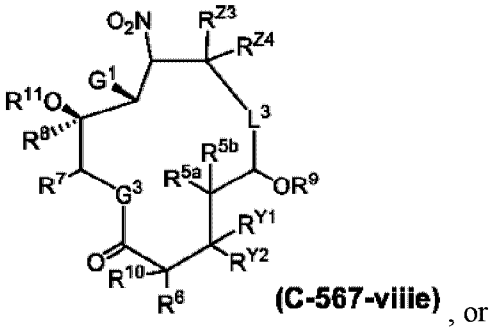
(C-567-viiic),

14-membered ring system



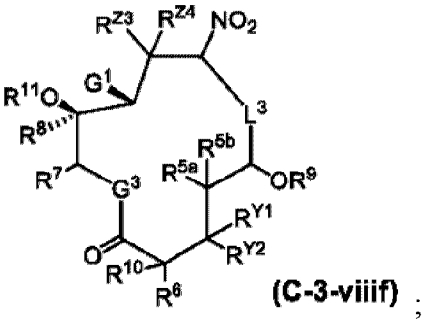
(C-567-viiid),

14-membered ring system



(C-567-viiie), or

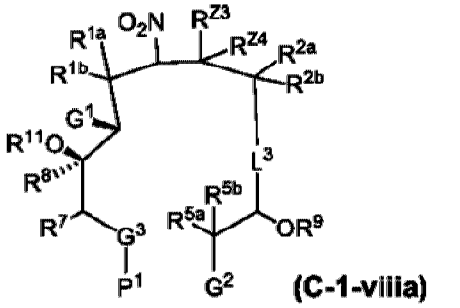
13-membered ring system



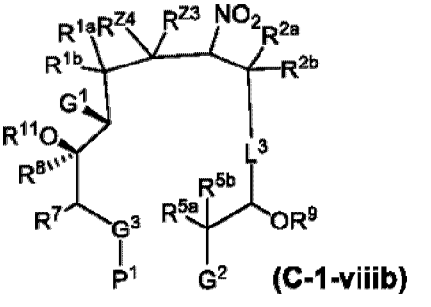
(C-3-viiif);

13-membered ring system

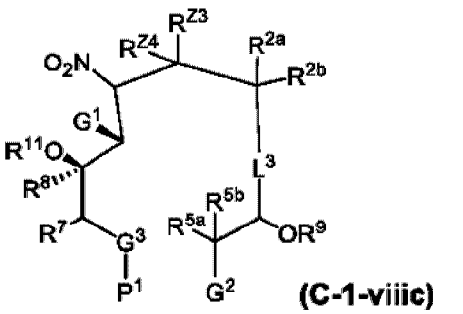
wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



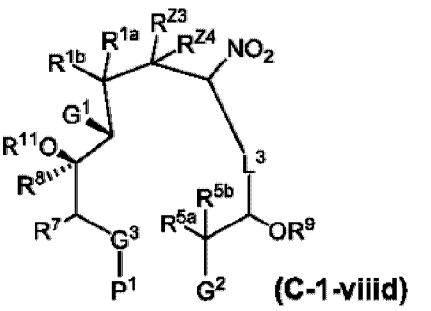
(C-1-viiia),



(C-1-viiib),

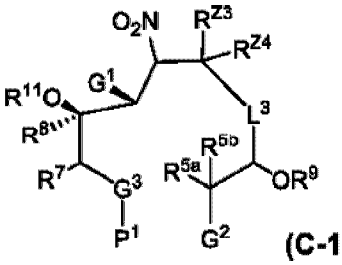


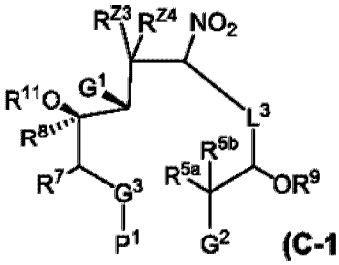
(C-1-viiic),



(C-1-viiid).

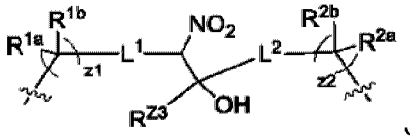
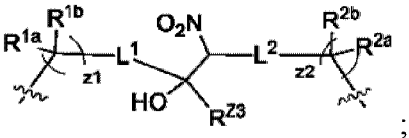
Date Reçue/Date Received 2020-06-25



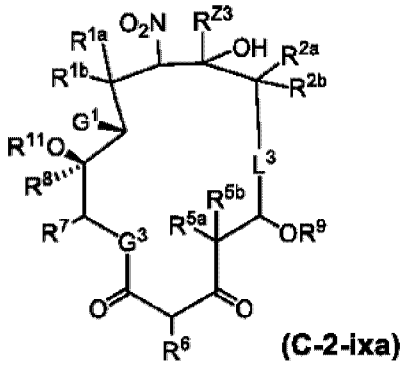
, or


;

[13] a group of formula:

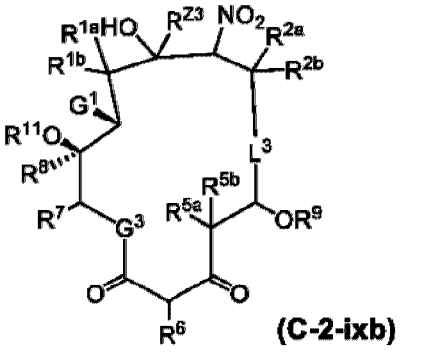

or

;

wherein L^1 and L^2 are each independently a bond or $-CH_2-$; z1 and z2 are 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:



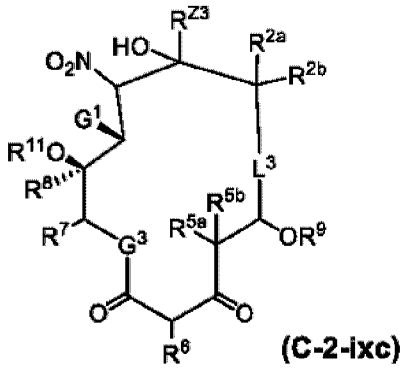
,

15-membered ring system



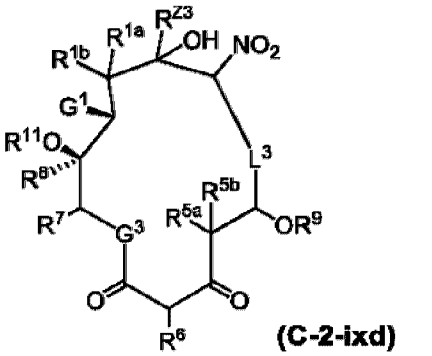
,

15-membered ring system



,

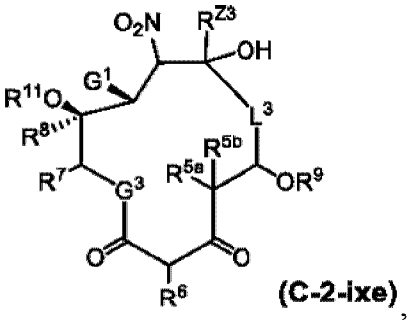
14-membered ring system



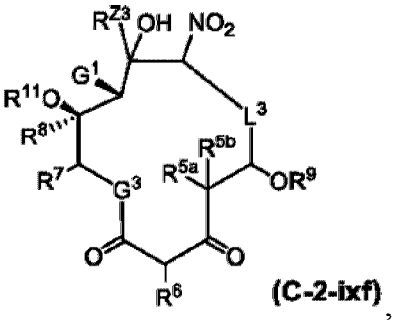
,

14-membered ring system

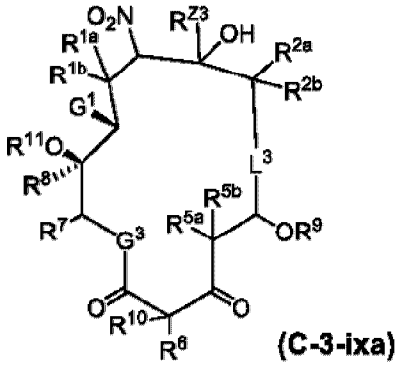
Date Reçue/Date Received 2020-06-25



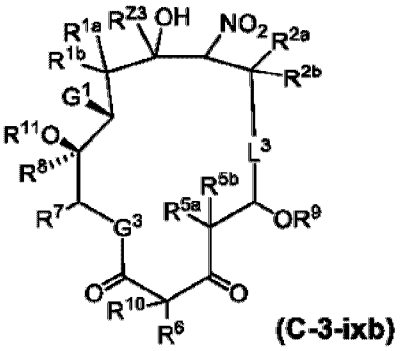
13-membered ring system



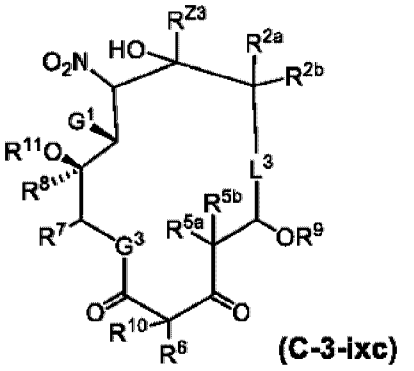
13-membered ring system



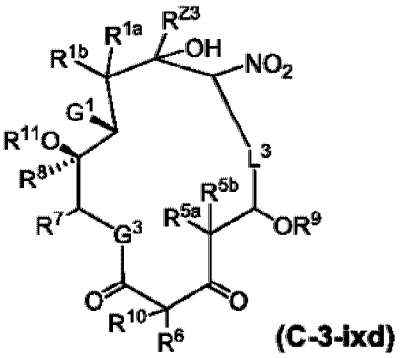
15-membered ring system



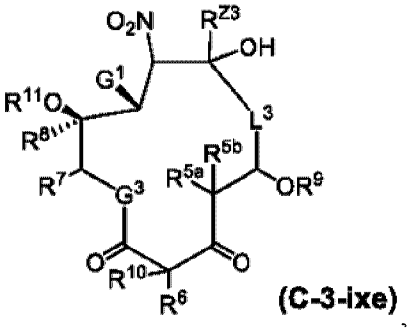
15-membered ring system



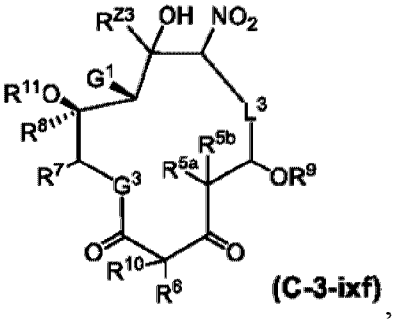
14-membered ring system



14-membered ring system

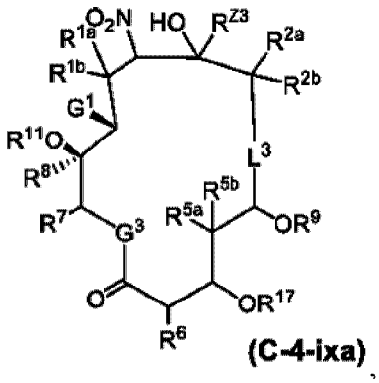


13-membered ring system



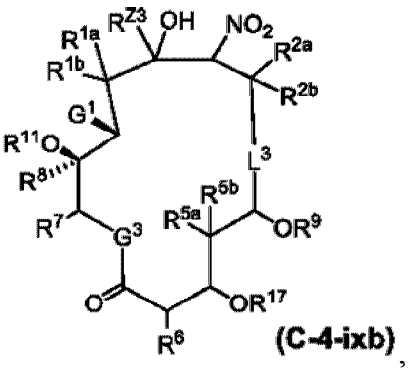
13-membered ring system

Date Reçue/Date Received 2020-06-25



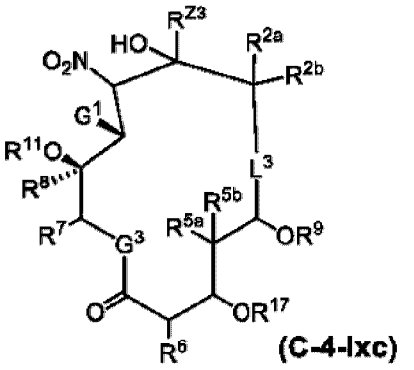
(C-4-ixa),

15-membered ring system



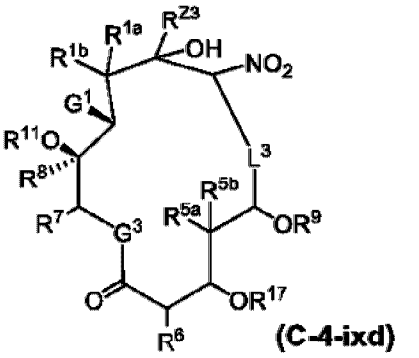
(C-4-ixb),

15-membered ring system



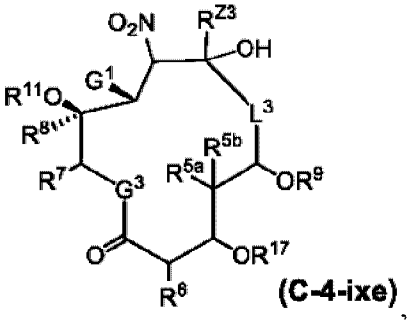
(C-4-ixc),

14-membered ring system



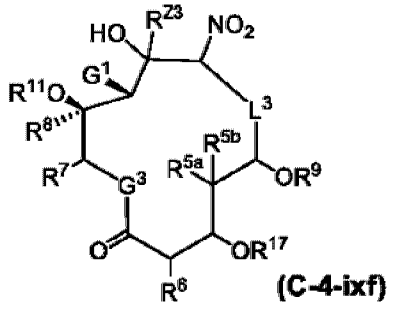
(C-4-ixd),

14-membered ring system



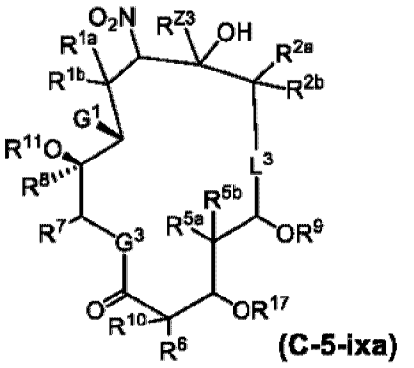
(C-4-ixe),

13-membered ring system



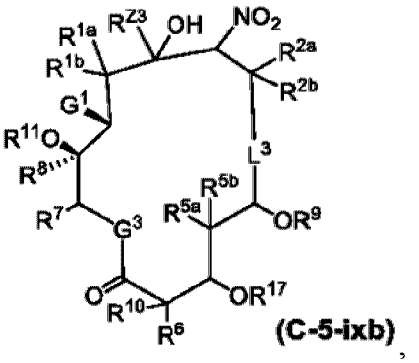
(C-4-ixf),

13-membered ring system



(C-5-ixa),

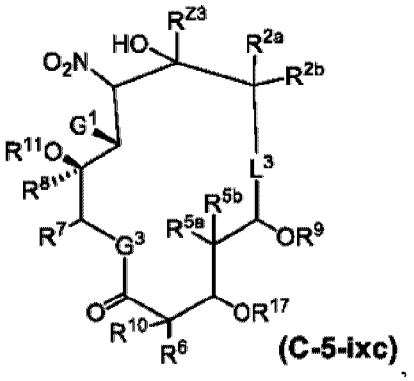
15-membered ring system



(C-5-ixb),

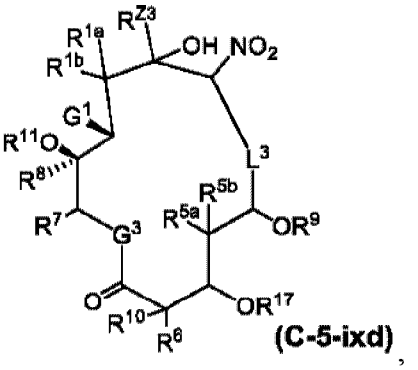
15-membered ring system

Date Reçue/Date Received 2020-06-25



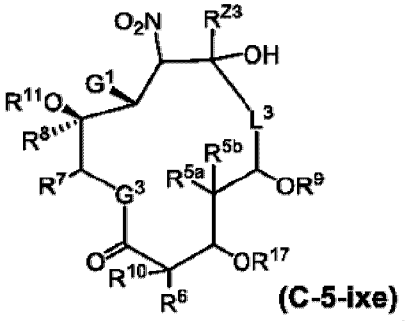
(C-5-ixc)

14-membered ring system



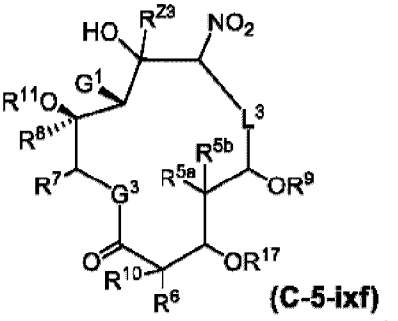
(C-5-ixd)

14-membered ring system



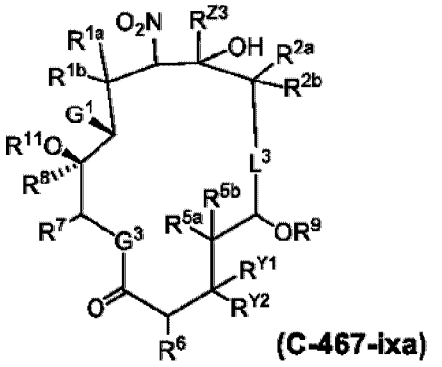
(C-5-ixe)

13-membered ring system



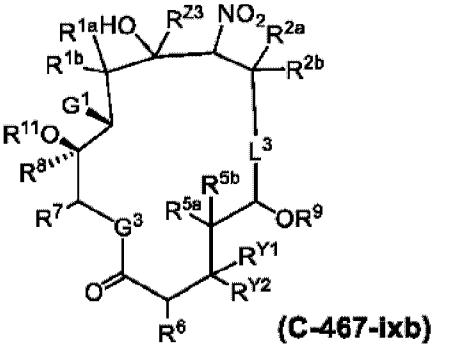
(C-5-ixf)

13-membered ring system



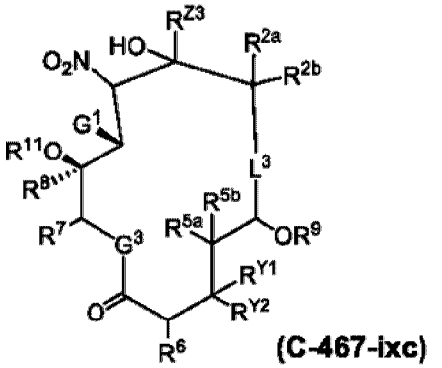
(C-467-ixa)

15-membered ring system



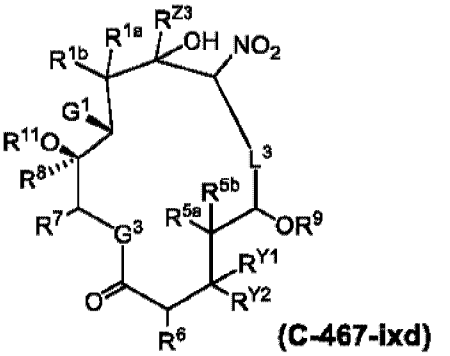
(C-467-ixb)

15-membered ring system



(C-467-ixc)

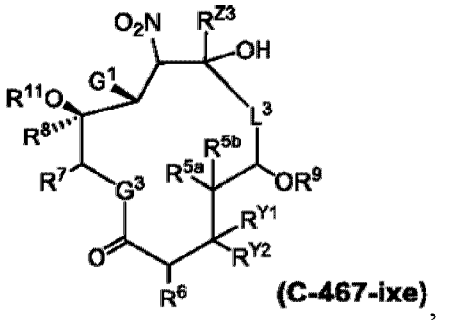
14-membered ring system



(C-467-ixd)

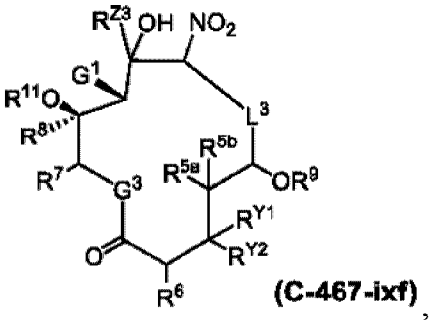
14-membered ring system

Date Reçue/Date Received 2020-06-25



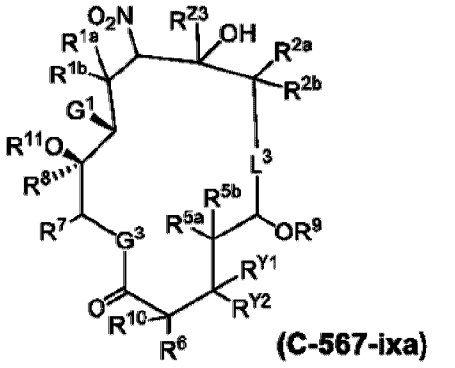
(C-467-ixe),

13-membered ring system



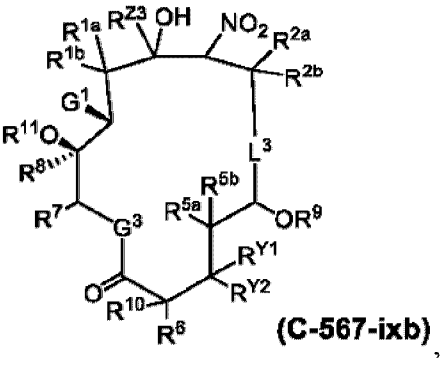
(C-467-ixf),

13-membered ring system



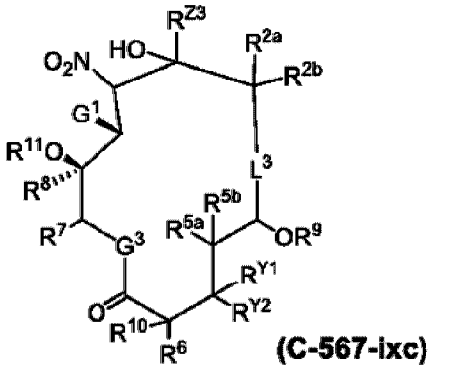
(C-567-ixa),

15-membered ring system



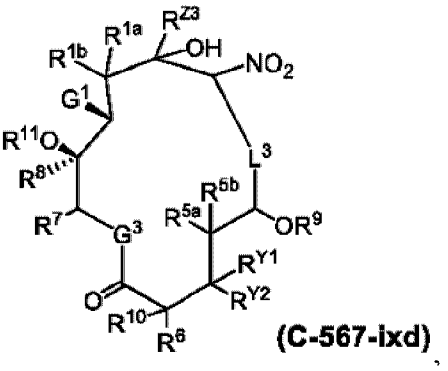
(C-567-ixb),

15-membered ring system



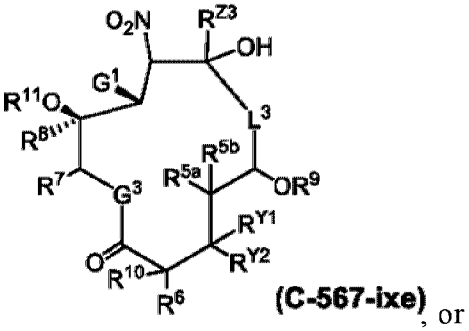
(C-567-ixc),

14-membered ring system



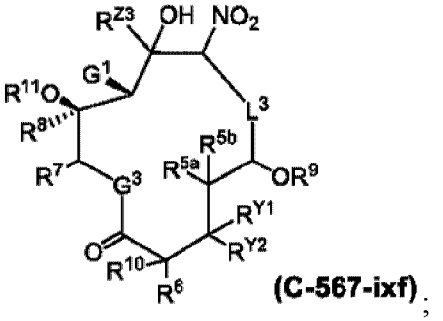
(C-567-ixd),

14-membered ring system



(C-567-ixe), or

13-membered ring system

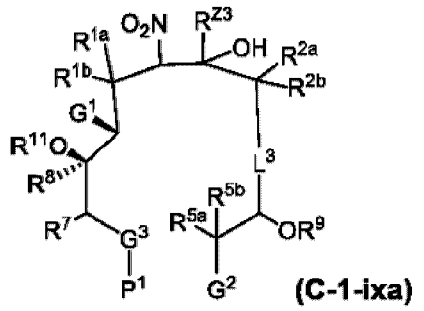


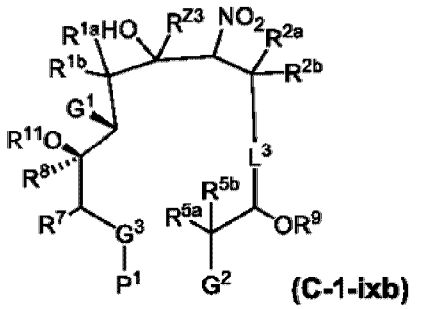
(C-567-ixf);

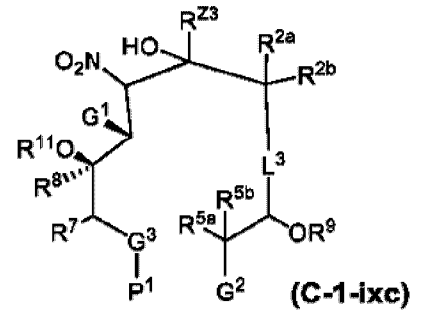
13-membered ring system

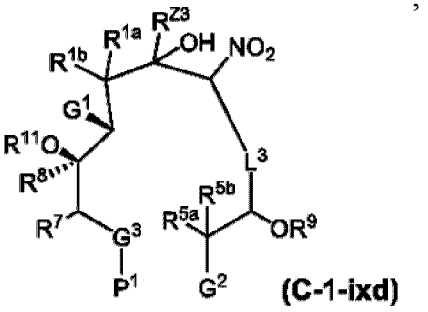
Date Reçue/Date Received 2020-06-25

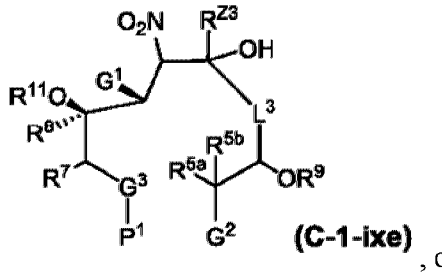
wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:

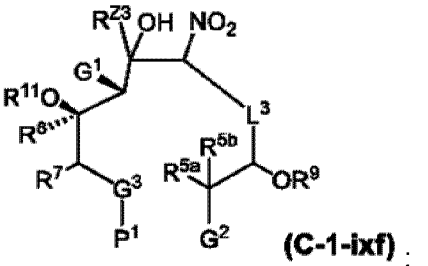

(C-1-ixa),


(C-1-ixb),

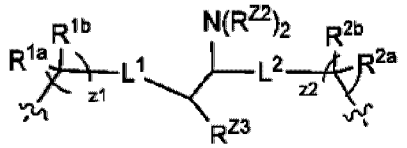
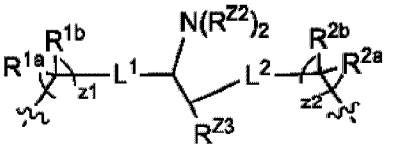

(C-1-ixc),


(C-1-ixd),


(C-1-ixe), or

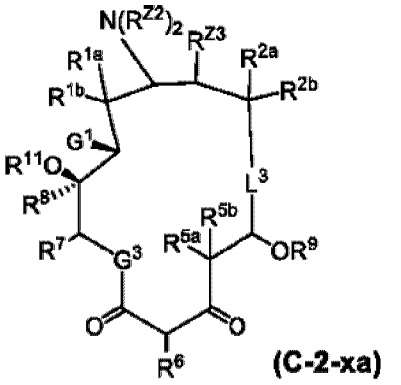

(C-1-ixf);

[14] a group of formula:


or

;

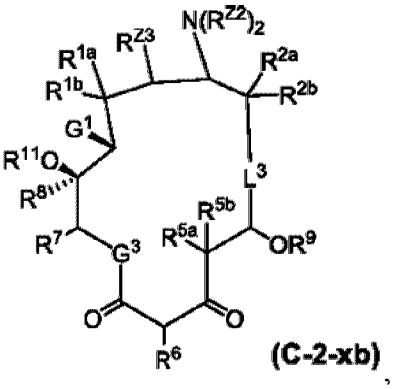
wherein L^1 and L^2 are each independently a bond or –CH_2–; z1 and z2 are 0, 1, or 2 *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:

Date Reçue/Date Received 2020-06-25



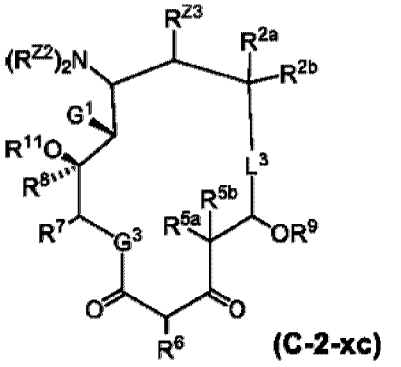
(C-2-xa),

15-membered ring system



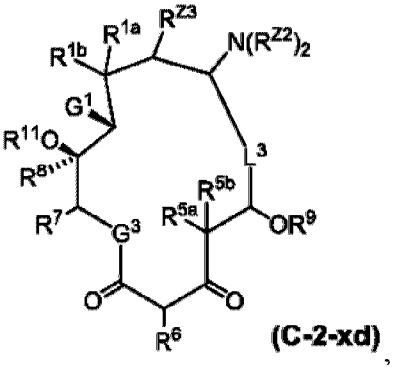
(C-2-xb),

15-membered ring system



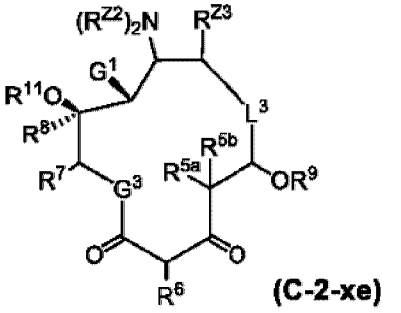
(C-2-xc),

14-membered ring system



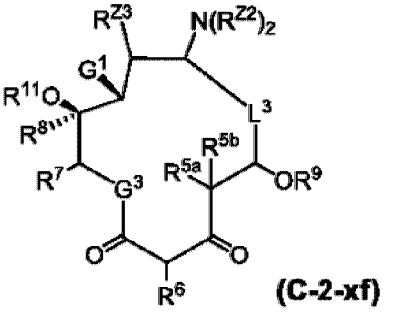
(C-2-xd),

14-membered ring system



(C-2-xe),

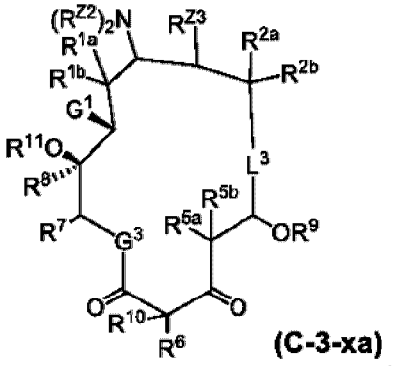
13-membered ring system



(C-2-xf),

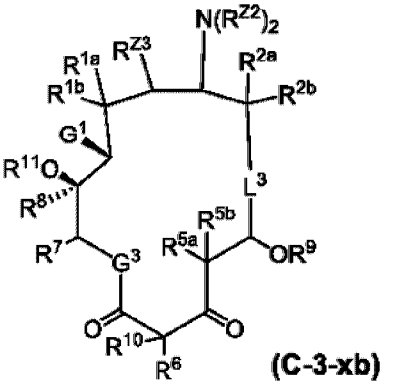
13-membered ring system

Date Reçue/Date Received 2020-06-25



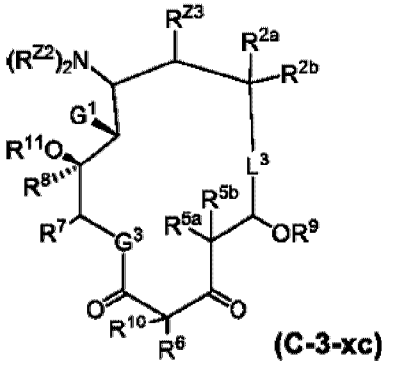
(C-3-xa),

15-membered ring system



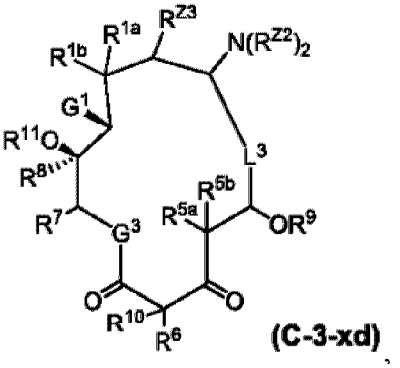
(C-3-xb),

15-membered ring system



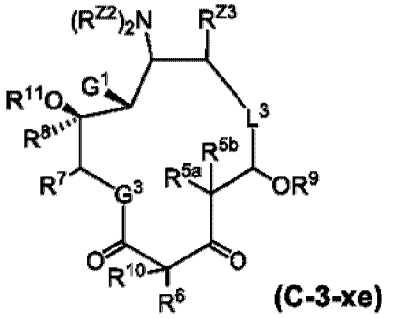
(C-3-xc),

14-membered ring system



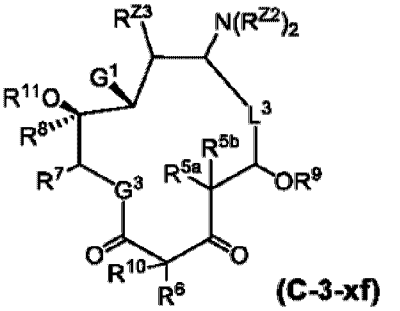
(C-3-xd),

14-membered ring system



(C-3-xe),

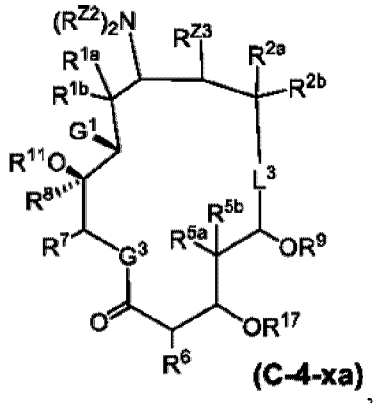
13-membered ring system



(C-3-xf),

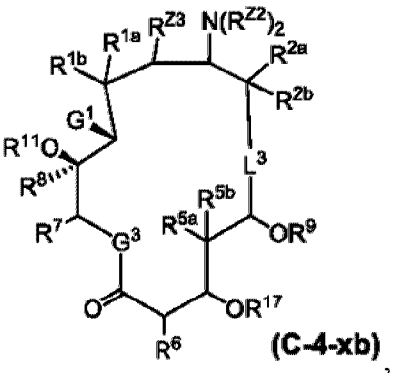
13-membered ring system

Date Reçue/Date Received 2020-06-25



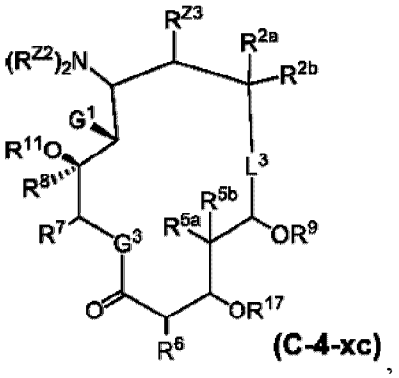
(C-4-xa)

15-membered ring system



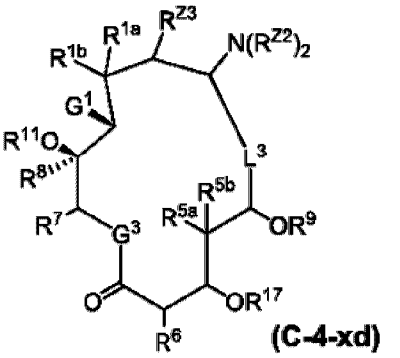
(C-4-xb)

15-membered ring system



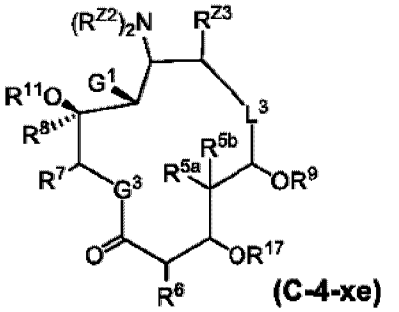
(C-4-xc)

14-membered ring system



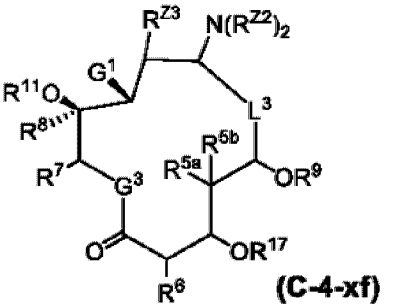
(C-4-xd)

14-membered ring system



(C-4-xe)

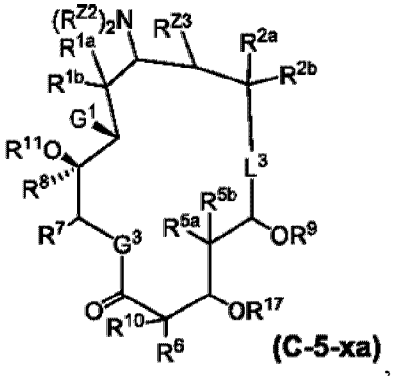
13-membered ring system



(C-4-xf)

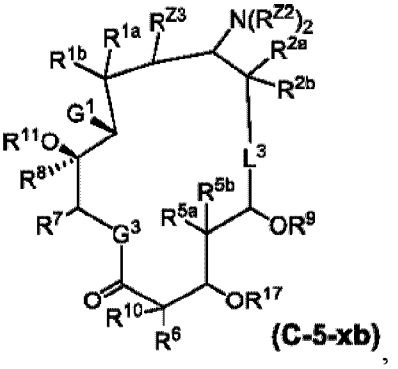
13-membered ring system

Date Reçue/Date Received 2020-06-25



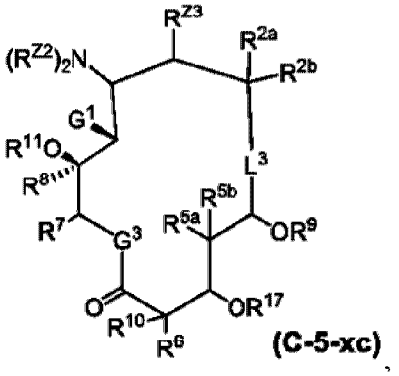
(C-5-xa)

15-membered ring system



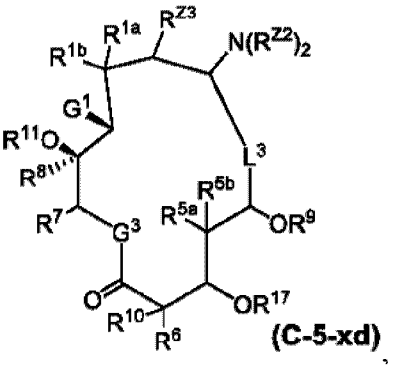
(C-5-xb)

15-membered ring system



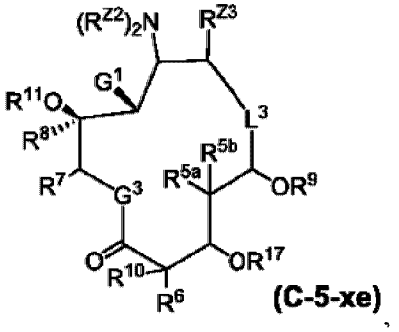
(C-5-xc)

14-membered ring system



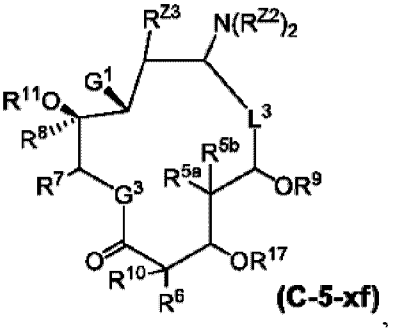
(C-5-xd)

14-membered ring system



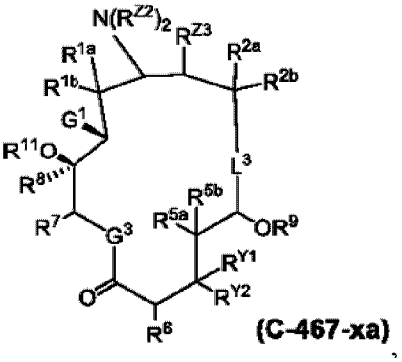
(C-5-xe)

13-membered ring system



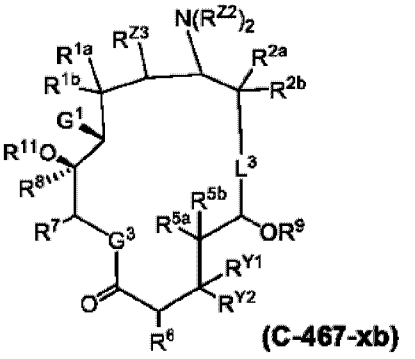
(C-5-xf)

13-membered ring system



(C-467-xa)

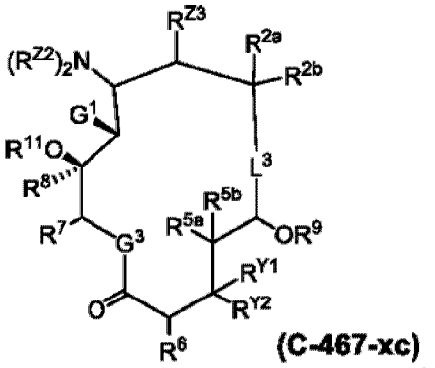
15-membered ring system



(C-467-xb)

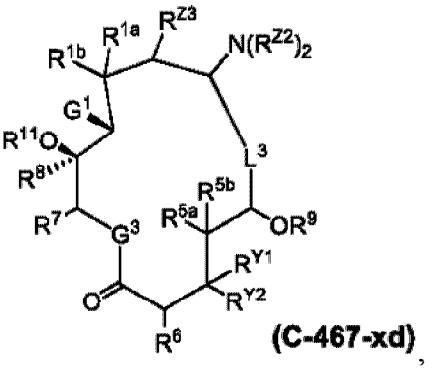
15-membered ring system

Date Reçue/Date Received 2020-06-25



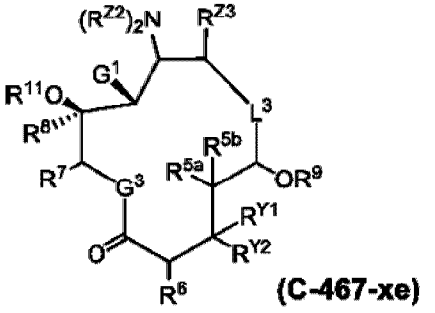
(C-467-xc)

14-membered ring system



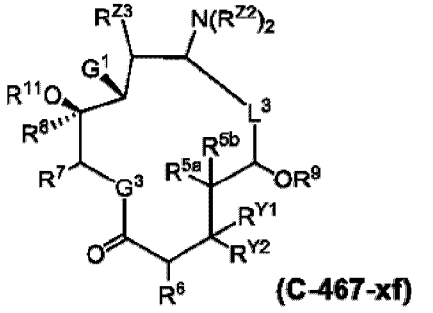
(C-467-xd)

14-membered ring system



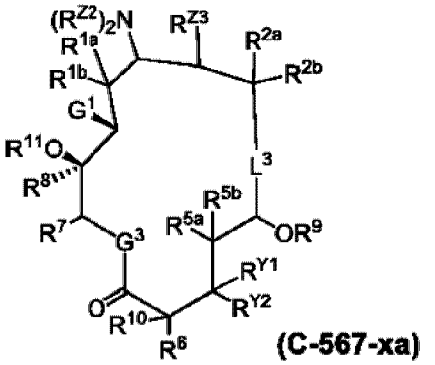
(C-467-xe)

13-membered ring system



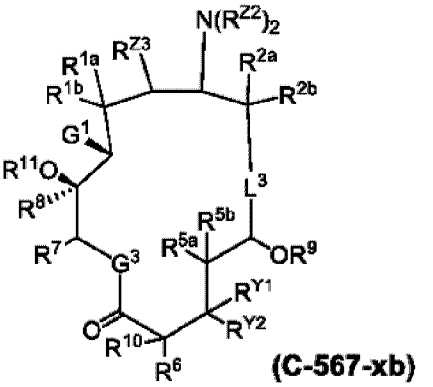
(C-467-xf)

13-membered ring system



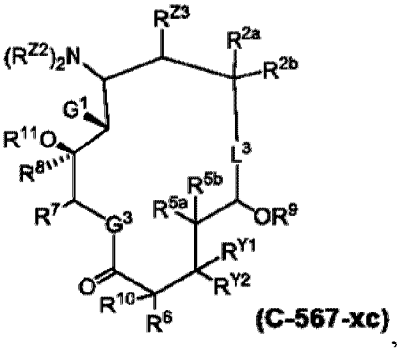
(C-567-xa)

15-membered ring system



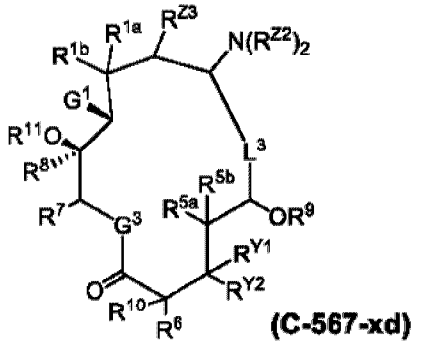
(C-567-xb)

15-membered ring system



(C-567-xc)

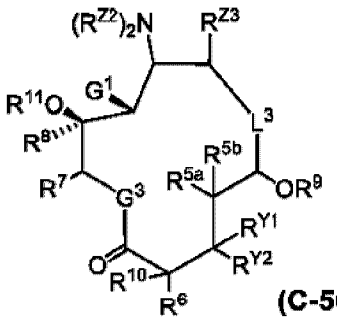
14-membered ring system



(C-567-xd)

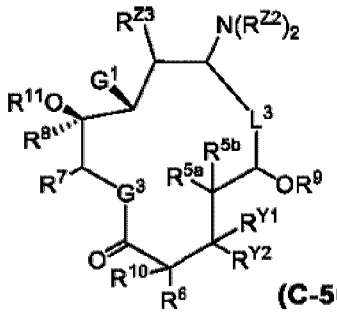
14-membered ring system

Date Reçue/Date Received 2020-06-25



, or

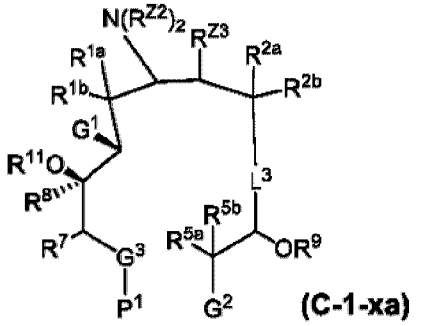
13-membered ring system



;

13-membered ring system

wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



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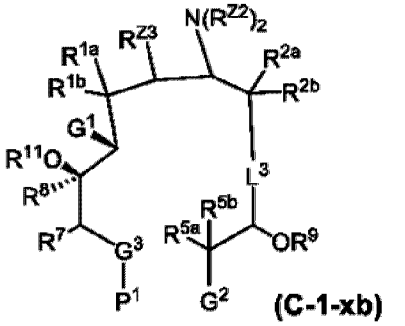

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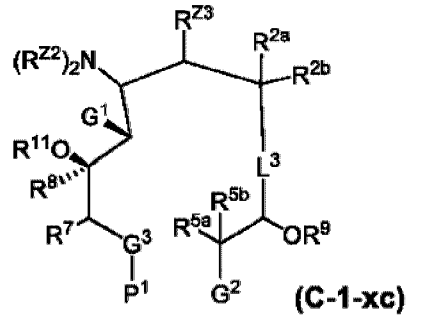

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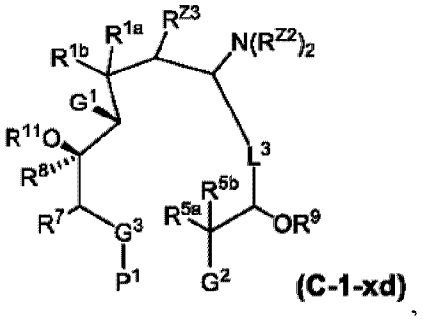

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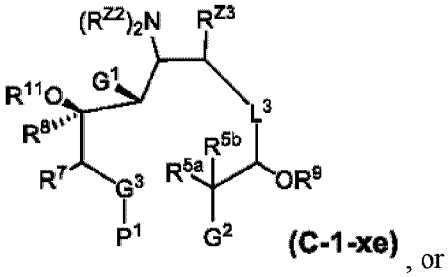
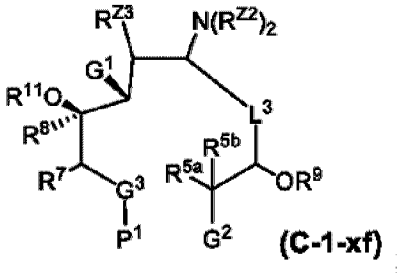
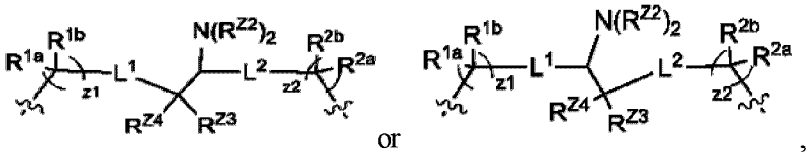


, or



[15] an amino group of formula:

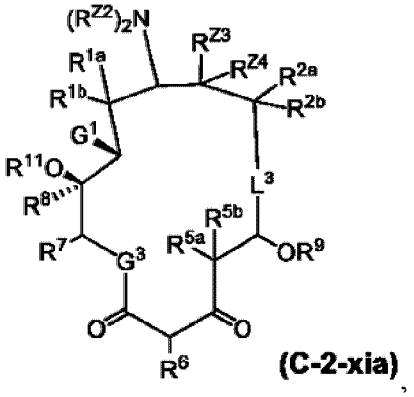
Date Reçue/Date Received 2020-06-25



or

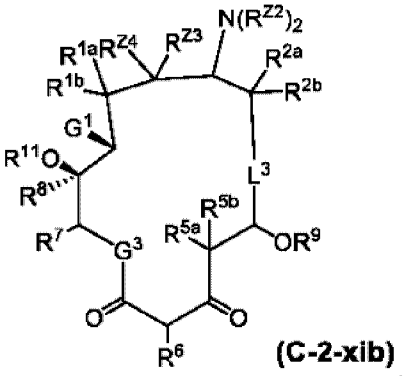
,

wherein L^1 and L^2 are each independently a bond or –CH_2–; z1 and z2 are 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:



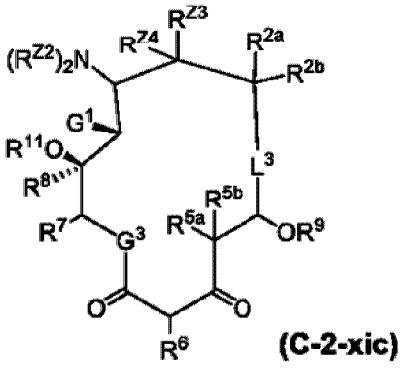
(C-2-xia),

15-membered ring system



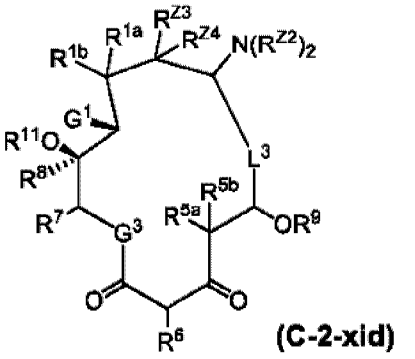
(C-2-xib),

15-membered ring system



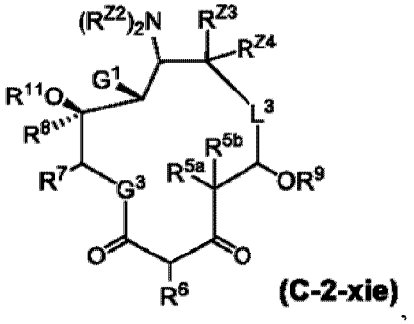
(C-2-xic),

14-membered ring system



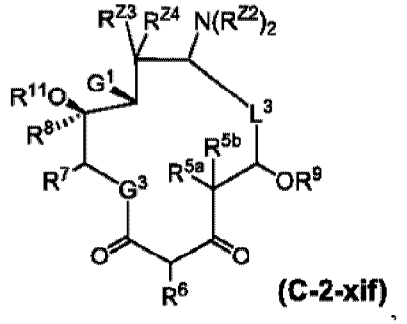
(C-2-xid),

14-membered ring system



(C-2-xie),

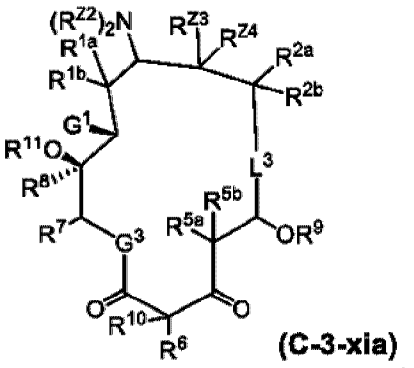
13-membered ring system



(C-2-xif),

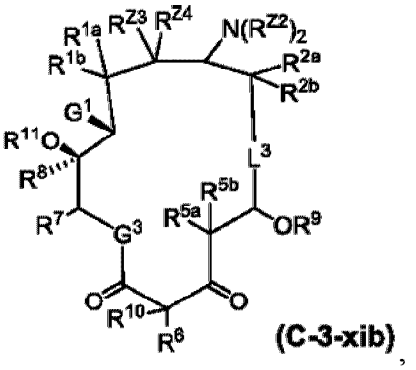
13-membered ring system

Date Reçue/Date Received 2020-06-25



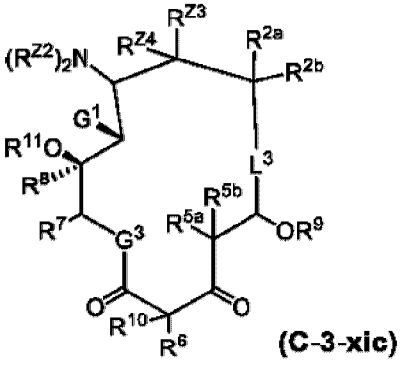
(C-3-xia)

15-membered ring system



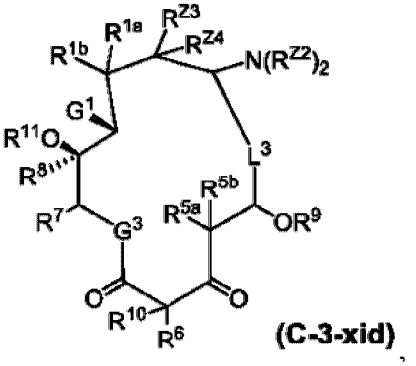
(C-3-xib)

15-membered ring system



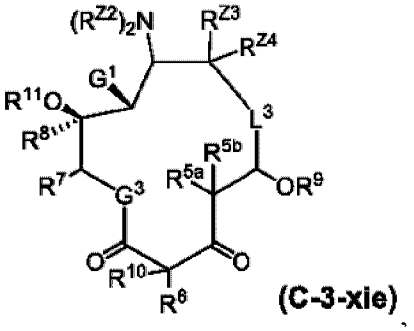
(C-3-xic)

14-membered ring system



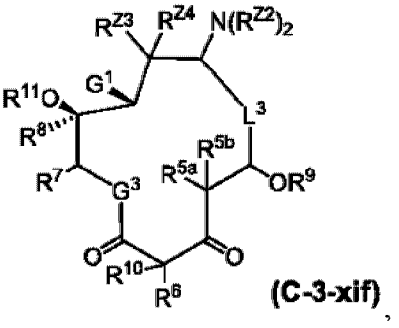
(C-3-xid)

14-membered ring system



(C-3-xie)

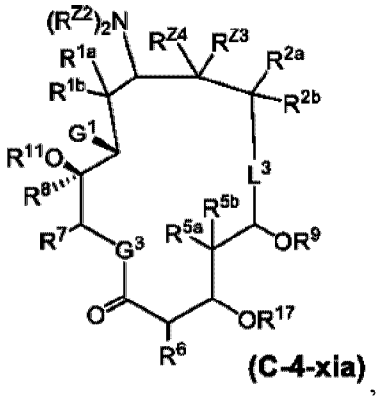
13-membered ring system



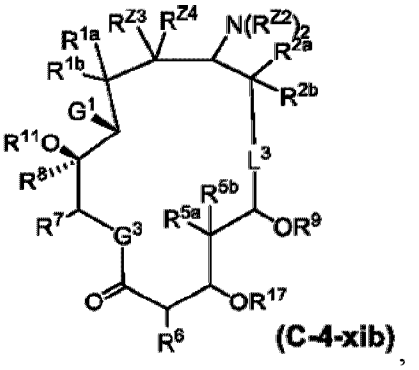
(C-3-xif)

13-membered ring system

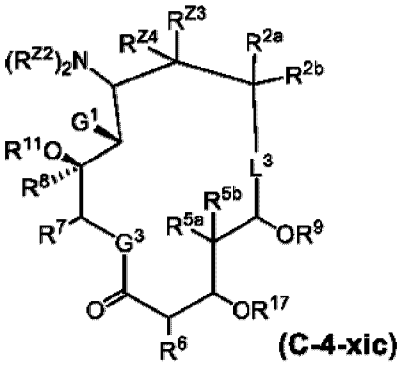
Date Reçue/Date Received 2020-06-25



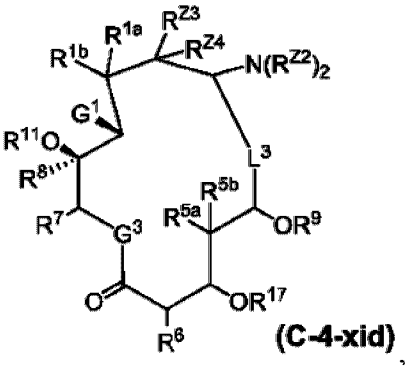
15-membered ring system



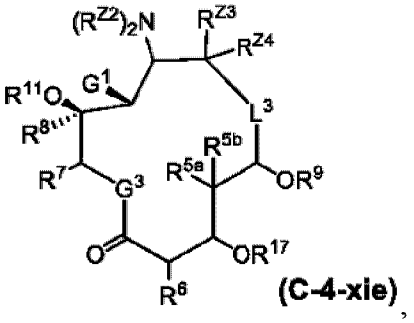
15-membered ring system



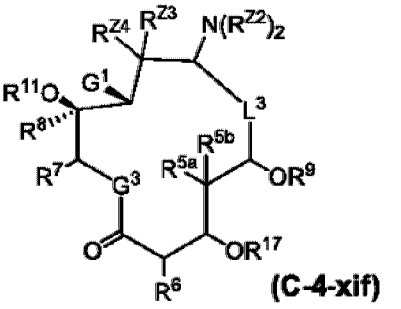
14-membered ring system



14-membered ring system

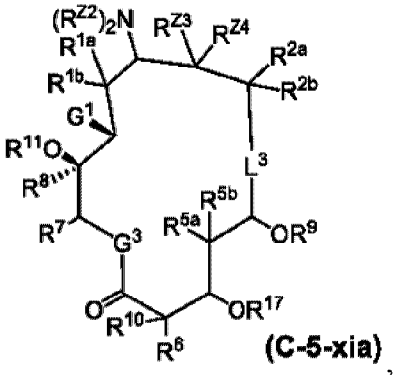


13-membered ring system



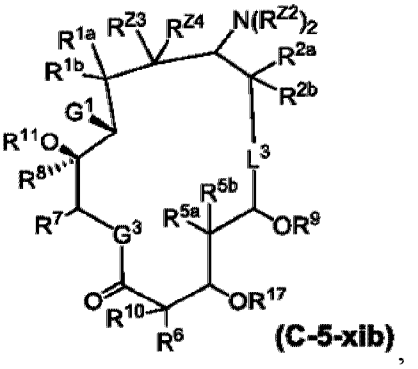
13-membered ring system

Date Reçue/Date Received 2020-06-25



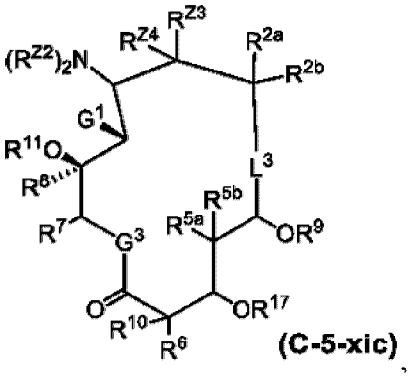
(C-5-xia)

15-membered ring system



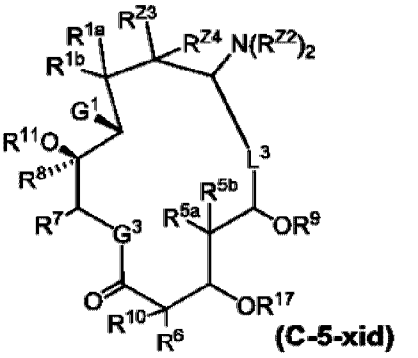
(C-5-xib)

15-membered ring system



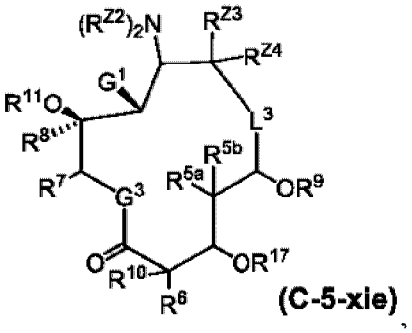
(C-5-xic)

14-membered ring system



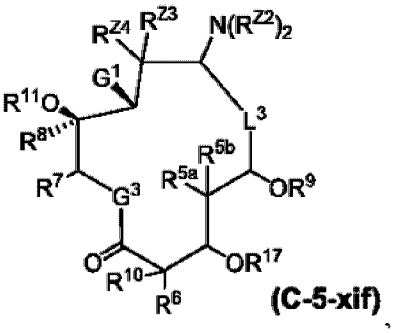
(C-5-xid)

14-membered ring system



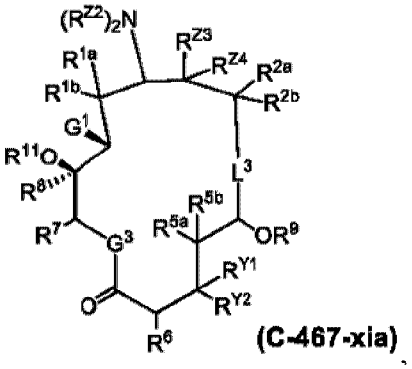
(C-5-xie)

13-membered ring system



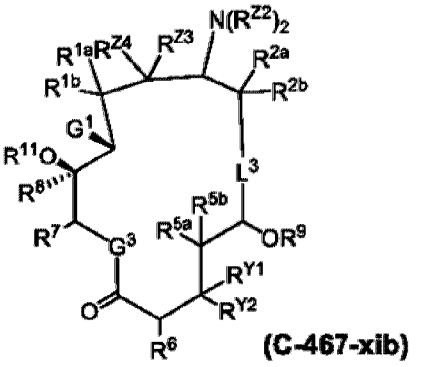
(C-5-xif)

13-membered ring system



(C-467-xia)

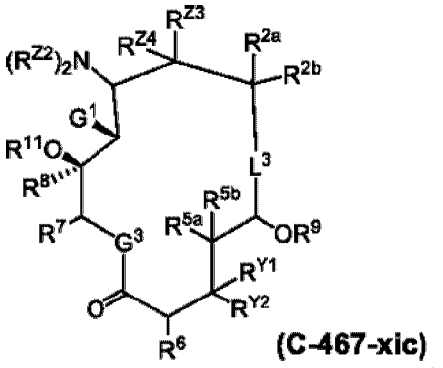
15-membered ring system



(C-467-xib)

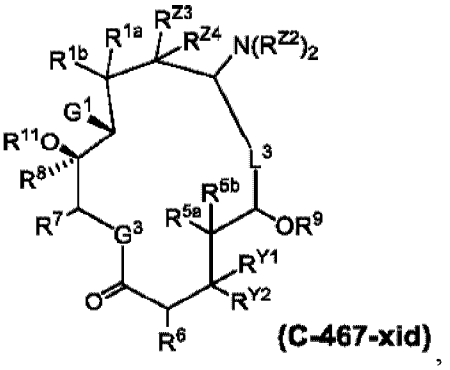
15-membered ring system

Date Reçue/Date Received 2020-06-25



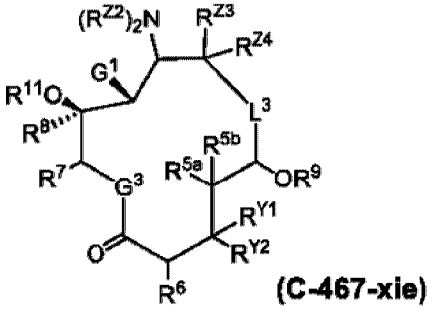
(C-467-xic),

14-membered ring system



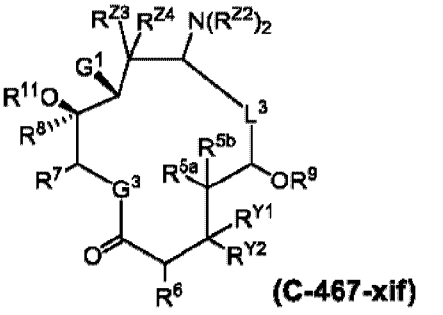
(C-467-xid),

14-membered ring system



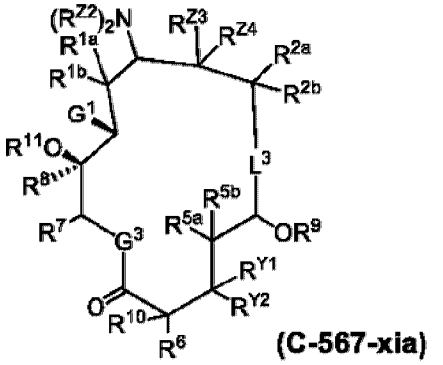
(C-467-xie),

13-membered ring system



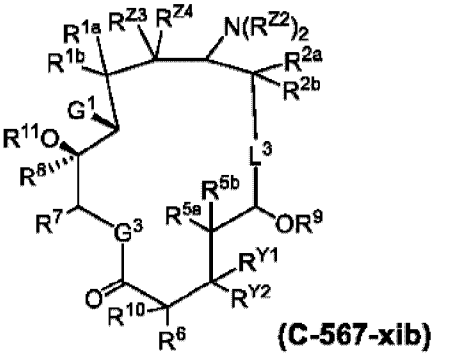
(C-467-xif),

13-membered ring system



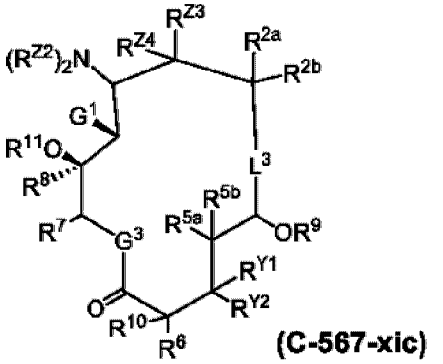
(C-567-xia),

15-membered ring system



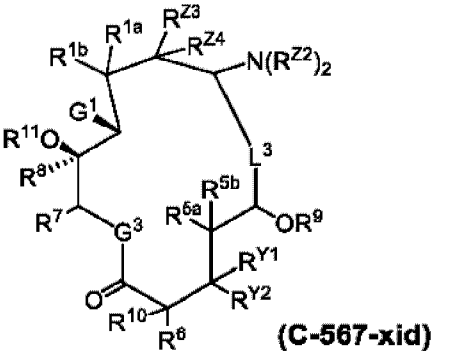
(C-567-xib),

15-membered ring system



(C-567-xic),

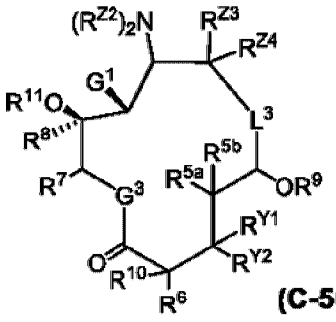
14-membered ring system



(C-567-xid),

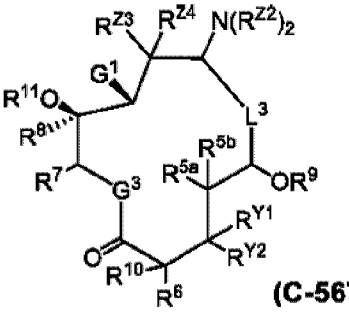
14-membered ring system

Date Reçue/Date Received 2020-06-25



, or

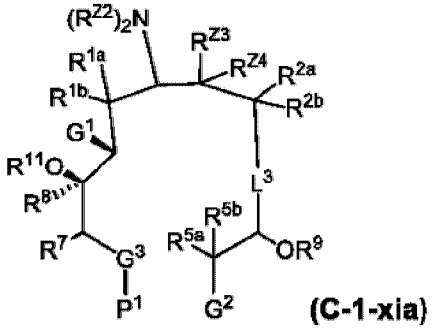
13-membered ring system



;

13-membered ring system

wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



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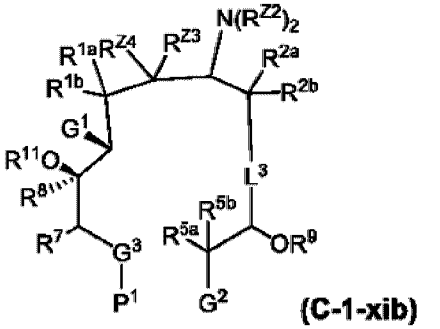

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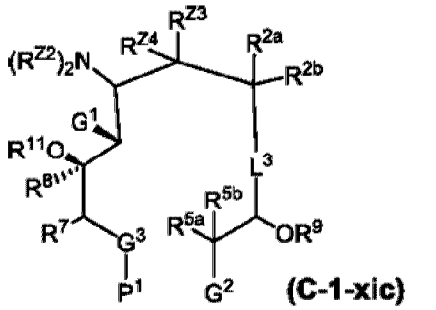

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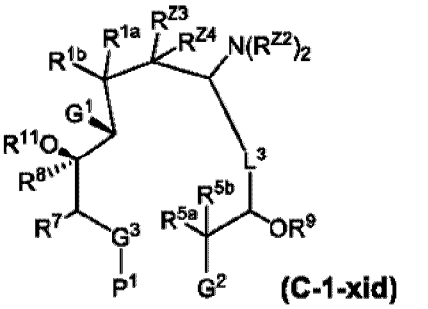

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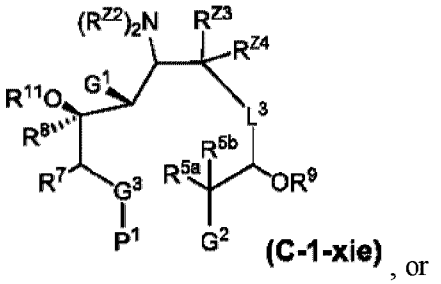
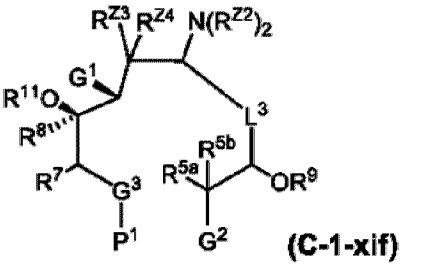
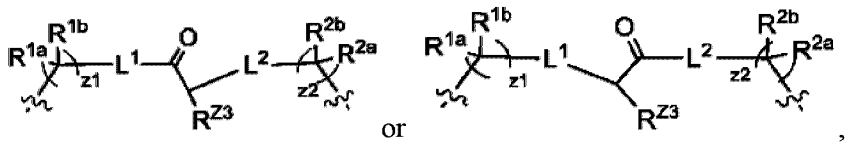


, or



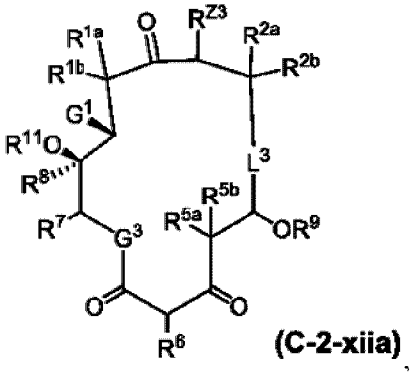
[16] an keto compound of formula:

Date Reçue/Date Received 2020-06-25



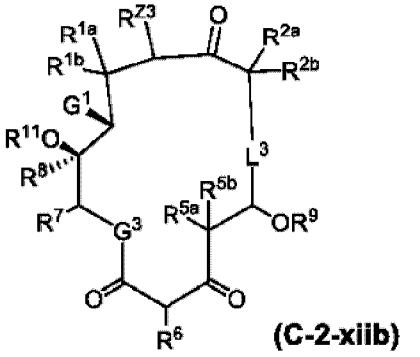
or ,

wherein L^1 and L^2 are each independently a bond or $–CH_2–$; z1 and z2 are 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:



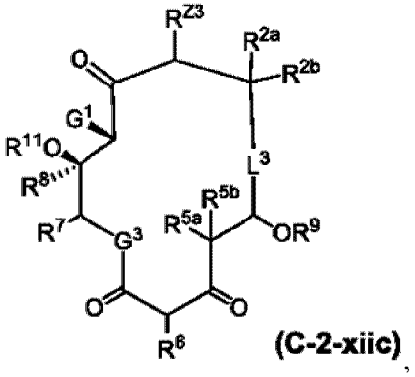
(C-2-xiia),

15-membered ring system



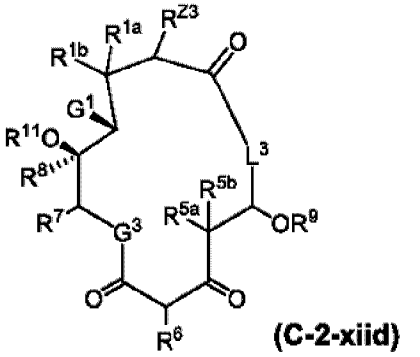
(C-2-xiib),

15-membered ring system



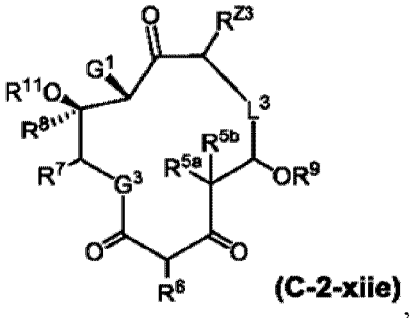
(C-2-xiic),

14-membered ring system



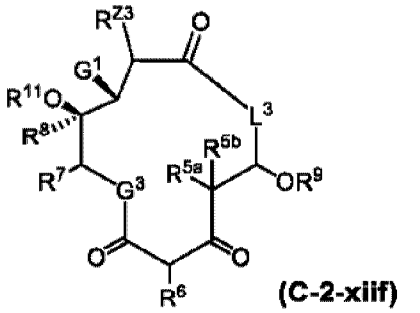
(C-2-xiid),

14-membered ring system



(C-2-xiie),

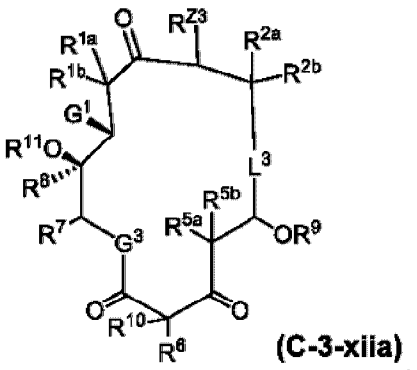
13-membered ring system



(C-2-xiif),

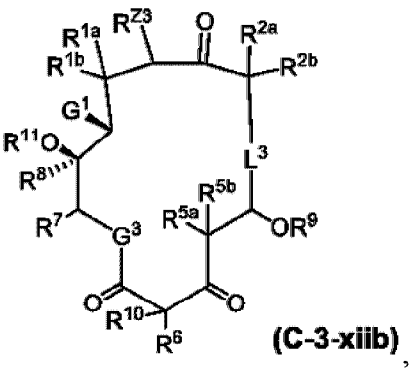
13-membered ring system

Date Reçue/Date Received 2020-06-25



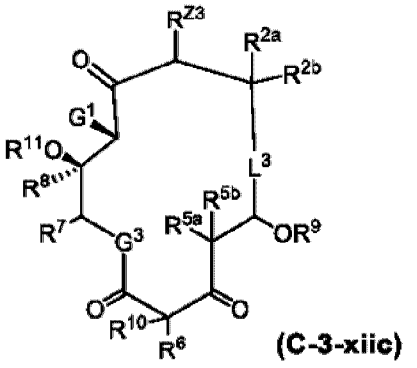
(C-3-xiia)

15-membered ring system



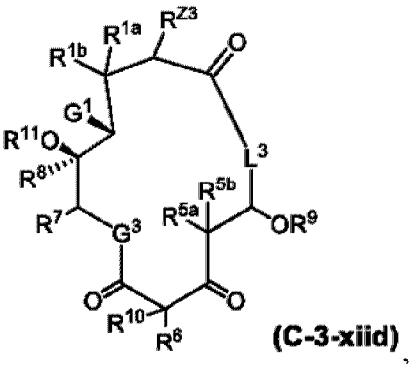
(C-3-xiib)

15-membered ring system



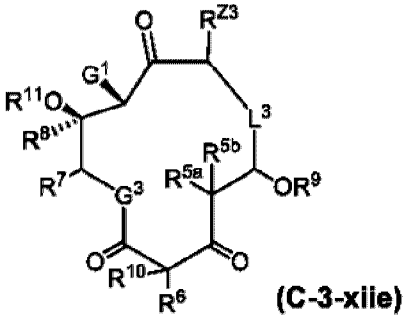
(C-3-xiic)

14-membered ring system



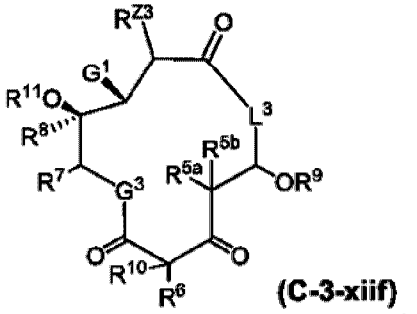
(C-3-xiid)

14-membered ring system



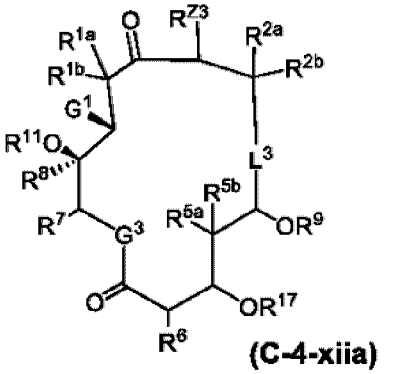
(C-3-xiie)

13-membered ring system



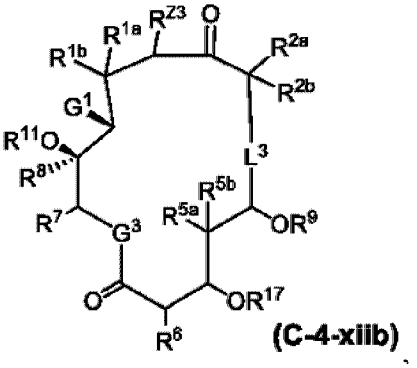
(C-3-xiif)

13-membered ring system



(C-4-xiia)

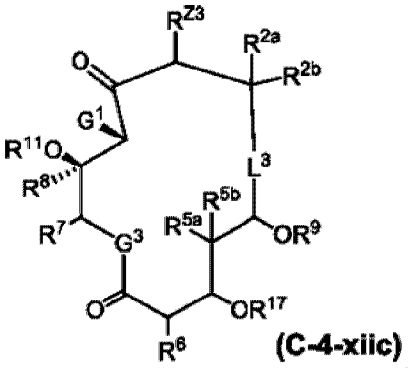
15-membered ring system



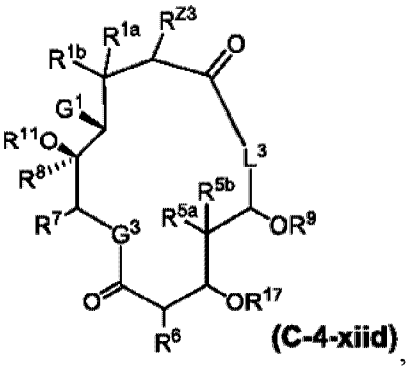
(C-4-xiib)

15-membered ring system

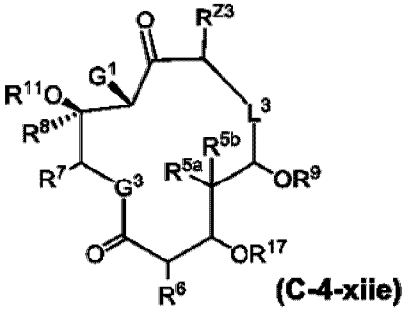
Date Reçue/Date Received 2020-06-25



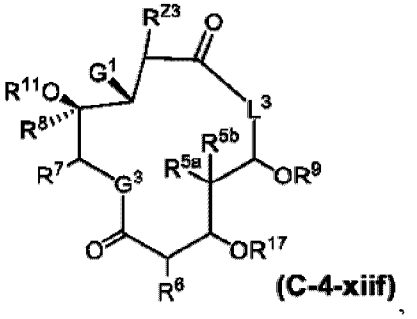
14-membered ring system



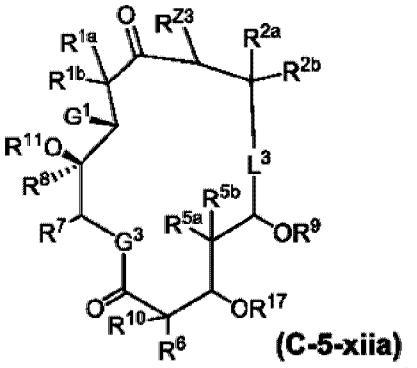
14-membered ring system



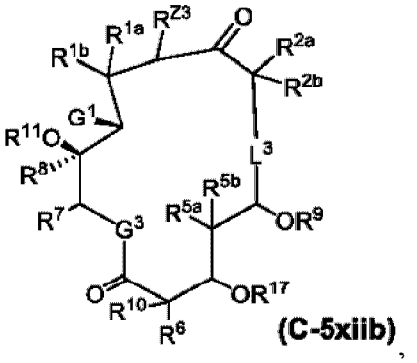
13-membered ring system



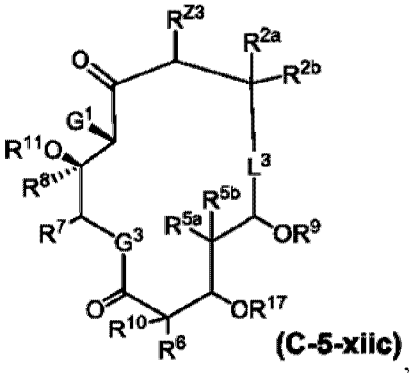
13-membered ring system



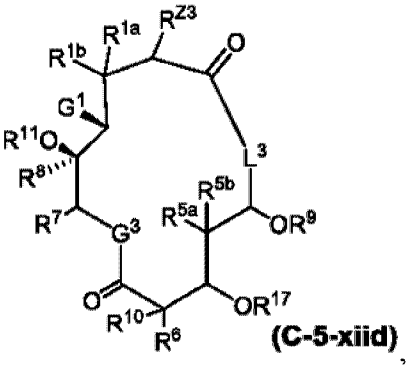
15-membered ring system



15-membered ring system

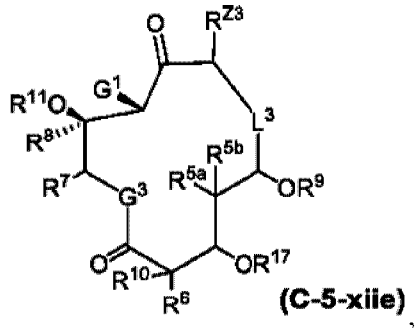


14-membered ring system

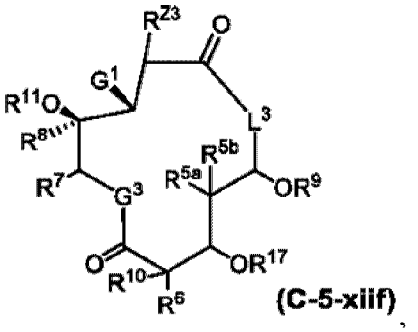


14-membered ring system

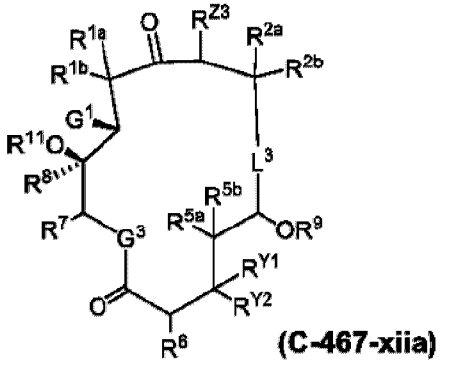
Date Reçue/Date Received 2020-06-25



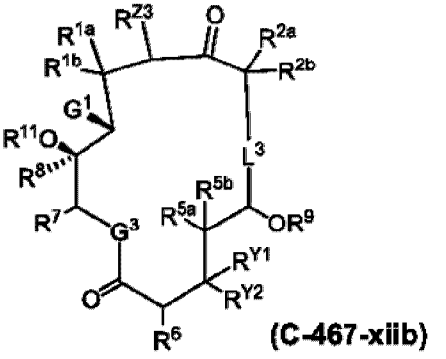
13-membered ring system



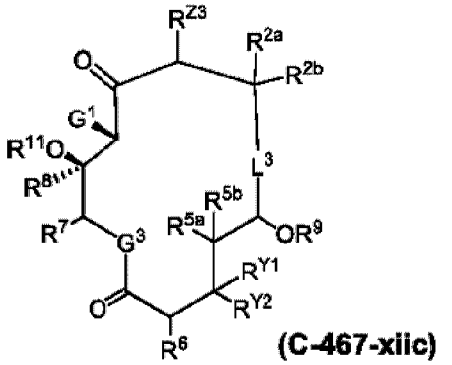
13-membered ring system



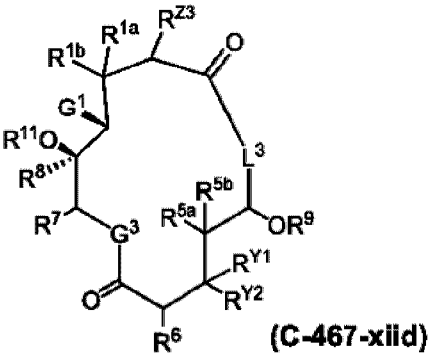
15-membered ring system



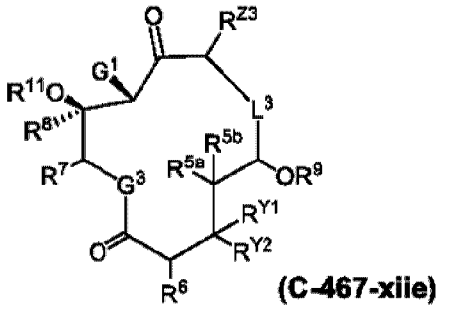
15-membered ring system



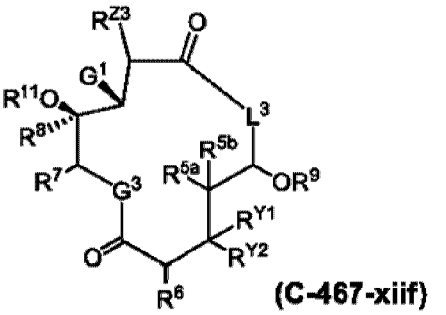
14-membered ring system



14-membered ring system

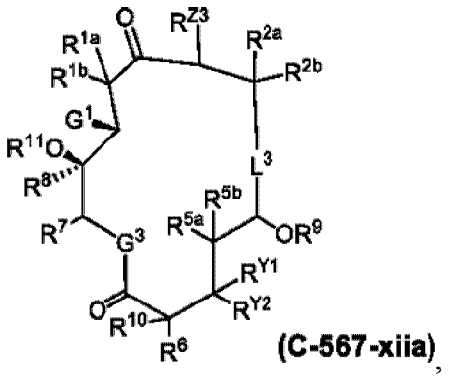


13-membered ring system



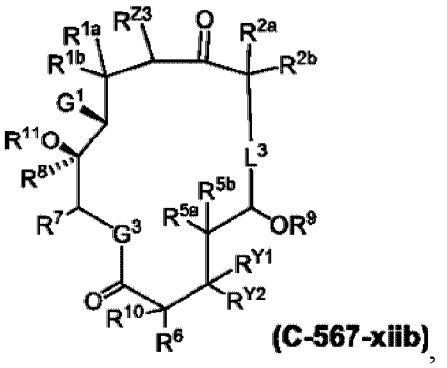
13-membered ring system

Date Reçue/Date Received 2020-06-25



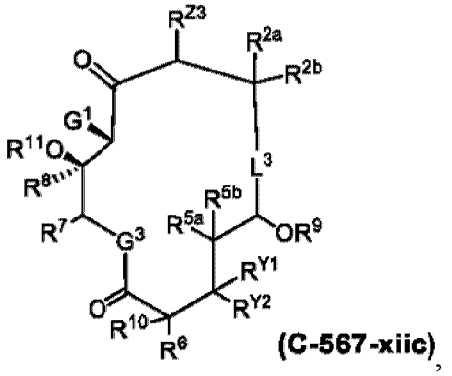
(C-567-xiia),

15-membered ring system



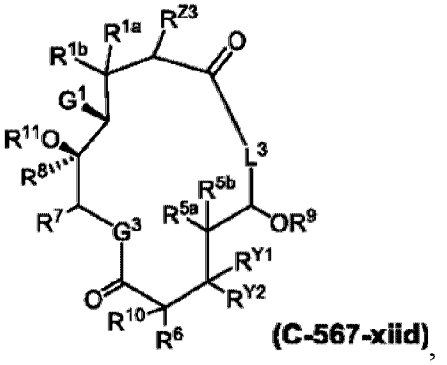
(C-567-xiib),

15-membered ring system



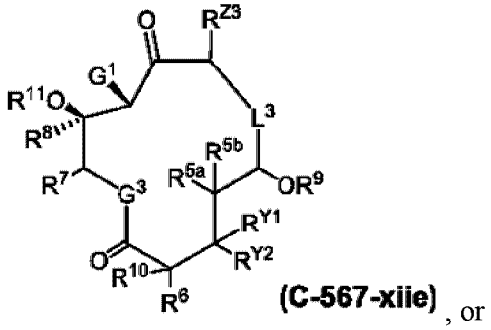
(C-567-xiic),

14-membered ring system



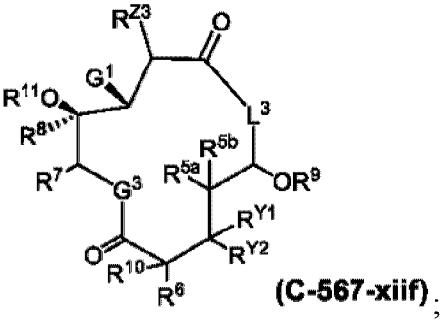
(C-567-xiid),

14-membered ring system



(C-567-xiie), or

13-membered ring system

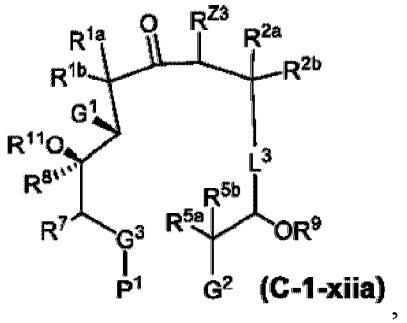


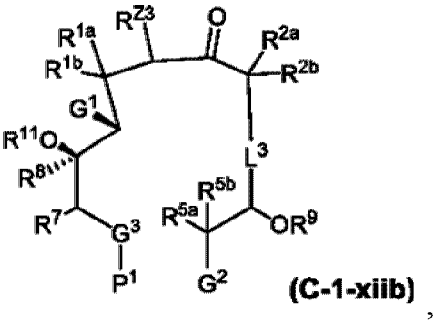
(C-567-xiif);

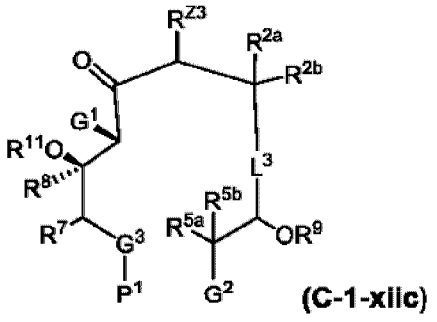
13-membered ring system

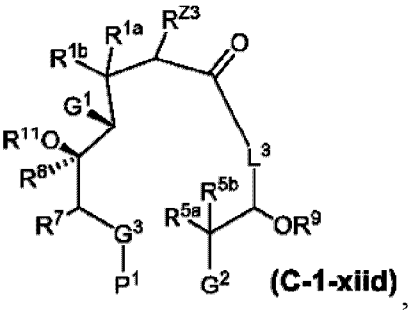
wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:

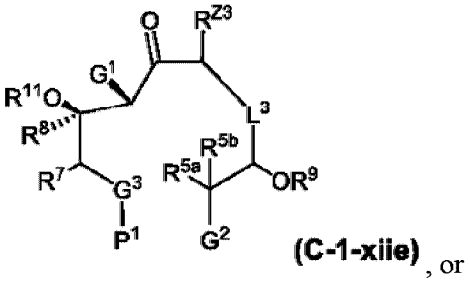
Date Reçue/Date Received 2020-06-25

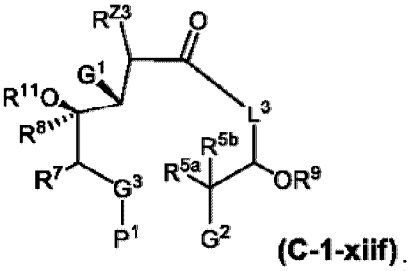

(C-1-xiia),


(C-1-xiib),

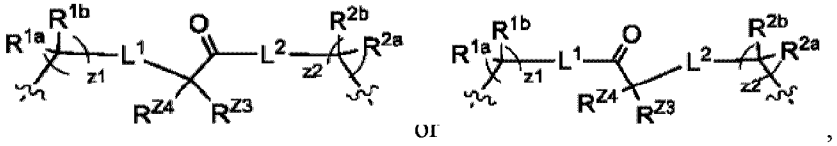

(C-1-xiic),


(C-1-xiid),

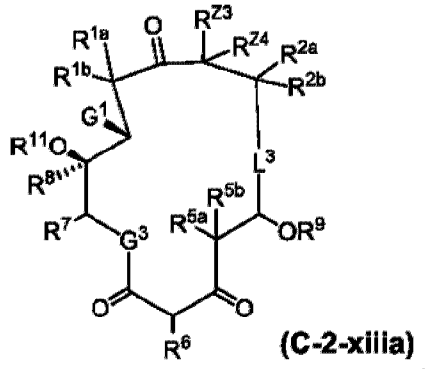

(C-1-xiie), or


(C-1-xiif);

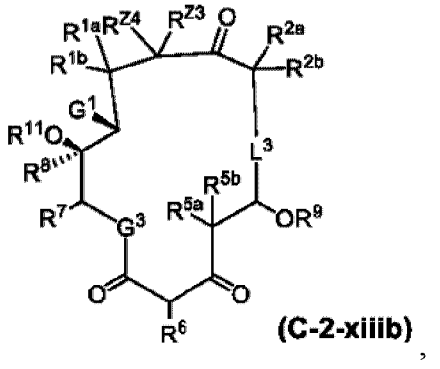
[17] an keto group of formula:


or

wherein L^1 and L^2 are each independently a bond or $–CH_2–$; z1 and z2 are 0, 1, or 2, *e.g.,* to provide a 13-, 14-, 15- or 16-membered ring system, *e.g.,* of formula:

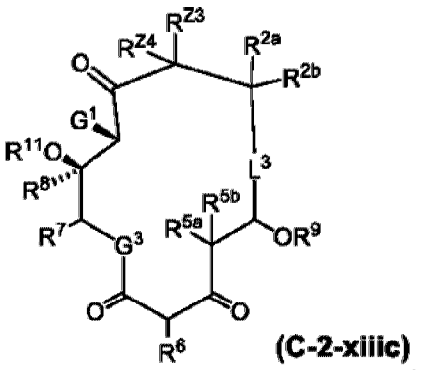

(C-2-xiia),

15-membered ring system


(C-2-xiib),

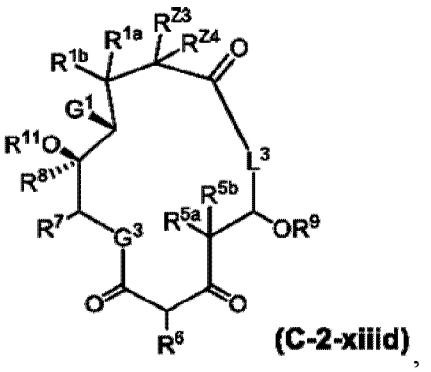
15-membered ring system

Date Reçue/Date Received 2020-06-25



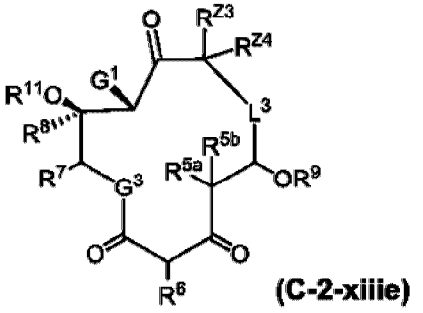
(C-2-xiiic)

14-membered ring system



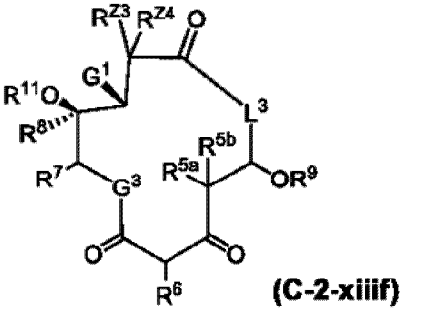
(C-2-xiiid)

14-membered ring system



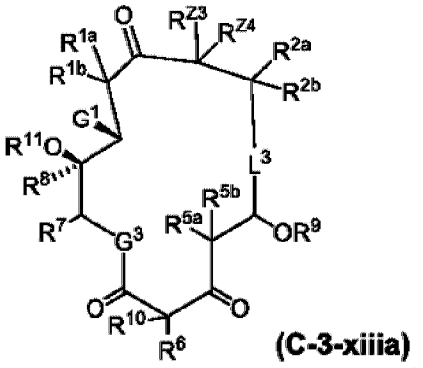
(C-2-xiiie)

13-membered ring system



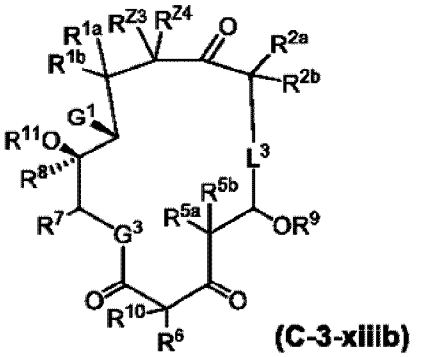
(C-2-xiiif)

13-membered ring system



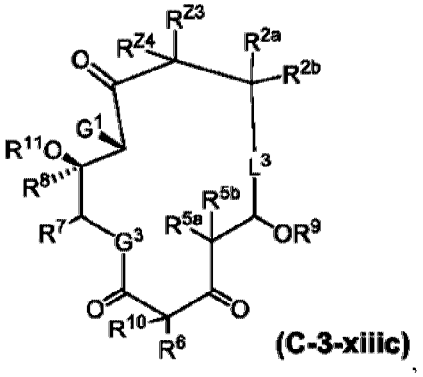
(C-3-xiiia)

15-membered ring system



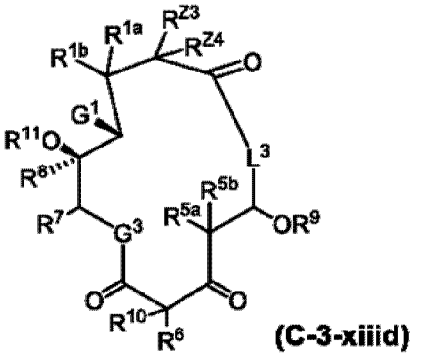
(C-3-xiiib)

15-membered ring system



(C-3-xiiic)

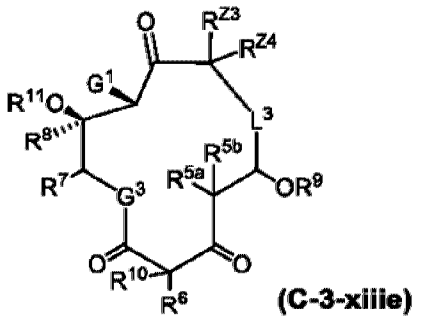
14-membered ring system



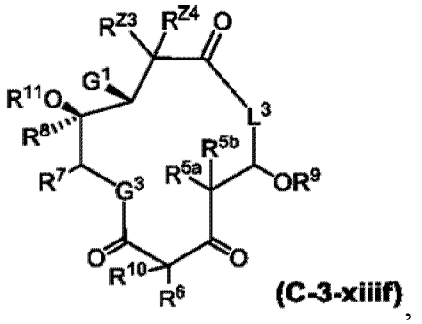
(C-3-xiiid)

14-membered ring system

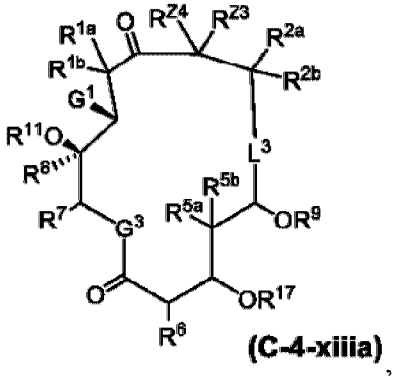
Date Reçue/Date Received 2020-06-25



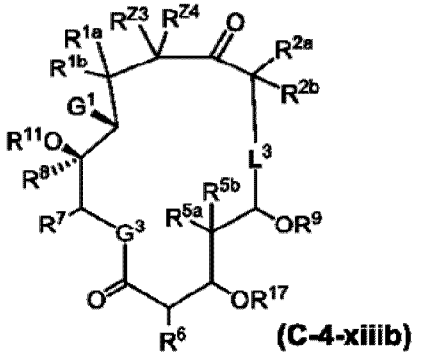
13-membered ring system



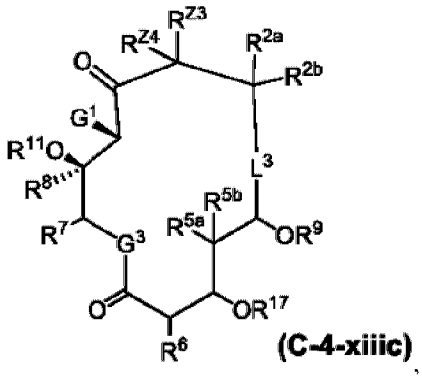
13-membered ring system



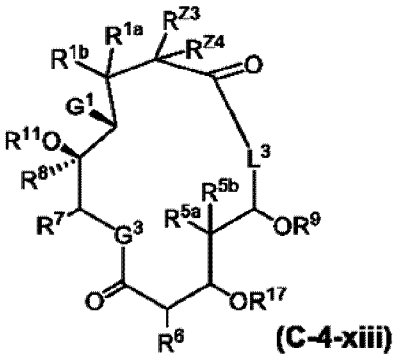
15-membered ring system



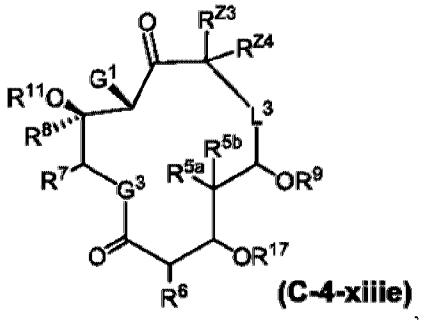
15-membered ring system



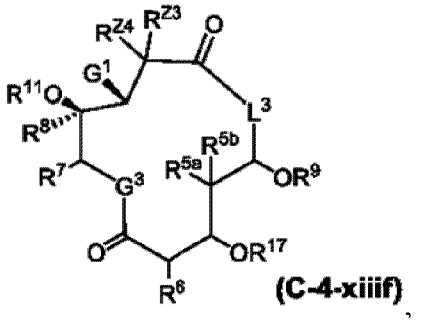
14-membered ring system



14-membered ring system

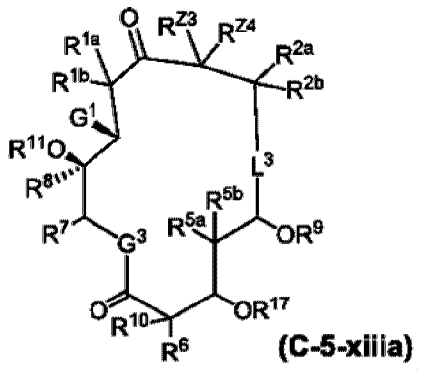


13-membered ring system



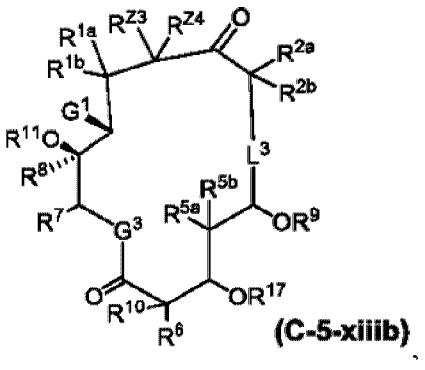
13-membered ring system

Date Reçue/Date Received 2020-06-25



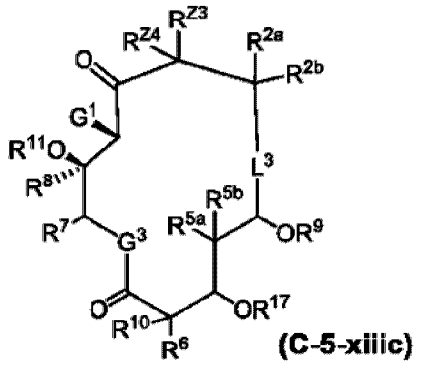
(C-5-xiiia)

15-membered ring system



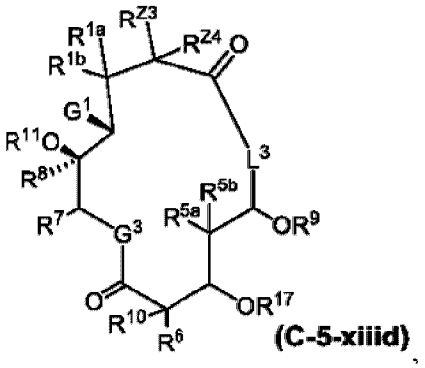
(C-5-xiiib)

15-membered ring system



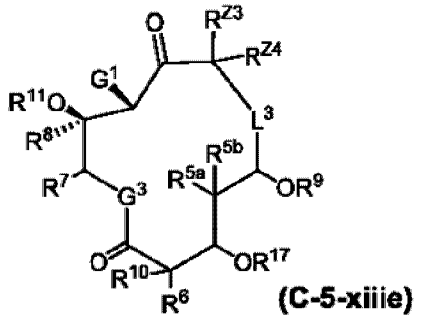
(C-5-xiiic)

14-membered ring system



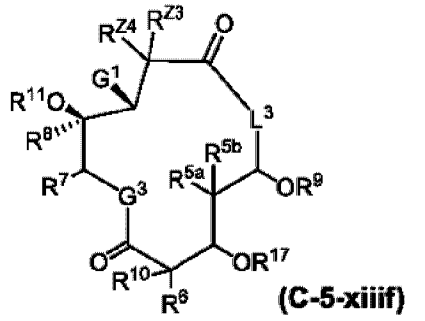
(C-5-xiiid)

14-membered ring system



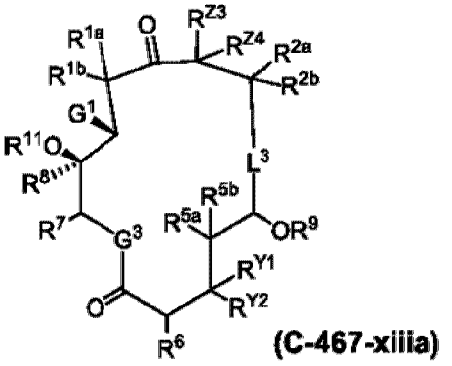
(C-5-xiiie)

13-membered ring system



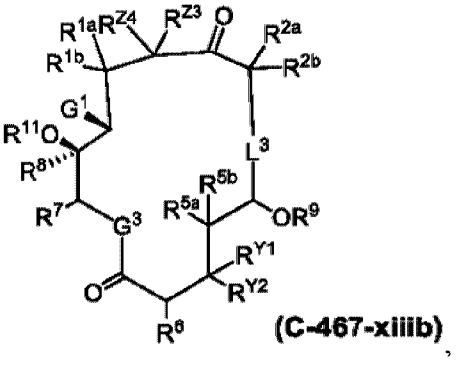
(C-5-xiiif)

13-membered ring system



(C-467-xiiia)

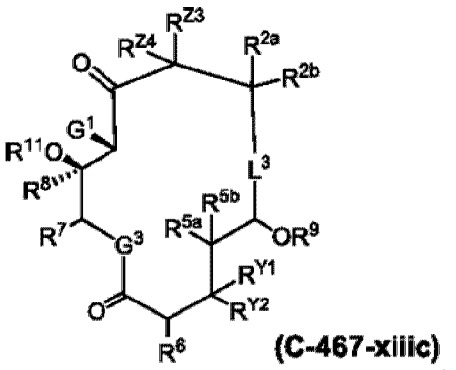
15-membered ring system



(C-467-xiiib)

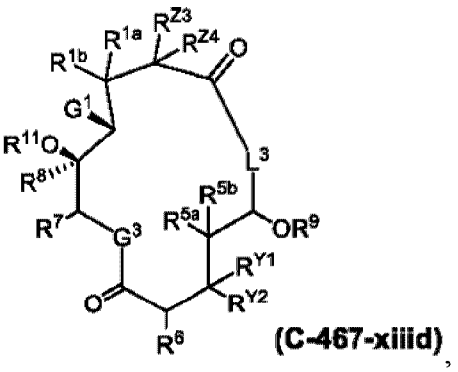
15-membered ring system

Date Reçue/Date Received 2020-06-25



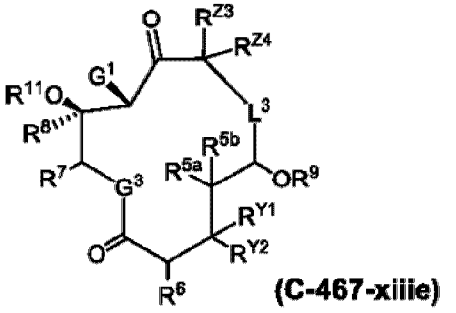
(C-467-xiiic)

14-membered ring system



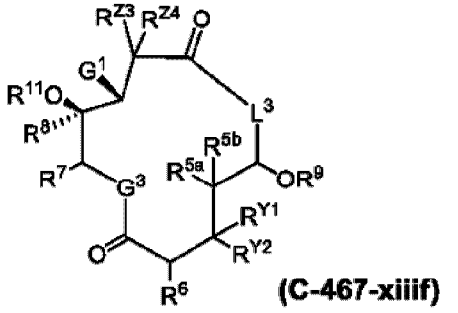
(C-467-xiiid)

14-membered ring system



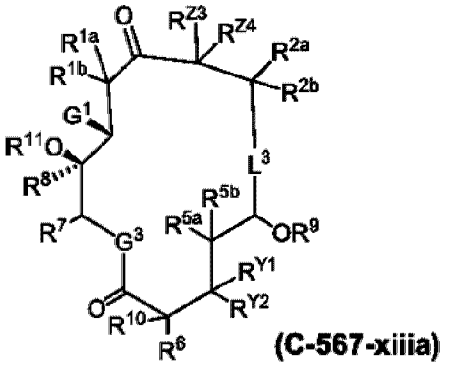
(C-467-xiiie)

13-membered ring system



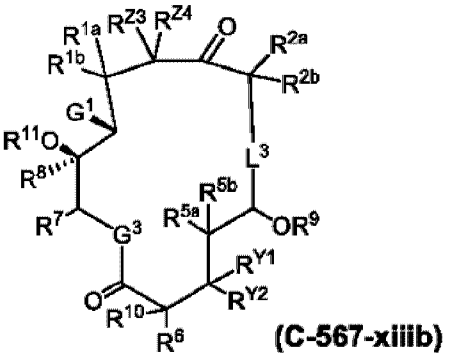
(C-467-xiiif)

13-membered ring system



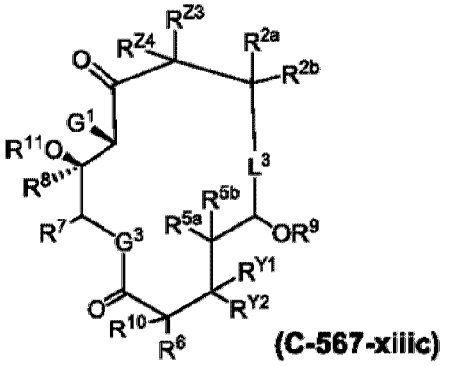
(C-567-xiiia)

15-membered ring system



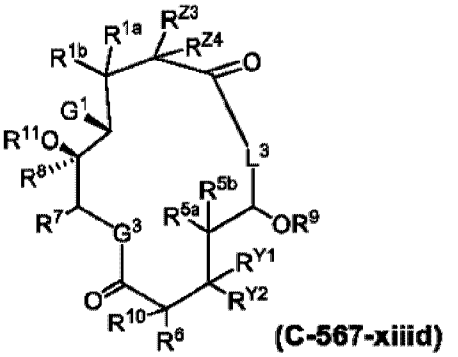
(C-567-xiiib)

15-membered ring system



(C-567-xiiic)

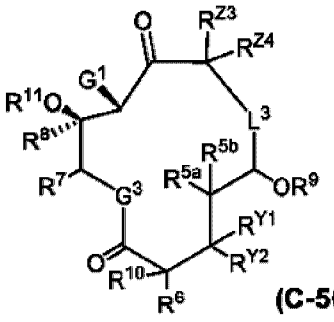
14-membered ring system



(C-567-xiiid)

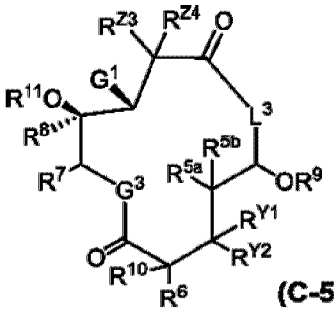
14-membered ring system

Date Reçue/Date Received 2020-06-25



(C-567-xiiie), or

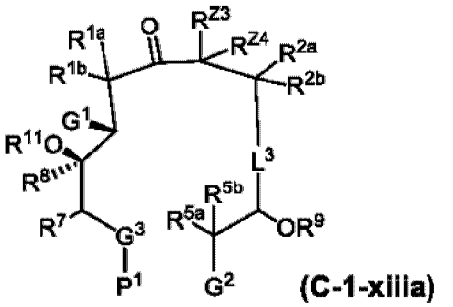
13-membered ring system



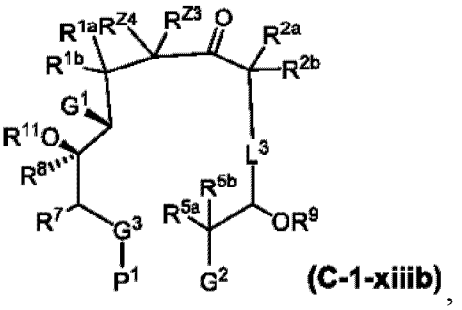
(C-567-xiiif);

13-membered ring system

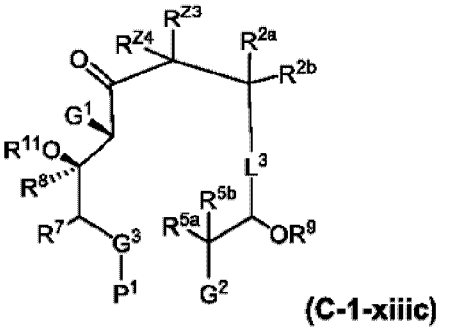
wherein in certain embodiments the macrolide is prepared, in part, from macrocyclization (*e.g.,* thermally induced) of the coupled precursor compound of the below formula, optionally followed by further synthetic manipulation, as described herein:



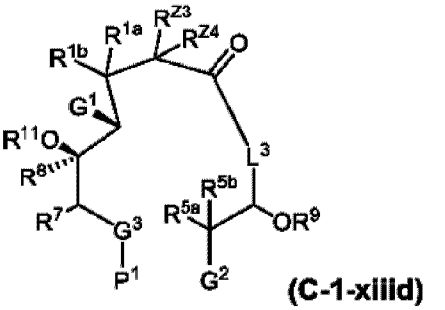
(C-1-xiiia),



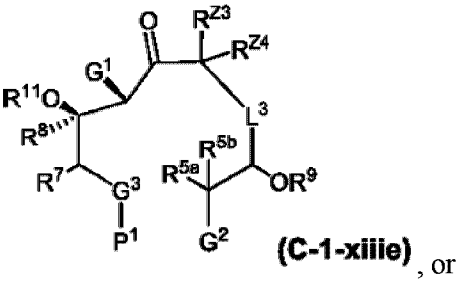
(C-1-xiiib),



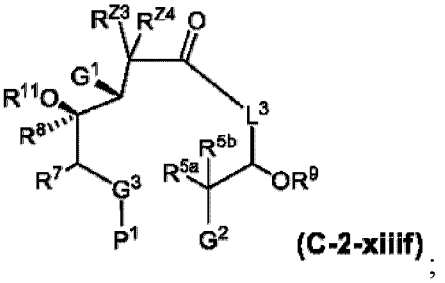
(C-1-xiiic),



(C-1-xiiid),



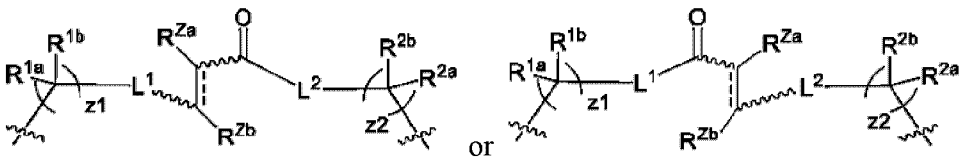
(C-1-xiiie), or



(C-2-xiiif);

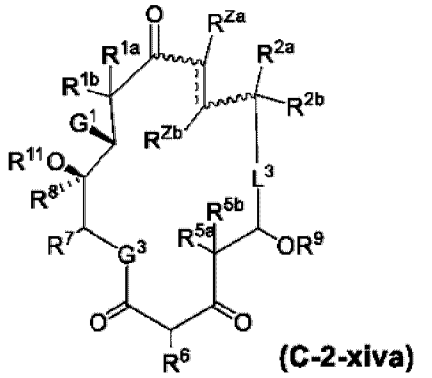
[18] a ketone of formula:

Date Reçue/Date Received 2020-06-25



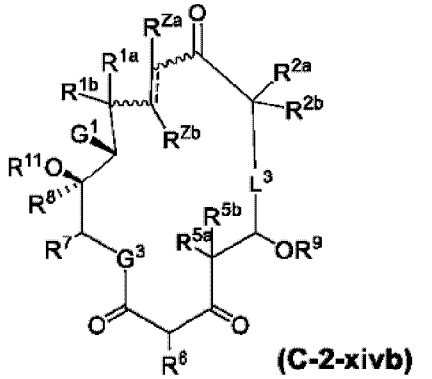
or

wherein L^1 and L^2 are each independently a bond or $-CH_2-$; z1 and z2 are each independently 0, 1, or 2, *e.g.,* to provide a 14-, 15- or 16-membered ring system, *e.g.,* of formula:



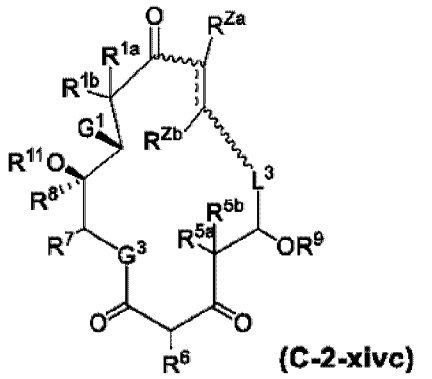
(C-2-xiva),

16-membered ring system



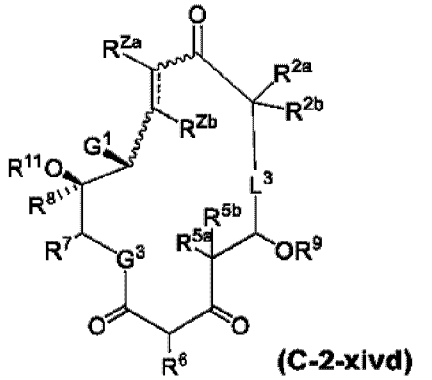
(C-2-xivb),

16-membered ring system



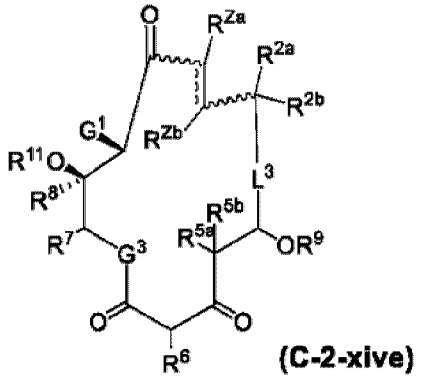
(C-2-xivc),

15-membered ring system



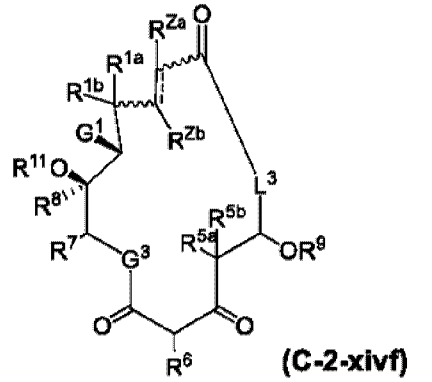
(C-2-xivd),

15-membered ring system



(C-2-xive),

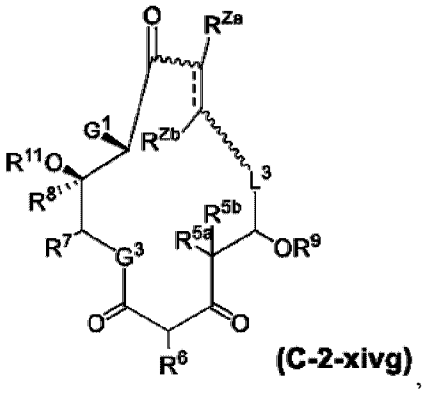
15-membered ring system



(C-2-xivf),

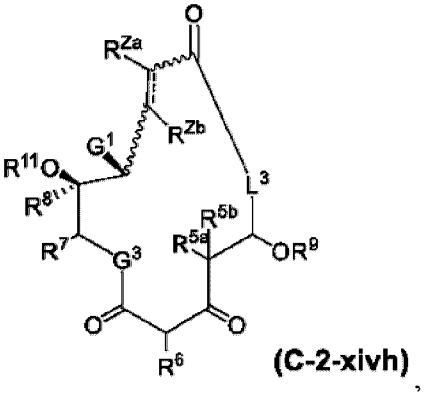
15-membered ring system

Date Reçue/Date Received 2020-06-25



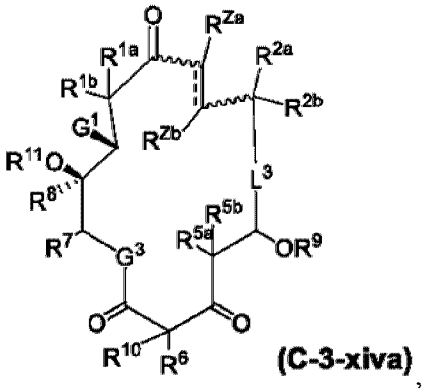
(C-2-xivg),

14-membered ring system



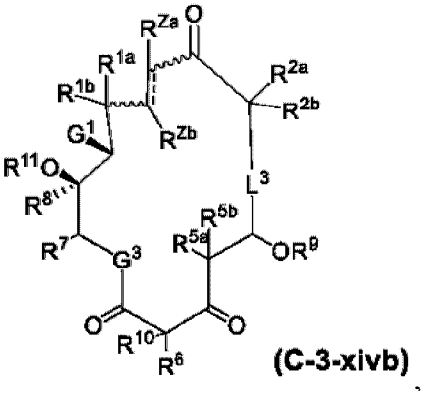
(C-2-xivh),

14-membered ring system



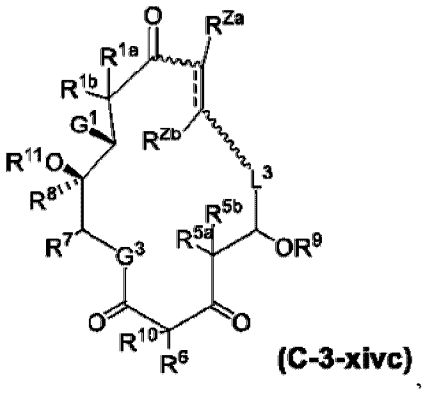
(C-3-xiva),

16-membered ring system



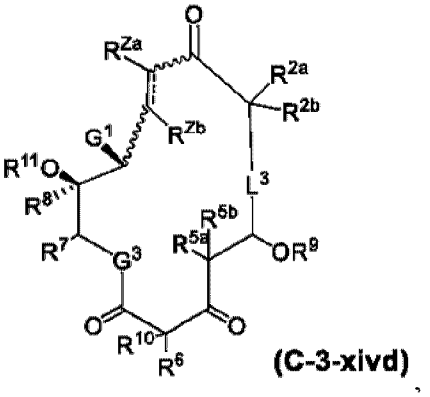
(C-3-xivb),

16-membered ring system



(C-3-xivc),

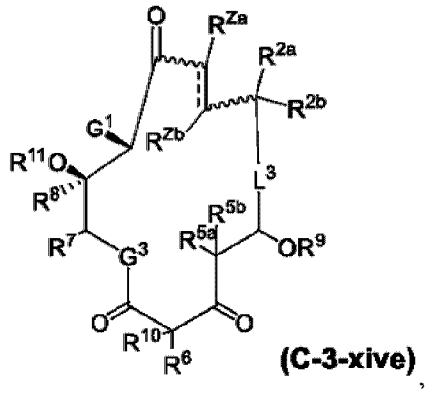
15-membered ring system



(C-3-xivd),

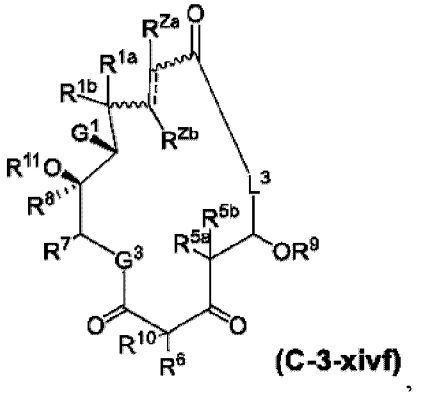
15-membered ring system

Date Reçue/Date Received 2020-06-25



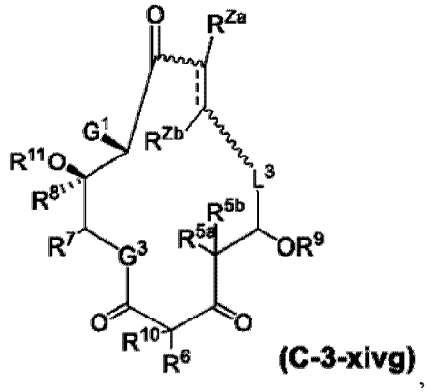
(C-3-xive)

15-membered ring system



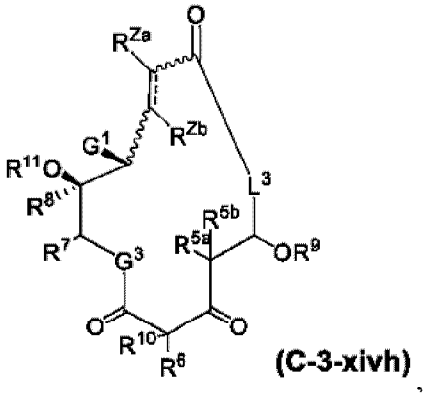
(C-3-xivf)

15-membered ring system



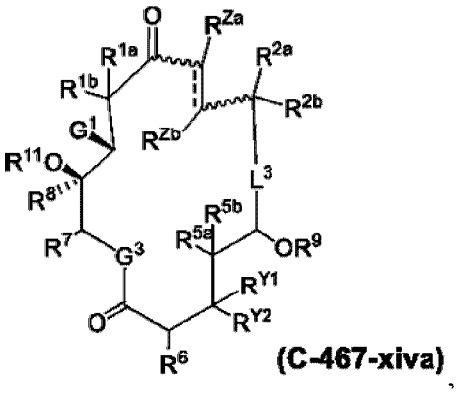
(C-3-xivg)

14-membered ring system



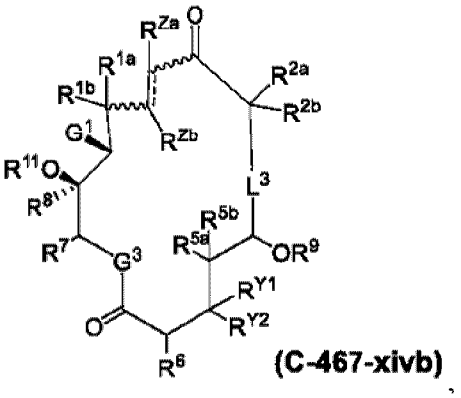
(C-3-xivh)

14-membered ring system



(C-467-xiva)

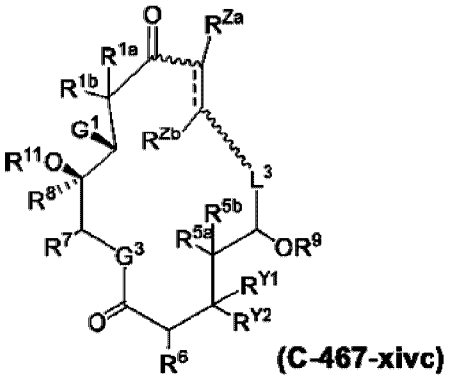
16-membered ring system



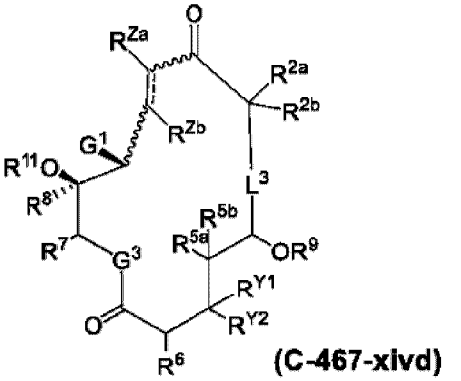
(C-467-xivb)

16-membered ring system

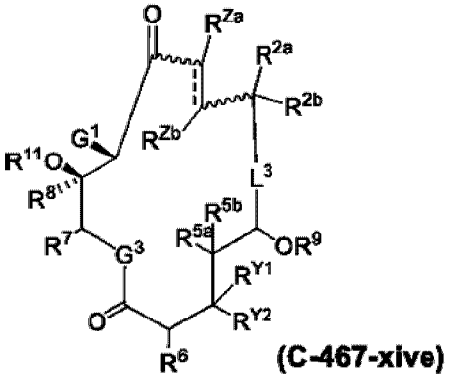
Date Reçue/Date Received 2020-06-25



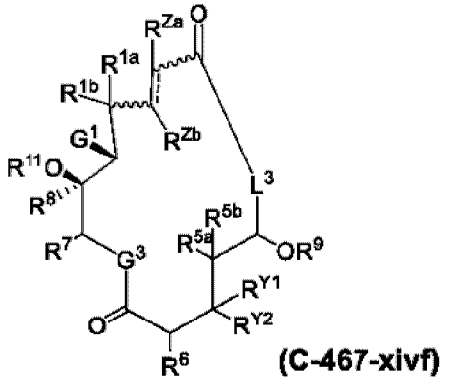
15-membered ring system



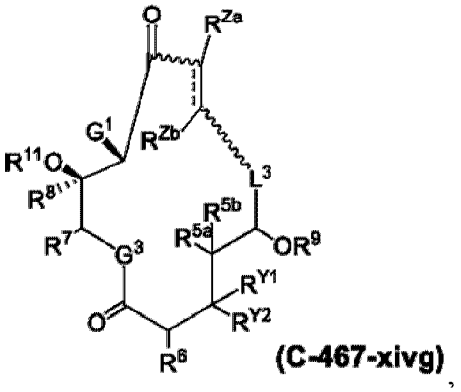
15-membered ring system



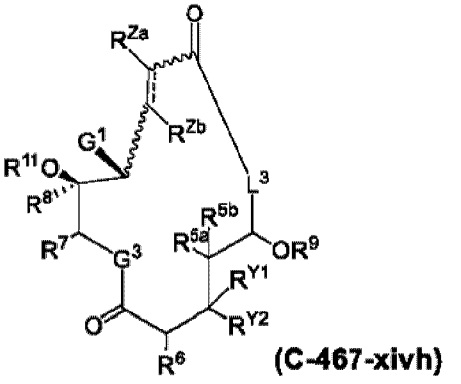
15-membered ring system



15-membered ring system

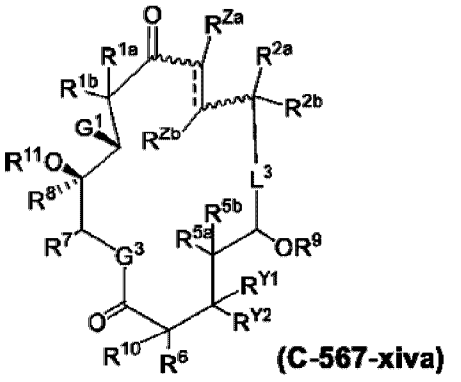


14-membered ring system



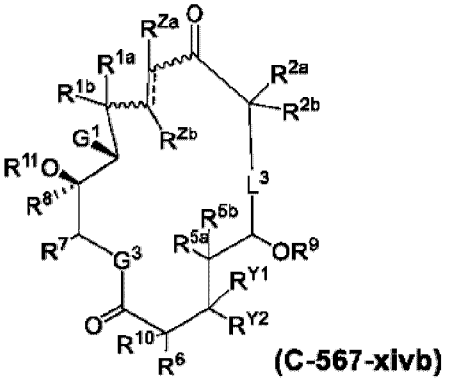
14-membered ring system

Date Reçue/Date Received 2020-06-25



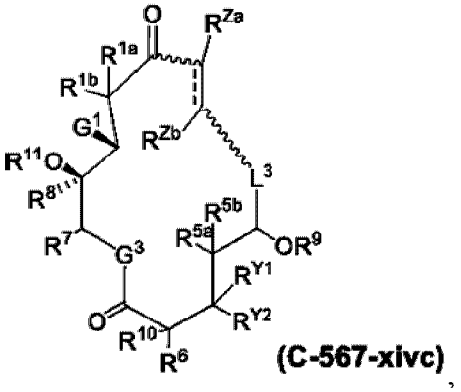
(C-567-xiva)

16-membered ring system



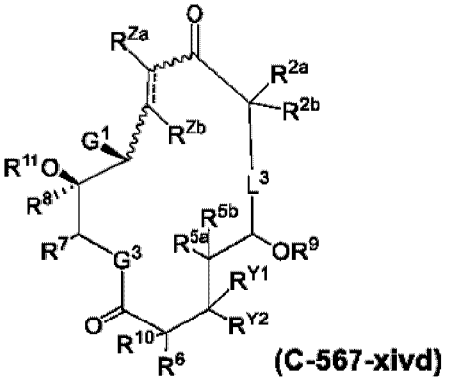
(C-567-xivb)

16-membered ring system



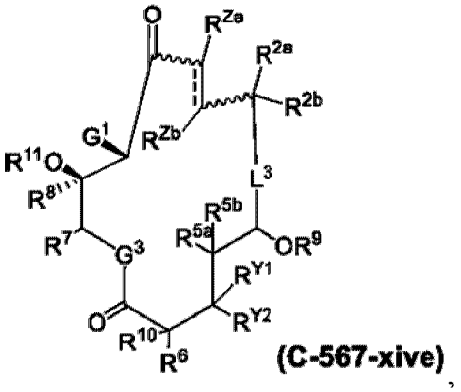
(C-567-xivc)

15-membered ring system



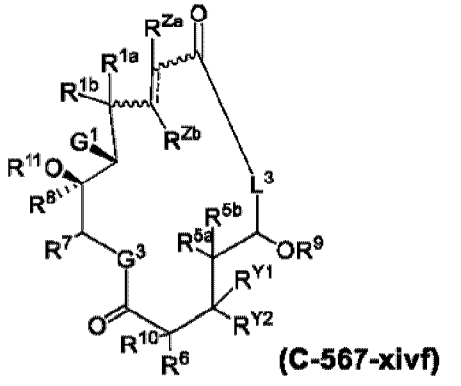
(C-567-xivd)

15-membered ring system



(C-567-xive)

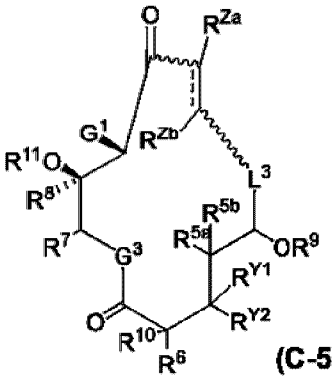
15-membered ring system



(C-567-xivf)

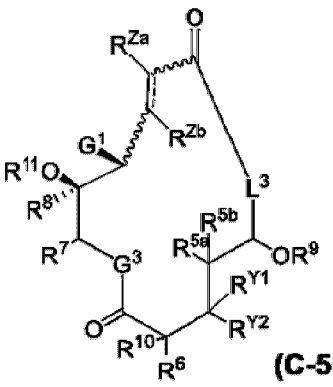
15-membered ring system

Date Reçue/Date Received 2020-06-25



(C-567-xivg), or

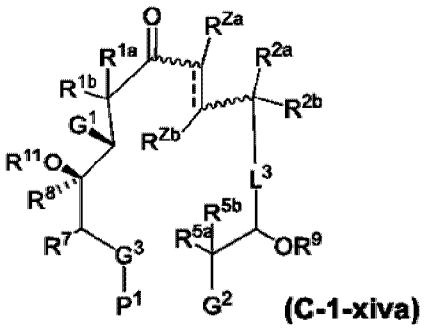
14-membered ring system



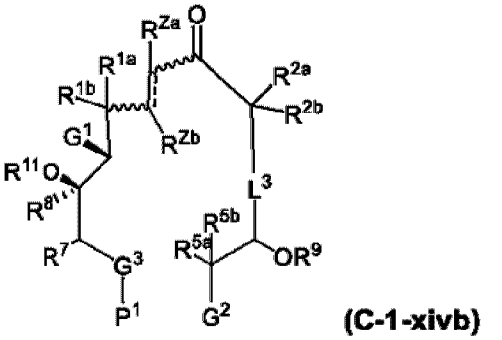
(C-567-xivh);

14-membered ring system

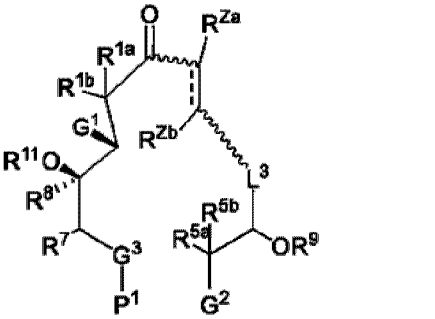
wherein the macrolide is prepared by macrocyclization (*e.g.,* thermally induced macrocyclization) of the coupled precursor of one of the formulae below, optionally followed by further synthetic manipulation, as described herein:



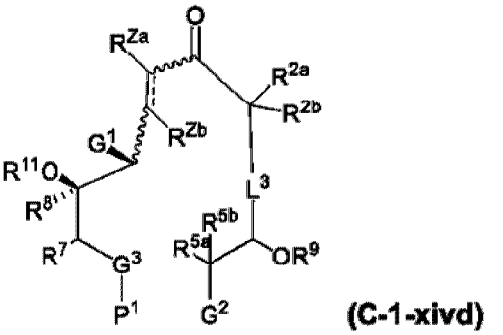
(C-1-xiva),



(C-1-xivb),

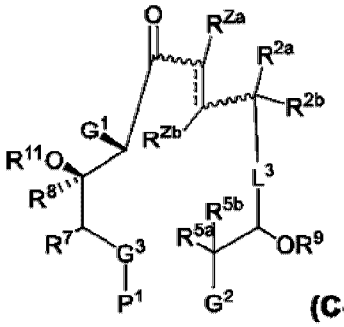


(C-1-xivc),

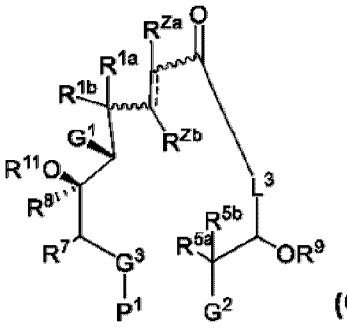


(C-1-xivd),

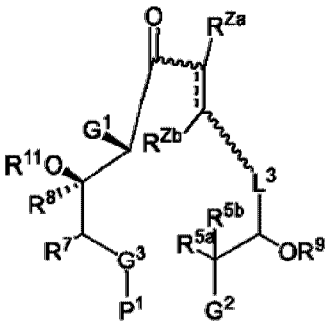
Date Reçue/Date Received 2020-06-25



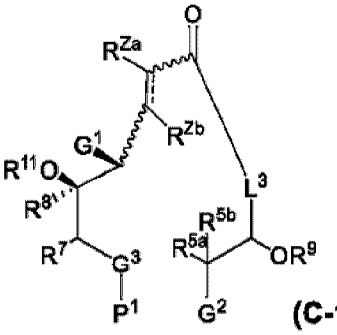
(C-1-xive),



(C-1-xivf),



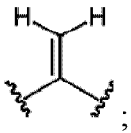
(C-1-xivg), or



(C-1-xivh);

wherein:

R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is halogen, or R^{Y1} and R^{Y2} are joined to form an oxo (=O) group;

each instance of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein R^{1a} and R^{1b} or R^{2a} and R^{2b} can be taken together to form  ;

R^{Za} and R^{Zb} are each independently hydrogen, halogen, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

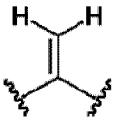
each instance of R^{Z2} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, $-C(=O)R^{Z8}$,

Date Reçue/Date Received 2020-06-25

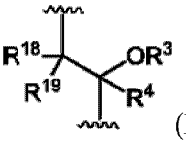
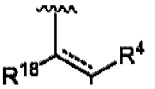
-C(=O)OR^{Z8}, -C(=O)N(R^{Z8})$_2$, or a nitrogen protecting group, or two R^{Z2} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring;

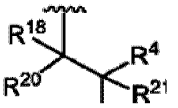
R$_{Z3}$ is hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl;

R$_{Z4}$ is halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl;

or wherein R^{Z3} and R^{Z4} can be taken together to form  ;

L$_3$ is a group of formula:

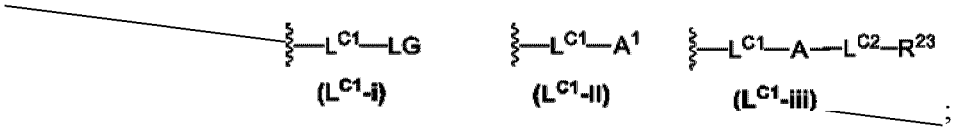
 (**L^3-i**),  (**L^3-ii**),



or (**L^3-iii**);

------ represents a single or double bond;

R$_3$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)R^{Z8}, -C(=O)OR^{Z8}, - C(=O)N(R^{Z8})$_2$, an oxygen protecting group, or a group of formula:


(L^{C1}-i) (L^{C1}-ii) (L^{C1}-iii)

R$_4$ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of R^{18} and R^{19} independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Date Reçue/Date Received 2020-06-25

each instance of R^{20} and R^{21} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, carbonyl, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring;

each instance of R^{5a} and R^{5b} is independently hydrogen, halogen, silyl, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substitued aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

$R_{7 \text{ and }} R^8$ are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

$R_{9 \text{ and }} R^{17}$ are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $–C(=O)R^{Z8}$, $–C(=O)OR^{Z8}$, $–C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a carbohydrate;

R_{10} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, and halogen;

G_3 is –O–, –S–, or $–N(R^{G1})–$, wherein R^{G1} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

P_1 is hydrogen, silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group;

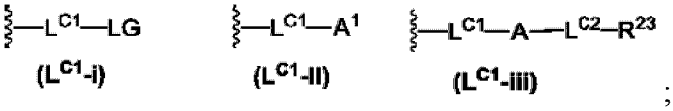
G_1 is $–OR^{12}$ or $–NR^{13}R^{14}$;

provided when G^1 is $–OR^{12}$, then:

Date Reçue/Date Received 2020-06-25

R^{11} and R^{12} are joined as a group of formula –C(=O)- to provide a cyclic carbonate, or

R^{11} and R^{12} are not joined, and R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, and R^{12} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group, or a group of formula:



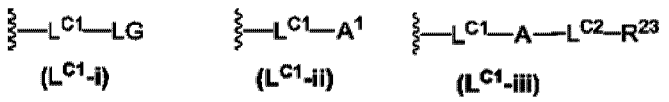
;

or provided when G^1 is $-NR^{13}R^{14}$, then:

R^{11} and R^{13} are joined as a group of formula –C(=O)- to provide a cyclic carbamate, or

R^{11} and R^{13} are not joined, R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, R^{13} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

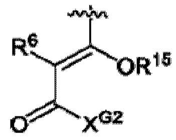
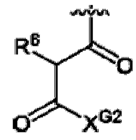
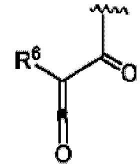
R^{14} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group, $-C(=O)R^{Z8}$, or $-C(=O)OR^{Z8}$, or a group of formula:

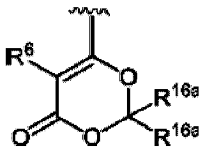
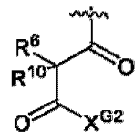


or R^{13} and R^{14} are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl;

G^2 is a group of formula:

Date Reçue/Date Received 2020-06-25

 ,
 ,
 ,

 or 

each instance of X^{G2} is $-OR^{15}$, $-SR^{15}$, or $-N(R^{15})_2$;

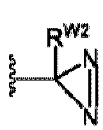
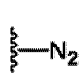
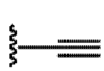
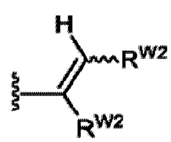
each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or two R^{15} groups can be taken together to form an optionally substituted heteroaryl or heterocyclic ring;

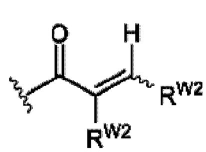
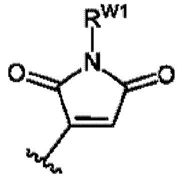
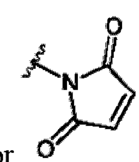
each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of L^{C1} and L^{C2} is independently a bond, or a linking group selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, and combinations thereof;

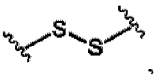
Leaving group (LG) is –Br, –I, –Cl, $-O(C{=}O)R^{LG}$, or $-O(SO)_2R^{LG}$, wherein R^{LG} is optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl;

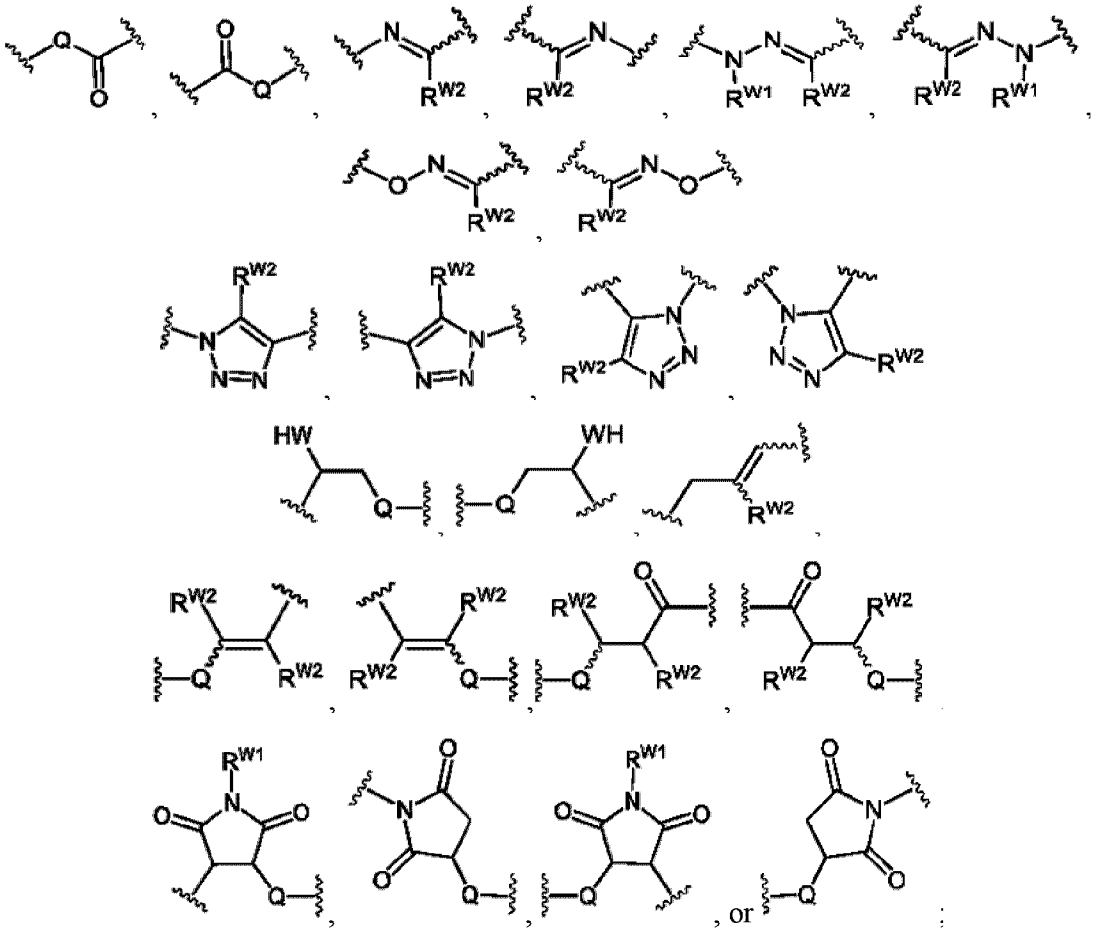
each instance of A^1 and A^2 is independently a leaving group (LG), –SH, –OH, –NH_2, $-NH-NH_2$, $-N_3$, $-O-NH_2$,

$-C(=O)R^{X1}$,  ,  ,  ,  ,  ,  .

 ,  , or  ;

Date Reçue/Date Received 2020-06-25

A is –NH–, –NH–NH–, –NH–O–, –O–NH–, –S–, –O–,  ,



Q is –NH–, –NH–NH–, –O–NH–,–NH–O–,–S–, or –O–;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; or a nitrogen protecting group;

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; or optionally substituted heteroaryl, or two R^{W2} groups are joined to form an optionally substituted cyclic moiety;

R^{X1} is hydrogen, halogen, or $–OR^{X2}$, wherein R^{X2} is hydrogen; optionally substituted alkyl; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted

Date Reçue/Date Received 2020-06-25

alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or an oxygen protecting group;

R_{23} is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; or optionally substituted heteroaryl; and

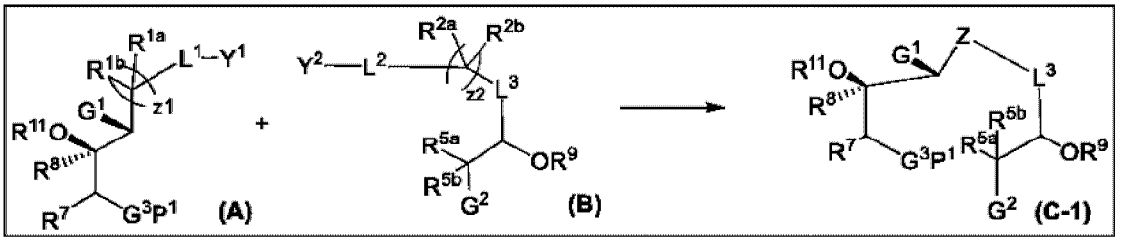
each instance of R^{Z8} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^{Z8} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring;

or A is a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl.

Coupling and Macrocyclization

[00101] As generally described herein, macrolides of the present invention are prepared by coupling of an western half (**A**) with an eastern half (**B**) to provide a compound of Formula (C-1), as depicted in Scheme 8:

Scheme 8.

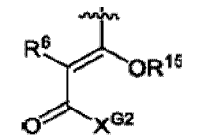


or salt thereof, wherein L^1, L^2, L^3, G^1, G^3, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{5a}, R^{5b}, R^7, R^8, R^9, R^{11}, z1, and z2 are as defined herein;

P_1 is hydrogen, silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group;

G_2 is a group of formula:

Date Reçue/Date Received 2020-06-25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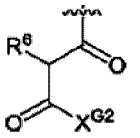
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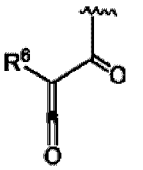
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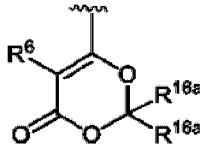
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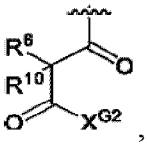
or

,

wherein R^6 and R^{10} are as defined herein;

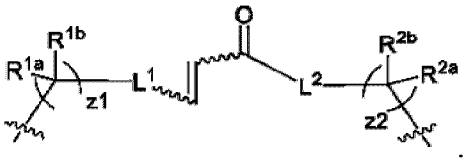
each instance of X^{G2} is $–OR^{15}$, $–SR^{15}$, or $–N(R^{15})_2$;

each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or two R^{15} groups can be taken together to form an optionally substituted heteroaryl or heterocyclic ring;

each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

one of Y^1 and Y^2 is $–Z^4H$ or $–CH_2NO_2$, and the other of Y^1 and Y^2 is a leaving group (LG), $–C(=O)R^{Z3}$, $–C(=O)OR^{Z3}$, $–C(=O)LG$, $–C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3})$, or $–C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3})$, wherein Z^4 is –O–, –S–, or $–NR^{Z2}–$, and wherein the leaving group (LG), R^{Z3}, R^{Z4}, R^{P1}, R^{P2}, and R^{P3} are as defined herein, to provide various linkages of formula Z.

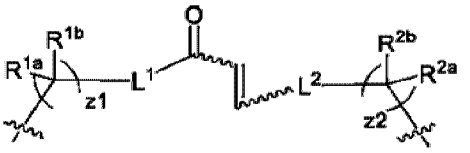
[00102] For example, in certain embodiments, when Y^1 is $–C(=O)R^{Z3}$ and R^{Z3} is hydrogen (*aka* wherein Y^1 is –CHO) and Y^2 is $–C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3})$ or $–C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3})$, coupling of the eastern and western halves *via* a Wittig or Horner-Emmons reaction forms the moiety –CH=CH-C(=O)–, and provides a compound of Formula (**C-1**), wherein Z is an $a_{\square}\square$-unsaturated ketone of formula:



[00103] In certain embodiments, the double bond of the above recited formula is provided in the *cis*-configuration. In certain embodiments, the double bond of the above recited formula is provided in the *trans*-configuration.

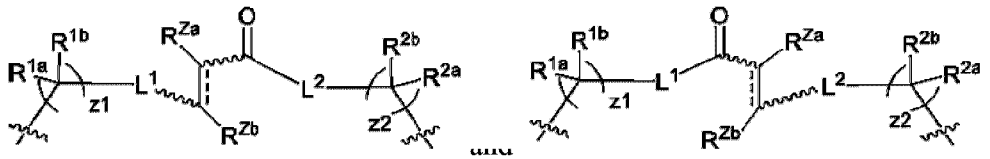
Date Reçue/Date Received 2020-06-25

[00104] In certain embodiments, when Y^2 is $-C(=O)R^{Z3}$ and R^{Z3} is hydrogen (*aka* wherein Y^1 is –CHO) and Y^1 is $-C(=O)\text{-}CH=P(R^{P1})(R^{P2})(R^{P3})$ or $-C(=O)\text{-}CH_2\text{-}P(O)(OR^{P2})(OR^{P3})$, coupling of the eastern and western halves *via* a Wittig reaction or Horner-Emmons reaction forms a moiety -C(=O)–CH=CH-, and provides a compound of Formula (**C-1**), wherein Z is an a,J3 -unsaturated ketone of formula:



[00105] In certain embodiments, the double bond of the above recited formula is provided in the *cis*-configuration. In certain embodiments, the double bond of the above recited formula is provided in the *trans*-configuration.

[00106] Optional synthetic modification of the moieties –CH=CH-C(=O)– and -C(=O)–CH=CH- is further contemplated herein. For example, the double bond may be reduced to a single bond, and optionally the carbon alpha to the ketone may be substituted by a non-hydrogen group R^{Za}. A nucleophile may react with the double bond via 1,4-addition of a non-hydrogen group R^{Zb} optionally followed by alpha substitution via a non-hydrogen group R^{Za}. Various synthetic modifications of the a,J3 -unsaturated ketone formula contemplated herein are thus encompassed by the formulae:

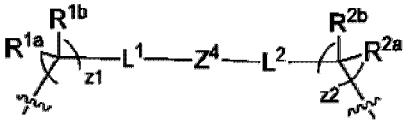


wherein represents a single or double bond, and R^{Za} and R^{Zb} are each independently hydrogen or a non-hydrogen group (*e.g.,* halogen, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl). The above formulae thus encompass the initial Wittig reaction or Horner-Emmons reaction linkages, *i.e.,* wherein represents a double bond and R^{Za} and R^{Zb} are each hydrogen, as well as additional synthetic modifications of the linkage, *e.g.,* wherein represents a single bond, and R^{Za} and R^{Zb} are each independently hydrogen or a non-hydrogen group, or wherein represents a single bond or double bond, and R^{Za} and R^{Zb} are each independently hydrogen or a non-hydrogen group, provided at least one of R^{Za} and R^{Zb} is a non-hydrogen group. In certain embodiments, wherein represents a double bond,

Date Reçue/Date Received 2020-06-25

R^{Za} and R^{Zb} are in a *cis*-configuration. In certain embodiments, wherein represents a double bond , R^{Za} and R^{Zb} are in a *trans*-configuration.

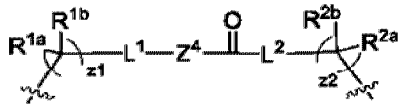
[00107] In certain embodiments, when Y^1 is $-Z^4H$ and Y^2 is a leaving group (LG), or when Y^2 is $-Z^4H$ and Y^1 is a leaving group (LG), coupling of the eastern and western halves by nucleophilic displacement (nucleophilic substitution), optionally in the presence of a base, provides a compound of Formula (**C-1**), wherein Z is an ether, thioether, or amine of formula:



,

wherein Z^4 is –O–, –S–, or $-NR^{Z2}$–, and wherein R^{Z2} is hydrogen or a non-hydrogen group. Exemplary bases include, but are not limited to, organic bases (*e.g.,* pyridine, DMAP, Hunig's base) and inorganic bases (*e.g.,* sodium bicarbonate, sodium carbonate). Exemplary leaving groups include bromine, chlorine, iodine, tosylate, triflate, mesylate, and besylate.

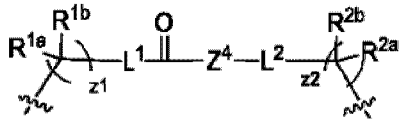
[00108] In certain embodiments, when Y^1 is $-Z^4H$, and Y^2 is $-C(=O)OR^{Z3}$ or –C(=O)LG, coupling of the eastern and western halves by 1,2-nucleophilic addition , optionally in the presence of a base, provides a compound of Formula (**C-1**), wherein Z is an ester, thioester, or amide of formula:



,

wherein Z^4 is –O–, –S–, or $-NR^{Z2}$–, and wherein R^{Z2} is hydrogen or a non-hydrogen group. In certain embodiments, wherein R^{Z3} is hydrogen, the reaction proceeds in the presence of a coupling agent, *e.g.,* a carbodiimide reagent. Exemplary bases include, but are not limited to, organic bases (*e.g.,* pyridine, DMAP, Hunig's base) and inorganic bases (*e.g.,* sodium bicarbonate, sodium carbonate). Exemplary leaving groups include bromine, chlorine, iodine, tosylate, mesylate, triflate, and besylate.

[00109] Alternatively, in certain embodiments, when Y^2 is $-Z^4H$, and Y^1 is $-C(=O)OR^{Z3}$ or –C(=O)LG, coupling of the eastern and western halves by 1,2-nucleophilic addition, optionally in the presence of a base, provides a compound of Formula (**C-1**), wherein Z is an ester, thioester, or amide of formula:



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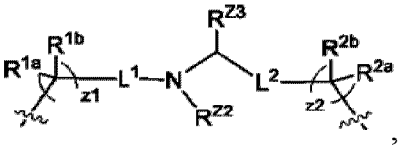
Date Reçue/Date Received 2020-06-25

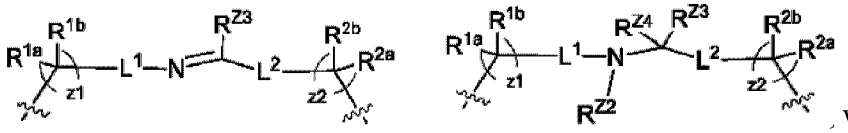
wherein Z^4 is –O–, –S–, or $–NR^{Z2}–$, and wherein R^{Z2} is hydrogen or a non-hydrogen group. In certain embodiments, wherein R^{Z3} is hydrogen, the reaction proceeds in the presence of a coupling agent, *e.g.,* a carbodiimide reagent. Exemplary bases include, but are not limited to, organic bases (*e.g.,* pyridine, DMAP, Hunig's base) and inorganic bases (*e.g.,* sodium bicarbonate, sodium carbonate). Exemplary leaving groups include bromine, chlorine, iodine, tosylate, mesylate, triflate, and besylate.

[00110] In certain embodiments, wherein Y^1 is $–NH_2$ or $–NHR^{Z2}$, and Y^2 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves by reductive amination, optionally followed by protection of the amine group by a non-hydrogen R^{Z2}, provides a compound of Formula (**C-1**), wherein Z is an amine of formula:



wherein R^{Z2} is hydrogen or a non-hydrogen group. Exemplary reductive amination conditions include, but are not limited to, use of $B_{10}H_{14}$, $InCl_3/Et_3SiH$, $NaBH_4$, $NaBH_4/H_3BO_3$, $NaBH_3CN$ or $NaBH(OAc)_3$, optionally in the prescence of an acid (*e.g.,* AcOH, TFA) or protic solvent (*e.g.,* MeOH). In certain embodiments, R^{Z2} is hydrogen. In certain embodiments, R^{Z2} is methyl. In certain embodiments, R^{Z2} is $-C(=O)R^{Z8}$. In certain embodiments, R^{Z2} is $–C(=O)Me$. In certain embodiments, R^{Z2} is a nitrogen protecting group.

[00111] In certain embodiments, wherein Y^1 is $–NH_2$, and Y^2 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves by imine formation, optionally followed by addition of a group R^{Z4} to the imine double bond, and optionally followed by protection of the amine group by a non-hydrogen R^{Z2}, provides a compound of Formula (**C-1**), wherein Z is an imine or amine of formula:

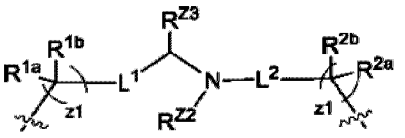


wherein R^{Z2} is hydrogen or a non-hydrogen group. In certain embodiments, R^{Z2} is hydrogen. In certain embodiments, R^{Z2} is protected as methyl, $-C(=O)R^{Z8}$, or a nitrogen protecting group. In certain embodiments, R^{Z4} is added to the imine double bond via a nucleophilic reagent, $R^{Z4}M$, wherein M is an anion, Li, K, CuX, or MgX, wherein X is halogen.

[00112] Alternatively, in certain embodiments, wherein Y^2 is $–NH_2$ or $–NHR^{Z2}$ and Y_1 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves by reductive amination, optionally

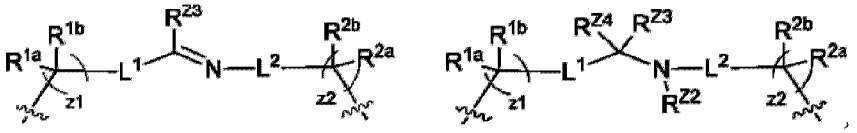
Date Reçue/Date Received 2020-06-25

followed by protection of the amine group by a non-hydrogen R^{Z2}, provides a compound of Formula (**C-1**), wherein Z is an amine of formula:



wherein R^{Z2} is hydrogen or a non-hydrogen group. Exemplary reductive amination conditions include, but are not limited to, use of $B_{10}H_{14}$, $InCl_3/Et_3SiH$, $NaBH_4$, $NaBH_4/H_3BO_3$, $NaBH_3CN$ or $NaBH(OAc)_3$, optionally in the prescence of an acid (*e.g.,* AcOH, TFA) or protic solvent (*e.g.,* MeOH). In certain embodiments, R^{Z2} is hydrogen. In certain embodiments, R^{Z2} is protected as methyl, $-C(=O)R^{Z8}$, or a nitrogen protecting group.

[00113] In certain embodiments, wherein Y^2 is $-NH_2$, and Y^1 is $-C(=O)R^{Z3}$, coupling of the eastern and western halves by imine formation, optionally followed by addition of a group R^{Z4} to the imine double bond, optionally followed by protection of the amine group by a non-hydrogen R^{Z2}, provides a compound of Formula (**C-1**), wherein Z is an imine or amine of formula:

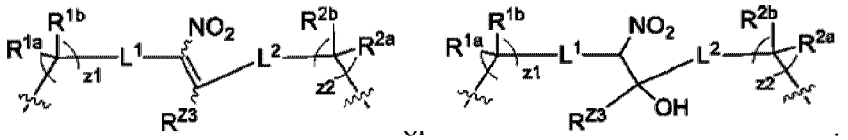


wherein R^{Z2} is hydrogen or a non-hydrogen group. In certain embodiments, R^{Z2} is hydrogen. In certain embodiments, R^{Z2} is protected as methyl, $-C(=O)R^{Z8}$, or a nitrogen protecting group. In certain embodiments, R^{Z4} is added to the imine double bond via a nucleophilic reagent, $R^{Z4}M$, wherein M is an anion, Li, K, CuX, or MgX, wherein X is halogen.

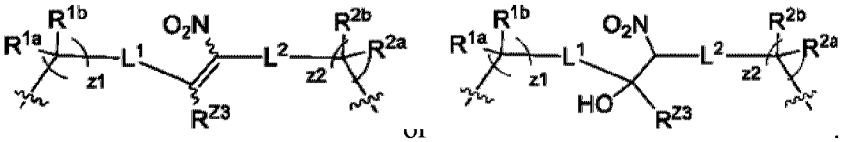
[00114] Further contemplated are nitro-aldol reaction (Henry reaction) coupling products, and oxidized, reduced, and/or addition products formed therefrom. The nitro aldol reaction may be catalyzed or promoted by many different sets of conditions, *e.g.,* use of an organic base, inorganic base, quaternary ammonium salt, and/or a catalyst; and use of protic or aprotic solvents and/or use of solventless conditions. See, *e.g.,* Luzzio *Tetrahedron* (2001) 915-945, for a review of various conditions employed in a nitro aldol reaction.

[00115] For example, in certain embodiments, wherein Y^1 is $-CH_2NO_2$, and Y^2 is $-C(=O)R^{Z3}$, coupling of the eastern and western halves provides a compound of Formula (**C-1**), wherein Z is a group of formula:

Date Reçue/Date Received 2020-06-25

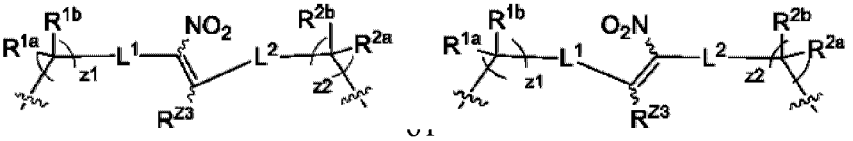


[00116] Alternatively, in certain embodiments, wherein Y^2 is $–CH_2NO_2$, and Y^1 is $–C(=O)R^{Z3}$, coupling of the eastern and western halves provides a compound of Formula (**C-1**), wherein Z is a group of formula:

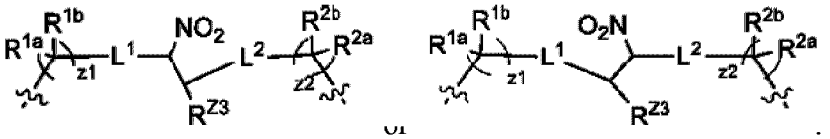


[00117] With the nitro-aldol coupling product in hand, the nitro ($-NO_2$) moiety may be manipulated at any stage in the synthesis.

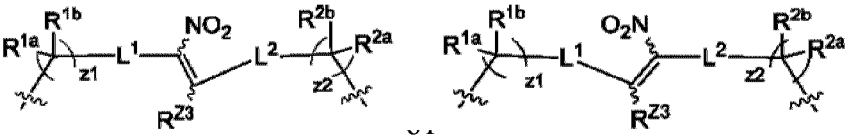
[00118] For example, reduction of the double bond of the nitro-aldol product of formula:



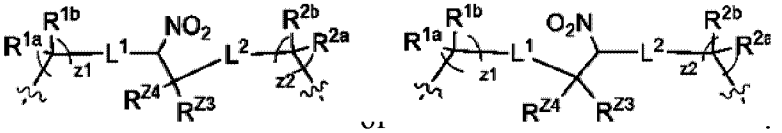
provides a Z group of formula:



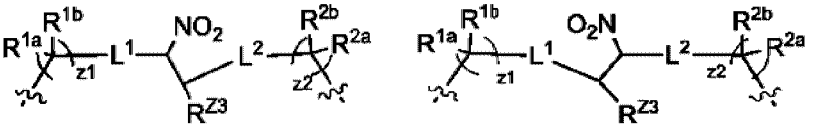
[00119] Addition of a group R^{Z4} to the nitro-aldol product of formula:



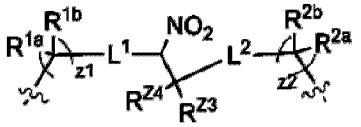
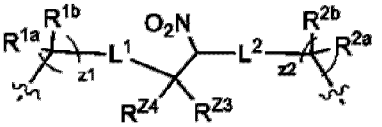
provides a Z group of formula:



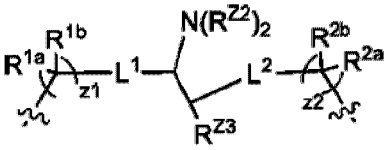
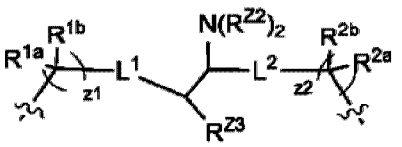
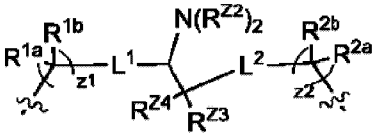
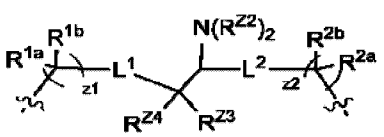
[00120] Reduction of the nitro group as provided in formulae:



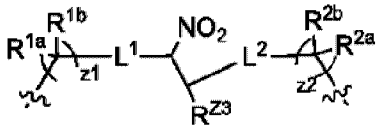
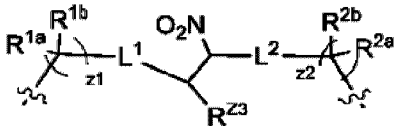
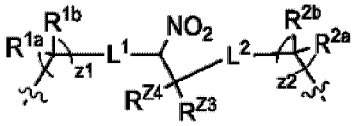
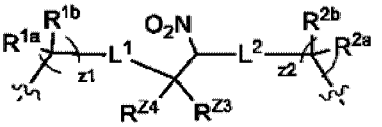
Date Reçue/Date Received 2020-06-25

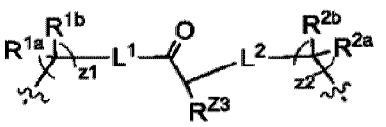
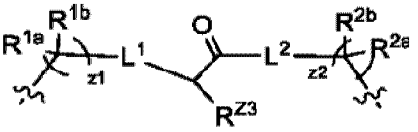
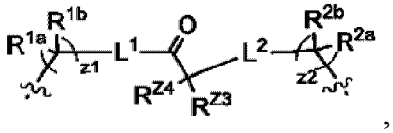
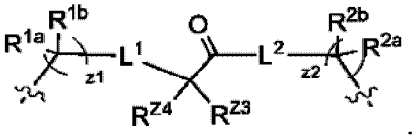
to the free amine, which may be optionally mono- or bis-protected, provides a Z group of formula:

[00121] Oxidation of the nitro group as provided in formula:

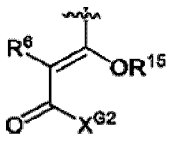
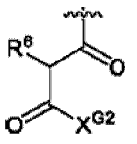
provides the keto (oxo) product of formula:

[00122] Alternative syntheses to form the keto (oxo) product are futher contemplated herein.

[00123] Various macrolides may be accessed from these coupled products of Formula (**C-1**), depending upon the nature of the group G^2, upon macrocyclization. For example, as depicted in Scheme 9, when G^2 is a group of formula:

Date Reçue/Date Received 2020-06-25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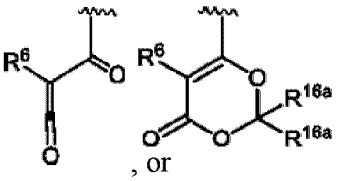
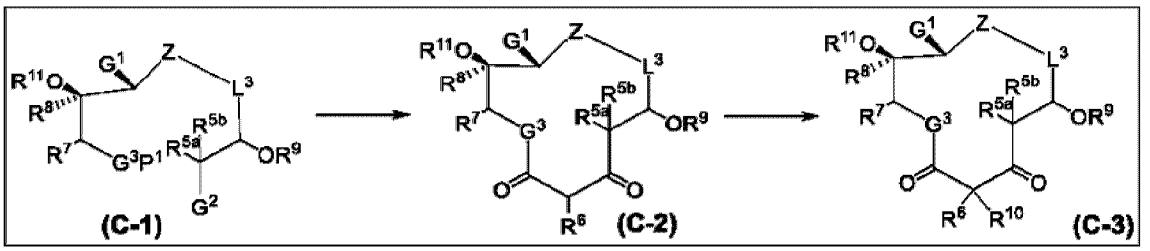
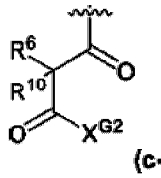

, or

and R^6 is a hydrogen or non-hydrogen group, macrocyclization of the compound of Formula (**C-1**), *e.g.,* wherein P^1 is hydrogen, provides a macrolide of Formula (**C-2**). Enolization of the macrolide of Formula (**C-2**), followed by addition of a non-hydrogen group R^{10} (*e.g.,* with a base and an R^{10} alkylating agent, *e.g.*, R^{10}-LG, or with a halogenating agent if R^{10} is halogen), provides a macrolide of Formula (**C-3**).

Scheme 9.

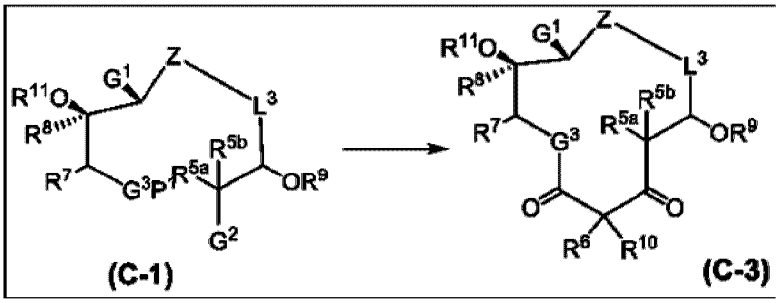


[00124] Alternatively, as depicted in Scheme 10, when G^2 is a group of formula:



and wherein each of R^6 and R^{10} is a hydrogen or non-hydrogen group, macrocyclization of the compound of Formula (**C-1**) *e.g.,* wherein P^1 is hydrogen, provides a macrolide of Formula (**C-3**).

Scheme 10.



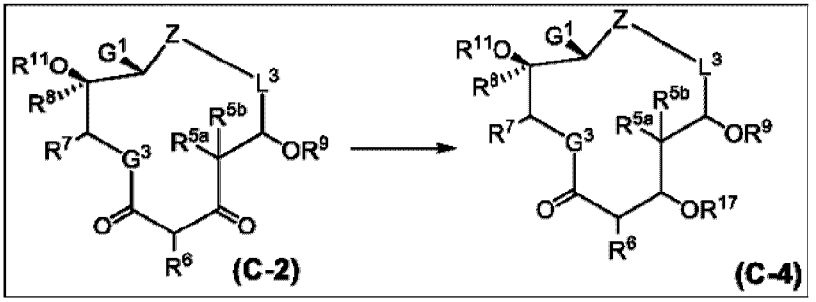
[00125] Further functionalization of the macrolide is also contemplated herein. For example, as depicted in Schemes 11 and 12, reduction of the C3 ketone of macrolides (**C-2**) and (**C-3**) to a hydroxyl group, optionally followed by protection, provides macrolides (**C-4**) and (**C-5**), respectively. Alternatively, the hydroxyl group at C3 can be modified through O-

Date Reçue/Date Received 2020-06-25

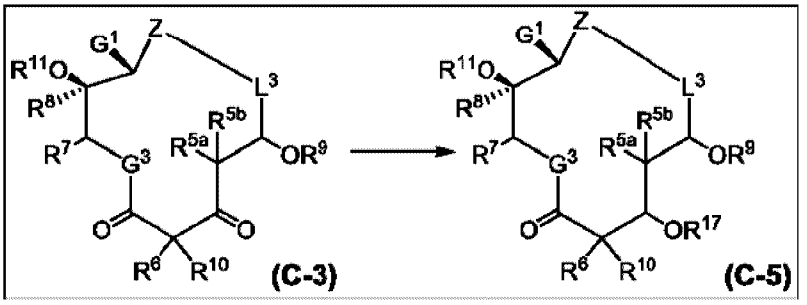
alkylation or acylation as depicted in Schemes 13A-13B, where LG is a leaving group as defined herein. In certain embodiments, R^{17} is $-C(=O)R^{Z8}$, wherein R^{Z8} is optionally substituted alkyl (*e.g.,* optionally substituted aralkyl or optionally substituted heteroaralkyl).

[00126] The ability to readily alter the oxidation state of oxygen at C3 enables the protection of this position as a carbonyl group while other free hydroxy groups are modified (*e.g.* O-alkylation). Therefore, oxidation or reduction of this position at various points along the specific synthetic sequence is contemplated herein.

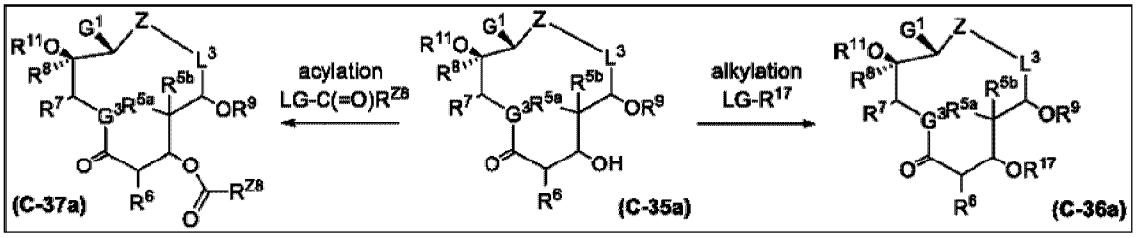
Scheme 11.



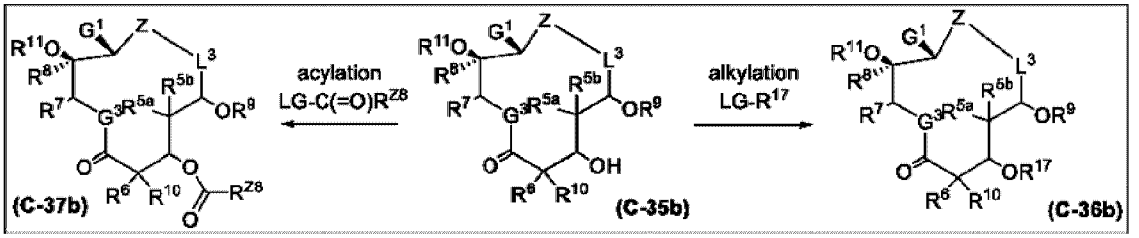
Scheme 12.



Scheme 13A.



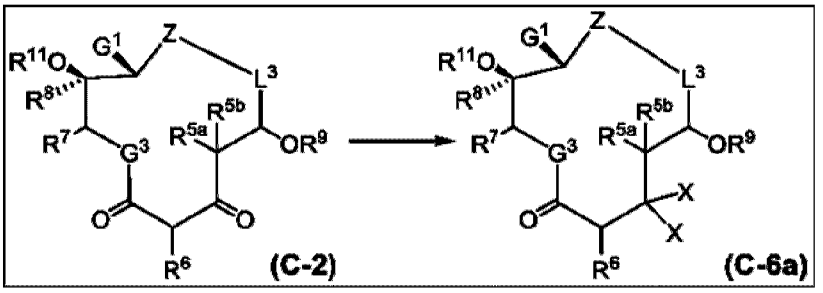
Scheme 13B.



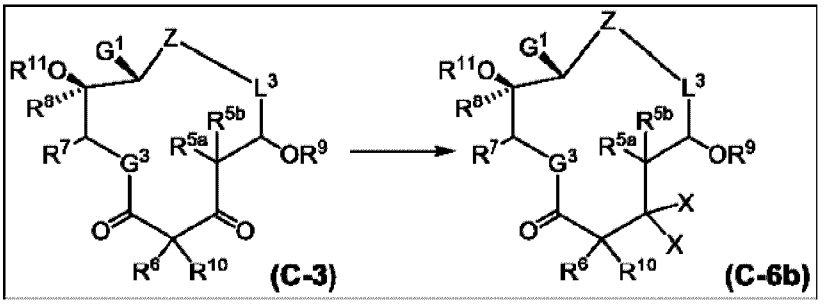
Date Reçue/Date Received 2020-06-25

[00127] Further modification of the ketone or reduced macrolide is also contemplated herein. For example, as depicted in Schemes 14A-14B, and 15A-15B, the C3 ketone **C-2** or **C-3**, or **C-4** or **C-5** (*e.g.,* hydroxyl at C3, wherein R^{17} is hydrogen), can be halogenated with an electrophilic halogenating agent (*e.g.* Deoxo-Fluor) to give geminal dihalides such as **C-6**, or monohalides such as **C-7**, respectively, wherein X is a halogen (*e.g.* fluorine, bromine, iodine).

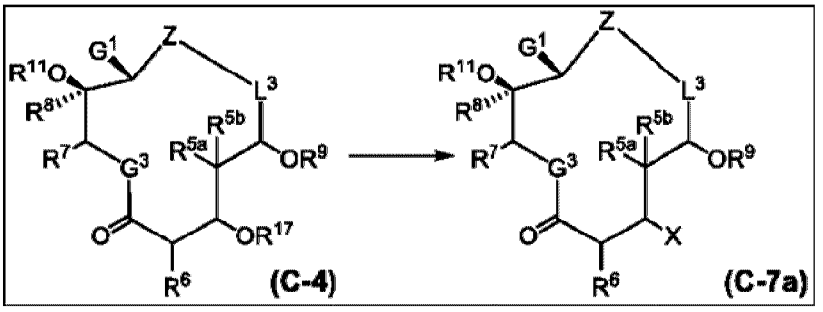
Scheme 14A.



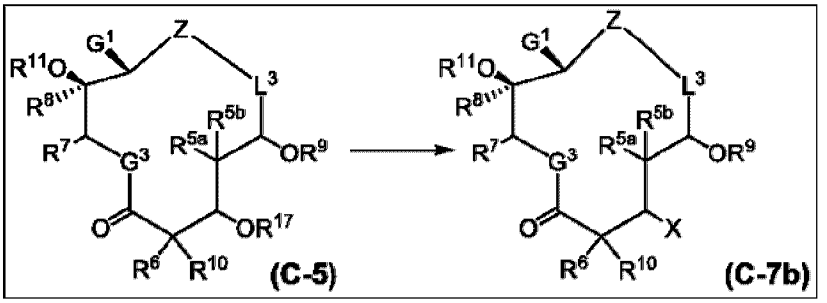
Scheme 14B.



Scheme 15A.

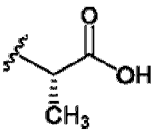


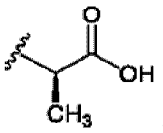
Scheme 15B.



Date Reçue/Date Received 2020-06-25

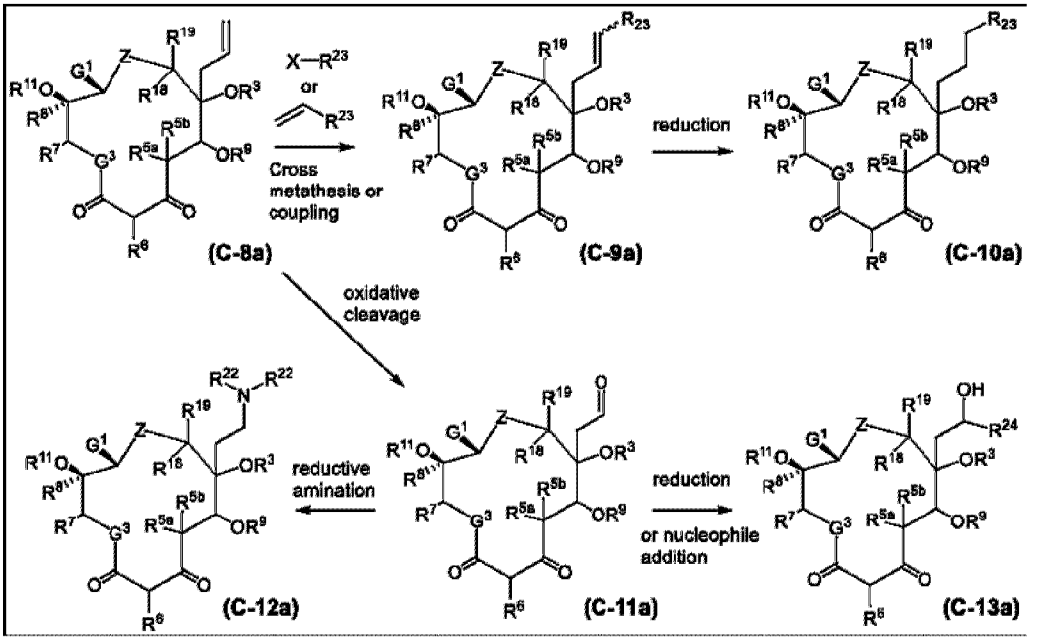
[00128] Instances wherein either R^3 or R^4 is allyl enable rapid derivitization into novel macrolides as demonstrated in Schemes 16A-16B and 17A-17B. A variety of groups, such as heteroaryl or aryl moieties, may be introduced through a transition metal catalyzed cross coupling (*e.g.* Heck reaction) or through an olefin metathesis reaction (*e.g.* cross methathesis using a Grubbs or Schrock metal carbene catalyst) leading to derivatives such as **C-9** or **C-15**. Subsequent manipulation of the olefin (*e.g.* hydrogenation) can access further structural diversity (*e.g.* **C-10a-b**, **C-16a-b**). Alternatively, the olefin functionality can be oxidatively cleaved to produce a carbonyl functionality (**C-11a-b** or **C-17a-b**) that may be further modified through transformations such as reduction, nucleophilic additions (**C-13a-b** or **C-19a-b**), or reductive amination (**C-12a-b** or **C-18a-b**), wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl and R^{24} is hydrogen, optionally substituted alkyl, or optionally substituted aryl. In certain embodiments, R^{22} is –



$CH_2C(=O)OH$. In certain embodiments, R^{22} is  . In certain embodiments, R^{22} is

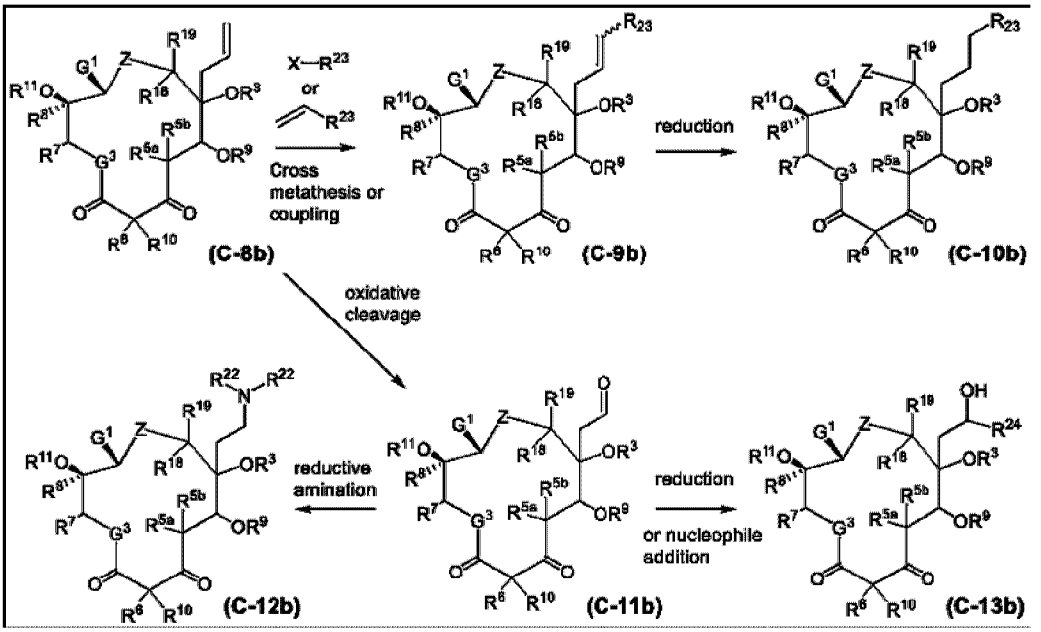
. While the modifications as drawn herein are demonstrated in the context of the preformed macrocycle, identical transformations on the macrolide building blocks prior to assembly are contemplated herein.

Scheme 16A.

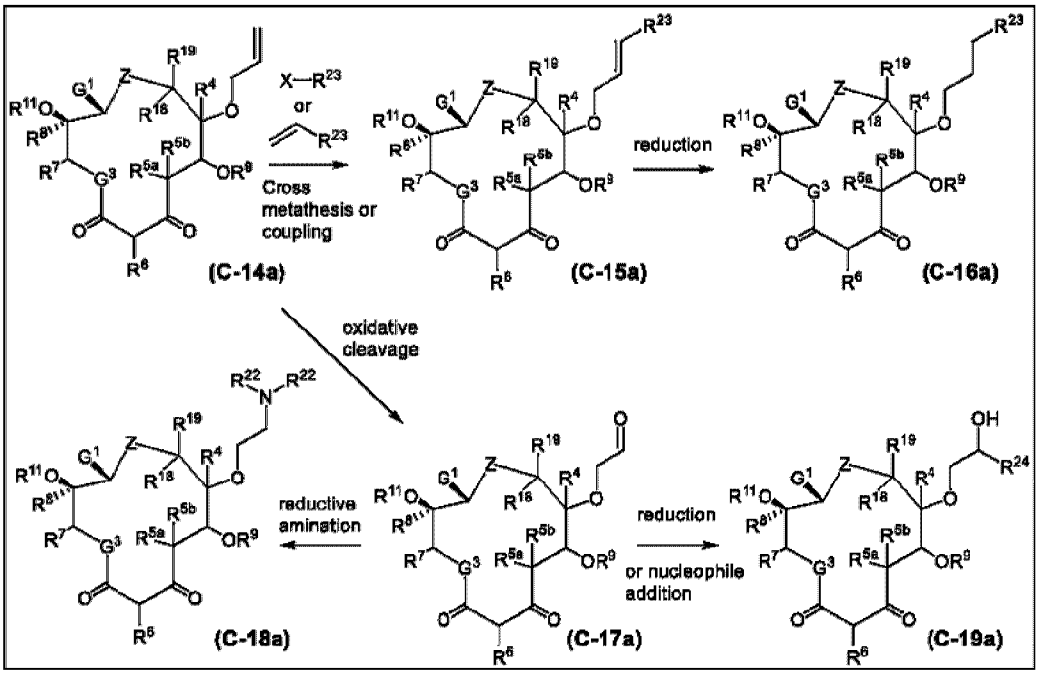


Date Reçue/Date Received 2020-06-25

Scheme 16B.

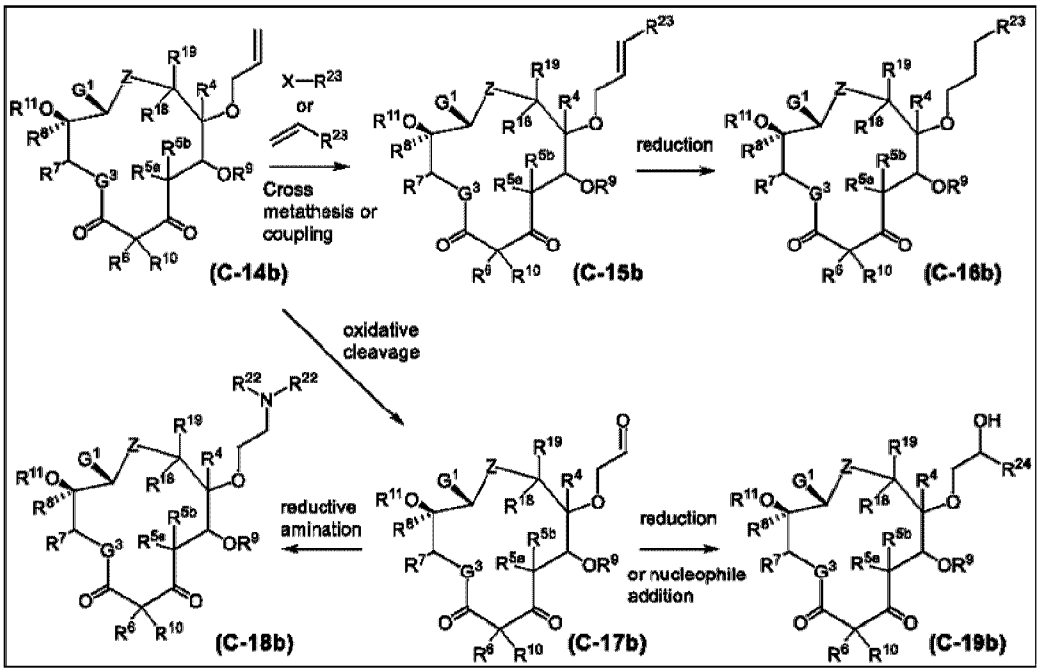


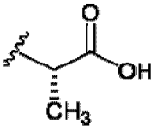
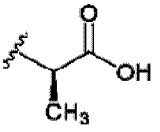
Scheme 17A.



Date Reçue/Date Received 2020-06-25

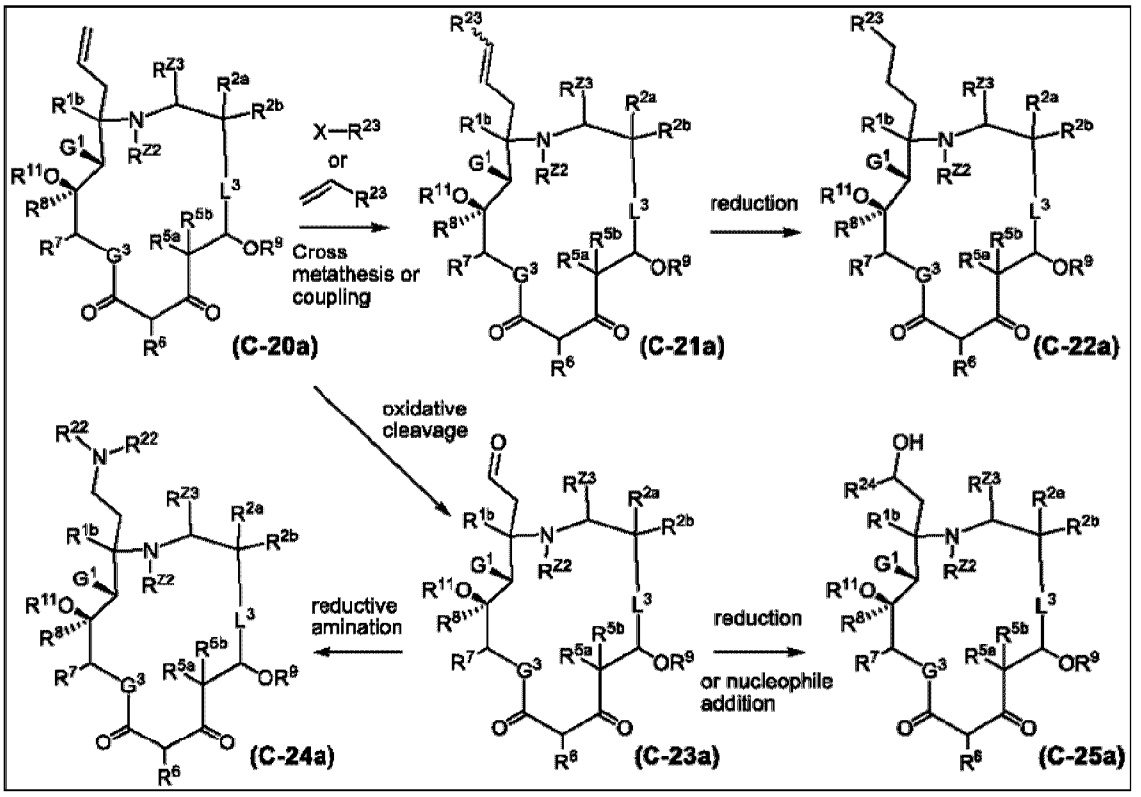
Scheme 17B.



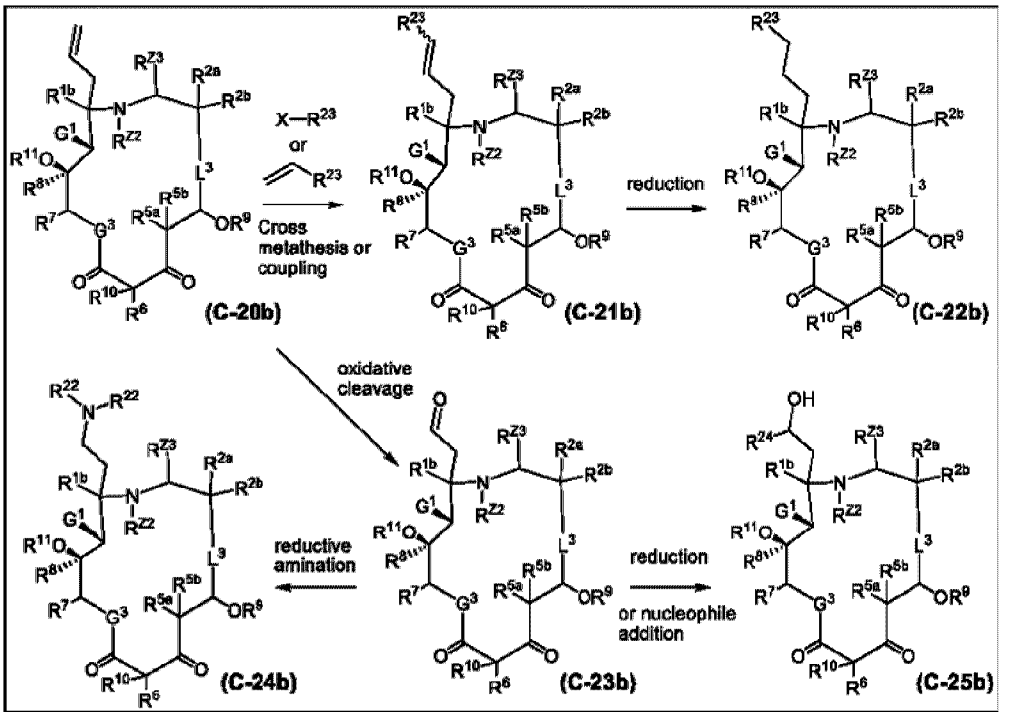
[00129] Further derivatization may be carried out using the transformations described herein pre- or post-macrocyclization when any of R^{1a}, R^{1b}, R^{2a}, R^{2b}, or R^{Z3} is allyl. While only depicted for macrocycles of **C-20a-b** in Scheme 18A-B, such modifications are contemplated for any macrocycle wherein at least one of R^{1a}, R^{1b}, R^{2a}, R^{2b}, or R^{Z3} is allyl. Derivitives wherein a -CH_2- moiety in the chain has been removed may be prepared using the precursor wherein any of R^{1a}, R^{1b}, R^{2a}, R^{2b}, or R^{Z3} is vinyl (Scheme 19A-19B). In certain embodiments, R^{22} is $-CH_2C(=O)OH$. In certain embodiments, R^{22} is  . In certain embodiments, R^{22} is  . While the modifications as drawn herein are demonstrated in the context of the preformed macrocycle, identical transformations on the macrolide building blocks prior to assembly are contemplated herein.

Date Reçue/Date Received 2020-06-25

Scheme 18A.

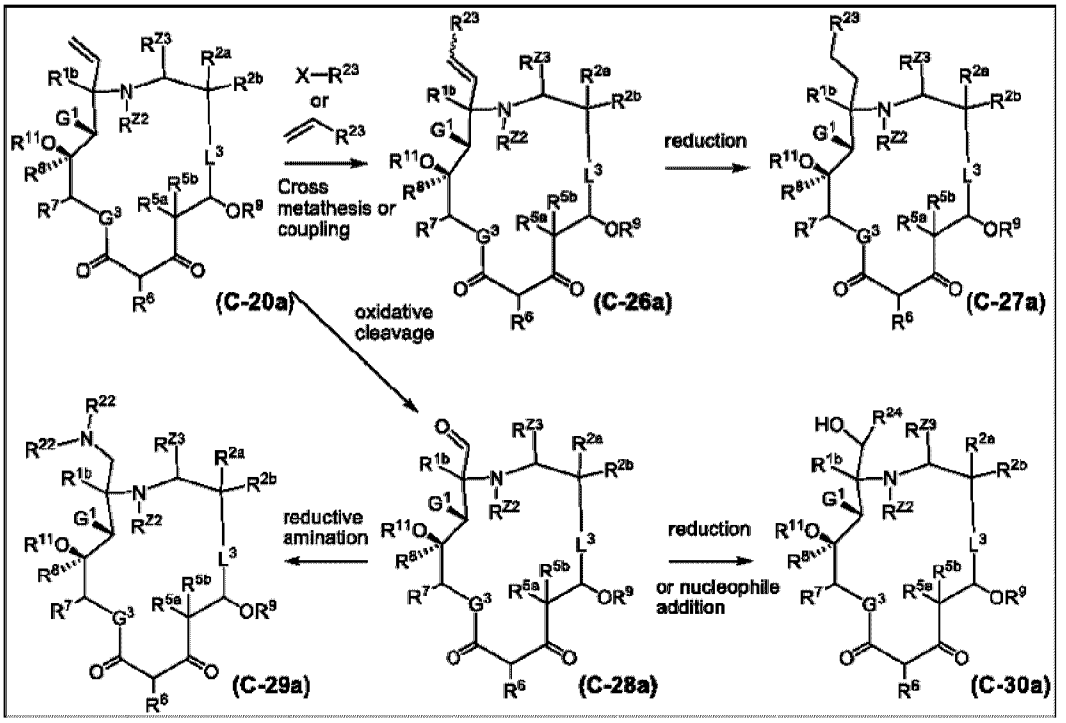


Scheme 18B.

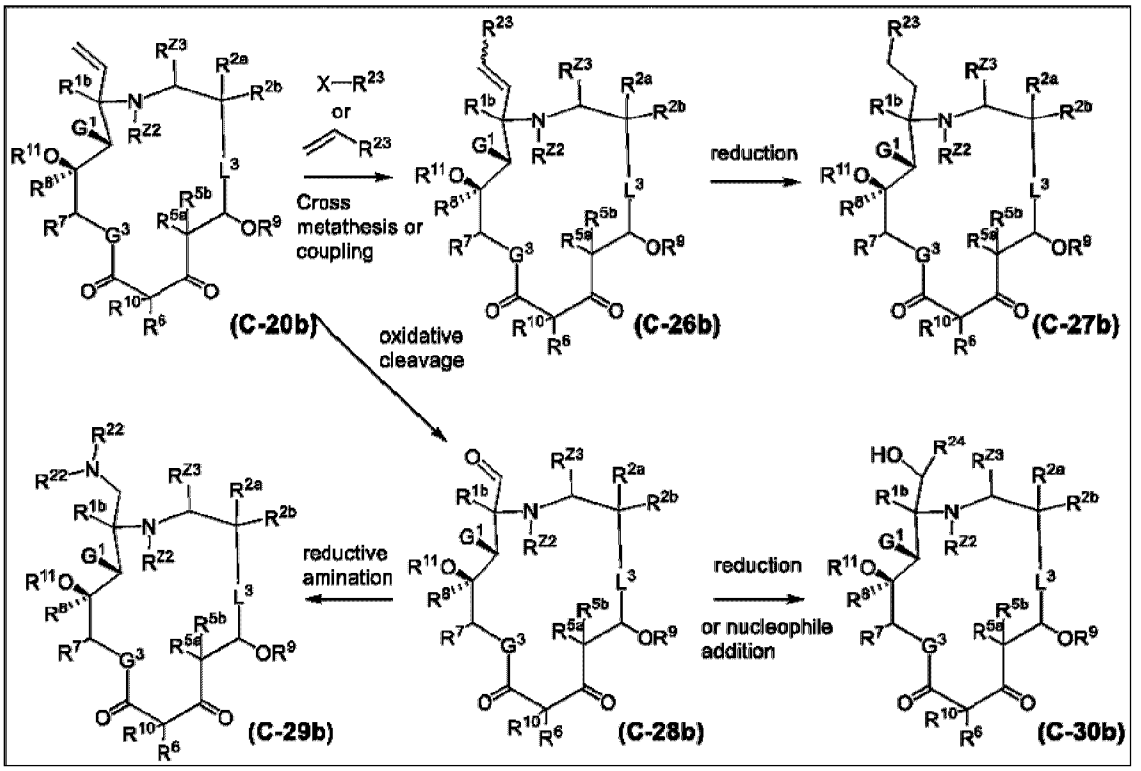


Date Reçue/Date Received 2020-06-25

Scheme 19A.

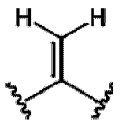
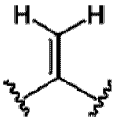


Scheme 19B.

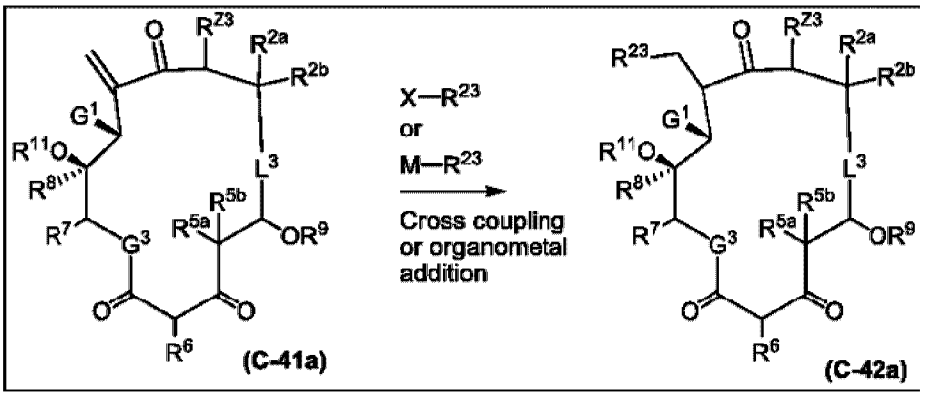


[00130] Further derivatization may be carried out using the transformations described herein pre- or post-macrocyclization when R^{1a} and R^{1b} or R^{2a} and R^{2b} can be taken together to

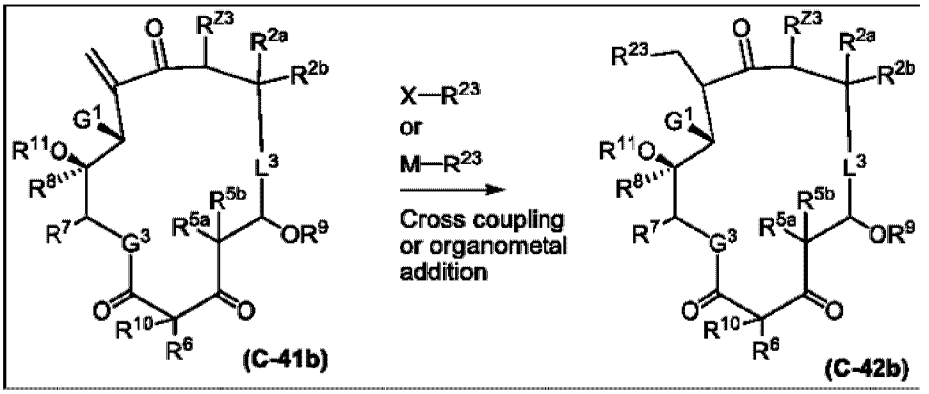
Date Reçue/Date Received 2020-06-25

form  *alpha* to an oxo (=O) moiety. Conjugate addition reactions using nucleophilic R_{23} species (such as X-R^{23} or M-R^{23}, wherein M is an anion, Li, Na, K, CuX, or MgX and wherein X is a halogen) provide compounds of formula **C-42a-b**. While only depicted for macrocycles of **C41a-b** in Scheme 20A-20B, such modifications are ancipated for any macrocycle wherein R^{1a} and R^{1b} or R^{2a} and R^{2b} is  *alpha* to an oxo (=O) moiety. While the modifications as drawn herein are demonstrated in the context of the preformed macrocycle, identical transformations on the macrolide building blocks prior to assembly are contemplated herein.

Scheme 20A.



Scheme 20B.

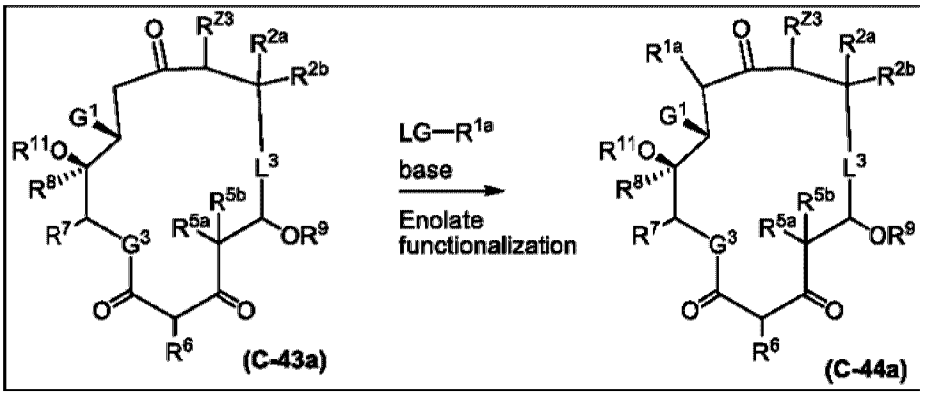


[00131] Further derivatization may be carried out using the transformations described herein pre- or post-macrocyclization when any of R^{1a}, R^{1b}, R^{2a}, R^{2b}, or R^{Z3} is hydrogen, attached *alpha* to an oxo (=O) moiety. Base-mediated deprotonation and nucleophilic addition of the enolate to leaving group conjugates of R^{1a}, wherein LG is a leaving group as

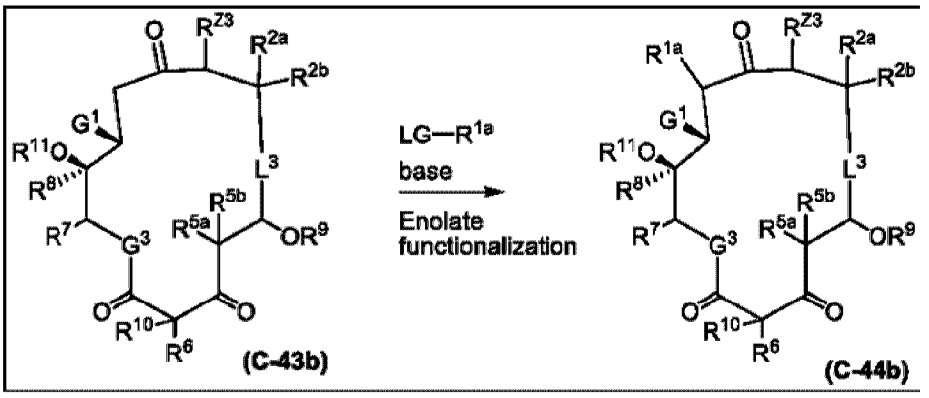
Date Reçue/Date Received 2020-06-25

definied herein, provide alpha-functionalized ketolides of formula **C-44a-b**. While only depicted for macrocycles of **C-43a-b** in Scheme 21A-21B, such modifications are ancipated for any macrocycle wherein at least one of R^{1a}, R^{1b}, R^{2a}, R^{2b}, or R^{Z3} is hydrogen and Z contains a ketone moiety. While the modifications as drawn herein are demonstrated in the context of the preformed macrocycle, identical transformations on the macrolide building blocks prior to assembly are contemplated herein.

Scheme 21A.



Scheme 21B.



[00132] As depicted in Scheme 22A-2B, the nitrogen of the macrocycle can be further functionalized with R^{Z2} groups. Non-limiting examples of double bond fuctionalization include:

(i) Amine N-alkylation with leaving group conjugates of R^{Z2} (*i.e.* **C32a-b**, R^{Z2}-LG, wherein LG is a leaving group as defined herein). In certain embodiments, the leaving group conjugate of R^{Z2} is an organohalide. In certain embodiments, the organohalide is a methyl halide (*e.g.* methyl iodide).

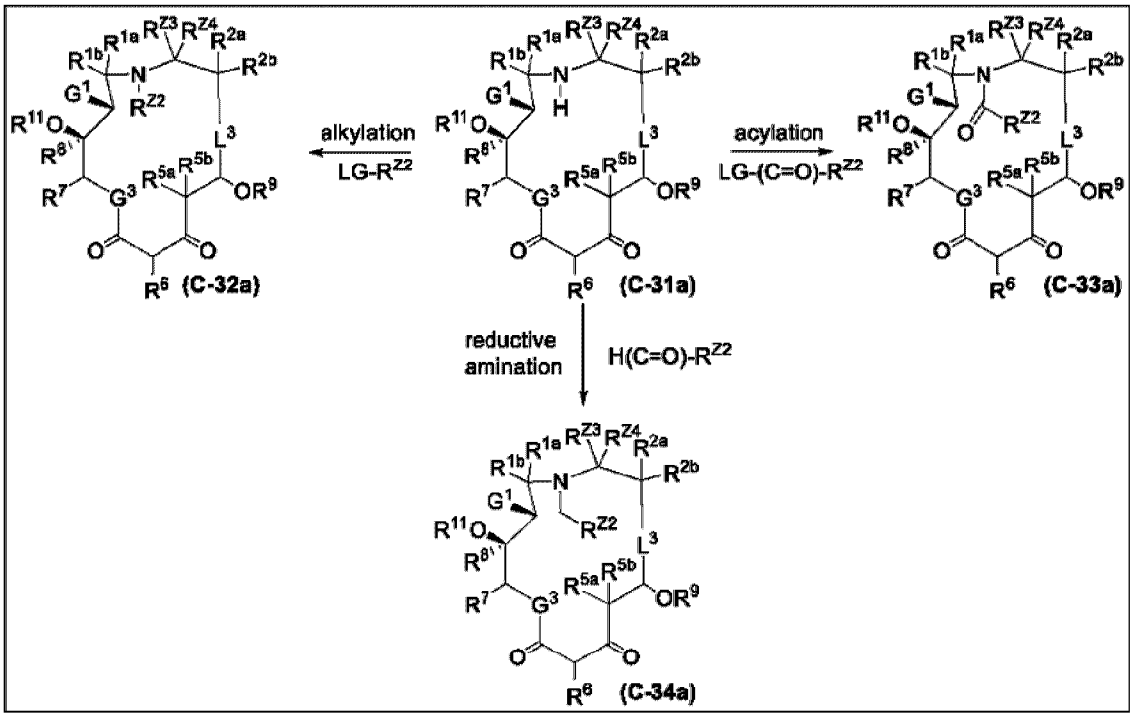
(ii) Amine acylation with reagents such as carboxylic acids, acid anhydrides, or other acid leaving group conjugates (i.e. **C33a-b**, $R^{Z2}(C{=}O)OH$, $R^{Z2}(C{=}O)O(C{=}O)R^{Z2}$, or

Date Reçue/Date Received 2020-06-25

R^{Z2}(C=O)-LG wherein LG is a leaving group as defined herein). In certain embodiments, the acid anhydride is acetic anhydride.

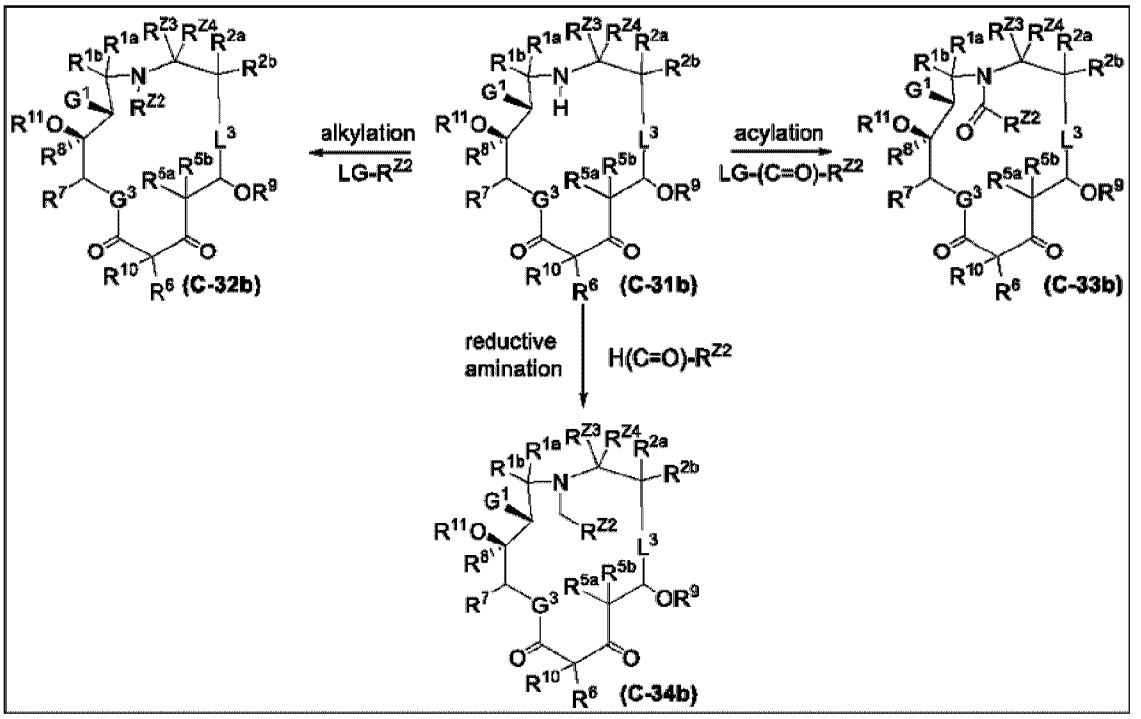
(iii) Reductive amination with reagents such as aldehydes or ketones (i.e. **C34a-b**, R^{Z2}(C=O)H or R^{Z2}(C=O)R^{Z2}). In certain embodiments, the aldehyde is formaldehyde. While only depicted for macrocycles of **C31a-b** in Scheme 21A-B, such modifications are ancipated for any macrocycle wherein Z contains an amine moiety. While the modifications as drawn herein are demonstrated in the context of the preformed macrocycle, identical transformations on the macrolide building blocks prior to assembly are contemplated herein.

Scheme 22A.

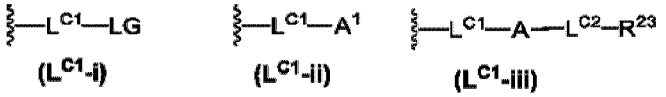


Date Reçue/Date Received 2020-06-25

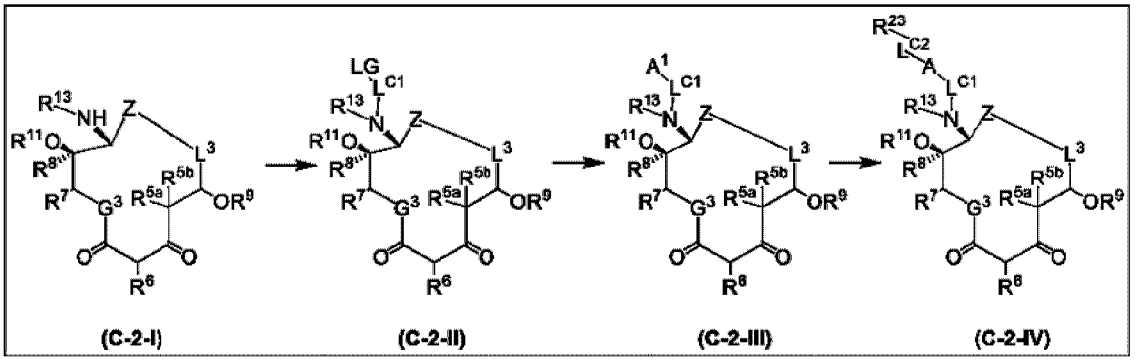
Scheme 22B.



[00133] Furthermore, as depicted in Schemes 23-26, wherein G^1 is $-NHR^{13}$, installation of a group of formula (**L^{C1}-i**) by reaction of the alcohol with a compound of formula LG-L^{C1}-LG, followed by displacement of the second leaving group with a nucleophilic group A^1 to provide a group of formula (**L^{C1}-ii**), followed by reaction of the group A^1 and with a compound of formula A^2-L^{C2}-R^{23} to install a group of formula (**L^{C1}-iii**), is contemplated herein.

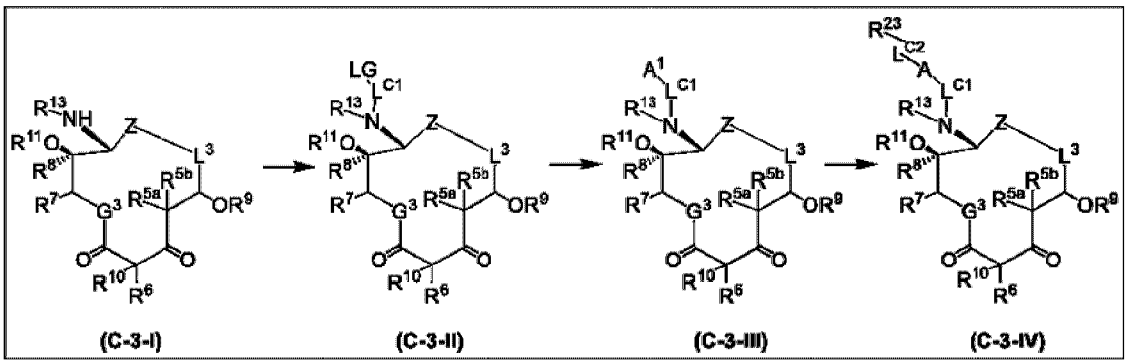


Scheme 23.

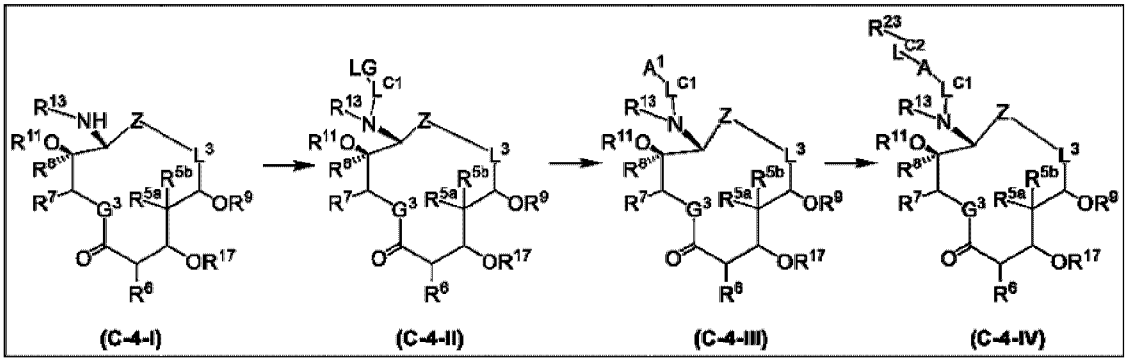


Date Reçue/Date Received 2020-06-25

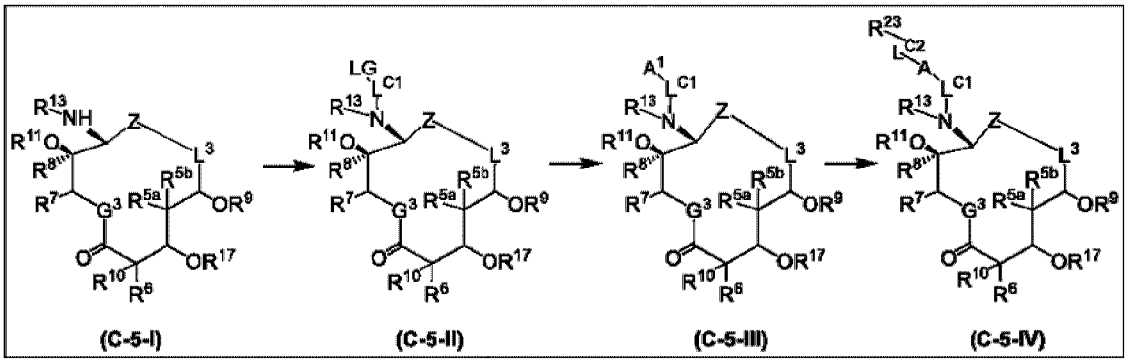
Scheme 24.



Scheme 25.



Scheme 26.

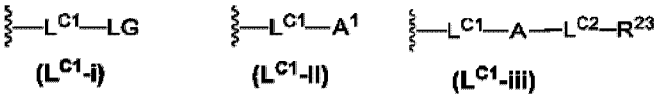


[00134] Alternatively, the group $–L^{C1}\text{-}A^1$ may be installed directly by reaction of the amine with a compound of formula $LG–L^{C1}\text{-}A^1$. Such reactions are also contemplated wherein G^1 is –OH.

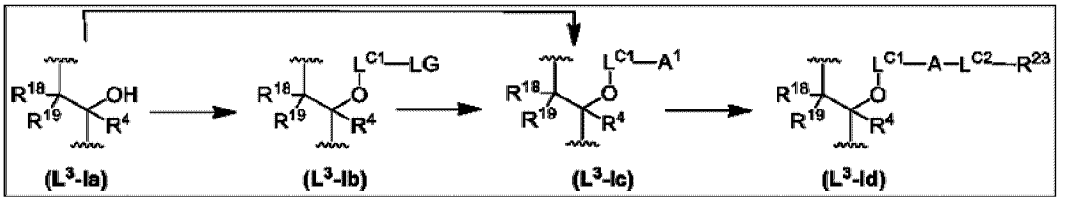
[00135] Additionally, as depicted in Scheme 27, wherein L^3 is a group of formula (**L^3-i**), wherein R^3 is hydrogen (referred to as (**L^3-ia**)), installation of a group of formula (**L^{C1}-i**) by reaction of the alcohol with a compound of formula $LG\text{-}L^{C1}\text{-}LG$, followed by conversion of (*e.g.,* by nucleophilic displacement or other synthetic manipulation) of the second leaving group with a group A^1 to provide a group of formula (**L^{C1}-ii**), followed by reaction of the

Date Reçue/Date Received 2020-06-25

group A^1 and with a compound of formula A^2-L^{C2}-R^{23} to install a group of formula (**L^{C1}-iii**), is also contemplated herein.



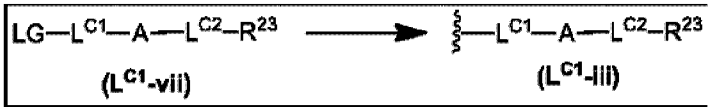
Scheme 27.



[00136] Alternatively, the group –L^{C1}-A^1 may be installed directly from (**L^3-ia**) to provide (**L^3-ic**) by reaction of the hydroxyl group with a compound of formula LG–L^{C1}-A^1.

[00137] Furthermore, there are many ways of adding a group of formula (**L^{C1}-iii**) which do not involve reaction of A^1 and A^2 to form A and thus A may be any group, e.g., for example, a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. For example, a group of formula (**L^{C1}-iii**) may be installed by reaction of the group -OR^{12}, -$NR^{13}R^{14}$, and/or -OR^3, wherein R^{12}, R^{14}, and/or R^3 are hydrogen, with a compound of formula (**L^{C1}-vii**), *e.g.,* by nucleophilic displacement, to provide a group wherein R^{12}, R^{14}, and/or R^3 is of formula (**L^{C1}-iii**). See, *e.g.*, Scheme 28.

Scheme 28.



[00138] Furthermore, as depicted in Scheme 28, wherein L^3 is a group of formula (**L^3-i**), elimination of the group –OR^3 provides an alkenyl moiety, which may be reduced (*e.g.*, by hydrogenation), or be further functionalized with groups R^{20} and R^{21}, as depicted in Scheme 29. Functionalization of double bonds to provide groups R^{20} and R^{21} are known in the art. See, *e.g.*, *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987. Non-limiting examples of double bond fuctionalization include:

Date Reçue/Date Received 2020-06-25

(i) reaction of the double bond with a cyclopropanting reagent to provide a group (**L^3-iii**) wherein R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl ring;

( ) reaction of the double bond with an epoxidizing reagent to provide a group (**L^3-iii**) wherein R^{20} and R^{21} are joined to form an oxiranyl ring;

(i) reaction of the double bond with a dihydroxylation reagent (*e.g.,* OsO_4), optionally followed by protection of the hydroxyl groups, to provide a group (**L^3-iii**) wherein R_{20} and R^{21} are each independently hydroxyl or substituted hydroxyl;

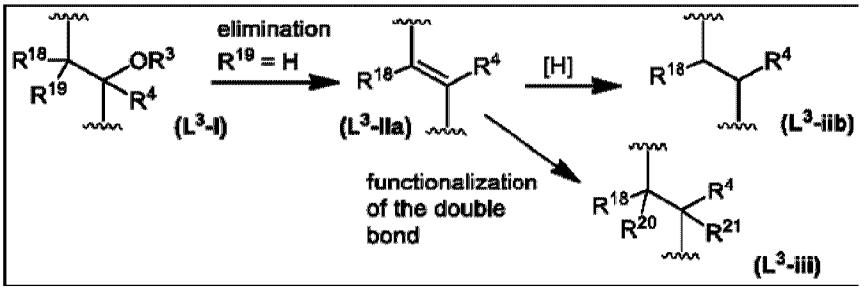
(ii) HX addition to the double bond, wherein X is a halogen or hydroxyl or substituted hydroxyl, to provide a group (**L^3-iii**) wherein one of R^{20} and R^{21} is halogen or hydroxyl or substituted hydroxyl, and one of R^{20} and R^{21} is hydrogen;

(iii) X_2 addition to the double bond, wherein X is halogen, to provide a group (**L^3-iii**) wherein R^{20} and R^{21} are each independently halogen;

(iv) X_2/H_2O or X_2/alcohol addition to the double bond, wherein X is halogen, to provide a group (**L^3-iii**) wherein one of R^{20} and R^{21} is hydroxyl or substituted hydroxyl, and one of R^{20} and R^{21} is halogen; and

(viii) oxidative hydroboration of the double bond to provide a group (**L^3-iii**) wherein one of R^{20} and R^{21} is hydroxyl or substituted hydroxyl, and one of R^{20} and R^{21} is hydrogen.

Scheme 29.

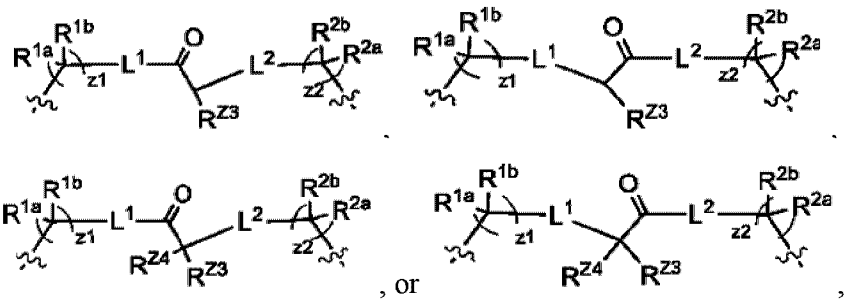


[00139] For all of the transformations pertaining to functionalization of the pre-formed macrocycle, incorporation of these groups through such general transformations at steps prior to ring formation is contemplated herein. Such reordering of steps as is appropriate to accomodate particular intermediates or functional groups is understood by those skilled in the art.

Alternative Method of Synthesizing Ketolides

[00140] As generally described herein, alternative methods of preparing the keto (oxo) product wherein Z is of formula:

Date Reçue/Date Received 2020-06-25



are further contemplated herein.

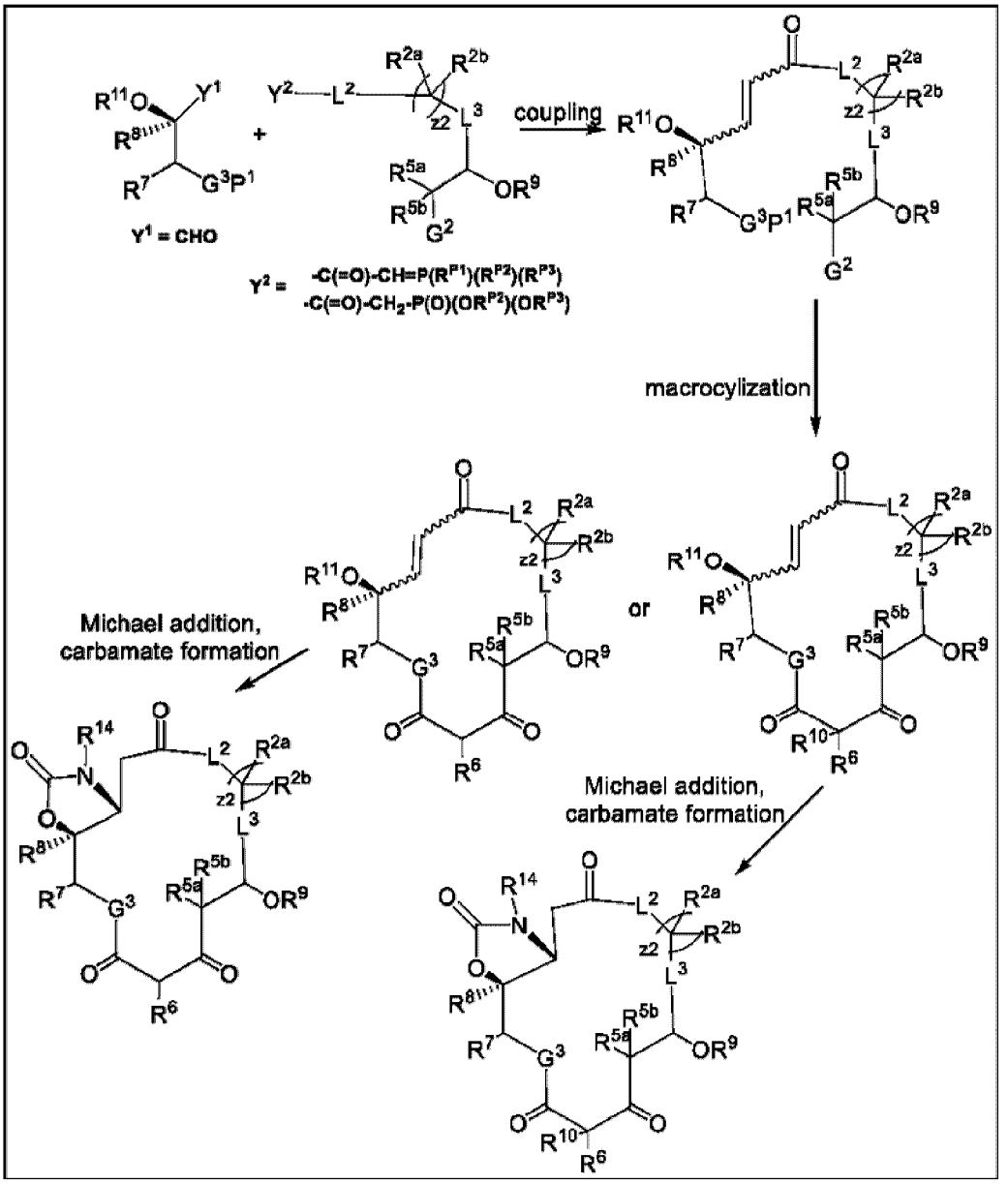
[00141] For example, the above recited Z linkage may be formed *via* Wittig or Horner Emmons reaction between an aldehyde and a ylide or phosphonate ester to form an a,J3-unsaturated keto linked intermediate. See, *e.g.,* Schemes 30 and 31. In certain embodiments, wherein represents a double bond, the ketone moeity and J3 -substitutent are in a *cis*-configuration. In certain embodiments, wherein represents a double bond, the ketone moeity and J3-substitutent are in a *trans*-configuration.

[00142] The cyclic carbamate, installed prior to macrocyclization (see, *e.g.,* Scheme 30) or after macrocylization (see, *e.g.,* Scheme 31), may be formed *via* Michael addition of the amine NH_2R^{14} to the a,J3 -unsaturated keto moiety, followed by reaction of the attached amino group $-NHR^{14}$ and vicinal hydroxyl group (*i.e.,* R^{11} is hydrogen) with reagent LG-C(=O)-LG, wherein each LG is a leaving group as defined herein (*e.g.,* chloro), substituted hydroxyl (*e.g.,* to provide a carbonate ester), substituted thiol, substituted amino (*e.g.,* imidazolyl). In certain embodiments, the free hydroxyl group is first treated with reagent LG-C(=O)-LG, following which an amine of NH_2R^{14} is added, leading to initial formation of an acyclic carbamate prior to conjugate addition of the intermediate $-NHR^{14}$ group to the unsaturated ketone.

[00143] Alternatively, the cyclic carbamate, installed prior to macrocyclization (see, *e.g.,* Scheme 30) or after macrocylization (see, *e.g.,* Scheme 31), may be formed *via* reaction of the free hydroxyl group (*i.e.*, R^{11} is hydrogen) with an isocyanate reagent $O=C=N-R^{14}$, followed by conjugate addition of the intermediate $-NHR^{14}$ group to the unsaturated ketone. In certain embodiments, the isocyanate reacts with the free hydroxyl group and $-NHR^{14}$ undergoes the conjugate addition reaction in a single step. In certain embodiments, the intermediate acyclic carbamate is isolated. In certain embodiments, base is added to the isolated acyclic carbamate to promote the conjugate addition reaction.

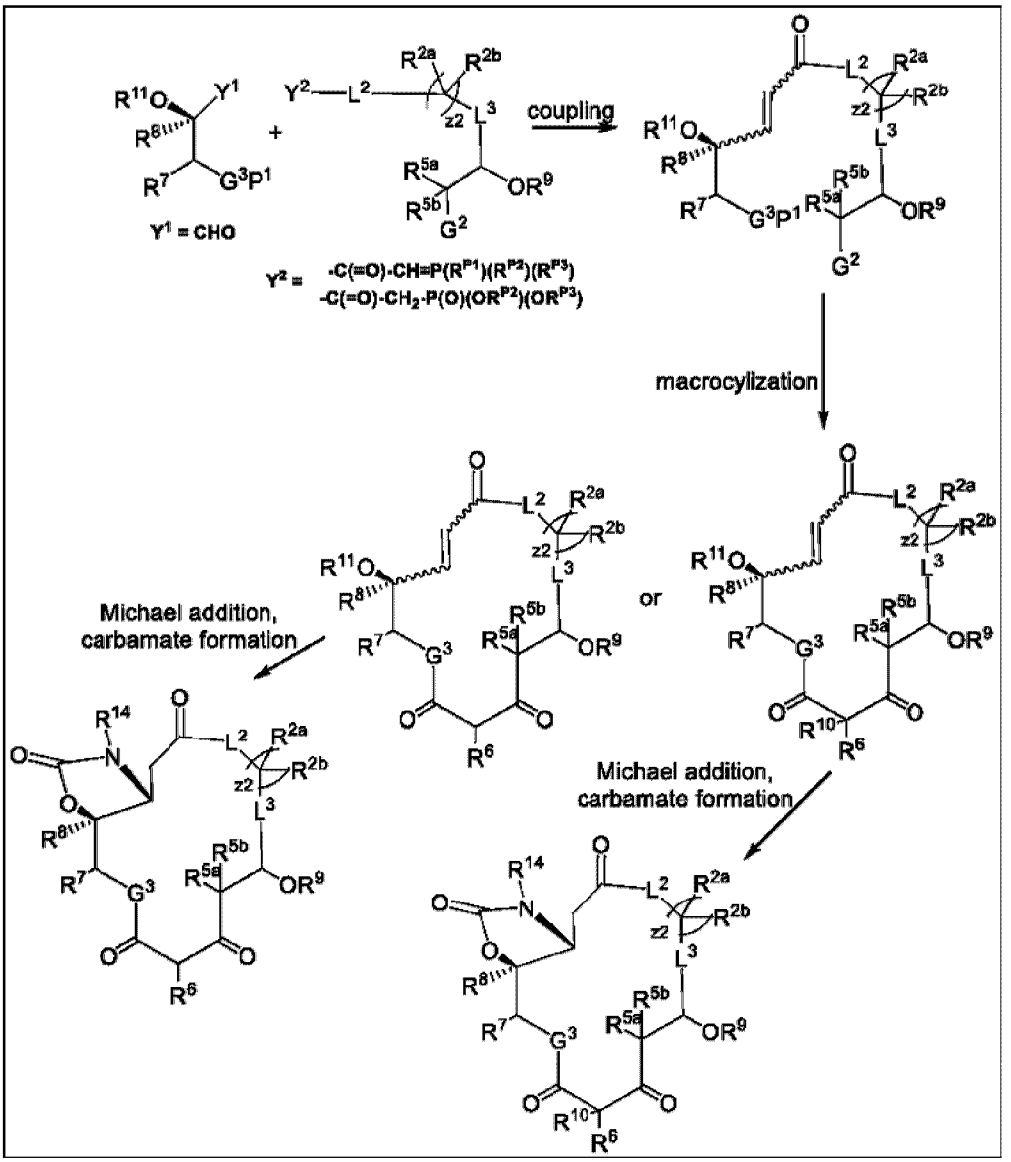
Date Reçue/Date Received 2020-06-25

Scheme 30.



Date Reçue/Date Received 2020-06-25

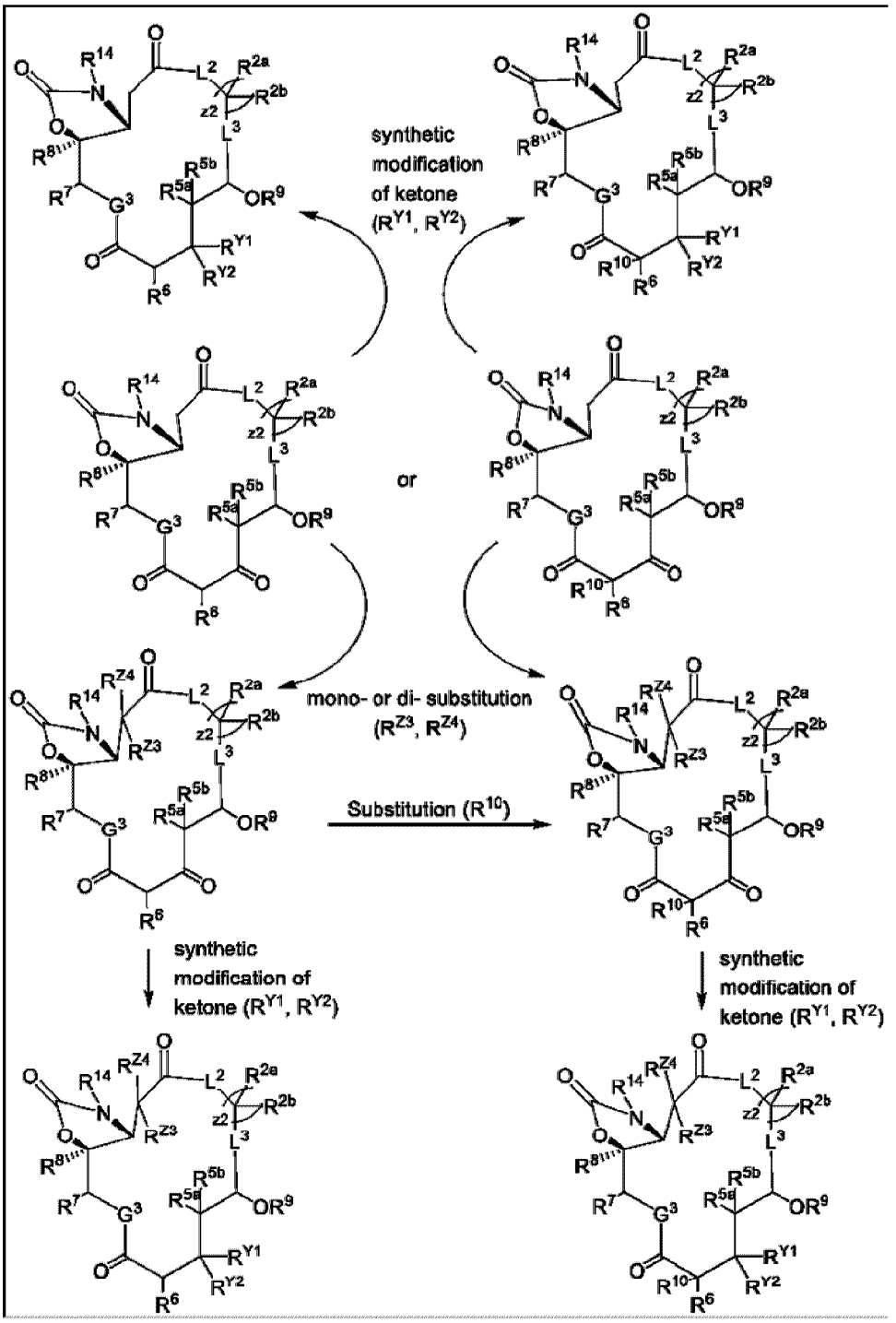
Scheme 31.



[00144] Scheme 32 depicts various synthetic modifications which are contemplated and further described in greater detail elsewhere. For example, after formation of the cyclic carbamate, the carbon alpha to the ketone moiety so installed may be monosubstituted (*e.g.*, wherein R^{Z3} is hydrogen and R^{Z4} is a non-hydrogen) or di-substituted (*i.e.,* wherein both R^{Z3} and R^{Z4} are non-hydrogen groups). Synthetic modification of the C3 ketone by dihalogenation (*e.g.,* wherein each of R^{Y1} and R^{Y2} is halogen (*e.g.,* fluoro)), or by reduction to provide an alcohol wherein R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, followed by monohalogenation to provide a product wherein R^{Y1} is halogen (*e.g.,* fluoro) and R^{Y2} is hydrogen is further contemplated.

Date Reçue/Date Received 2020-06-25

Scheme 32.

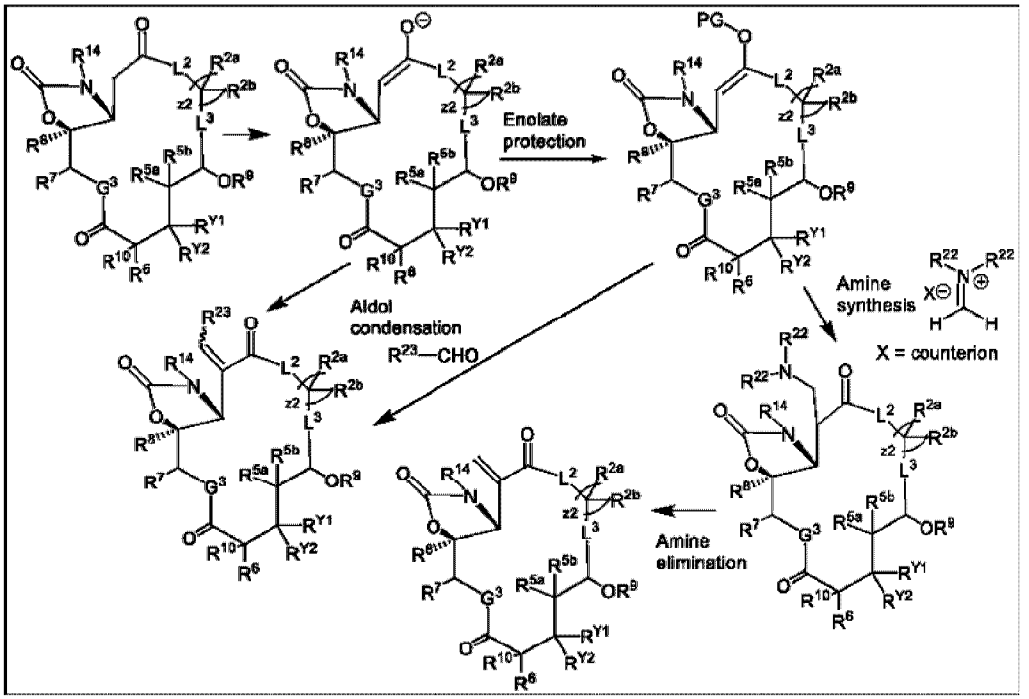


[00145] Scheme 33 depicts additional functionalization of ketolides prepared by the methods described herein via an enolate or trapped enolate, wherein PG is an oxygen protecting group as defined herein. In certain embodiments, the trapped enolate is trapped as a protected enol ether using a reagent of formula LG–PG wherein LG is leaving group and

Date Reçue/Date Received 2020-06-25

PG is protecting group as defined herein. In certain embodiments, either the protected enol ether or the enolate can be utilized to carry out an aldol condensation reaction with aldehydes of formula R^{23}–CHO. Alternatively, the protected enol ether can be contacted with iminium salts under suitable conditions to afford amino substituted products. Amines produced *via* this method can be eliminated to provide exocyclic alkenes.

Scheme 33.



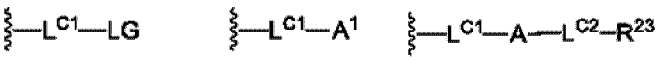
Group G^1 and R_{11}

[00146] As generally defined herein, G^1 is $–OR^{12}$ or $–NR^{13}R^{14}$.

[00147] In certain embodiments, G^1 is $–OR^{12}$, then R^{11} and R^{12} are joined as a group of formula –C(=O)- to provide a cyclic carbonate.

[00148] In certain embodiments, G^1 is $–OR^{12}$ and R^{11} and R^{12} are not joined to form a cyclic carbonate. In that instance, in certain embodiments, R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, and R^{12} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group, or a group of formula:

Date Reçue/Date Received 2020-06-25


(L^C1-i) (L^C1-ii) (L^C1-iii)

, as defined herein.

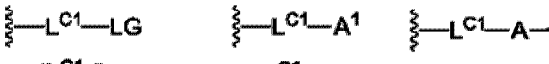
[00149] In certain embodiments, wherein R^{12} is not hydrogen, R^{12} is optionally substituted with a non-hydrogen group of formula R^{23} as defined herein.

[00150] In certain embodiments, G^1 is $-NR^{13}R^{14}$, and R^{11} and R^{13} are joined as a group of formula $-C(=O)-$ to provide a cyclic carbamate.

[00151] In certain embodiments, G^1 is $-NR^{13}R^{14}$, and R^{11} and R^{13} are not joined to form a cyclic carbamate. In that instance, in certain embodiments, R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, R^{13} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group.

[00152] In certain embodiments, wherein R^{13} is not hydrogen, R^{13} is optionally substituted with a non-hydrogen group of formula R^{23} as defined herein.

[00153] In certain embodiments, wherein G^1 is $-NR_{13}R_{14}$, R^{14} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group, $-C(=O)R^{Z8}$, or $-C(=O)OR^{Z8}$, or


(L^C1-i) (L^C1-ii) (L^C1-iii)

a group of formula:

, as defined herein.

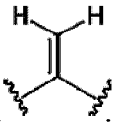
[00154] In certain embodiments, wherein R^{14} is not hydrogen, R^{14} is optionally substituted with a non-hydrogen group of formula R^{23} as defined herein.

[00155] In certain embodiments, wherein G^1 is $-NR_{13}R_{14}$, R^{13} and R^{14} are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl. In certain embodiments, the heterocyclyl or heteroaryl ring system formed from the joining of R^{13} and R_{14} is optionally substituted with a non-hydrogen group of formula R^{23} as defined herein.

Groups R^{1a}, R^{1b}, R^{2a}, and R_{2b}

[00156] As generally defined herein, each instance of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally

Date Reçue/Date Received 2020-06-25

substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein R^{1a} and R^{1b} or R^{2a} and R^{2b} can be taken together to form  .

[00157] In certain embodiments, the carbon to which R^{1a} and R^{1b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{1a} and R^{1b} is attached is a stereocenter of the (S)-configuration

[00158] In certain embodiments, at least one of R^{1a} and R^{1b} is hydrogen. In certain embodiments, both R^{1a} and R^{1b} are hydrogen.

[00159] In certain embodiments, at least one of R^{1a} and R^{1b} is halogen; *e.g.* –F, -Cl, -Br, or I. In certain embodiments, both R^{1a} and R^{1b} are halogen; *e.g.* –F, -Cl, -Br, or I.

[00160] In certain embodiments, at least one of R^{1a} and R^{1b} is carbonyl. In certain embodiments, at least one of R^{1a} and R^{1b} is a carboxylic acid. In certain embodiments, at least one of R^{1a} and R^{1b} is a ketone. In certain embodiments, at least one of R^{1a} and R^{1b} is an aldehyde (-CHO).

[00161] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted alkyl, *e.g.*, optionally substituted $C_{1–6}$alkyl optionally substituted $C_{1–2}$alkyl, optionally substituted $C_{2–3}$alkyl, optionally substituted $C_{3–4}$alkyl, optionally substituted $C_{4–5}$alkyl, or optionally substituted $C_{5–6}$alkyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is $–CH_3$. In certain embodiments, both instances of R^{1a} and R^{1b} are $–CH_3$. In certain embodiments, at least one instance of R^{1a} and R^{1b} is alkyl substituted with one or more halogen atoms, *e.g.,* optionally substituted haloalkyl; *e.g.*, $-CF_3$, $-CF_2CF_3$, or $-CF_2H$. In certain embodiments, at least one of R^{1a} and R^{1b} is $–CH_2CHO$.

[00162] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted alkenyl, *e.g.*, optionally substituted $C_{2–6}$alkenyl, optionally substituted $C_{2–3}$alkenyl, optionally substituted $C_{3–4}$alkenyl, optionally substituted $C_{4–5}$alkenyl, or optionally substituted $C_{5–6}$alkenyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is vinyl, allyl, or prenyl.

[00163] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted alkynyl, *e.g.*, optionally substituted $C_{2–6}$alkynyl, optionally substituted $C_{2–3}$alkynyl, optionally substituted $C_{3–4}$alkynyl, optionally substituted $C_{4–5}$alkynyl, or optionally substituted $C_{5–6}$alkynyl.

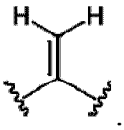
Date Reçue/Date Received 2020-06-25

[00164] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted cyclopropyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is unsubstituted cyclopropyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted cyclobutyl. In certain embodiments, at least one instance of R^{1a} and R_{1b} is unsubstituted cyclobutyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted cyclopentyl. In certain embodiments, at least one instance of R^{1a} and R_{1b} is unsubstituted cyclopentyl. In certain embodiments, at least one instance of R^{1a} and R_{1b} is optionally substituted cyclohexyl. In certain embodiments, at least one instance of R^{1a} and R_{1b} is unsubstituted cyclohexyl.

[00165] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted heterocylyl, *e.g.*, *e.g.,* optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00166] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00167] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00168] In certain embodiments, R^{1a} and R^{1b} are taken together to form  .

[00169] In certain embodiments, the carbon to which R^{2a} and R^{2b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{2a} and R_{2b} is attached is a stereocenter of the (S)-configuration.

[00170] In certain embodiments, at least one instance of R^{2a} and R^{2b} is hydrogen. In certain embodiments, both R^{2a} and R^{2b} are hydrogen.

[00171] In certain embodiments, at least one of R^{2a} and R^{2b} is halogen; *e.g.* –F, -Cl, -Br, or I. In certain embodiments, both R^{2a} and R^{2b} are halogen; *e.g.* –F, -Cl, -Br, or I.

[00172] In certain embodiments, at least one of R^{2a} and R^{2b} is carbonyl. In certain embodiments, at least one of R^{2a} and R^{2b} is a carboxylic acid. In certain embodiments, at least one of R^{2a} and R^{2b} is a ketone. In certain embodiments, at least one of R^{2a} and R^{2b} is an aldehyde (-CHO).

Date Reçue/Date Received 2020-06-25

[00173] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, at least one instance of R^{2a} and R^{2b} is $-CH_3$. In certain embodiments, both instances of R^{2a} and R^{2b} are $-CH_3$. In certain embodiments, at least one instance of R^{2a} and R^{2b} is alkyl optionally substituted with one or more halogen atoms, *e.g.,* optionally substituted haloalkyl; *e.g.*, $-CF_3$, $-CF_2CF_3$, or $-CF_2H$. In certain embodiments, at least one of R^{2a} and R^{2b} is $-CH_2CHO$.

[00174] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, at least one instance of R^{2a} and R^{2b} is vinyl, allyl, or prenyl.

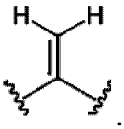
[00175] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00176] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00177] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted heterocylyl, *e.g.,* optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00178] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00179] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00180] In certain embodiments, R^{2a} and R^{2b} are taken together to form 

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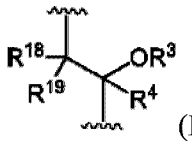
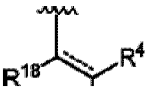
Date Reçue/Date Received 2020-06-25

Group L^3 and Groups R^3, R^4, R^{18}, R^{19}, R^{20}, and R^{21}

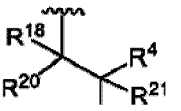
[00181] As generally defined herein, L^3 is a group of the formula:



(L^3-i),



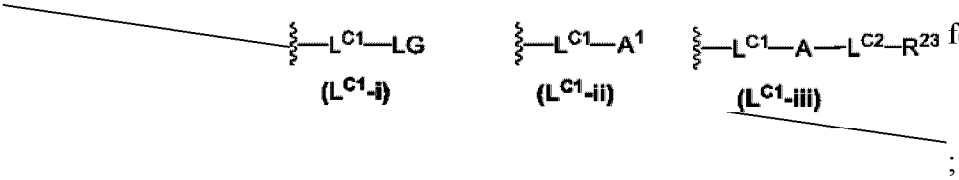
(L^3-ii),



or **(L^3-iii)**;

------ represents a single or double bond;

R_3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -$C(=O)R^{Z8}$, -$C(=O)OR^{Z8}$, - $C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a group of formula:



;

R_4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl;

each instance of R^{18} and R^{19} independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

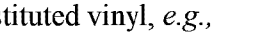
each instance of R^{20} and R^{21} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, carbonyl, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring.

[00182] In certain embodiments, the carbon to which R^3 is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^3 is attached is a stereocenter of the (S)-configuration.

[00183] In certain embodiments, R^3 is hydrogen.

Date Reçue/Date Received 2020-06-25

[00184] In certain embodiments, R^3 is optionally substituted alkyl; *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or an optionally substituted C_{5-6}alkyl. In certain embodiments, R^3 is $-CH_3$. In certain embodiments, R^3 is $-CH_2CHO$. In certain embodiments, R^3 is $-CH_2N(R^{22})_2$ wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl. In certain embodiments, R^3 is $-CH_2NH(R^{22})$. In certain embodiments, R^3 is $-CH_2NH_2$. In certain embodiments, R^3 is $-CH_2CH(OH)R^{24}$ wherein R^{24} is hydrogen, optionally substituted alkyl, or optionally substituted aryl. In certain embodiments, R^3 is $-CH_2CH_2OH$. In certain embodiments, R^3 is $-CH_2CH_2R^{23}$ wherein R^{23} is as defined herein.

[00185] In certain embodiments, R^3 is optionally substituted alkenyl; *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, R^3 is vinyl, allyl, or prenyl. In certain embodiments, R^3 is optionally substituted allyl, *e.g.,* substituted allyl, *e.g.,*  wherein R^{23} is as defined herein, or unsubstituted allyl  . In certain embodiments, R^3 is optionally substituted vinyl, *e.g.,* substituted vinyl, *e.g.,*  wherein R^{23} is as defined herein, or unsubstituted vinyl  .

[00186] In certain embodiments, R^3 is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00187] In certain embodiments, R^3 is optionally substituted carbocyclyl; *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00188] In certain embodiments, R^3 is optionally substituted heterocyclyl, *e.g.,* optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

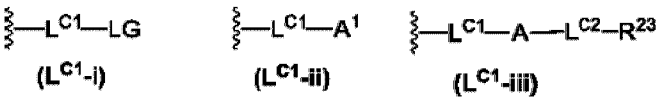
[00189] In certain embodiments, R^3 is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00190] In certain embodiments, R^3 is optionally substituted heteroaryl, *e.g.,* optionally substituted 5– to 6–membered heteroaryl.

Date Reçue/Date Received 2020-06-25

[00191] In certain embodiments, R^3 is $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, or an oxygen protecting group.

[00192] In certain embodiments, R^3 is or a group of formula:



,

wherein L^{C1}, LG, A^1, A, L^{C2}, and R^{23} are as defined herein.

[00193] In certain embodiments, the carbon to which R^4 is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^4 is attached is a stereocenter of the (S)-configuration.

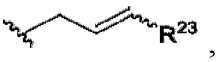
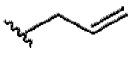
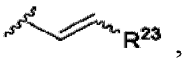
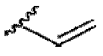
[00194] In certain embodiments, R^4 is hydrogen.

[00195] In certain embodiments, R^4 is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, R^4 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CHO$. In certain embodiments, R^4 is $-CH_2N(R^{22})_2$ wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl. In certain embodiments, R^4 is $-CH_2NH(R^{22})$. In certain embodiments, R^4 is $-CH_2NH_2$. In certain embodiments, R^4 is $-CH_2CH(OH)R^{24}$ wherein R^{24} is hydrogen, optionally substituted alkyl, or optionally substituted aryl. In certain embodiments, R^4 is $-CH_2CH_2OH$. In certain embodiments, R^4 is $-CH_2CH_2R^{23}$ wherein R^{23} is as defined herein.

[00196] In certain embodiments, R^4 is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, R^4 is optionally substituted allyl, *e.g.,* substituted allyl, *e.g.,*  wherein R^{23} is as defined herein, or unsubstituted allyl  . In certain embodiments, R_4 is optionally substituted vinyl, *e.g.,* substituted vinyl, *e.g.,*  wherein R^{23} is as defined herein, or unsubstituted vinyl  .

[00197] Various combinations of R^4 and R^{21} are contemplated herein. For example, in certain embodiments, R^4 is optionally substituted C_{1-3}alkyl and R^{21} is hydrogen. In certain embodiments, R^3 is $-CH_2CHO$, $-CH_2N(R^{22})_2$, $-CH_2CH(OH)R^{24}$, or $-CH_2CH_2R^{23}$ and R^{21} is hydrogen. In certain embodiments, R^4 is optionally substituted C_{2-3}alkenyl, and R^{21} is

Date Reçue/Date Received 2020-06-25

hydrogen. In certain embodiments, R^4 is  ,  ,  , or  and R^{21} is hydrogen.

[00198] In certain embodiments, R^4 is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00199] In certain embodiments, R^4 is optionally substituted carbocyclyl, *e.g.*, optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00200] In certain embodiments, R^4 is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

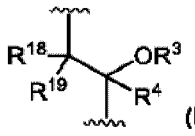
[00201] In certain embodiments, R^4 is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00202] In certain embodiments, R^4 is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00203] In certain embodiments, each instance of R^{18} and R^{19} is independently hydrogen or optionally substituted alkyl, *e.g.*, hydrogen or $-CH_3$. In certain embodiments, the carbon to which R^{18} and R^{19} are attached is a stereocenter in the (R) configuration. In certain embodiments, the carbon to which R^{18} and R^{19} are attached is a stereocenter in the (S) configuration.

[00204] In certain embodiments, each instance of R^{20} and R^{21} is independently hydrogen, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring. In certain embodiments, R^{20} and R^{21} are syn to each other. In certain embodiments, R^{20} and R^{21} are anti to each other.

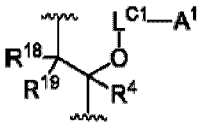
[00205] In certain embodiments, L^3 is:



$(L^3\text{-}i)$.

[00206] In certain embodiments, L^3 is:

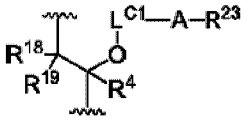
Date Reçue/Date Received 2020-06-25



(L^3-ic)

wherein L^{C1} and A^1 are as defined herein.

[00207] In certain embodiments, L^3 is of the formula:



(L^3-id)

wherein L^{C1}, A, L^{C2}, and R^{23} are as defined herein.

Groups R^{5a} and R^{5b}

[00208] As generally defined herein, each instance of R^{5a} and R^{5b} is independently hydrogen, halogen, silyl, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl.

[00209] In certain embodiments, one instance of R^{5a} and R^{5b} is hydrogen, and the other of R^{5a} and R^{5b} is a non-hydrogen group. In certain embodiments, each instance of R^{5a} and R^{5b} is hydrogen. In certain embodiments, each instance of R^{5a} and R^{5b} is a non-hydrogen group, *e.g.,* halogen, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl.

[00210] In certain embodiments, the carbon to which R^{5a} and R^{5b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{5a} and R^{5b} is attached is a stereocenter of the (S)-configuration.

[00211] In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, at least one instance of R^{5a} and R^{5b} is $-CH_3$. In certain embodiments, both instances of R^{5a} and R^{5b} are $-CH_3$.

[00212] In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted carbocyclyl, *e.g.*, optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

Date Reçue/Date Received 2020-06-25

[00213] In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00214] In certain embodiments, at least one instance of R^{5a} and R^{5b} is halogen, *e.g.*, bromo, iodo, chloro, or fluoro. In certain embodiments, at least one instance of R^{5a} and R^{5b} is fluoro. In certain embodiments, both instances of R^{5a} and R^{5b} are fluoro. In certain embodiments, one of R^{5a} and R^{5b} is hydrogen and the other of R^{5a} and R^{5b} is fluoro.

[00215] In certain embodiments, at least one instance of R^{5a} and R^{5b} is silyl.

Groups R^6 and R_{10}

[00216] As generally defined herein, R^6 and/or R^{10} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen.

[00217] In certain embodiments, R^6 and/or R^{10} is hydrogen. In certain embodiments, R_6 is hydrogen. In certain embodiments, R^{10} is hydrogen. In certain embodiments, R^6 is hydrogen, and R^{10} is hydrogen. In certain embodiments, both of R^6 and R^{10} are non-hydrogen groups.

[00218] In certain embodiments, the carbon to which R^6 and R^{10} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^6 and R_{10} is attached is a stereocenter of the (S)-configuration.

[00219] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted alkyl; *e.g.*, optionally substituted $C_{1–6}$alkyl optionally substituted $C_{1–2}$alkyl, optionally substituted $C_{2–3}$alkyl, optionally substituted $C_{3–4}$alkyl, optionally substituted $C_{4–5}$alkyl, or optionally substituted $C_{5–6}$alkyl. In certain embodiments, at least one instance of R_6 and R^{10} is $–CH_3$. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_3$. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_2CN$. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_2C(=O)OR^{23}$, wherein R^{32} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocycyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl. In certain embodiments, R^{32} is optionally substituted alkyl,

Date Reçue/Date Received 2020-06-25

e.g. C_{1-6} alkyl. In certain embodiments, R^{32} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{32} is methyl, ethyl, or propyl. In certain embodiments, R^{32} is substituted C_{1-6} alkyl. In certain embodiments, R^{32} is hydrogen.

[00220] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, at least one instance of R^6 and R^{10} is substituted or unsubstituted allyl. In certain embodiments, at least one instance of R^6 and R_{10} is substituted or unsubstituted vinyl. Such groups are contemplated after the macrocyclization step, converted, for example, from the enolate of the macrolide wherein R^6 and/or R^{10} is hydrogen.

[00221] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl. Such groups are contemplated after the macrocyclization step, converted, for example, from the enolate of the macrolide wherein R^6 and/or R^{10} is hydrogen.

[00222] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00223] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00224] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted aryl; *e.g.*, optionally substituted phenyl.

[00225] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted aralkyl; *e.g.*, optionally substituted benzyl.

[00226] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted heteroaryl, *e.g.,* optionally substituted 5– to 6–membered heteroaryl.

[00227] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted heteroaralkyl; *e.g.*, optionally substituted pyrazolylalkyl, imidazolylalkyl, thiazolylalkyl, oxazolylalkyl, pyridinylalkyl, pyrimidinylalkyl, or pyrazinylalkyl.

Date Reçue/Date Received 2020-06-25

[00228] In certain embodiments, at least one instance of R^6 and R^{10} is hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, or substituted amino. Such groups are contemplated after the macrocyclization step, converted, for example, from wherein R_6 and/or R^{10} is a halogen.

[00229] In certain embodiments, at least one instance of R^6 and R^{10} is carbonyl, *e.g.,* acetyl.

[00230] In certain embodiments, at least one instance of R^6 and R^{10} is silyl. In certain embodiments, R^6 is silyl prior to macrocyclization, but is removed after the macrolide is formed and replaced with, for example, hydrogen.

[00231] In certain embodiments, at least one instance of R^6 and R^{10} is halogen, *e.g.,* fluoro, bromo, chloro, or iodo.

Groups R^7 and R_8

[00232] As generally defined herein, R^7 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

[00233] In certain embodiments, R^7 is hydrogen. However, in certain embodiments, R_7 is a non-hydrogen group, and the the carbon to which R^7 is attached is a stereocenter of the (R)-configuration. In certain embodiments, R^7 is a non-hydrogen group, and the the carbon to which R^7 is attached is a stereocenter of the (S)-configuration.

[00234] In certain embodiments, R^7 is optionally substituted alkyl, *e.g.*, optionally substituted $C_{1–6}$alkyl optionally substituted $C_{1–2}$alkyl, optionally substituted $C_{2–3}$alkyl, optionally substituted $C_{3–4}$alkyl, optionally substituted $C_{4–5}$alkyl, or optionally substituted $C_{5–6}$alkyl. In certain embodiments, R^7 is $–CH_3$ or $–CH_2CH_3$.

[00235] In certain embodiments, R^7 is optionally substituted alkenyl, *e.g.*, optionally substituted $C_{2–6}$alkenyl, optionally substituted $C_{2–3}$alkenyl, optionally substituted $C_{3–4}$alkenyl, optionally substituted $C_{4–5}$alkenyl, or optionally substituted $C_{5–6}$alkenyl. In certain embodiments, R^7 is vinyl, allyl, or prenyl.

[00236] In certain embodiments, R^7 is optionally substituted alkynyl, *e.g.*, optionally substituted $C_{2–6}$alkynyl, optionally substituted $C_{2–3}$alkynyl, optionally substituted $C_{3–4}$alkynyl, optionally substituted $C_{4–5}$alkynyl, or optionally substituted $C_{5–6}$alkynyl.

Date Reçue/Date Received 2020-06-25

[00237] In certain embodiments, R^7 is optionally substituted carbocyclyl, *e.g.,* optionally substituted $C_{3–6}$carbocyclyl, optionally substituted $C_{3–4}$carbocyclyl, optionally substituted $C_{4–5}$ carbocyclyl, or optionally substituted $C_{5–6}$ carbocyclyl.

[00238] In certain embodiments, R^7 is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00239] In certain embodiments, R^7 is optionally substituted aryl; *e.g.*, optionally substituted phenyl.

[00240] In certain embodiments, R^7 is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00241] As generally defined herein, R^8 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

[00242] In certain embodiments, R^8 is hydrogen.

[00243] In certain embodiments, R^8 is optionally substituted alkyl, *e.g.*, optionally substituted $C_{1–6}$alkyl optionally substituted $C_{1–2}$alkyl, optionally substituted $C_{2–3}$alkyl, optionally substituted $C_{3–4}$alkyl, optionally substituted $C_{4–5}$alkyl, or optionally substituted $C_{5–6}$alkyl. In certain embodiments, R^8 is $–CH_3$ or $–CH_2CH_3$.

[00244] In certain embodiments, R^8 is optionally substituted alkenyl, *e.g.*, optionally substituted $C_{2–6}$alkenyl, optionally substituted $C_{2–3}$alkenyl, optionally substituted $C_{3–4}$alkenyl, optionally substituted $C_{4–5}$alkenyl, or optionally substituted $C_{5–6}$alkenyl. In certain embodiments, R^8 is vinyl, allyl, or prenyl

[00245] In certain embodiments, R^8 is optionally substituted alkynyl, *e.g.*, optionally substituted $C_{2–6}$alkynyl, optionally substituted $C_{2–3}$alkynyl, optionally substituted $C_{3–4}$alkynyl, optionally substituted $C_{4–5}$alkynyl, or optionally substituted $C_{5–6}$alkynyl.

[00246] In certain embodiments, R^8 is optionally substituted carbocyclyl, *e.g.,* optionally substituted $C_{3–6}$carbocyclyl, optionally substituted $C_{3–4}$carbocyclyl, optionally substituted $C_{4–5}$ carbocyclyl, or optionally substituted $C_{5–6}$ carbocyclyl.

[00247] In certain embodiments, R^8 is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

Date Reçue/Date Received 2020-06-25

[00248] In certain embodiments, R^8 is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00249] In certain embodiments, R^8 is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

Groups R^{Za} and R^{Zb}

[00250] As generally defined herein, R^{Za} and R^{Zb} are each independently hydrogen, halogen, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

[00251] In certain embodiments, the bond between the two carbons to which R^{Za} and R^{Zb} are attached represents a double bond, and R^{Za} and R^{Zb} are each independently hydrogen.

[00252] In certain embodiments, the bond between the two carbons to which R^{Za} and R^{Zb} are attached represents a single bond (*e.g.,* provided by hydrogenation of the double bond), and R^{Za} and R^{Zb} are each independently hydrogen.

[00253] In certain embodiments, at least one of R^{Za} and R^{Zb} is a hydrogen and at least one of R^{Za} and R^{Zb} is a non-hydrogen group, *e.g.,* halogen, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{Za} is hydrogen and R^{Zb} is a non-hydrogen group. In certain embodiments, R^{Za} is a non-hydrogen group and R^{Zb} ishydrogen. In certain embodiments, both of R^{Za} and R^{Zb} are non-hydrogen groups. In any of the above instance, in certain embodiments, the bond between the two carbons to which R^{Za} and R^{Zb} are attached represents a single bond. Alternatively, in any of the above instance, in certain embodiments, the bond between the two carbons to which R^{Za} and R^{Zb} are attached represents a double bond.

[00254] In certain embodments, R^{Za} is hydrogen, R^{Zb} is hydrogen, and the bond ---- between the two carbons to which R^{Za} and R^{Zb} are attached represents a double bond.

[00255] In certain embodiments, R^{Za} is halogen (*e.g.,* fluoro) or optionally substituted alkyl (*e.g.,* methyl), R^{Zb} is hydrogen, and the bond between the two carbons to which R^{Za} and R^{Zb} are attached represents a single bond.

Date Reçue/Date Received 2020-06-25

[00256] In certain embodiments, the bond between the two carbons to which R^{Za} and R^{Zb} are attached represents a double bond and R^{Za} and R^{Zb} are in a *cis*-configuration. In certain embodiments, the bond between the two carbons to which R^{Za} and R^{Zb} are attached represents a double bond and R^{Za} and R^{Zb} are in a *trans*-configuration.

Groups R^{Z2}, R^{Z3} and R^{Z4}

[00257] As generally defined herein, each instance of R^{Z2} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, or a nitrogen protecting group, or two R^{Z2} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring.

[00258] In certain embodiments, R^{Z2} is hydrogen.

[00259] In certain embodiments, R^{Z2} is optionally substituted alkyl; *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, R^{Z2} is $-CH_3$.

[00260] In certain embodiments, R^{Z2} is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl.

[00261] In certain embodiments, R^{Z2} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00262] In certain embodiments, R^{Z2} is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00263] In certain embodiments, R^{Z2} is optionally substituted heterocyclyl, *e.g.,* optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00264] In certain embodiments, R^{Z2} is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

Date Reçue/Date Received 2020-06-25

[00265] In certain embodiments, R^{Z2} is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00266] In certain embodiments, R^{Z2} is hydroxyl, substituted hydroxyl, amino, or substituted amino.

[00267] In certain embodiments, R^{Z2} is $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$.

[00268] In certain embodiments, R^{Z2} is a nitrogen protecting group.

[00269] In certain embodiments, two R^{Z2} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring.

[00270] As generally defined herein, R^{Z3} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl.

[00271] In certain embodiments, R^{Z3} is hydrogen.

[00272] In certain embodiments, R^{Z3} is optionally substituted alkyl; *e.g.*, optionally substituted $C_{1–6}$alkyl optionally substituted $C_{1–2}$alkyl, optionally substituted $C_{2–3}$alkyl, optionally substituted $C_{3–4}$alkyl, optionally substituted $C_{4–5}$alkyl, or optionally substituted $C_{5–6}$alkyl. In certain embodiments, R^{Z3} is $–CH_3$. In certain embodiments, R^{Z3} is $–CH_2CHO$. In certain embodiments, R^{Z3} is $–CH_2CH_2OH$. In certain embodiments, R^{Z3} is $–CH_2CH_2N(R^{22})_2$. In certain embodiments, R^{Z3} is $–CH_2CH_2N(CH_3)_2$. In certain embodiments, R^{Z3} is $–CH_2CH(OH)R^{24}$. In certain embodiments, R^{Z3} is alkyl optionally substituted with one or more halogen atoms, *e.g.,* optionally substituted haloalkyl; *e.g.*, $-CF_3$, $-CF_2CF_3$, or $-CF_2H$. In certain embodiments, R^{Z3} is $–CF_3$.

[00273] In certain embodiments, R^{Z3} is optionally substituted alkenyl, *e.g.*, optionally substituted $C_{2–6}$alkenyl, optionally substituted $C_{2–3}$alkenyl, optionally substituted $C_{3–4}$alkenyl, optionally substituted $C_{4–5}$alkenyl, or optionally substituted $C_{5–6}$alkenyl. In certain embodiments, R^{Z3} is optionally substituted vinyl. In certain embodiments, R^{Z3} is unsubstituted vinyl. In certain embodiments, R^{Z3} is optionally substituted allyl. In certain embodiments, R^{Z3} is unsubstituted allyl.

[00274] In certain embodiments, R^{Z3} is optionally substituted alkynyl, *e.g.*, optionally substituted $C_{2–6}$alkynyl, optionally substituted $C_{2–3}$alkynyl, optionally substituted $C_{3–4}$alkynyl, optionally substituted $C_{4–5}$alkynyl, or optionally substituted $C_{5–6}$alkynyl.

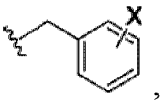
[00275] In certain embodiments, R^{Z3} is optionally substituted carbocyclyl, *e.g.,* optionally substituted $C_{3–6}$carbocyclyl, optionally substituted $C_{3–4}$carbocyclyl, optionally substituted $C_{4–5}$ carbocyclyl, or optionally substituted $C_{5–6}$ carbocyclyl. In certain

Date Reçue/Date Received 2020-06-25

embodiments, R^{Z3} is optionally substituted cyclopropyl. In certain embodiments, R^{Z3} is unsubstituted cyclopropyl. In certain embodiments, R^{Z3} is optionally substituted cyclobutyl. In certain embodiments, R^{Z3} is unsubstituted cyclobutyl.

[00276] In certain embodiments, R^{Z3} is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00277] In certain embodiments, R^{Z3} is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00278] In certain embodiments, R^{Z3} is optionally substituted aralkyl. In certain embodiments, R^{Z3} is unsubstituted aralkyl. In certain embodiments, R^{Z3} is optionally substituted benzyl. In certain embodiments, R^{Z3} is  , wherein X is halogen. In certain embodiments, R^{Z3} is unsubstituted benzyl.

[00279] In certain embodiments, R^{Z3} is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00280] In certain embodiments, R^{Z3} is optionally substituted heteroaralkyl. In certain embodiments, R^{Z3} is unsubstituted heteroaralkyl.

[00281] As generally defined herein, R^{Z4} is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl.

[00282] In certain embodiments, R^{Z4} is optionally substituted alkyl, *e.g.*, optionally substituted $C_{1–6}$alkyl optionally substituted $C_{1–2}$alkyl, optionally substituted $C_{2–3}$alkyl, optionally substituted $C_{3–4}$alkyl, optionally substituted $C_{4–5}$alkyl, or optionally substituted $C_{5–6}$alkyl. In certain embodiments, R^{Z4} is $–CH_3$. In certain embodiments, R^{Z4} is alkyl optionally substituted with one or more halogen atoms, *e.g.,* optionally substituted haloalkyl; *e.g.*, $-CF_3$, $-CF_2CF_3$, or $-CF_2H$.

[00283] In certain embodiments, R^{Z4} is optionally substituted alkenyl, *e.g.*, optionally substituted $C_{2–6}$alkenyl, optionally substituted $C_{2–3}$alkenyl, optionally substituted $C_{3–4}$alkenyl, optionally substituted $C_{4–5}$alkenyl, or optionally substituted $C_{5–6}$alkenyl.

Date Reçue/Date Received 2020-06-25

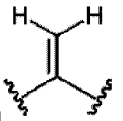
[00284] In certain embodiments, R^{Z4} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00285] In certain embodiments, R^{Z4} is optionally substituted carbocyclyl, *e.g.*, optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00286] In certain embodiments, R^{Z4} is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00287] In certain embodiments, R^{Z4} is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00288] In certain embodiments, R^{Z4} is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00289] In certain embodiments, R^{Z3} and R^{Z4} are taken together to form  .

Groups R^9 and R^{17}, R_{Y1}, R_{Y2}

[00290] As generally defined herein, R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is halogen, or R^{Y1} and R^{Y2} are joined to form an oxo (=O) group.

[00291] In certain embodiments, R^{Y1} and R^{Y2} are joined to form an oxo (=O) group.

[00292] In certain embodiments, R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen.

[00293] In certain embodments, R^{Y1} is halogen (*e.g.,* fluoro) and R^{Y2} is hydrogen.

[00294] In certain embodments, R^{Y1} is halogen (*e.g.,* fluoro) and R^{Y2} is halogen (*e.g.,* fluoro).

[00295] As generally defined herein, R^9 and/or R^{17} are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a carbohydrate, wherein each instance of R^{Z8} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted

Date Reçue/Date Received 2020-06-25

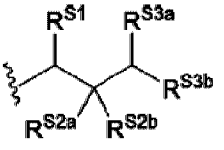
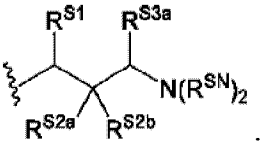
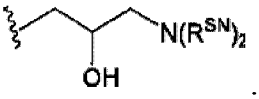
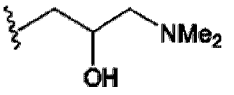
aryl, or optionally substituted heteroaryl, or two R^{Z8} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring.

[00296] In certain embodiments, the carbon to which R^9 is attached is of the (R)-configuration. In certain embodiments, the carbon to which R^9 is attached is of the (S)-configuration.

[00297] In certain embodiments, the carbon to which R^{17} is attached is of the (R)-configuration. In certain embodiments, the carbon to which R^{17} is attached is of the (S)-configuration.

[00298] In certain embodiments, R^9 is hydrogen. In certain embodiments, R^{17} is hydrogen.

[00299] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl, *e.g.*, $-CH_3$.

[00300] In certain embodiments, R^9 is  , where R^{S1}, R^{S2a}, R_{S2b}, R_{S3a}, and R^{S3b} are defined herein. In certain embodiments, R^9 is  . In certain embodiments, R^9 is  . In certain embodiments, R^9 is  .

[00301] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted alkenyl, *e.g.*, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-3}alkenyl, substituted or unsubstituted C_{3-4}alkenyl, substituted or unsubstituted C_{4-5}alkenyl, or substituted or unsubstituted C_{5-6}alkenyl.

[00302] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted alkynyl, *e.g.*, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-3}alkynyl, substituted or unsubstituted C_{3-4}alkynyl, substituted or unsubstituted C_{4-5}alkynyl, or substituted or unsubstituted C_{5-6}alkynyl.

[00303] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted carbocyclyl, *e.g.*, substituted or unsubstituted C_{3-6}carbocyclyl, substituted or

Date Reçue/Date Received 2020-06-25

unsubstituted C_{3-4}carbocyclyl, substituted or unsubstituted C_{4-5} carbocyclyl, or substituted or unsubstituted C_{5-6} carbocyclyl.

[00304] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00305] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted aryl, *e.g.*, optionally substituted phenyl.

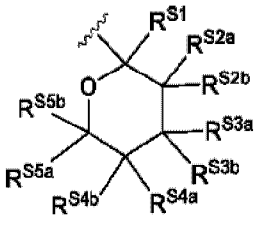
[00306] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00307] In certain embodiments, R^9 and/or R^{17} are each independently $–C(=O)R^{Z8}$, $–C(=O)OR^{Z8}$, or $–C(=O)N(R^{Z8})_2$. For example, in certain embodiments, R^{17} is $–C(=O)R^{Z8}$, wherein R^{Z8} is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, R^{17} is $–C(=O)R^{Z8}$, wherein R^{Z8} is optionally substituted aralkyl or optionally substituted heteroaralkyl.

[00308] In certain embodiments, R^9 and/or R^{17} are each independently an oxygen protecting group.

[00309] In certain embodiments, R^9 and/or R^{17} are each independently a carbohydrate.

[00310] In certain embodiments, R^9 and/or R^{17} is a group of Formula (**s - 1**), which encompasses carbohydrates, but also encompasses optionally substituted heterocylyl:



(s - 1)

wherein:

each of R^{S1}, R^{S2a}, R^{S2b}, R^{S3a}, R^{S3b}, R^{S4a}, R^{S4b}, R^{S5a}, and R^{S5b} is independently hydrogen, optionally substituted alkyl, $–OR^{SO}$, $–N(R^{SN})_2$, or wherein R^{S2a} or R^{S2b} may be taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused heterocyclic ring;

each instance of R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group; and

Date Reçue/Date Received 2020-06-25

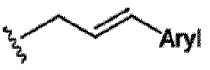
each instance of R^{SN} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; or optionally two R^{SN} are taken with the intervening atoms to form a heterocyclic ring.

[00311] As generally defined herein, each instance of R^{S1} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, or $-N(R^{SN})_2$.

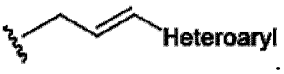
[00312] In certain embodiments, R^{S1} is hydrogen.

[00313] In certain embodiments, R^{S1} is optionally substituted alkyl. In certain embodiments, R^{S1} is substituted C_{1-6} alkyl. In certain embodiments, R^{S1} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{S1} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, R^{S1} is isopropyl, isobutyl, or isoamyl. In certain embodiments, R^{S1} is isobutyl. In certain embodiments, R^{S1} is *tert*–butyl.

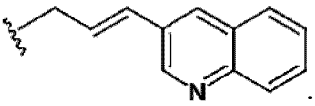
[00314] In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, R^{S1} is –OH. In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, R^{S1} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, R^{S1} is optionally substituted –O–alkyl–aryl. In certain embodiments, R^{S1} is –O–Bz. In certain embodiments, R^{S1} is optionally substituted –O–alkyl–heteroaryl. In certain embodiments, R_{S1} is optionally substituted –O–alkenyl–aryl. In certain embodiments, R^{S1} is optionally substituted –O–alkenyl–heteroaryl. In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is



. In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is



. In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is



. In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, R^{S1} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00315] In certain embodiments, R^{S1} is $-N(R^{SN})_2$. In some embodiments, R^{S1} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, R^{S1} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

[00316] In certain embodiments, R^{S1} is $-NH_2$.

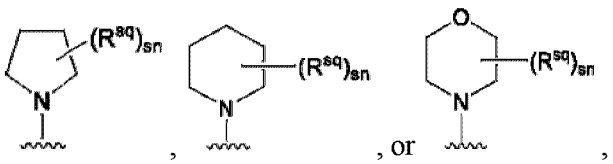
Date Reçue/Date Received 2020-06-25

[00317] In certain embodiments, R^{S1} is $-NHR^{SN}$. In certain embodiments, R^{S1} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-NHR^{SN}$, wherein R^{SN} is substituted C_{1-6} alkyl. In certain embodiments, R^{S1} is –NH–benzyl.

[00318] In certain embodiments, R^{S1} is $-NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiments, R^{S1} is –NHFmoc. In certain embodiment, R^{S1} is –NHBoc.

[00319] In certain embodiments, R^{S1} is $-N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(R^{SN})_2$, wherein each R_{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, R_{S1} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00320] In some embodiments, R^{S1} is $-N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, R^{S1} is of the formula:



, , or ,

wherein R^s_q is as defined herein, and sn is 0, 1, 2, or 3.

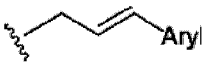
[00321] As generally defined above, each instance of R^{S2a} and R^{S2b} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, or $-N(R^{SN})_2$.

[00322] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is hydrogen.

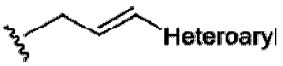
[00323] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, at least one instance of R^{S2a} and R_{S2b} is isopropyl, isobutyl, or isoamyl. In certain embodiments, at least one instance of R^{S2a} and R_{S2b} is isobutyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is *tert*–butyl.

Date Reçue/Date Received 2020-06-25

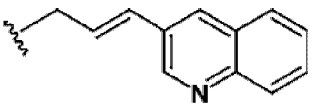
[00324] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –OH. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is optionally substituted –O– alkyl–aryl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –O–Bz. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –O–alkyl–heteroaryl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is optionally substituted –O–alkenyl–aryl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is optionally substituted –O– alkenyl–heteroaryl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$,

wherein R^{SO} is 

wherein Aryl is an optionally substituted aryl group. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is



, wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –OR^{SO}, wherein R^{SO} is



. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –OR^{SO}, wherein R^{SO} is an oxygen protecting group. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00325] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$. In some embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

[00326] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-NH_2$.

[00327] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-NHR^{SN}$. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R_{S2b} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiment, at least one

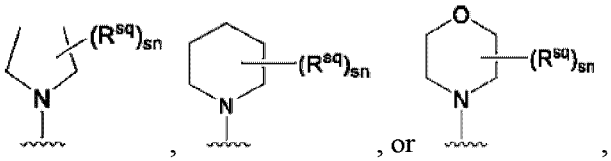
Date Reçue/Date Received 2020-06-25

instance of R^{S2a} and R^{S2b} is $–NHR^{SN}$, wherein R^{SN} is substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –NH–benzyl.

[00328] In certain embodiment, at least one instance of R^{S2a} and R^{S2b} is $–NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiment, at least one instance of $R_{S2a\ and}$ R^{S2b} is –NHFmoc. In certain embodiment, at least one instance of R^{S2a} and R^{S2b} is –NHBoc.

[00329] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $–N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $–N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $– N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $–N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R_{S2a} and R^{S2b} is $–N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $–N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $–N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00330] In some embodiments, at least one instance of R^{S2a} and R^{S2b} is $–N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, at least one instance of $R_{S2a\ and}$ R^{S2b} is of the formula:



, , or ,

wherein R^s_q is as defined herein, and sn is 0, 1, 2, or 3.

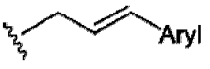
[00331] As generally defined above, each instance of R^{S3a} and R^{S3b} is independently hydrogen, optionally substituted alkyl, $–OR^{SO}$, or $–N(R^{SN})_2$.

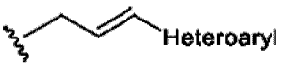
[00332] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is hydrogen.

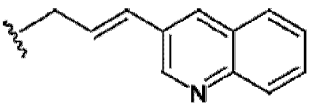
[00333] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is unsubstituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is methyl, ethyl,

Date Reçue/Date Received 2020-06-25

propyl, butyl, pentyl, or hexyl. In certain embodiments, at least one instance of R^{S3a} and R_{S3b} is isopropyl, isobutyl, or isoamyl. In certain embodiments, at least one instance of R^{S3a} and R_{S3b} is isobutyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is *tert*–butyl.

[00334] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is –OH. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, at least one instance of R_{S3a} and R^{S3b} is optionally substituted –O–alkyl–aryl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} –O–Bz. In certain embodiments, at least one instance of R^{S3a} and R_{S3b} is –O–alkyl–heteroaryl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is optionally substituted –O–alkenyl–aryl. In certain embodiments, at least one instance of R_{S3a} and R^{S3b} is optionally substituted –O–alkenyl–heteroaryl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Aryl is an optionally substituted aryl group. In certain embodiments, at least one instance of R^{S3a} and R_{S3b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, at least one instance of R^{S2a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is 

. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00335] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$. In some embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

[00336] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-NH_2$.

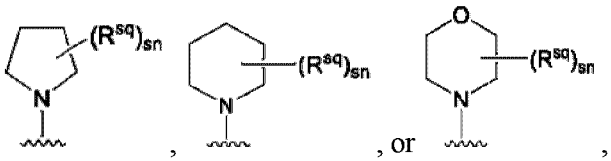
Date Reçue/Date Received 2020-06-25

[00337] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-NHR^{SN}$. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiment, at least one instance of R^{S3a} and R^{S3b} is $-NHR^{SN}$, wherein R^{SN} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is –NH–benzyl.

[00338] In certain embodiment, at least one instance of R^{S3a} and R^{S3b} is $-NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiment, at least one instance of R^{S3a} and R^{S3b} is –NHFmoc. In certain embodiment, at least one instance of R^{S3a} and R^{S3b} is –NHBoc.

[00339] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00340] In some embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, at least one instance of R^{S3a} and R^{S3b} is of the formula:



, , or ,

wherein R^s_q is as defined herein, and sn is 0, 1, 2, or 3.

[00341] In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused heterocyclic ring. In certain embodiments, R^{S2a} is taken together with R^{S3a} to form an optionally substituted fused heterocyclic ring. In certain

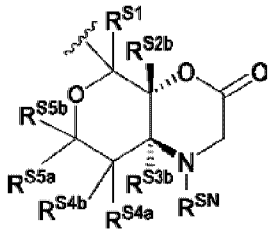
Date Reçue/Date Received 2020-06-25

embodiments, R^{S2b} is taken together with R^{S3b} to form an optionally substituted fused heterocyclic ring. In certain embodiments, R^{S2a} is taken together with R^{S3b} to form an optionally substituted fused heterocyclic ring. In certain embodiments, R^{S2b} is taken together with R^{S3a} to form an optionally substituted fused heterocyclic ring.

[00342] In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused pyrrolidine. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperidine. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperidinone. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R_{S3a} R^{S3b} to form an optionally substituted fused piperazine. In certain embodiments, R_{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperazinone. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused morpholine. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused morpholinone.

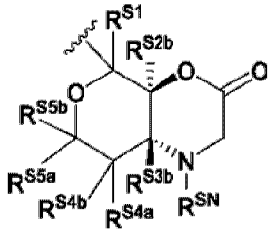
[00343] In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused pyrrolidine; and R^{SN} is methyl. In certain embodiments, R_{S2a} R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperidine; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R_{S3a} R^{S3b} to form an optionally substituted fused piperidinone; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperazine; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperazinone; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused morpholine; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R_{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused morpholinone; and R^{SN} is methyl.

[00344] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



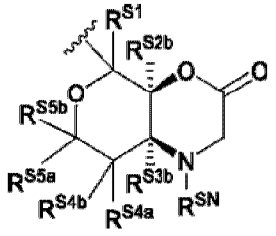
Date Reçue/Date Received 2020-06-25

[00345] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



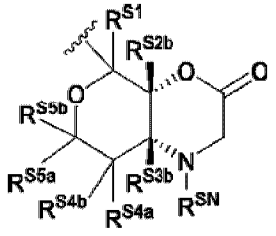
.

[00346] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



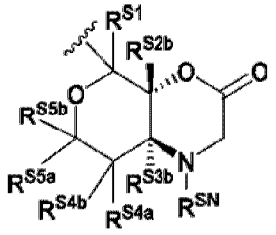
.

[00347] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



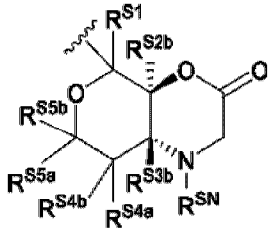
.

[00348] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



; and R^{SN} is methyl.

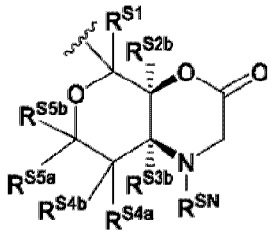
[00349] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



; and R^{SN} is methyl.

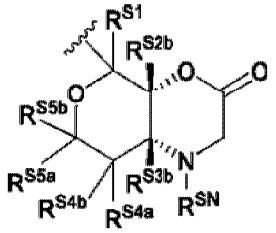
Date Reçue/Date Received 2020-06-25

[00350] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



; and R^{SN} is methyl.

[00351] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form

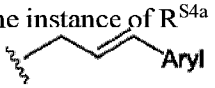


; and R^{SN} is methyl.

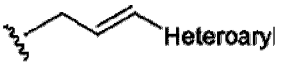
[00352] As generally defined above, each instance of R^{S4a} and R^{S4b} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, or $-N(R^{SN})_2$.

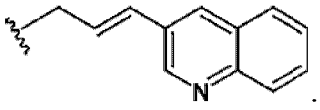
[00353] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is hydrogen.

[00354] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is isopropyl, isobutyl, or isoamyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is isobutyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is *tert*–butyl.

[00355] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is –OH. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is optionally substituted –O–alkyl–aryl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is –O–Bz. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is  wherein Aryl is an optionally substituted aryl group. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein

Date Reçue/Date Received 2020-06-25

R_{SO} is 

wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R_{SO} is 

. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00356] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$. In some embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

[00357] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-NH_2$.

[00358] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R_{S4b} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$, wherein R^{SN} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is –NH–benzyl.

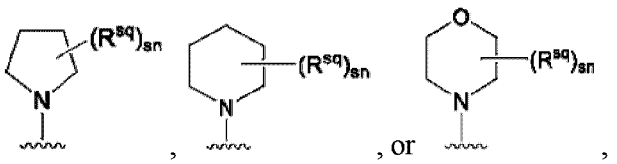
[00359] In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiment, at least one instance of R_{S4a} and R^{S4b} is –NHFmoc. In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is –NHBoc.

[00360] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R_{S4a} and R^{S4b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6}

Date Reçue/Date Received 2020-06-25

alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00361] In some embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, at least one instance of R^{S4a} and R^{S4b} is of the formula:



, , or ,

wherein R^s_q is as defined herein, and sn is 0, 1, 2, or 3.

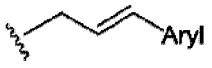
[00362] As generally defined above, each instance of R^{S5a} and R^{S5b} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, or $-N(R^{SN})_2$.

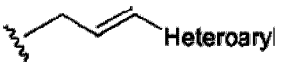
[00363] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is hydrogen.

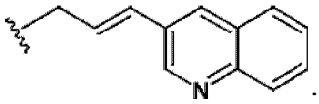
[00364] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is isopropyl, isobutyl, or isoamyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is isobutyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is *tert*–butyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is alkoxyalkyl, *e.g.* $-CH_2OMe$, $-CH_2OEt$, or $-CH_2OBn$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2OH$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2OBz$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2OPG$, wherein PG is an oxygen protecting group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is aminoalkyl, *e.g.* $-CH_2NHMe$, $-CH_2NMe_2$, or $-CH_2NHBn$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2NH_2$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2NHPG$, wherein PG is an nitrogen protecting group.

[00365] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted heterocyclyl, or an oxygen

Date Reçue/Date Received 2020-06-25

protecting group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is –OH. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is optionally substituted –O–alkyl–aryl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is –O–Bz. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Aryl is an optionally substituted aryl group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is 

. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00366] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$. In some embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

[00367] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-NH_2$.

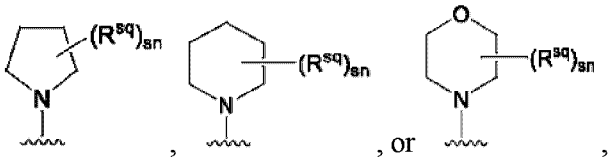
[00368] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-NHR^{SN}$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiment, at least one instance R^{S5a} and R^{S5b} is $-NHR^{SN}$, wherein R^{SN} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is –NH–benzyl.

[00369] In certain embodiment, at least one instance of R^{S5a} and R^{S5b} is $-NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is –NHFmoc. In certain embodiment, at least one instance of R^{S5a} and R^{S5b} is –NHBoc.

Date Reçue/Date Received 2020-06-25

[00370] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R_{S5a} and R^{S5b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00371] In some embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, at least one instance of R_{S5a} and R^{S5b} is of the formula:



, , or ,

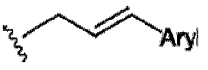
wherein R^{s}_{q} is as defined herein, and sn is 0, 1, 2, or 3.

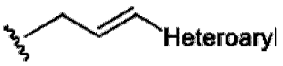
[00372] As used herein, each instance R^{s}_{q} is independently halogen, optionally substituted alkyl, $-OR^{SO1}$, or $-N(R^{SN1})_2$, wherein R^{SO1} is independently hydrogen, optionally substituted alkyl, or an oxygen protecting group; and R^{SN1} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; or optionally two R^{SN1} are taken together with the intervening atoms to form an optionally substituted heterocyclic ring.

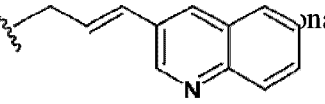
[00373] As generally defined herein, each instance of R^{SO} is independently hydrogen, optionally substituted alkyl, carbonyl, optionally substituted heterocyclyl, or an oxygen protecting group.

[00374] In certain embodiments, R^{SO} is hydrogen. In certain embodiments, R^{SO} is optionally substituted alkyl. In certain embodiments, R^{SO} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{SO} is methyl, ethyl, or propyl. In certain embodiments, R^{SO} is optionally substituted aralkyl, *e.g.,* optionally substituted benzyl (Bn). In certain embodiments, R^{SO} is optionally substituted heterocyclyl. In certain embodiments, R^{SO} is

Date Reçue/Date Received 2020-06-25

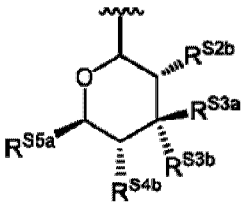
carbonyl. In certain embodiments, R^{SO} is –C(=O)CH_3 (acetyl, Ac). In certain embodiments, R_{SO} is –C(=O)Ph (benzoyl, Bz). In certain embodiments, R^{SO} is 

wherein Aryl is an optionally substituted aryl group. In certain embodiments, R^{SO} is 

wherein 

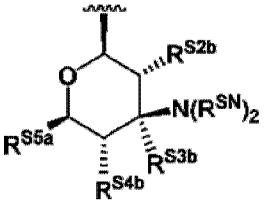
nally substituted heteroaryl group. In certain embodiments, R^{SO} is . In certain embodiments, R^{SO} is an oxygen protecting group.

[00375] As generally defined herein, each instance of R^{SN} is independently hydrogen, optionally substituted alkyl, optionally substituted heterocyclyl, or a nitrogen protecting group; or optionally two R^{SN} are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. In certain embodiments, R^{SN} is hydrogen. In certain embodiments, R^{SN} is optionally substituted alkyl. In certain embodiments, R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{SN} is methyl, ethyl, or propyl. In certain embodiments, R^{SN} is substituted aralkyl, *e.g.,* optionally substituted benzyl (Bn). In certain embodiments, R^{SN} is optionally substituted heterocyclyl. In certain embodiments, R^{SN} is carbonyl. In certain embodiments, R^{SN} is carbonyl. In certain embodiments, R^{SN} is C(=O)CH_3 (acetyl, Ac). In certain embodiments, R^{SN} is –C(=O)Ph (benzoyl, Bz). In certain embodiments, R^{SN} is a nitrogen protecting group.

[00376] In certain embodiments, R^9 and/or R^{17} is of Formula (**s - 2**): 

(**s - 2**).

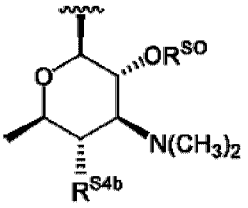
[00377] In certain embodiments, R^9 and/or R^{17} is of Formula (**s - 2a**):



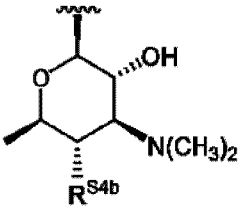
(**s - 2a**).

Date Reçue/Date Received 2020-06-25

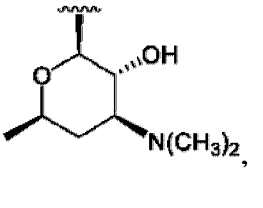
[00378] In certain embodiments, R^9 and/or R^{17} is of one of the following formulae:



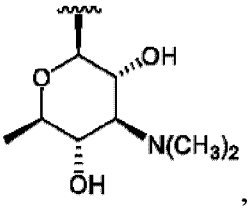
(s-2a-i),



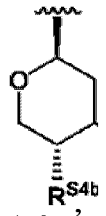
(s-2a-i-1),



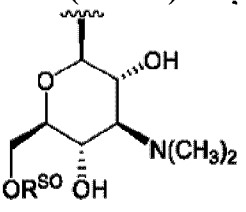
(s-2a-i-2),



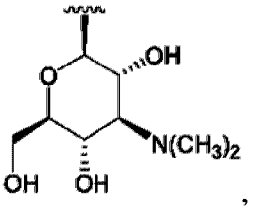
(s-2a-i-3),



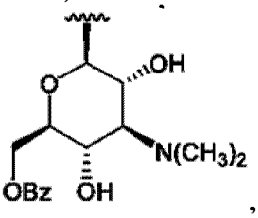
(s-2a-ii),



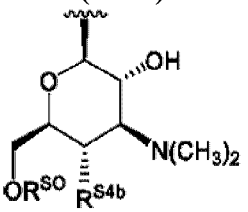
(s-2a-ii-1),



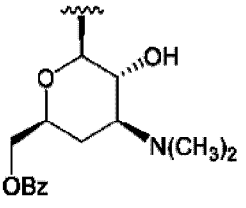
(s-2a-ii-2),



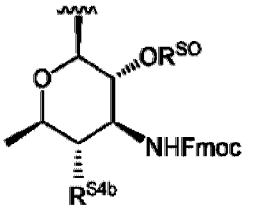
(s-2a-iii),



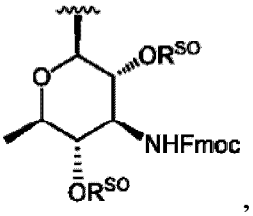
(s-2a-iii-1),



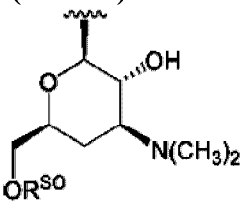
(s-2a-iii-2),



(s-2a-iii-3),



(s-2a-iii-4),

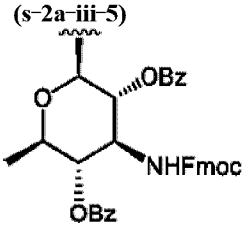


(s-2a-iii-5),

(s-2a-iii-6),

(s-2a-iv),

(s-2a-iv-1),



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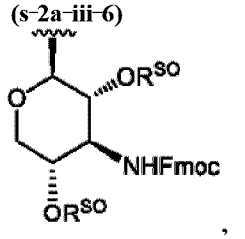
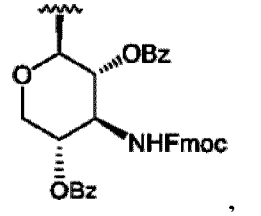


(s-2a-iv-3),



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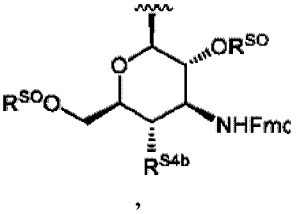

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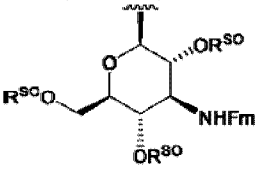
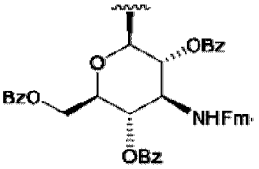
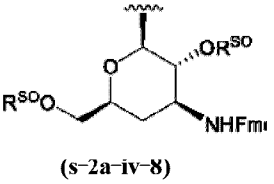


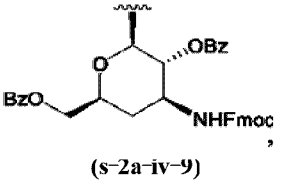
(s-2a-iv-6),



(s-2a-iv-7),

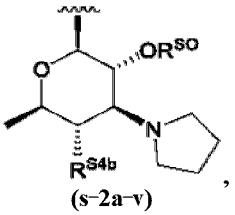


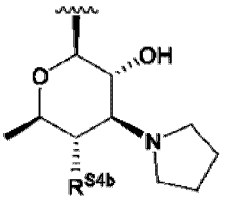
(s-2a-iv-8),

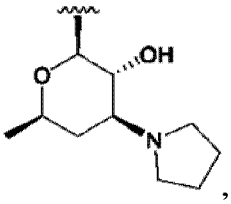


(s-2a-iv-9),

Date Reçue/Date Received 2020-06-25


(s-2a-v),


(s-2a-v-1),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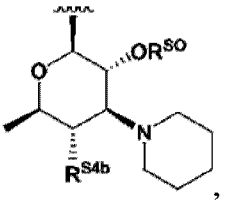
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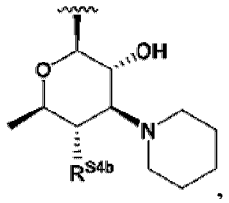
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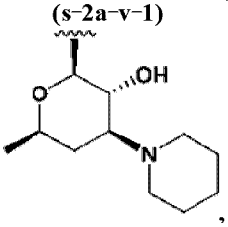
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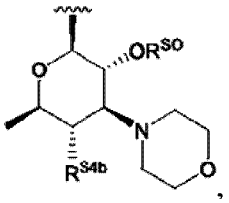
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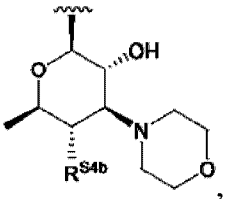
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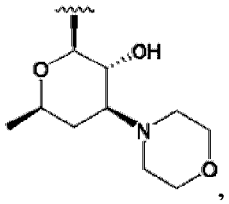
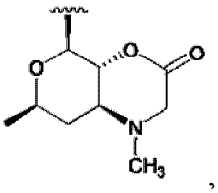

(s-2a-vii-2),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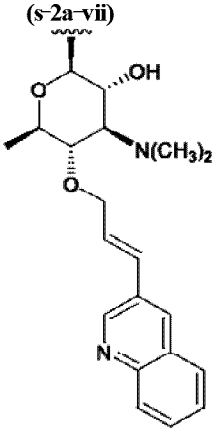
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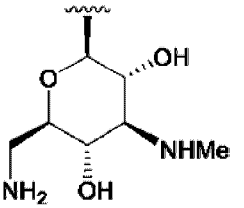
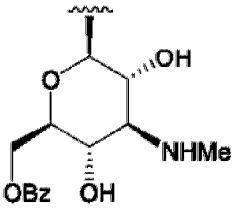
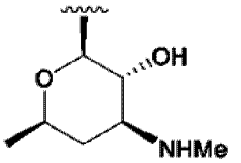
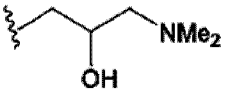
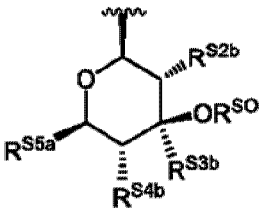

(s-2a-vii-5),


(s-2a-vii-5),

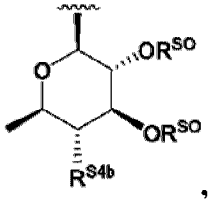

and (s-2a-vii-5)

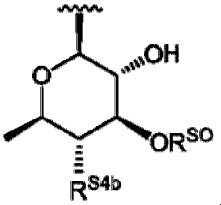

(s-2a-vii-5)

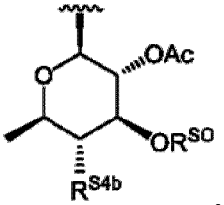
[00379] In certain embodiments, R^9 and/or R^{17} is of Formula (**s－2b**):


(**s－2b**).

[00380] In certain embodiments, R^9 and/or R^{17} is of one of the following formulae:


(**s-2b-i**),


,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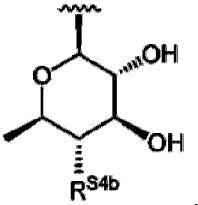
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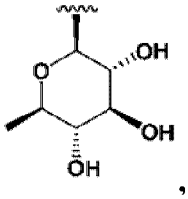
Date Reçue/Date Received 2020-06-25

(s-2b-i-1) (s-2b-i-2) (s-2b-i-3)



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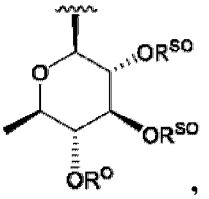

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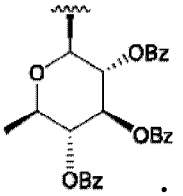
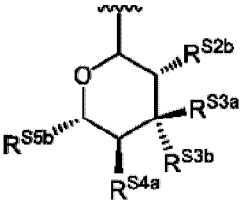


.

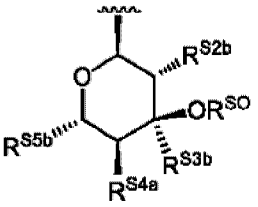
(s-2b-i-4) (s-2b-i-5) (s-2b-i-5)

[00381] In certain embodiments, R^9 and/or R^{17} is of Formula (**s-3**):



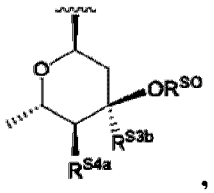
(**s-3**).

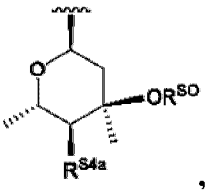
[00382] In certain embodiments, R^9 and/or R^{17} is of Formula (**s-3a**):



(**s-3a**).

[00383] In certain embodiments, R^9 and/or R^{17} is one of the following formulae:



,


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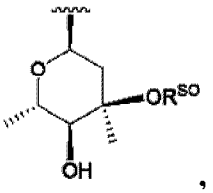
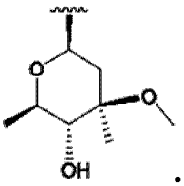


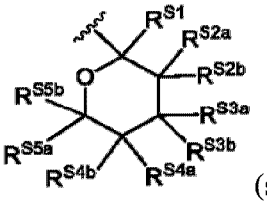
,


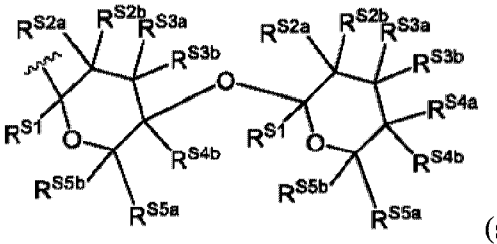
.

(s-3a-i) (s-3a-i-1) and (s-3a-i-2) (s-3a-i-3)

[00384] In certain embodiments, R^{SO} is an optionally substituted heterocycyl.

[00385] For example, in certain embodiments, R^{SO} is of the formula:

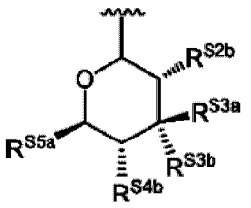


(**s-4**) or


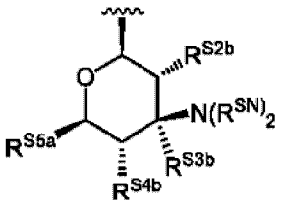
(**s-5**).

[00386] In certain embodiments, R^{SO} is of the formula:

Date Reçue/Date Received 2020-06-25



[00387] In certain embodiments, R^{SO} is of the formula: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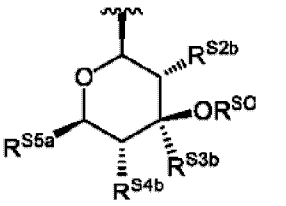
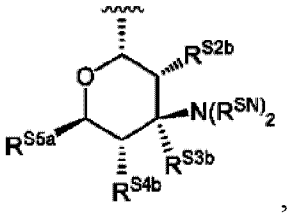
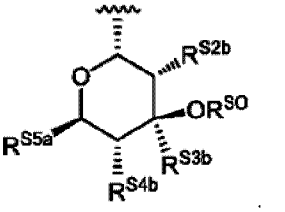
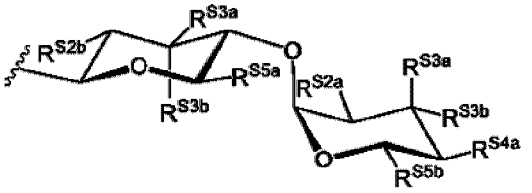

,

, or

.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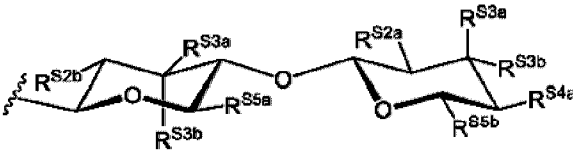
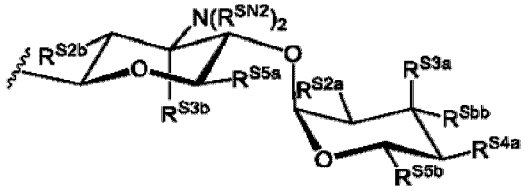

.

[00388] In certain embodiments, R^{SO} is of the formula: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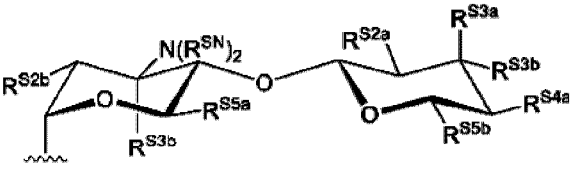
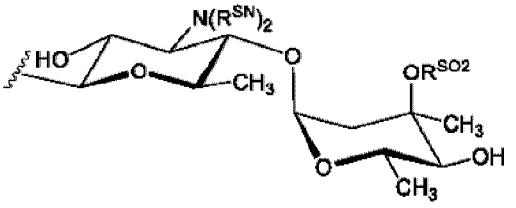

,

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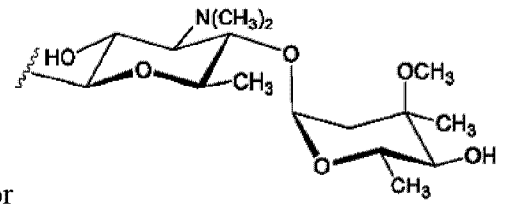
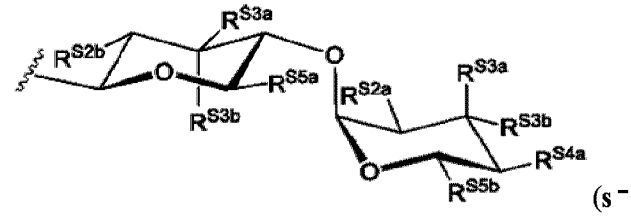
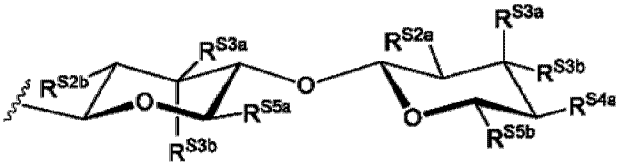

or

[00389] In certain embodiments, R^{9} and/or R^{17} is of the formula:

Date Reçue/Date Received 2020-06-25

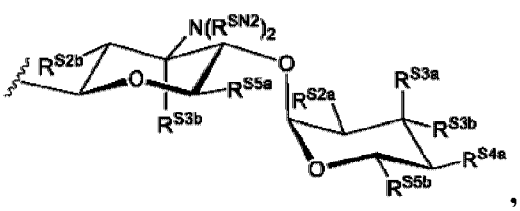


(s-2c) or

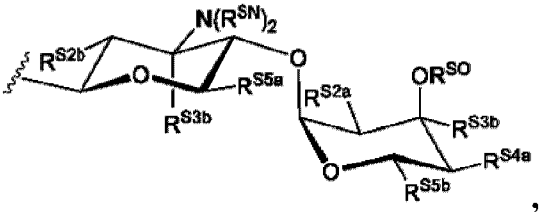


(s-2d).

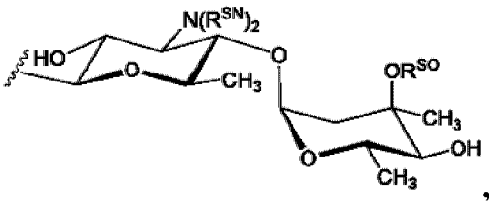
[00390] In certain embodiments, R^9 and/or R^{17} is one of the following formulae:



(s-2c-i),

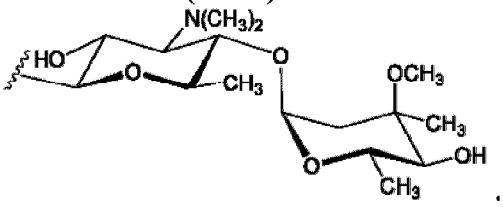


(s-2c-ii),



(s-2c-iii),

or



(s-2c-iv).

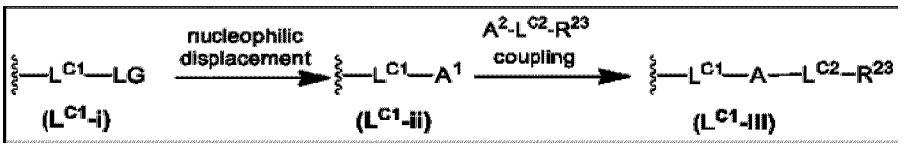
Groups A^1, A^2, and A

[00391] As is generally understood from the above disclosure, in certain embodiments, R^{12}, R^{14}, and/or R3

is a group of Formula (**L^{C1}-i**), wherein LG is a leaving group as defined herein. In certain embodiments, nucleophilic displacement of the leaving group provides a group of Formula (**L^{C1}-ii**). See Scheme A1. It is generally understood that A^1 is a group which is reactive with A^2 of a compound of Formula A^2–L^{C2}–R^{23}, and reaction between the two halves provides a group of Formula (**L^{C1}-iii**). See, Scheme A1. These reactions, from (**L^{C1}-i**) to (**L^{C1}-ii**),

and (**L^{C1}-ii**) to (**L^{C1}-iii**), are envisioned to take place at any stage of the synthesis, for example, during construction of the eastern or western halves, after coupling of the eastern or western halves, or after the macrocyclization step.

Scheme A1.

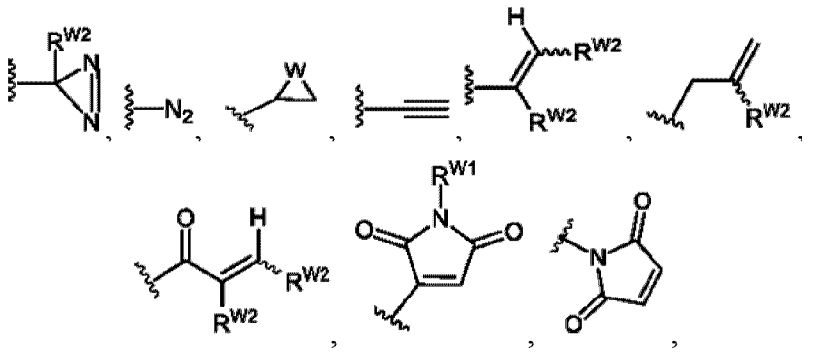


Date Reçue/Date Received 2020-06-25

[00392] In certain embodiments, the coupling reaction from (**L^{C1}-ii**) to (**L^{C1}-iii**) comprises a reaction typically referred to as "click chemistry." Click chemistry is a chemical approach introduced by Sharpless in 2001 and describes chemistry tailored to generate substances quickly and reliably by joining small units together. See, *e.g.*, Kolb, Finn and Sharpless *Angewandte Chemie International Edition* (2001) 40: 2004–2021; Evans, *Australian Journal of Chemistry* (2007) 60: 384–395). Exemplary coupling reactions (some of which may be classified as "Click chemistry") include, but are not limited to, formation of esters, thioesters, amides (*e.g.,* such as peptide coupling) from activated acids or acyl halides; nucleophilic displacement reactions (*e.g.,* such as nucleophilic displacement of a halide or ring opening of strained ring systems); azide–alkyne Huisgon cycloaddition; thiol–yne addition; imine formation; and Michael additions (*e.g.,* maleimide addition).

[00393] In general, for the group (**L_{C1}-ii**), A^1 should be complimentary and reactive with the group A^2 in order to form the group (**L^{C1}-iii**). For example, if the group A^2 of A^2–L^{C2}–R^{23} is a nucleophilic group, the group A^1 must be a electrophilic group. Likewise, if the group A^2 of A^2–L^{C2}–R^{23} is an electrophilic group, the group A^1 must be a nucleophilic group. While A^1 and A^2 are defined the same in the present invention, it is thus understood that such groups are paired complements.

[00394] As genererally defined herein, A^1 and A^2 may be selected from the group consisting of a leaving group (LG), –SH, –OH, –NH_2, –NH–NH_2, –N_3, –O–NH_2, –C(=O)R^{X1},



wherein:

R_{X1} is hydrogen, a leaving group, or –OR^{X2}, wherein R^{X2} is hydrogen; optionally substituted alkyl; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; an oxygen protecting group;

Leaving group (LG) is –Br, –I, –Cl, -O(C=O)R^{LG}, or -O$(SO)_2R^{LG}$, wherein R^{LG} is optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl;

W is O, S, or NR^{W1};

Date Reçue/Date Received 2020-06-25

R^{W1} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or a nitrogen protecting group; and

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl, or two R^{W2} groups are joined to form a optionally substituted cyclic moiety.

[00395] In certain embodiments, A^2 is –SH. In certain embodiments, A^1 is –SH.

[00396] In certain embodiments, A^2 is –OH. In certain embodiments, A^1 is –OH.

[00397] In certain embodiments, A^2 is $–NH_2$. In certain embodiments, A^1 is $–NH_2$.

[00398] In certain embodiments, A^2 is $–NH–NH_2$. In certain embodiments, A^1 is $–NH–NH_2$.

[00399] In certain embodiments, A^2 is $–O–NH_2$. In certain embodiments, A^1 is $–O–NH_2$.

[00400] In certain embodiments, A^2 is $–N_3$. In certain embodiments, A^1 is $–N_3$.

[00401] In certain embodiments, A^2 is a leaving group, *e.g.*, –Cl, –Br, or –I. In certain embodiments, A^1 is a leaving group, *e.g.*, –Cl, –Br, or –I.

[00402] In certain embodiments, A^2 is $–C(=O)R^{X1}$, wherein R^{X1} is hydrogen, *i.e.,* to provide A^2 as an aldehyde –CHO. In certain embodiments, A^1 is $–C(=O)R^{X1}$, wherein R^{X1} is hydrogen, *i.e.,* to provide A^1 as an aldehyde –CHO.

[00403] In certain embodiments, A^2 is $–C(=O)R^{X1}$, wherein R^{X1} is a leaving group (LG).

[00404] In certain embodiments, A^1 is $–C(=O)R^{X1}$, wherein R^{X1} is a leaving group (LG).

[00405] In certain embodiments, A^2 is $–C(=O)R^{X1}$, wherein R^{X1} is $–OR^{X2}$, and wherein R^{X2} is hydrogen, *i.e.,* to provide A^2 as a carboxylic acid –C(=O)OH.

[00406] In certain embodiments, A^1 is $–C(=O)R^{X1}$, wherein R^{X1} is $–OR^{X2}$, and wherein R^{X2} is hydrogen, *i.e.,* to provide A^1 as a carboxylic acid –C(=O)OH.

[00407] In certain embodiments, A^2 is $–C(=O)R^{X1}$, wherein R^{X1} is $–OR^{X2}$, and wherein R^{X2} is a non-hydrogen group, *i.e.,* to provide A^2 as an ester $–C(=O)OR^{X2}$.

[00408] In certain embodiments, A^1 is $–C(=O)R^{X1}$, wherein R^{X1} is $–OR^{X2}$, and wherein R^{X2} is non-hydrogen group, *i.e.,* to provide A^1 as an ester $–C(=O)OR^{X2}$.

Date Reçue/Date Received 2020-06-25

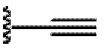
[00409] In certain embodiments, A^2 is an oxiranyl, thiorenyl, or azirdinyl group of formula:

wherein W is O, S, or NR^{W1}. In certain embodiments, W is O. In certain embodiments, W is S. In certain embodiments, W is NR^{W1}.

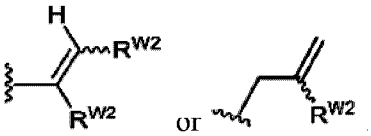
[00410] In certain embodiments, A^1 is an oxiranyl, thiorenyl, or azirdinyl group of formula:

wherein W is O, S, or NR^{W1}. In certain embodiments, W is O. In certain embodiments, W is S. In certain embodiments, W is NR^{W1}.

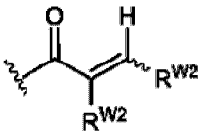
[00411] In certain embodiments, A^1 or A^2 is ethynyl:



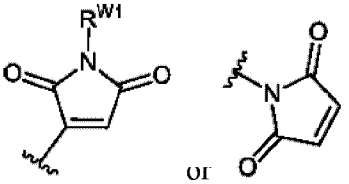
[00412] In certain embodiments, A^1 or A^2 is ethenyl or propenyl:



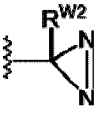
[00413] In certain embodiments, A^1 or A^2 is an α,β - unsaturated carbonyl:



[00414] In certain embodiments, A^1 or A^2 is a maleimide group:



[00415] In certain embodiments, A^1 or A^2 is a group:

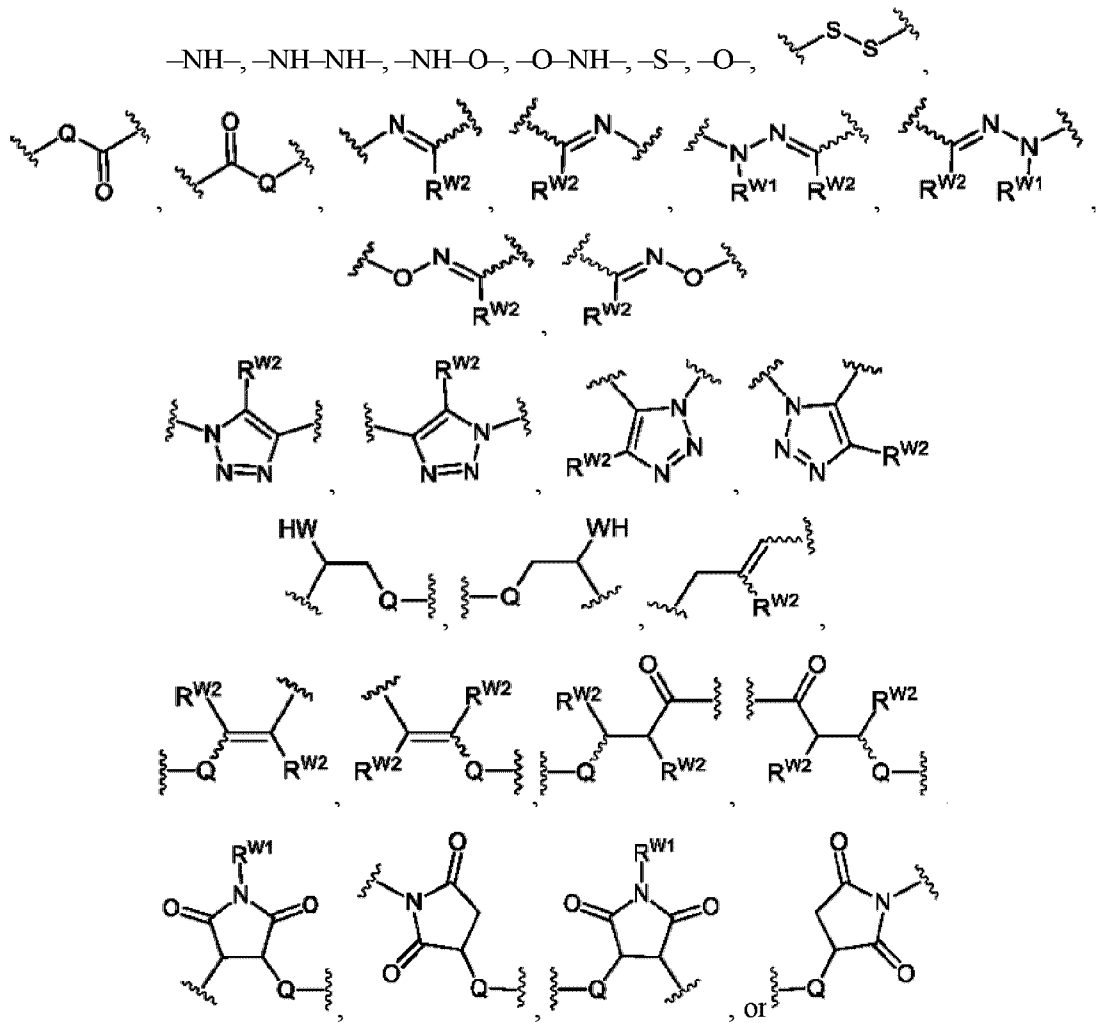


wherein R^{W2} is alkyl, *e.g.*, methyl.

Date Reçue/Date Received 2020-06-25

[00416] In certain embodiments, A^1 or A^2 is a group:

[00417] Furthermore, as generally defined herein, A^1 or A^2 react together to form a group A, wherein A is a group of the formula:



wherein:

Q is –NH–, –NH–NH–, –O–NH–,–NH–O–,–S–, or –O–;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or a nitrogen protecting group; and

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted

Date Reçue/Date Received 2020-06-25

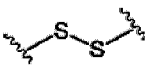
heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl, or two R_{W2} groups are joined to form an optionally substituted cyclic moiety.

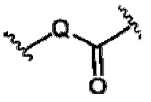
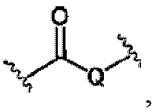
[00418] In certain embodiments, A is –NH–.

[00419] In certain embodiments, A is –NH–NH–.

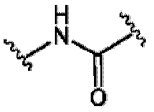
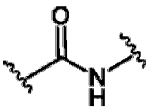
[00420] In certain embodiments, A is –S–.

[00421] In certain embodiments, A is –O–.

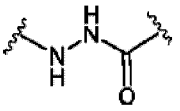
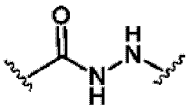
[00422] In certain embodiments, A is a disulfide group  .

[00423] In certain embodiments, A is  or  , wherein Q is –NH–, –NH–NH–, –O–NH–,–NH–O–,–S–, –O–.

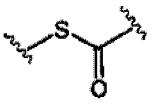
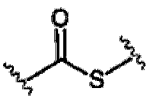
[00424] For example, in certain embodiments, wherein Q is –NH–, A is an amide group of the formula:

 or  .

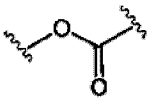
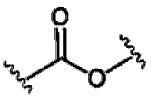
[00425] In certain embodiments, wherein Q is –NH–NH–, A is an amide hydrazide group of the formula:

 or  .

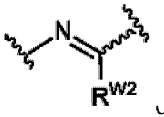
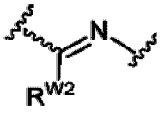
[00426] In certain embodiments, wherein Q is –S–, A is an thioester group of the formula:

 or  .

[00427] In certain embodiments, wherein Q is –O–, A is an ester group of the formula:

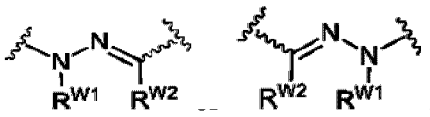
 or  .

[00428] In certain embodiments, A is:

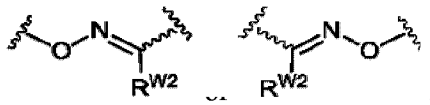
 or  . In certain embodiments, R^{W2} is alkyl, *e.g.,* methyl.

[00429] In certain embodiments, A is:

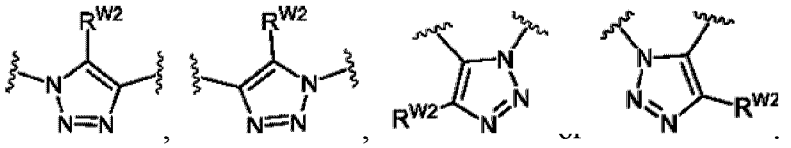
Date Reçue/Date Received 2020-06-25

 . In certain embodiments, R^{W2} is alkyl, *e.g.,* methyl. In certain embodiments, R^{W1} is hydrogen.

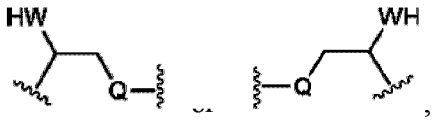
[00430] In certain embodiments, A is:

 . In certain embodiments, R^{W2} is alkyl, *e.g.,* methyl.

[00431] In certain embodiments, A is:

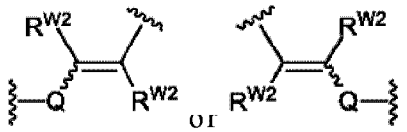


[00432] In certain embodiments, A is:



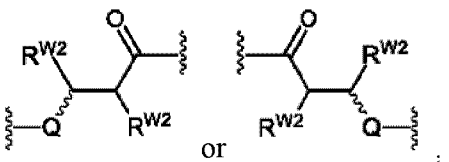
wherein W is O, S, or NR_{W1}, R^{W1} is hydrogen, optionally substituted alkyl, or an amino protecting group; and Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–. In certain embodiments, W is O. In certain embodiments, W is S. In certain embodiments, W is NR^{W1}. In certain embodiments, Q is –NH–. In certain embodiments, Q is –NH–NH–. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–.

[00433] In certain embodiments, A is:



wherein Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–. In certain embodiments, Q is –NH–. In certain embodiments, Q is –NH–NH–. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–.

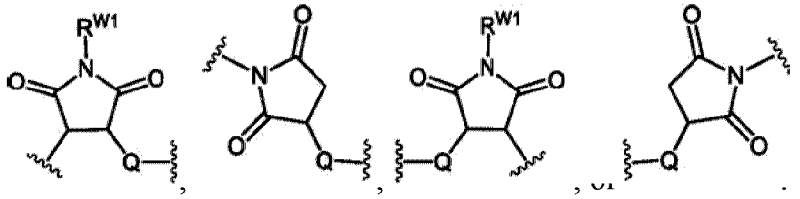
[00434] In certain embodiments, A is:



Date Reçue/Date Received 2020-06-25

wherein Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–. In certain embodiments, Q is –NH–. In certain embodiments, Q is –NH–NH–. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–.

[00435] In certain embodiments, A is:



wherein Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–. In certain embodiments, Q is –NH–. In certain embodiments, Q is –NH–NH–. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–.

[00436] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is –C(=O)R^{X1}, wherein R^{X1} is a leaving group (LG) or –OR^{X2}, and the other of A^1 and A^2 is –SH, –OH, –NH_2, or –NH–NH_2 to provide a moiety A, wherein A is an amide, thioester, or ester group. See, for example, Scheme A2 and Table A1.

Scheme A2. Preparation via amide, thioester, and ester formation

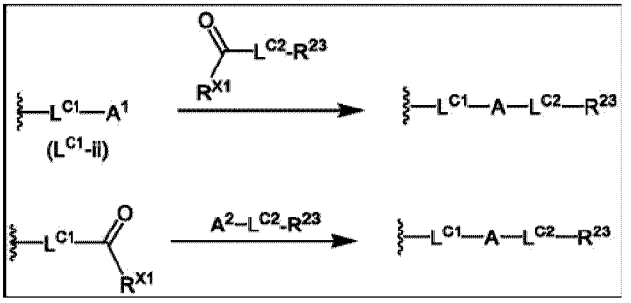


Table A1.			
RX1	A1	A2	**A** –C(=O)O–, –OC(=O)–
LG or –OR^{X2}	–SH	—	–C(=O)S–
	—	–SH	–SC(=O)–
	–OH	—	–C(=O)O–
	—	–OH	–OC(=O)–
	–NH_2	—	–C(=O)NH–
		–NH_2	–NHC(=O)–
	–NH–NH_2	—	–C(=O)NHNH–
	—	–NH–NH_2	–NHNHC(=O)–

Date Reçue/Date Received 2020-06-25

[00437] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is a leaving group (LG), and the other of A^1 and A^2 is –SH, –OH, –NH_2, or –NH–NH_2 to provide a group of formula (**L^{C1}-iii**) wherein A is, respectively, –S–, –O–, –NH–, or –NH–NH–. See, for example, Scheme A3 and Table A2.

Scheme A3. Nucleophilic displacement of a halide or other leaving group

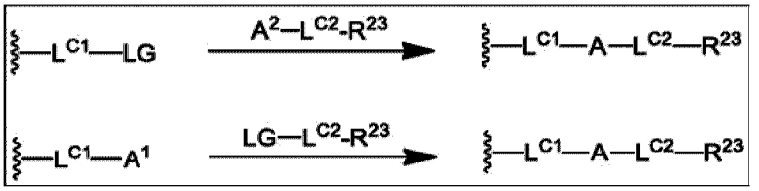


Table A2		
A1	A2	A
LG	–SH	–S–
	–OH	–O–
	–NH_2	–NH–
	–NH–NH_2	–NH–NH–
	–O–NH_2	–O–NH–
–SH	LG	–S–
–OH		–O–
–NH_2		–NH–
–NH–NH_2		–NH–NH–
–O–NH_2		–NH–O–

[00438] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is 

, and the other of A^1 and A^2 is –SH, –OH, –NH_2, or –NH–NH_2 to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A4 and Table A3.

Scheme A4. Nucleophilic addition to strained ring systems

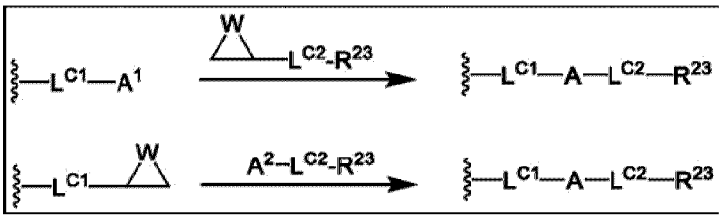
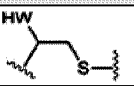


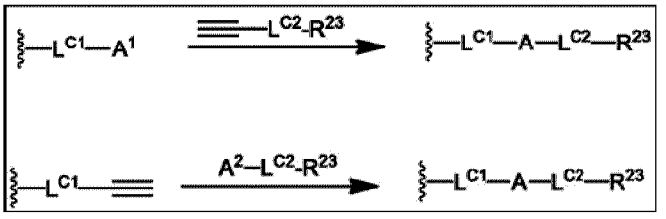
Table A3.			
W	A2	A1	A
O, S, NR^{W1}	–SH	—	

Date Reçue/Date Received 2020-06-25

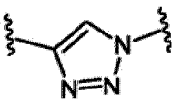
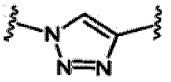
Table A3.			
W	**A2**	**A1**	**A**
	–OH	—	
	–NH_2	—	
	–NH–NH_2	—	
	–O–NH_2	—	
O, S, NR^{W1}	—	–SH	
	—	–OH	
	—	–NH_2	
	—	–NH–NH_2	
	—	–O–NH_2	

[00439] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is , and the other of A^1 and A^2 is –N_3 to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A5 and Table A4.

Scheme A5. Azide–alkyne Huisgen cycloaddition



Date Reçue/Date Received 2020-06-25

Table A4.			
A1	A2	A	
		1,4–adduct	*1,5–adduct*
—	–N_3		
–N_3	—		

[00440] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is , and the other of A^1 and A^2 is –SH to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A6 and Table A5.

Scheme A6. Thiol–yne addition

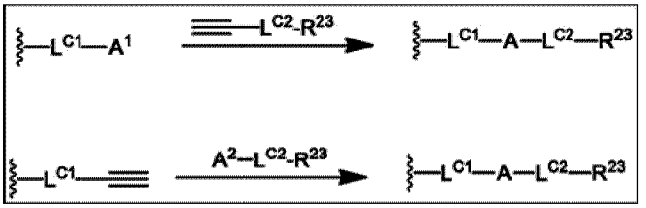
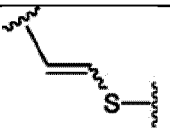
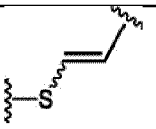


Table A5.		
A1	A2	A
—	–SH	
–SH	—	

[00441] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is an aldehyde –CHO or ketone, and the other of A^1 and A^2 is –NH_2, –NH–NH_2, or –O–NH_2 to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A7 and Table A6.

Date Reçue/Date Received 2020-06-25

Scheme A7. Imine formation

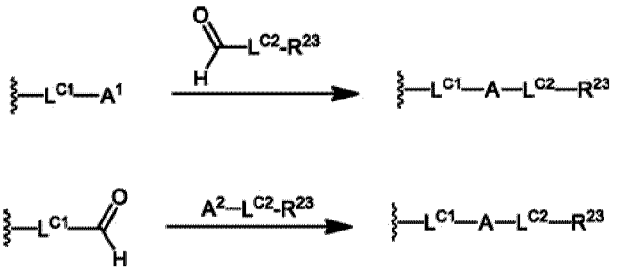
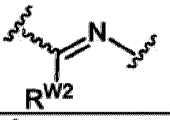
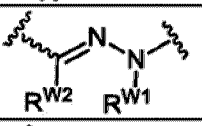
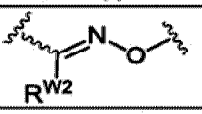
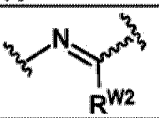
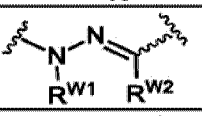
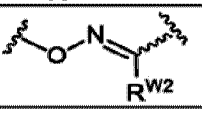
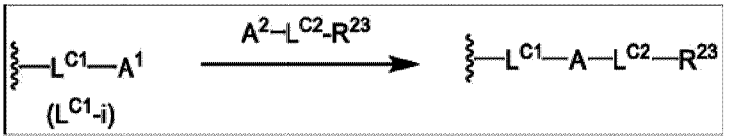


Table A6.

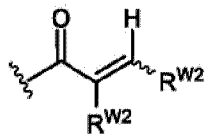
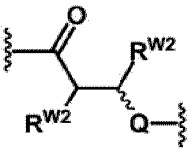
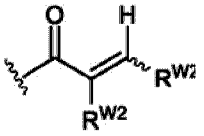
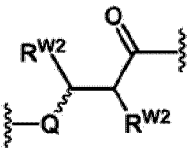
A 1	A 2	A
––	–NH2	
––	–NH–NH2	
––	–O–NH2	
–NH2	––	
–NH–NH2	––	
–O–NH2	––	

[00442] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is an □,□-□-unsaturated carbonyl, and the other of A^1 and A^2 is –OH, –SH, –NH2, –NHNH2, or –O–NH2 to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A8 and Table A7.

Scheme A8. Michael addition



Date Reçue/Date Received 2020-06-25

Table A7.		
A1	A2	A
	–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2	
–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2		

[00443] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is a maleimide group, and the other of A^1 and A^2 is –OH, –SH, –NH_2, –$NHNH_2$, or –O–NH_2 to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A9 and Table A8.

Scheme A9. Maleimide addition

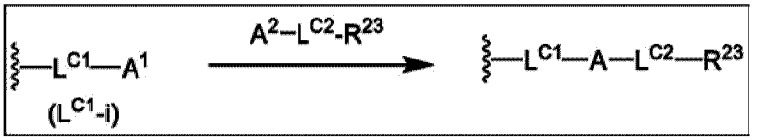
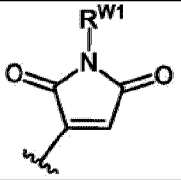
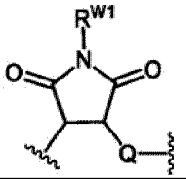
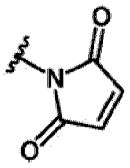
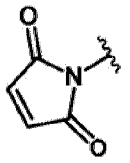
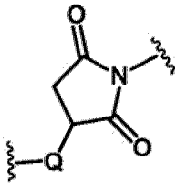
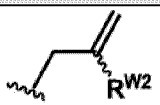


Table A8.		
A1	A2	A
	–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2	
	–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2	
–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2		

Date Reçue/Date Received 2020-06-25

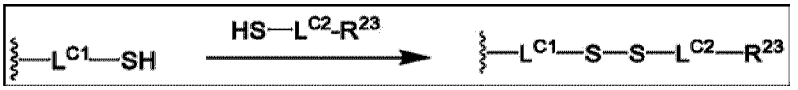
Table A8.		
A1	A2	A
–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2		

[00444] In certain embodiments, the method comprises coupling (*e.g.*, palladium catalyzed coupling) of a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is an propenyl group, and one of A^1 and A^2 is a leaving group, to provide a group of formula (**L^{C1}-iii**) upon treatment with a palladium catalyst. See, for example, Table A9.

Table A9.		
A1	A2	A
	LG	
LG		

[00445] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is –SH to provide, upon treatment with an oxidant, a group of formula (**L^{C1}-iii**), wherein A is a disulfide bond. See, for example, Scheme A8.

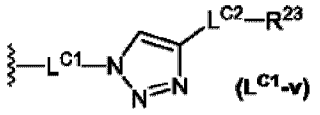
Scheme A8. Disulfide formation



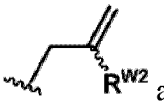
[00446] In certain preferred embodiments, A^1 is –N_3 and A^2 is , such that the compound of formula A^2–L^{C2}–R^{23} is of the formula:

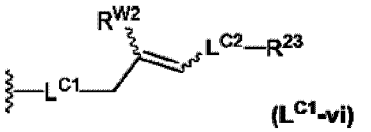
Date Reçue/Date Received 2020-06-25

and A^1 and A^2–L^{C2}–R^{23} react together to provide a group of formula:



(L^{C1}-v)

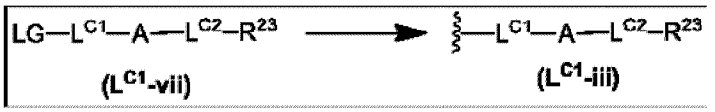
[00447] In certain preferred embodiments, A^1 is  and A^2 is a leaving group, and A^1 and A^2–L^{C2}–R^{23} react together (*e.g.,* via palladium catalysis) to provide a group of formula:



(L^{C1}-vi)

[00448] Furthermore, as described herein, there are many ways of adding a group of formula (**L^{C1}-iii**) which do not involve reaction of A^1 and A^2 to form A. For example, a group of formula (**L^{C1}-iii**) may be installed by reaction of the group -OR^{12}, -$NR^{13}R^{14}$, and/or - OR^3, wherein R^{12}, R^{14}, and/or R^3 are hydrogen, with a compound of formula (**L^{C1}-vii**), *e.g.,* by nucleophilic displacement, to provide a group wherein R^{12}, R^{14}, and/or R^3 is of formula (**L^{C1}-iii**). See, *e.g.*, Scheme A9.

Scheme A9.

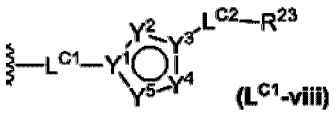


(L^{C1}-vii) (L^{C1}-iii)

[00449] Thus, in certain embodiments, A may be any group as defined above, and further may be any cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl.

[00450] In certain embodiments, A is an optionally substituted heteroaryl, *e.g.,* a 5- to 6- membered optionally substituted heteroaryl.

[00451] In certain embodiments, wherein A is a 5-membered optionally substituted heteroaryl, the group of formula (**L^{C1}-iii**) is of the formula (**L^{C1}-v**):

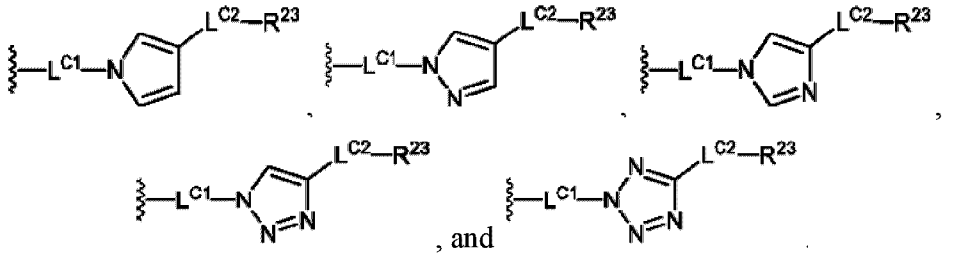


(L^{C1}-viii)

wherein each instance of Y^1, Y^2, Y^3, Y^4, and Y^5 is independently CR^Y, O, S, N, or NR^Y, wherein R^Y is hydrogen or optionally substituted alkyl.

Date Reçue/Date Received 2020-06-25

[00452] In certain embodiments wherein A is a 5-membered heteroaryl, the group of formula (**L^{C1}-iii**) is selected from:



, and .

L_{C1}, L^{C2} and Group R_{23}

[00453] As generally defined above, each instance of L^{C1} and L^{C2} is independently a bond, or a linking group selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, and combinations thereof.

[00454] In certain embodiments, L^{C1} is a bond. It is generally understood that if L^{C1} is a bond, then the group -LG, $-A^1$, or $-A-L^{C2}-R^{23}$, as described herein, is directly attached to the parent moiety, *e.g.,* the macrolide or intermediate compounds. Furthermore, in certain embodiments, L^{C2} is a bond. It is generally understood that if L^{C2} is a bond, then the group R_{23} is directly attached to A, as described herein.

[00455] Alternatively, in certain embodiments, L^{C1} is a linking group. In certain embodiments, L^{C2} is a linking group.

[00456] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of optionally substituted alkylene, *e.g.,* substituted or unsubstituted C_{1-6}alkylene, substituted or unsubstituted C_{2-6}alkylene, substituted or unsubstituted C_{3-6}alkylene, substituted or unsubstituted C_{4-6}alkylene, substituted or unsubstituted C_{5-6}alkylene, substituted or unsubstituted C_{2-5}alkylene, substituted or unsubstituted C_{2-4}alkylene, substituted or unsubstituted C_{2-3}alkylene, substituted or unsubstituted C_1alkylene, substituted or unsubstituted C_2alkylene, substituted or unsubstituted C_3alkylene, substituted or unsubstituted C_4alkylene, substituted or unsubstituted C_5alkylene, or substituted or unsubstituted C_6alkylene. In certain embodiments, L_{C1} and L^{C2} are each optionally and independently an alkylene linking group of the formula $-(CH_2)_n-$, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

Date Reçue/Date Received 2020-06-25

[00457] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted alkenylene, *e.g.,* substituted or unsubstituted C_{2-6}alkenylene, substituted or unsubstituted C_{3-6}alkenylene, substituted or unsubstituted C_{4-6}alkenylene, substituted or unsubstituted C_{5-6}alkenylene, substituted or unsubstituted C_{2-5}alkenylene, substituted or unsubstituted C_{2-4}alkenylene, substituted or unsubstituted C_{2-3}alkenylene, substituted or unsubstituted C_2alkenylene, substituted or unsubstituted C_3alkenylene, substituted or unsubstituted C_4alkenylene, substituted or unsubstituted C_5alkenylene, or substituted or unsubstituted C_6alkenylene.

[00458] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted alkynylene, *e.g.,* substituted or unsubstituted C_{2-6}alkynylene, substituted or unsubstituted C_{3-6}alkynylene, substituted or unsubstituted C_{4-6}alkynylene, substituted or unsubstituted C_{5-6}alkynylene, substituted or unsubstituted C_{2-5}alkynylene, substituted or unsubstituted C_{2-4}alkynylene, substituted or unsubstituted C_{2-3}alkynylene, substituted or unsubstituted C_2alkynylene, substituted or unsubstituted C_3alkynylene, substituted or unsubstituted C_4alkynylene, substituted or unsubstituted C_5alkynylene, or substituted or unsubstituted C_6alkynylene.

[00459] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted heteroalkylene, *e.g.,* substituted or unsubstituted heteroC_{1-6}alkylene, substituted or unsubstituted heteroC_{2-6}alkylene, substituted or unsubstituted heteroC_{3-6}alkylene, substituted or unsubstituted heteroC_{4-6}alkylene, substituted or unsubstituted heteroC_{5-6}alkylene, substituted or unsubstituted heteroC_{2-5}alkylene, substituted or unsubstituted heteroC_{2-4}alkylene, substituted or unsubstituted heteroC_{2-3}alkylene, substituted or unsubstituted heteroC_1alkylene, substituted or unsubstituted heteroC_2alkylene, substituted or unsubstituted heteroC_3alkylene, substituted or unsubstituted heteroC_4alkylene, substituted or unsubstituted heteroC_5alkylene, or substituted or unsubstituted heteroC_6alkylene.

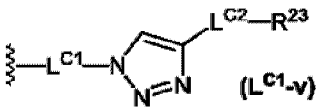
[00460] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted heteroalkenylene, *e.g.,* substituted or unsubstituted heteroC_{2-6}alkenylene, substituted or unsubstituted heteroC_{3-6}alkenylene, substituted or unsubstituted heteroC_{4-6}alkenylene, substituted or unsubstituted heteroC_{5-6}alkenylene, substituted or unsubstituted heteroC_{2-5}alkenylene, substituted or unsubstituted heteroC_{2-4}alkenylene, substituted or unsubstituted heteroC_{2-3}alkenylene, substituted or unsubstituted heteroC_2alkenylene, substituted or unsubstituted heteroC_3alkenylene, substituted or unsubstituted heteroC_4alkenylene,

Date Reçue/Date Received 2020-06-25

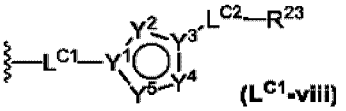
substituted or unsubstituted heteroC5alkenylene, or substituted or unsubstituted heteroC6alkenylene.

[00461] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted heteroalkynylene, *e.g.,* substituted or unsubstituted heteroC2–6alkynylene, substituted or unsubstituted heteroC3–6alkynylene, substituted or unsubstituted heteroC4–6alkynylene, substituted or unsubstituted heteroC5–6alkynylene, substituted or unsubstituted heteroC2–5alkynylene, substituted or unsubstituted heteroC2–4alkynylene, substituted or unsubstituted heteroC2–3alkynylene, substituted or unsubstituted heteroC2alkynylene, substituted or unsubstituted heteroC3alkynylene, substituted or unsubstituted heteroC4alkynylene, substituted or unsubstituted heteroC5alkynylene, or substituted or unsubstituted heteroC6alkynylene.

[00462] In certain embodiments, L^{C1} is an optionally substituted alkylene, and L^{C2} is a bond, *e.g.,* L^{C1} is an optionally substituted alkylene of the formula $-(CH_2)_n-$, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and L^{C2} is a bond in groups of formula (**L^{C1}-v**) or (**L^{C1}-viii**) as described herein.

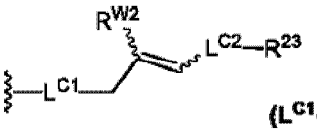


(**L^{C1}-v**)



(**L^{C1}-viii**)

[00463] In other embodiments, both of L^{C1} and L^{C2} are bonds, *e.g.,* both of L^{C1} and L^{C2} are bonds in the group of formula (**L^{C1}-vi**) as described herein.



(**L^{C1}-vi**)

[00464] Furthermore, it is also generally understood that R^{23} may be an acyclic moiety or a cyclic moiety selected from the group consisting of optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; and optionally substituted heteroaryl.

[00465] For example, in certain embodiments, R^{23} is an acyclic moiety selected from the group consisting of optionally substituted alkyl; optionally substituted alkenyl; and optionally substituted alkynyl.

[0001] In certain embodiments, R^{23} is optionally substituted alkyl, *e.g.*, optionally substituted C1–6alkyl, substituted or unsubstituted C1–2alkyl, optionally substituted C2–

Date Reçue/Date Received 2020-06-25

$_{3}$alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. Exemplary R^{23} C_{1-6} alkyl groups include, but are not limited to, optionally substituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6).

[00466] In certain embodiments, R^{23} is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl.

[00467] In certain embodiments, R^{23} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00468] In certain embodiments, R^{23} is a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; and optionally substituted heteroaryl.

[00469] In certain embodiments, R^{23} is optionally substituted carbocyclyl, *e.g.*, optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

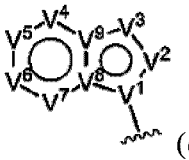
[00470] In certain embodiments, R^{23} is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

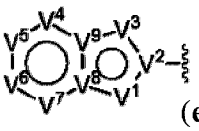
[00471] In certain embodiments, R^{23} is optionally substituted aryl, *e.g.*, optionally substituted monocyclic aryl, optionally substituted 5,6-fused bicyclic aryl, or optionally substituted 6,6-fused aryl. In certain embodiments, R^{23} is optionally substituted phenyl. In certain embodiments, R^{23} is optionally substituted napthyl.

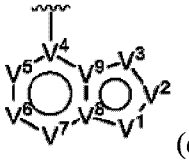
[00472] In certain embodiments, R^{23} is optionally substituted heteroaryl, *e.g.*, optionally substituted monocyclic heteoaryl or optionally substituted bicyclic heteroaryl, *e.g.,* optionally substituted 5–6 membered heteroaryl, optionally substituted 5,6 fused-bicyclic heteroaryl, or optionally substituted 6,6 fused-bicyclic heteroaryl.

[00473] Specific aryl and heteroaryl R^{23} groups are further contemplated herein. For example, in certain embodiments, R^{23} is an aryl or heteroaryl ring system of formula:

Date Reçue/Date Received 2020-06-25


(e-1)


(e-2)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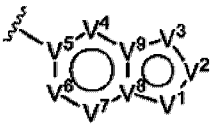
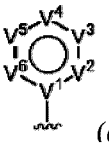

(e-4)


(e-5),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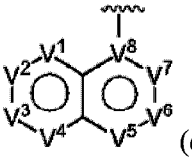
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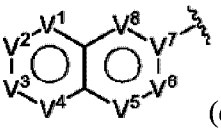
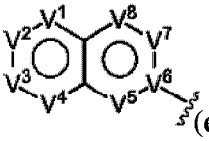

(e-8), or


(e-9),

wherein:

each instance of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 may independently be O, S, N, NR^{23N}, C, or CR^{23C}, as valency permits;

R^{23N} is independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or a nitrogen protecting group; and

R^{23C} is hydrogen, halogen, –CN, $–NO_2$, $–N_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, or carbonyl.

[00474] In certain embodiments, V^1 is O, S, N or NR^{23N}. In certain embodiments, V^1 is N or NR^{23N}. In certain embodiments, V^1 is O. In certain embodiments, V^1 is S.

[00475] In certain embodiments, V^2 is O, S, N or NR^{23N}. In certain embodiments, V^2 is N or NR^{23N}. In certain embodiments, V^2 is O. In certain embodiments, V^2 is S.

[00476] In certain embodiments, V^3 is O, S, N or NR^{23N}. In certain embodiments, V^3 is N or NR^{23N}. In certain embodiments, V^3 is O. In certain embodiments, V^3 is S.

Date Reçue/Date Received 2020-06-25

[00477] In certain embodiments, V^4 is O, S, N or NR^{23N}. In certain embodiments, V^4 is N or NR^{23N}. In certain embodiments, V^4 is O. In certain embodiments, V^4 is S.

[00478] In certain embodiments, V^5 is O, S, N or NR^{23N}. In certain embodiments, V^5 is N or NR^{23N}. In certain embodiments, V^5 is O. In certain embodiments, V^5 is S.

[00479] In certain embodiments, V^6 is O, S, N or NR^{23N}. In certain embodiments, V^6 is N or NR^{23N}. In certain embodiments, V^6 is O. In certain embodiments, V^6 is S.

[00480] In certain embodiments, V^7 is O, S, N or NR^{23N}. In certain embodiments, V^7 is N or NR^{23N}. In certain embodiments, V^7 is O. In certain embodiments, V^7 is S.

[00481] In certain embodiments, V^8 is O, S, N or NR^{23N}. In certain embodiments, V^8 is N or NR^{23N}. In certain embodiments, V^8 is O. In certain embodiments, V^8 is S.

[00482] In certain embodiments, V^9 is O, S, N or NR^{23N}. In certain embodiments, V^9 is N or NR^{23N}. In certain embodiments, V^9 is O. In certain embodiments, V^9 is S.

[00483] In certain embodiments, only one of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 is selected from the group consisting of N and NR^{23N}. In certain embodiments, only one of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 is O. In certain embodiments, only one of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 is S. In any of the above instances, in certain embodiments, the rest of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are independently C or CR^{23C} as valency permits.

[00484] In certain embodiments, only two of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently selected from the group consisting of N and NR^{23N}. In certain embodiments, only two of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently selected from the group consisting of O, N and NR^{23N}. In certain embodiments, only two of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently selected from the group consisting of S, N and NR^{23N}. In any of the above instances, in certain embodiments, the rest of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are independently C or CR^{23C} as valency permits.

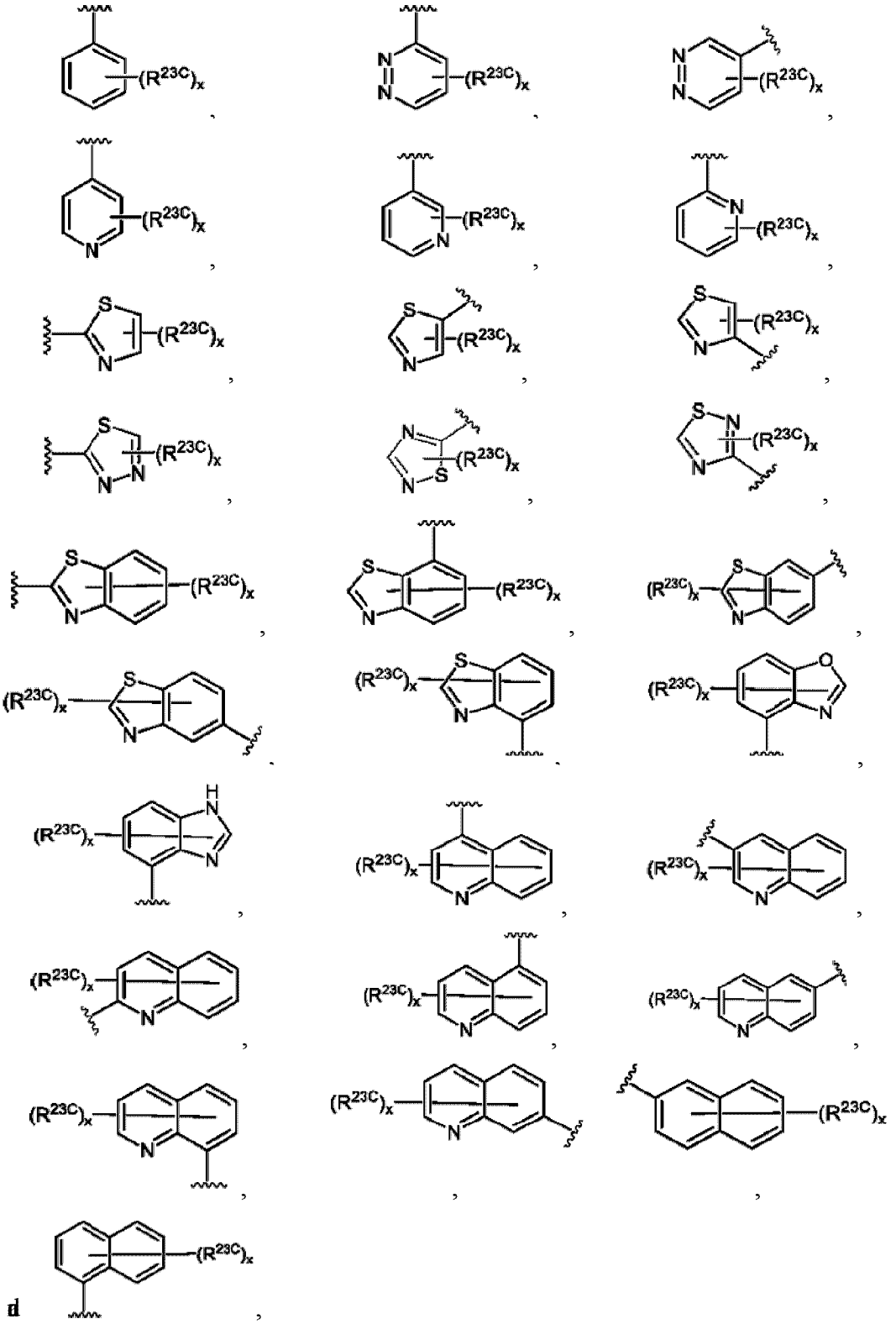
[00485] In certain embodiments, all V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are independently C or CR^{23C} as valency permits.

[00486] In certain embodiments, R^{23C} is hydrogen, halogen, –CN, hydroxyl, substituted hydroxyl, amino, or substituted amino.

[00487] In certain embodiments, R^{23N} is independently hydrogen or optionally substituted alkyl (*e.g.*, $-CH_3$).

Date Reçue/Date Received 2020-06-25

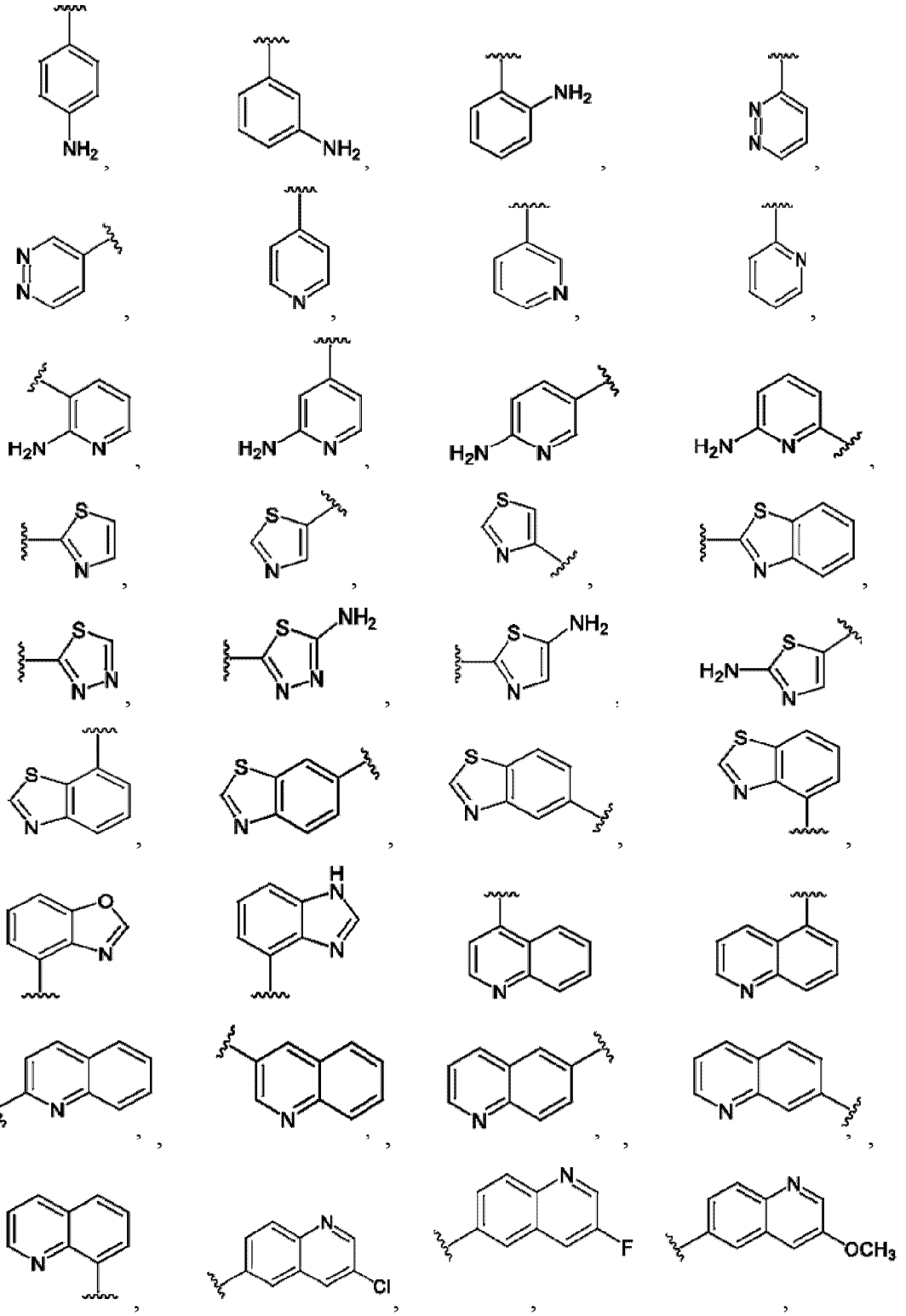
[00488] In certain embodiments, R^{23} is selected from any one of the following aryl or heteroaryl ring systems:



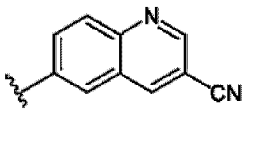
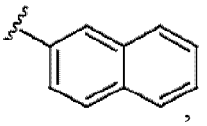
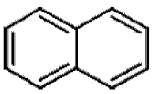
wherein R^{23C} is as defined herein, and x is 0, 1, or 2.

Date Reçue/Date Received 2020-06-25

[00489] In certain embodiments, R^{23} is selected from any one of the following aryl or heteroaryl ring systems:



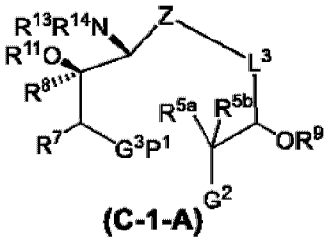
Date Reçue/Date Received 2020-06-25

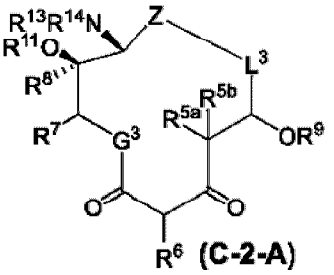
and

Further Embodiments of the Invention

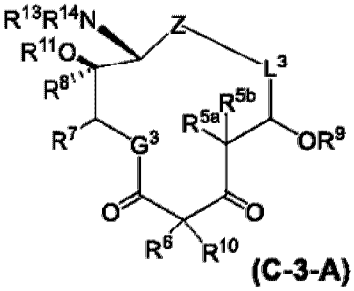
[00490] Various combinations of the above described embodiments are further contemplated herein. For example, in certain embodiments, G^1 is $-NR^{13}NR^{14}$, to provide a compound or macrolide of formula:



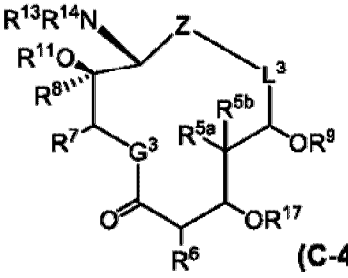
(C-1-A),



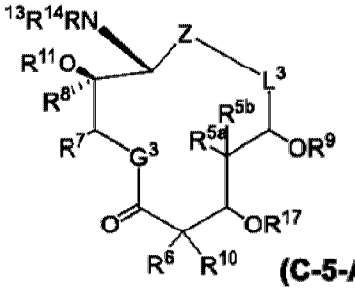
(C-2-A)



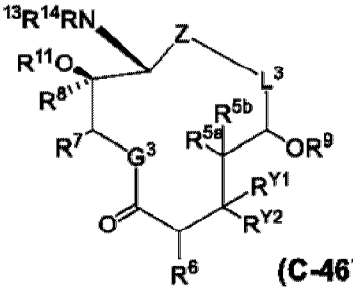
(C-3-A),



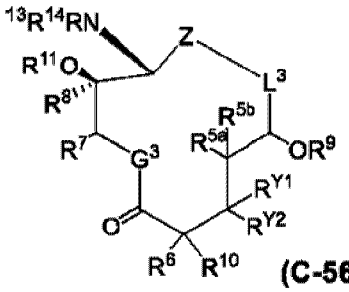
(C-4-A),



(C-5-A),



(C-467-A)

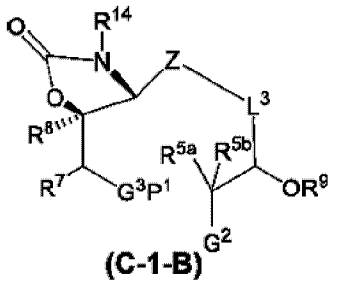


(C-567-A)

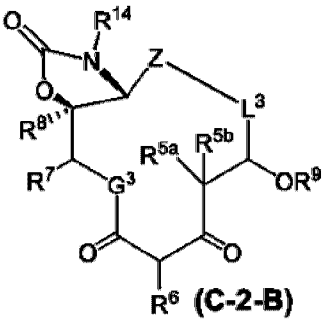
or a salt thereof.

Date Reçue/Date Received 2020-06-25

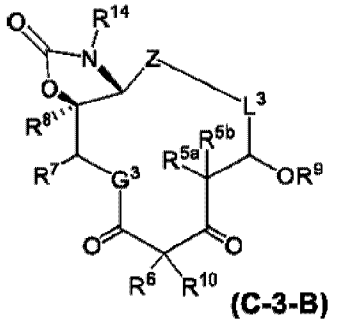
[00491] In certain embodiments, G^1 is $-NR^{13}NR^{14}$, and R^{13} and R^{11} are joined to form a carbamate group to provide a compound or macrolide of formula:



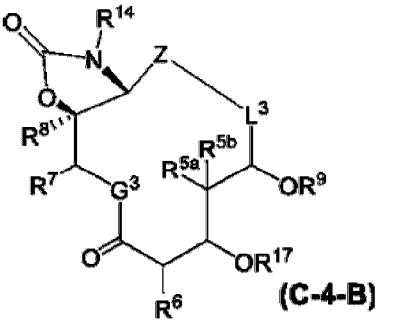
(C-1-B),



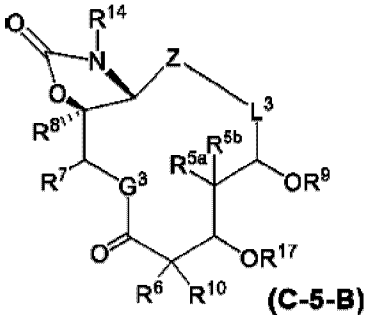
(C-2-B),



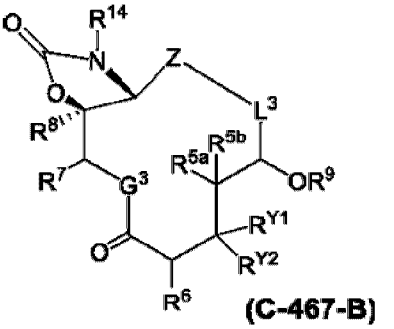
(C-3-B),



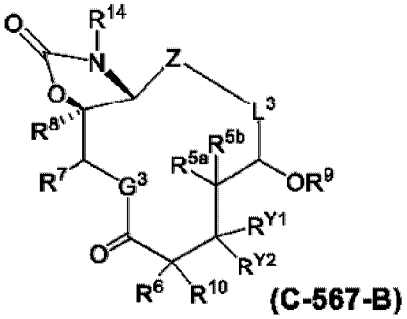
(C-4-B),



(C-5-B),



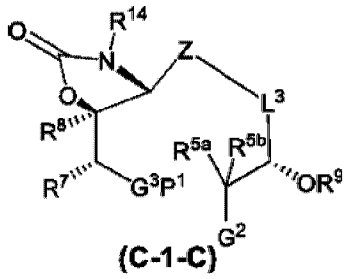
(C-467-B),



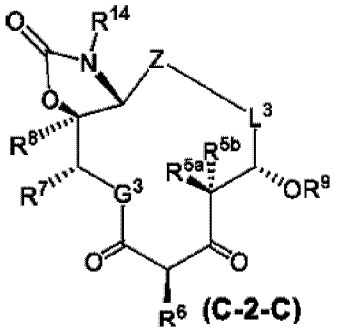
(C-567-B) or a salt thereof.

Date Reçue/Date Received 2020-06-25

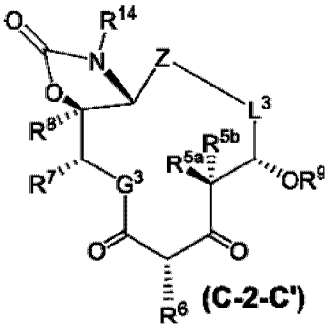
[00492] In certain embodiments, G^1 is $-NR^{13}NR^{14}$, and R^{13} and R^{11} are joined to form a carbamate group to provide a compound or macrolide having the following stereochemistry:



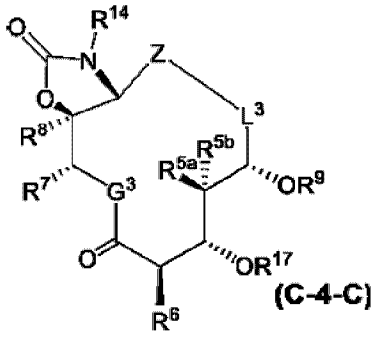
(C-1-C),



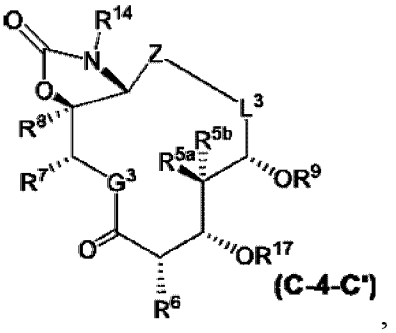
(C-2-C),



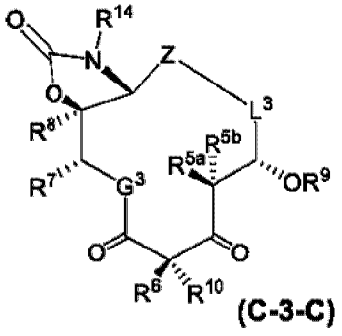
(C-2-C'),



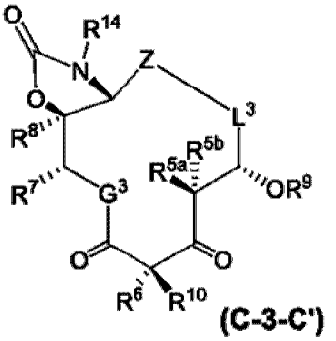
(C-4-C),



(C-4-C'),

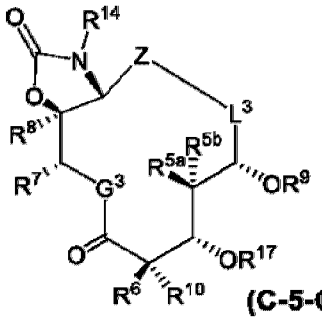
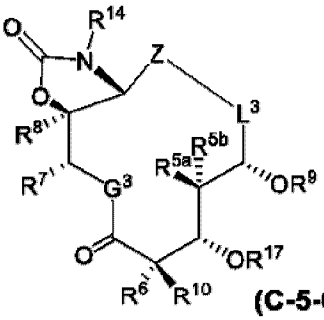
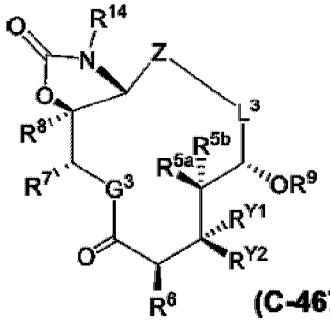
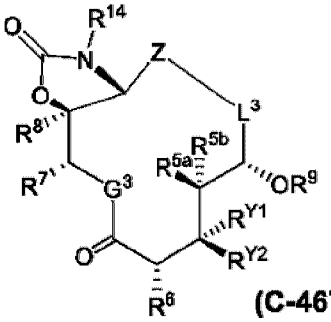
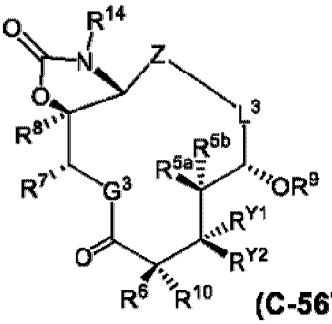
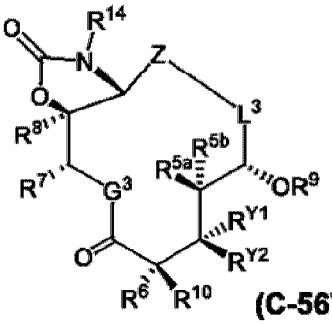


(C-3-C),



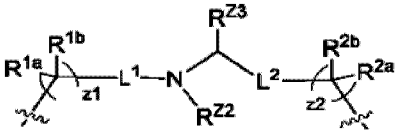
(C-3-C')

Date Reçue/Date Received 2020-06-25

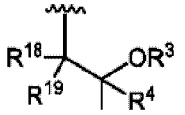
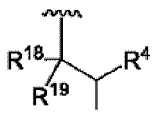

(C-5-C),

(C-5-C'),
or

(C-467-C)

(C-467-C')
salts

(C-567-C)

(C-567-C')
thereof.

[00493] Various embodiments are further contemplated in combination with any formulae depicted herein, *e.g.,* for example, any of the above depicted formulae (**C-1-A**) to (**C-567-C'**).

[00494] For example, in certain embodiments of any of the above formulae, Z is of formula:



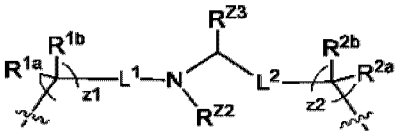
wherein z1 and z2 are 1, L^1 and L^2 are both a bond, R^7 is $–CH_2CH_3$, R^8 is $–CH_3$, G^3 is –O–,

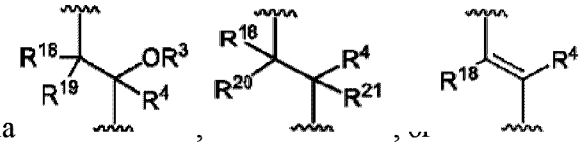



L_3 is a group of formula or , and R^{18} and R^{19} are both hydrogen;

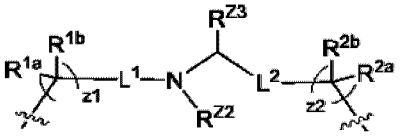
Date Reçue/Date Received 2020-06-25

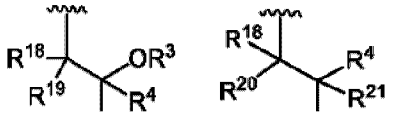
[00495] In certain embodiments of any of the above formulae, Z is of formula:



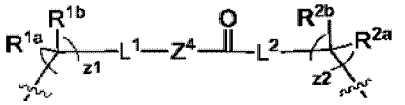
wherein z1 is 1, z2 is 0, L^1 and L^2 are both a bond, R^7 is $-CH_2CH_3$, R^8 is $-CH_3$, G^3 is –O–, L^3 is a group of formula  , and R^{18} is hydrogen.

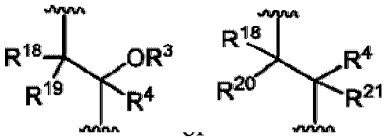
[00496] In certain embodiments of any of the above formulae, Z is of formula:



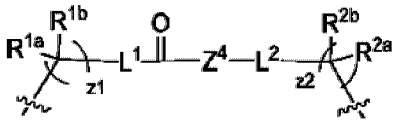
wherein z1 is 1, z2 is 2, L^1 and L^2 are both a bond, R^7 is $-CH_2CH_3$, R^8 is $-CH_3$, G^3 is –O–, L^3 is a group of formula  , and R^{18} and R^{19} are both hydrogen.

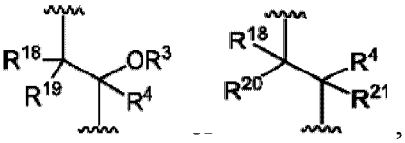
[00497] In certain embodiments of any of the above formulae, Z is of formula:



wherein z1 and z2 are 1, L^1 and L^2 are both a bond, Z^4 is –O– or –NH–, R^7 is $-CH_2CH_3$, R^8 is $-CH_3$, G^3 is –O–, L^3 is a group of formula  , and R^{18} is hydrogen.

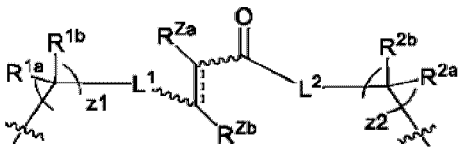
[00498] In certain embodiments of any of the above formulae, Z is of formula:



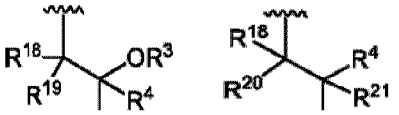
wherein z1 is 0, z2 is 1, L^1 is a bond, L^2 is $-CH_2-$, Z^4 is –O– or –NH–, R^7 is $-CH_2CH_3$, R^8 is $-CH_3$, G^3 is –O–, L^3 is a group of formula  , and R^{18} is hydrogen.

Date Reçue/Date Received 2020-06-25

[00499] In certain embodiments of any of the above formulae, Z is of formula:

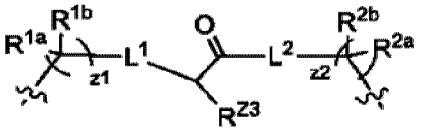


wherein z1 and z2 are 1, L^1 and L^2 are both a bond, R^7 is $-CH_2CH_3$, R^8 is $-CH_3$, G^3 is –O–,

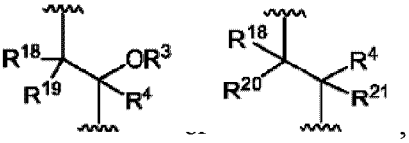


L_3 is a group of formula or , and R^{18} is hydrogen.

[00500] In certain embodiments of any of the above formulae, Z is of formula:



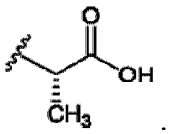
wherein z1 is 0, z2 is 1, L^1 and L^2 are both a bond, R^7 is $-CH_2CH_3$, R^8 is $-CH_3$, G^3 is –O–,



and L^3 is a group of formula , and R^{18} is hydrogen.

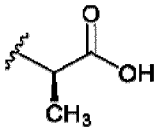
[00501] In certain aspects of the formulae depicted herein, *e.g.,* for example, any of the above depicted formulae (**C-1-A**) to (**C-567-C'**), further specific combinations are contemplated, as provided below.

[00502] For example, in certain embodiments, R^{Z3} is hydrogen. In certain embodiments, R^{Z3} is not hydrogen. In certain embodiments, the carbon to which R^{Z3} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{Z3} is attached is a stereocenter of the (S)-configuration. In certain embodiments, R_{Z3} is optionally substituted C_{1-6}alkyl. In certain embodiments, R^{Z3} is optionally substituted C_{1-2}alkyl. In certain embodiments, R^{Z3} is $-CH_3$. In certain embodiments, R^{Z3} is optionally substituted haloalkyl. In certain embodiments, R^{Z3} is -CF_3. In certain embodiments, R^{Z3} is $-CH_2CH_2OH$. In certain embodiments, R^{Z3} is $-CH_2CH_2N(R^{22})_2$. In certain embodiments, R_{Z3} is $-CH_2CH_2N(R^{22})_2$. In certain embodiments, R^{Z3} is $-CH_2CH_2NHR^{22}$. In certain embodiments, R^{Z3} is $-CH_2CH_2NHR^{22}$; and R^{22} is $-CH_2C(=O)OH$. In certain embodiments,



R_{Z3} is $-CH_2CH_2NHR^{22}$; and R^{22} is . In certain embodiments, R^{Z3} is –

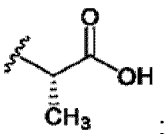
Date Reçue/Date Received 2020-06-25

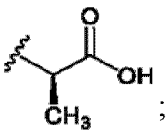
$CH_2CH_2NHR^{22}$; and R^{22} is  . In certain embodiments, R^{Z3} is optionally substituted aralkyl. In certain embodiments, R^{Z3} is optionally substituted benzyl. In certain embodiments, R^{Z3} is unsubstituted benzyl. In certain embodiments, R^{Z3} is substituted benzyl. In certain embodiments, R^{Z3} is monosubstituted benzyl. In certain embodiments, R^{Z3} is benzyl substituted by one instance of halogen. In certain embodiments, R^{Z3} is optionally substituted C_{2-6}alkenyl. In certain embodiments, R^{Z3} is optionally substituted vinyl. In certain embodiments, R^{Z3} is unsubstituted vinyl. In certain embodiments, R^{Z3} is optionally substituted allyl. In certain embodiments, R^{Z3} is unsubstituted allyl. In certain embodiments R^{Z3} is optionally substituted carbocyclyl. In certain embodiments, R^{Z3} is optionally substituted C_{3-6}carbocyclyl. In certain embodiments, R^{Z3} is optionally substituted cyclopropyl. In certain embodiments, R^{Z3} is unsubstituted cyclopropyl.

[00503] In certain embodiments, R^{Z2} is hydrogen. In certain embodiments, R^{Z2} is optionally substituted C_{1-6}alkyl. In certain embodiments, R^{Z2} is optionally substituted C_{1-2}alkyl. In certain embodiments, R^{Z2} is $-CH_3$. In certain embodiments, R^{Z2} is $-C(=O)R^{Z8}$; and R^{Z8} is optionally substituted alkyl. In certain embodiments, R^{Z2} is acetyl. In certain embodiments, R^{Z2} is a nitrogen protecting group.

[00504] In certain embodiments, at least one of R^{1a} and R^{1b} is hydrogen. In certain embodiments, both R^{1a} and R^{1b} are hydrogen. In certain embodiments, neither R^{1a} nor R^{1b} are hydrogen. In certain embodiments, the carbon to which R^{1a} and R^{1b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{1a} and R^{1b} is attached is a stereocenter of the (S)-configuration. In certain embodiments, R^{1a} is optionally substituted C_{1-6}alkyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted C_{1-2}alkyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_3$; and R^{1b} is hydrogen. In certain embodiments, both R^{1a} and R^{1b} are $-CH_3$. In certain embodiments, R^{1a} is optionally substituted haloalkyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CF_3$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2OH$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2N(R^{22})_2$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2N(R_{22})_2$; R^{22} is $-CH_3$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2NHR^{22}$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2NHR_{22}$; R^{22} is $-CH_2C(=O)OH$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is –

Date Reçue/Date Received 2020-06-25

$CH_2CH_2NHR_{22}$; R^{22} is  ; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is –

$CH_2CH_2NHR_{22}$; R^{22} is  ; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted aralkyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted benzyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is unsubstituted benzyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is substituted benzyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is monosubstituted benzyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is benzyl substituted by one instance of halogen; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted C_{2-6}alkenyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted vinyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is unsubstituted vinyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted allyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is unsubstituted allyl; and R^{1b} is hydrogen. In certain embodiments R^{1a} is optionally substituted carbocyclyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted C_{3-6}carbocyclyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted cyclopropyl; and R_{1b} is hydrogen. In certain embodiments, R^{1a} is unsubstituted cyclopropyl; and R^{1b} is hydrogen.

[00505] In certain embodiments, at least one of R^{2a} and R^{2b} is hydrogen. In certain embodiments, both R^{2a} and R^{2b} are hydrogen. In certain embodiments, neither R^{2a} nor R^{2b} are hydrogen. In certain embodiments, R^{2a} is optionally substituted C_{1-6}alkyl; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is optionally substituted C_{1-2}alkyl; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is $–CH_3$; and R^{2b} is hydrogen. In certain embodiments, both R^{2a} and R^{2b} are $–CH_3$. In certain embodiments, R^{2a} is optionally substituted haloalkyl; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is $-CF_3$; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is halogen; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is –F; and R_{2b} is hydrogen. In certain embodiments, R^{2a} is halogen; and R^{2b} is C_{1-6}alkyl. In certain embodiments, R^{2a} is –F; and R^{2b} is C_{1-6}alkyl. In certain embodiments, R^{2a} is halogen; and R_{2b} is $–CH_3$. In certain embodiments, R^{2a} is –F; and R^{2b} is $–CH_3$.

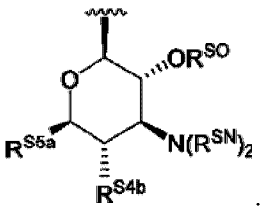
[00506] In certain embodiments, the carbon to which R^4 is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^4 is attached is a

Date Reçue/Date Received 2020-06-25

stereocenter of the (S)-configuration. In certain embodiments, R^3 is hydrogen; and R^4 is not hydrogen. In certain embodiments, neither R^3 nor R^4 are hydrogen. In certain embodiments, R_3 is hydrogen. In certain embodiments, R^3 is optionally substituted C_{1-6}alkyl. In certain embodiments, R^3 is optionally substituted C_{1-2}alkyl. In certain embodiments, R^3 is $-CH_3$. In certain embodiments, R^3 is optionally substituted C_{2-6}alkenyl. In certain embodiments, R^3 is optionally substituted allyl. In certain embodiments, R^3 is unsubstituted allyl. In certain embodiments, R^3 is allyl substituted with one optionally substituted heteroaryl ring. In certain embodiments, R^3 is allyl substituted with one optionally substituted quinoline ring. In certain embodiments, R^3 is hydrogen; and R^4 is $-CH_3$. In certain embodiments, R^3 is optionally substituted C_{1-6}alkyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is optionally substituted C_{1-2}alkyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is $-CH_3$; and R^4 is $-CH_3$. In certain embodiments, R^3 is optionally substituted C_{2-6}alkenyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is optionally substituted allyl; and R^4 is $-CH_3$. In certain embodiments, R_3 is unsubstituted allyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is allyl substituted with one optionally substituted heteroaryl ring; and R^4 is $-CH_3$. In certain embodiments, R^3 is allyl substituted with one optionally substituted quinoline ring; and R^4 is $-CII_3$. In certain embodiments, R^4 is optionally substituted C_{1-6}alkyl. In certain embodiments, R^4 is optionally substituted C_{1-2}alkyl. In certain embodiments, R^4 is $-CH_3$. In certain embodiments, R^4 is optionally substituted C_{2-6}alkenyl. In certain embodiments, R^4 is optionally substituted allyl. In certain embodiments, R^4 is unsubstituted allyl. In certain embodiments, R^4 is allyl substituted with one optionally substituted heteroaryl ring. In certain embodiments, R^4 is allyl substituted with one optionally substituted quinoline ring. In certain embodiments, R^4 is $-CH_2CH_2OH$. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$; and R^{22} is $-CH_3$. In certain embodiments, R^4 is $-CH_2CHO$. In certain embodiments, R^4 is optionally substituted C_{1-6}alkyl; and R^3 is $-CH_3$. In certain embodiments,
R_4 is optionally substituted C_{1-2}alkyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is optionally substituted C_{2-6}alkenyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is optionally substituted allyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is unsubstituted allyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is allyl substituted with one optionally substituted heteroaryl ring; and R^3 is $-CH_3$. In certain embodiments, R^4 is allyl substituted with one optionally substituted quinoline ring; and R^3 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CH_2OH$; and R^3 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$; and R^3 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CH_2N(R_{22})_2$; R^{22} is $-CH_3$; and R^3 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CHO$; and R^3 is $-CH_3$. In certain embodiments, R^4 is optionally

Date Reçue/Date Received 2020-06-25

substituted C_{1-6}alkyl; and R^3 is hydrogen. In certain embodiments, R^4 is optionally substituted C_{1-2}alkyl; and R^3 is hydrogen. In certain embodiments, R^4 is optionally substituted C_{2-6}alkenyl; and R^3 is hydrogen. In certain embodiments, R^4 is optionally substituted allyl; and R^3 is hydrogen. In certain embodiments, R^4 is unsubstituted allyl; and R_3 is hydrogen. In certain embodiments, R^4 is allyl substituted with one optionally substituted heteroaryl ring; and R^3 is hydrogen. In certain embodiments, R^4 is allyl substituted with one optionally substituted quinoline ring; and R^3 is hydrogen. In certain embodiments, R^4 is $-CH_2CH_2OH$; and R^3 is hydrogen. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$; and R^3 is hydrogen. In certain embodiments, R^4 is $-CH_2CH_2N(R_{22})_2$; R^{22} is $-CH_3$; and R^3 is hydrogen. In certain embodiments, R^4 is $-CH_2CHO$; and R^3 is hydrogen. In certain embodiments, R^4 is optionally substituted C_{1-6}alkyl; and R^{21} is hydrogen. In certain embodiments, R^4 is optionally substituted C_{1-2}alkyl; and R^{21} is hydrogen. In certain embodiments, R^4 is optionally substituted C_{2-6}alkenyl; and R^{21} is hydrogen. In certain embodiments, R^4 is optionally substituted allyl; and R^{21} is hydrogen. In certain embodiments, R^4 is unsubstituted allyl; and R^{21} is hydrogen. In certain embodiments, R^4 is allyl substituted with one optionally substituted heteroaryl ring; and R^{21} is hydrogen. In certain embodiments, R^4 is allyl substituted with one optionally substituted quinoline ring; and R^{21} is hydrogen. In certain embodiments, R^4 is $-CH_2CH_2OH$; and R^{21} is hydrogen. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$; and R^{21} is hydrogen. In certain embodiments, R^4 is $-CH_2CH_2N(R_{22})_2$; R^{22} is $-CH_3$; and R^{21} is hydrogen. In certain embodiments, R^4 is $-CH_2CHO$; and R^{21} is hydrogen.

[00507] In certain embodiments, R^9 is hydrogen. In certain embodiments, R^9 is not hydrogen. In certain embodiments, R^9 is an oxygen protecting group. In certain embodiments, R_9 is 

. In certain embodiments, R^{SO} is hydrogen. In certain embodiments, R^{SO} is an oxygen protecting group. In certain embodiments, R^9 is methyl carbonate. In certain embodiments, at least one R^{SN} is hydrogen. In certain embodiments, at least one R^{SN} is $-CH_3$. In certain embodiments, one R^{SN} is $-CH_3$; and the second R^{SN} is hydrogen. In certain embodiments, both R^{SN} groups are $-CH_3$. In certain embodiments, R_{S4b} is hydrogen. In certain embodiments, R^{S4b} is not hydrogen. In certain embodiments, R^{S4b} is $-OR^{SO}$; and R^{SO} is hydrogen. In certain embodiments, R^{S4b} is $-OR^{SO}$; and R^{SO} is an oxygen protecting group. In certain embodiments, R^{S5a} is optionally substituted alkyl. In certain

Date Reçue/Date Received 2020-06-25

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2 __

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

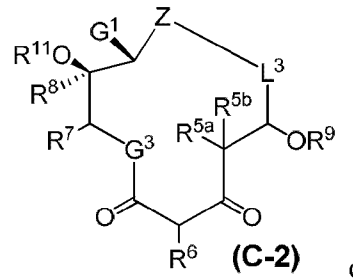
THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

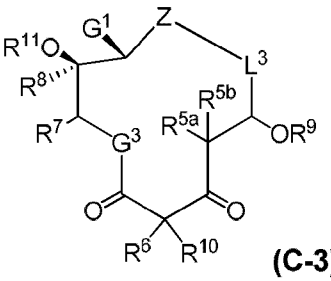
CLAIMS

What is claimed is:

1. A compound of formula:



(C-2) or

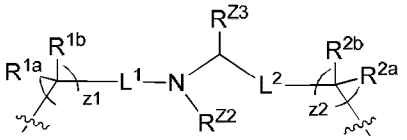


(C-3),

or a salt thereof;

wherein:

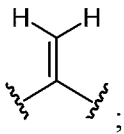
Z is a group of formula:



wherein:

L^1 and L^2 are each independently a bond or $–CH_2–$;

z1 and z2 are each independently 0, 1, or 2;

each instance of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or wherein R^{1a} and R^{1b} or R^{2a} and R^{2b} can be taken together to form 

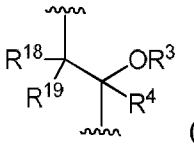
;

R^{Z2} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, or a nitrogen protecting group;

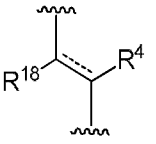
Date Reçue/Date Received 2021-01-08

R^{Z3} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl;

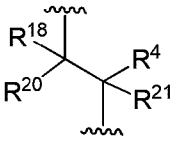
L^3 is a group of formula:



(L^3-i),



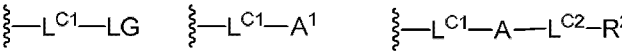
(L^3-ii),



or **(L^3-iii)**;

------ represents a single or double bond;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a group of formula:



(L^{C1}-i) , **(L^{C1}-ii)** , or **(L^{C1}-iii)** ;

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of R^{18} and R^{19} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of R^{20} and R^{21} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, or carbonyl, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or oxiranyl ring;

each instance of R^{5a} and R^{5b} is independently hydrogen, halogen, silyl, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

Date Reçue/Date Received 2021-01-08

R^6 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

R^7 and R^8 are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^9 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $–C(=O)R^{Z8}$, $–C(=O)OR^{Z8}$, $–C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a carbohydrate;

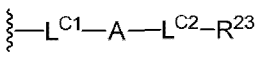
R^{10} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

G^3 is –O–, –S–, or $–N(R^{G1})–$, wherein R^{G1} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

G^1 is $–NR^{13}R^{14}$;

R^{11} and R^{13} are joined as a group of formula –C(=O)- to provide a cyclic carbamate;

R^{14} is hydrogen, or a group of formula:

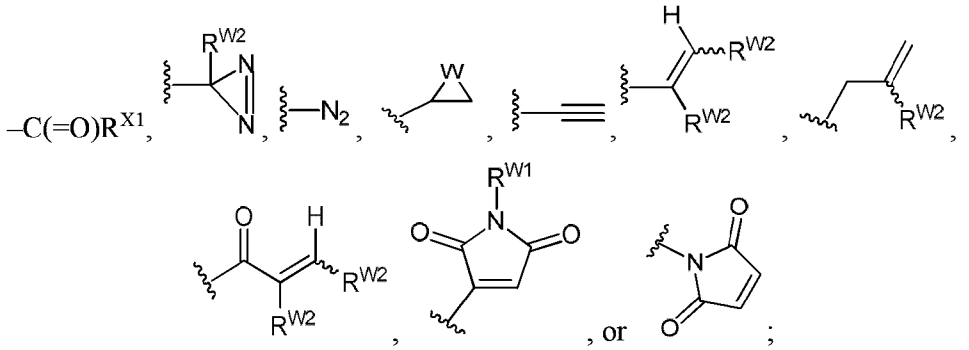


$(L^{C1}\text{-iii})$;

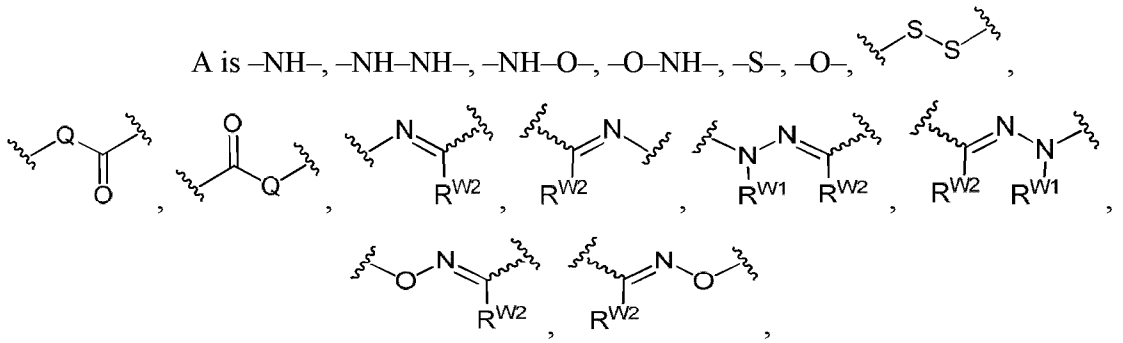
each instance of L^{C1} and L^{C2} is independently a bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or a combination thereof;

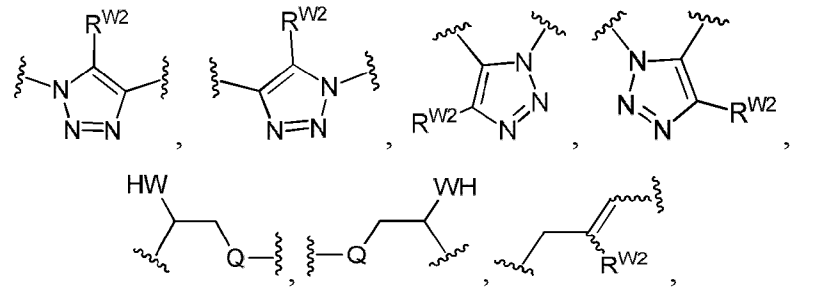
each instance of A^1 is independently a leaving group (LG), –SH, –OH, $–NH_2$, $–NH–NH_2$, $–N_3$, $–O–NH_2$,

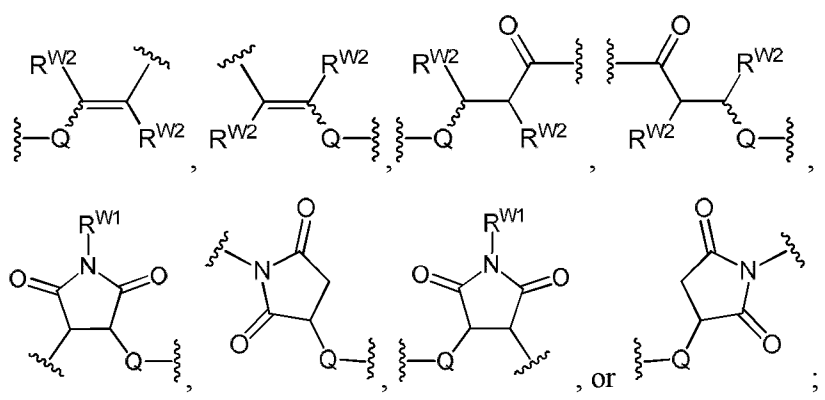
Date Reçue/Date Received 2021-01-08



A is –NH–, –NH–NH–, –NH–O–, –O–NH–, –S–, –O–,







Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; or a nitrogen protecting group;

Date Reçue/Date Received 2021-01-08

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; or optionally substituted heteroaryl, or two R^{W2} groups are joined to form an optionally substituted cyclic moiety;

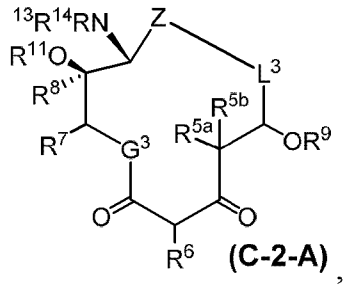
R^{X1} is hydrogen, halogen, or $-OR^{X2}$, wherein R^{X2} is hydrogen; optionally substituted alkyl; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or an oxygen protecting group;

R^{23} is optionally substituted aryl or optionally substituted heteroaryl; and

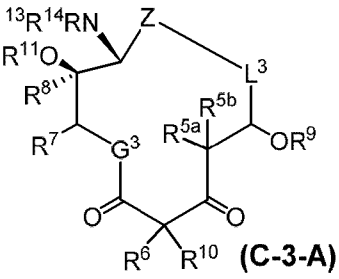
each instance of R^{Z8} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^{Z8} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring;

or A is a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl.

2. The compound of claim 1, wherein the compound is of formula:



(C-2-A), or

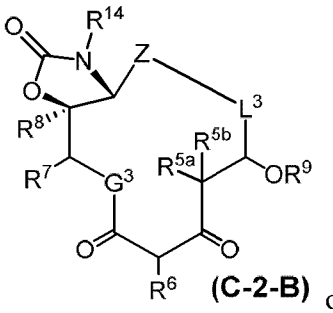


(C-3-A),

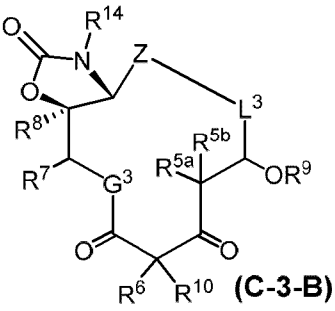
or a salt thereof.

3. The compound of claim 1, wherein the compound is of formula:

Date Reçue/Date Received 2021-01-08



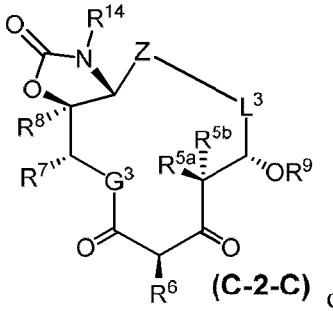
(C-2-B) or



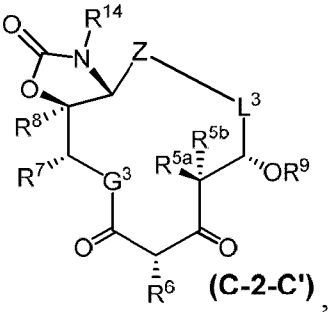
(C-3-B),

or a salt thereof.

4. The compound of claim 1, wherein the compound is of formula:



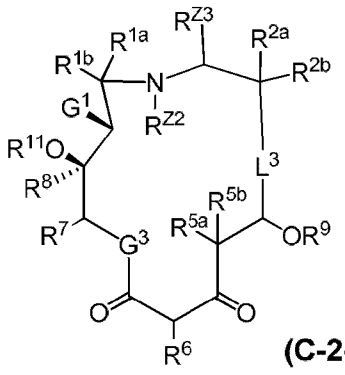
(C-2-C) or



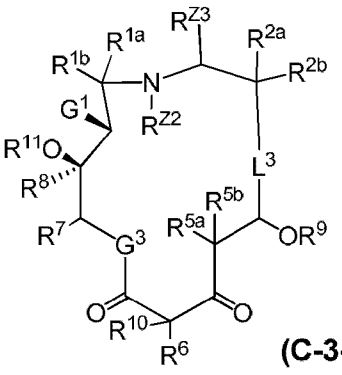
(C-2-C'),

or a salt thereof.

5. The compound of claim 1, wherein the compound is of formula:

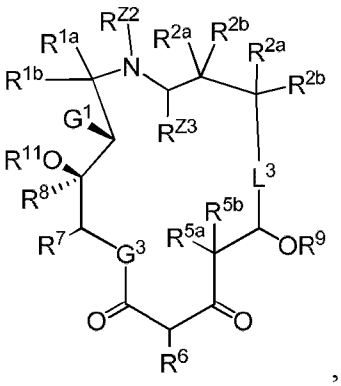
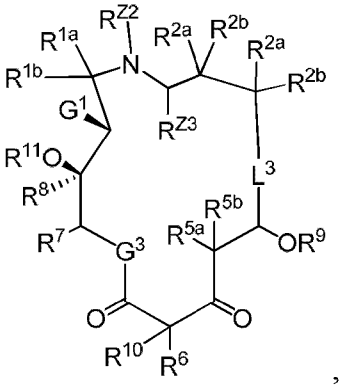
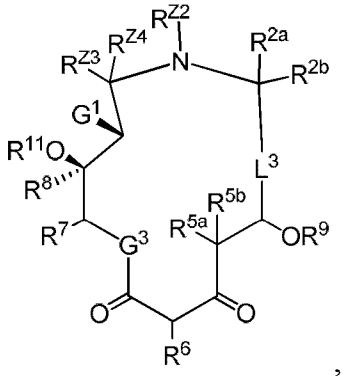
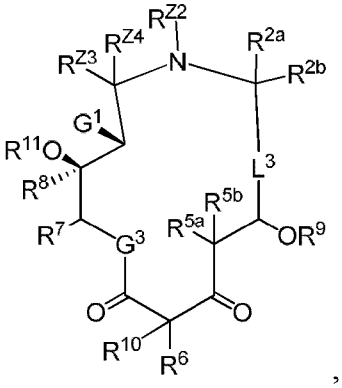


(C-2-iiia),



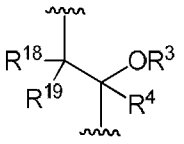
(C-3-iiia),

Date Reçue/Date Received 2021-01-08

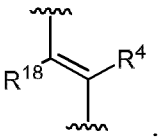

,

,

, or

,

or a salt thereof.

6. The compound of any one of claims 1-5, or a salt thereof, wherein L^3 is a group of formula:

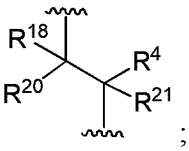

(**L^3-i**).

7. The compound of any one of claims 1-5, or a salt thereof, wherein L^3 is a group of formula:

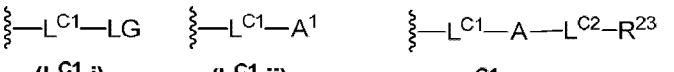

.

8. The compound of any one of claims 1-5, or a salt thereof, wherein L^3 is a group of formula:

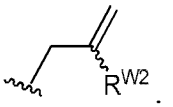
Date Reçue/Date Received 2021-01-08


; and R^{21} is hydrogen.

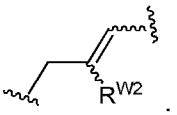
9. The compound of claim 1, or a salt thereof, wherein R^3 is a group of formula:


(L^{C1}-i) , **(L^{C1}-ii)** , or **(L^{C1}-iii)** .

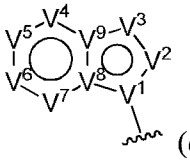
10. The compound of claim 9, or a salt thereof, wherein A^1 is:

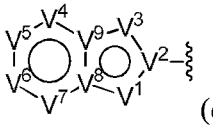

.

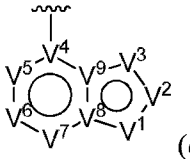
11. The compound of claim 9, or a salt thereof, wherein A is:

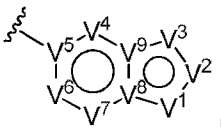

.

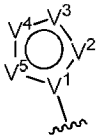
12. The compound of claim 9, or a salt thereof, wherein R^{23} is

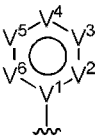

(e–1)

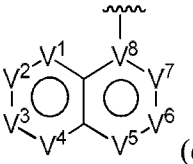

(e–2)

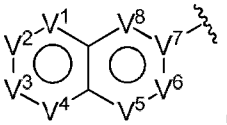

(e–3)


(e–4)

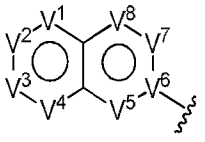

(e–5),


(e–6),


(e-7),


(e-8), or

Date Reçue/Date Received 2021-01-08


(**e-9**),

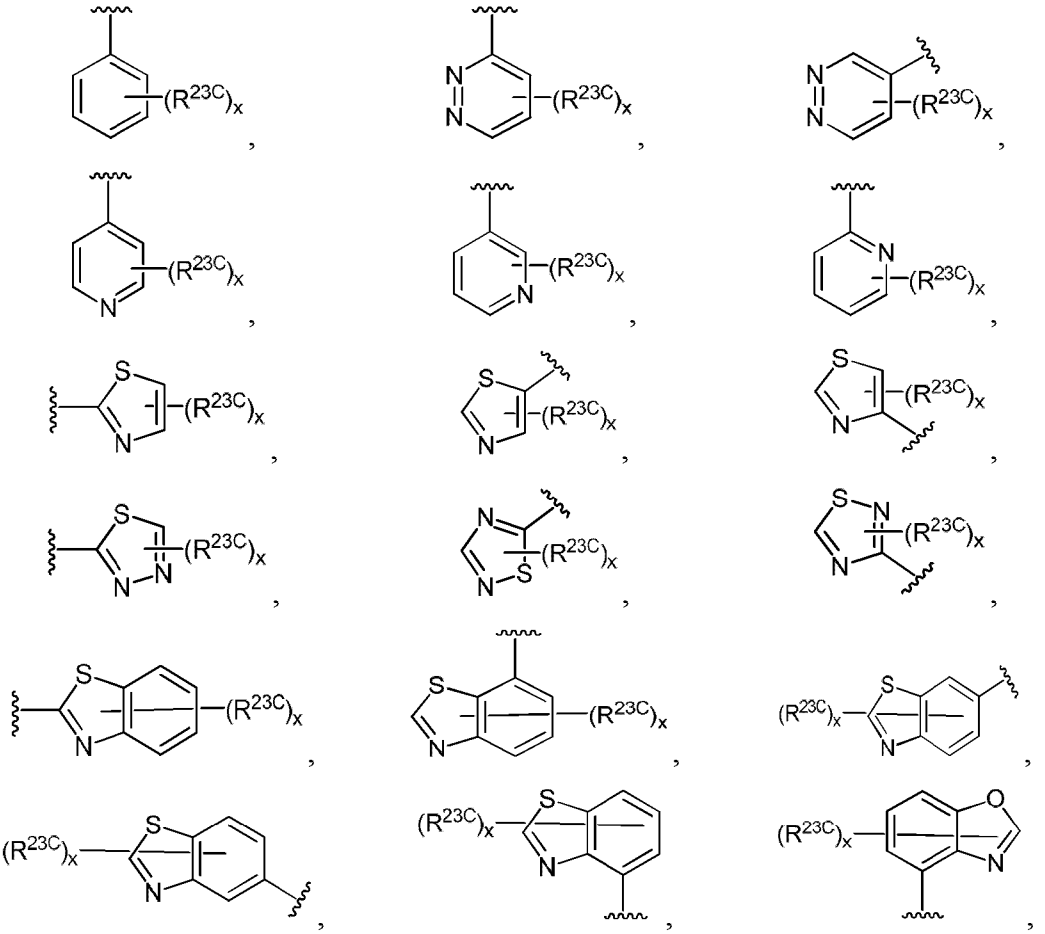
wherein:

each instance of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 may independently be O, S, N, NR^{23N}, C, or CR^{23C}, as valency permits;

R^{23N} is independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or a nitrogen protecting group; and

R^{23C} is hydrogen, halogen, –CN, $–NO_2$, $–N_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, or carbonyl.

13. The compound of claim 14, or a salt thereof, wherein R^{23} is of formula:



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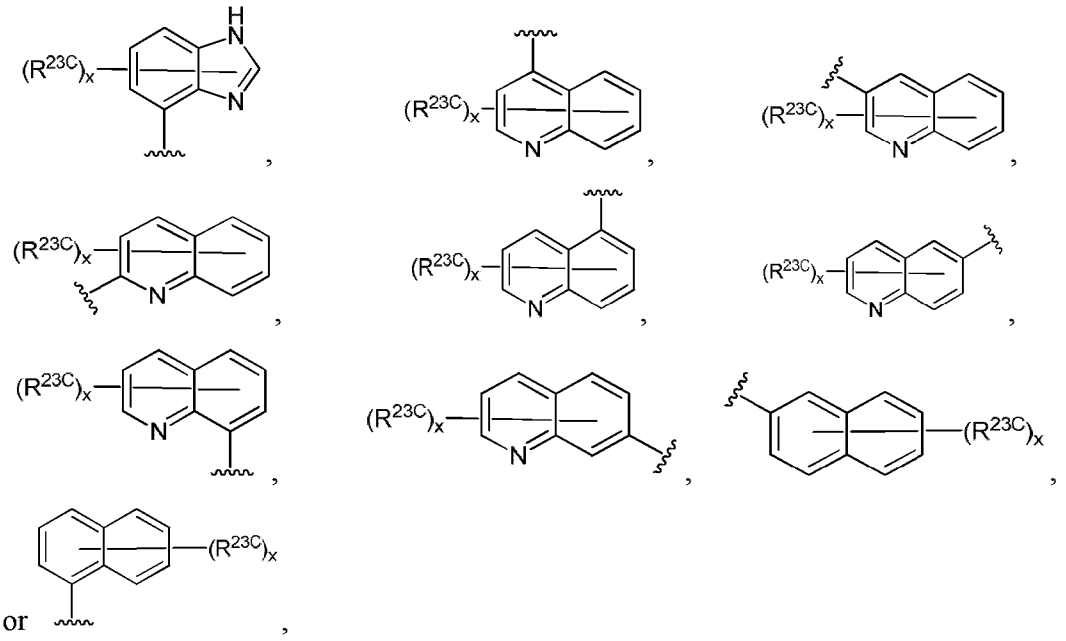


wherein x is 0, 1, or 2.

14. The compound of any one of claims 1-13, or a salt thereof, wherein R^4 is hydrogen, optionally substituted C_{1-6}alkyl, or optionally substituted C_{2-6}alkenyl.

15. The compound of any one of claims 1-13, wherein R^4 is $–CH_3$, $–CH_2CH_2OH$, $–CH_2C(H)=O$, $–CH_2CH_2N(R^{22})_2$, or $–CH_2CH_2NHR^{22}$, wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl.

16. The compound of any one of claims 1-13, or a salt thereof, wherein R^4 is substituted allyl or unsubstituted allyl.

17. The compound of any one of claims 1-13, or a salt thereof, wherein R^4 is hydrogen, optionally substituted C_{1-6}alkyl, or optionally substituted C_{2-6}alkenyl; and R^{21} is hydrogen.

18. The compound of any one of claims 1-13, or a salt thereof, wherein R^4 is $–CH_3$, $–CH_2CH_2OH$, $–CH_2C(H)=O$, $–CH_2CH_2N(R^{22})_2$, or $–CH_2CH_2NHR^{22}$, wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl; and R^{21} is hydrogen.

Date Reçue/Date Received 2021-01-08

19. The compound of any one of claims 1-13, or a salt thereof, wherein R^4 is substituted allyl or unsubstituted allyl; and R^{21} is hydrogen.

20. The compound of any one of claims 1-13, or a salt thereof, wherein each instance of R^{5a} and R^{5b} is independently hydrogen, optionally substituted alkyl, or halogen.

21. The compound of any one of claims 1-13, or a salt thereof, wherein R^{5a} and R^{5b} are both hydrogen.

22. The compound of any one of claims 1-13, or a salt thereof, wherein R^{5a} is $-CH_3$; and R^{5b} is hydrogen.

23. The compound of any one of claims 1-13, or a salt thereof, wherein R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aralkyl, or optionally substituted heteroaralkyl.

24. The compound of any one of claims 1-13, or a salt thereof, wherein R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aralkyl, or optionally substituted heteroaralkyl; and R^{10} is fluorine.

25. The compound of any one of claims 1-13, or a salt thereof, wherein R^6 is optionally substituted pyrazolylalkyl, imidazolylalkyl, thiazolylalkyl, oxazolylalkyl, pyridinylalkyl, pyrimidinylalkyl, or pyrazinylalkyl.

26. The compound of any one of claims 1-13, or a salt thereof, wherein R^6 is optionally substituted pyrazolylalkyl, imidazolylalkyl, thiazolylalkyl, oxazolylalkyl, pyridinylalkyl, pyrimidinylalkyl, or pyrazinylalkyl; and R^{10} is fluorine.

27. The compound of any one of claims 1-13, or a salt thereof, wherein R^6 is optionally substituted allyl or optionally substituted benzyl.

28. The compound of any one of claims 1-13, or a salt thereof, wherein R^6 is optionally substituted allyl or optionally substituted benzyl; and R^{10} is fluorine.

Date Reçue/Date Received 2021-01-08

29. The compound of any one of claims 1-13, or a salt thereof, wherein R^6 is $–CH_2CN$ or $–CH_2C(=O)OR^{32}$, wherein R^{32} is hydrogen or optionally substituted alkyl.

30. The compound of any one of claims 1-13, or a salt thereof, wherein R^7 is optionally substituted alkyl.

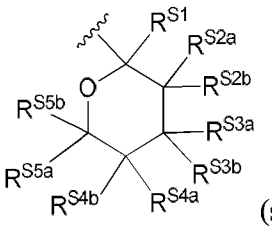
31. The compound of any one of claims 1-13, or a salt thereof, wherein R^7 is $–CH_2CH_3$.

32. The compound of any one of claims 1-13, or a salt thereof, wherein R^8 is optionally substituted alkyl.

33. The compound of any one of claims 1-13, or a salt thereof, wherein R^8 is $–CH_3$.

34. The compound of any one of claims 1-13, or a salt thereof, wherein R^{18} and R^{19} are hydrogen.

35. The compound of any one of claims 1-13, or a salt thereof, wherein R^9 is a group of formula:



(s–1)

wherein:

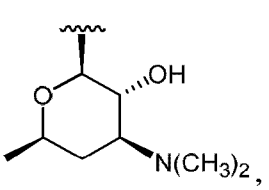
each of R^{S1}, R^{S2a}, R^{S2b}, R^{S3a}, R^{S3b}, R^{S4a}, R^{S4b}, R^{S5a}, and R^{S5b} is independently hydrogen, optionally substituted alkyl, $–OR^{SO}$, $–N(R^{SN})_2$, or wherein R^{S2a} or R^{S2b} may be taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused heterocyclic ring;

each instance of R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group; and

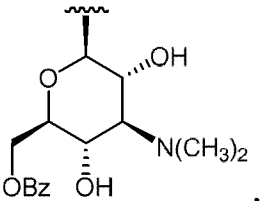
Date Reçue/Date Received 2021-01-08

each instance of R^{SN} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; or optionally two R^{SN} are taken with the intervening atoms to form a heterocyclic ring.

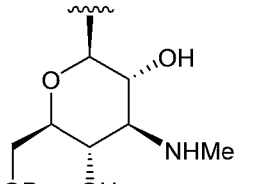
36. The compound of any one of claims 1-13, or a salt thereof, wherein R^9 is a group of formula:



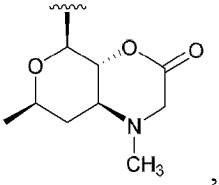
(s–2a–i–2),



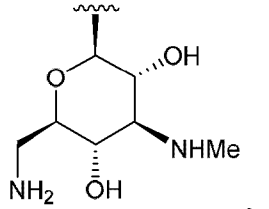
(s–2a–iii–4),



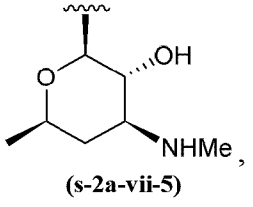
(s-2a-vii-5),



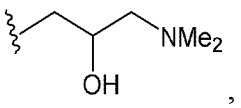
(s–2a–vii–3),



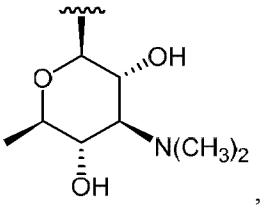
(s-2a-vii-5),



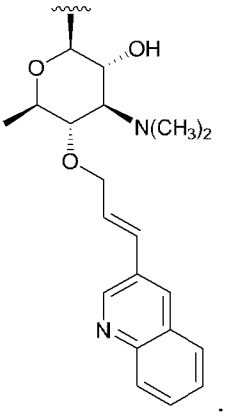
(s-2a-vii-5),



(s-2a-vii-5),



(s–2a–i–3),



or (s–2a–vii–4).

37. The compound of any one of claims 1-13, or a salt thereof, wherein R^{14} is hydrogen.

38. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is optionally substituted C_{1-6}alkyl, optionally substituted haloalkyl, optionally substituted aralkyl, optionally substituted C_{2-6}alkenyl, or optionally substituted C_{3-6}carbocyclyl.

Date Reçue/Date Received 2021-01-08

39. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is –CH_3, –CF_3, –CH_2CH_2OH, –$CH_2C(H)=O$, –$CH_2CH_2N(R^{22})_2$, or –$CH_2CH_2NHR^{22}$.

40. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is optionally substituted vinyl or optionally substituted allyl.

41. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is unsubstituted vinyl or unsubstituted allyl.

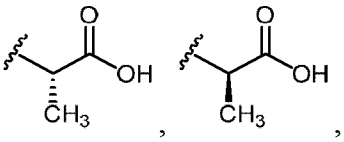
42. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is substituted benzyl or unsubstituted benzyl.

43. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is monosubstituted benzyl.

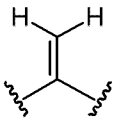
44. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is benzyl substituted by one instance of halogen.

45. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is substituted cyclopropyl or unsubstituted cyclopropyl.

46. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} or R^{Z3} is –$CH_2CH_2N(R^{22})_2$ or –$CH_2CH_2NHR^{22}$; and each instance of R^{22} is independently hydrogen,-$CH_2C(=O)OH$,



, or –CH_3.

47. The compound of any one of claims 1-13, or a salt thereof, wherein R^{1a} and R^{2a} are taken together to form 

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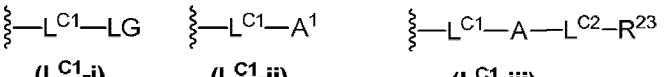
Date Reçue/Date Received 2021-01-08

48. The compound of any one of claims 1-13, or a salt thereof, wherein R^{2a} is optionally substituted C_{1-6}alkyl, optionally substituted haloalkyl, or halogen.

49. The compound any one of claims 1-13, or a salt thereof, wherein R^{2a} is $–CH_3$, $–CF_3$, or –F.

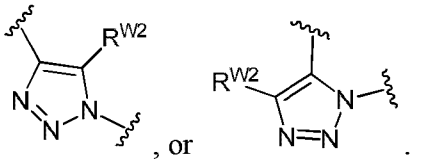
50. The compound of any one of claims 1-13, or a salt thereof, wherein R^{14} is a group of formula:



(L^{C1}-i) , **(L^{C1}-ii)** , or **(L^{C1}-iii)** .

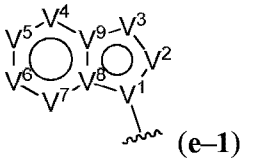
51. The compound of claim 50, or a salt thereof, wherein A^1 is $–N_3$.

52. The compound of claim 50, or a salt thereof, wherein A is:

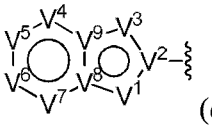


, or .

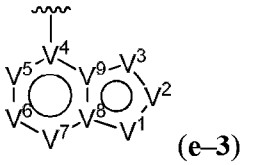
53. The compound of claim 50, or a salt thereof, wherein R^{23} is of formula:



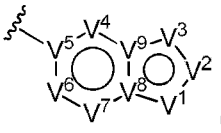
(e–1)



(e–2)

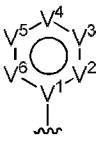


(e–3)

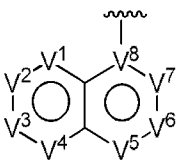


(e–4)

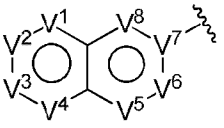
(e–5),



(e–6),

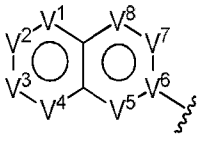


(e-7),



(e-8), or

Date Reçue/Date Received 2021-01-08


(**e-9**),

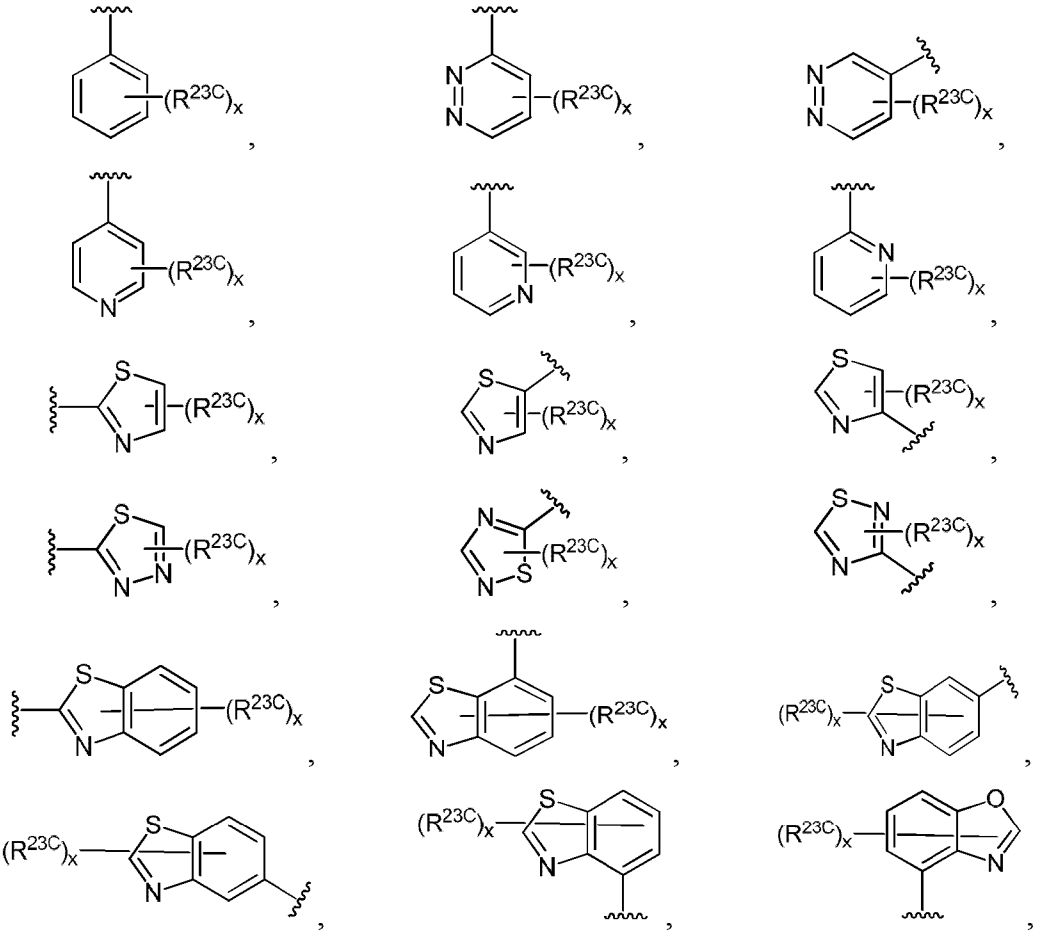
wherein:

each instance of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 may independently be O, S, N, NR^{23N}, C, or CR^{23C}, as valency permits;

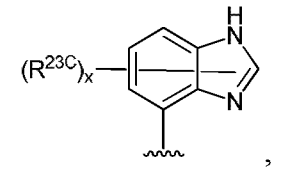
R^{23N} is independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or a nitrogen protecting group; and

R^{23C} is hydrogen, halogen, –CN, $–NO_2$, $–N_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, or carbonyl.

54. The compound of claim 53, or a salt thereof, wherein R^{23} is of formula:



Date Reçue/Date Received 2021-01-08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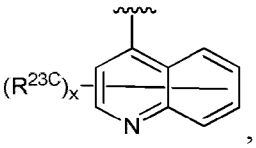
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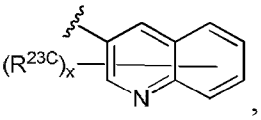
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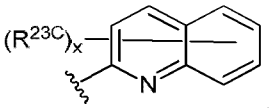
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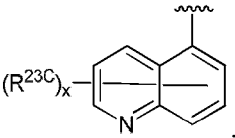
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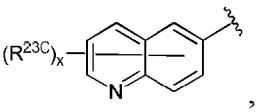
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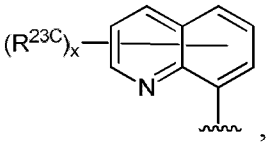
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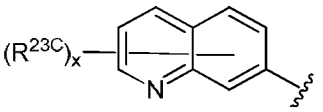
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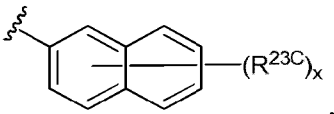
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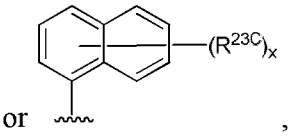
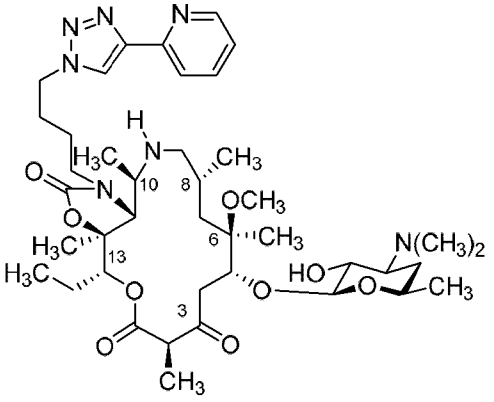
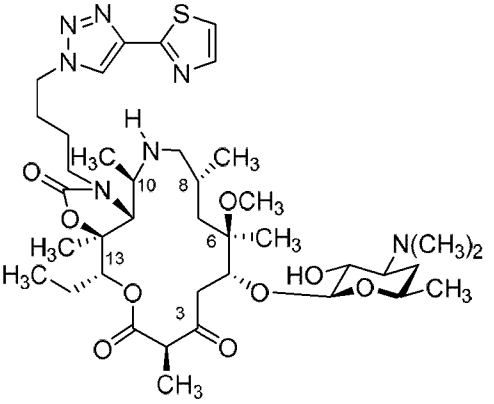
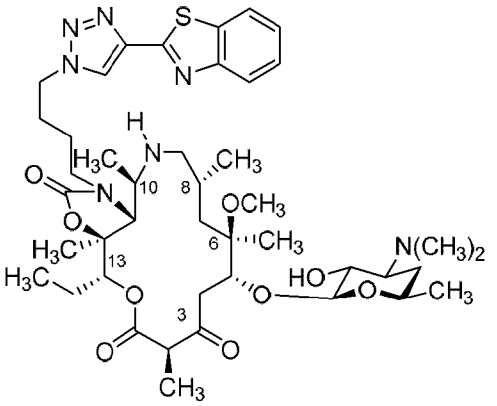
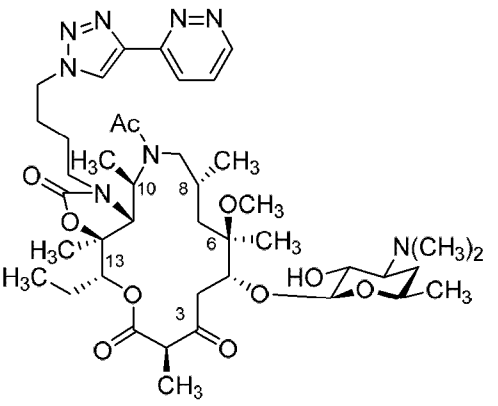
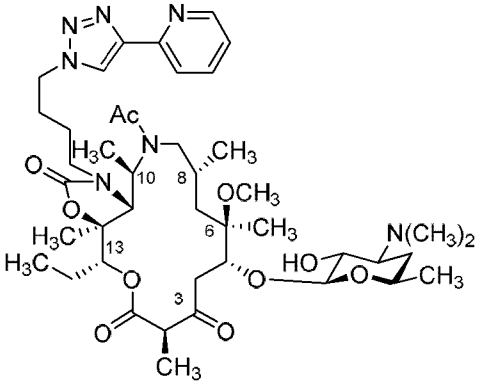
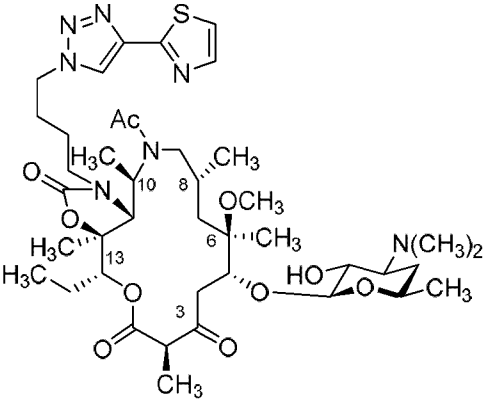
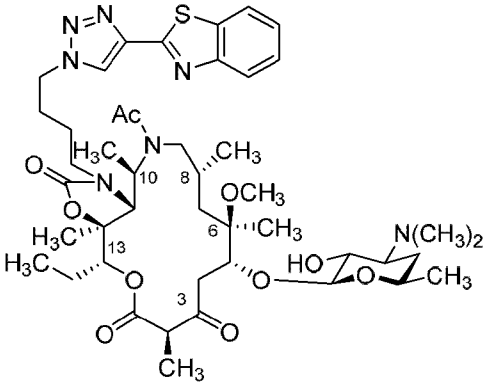
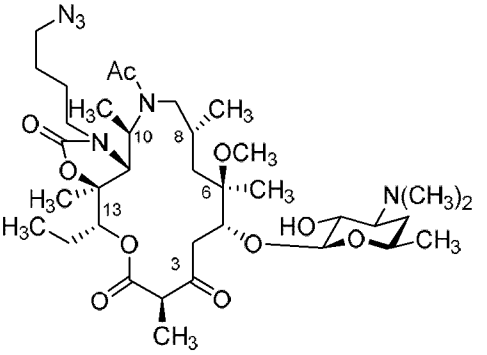

or ,

wherein x is 0, 1, or 2.

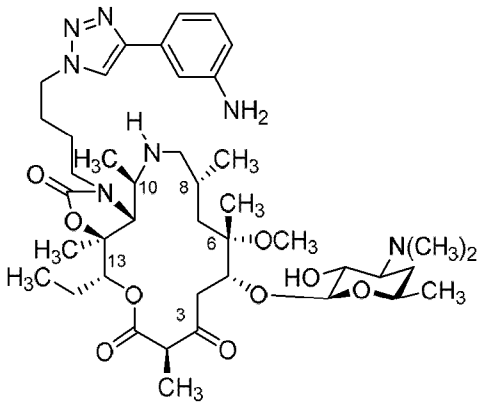
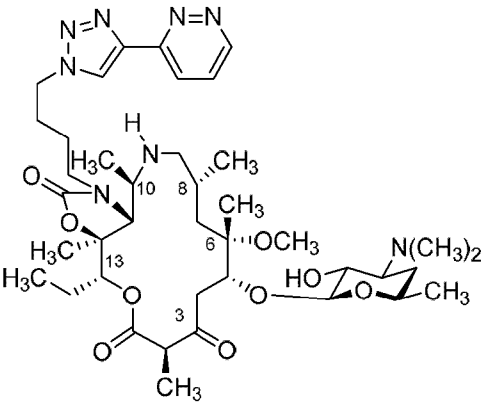
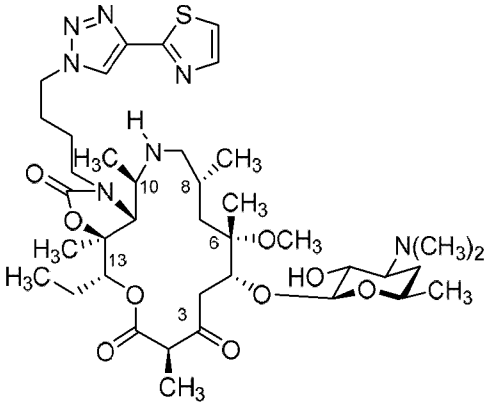
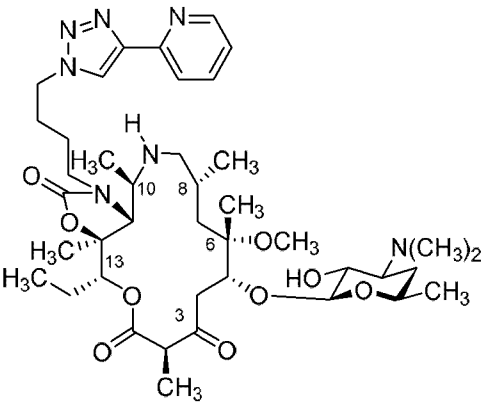
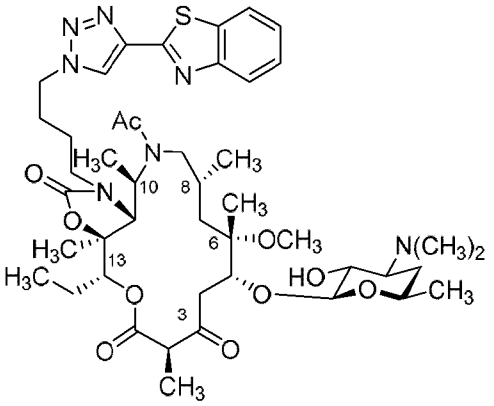
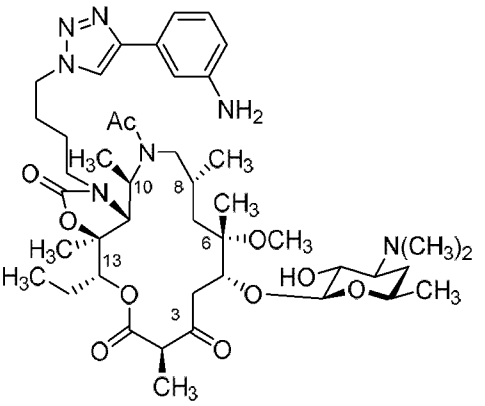
55. The compound of claim 1, wherein the compound is:

 **FSM-10786**	 **FSM-10787**

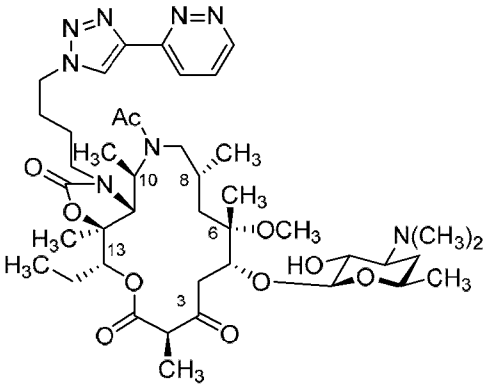
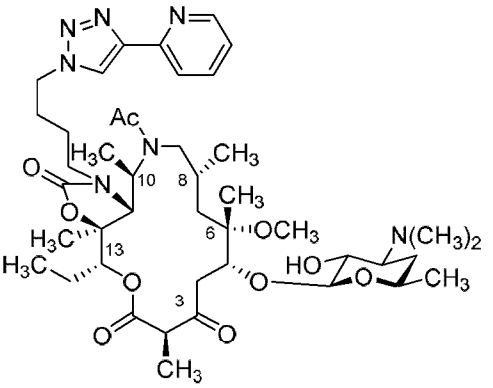
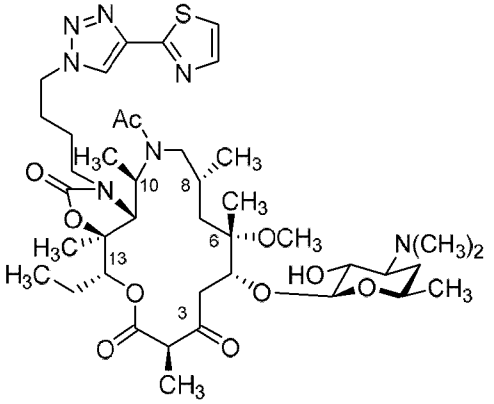
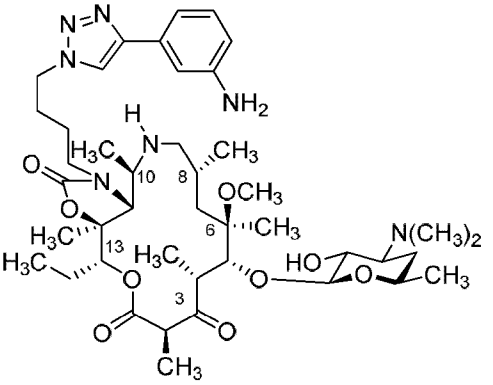
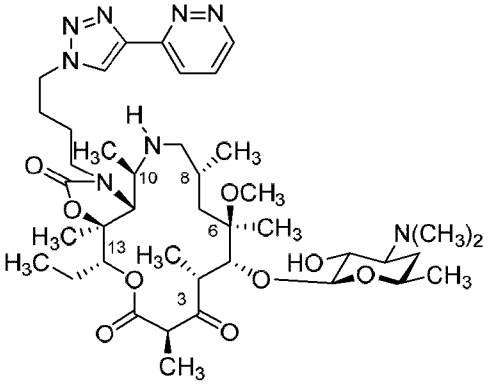
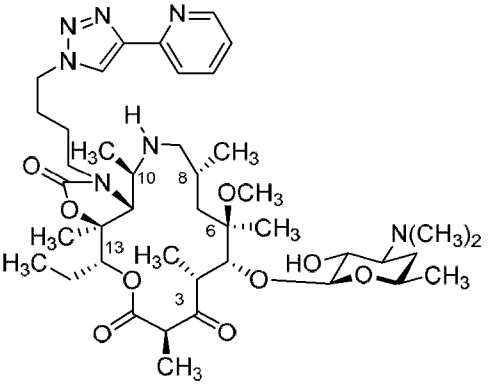
Date Reçue/Date Received 2021-01-08

 **FSM-10788**	 **FSM-10794**
 **FSM-10792**	 **FSM-10790**
 **FSM-10791**	 **FSM-10789**

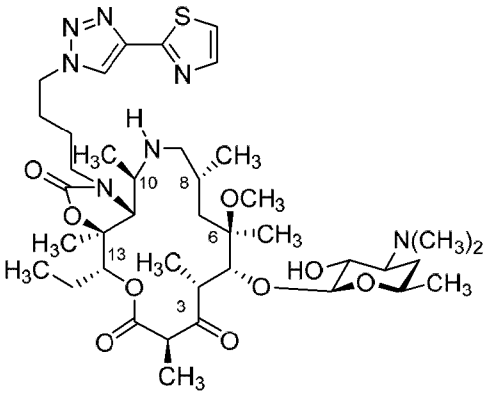
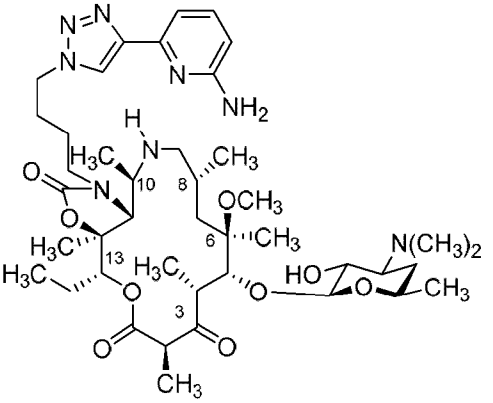
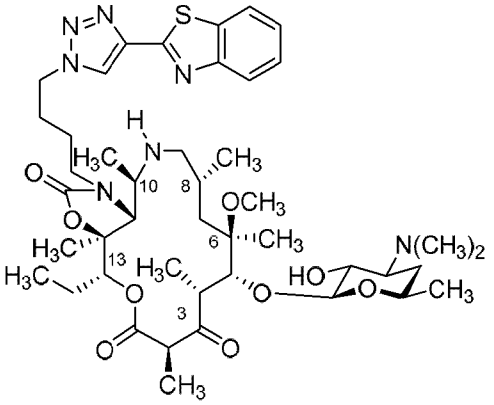
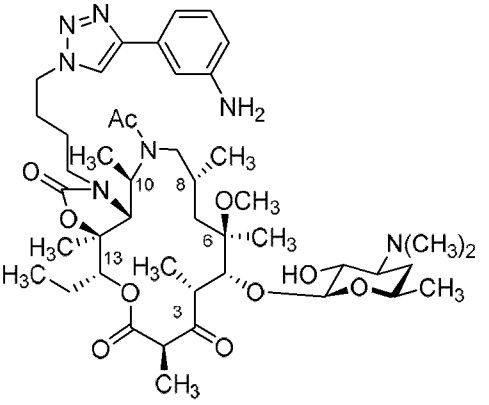
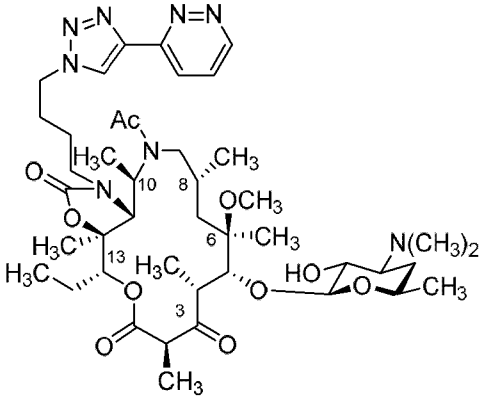
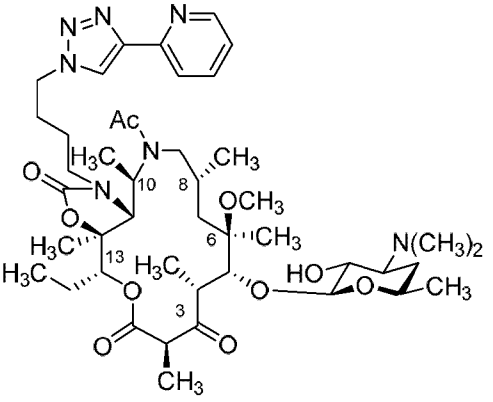
Date Reçue/Date Received 2021-01-08

 **FSM-30502**	 **FSM-30506**
 **FSM-30501**	 **FSM-30517**
 **FSM-30514**	 **FSM-30512**

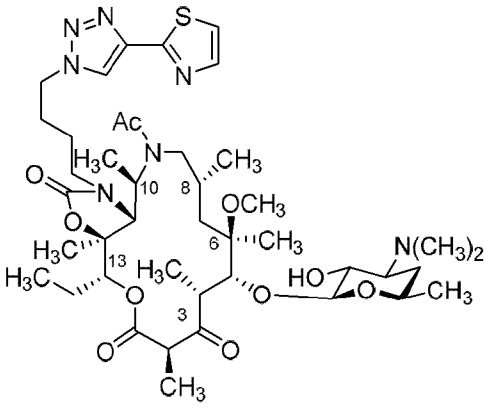
Date Reçue/Date Received 2021-01-08

 **FSM-30513**	 **FSM-30515**
 **FSM-30503**	 **FSM-20707**
 **FSM-20710**	 **FSM-20706**

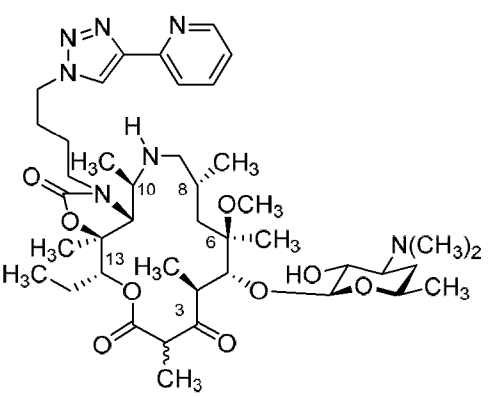
Date Reçue/Date Received 2021-01-08

 **FSM-20708**	 **FSM-20715**
 **FSM-20711**	 **FSM-20767**
 **FSM-20764**	 **FSM-20766**

Date Reçue/Date Received 2021-01-08



FSM-20763



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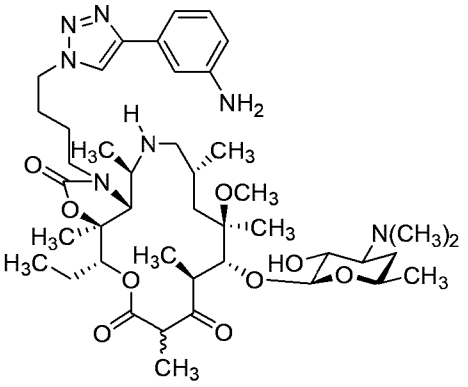

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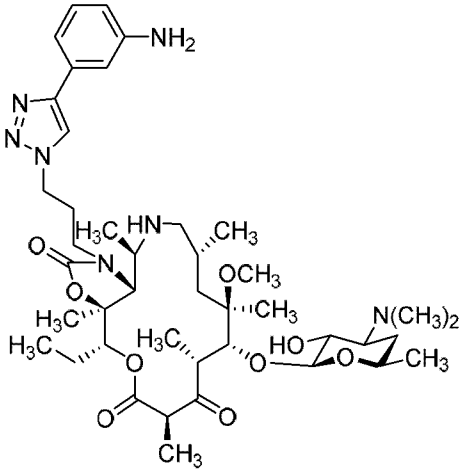
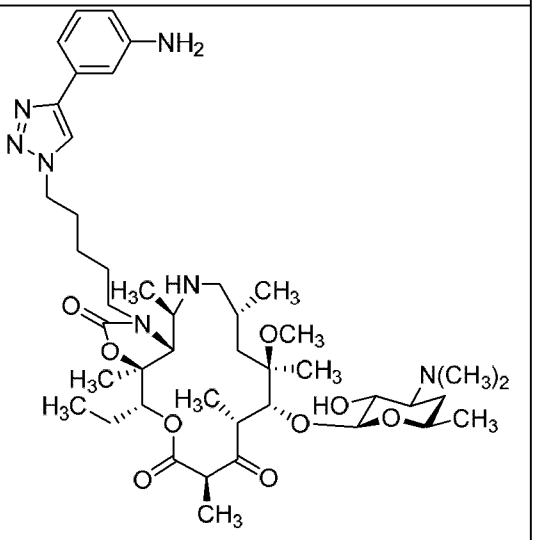


FSM-40347



FSM-40349

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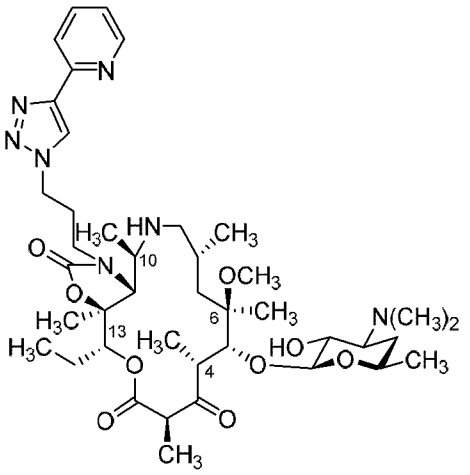

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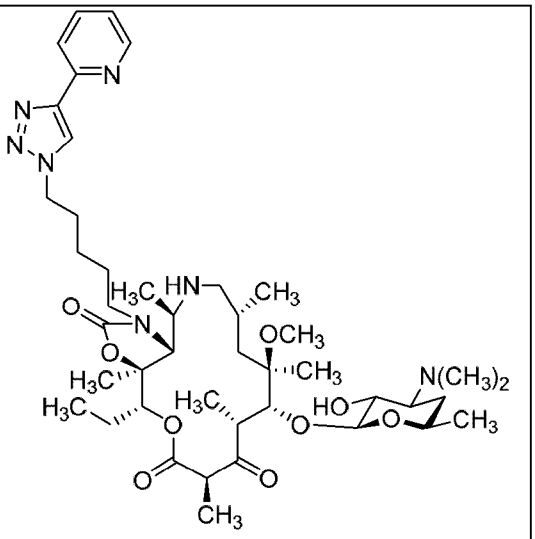

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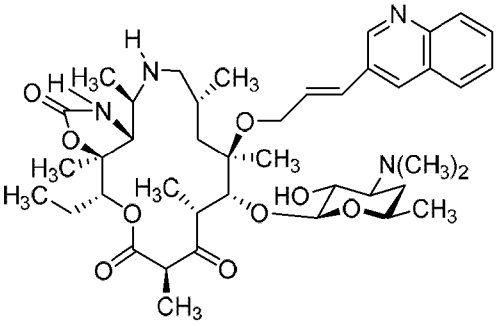

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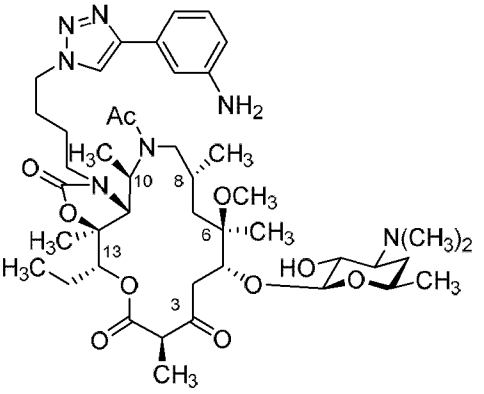
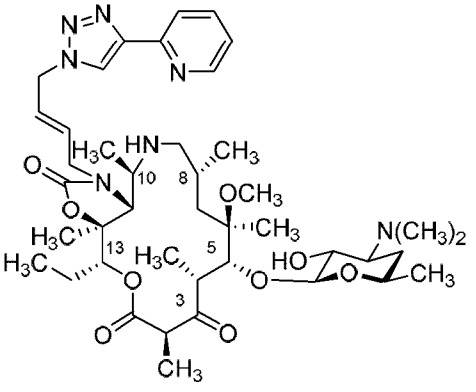
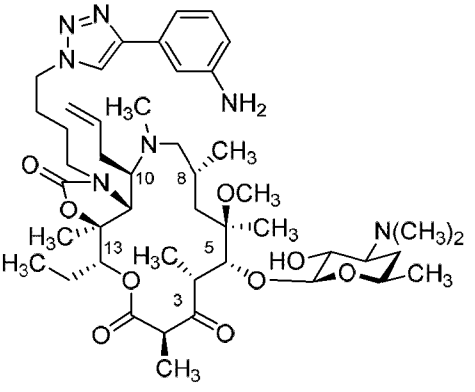


FSM-10793

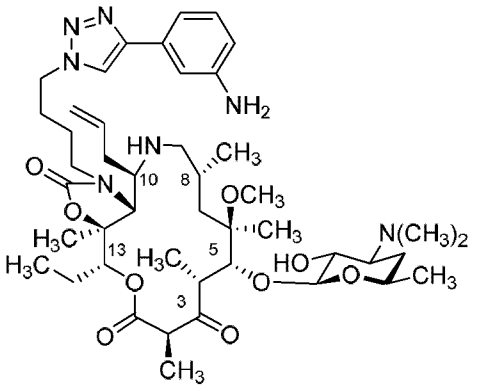


FSM-70153

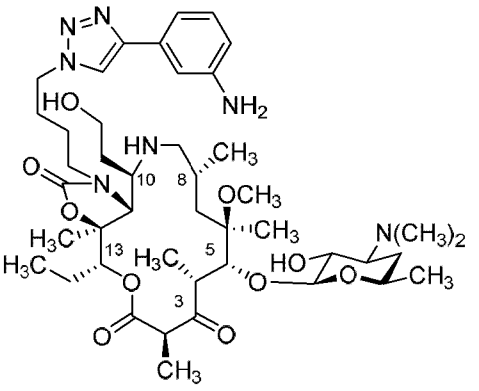


FSM-11094

Date Reçue/Date Received 2021-01-08



FSM-11044



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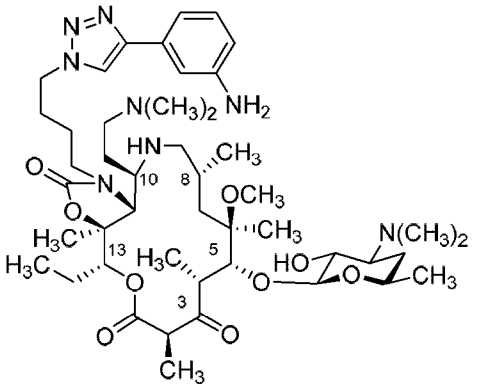

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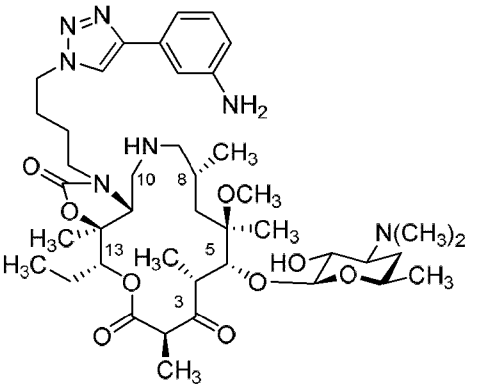

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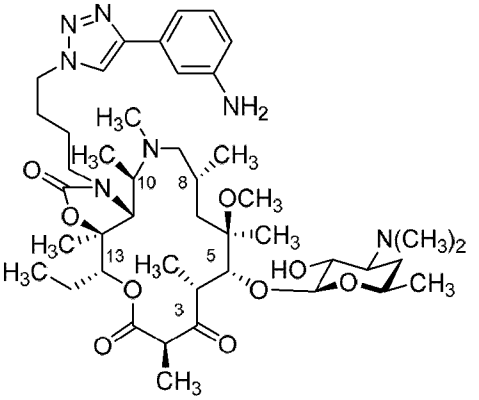
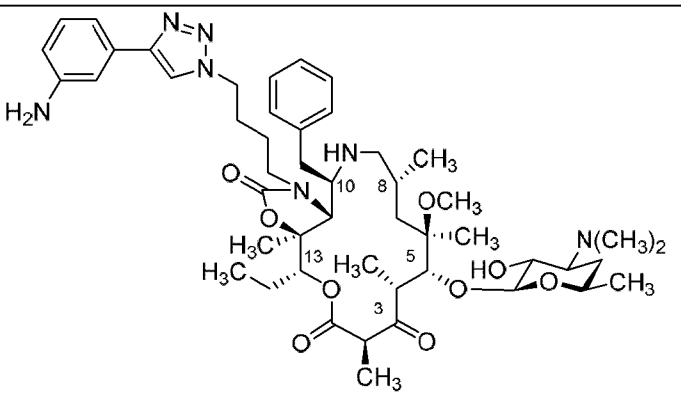
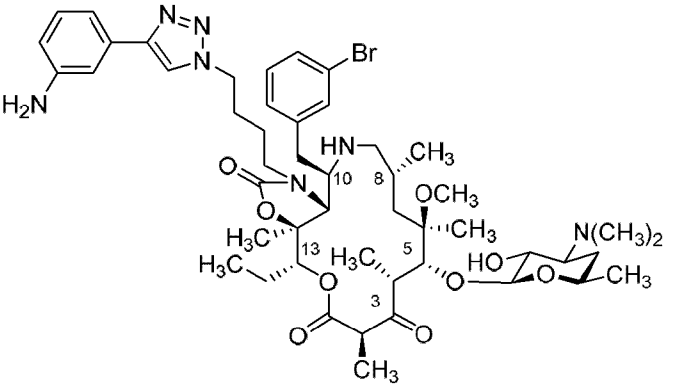


FSM-21339

Date Reçue/Date Received 2021-01-08



FSM-60353



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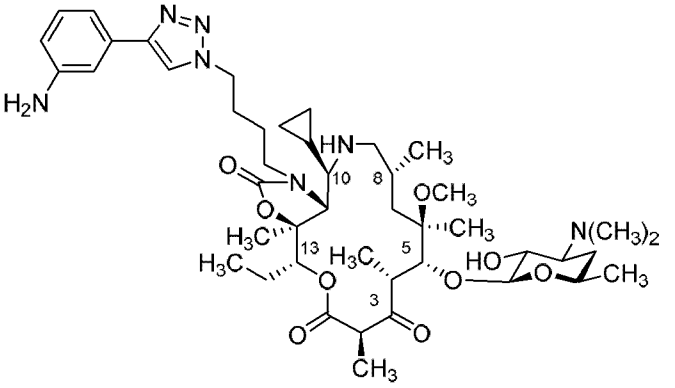

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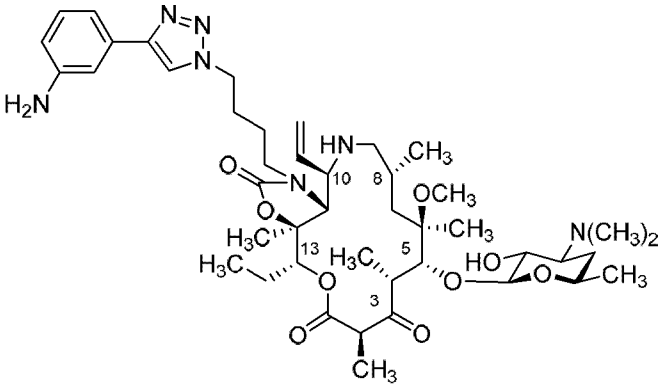

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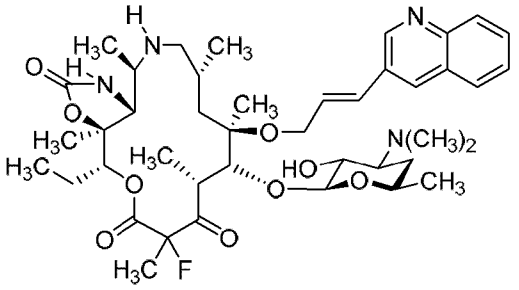
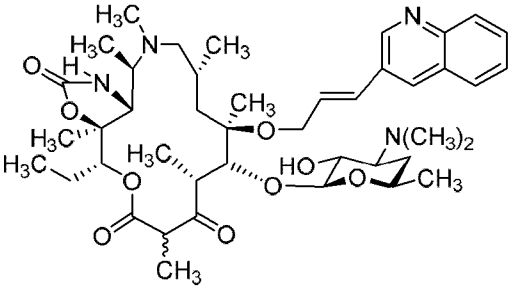


FSM-21088



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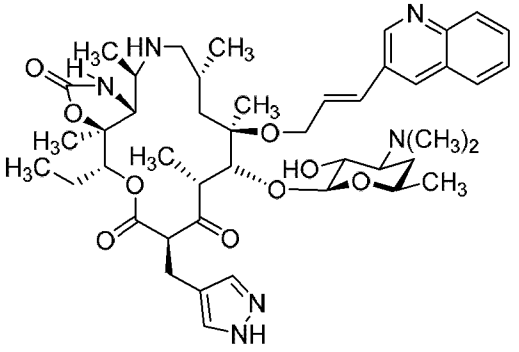
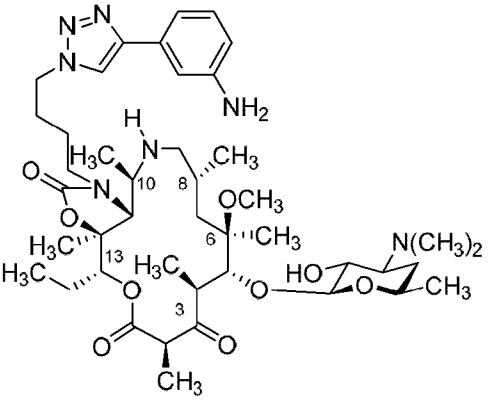
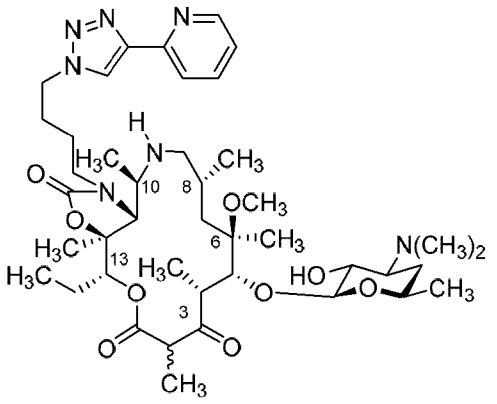
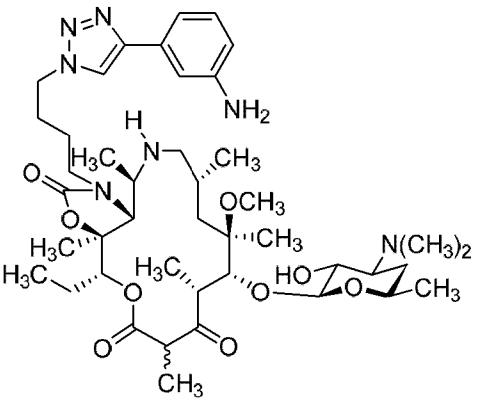
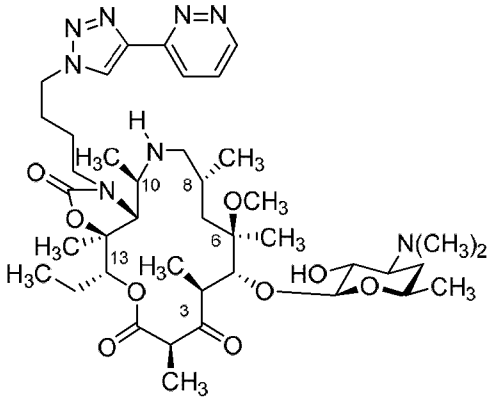
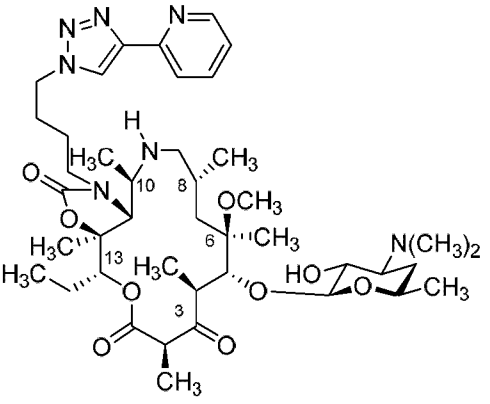
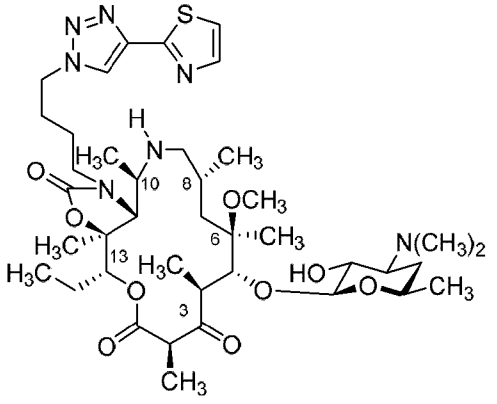
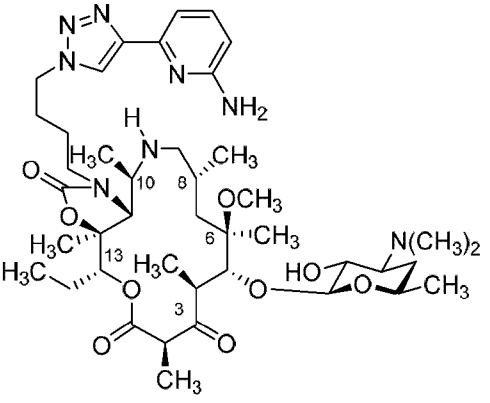


FSM-21064



FSM-20707a

Date Reçue/Date Received 2021-01-08

 **FSM-20754a**	 **FSM-20789a**
 **FSM-20710a**	 **FSM-20706a**
 **FSM-20708a**	 **FSM-20715a**

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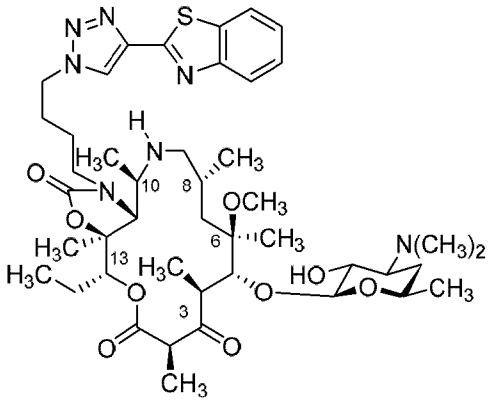
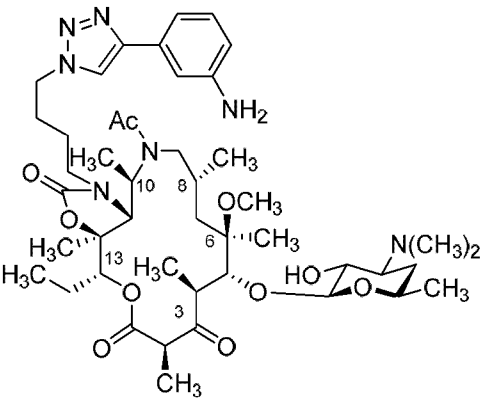
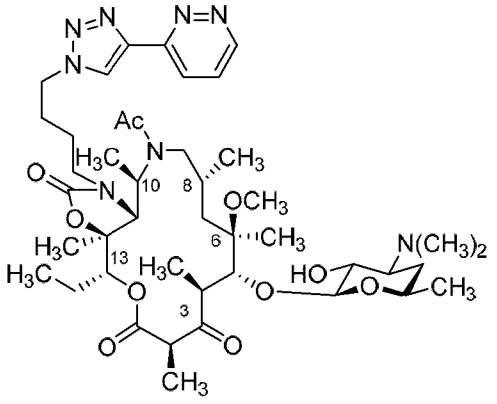
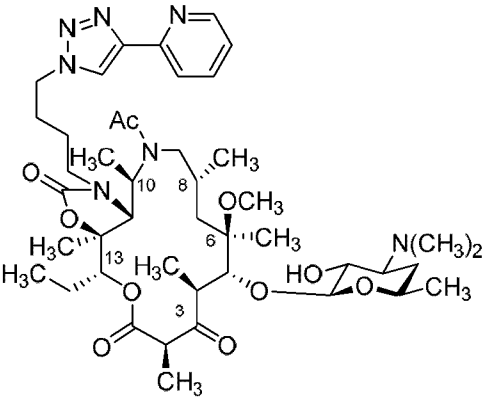
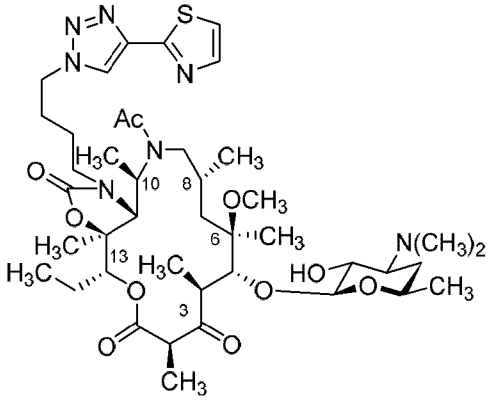
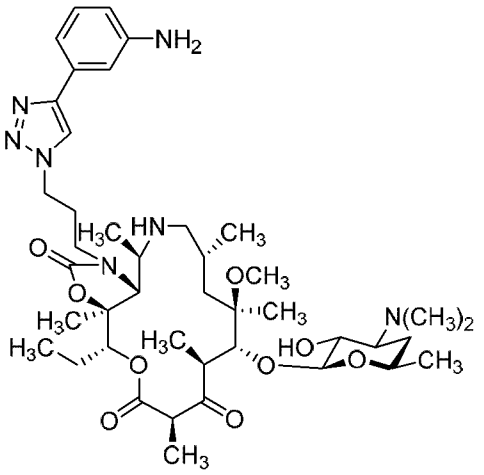
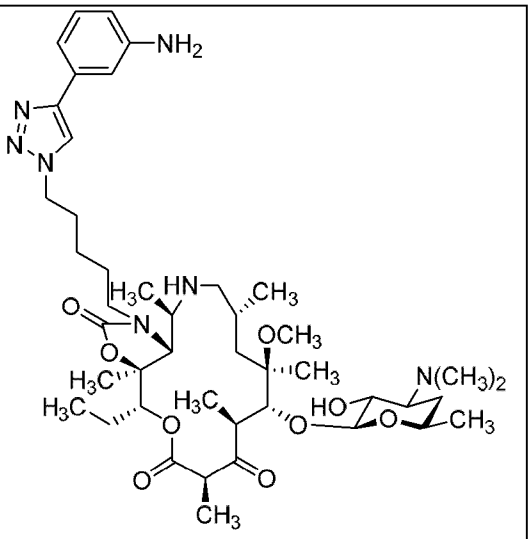
 **FSM-20711a**	 **FSM-20767a**
 **FSM-20764a**	 **FSM-20766a**
 **FSM-20763a**	

Date Reçue/Date Received 2021-01-08



FSM-40347a



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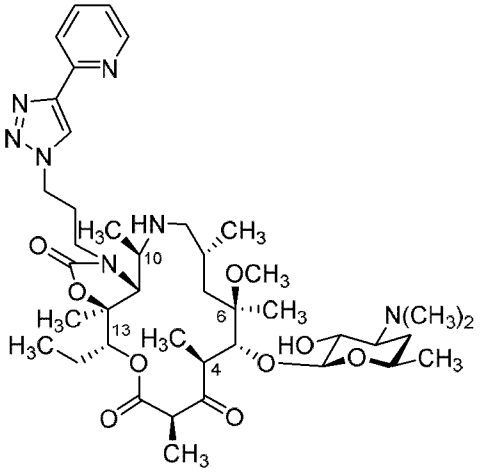

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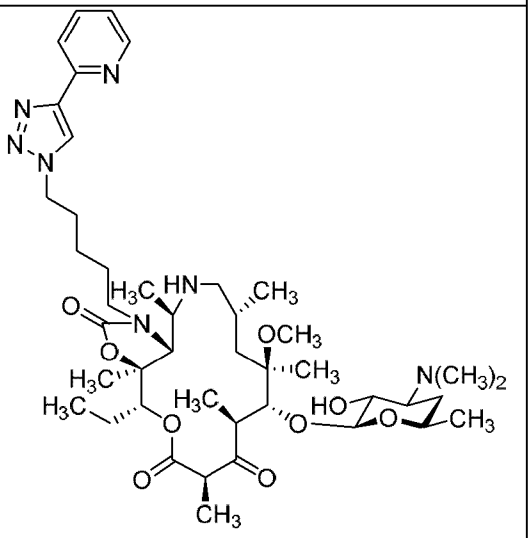

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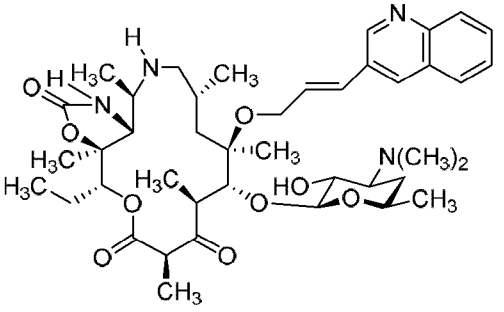

FSM-20919a

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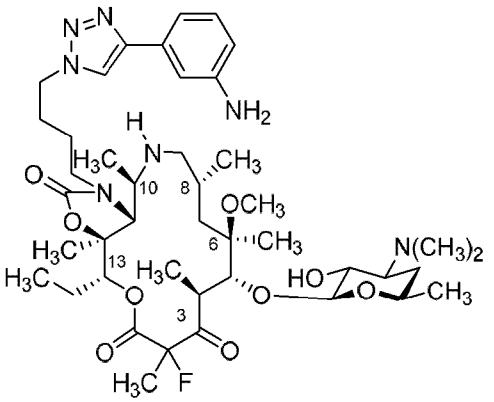
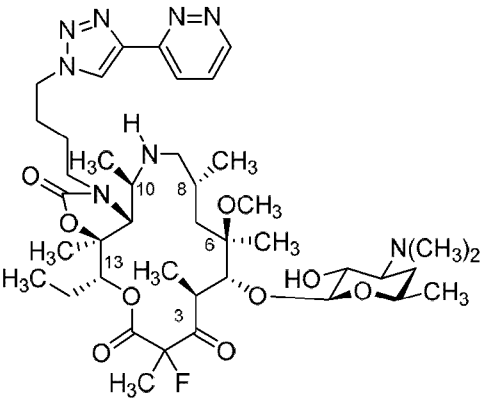
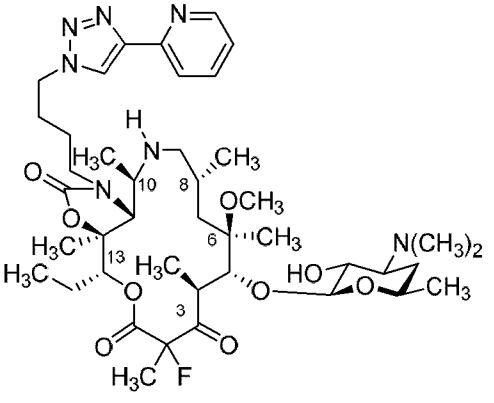
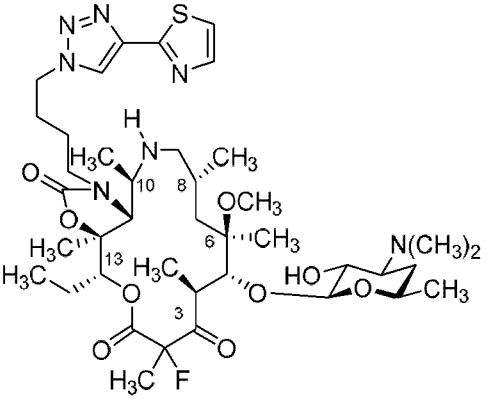
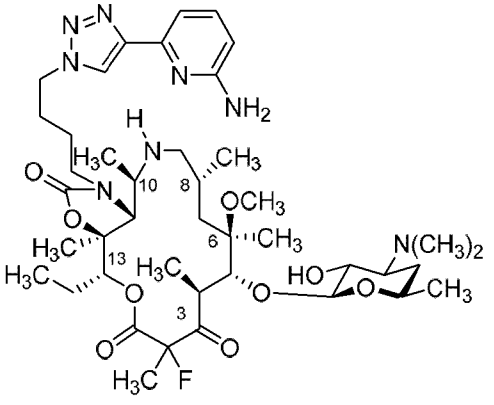
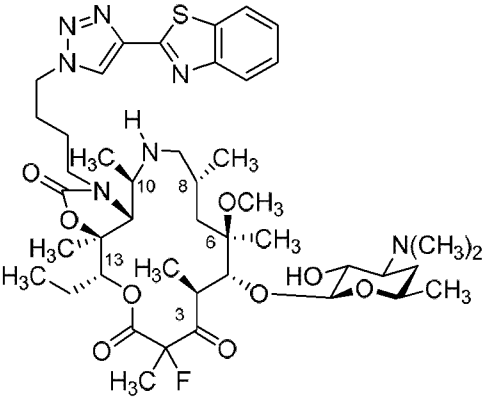
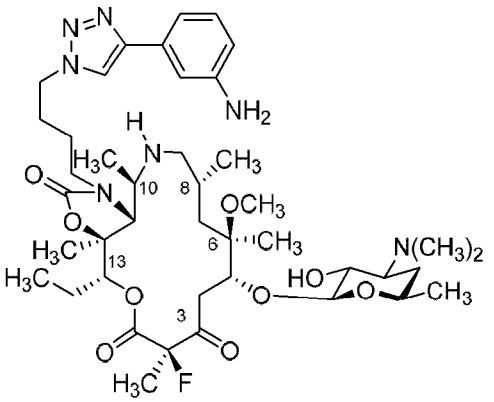
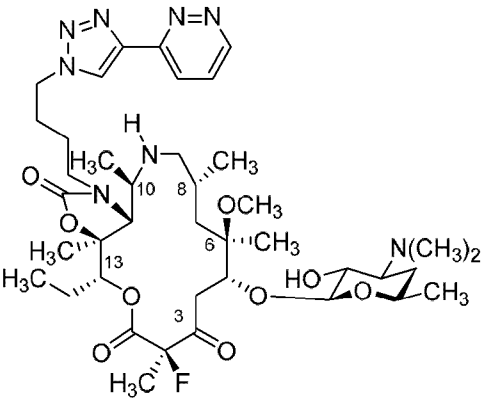
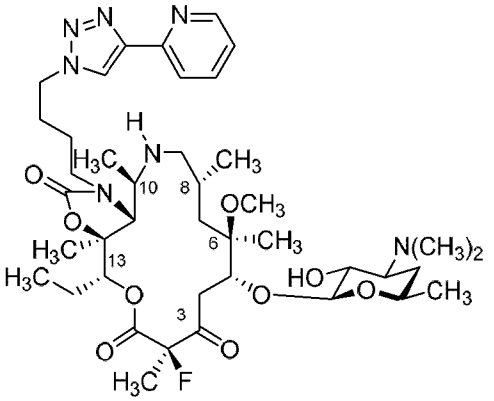
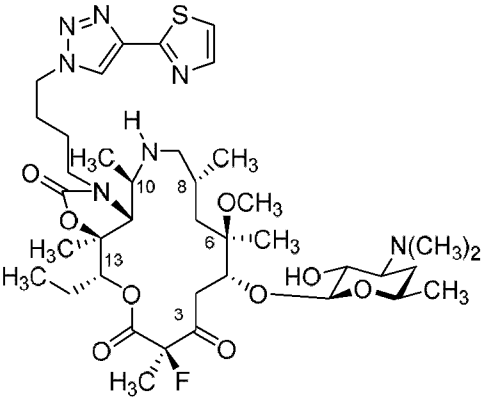
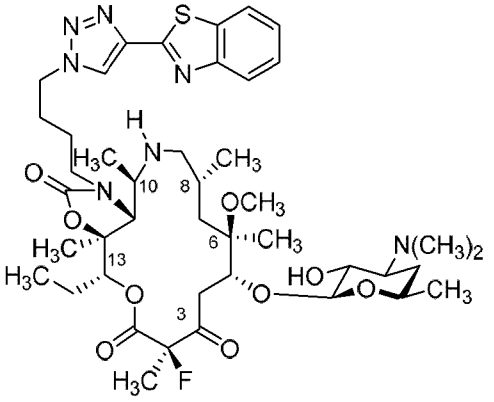
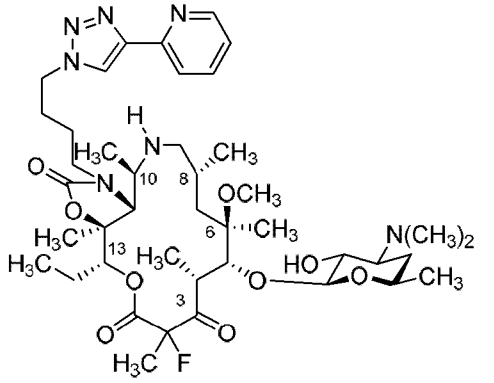
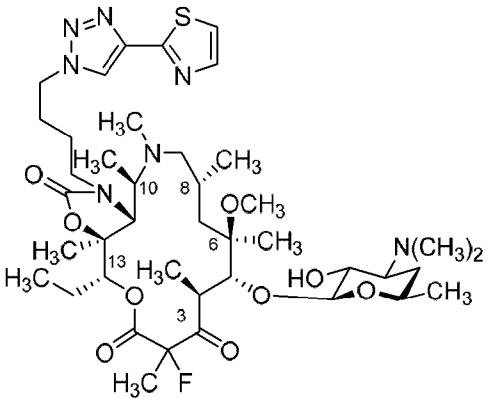
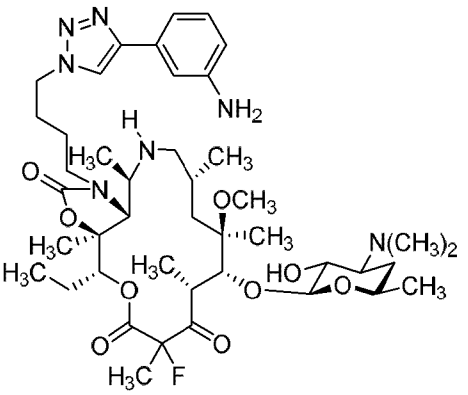
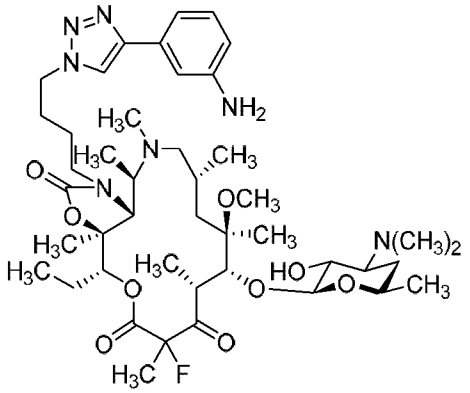
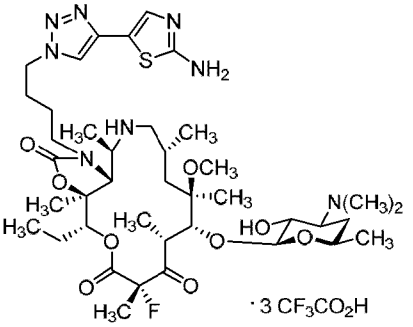
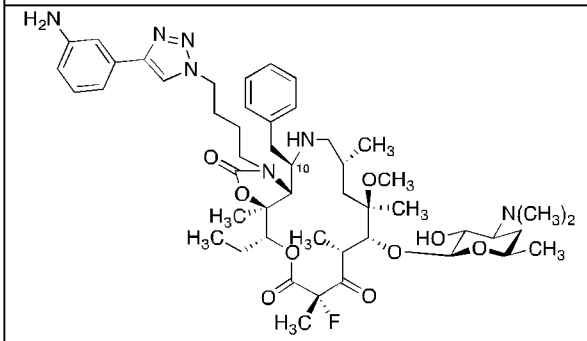
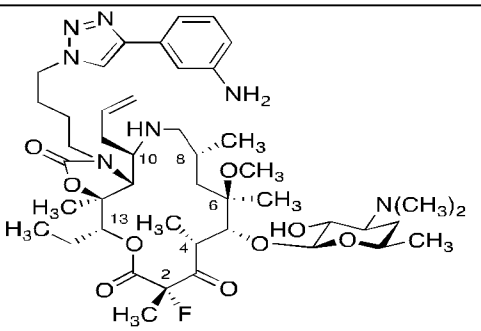
 **FSM-20720**	 **FSM-20717**
 **FSM-20716**	 **FSM-20721**
 **FSM-20718**	 **FSM-20722**

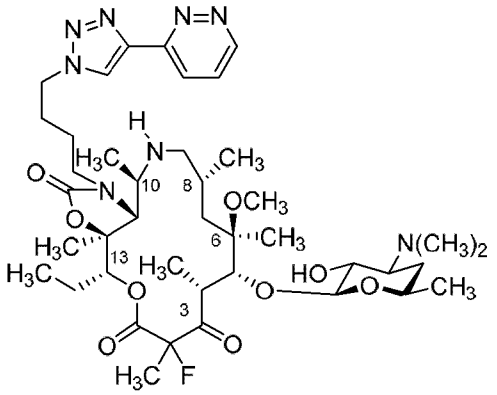
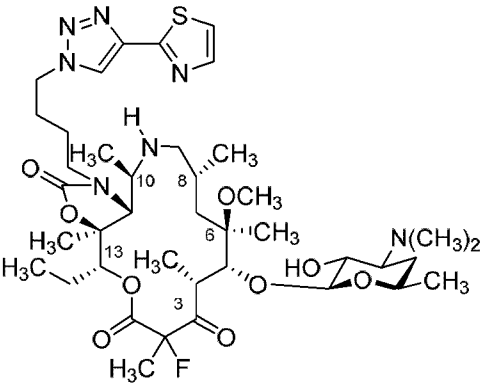
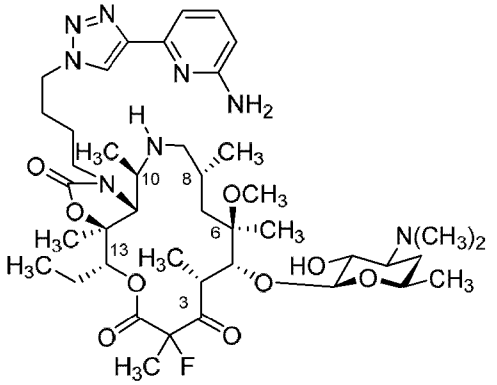
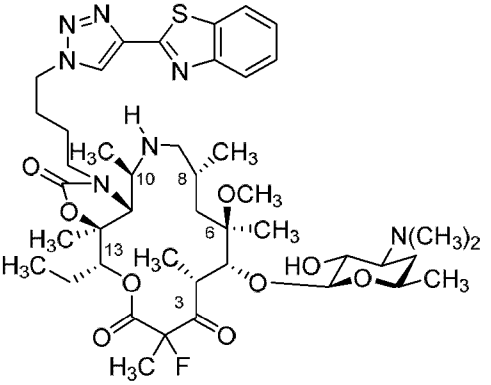
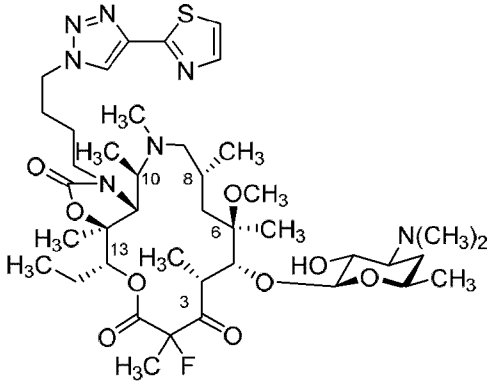
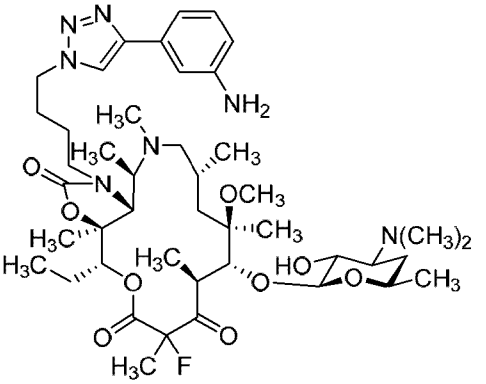
Date Reçue/Date Received 2021-01-08

 **FSM-10661**	 **FSM-10667**
 **FSM-10662**	 **FSM-10666**
 **FSM-10671**	 **FSM-20738**

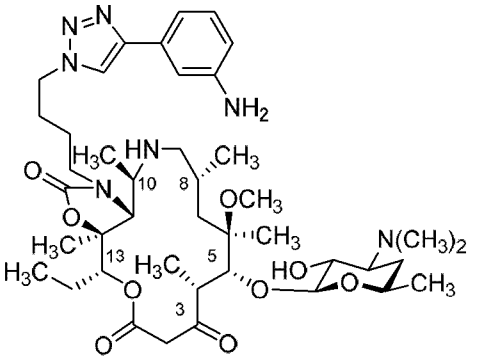
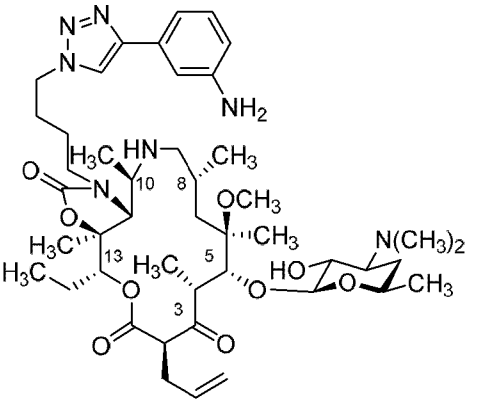
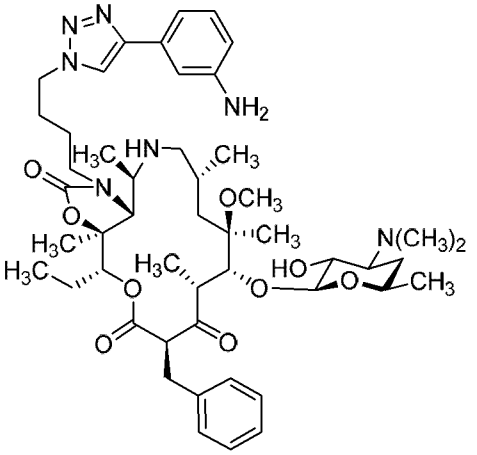
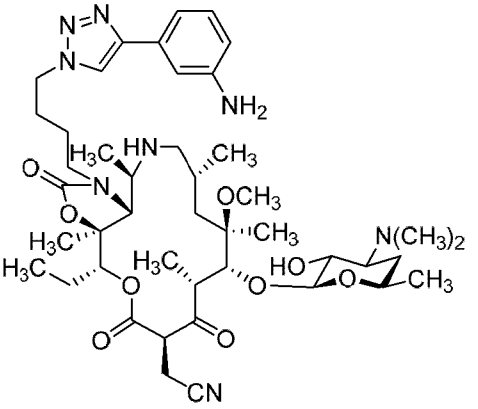
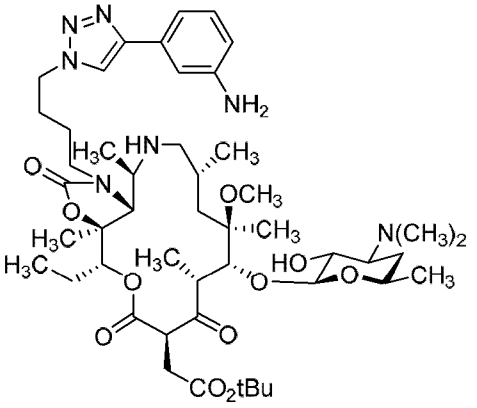
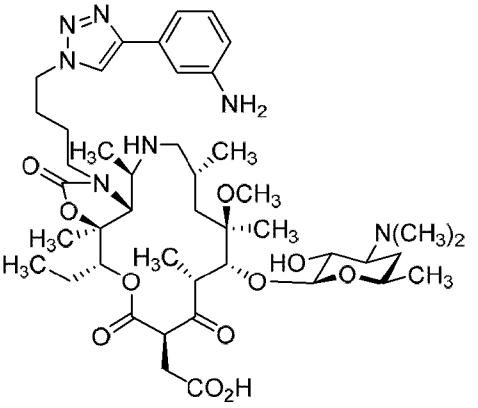
Date Reçue/Date Received 2021-01-08

 **FSM-20705**	 **FSM-20795**
 **FSM-20797**	 **FSM-21760**
 **FSM-60506**	 **FSM-11203**

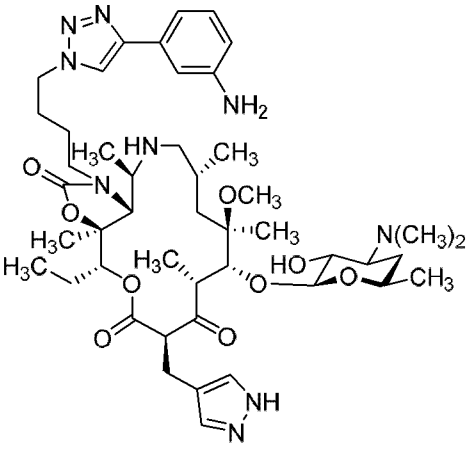
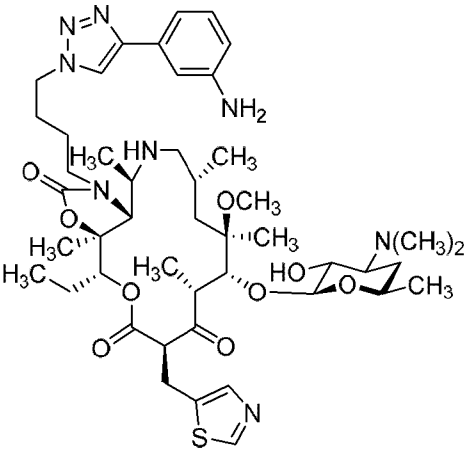
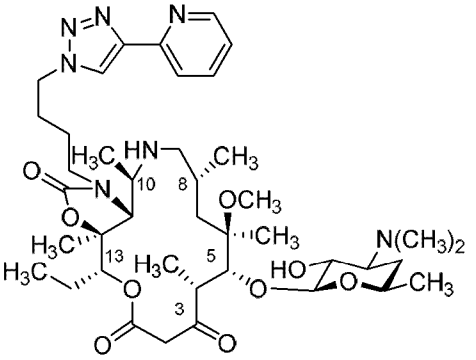
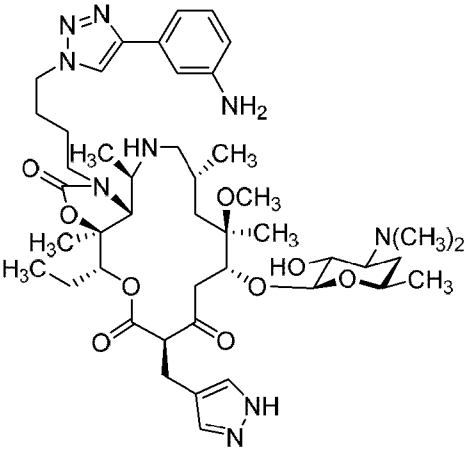
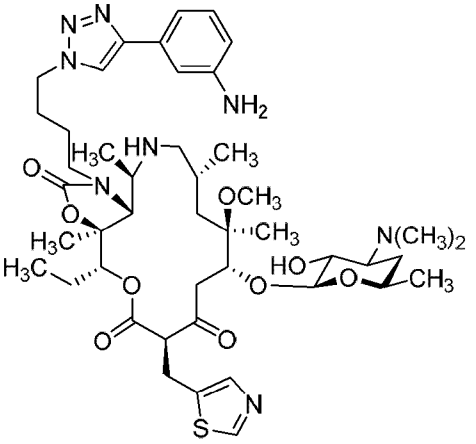
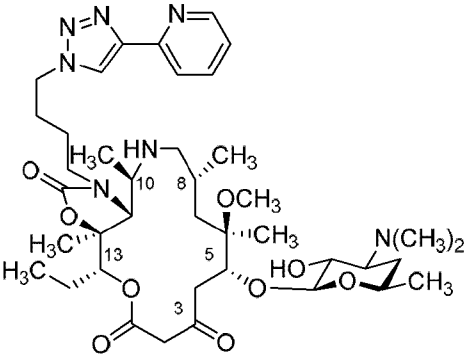
Date Reçue/Date Received 2021-01-08

 **FSM-20717a**	 **FSM-20721a**
 **FSM-20718a**	 **FSM-20722a**
 **FSM-20705a**	 **FSM-20797a**

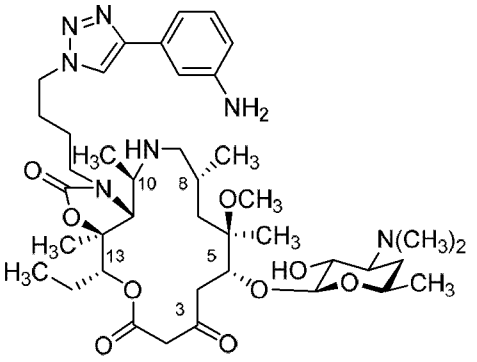
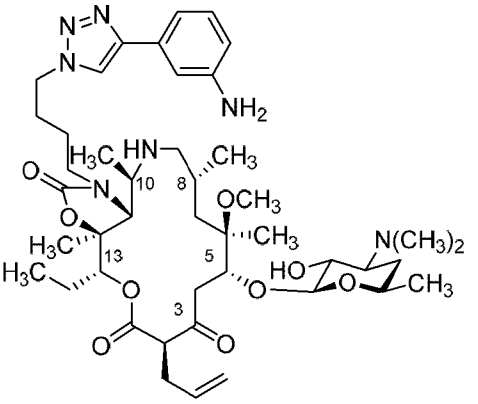
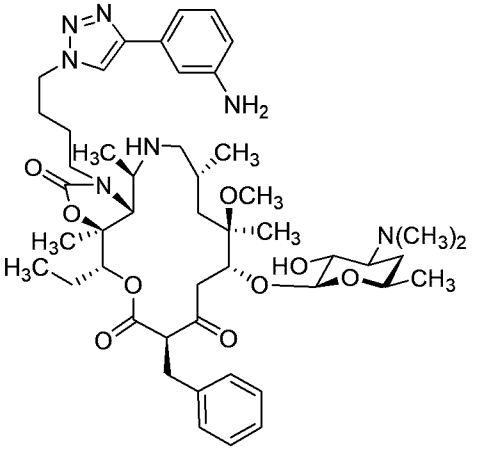
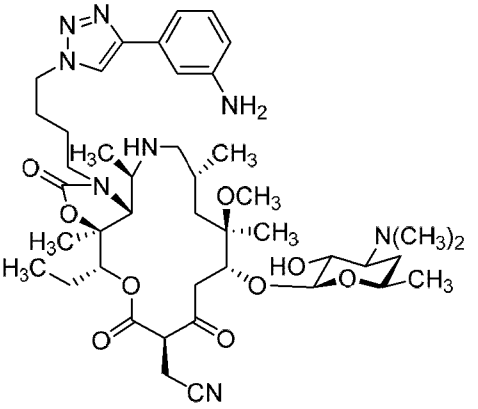
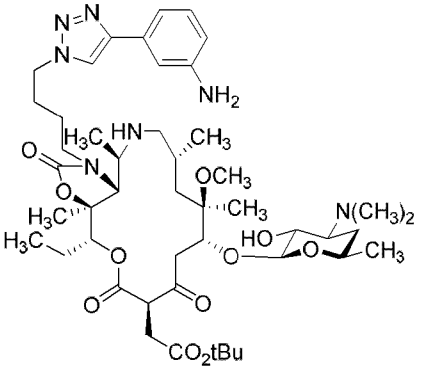
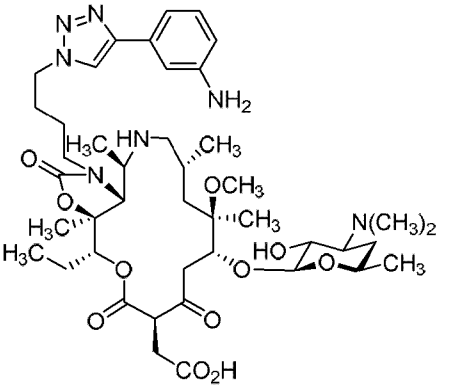
Date Reçue/Date Received 2021-01-08

 **FSM-56133**	 **FSM-56156**
 **FSM-56158**	 **FSM-56160**
 **FSM-56178**	 **FSM-56185**

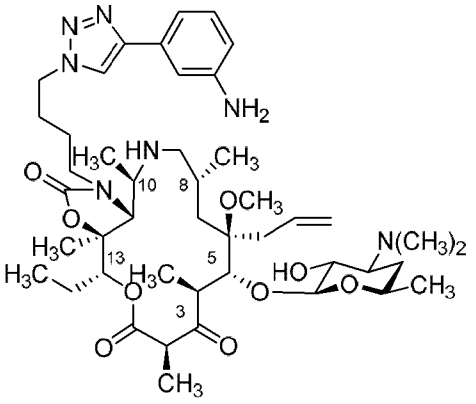
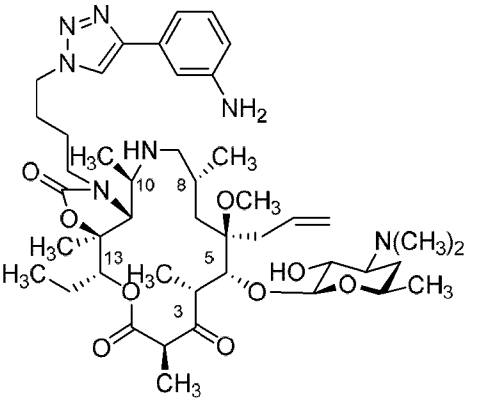
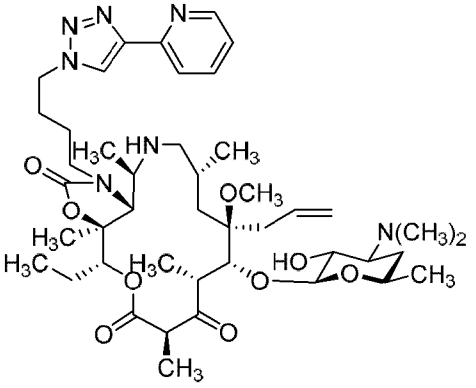
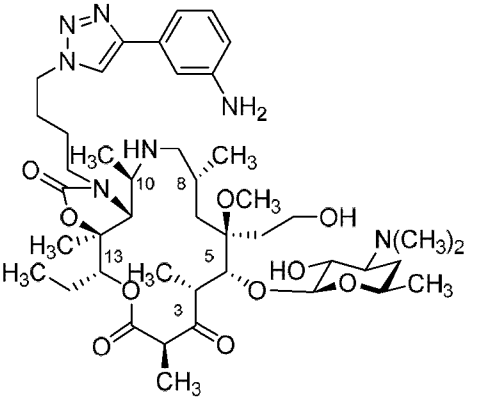
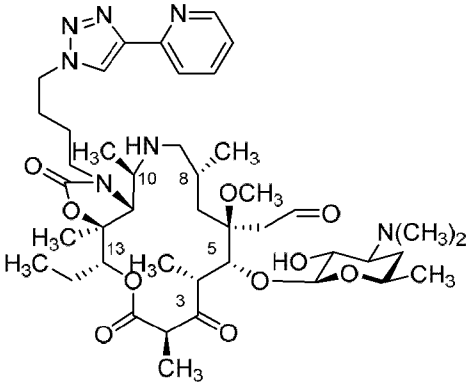
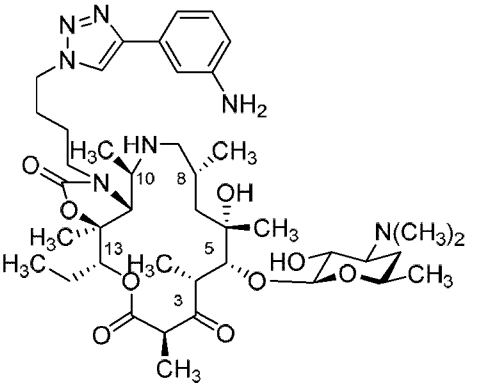
Date Reçue/Date Received 2021-01-08

 **FSM-56192**	 **FSM-56216**
 **FSM-56139**	 **FSM-56192a**
 **FSM-56216a**	 **FSM-56139a**

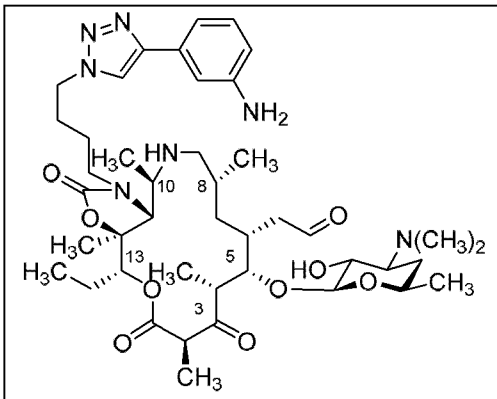
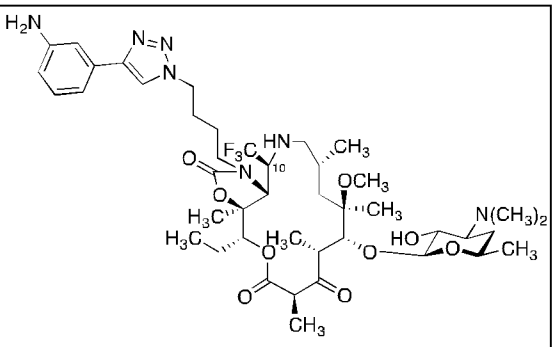
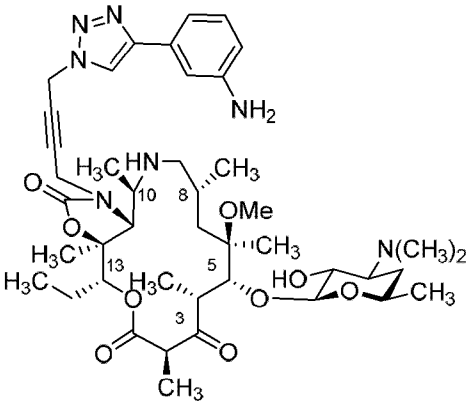
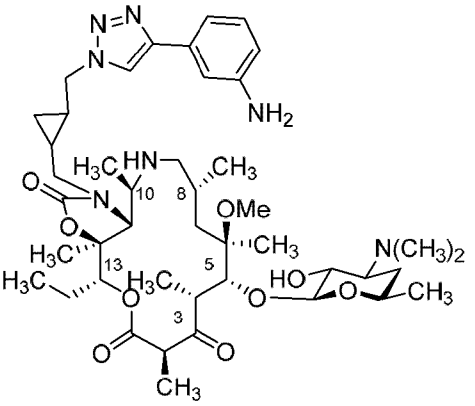
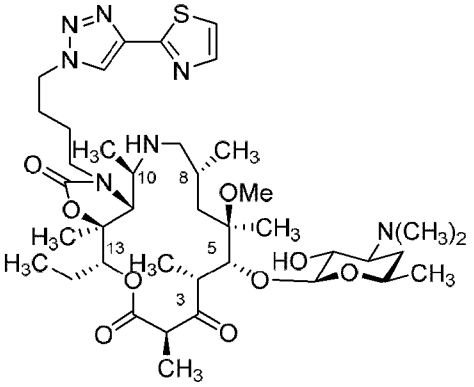
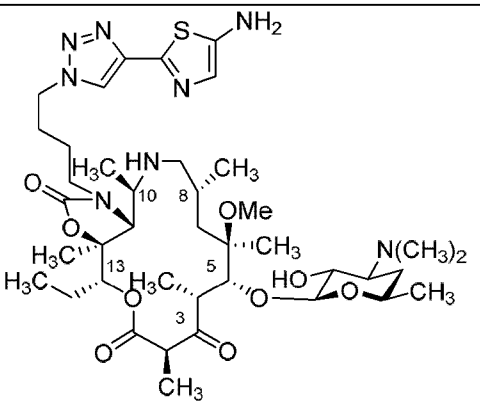
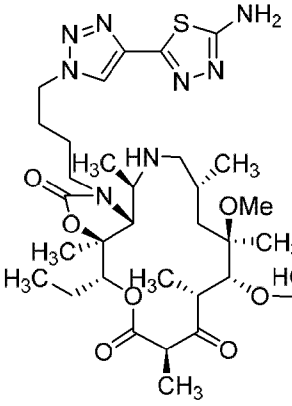
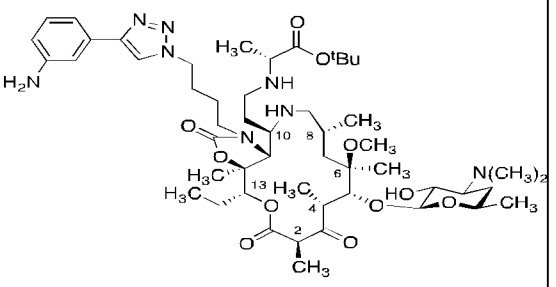
Date Reçue/Date Received 2021-01-08

 **FSM-56133a**	 **FSM-56156a**
 **FSM-56158a**	 **FSM-56160a**
 **FSM-56178a**	 **FSM-56185a**

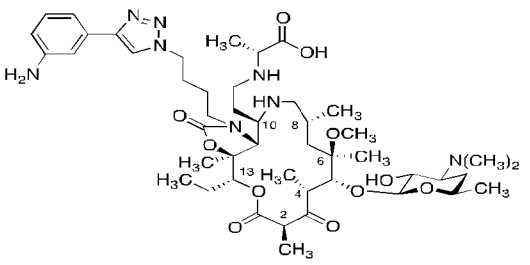
Date Reçue/Date Received 2021-01-08

 **FSM-21368**	 **FSM-21367**
 **FSM-21423**	 **FSM-21422**
 **FSM-21428**	

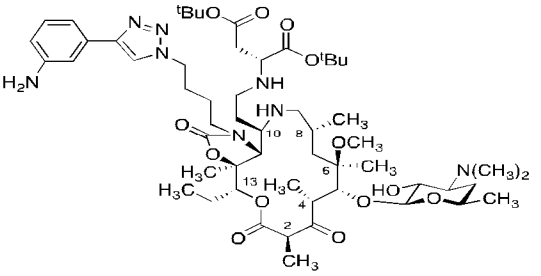
Date Reçue/Date Received 2021-01-08

	 **FSM-60546**
	
	
	 **FSM-11238**

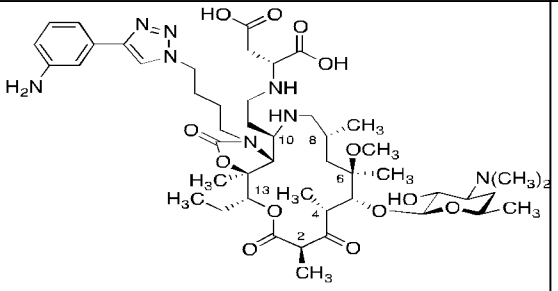
Date Reçue/Date Received 2021-01-08



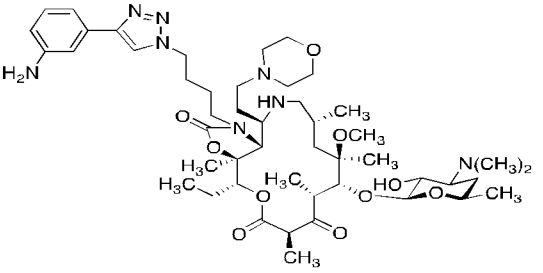
FSM-11258



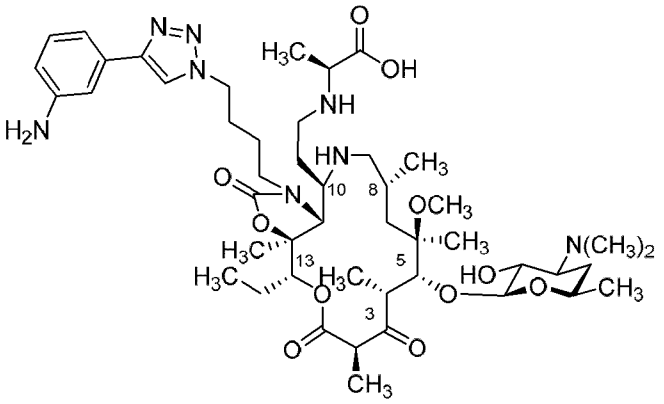
FSM-11252

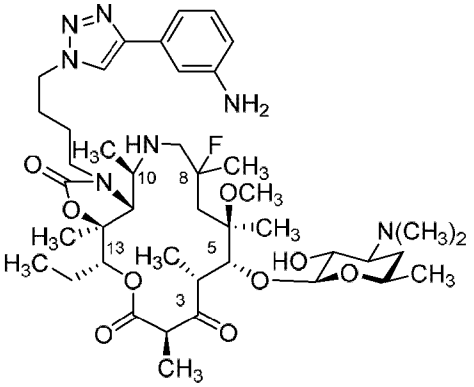


FSM-11259

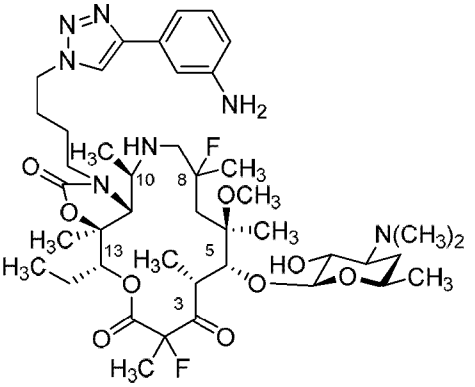


FSM-11253



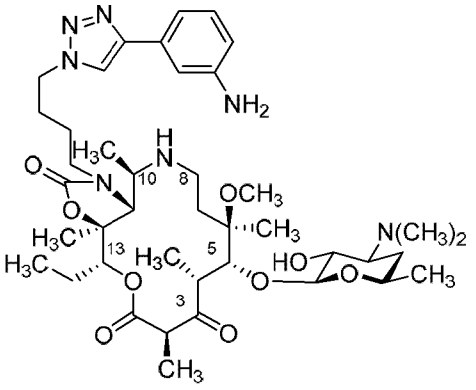
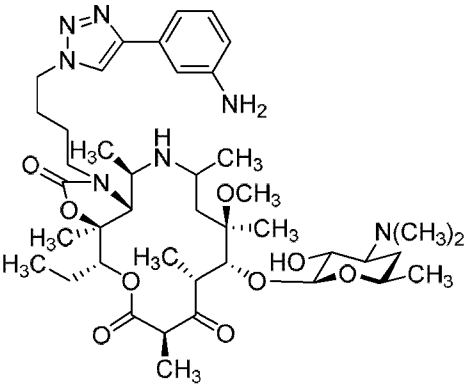
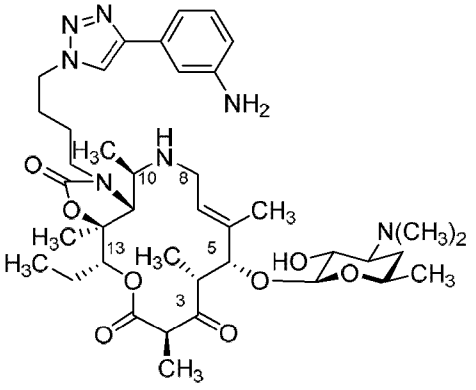
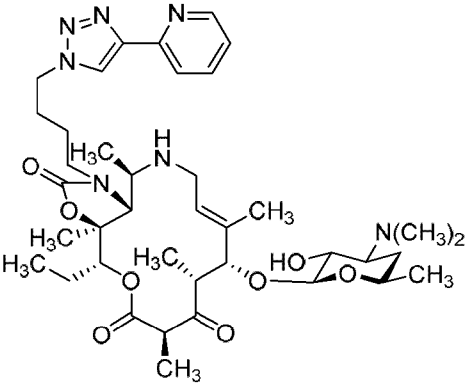
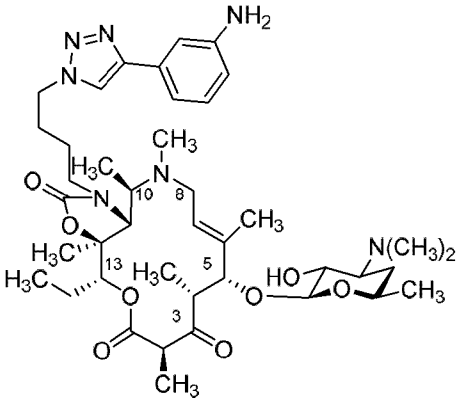
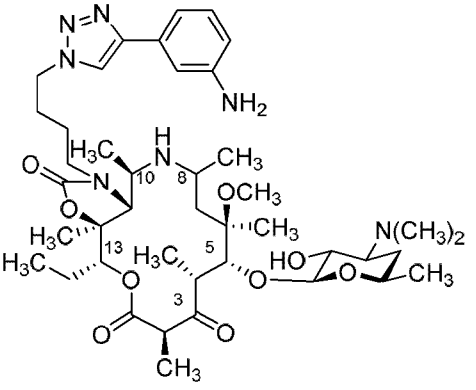


FSM-30686

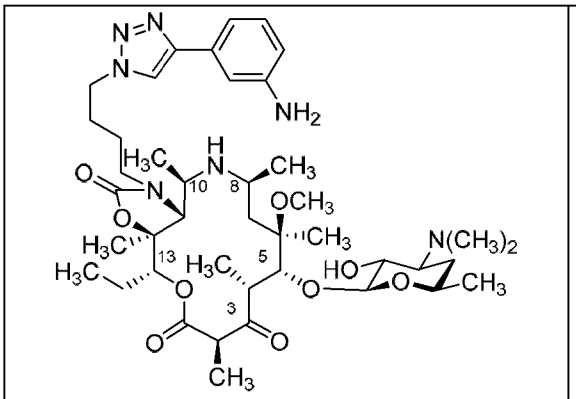


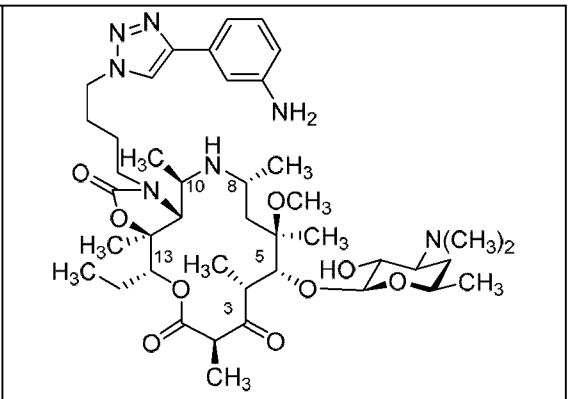
FSM-30704

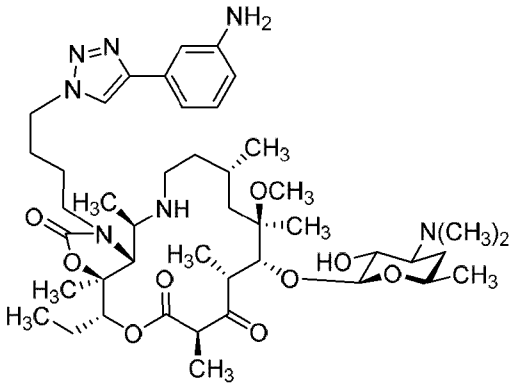
Date Reçue/Date Received 2021-01-08

 **FSM-30622**	 **FSM-30690**
 **FSM-30624**	 **FSM-30625**
 **FSM-30633**	 **FSM-30689**

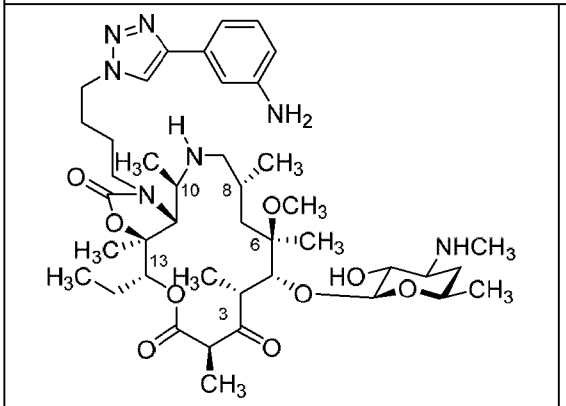
Date Reçue/Date Received 2021-01-08

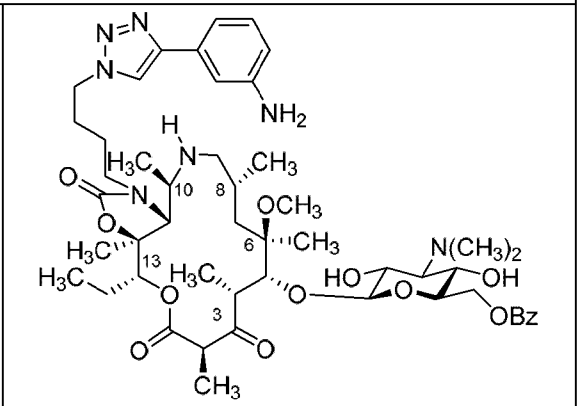




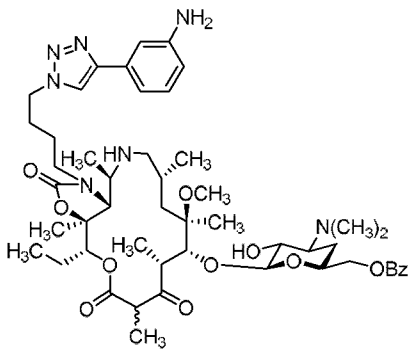


FSM-21397





Date Reçue/Date Received 2021-01-08



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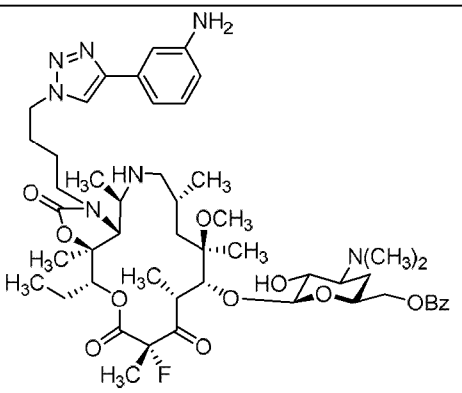

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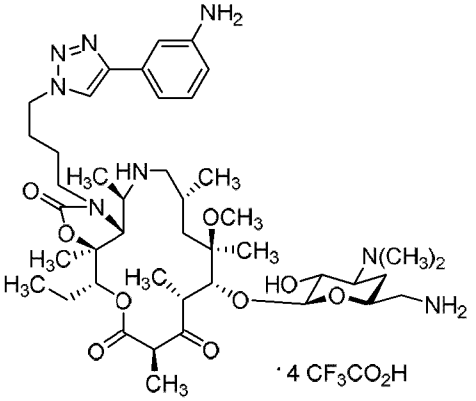
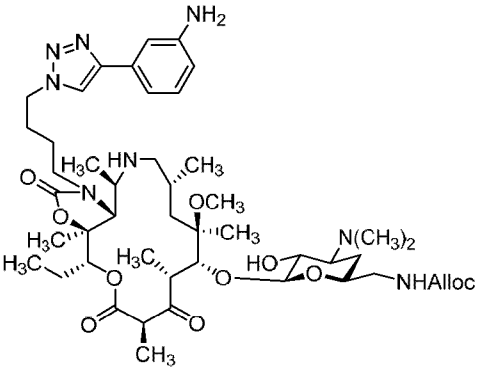
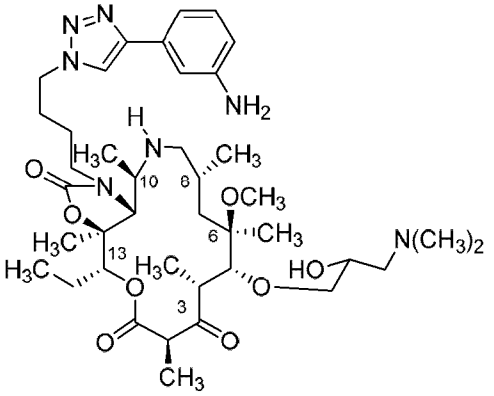


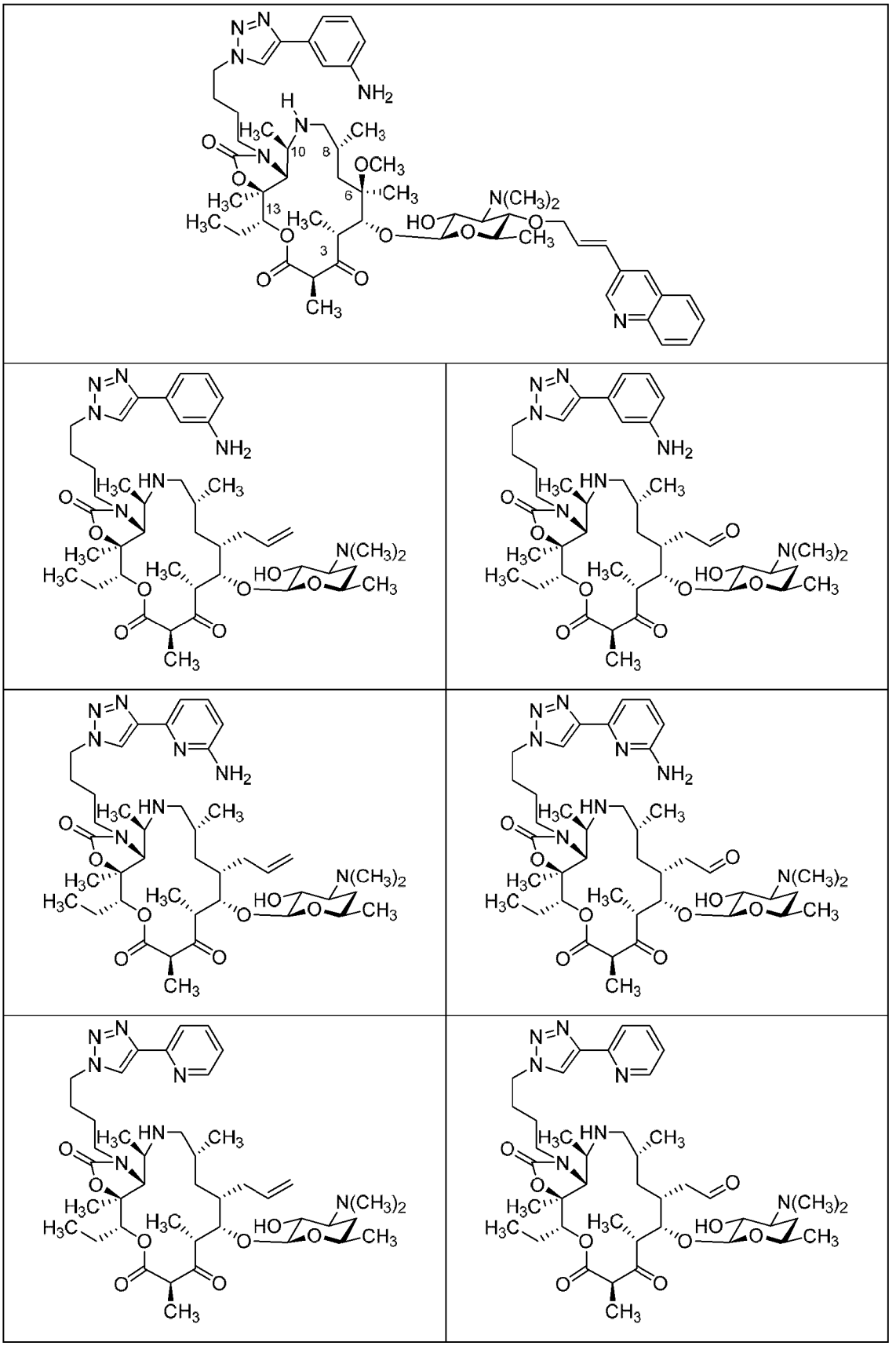
FSM-21700



FSM-21795



Date Reçue/Date Received 2021-01-08



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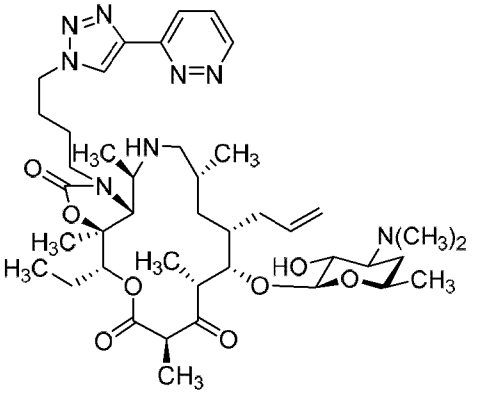
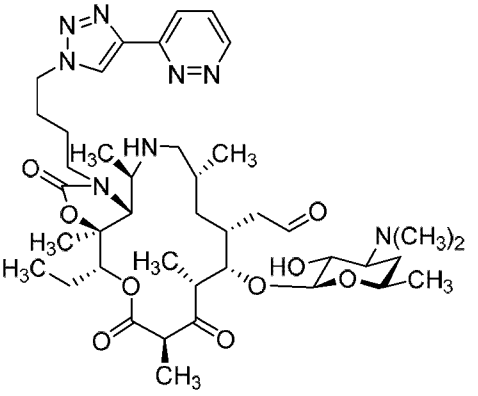
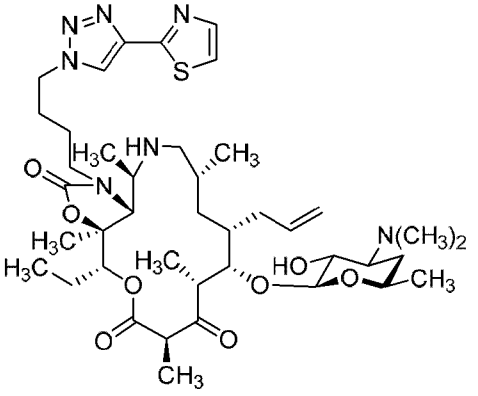
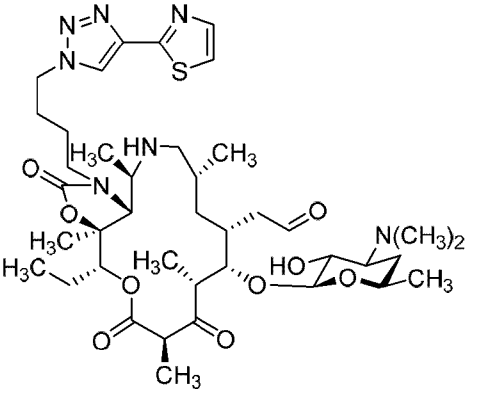
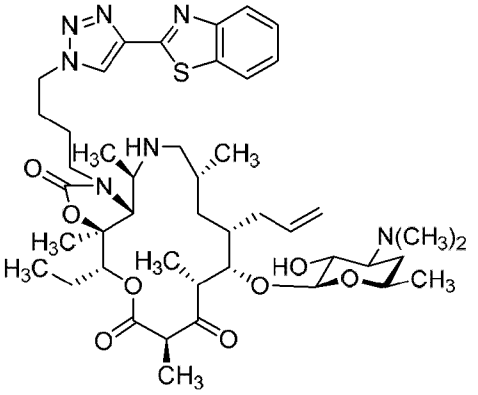
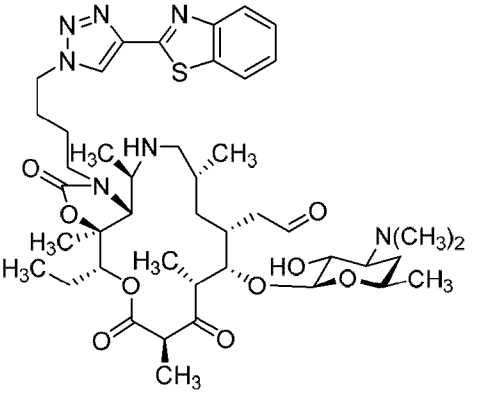


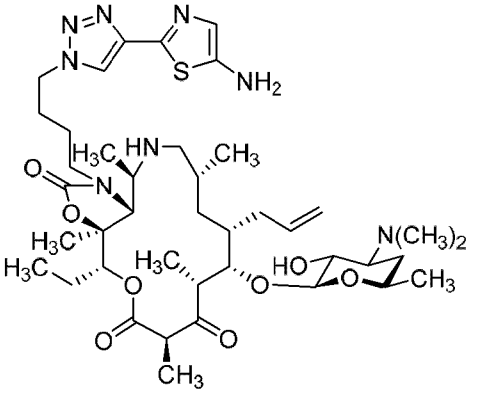


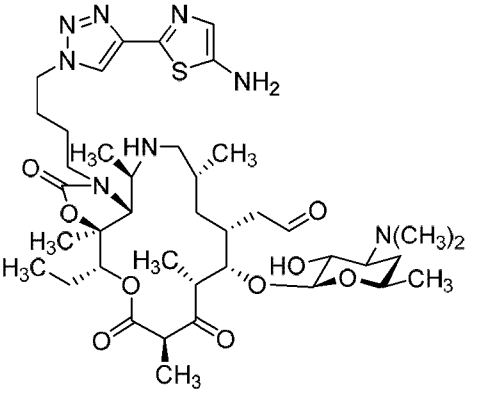




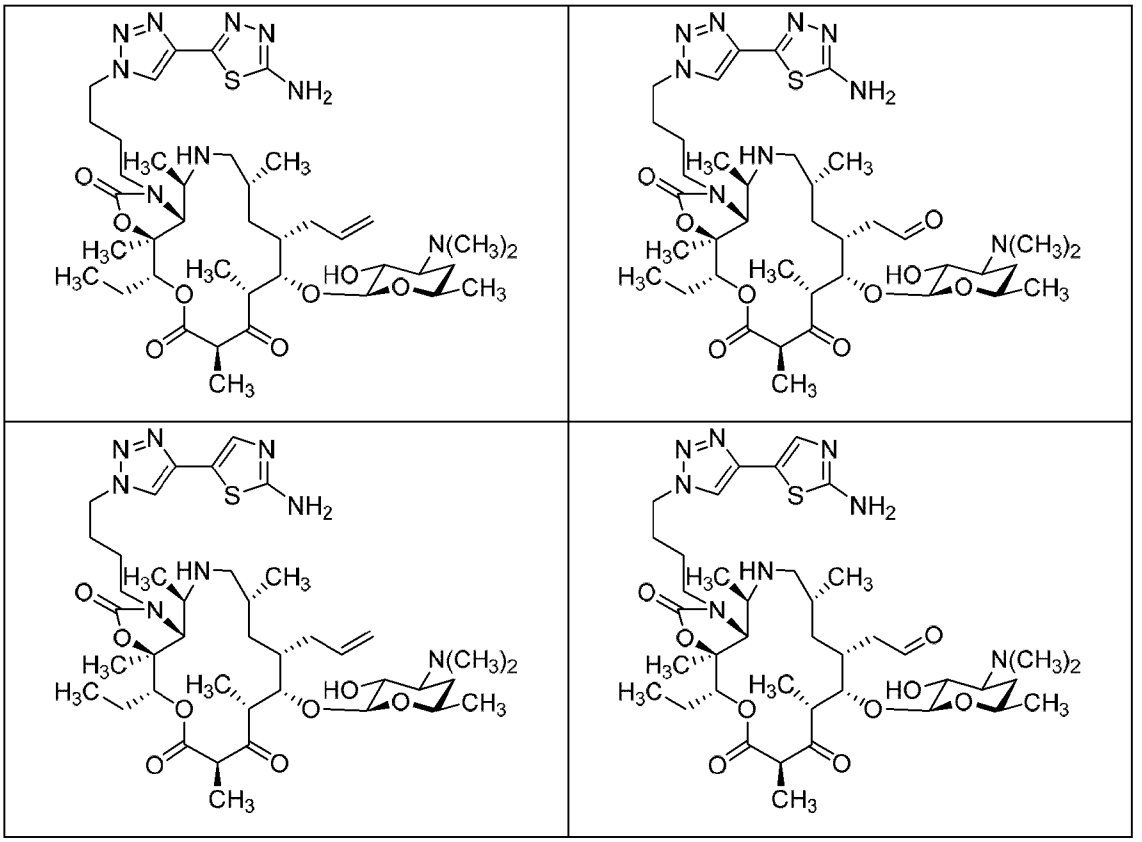








Date Reçue/Date Received 2021-01-08



or salt thereof.

56. A pharmaceutical composition comprising a compound of any one of claims 1-55, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

57. Use of a compound of any one of claims 1-55, or pharmaceutically acceptable salt thereof, for treatment of an infectious disease, wherein the compound or pharmaceutically acceptable salt thereof is for administration to a subject in need thereof.

58. The use of claim 57, wherein the infectious disease is a bacterial infection.

59. The use of claim 58, wherein the bacterial infection is an infection with a Gram positive bacteria.

Date Reçue/Date Received 2021-01-08

60. The use of claim 58, wherein the bacterial infection is an infection with a Gram negative bacteria.

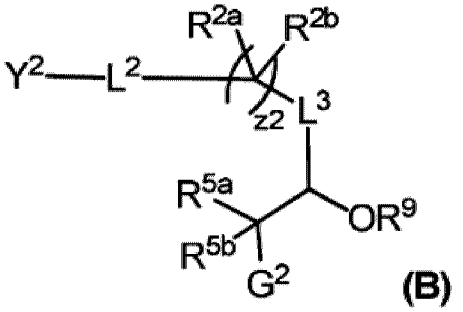
61. The use of claim 58, wherein the bacterial infection is a *Staphylococcus* infection, a *Bacillus* infection, a *Strepococcus* infection, an *Escherichia* infection, or a *Haemophilus* infection.

62. The use of claim 57, wherein the infectious disease is a parasitic infection.

63. Use of a compound of any one of claims 1-55, or a pharmaceutically acceptable salt thereof, for treatment of an inflammatory condition in a subject in need thereof.

64. The use of claim 63, wherein the inflammatory condition is a chronic pulmonary inflammatory syndrome.

65. A compound of formula:



(B)

or a salt thereof;

wherein:

Y^2 is $-Z^4H$, $-CH_2NO_2$, a leaving group (LG), $-C(=O)R^{Z3}$, $-C(=O)OR^{Z3}$, $-C(=O)LG$, $-C(=O)\text{-}CH=P(R^{P1})(R^{P2})(R^{P3})$, or $-C(=O)\text{-}CH_2\text{-}P(O)(OR^{P2})(OR^{P3})$;

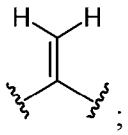
Z^4 is –O–, –S–, or $-NR^{Z2}-$,

R^{P1}, R^{P2}, and R^{P3} are each independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocycyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

L^2 is a bond or $-CH_2-$;

z2 is 0, 1, or 2;

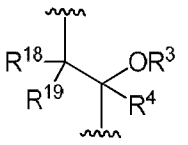
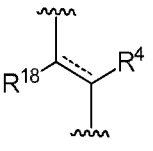
Date Reçue/Date Received 2021-01-08

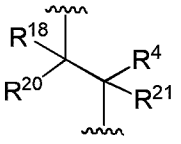
each instance of R^{2a}, and R^{2b} is independently hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or wherein R^{2a} and R^{2b} can be taken together to form  ;

each instance of R^{Z2} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, or a nitrogen protecting group, or two R^{Z2} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring;

R^{Z3} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl;

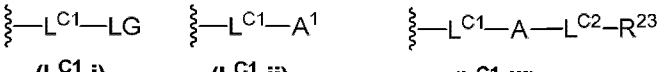
L^3 is a group of formula:

 **(L^3-i)**,  **(L^3-ii)**,

 or **(L^3-iii)**;

====== represents a single or double bond;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a group of formula:



(L^{C1}-i), **(L^{C1}-ii)**, or **(L^{C1}-iii)**;

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Date Reçue/Date Received 2021-01-08

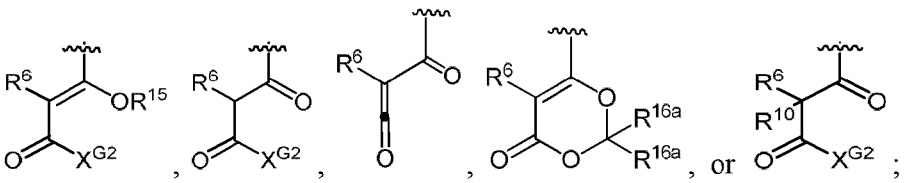
each instance of R^{18} and R^{19} independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of R^{20} and R^{21} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, or carbonyl, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring;

each instance of R^{5a} and R^{5b} is independently hydrogen, halogen, silyl, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^9 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $–C(=O)R^{Z8}$, $–C(=O)OR^{Z8}$, $–C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a carbohydrate;

G^2 is a group of formula:



R^6 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

R^{10} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

each instance of X^{G2} is $–OR^{15}$, $–SR^{15}$, or $–N(R^{15})_2$;

each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted

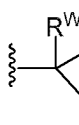
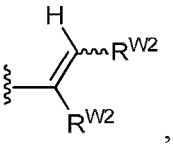
Date Reçue/Date Received 2021-01-08

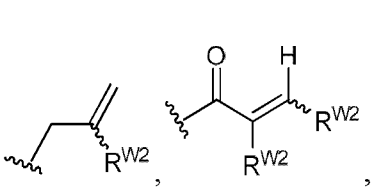
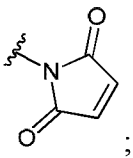
heteroaryl, or two R^{15} groups can be taken together to form an optionally substituted heteroaryl or heterocyclic ring; and

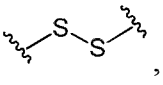
each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

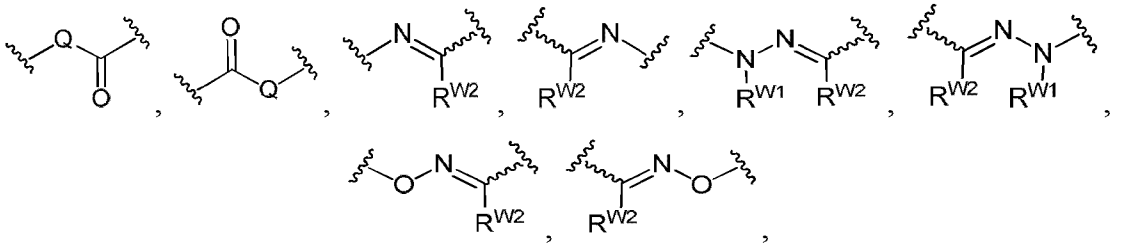
each instance of L^{C1} and L^{C2} is independently a bond, optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, or combinations thereof;

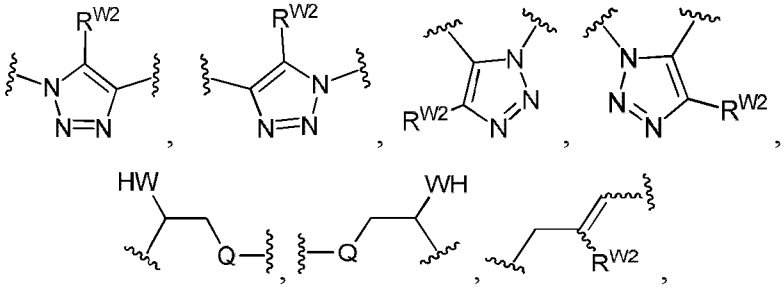
each instance of A^1 is independently a leaving group (LG), –SH, –OH, $–NH_2$, –NH–

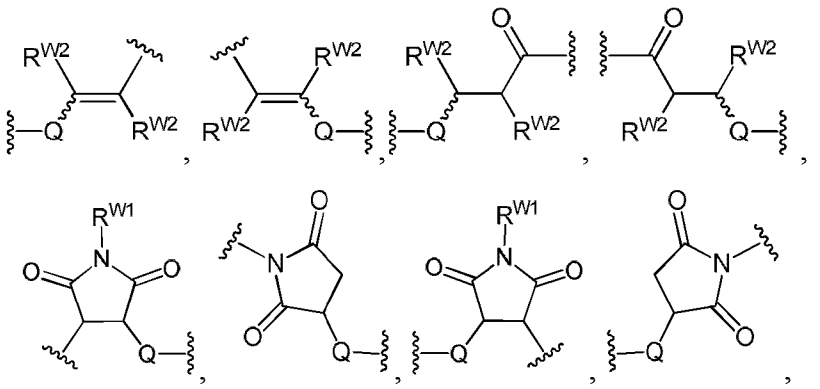
NH_2, $–N_3$, $–O–NH_2$, $–C(=O)R^{X1}$,  ,  ,  ,  ,

 , or  ;

A is –NH–, –NH–NH–, –NH–O–, –O–NH–, –S–, –O–,  ,







optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; or a nitrogen protecting group;

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; or optionally substituted heteroaryl, or two R^{W2} groups are joined to form an optionally substituted cyclic moiety;

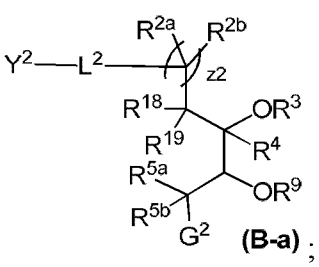
R^{X1} is hydrogen, halogen, or $–OR^{X2}$, wherein R^{X2} is hydrogen; optionally substituted alkyl; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or an oxygen protecting group;

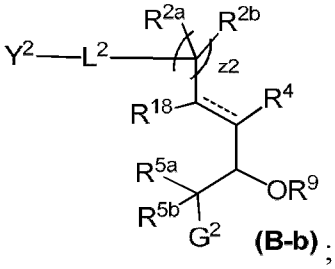
R^{23} is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; or optionally substituted heteroaryl; and

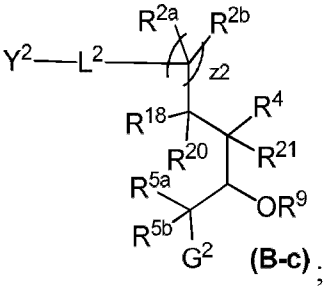
each instance of R^{Z8} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^{Z8} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring.

Date Reçue/Date Received 2021-01-08

66. The compound of claim 65, wherein the compound is of formula

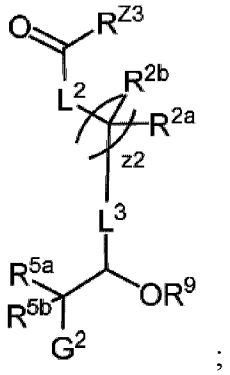

(B-a);


(B-b); or


(B-c);

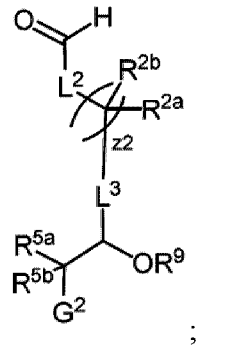
or a salt thereof.

67. The compound of claim 65 or 66, wherein the compound is of formula


;

or a salt thereof.

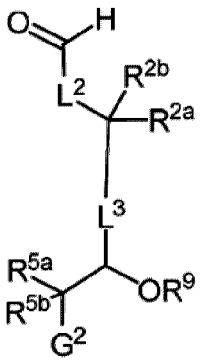
68. The compound of any one of claims 65-67, wherein the compound is of formula


;

or a salt thereof.

Date Reçue/Date Received 2021-01-08

69. The compound of any one of claims 65-68, wherein the compound is of formula



;

or a salt thereof.

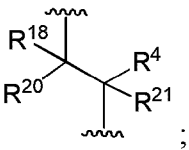
70. The compound of claim 65 or 66, or a salt thereof, wherein Y^2 is a leaving group (LG), $-C(=O)R^{Z3}$, $-C(=O)OR^{Z3}$, –C(=O)LG, $-C(=O)\text{-}CH=P(R^{P1})(R^{P2})(R^{P3})$, or $-C(=O)\text{-}CH_2\text{-}P(O)(OR^{P2})(OR^{P3})$.

71. The compound of any one of claims 65, 66 or 70, or a salt thereof, wherein Y^2 is $-C(=O)\text{-}CH=P(R^{P1})(R^{P2})(R^{P3})$ or $-C(=O)\text{-}CH_2\text{-}P(O)(OR^{P2})(OR^{P3})$.

72. The compound of any one of claims 65-68 or 70 or a salt thereof, wherein Y^2 is $-C(=O)R^{Z3}$.

73. The compound of any one of claims 65-70 or 72, or a salt thereof, wherein Y^2 is $-C(=O)R^{Z3}$, and R^{Z3} is hydrogen.

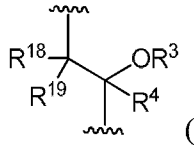
74. The compound of any one of claims 65-73, or a salt thereof, wherein L^3 is a group of formula:



; and R^{21} is hydrogen.

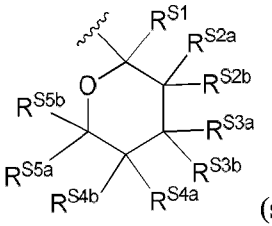
Date Reçue/Date Received 2021-01-08

75. The compound of any one of claims 65-73, or a salt thereof, wherein L^3 is a group of formula:



(L^3-i).

76. The compound of any one of claims 65-75, or a salt thereof, wherein R^9 is a group of formula:



(s–1)

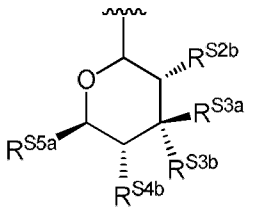
wherein:

each of R^{S1}, R^{S2a}, R^{S2b}, R^{S3a}, R^{S3b}, R^{S4a}, R^{S4b}, R^{S5a}, and R^{S5b} is independently hydrogen, optionally substituted alkyl, $–OR^{SO}$, or $–N(R^{SN})_2$, or wherein R^{S2a} or R^{S2b} may be taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused heterocyclic ring;

each instance of R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group; and

each instance of R^{SN} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; or optionally two R^{SN} are taken with the intervening atoms to form a heterocyclic ring.

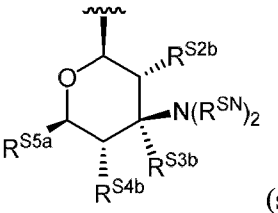
77. The compound of any one of claims 65-76, or a salt thereof, wherein R^9 is a group of formula:



(s–2).

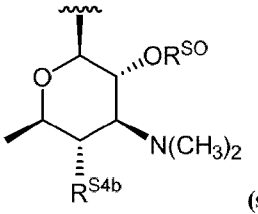
Date Reçue/Date Received 2021-01-08

78. The compound of any one of claims 65-77, or a salt thereof, wherein R^9 is a group of formula:



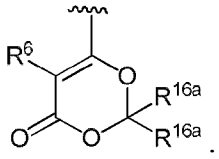
(s–2a).

79. The compound of any one of claims 65-78, or a salt thereof, wherein R^9 is a group of formula:



(s–2a–i).

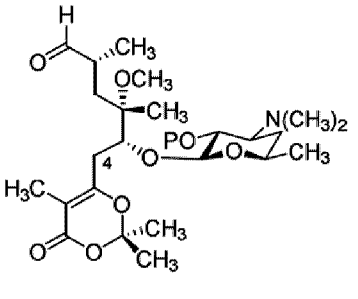
80. The compound of any one of claims 65-79, or a salt thereof, wherein G^2 is a group of formula:



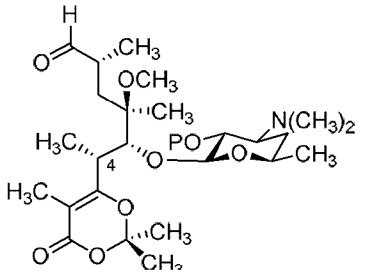
.

81. The compound of any one of claims 65-80, or a salt thereof, wherein each instance of R^{16a} is independently optionally substituted alkyl.

82. The compound of any one of claims 65-69, wherein the compound is of formula:

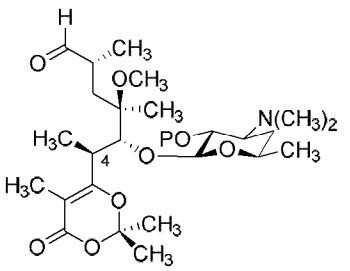
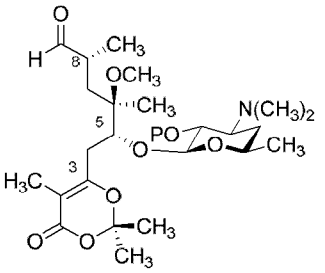


;



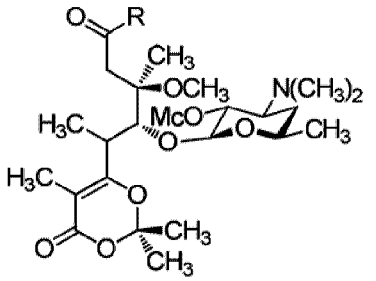
;

Date Reçue/Date Received 2021-01-08


; or 
;

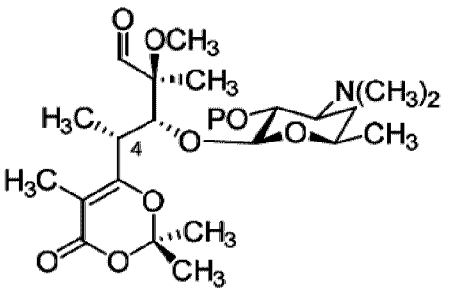
or a salt thereof, wherein P is an oxygen protecting group.

83. The compound of any one of claims 65-67, wherein the compound is of formula:


;

or a salt thereof, wherein R is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl.

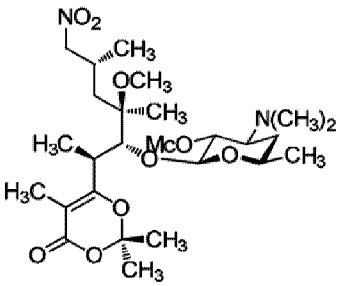
84. The compound of any one of claims 65-69, wherein the compound is of formula:


;

or a salt thereof, wherein P is an oxygen protecting group.

Date Reçue/Date Received 2021-01-08

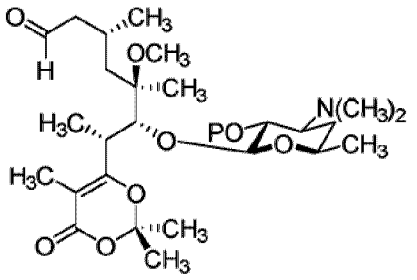
85. The compound of claim 65 or 66, wherein the compound is of formula:



;

or a salt thereof.

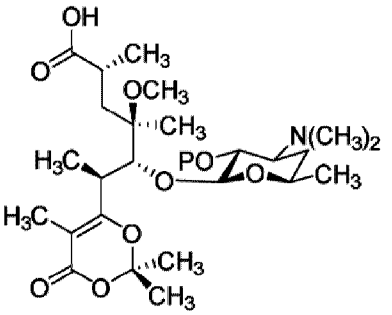
86. The compound of any one of claims 65-69, wherein the compound is of formula:



;

or a salt thereof, wherein P is an oxygen protecting group.

87. The compound of claim 65 or 66, wherein the compound is of formula:

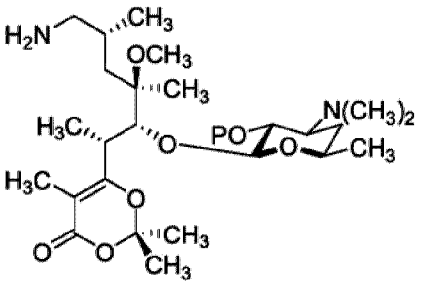


;

or a salt thereof, wherein P is an oxygen protecting group.

Date Reçue/Date Received 2021-01-08

88. The compound of claim 65 or 66, wherein the compound is of formula:



;

or a salt thereof, wherein P is an oxygen protecting group.

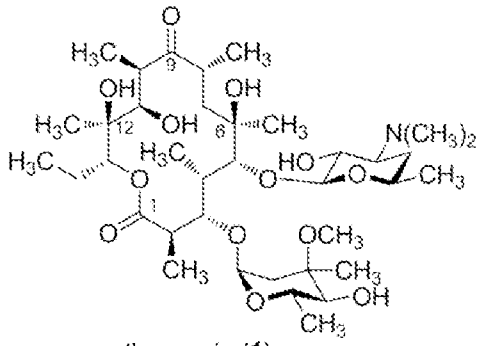
89. The compound of any one of claims 82, 84, or 86-88, or a salt thereof, wherein P is methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, *t*–butyl, allyl, *p*–chlorophenyl, *p*–methoxyphenyl, 2,4–dinitrophenyl, benzyl (Bn), *p*–methoxybenzyl, 3,4–dimethoxybenzyl, *o*–nitrobenzyl, *p*–nitrobenzyl, *p*–halobenzyl, 2,6–dichlorobenzyl, *p*–cyanobenzyl, *p*–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl *N*–oxido, diphenylmethyl, *p,p'*–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, *p*–methoxyphenyldiphenylmethyl, di(*p*–methoxyphenyl)phenylmethyl, tri(*p*–methoxyphenyl)methyl, 4–(4'–bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4′,4″–tris(levulinoyloxyphenyl)methyl, 4,4′,4″–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4′,4″–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1′–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–

Date Reçue/Date Received 2021-01-08

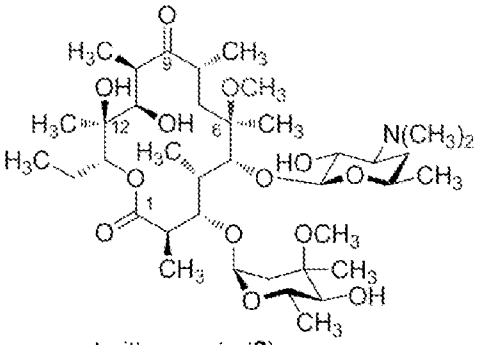
10–oxo)anthryl, 1,3–benzodithiolan–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*–butyldimethylsilyl (TBDMS), *t*–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–*p*–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, *p*–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *t*–butyl carbonate (BOC), *p*–nitrophenyl carbonate, benzyl carbonate, *p*–methoxybenzyl carbonate, 3,4–dimethoxybenzyl carbonate, *o*–nitrobenzyl carbonate, *p*–nitrobenzyl carbonate, *S*–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, *o*–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)–2–methyl–2–butenoate, *o*–(methoxyacyl)benzoate, α–naphthoate, nitrate, alkyl *N,N,N',N'*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, or tosylate (Ts).

90. The compound of any one of claims 82, 84, or 86-89, or a salt thereof, wherein P is methyl carbonate.

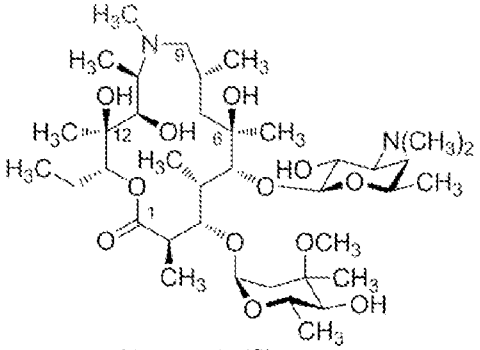
Date Reçue/Date Received 2021-01-08



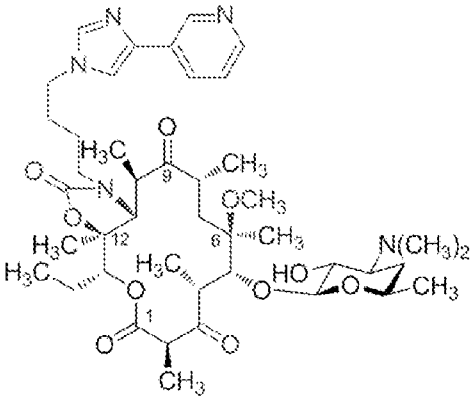
erythromycin (**1**)
14-membered macrolide
Preparation: **fermentation** from *S. erythraea*
US FDA Approval: **1952**



clarithromycin (**2**)
14-membered macrolide
semi-synthesis: 6 steps from erythromycin
1991

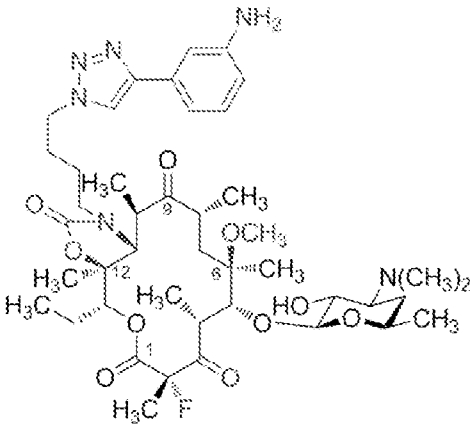


azithromycin (**3**)
15-membered azalide
semi-synthesis: 4 steps from erythromycin
1991

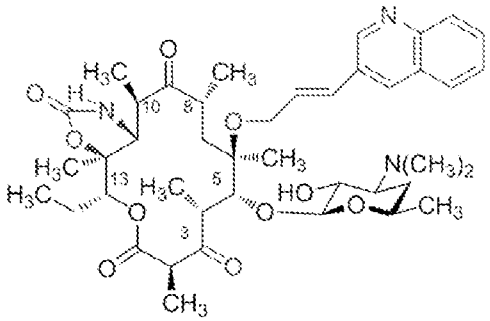


telithromycin (**4**)
14-membered ketolide
semi-synthesis: 12 steps from erythromycin
2004

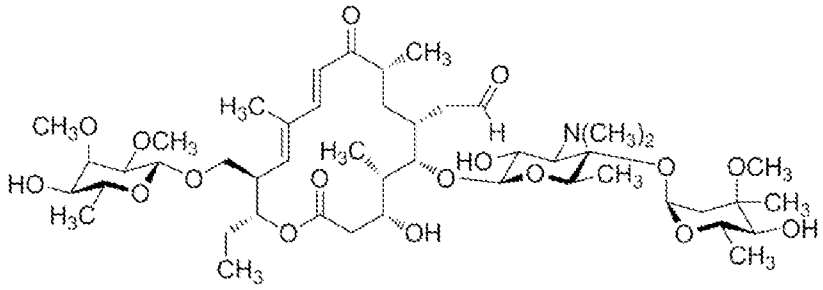
Figure 1



solithromycin (**5**)
14-membered ketolide
semi-synthesis: 16 steps from erythromycin
(Clinic Phase II)



cethromycin (**7**)
14-membered ketolide
(Clinic Phase III)



tylosin (**6**)
16-membered macrolide
fermentation from *S. fradiae*
(veterinary medicine)

Figure 1
(continued)

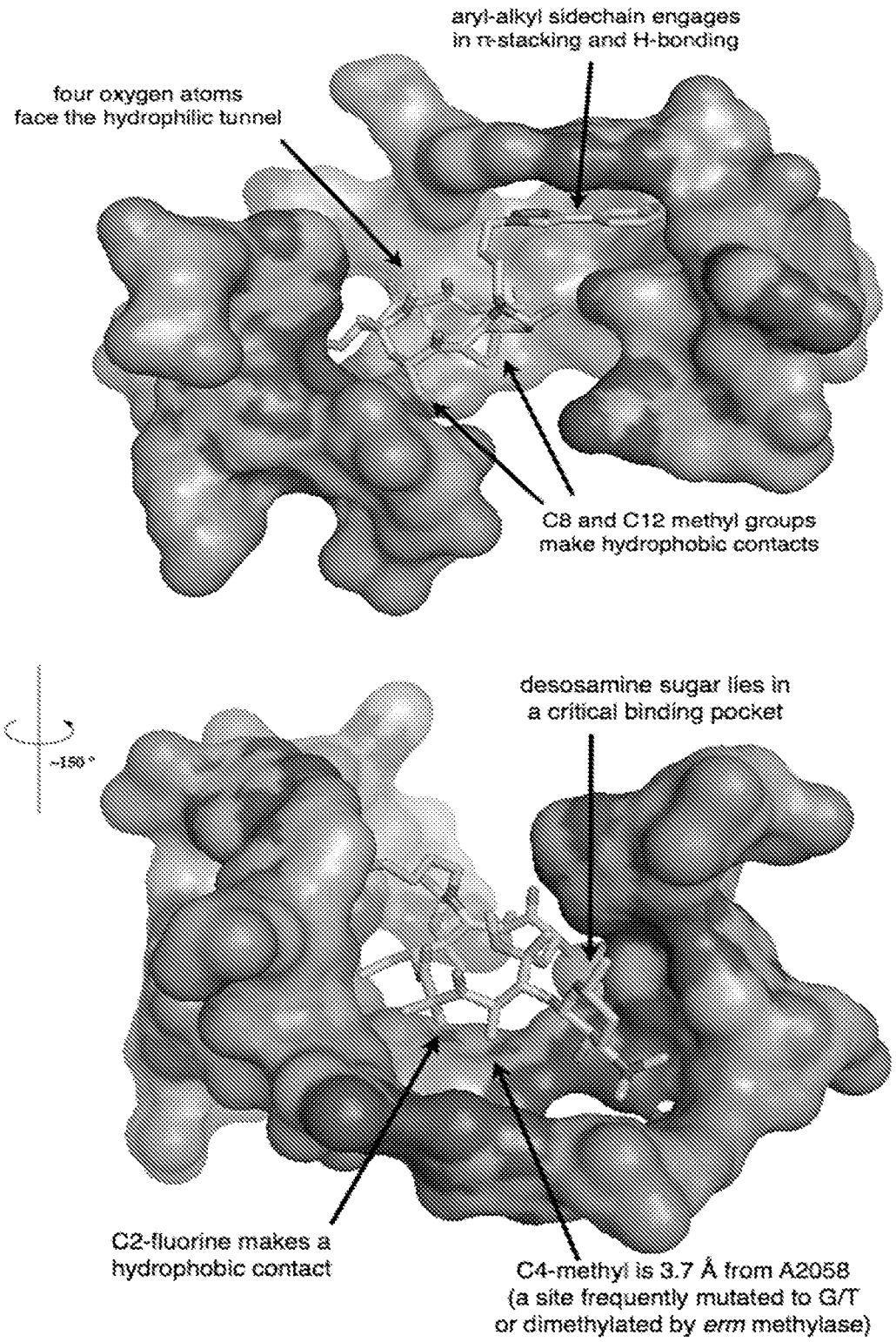
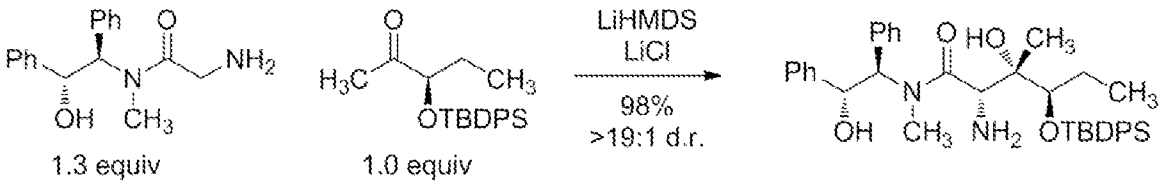
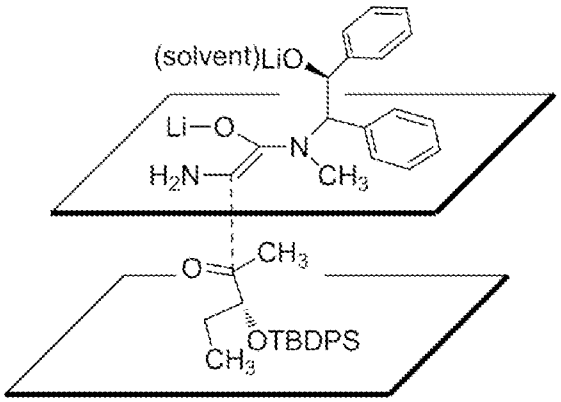

aryl-alkyl sidechain engages
in π-stacking and H-bonding
four oxygen atoms
face the hydrophilic tunnel
C8 and C12 methyl groups
make hydrophobic contacts
~150°
desosamine sugar lies in
a critical binding pocket
C2-fluorine makes a
hydrophobic contact
C4-methyl is 3.7 Å from A2058
(a site frequently mutated to G/T
or dimethylated by *erm* methylase)

Figure 2



Pseudoephenamine and Zimmerman Traxler:



Felkin-Ahn:

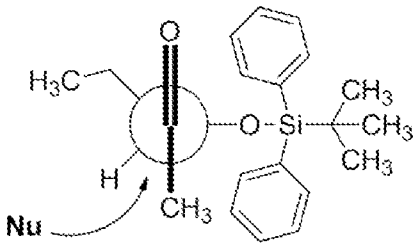


Figure 3