



(22) Date de dépôt/Filing Date: 2001/01/29  
(41) Mise à la disp. pub./Open to Public Insp.: 2001/07/31  
(30) Priorité/Priority: 2000/01/31 (60/179,324) US

(51) Cl.Int.<sup>7</sup>/Int.Cl.<sup>7</sup> C07H 17/00, A61K 31/7052,  
A61K 31/7048, A61P 31/04, A61K 38/04, A61P 33/02,  
C07K 5/04

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(54) Titre : MACROLIDES ANTIBACTERIENS ET PRO-CINETIQUES NOUVEAUX A 13 ET A 14 ATOMES ET LEURS INTERMEDIAIRES

(54) Title: NOVEL 13 AND 14-MEMBERED ANTIBACTERIAL AND PROKINETIC MACROLIDES AND THEIR INTERMEDIATES

(57) **Abrégé/Abstract:**

This invention relates to novel 13 and 14-membered erythromycin derivatives useful as antibacterial, antiprotozoal and/or prokinetic, and to intermediates that are useful in the preparation of said compounds. The active compounds of the present invention are antibacterial and antiprotozoal agents that may be used to treat various bacterial and protozoal infections and disorders related to such infections. The invention also relates to pharmaceutical compositions containing the compounds of the present invention and to methods of treating bacterial and protozoal infections by administering said compounds.



Abstract

This invention relates to novel 13 and 14-membered erythromycin derivatives useful as antibacterial, antiprotozoal and/or prokinetic, and to intermediates that are useful in the preparation of said compounds. The active compounds of the present invention are  
5 antibacterial and antiprotozoal agents that may be used to treat various bacterial and protozoal infections and disorders related to such infections. The invention also relates to pharmaceutical compositions containing the compounds of the present invention and to methods of treating bacterial and protozoal infections by administering said compounds.

NOVEL 13 AND 14-MEMBERED ANTIBACTERIAL AND PROKINETIC  
MACROLIDES AND THEIR INTERMEDIATES

Background Of The Invention

5 This invention relates to novel macrolide compounds that are useful as antibacterial, antiprotozoal and/or prokinetic agents in mammals, including man, as well as in fish and birds. This invention also relates to pharmaceutical compositions containing the novel compounds and to methods of treating bacterial and protozoal infections and gastrointestinal disorders in mammals, fish and birds by administering the novel compounds to mammals, fish and birds requiring such treatment.

10 Macrolides are known to be useful in the treatment of a broad spectrum of bacterial and protozoal infections in mammals, fish and birds. Such antibiotics include various derivatives of erythromycin A such as azithromycin which is commercially available and is referred to in United States patents 4,474,768 and 4,517,359, both of which are incorporated herein by reference in their entirety. Other macrolide antibiotics are disclosed and claimed in  
15 PCT international application number PCT/IB98/00741, filed May 15, which designates the United States, and United States Patent 5,527,780, issued June 18, 1996, each of which are incorporated herein by reference in their entirety. Like azithromycin and other macrolide antibiotics, the novel macrolide compounds of the present invention possess activity against various bacterial and protozoal infections as described below.

20 Macrolides are also known to be useful as prokinetic agents in the treatment of gastrointestinal disorders. Prokinetic agents (also called motility-enhancing agents) are compounds that induce gastrointestinal smooth muscle contractions, both in vitro and in vivo. These agents include agonists of motilin, a 22-amino-acid polypeptide that causes increased motility of several portions of the gut. For an overview of the clinical development of erythromycin derivatives with prokinetic activity, see R. Faghih et al., Drugs of the Future,  
25 23(8):861-872 (1998).

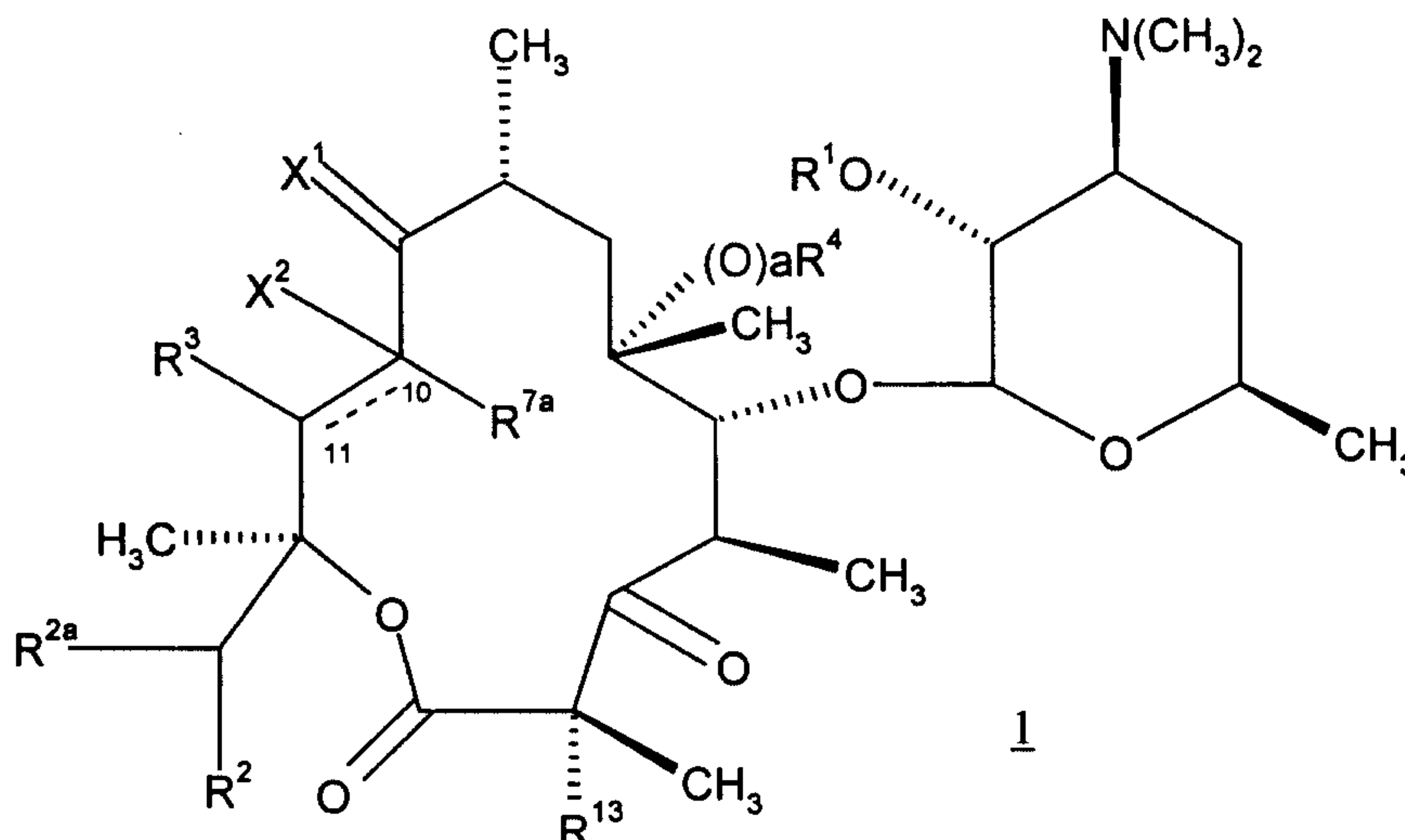
Defects in the normal gastrointestinal motility pattern can lead to the development of painful, debilitating and chronic disorders. Examples of these disorders include gastroesophageal reflux disease, delayed gastric emptying, diabetic gastroparesis, pediatric  
30 gastroparesis, anorexia, gall bladder stasis, postoperative paralytic ileus, systemic sclerosis, chronic constipation (colonic inertia), emesis, gastritis, and intestinal pseudoobstruction. Patients suffering from intestinal pseudoobstruction, for example, suffer from constipation, colicky pain and vomiting. These patients cannot tolerate oral feedings and require total parenteral nutrition. A successful prokinetic agent could alleviate the distress associated with  
35 such disorders.

Prokinetic agents can additionally be useful in the placement of diagnostic and therapeutic instruments. For example, prokinetic agents may facilitate the insertion of enteral

feeding tubes into the proximal small intestine. In intestinal pseudoobstruction, these agents may assist in the decompression of the upper gastrointestinal tract by nasogastric tubal aspiration. Accordingly, there is a need for the development of an effective prokinetic agent.

#### Summary of the Invention

5 The present invention relates to compounds and intermediates of the formula



and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:  
the dashed line between positions 10 and 11 represents an optional double bond;  
a is 0 or 1;

10

$R^1$  is hydrogen or a hydroxy protecting group;

$R^2$  is hydrogen,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl,  $C_5$ - $C_{10}$  cycloalkenyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $(C_1$ - $C_6$  alkoxy) $C_1$ - $C_6$  alkyl,  $(C_1$ - $C_6$  alkylthio) $C_1$ - $C_6$  alkyl,  $-(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl), and  $-(CR^{10}R^{11})_m$  (4 to 10 membered heterocyclic), wherein each  $m$  is independently an integer from 0 to 6, and the foregoing  $R^2$  groups, except hydrogen, are optionally substituted by one to three  $R^8$  substituents;

15

$R^{2a}$  is  $-NH_2$ ,  $-NR^9R^{14}$ ,  $-NHC(O)R^6$ ,  $-NHC(O)OR^6$ ,  $-OR^6$ ,  $-OC(O)R^6$ ,  $-OC(O)NR^9R^{14}$  or  $R^{2b}$ ;

each  $R^{2b}$  is hydroxy, azido, cyano,  $-OCN$ ,  $-SH$  or  $-SCN$ ;

20

$R^3$  is hydrogen, hydroxy, amino,  $-OR^6$ ,  $-NHR^6$  or  $-SR^6$ ;

$R^4$  is hydrogen or  $C_1$ - $C_{10}$  alkyl optionally substituted by one or two  $R^8$  groups;

each  $R^6$  is independently selected from hydrogen,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_{12}$  alkenyl,  $C_2$ - $C_{12}$  alkynyl,  $(C_3$ - $C_{10}$  cycloalkyl) $C_1$ - $C_6$  alkyl,  $-(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl), and  $-(CR^{10}R^{11})_m$  (4 to 10 membered heterocyclic), wherein each  $m$  is independently an integer from 0 to 6; and the foregoing  $R^6$  groups, except hydrogen, are optionally substituted by one to three  $R^8$  substituents;

25

$R^{7a}$  is hydrogen or methyl;

each  $R^8$  is independently selected from  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{10}$  alkynyl, oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido,  $-OR^9$ ,  $-C(O)R^9$ ,  $-C(O)OR^9$ ,  $-NR^{10}C(O)OR^{12}$ ,  $-OC(O)R^9$ ,  $-NR^{10}SO_2R^{12}$ ,  $-SO_2NR^9R^{10}$ ,  $-NR^{10}C(O)R^9$ ,  $-C(O)NR^9R^{10}$ ,  $-NR^9R^{10}$ ,  $-S(O)_j(CR^{10}R^{11})_m(C_6-C_{10}$  aryl),  $-S(O)_j(C_1-C_6$  alkyl), wherein  $j$  is an integer from 0 to 2,  $-(CR^{10}R^{11})_m(C_6-C_{10}$  aryl),  $-O(CR^{10}R^{11})_m(C_6-C_{10}$  aryl),  $-NR^{10}(CR^{10}R^{11})_m(C_6-C_{10}$  aryl), and  $-(CR^{10}R^{11})_m(4$  to 10 membered heterocyclic), wherein each  $m$  is independently an integer from 0 to 4; said alkyl, alkenyl and alkynyl groups optionally contain 1 or 2 hetero moieties selected from O,  $-S(O)_j$ - wherein  $j$  is an integer from 0 to 2, and  $-N(R^9)$ - with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a triple bond or a non-aromatic double bond; said cycloalkyl, aryl and heterocyclic  $R^2$  groups are optionally fused to a  $C_6$ - $C_{10}$  aryl group, a  $C_5$ - $C_8$  cycloalkyl group, or a 4 to 10 membered heterocyclic group; and said alkyl, cycloalkyl, aryl and heterocyclic  $R^2$  groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido,  $-NR^{10}SO_2R^{12}$ ,  $-SO_2NR^9R^{10}$ ,  $-C(O)R^9$ ,  $-C(O)OR^9$ ,  $-OC(O)R^9$ ,  $-NR^{10}C(O)OR^{12}$ ,  $-NR^{10}C(O)R^9$ ,  $-C(O)NR^9R^{10}$ ,  $-NR^9R^{10}$ ,  $-OR^9$ ,  $C_1$ - $C_{10}$  alkyl,  $-(CR^{10}R^{11})_m(C_6-C_{10}$  aryl), and  $-(CR^{10}R^{11})_m(4$  to 10 membered heterocyclic), wherein each  $m$  is independently an integer ranging from 0 to 4;

each  $R^9$  is independently selected from H,  $C_1$ - $C_{10}$  alkyl,  $-(CR^{10}R^{11})_m(C_6-C_{10}$  aryl), and  $-(CR^{10}R^{11})_m(4$  to 10 membered heterocyclic), wherein each  $m$  is independently an integer from 0 to 4; said alkyl group optionally includes 1 or 2 hetero moieties selected from O,  $-S(O)_j$ - wherein  $j$  is an integer ranging from 0 to 2, and  $-N(R^{10})$ - with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said cycloalkyl, aryl and heterocyclic  $R^9$  groups are optionally fused to a  $C_6$ - $C_{10}$  aryl group, a  $C_5$ - $C_8$  cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing  $R^9$  substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido,  $-C(O)R^{10}$ ,  $-C(O)OR^{10}$ ,  $-OC(O)R^{10}$ ,  $-NR^{10}C(O)R^{11}$ ,  $-C(O)NR^{10}R^{11}$ ,  $-NR^{10}R^{11}$ , hydroxy,  $C_1$ - $C_6$  alkyl, and  $C_1$ - $C_6$  alkoxy, and with the proviso that  $R^9$  must be attached through a carbon atom unless  $R^9$  is H;

each  $R^{10}$  and  $R^{11}$  is independently H or  $C_1$ - $C_6$  alkyl;

each  $R^{12}$  is selected from the substituents provided in the definition of  $R^9$  except  $R^{12}$  is not H;

$R^{13}$  is hydrogen or halogen;

each  $R^{14}$  is  $-R^6$ ,  $-OR^6$  or  $-NHR^6$ ;

$X^1$  is  $=O$  or  $=NOR^6$ ;

$X^2$  is absent, hydrogen or hydroxy;

$R^3$  and  $R^{2a}$  can be taken together;

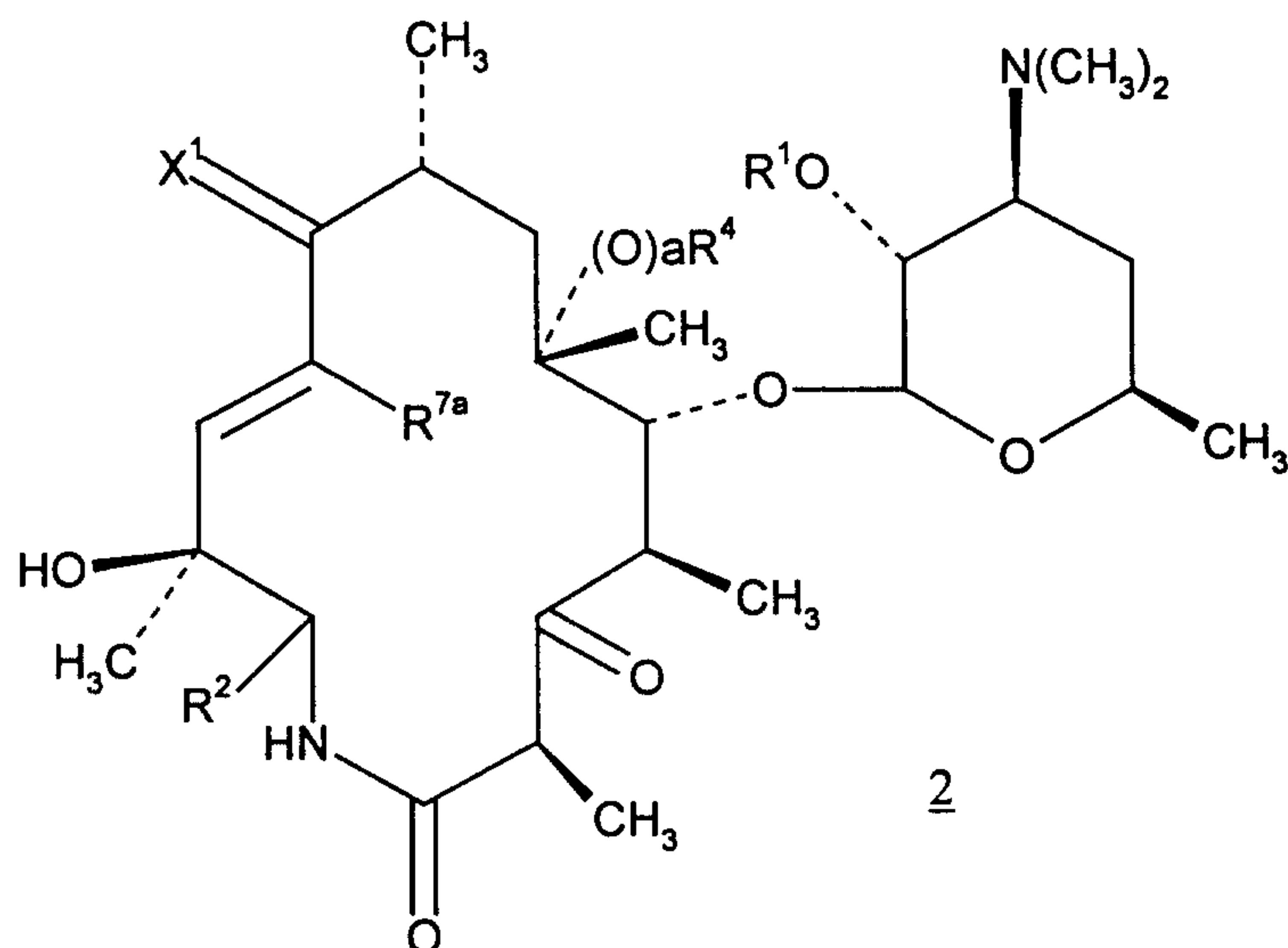
when taken together  $R^3$  and  $R^{2a}$  can form the diradical  $-OC(O)NR^{14}-$ ;

when taken together  $R^3$  and  $R^{2a}$  can also form the diradical  $-Y^aR^{16}Y^b-$ , wherein  $Y^a$  is -NH-, -O- or -S-;  $R^{16}$  is  $(C_2-C_4)$ alkylene wherein the alkylene group is optionally substituted by one to three  $R^8$  substituents; and  $Y^b$  is  $-NR^6-$ , -O- or -S-;

5 with the proviso that when a is zero,  $R^4$  is hydrogen; and

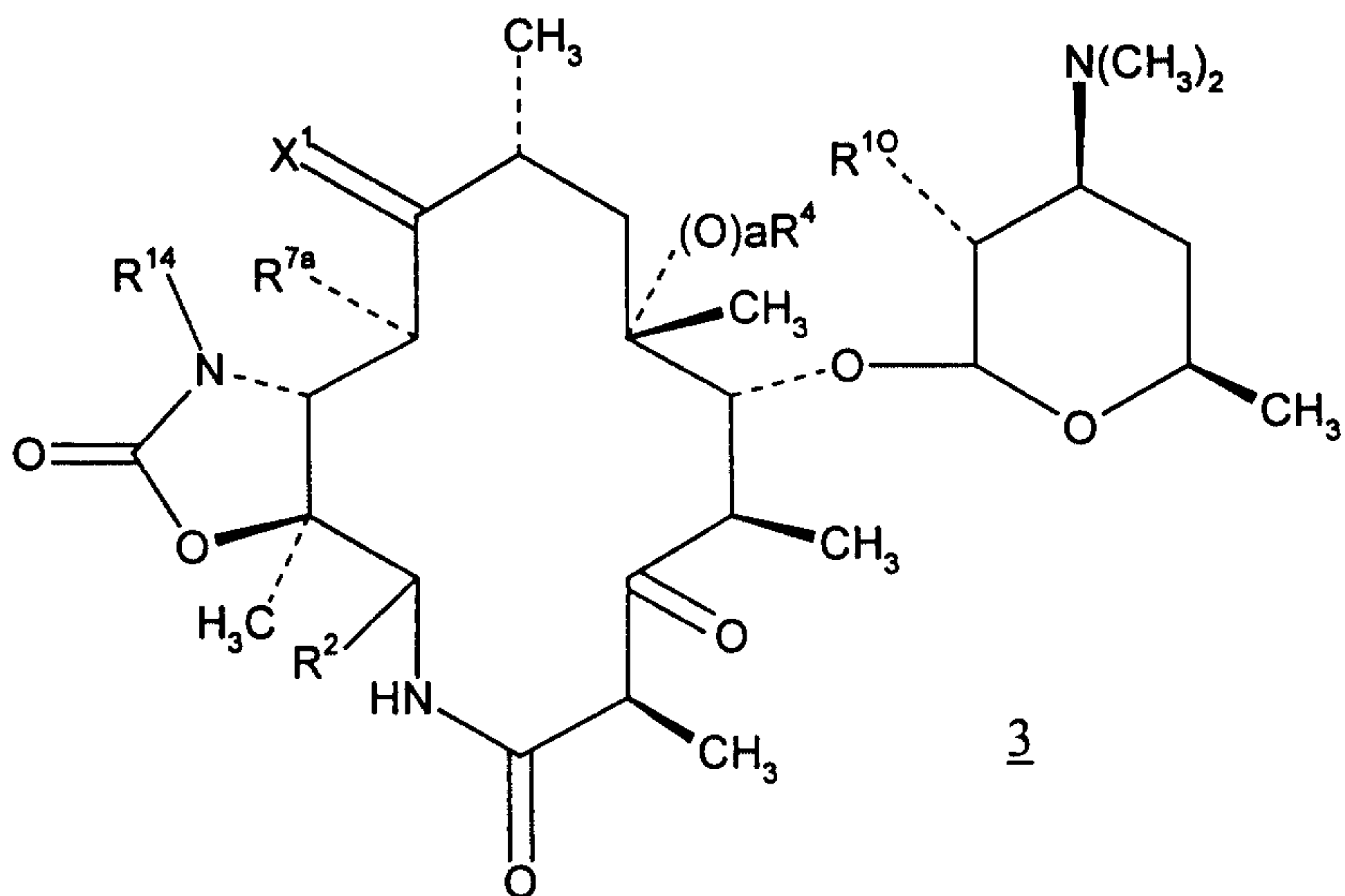
with the proviso that when the dashed line between positions 10 and 11 represents a double bond,  $X^2$  is absent and  $R^3$  is hydrogen.

The present invention also relates to compounds of the formula



10 and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:  
a,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^{7a}$  and  $X^1$  are as defined above for said compound of formula 1.

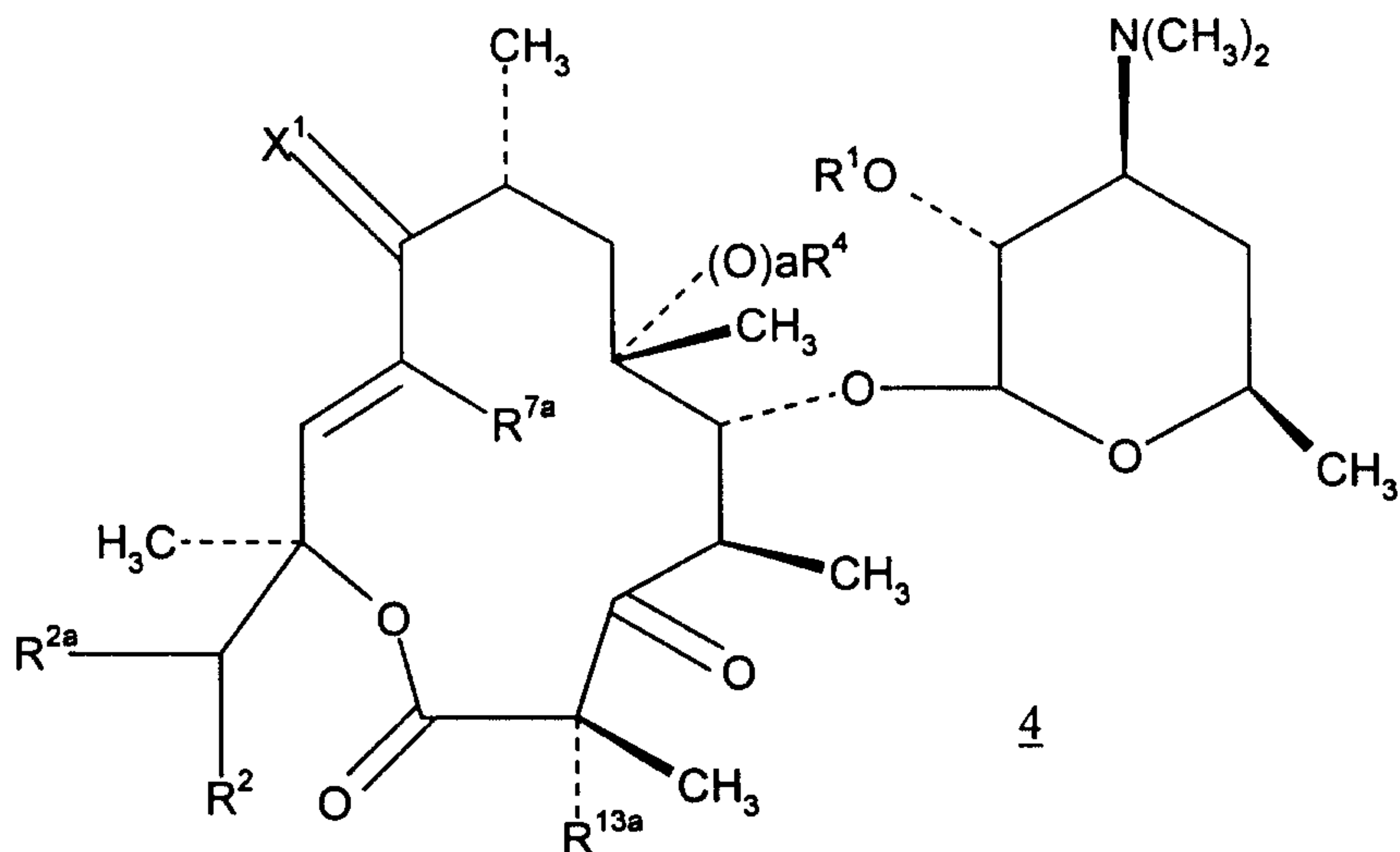
The present invention also relates to compounds of the formula



and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:

15 a,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^{7a}$ ,  $R^{14}$  and  $X^1$  are as defined above for said compound of formula 1.

Specific preferred intermediates of formula 1 include those having the structure of formula



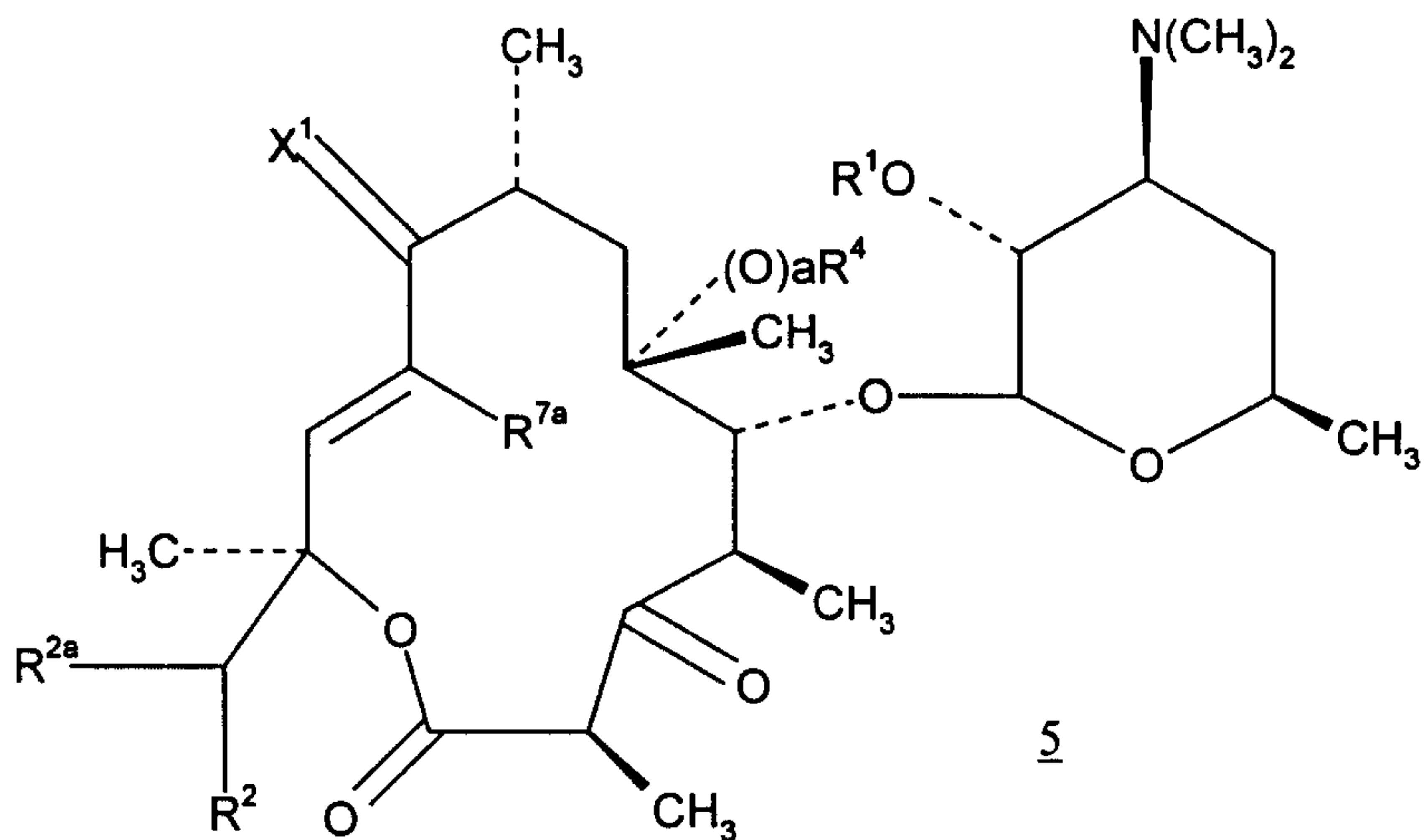
and to salts and solvates thereof, wherein:

5 a,  $R^1$ ,  $R^2$ ,  $R^{2a}$ ,  $R^4$ ,  $R^{7a}$  and  $X^1$  are as defined above for said compound of formula 1;

and

$R^{13a}$  is halogen.

Other specific preferred intermediates of formula 1 include those having the structure of formula

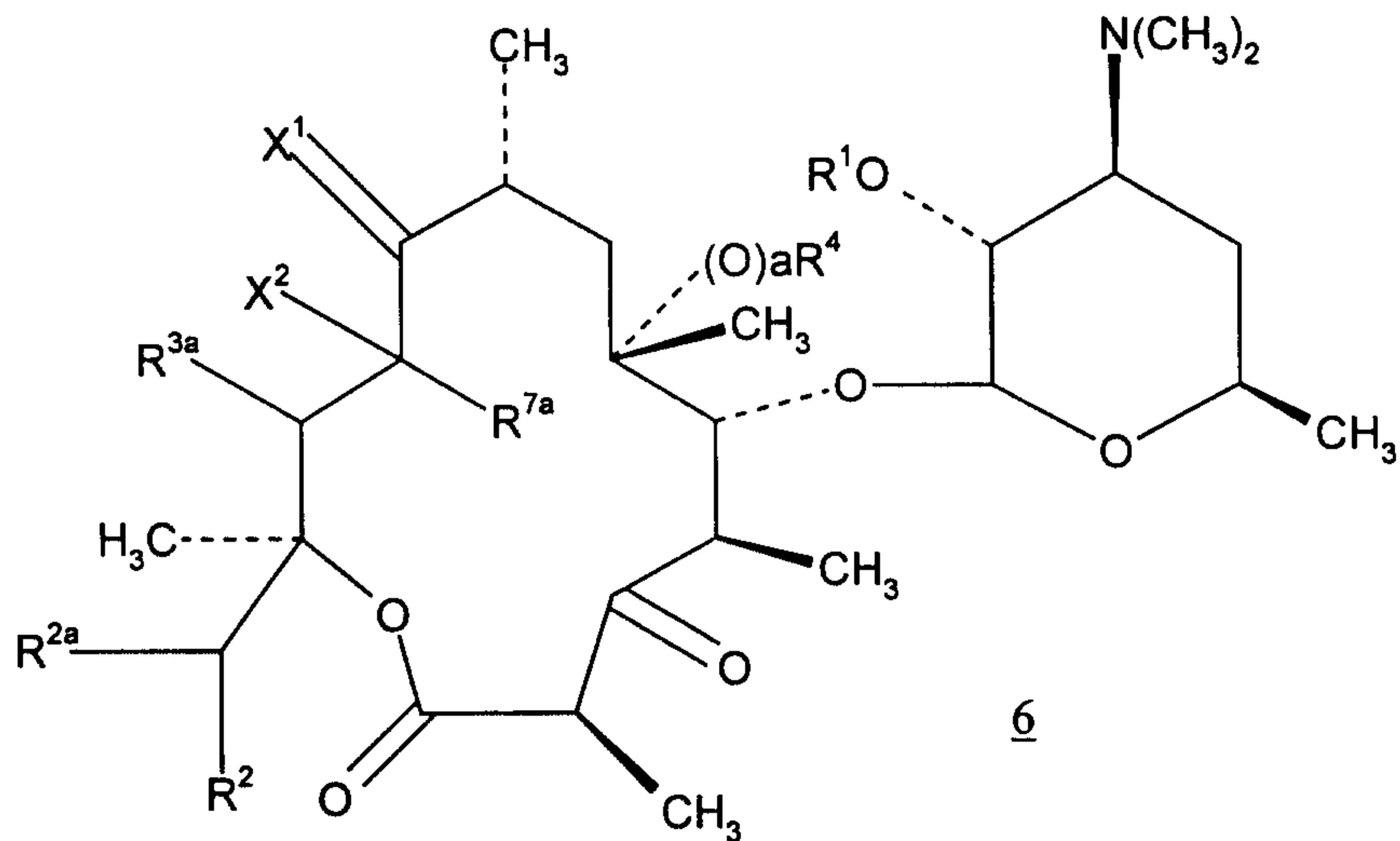


10

and to salts and solvates thereof, wherein:

a,  $R^1$ ,  $R^2$ ,  $R^{2a}$ ,  $R^4$ ,  $R^{7a}$  and  $X^1$  are as defined above for said compound of formula 1.

Other specific preferred intermediates of formula 1 include those having the structure of formula



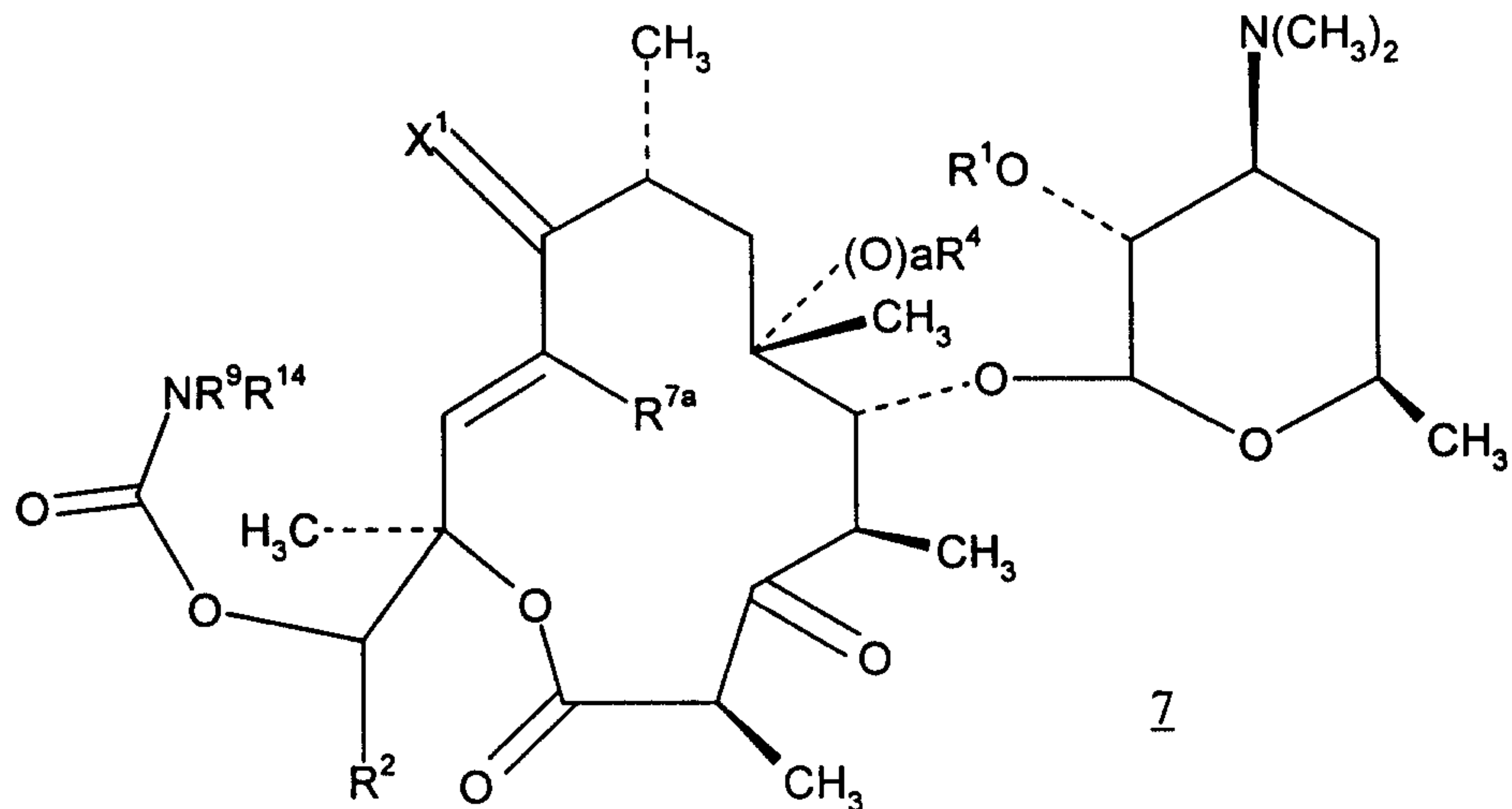
and to salts and solvates thereof, wherein:

a,  $R^1$ ,  $R^2$ ,  $R^{2a}$ ,  $R^4$ ,  $R^{7a}$ , and  $X^1$  are as defined above for said compound of formula 1;

$R^{3a}$  is hydrogen, hydroxy or amino; and

5  $X^2$  is hydrogen or hydroxy.

Other specific preferred intermediates of formula 1 include those having the structure of formula



and to salts and solvates thereof, wherein:

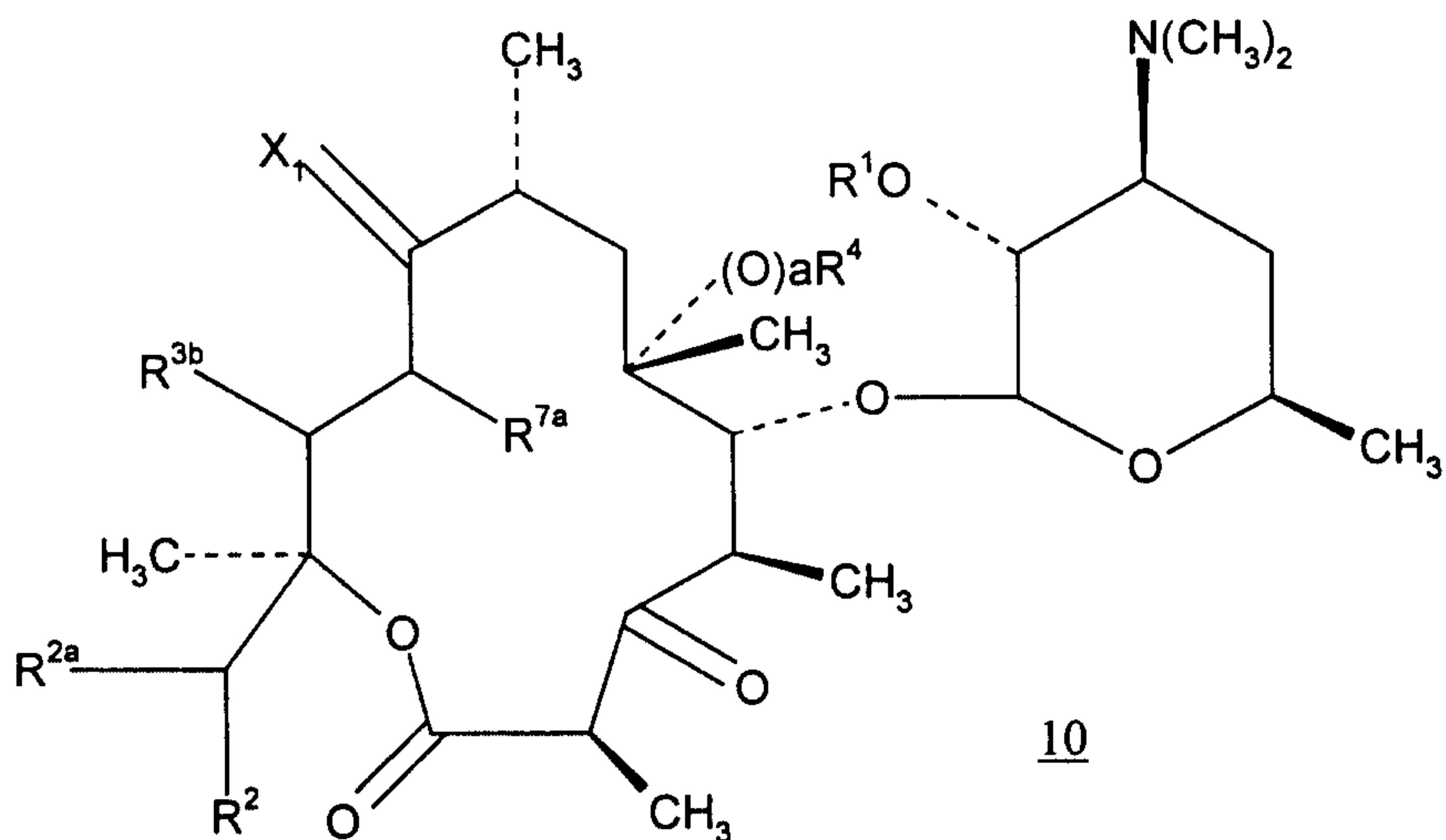
10 a,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^{7a}$ ,  $R^9$ ,  $R^{14}$  and  $X^1$  are as defined above for said compound of formula

1.

Other specific preferred compounds of formula 1 include those having the structure of formula







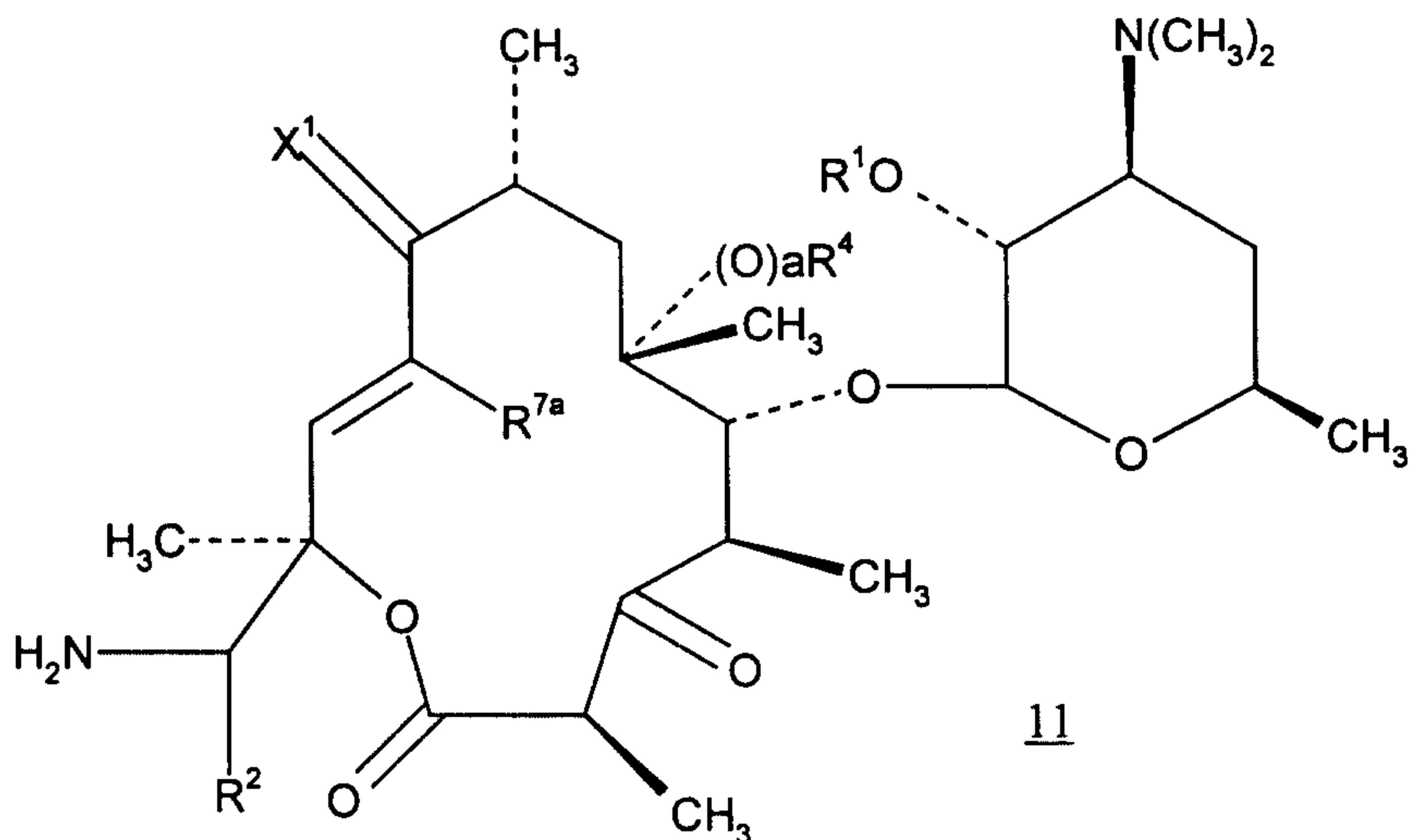
and to salts and solvates thereof, wherein:

a,  $R^1$ ,  $R^2$ ,  $R^{2a}$ ,  $R^4$ ,  $R^{7a}$  and  $X^1$  are as defined above for said compound of formula 1;

and

5  $R^{3b}$  is  $-OR^6$ ,  $-NHR^6$  or  $-SR^6$  wherein  $R^6$  is as defined above for said compound of formula 1.

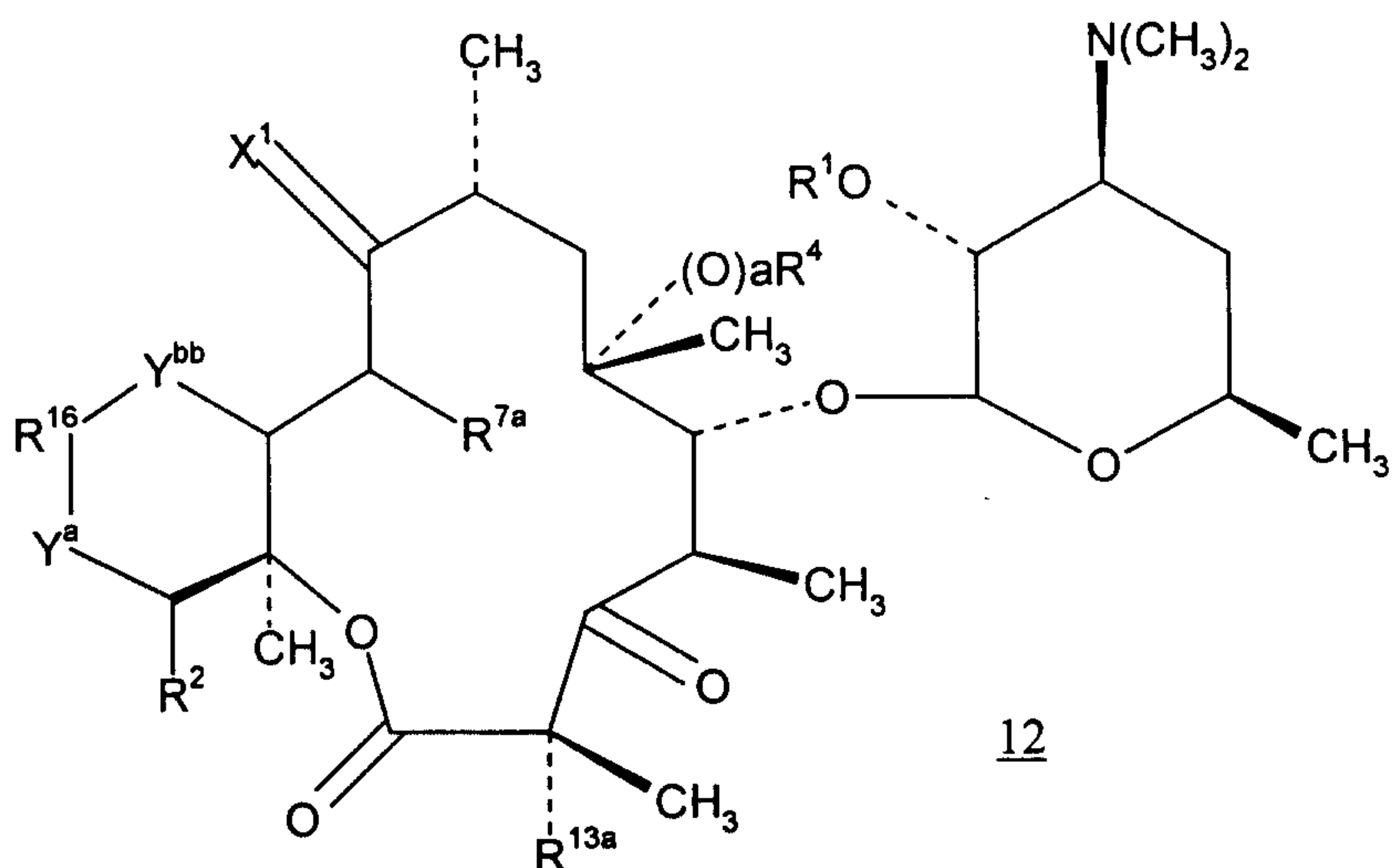
Other specific preferred intermediates of formula 1 include those having the structure of formula



10 and to salts and solvates thereof, wherein:

a,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^{7a}$  and  $X^1$  are as defined above for said compound of formula 1.

Other specific preferred compounds of formula 1 include those having the structure of formula

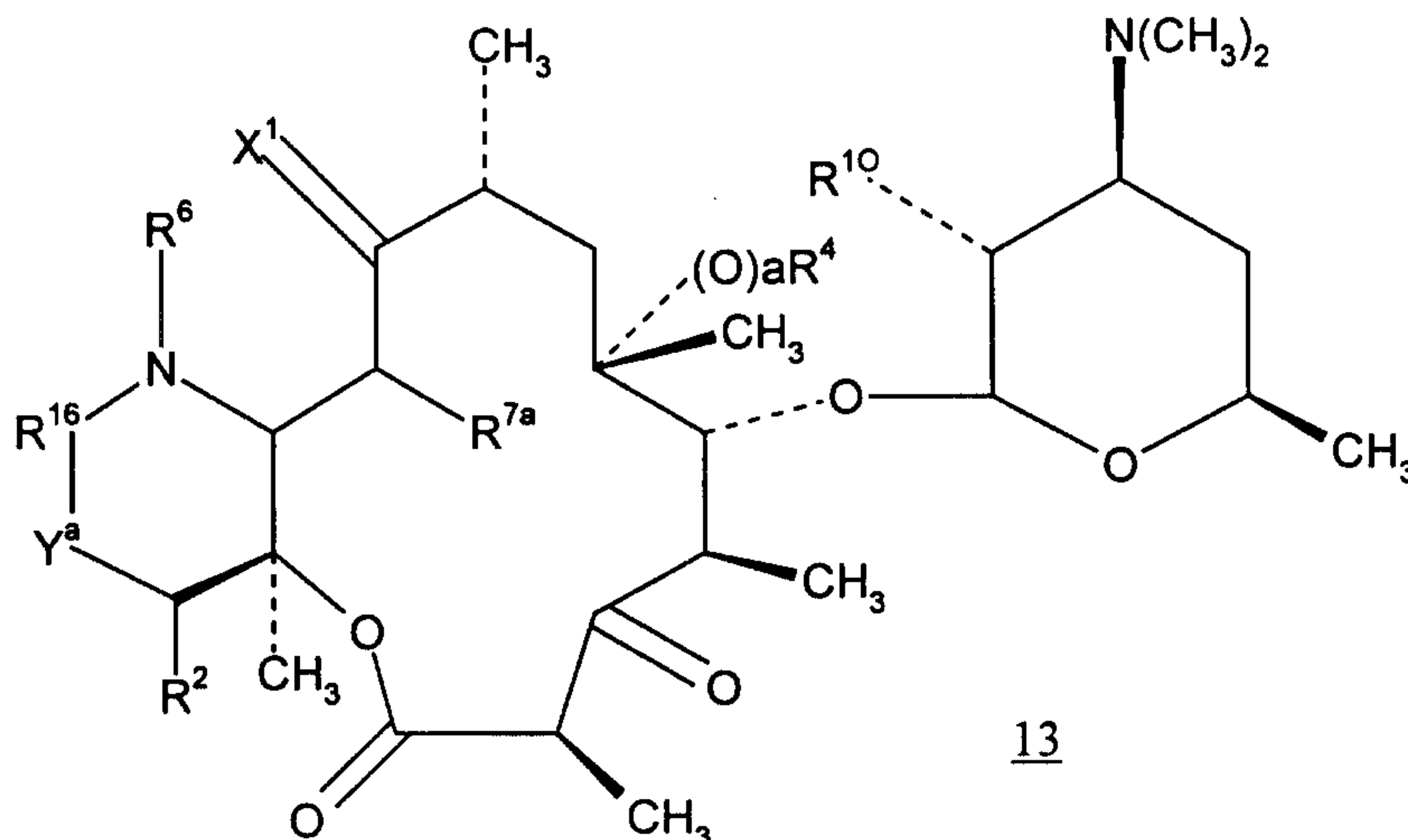


and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:

a,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^{7a}$ ,  $R^{13a}$ ,  $R^{16}$ ,  $X^1$  and  $Y^a$  are as defined above for said compounds of formula 1 and 4; and

5  $Y^{bb}$  is -NH-, -O- or -S-.

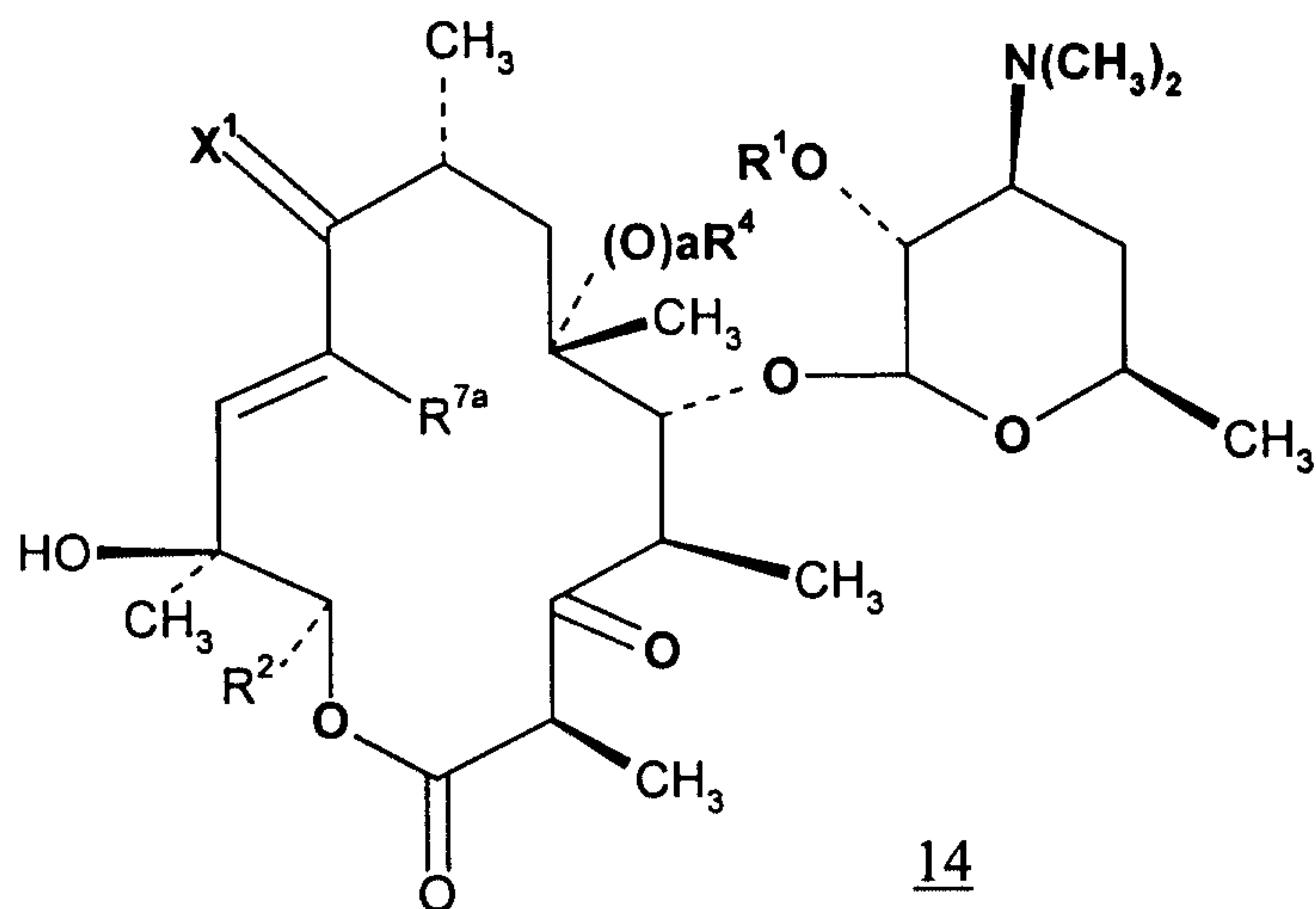
Other specific preferred compounds of formula 1 include those having the structure of formula



and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:

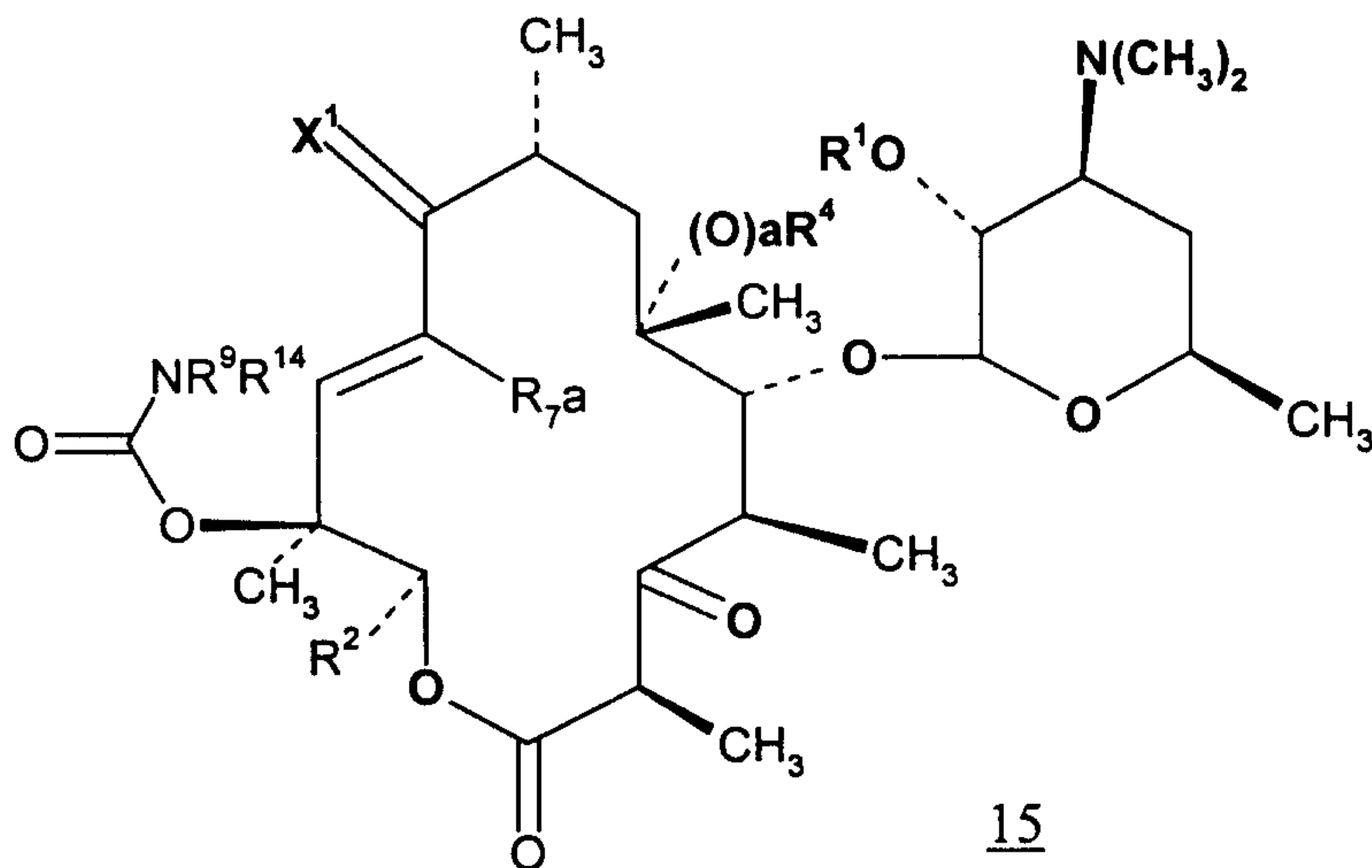
10 a,  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^6$ ,  $R^{7a}$ ,  $R^{16}$ ,  $X^1$  and  $Y^a$  are as defined above for said compound of formula 1;

The present invention also relates to compounds of the formula



and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:  
a, R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>7a</sup> and X<sup>1</sup> are as defined above for said compound of formula 1.

The present invention also relates to compounds of the formula

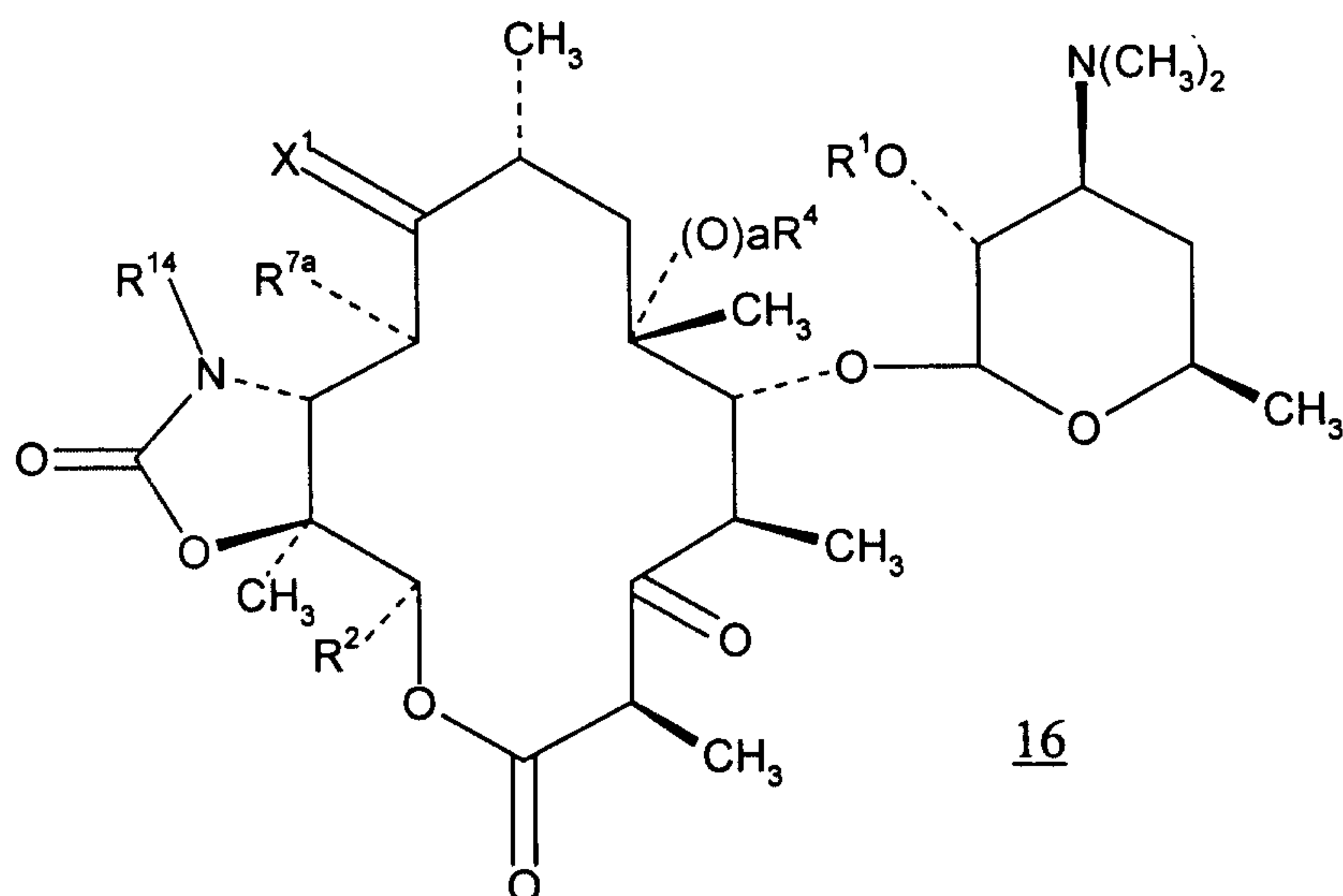


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and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:  
a, R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>7a</sup>, R<sup>9</sup>, R<sup>14</sup> and X<sup>1</sup> are as defined above for said compound of formula

1.

The present invention also relates to compounds of the formula



and to pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein:  
 a, R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>7a</sup>, R<sup>14</sup> and X<sup>1</sup> are as defined above for said compound of formula 1.

The invention also relates to a pharmaceutical composition for the treatment of a  
 5 bacterial infection or a protozoa infection, or a disorder related to a bacterial or protozoal  
 infection, in a mammal, fish, or bird, which comprises a therapeutically effective amount of a  
 compound of formulas 2, 3, 8, 9, 12-16 or a pharmaceutically acceptable salt, prodrug or  
 solvate thereof, and a pharmaceutically acceptable carrier.

The invention also relates to a method of treating a bacterial infection or a protozoa  
 10 infection, or a disorder related to a bacterial or protozoal infection, in a mammal, fish, or bird  
 which comprises administering to said mammal, fish or bird a therapeutically effective amount  
 of a compound of formulas 2, 3, 8, 9, 12-16 or a pharmaceutically acceptable salt, prodrug or  
 solvate thereof.

The invention also relates to a method of treating cancer or atherosclerosis in a  
 15 mammal which comprises administering to said mammal a therapeutically effective amount of  
 a compound of formulas 2, 3, 8, 9, 12-16 or a pharmaceutically acceptable salt, prodrug or  
 solvate thereof.

The term "treating", as used herein, unless otherwise indicated, means reversing,  
 alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term  
 20 applies, or one or more symptoms of such disorder or condition. The term "treatment", as used  
 herein, refers to the act of treating, as "treating" is defined immediately above.

As used herein, unless otherwise indicated, the terms or phrases "bacterial  
 infection(s)", "protozoal infection(s)", and "disorders related to bacterial infections or protozoal  
 infections" include the following: pneumonia, otitis media, sinusitis, bronchitis, tonsillitis, and  
 25 mastoiditis related to infection by *Streptococcus pneumoniae*, *Haemophilus influenzae*,  
*Moraxella catarrhalis*, *Staphylococcus aureus*, *Enterococcus faecalis*, *E. faecium*, *E.*

*casselflavus*, *S. epidermidis*, *S. haemolyticus*, or *Peptostreptococcus* spp.; pharyngitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Corynebacterium diphtheriae*, or *Actinobacillus haemolyticum*; respiratory tract infections related to infection by *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Chlamydia pneumoniae*; blood and tissue infections, including endocarditis and osteomyelitis, caused by *S. aureus*, *S. haemolyticus*, *E. faecalis*, *E. faecium*, *E. durans*, including strains resistant to known antibacterials such as, but not limited to, beta-lactams, vancomycin, aminoglycosides, quinolones, chloramphenicol, tetracyclines and macrolides; uncomplicated skin and soft tissue infections and abscesses, and puerperal fever related to infection by *Staphylococcus aureus*, coagulase-negative staphylococci (i.e., *S. epidermidis*, *S. hemolyticus*, etc.), *Streptococcus pyogenes*, *Streptococcus agalactiae*, Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, *Corynebacterium minutissimum*, *Clostridium* spp., or *Bartonella henselae*; uncomplicated acute urinary tract infections related to infection by *Staphylococcus aureus*, coagulase-negative staphylococcal species, or *Enterococcus* spp.; urethritis and cervicitis; sexually transmitted diseases related to infection by *Chlamydia trachomatis*, *Haemophilus ducreyi*, *Treponema pallidum*, *Ureaplasma urealyticum*, or *Neisseria gonorrhoeae*; toxin diseases related to infection by *S. aureus* (food poisoning and toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori*; systemic febrile syndromes related to infection by *Borrelia recurrentis*; Lyme disease related to infection by *Borrelia burgdorferi*; conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium*, or *Mycobacterium intracellulare*; infections caused by *Mycobacterium tuberculosis*, *M. leprae*, *M. paratuberculosis*, *M. kansasii*, or *M. chelonae*; gastroenteritis related to infection by *Campylobacter jejuni*; intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis*; gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis or cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae*. Bacterial infections and protozoal infections, and disorders related to such infections, which may be treated or prevented in animals include the following: bovine respiratory disease related to infection by *P. haemolytica*, *P. multocida*, *Mycoplasma bovis*, or *Bordetella* spp.; cow enteric disease related to infection by *E. coli* or protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by *S. aureus*, *Strep. uberis*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Klebsiella* spp., *Corynebacterium*, or *Enterococcus* spp.; swine respiratory disease related to infection by *A. pleuro.*, *P. multocida*,

or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli*, *Lawsonia intracellularis*, *Salmonella*, or *Serpulina hyodysintariae*; cow footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli*; cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus*; cow pink-eye related to infection by *Moraxella bovis*; cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by *E. coli*; skin and soft tissue infections in dogs and cats related to infection by *S. epidermidis*, *S. intermedius*, coagulase neg. *Staphylococcus* or *P. multocida*; and dental or mouth infections in dogs and cats related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium*, *Peptostreptococcus*, *Porphyromonas*, or *Prevotella*. Other bacterial infections and protozoal infections, and disorders related to such infections, which may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

15 The term "halo" or "halogen", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Said alkyl group may include one or two double or triple bonds. It is understood that for said alkyl group to include a carbon-carbon double or triple bond at least two carbon atoms are required in said alkyl group.

20 The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "4-10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4-10 atoms in its ring system. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or more oxo moieties. An example of a 4 membered heterocyclic group is azetidiny (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridiny, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexanyl, 3-

azabicyclo[4.1.0]heptyl, 3H-indolyl and quinoliziny. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, 5 triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazoliny, quinoxaliny, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

10 The term "protecting group" refers to a suitable chemical group that may be attached to a functional group and removed at a later stage to reveal the intact functional group. Examples of suitable protecting groups for various functional groups are described in T.W. Greene and P.G.M Wuts, Protective Groups in Organic Synthesis, 2d Ed., John Wiley and Sons (1991) (hereinafter, "Greene and Wuts"); L. Fieser and M. Fieser, Fieser and Fieser's Réagents for 15 Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).

The term "therapeutically effective amount" refers to an amount effective in treating or ameliorating disorders involving gastrointestinal motility or an amount effective in enhancing gastrointestinal motility in a patient, either as monotherapy or in combination with other agents. 20 The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder involving gastrointestinal motility in a patient, the improvement of an ascertainable measurement associated with a particular disorder, or the enhancement of gastrointestinal motility, e.g., to facilitate the placement of diagnostic or therapeutic instruments. As used herein, the term "patient" refers to mammals (including humans), fish and birds suffering from 25 disorders characterized by impaired gastrointestinal motility or in need of enhanced gastrointestinal motility.

The term "pharmaceutically acceptable carrier" refers to a carrier that may be administered to a patient together with a compound of this invention. The carrier does not destroy the pharmacological activity of the prokinetic agent and is nontoxic when administered 30 in doses sufficient to deliver a therapeutic amount of the prokinetic agent.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids 35 that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide,



nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-  
5 (2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include a basic moiety, such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

As used herein, unless otherwise indicated, "Ac" indicates an acetyl group.

As used herein, unless otherwise indicated, "Me" indicates a methyl group.

10 As used herein, unless otherwise indicated, "Et" indicates an ethyl group.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and, particularly, the calcium, magnesium, sodium and potassium salts of the compounds of the present invention.

15 The subject invention also includes isotopically-labeled compounds, and the pharmaceutically acceptable salts thereof, which are identical to those recited in formulas 1-16, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include  
20 isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the  
25 present invention, for example those into which radioactive isotopes such as  $^3\text{H}$  and  $^{14}\text{C}$  are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*,  $^3\text{H}$ , and carbon-14, *i.e.*,  $^{14}\text{C}$ , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, *i.e.*,  $^2\text{H}$ , can afford certain therapeutic advantages resulting from greater metabolic stability, for example  
30 increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formulas 1-16 of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

35 This invention also encompasses pharmaceutical compositions containing and methods of treating bacterial infections through administering prodrugs of compounds of the formulas 2, 3, 8, 9, 12-16. Compounds of formulas 2, 3, 8, 9, 12-16 having free amino, amido,

hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formulas 2, 3, 8, 9, 12-16. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone.

Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. The amide and ester moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in D. Fleisher, R. Bong, B.H. Stewart, *Advanced Drug Delivery Reviews* (1996) 19, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs and sulfate esters or phosphate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in R.P. Robinson et al., *J. Medicinal Chemistry* (1996) 39, 10.

The present invention also includes pharmaceutical compositions for enhancing the motility of the gastrointestinal tract comprising a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier or diluent. These pharmaceutical compositions may comprise one or more additional agents having a prokinetic effect or other therapeutic or prophylactic effect.

The present invention also includes a method of enhancing gastrointestinal motility in humans, other mammals, fish and birds in need of such treatment. This method can be used to treat disorders characterized by impaired gastrointestinal motility such as gastro-esophageal reflux disease, diabetic gastroparesis, delayed gastric emptying, pediatric gastroparesis, postoperative paralytic ileus, intestinal pseudoobstruction, gall bladder stasis, systemic sclerosis, anorexia, gastritis, emesis and chronic constipation. Alternatively, this method can be used to facilitate the placement of diagnostic and therapeutic instruments, such as the insertion of enteral feeding tubes into the proximal small intestine. The methods of the present invention comprise administering to a human, other mammal, fish or bird in need of such treatment a therapeutically effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the

compound as defined above. This invention contemplates treatment methods in which the compounds of the present invention are administered either as a single agent or in combination with other therapeutic agents.

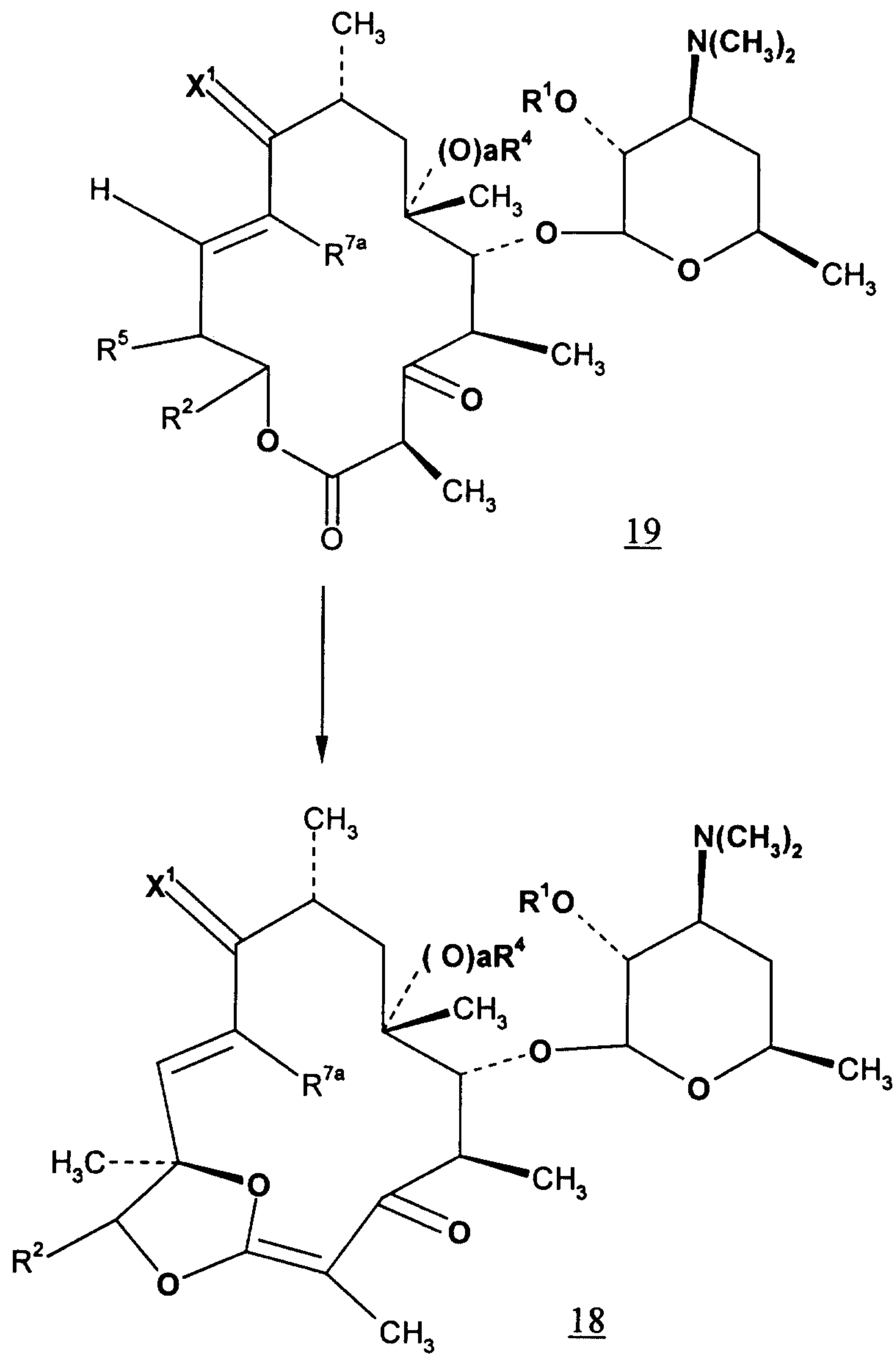
5 Unless otherwise indicated, references herein to gastrointestinal disorders include disorders that occur in mammals, fish and birds, as well as related disorders that may be treated or prevented by administering the compounds of the present invention.

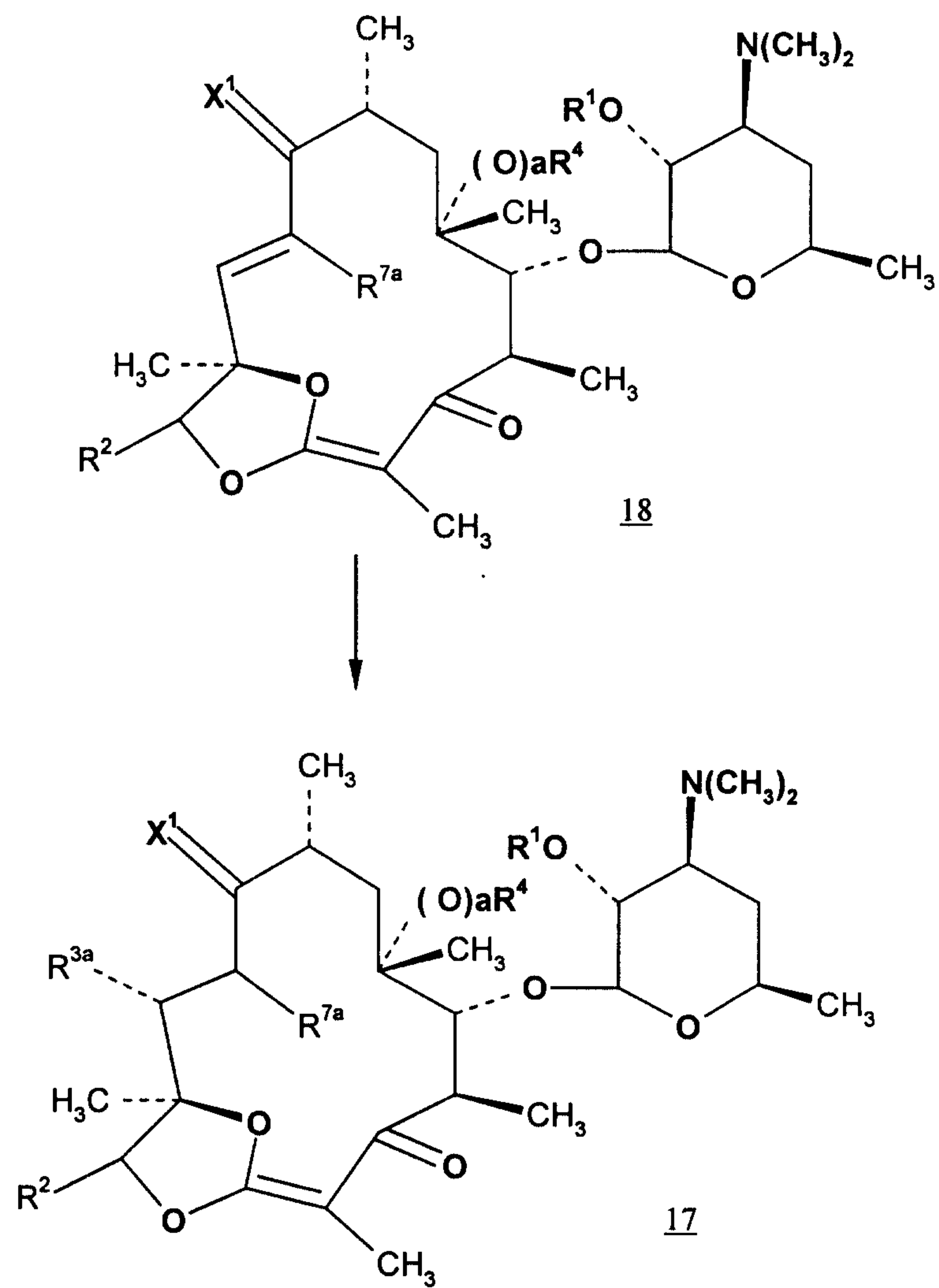
10 Certain compounds of formulas 1-16 may contain one or more asymmetric carbons and may therefore exist in different isomeric forms. This invention includes all pure individual enantiomers and individual diastereomers of the compounds of formulas 1-16 and mixtures comprising any combination of these isomers. Each stereogenic carbon may be of the R or S configuration. In particular, the invention includes both the R and S configurations of the methyl group at C-8 and C-10 of the macrolide ring of formulas 1-16, and both the E and Z isomers of the  $-OR^6$  group connected to the nitrogen of the oxime moiety at C-9 of the macrolide ring of formulas 1-16. Although specific compounds exemplified in this application may be depicted in  
15 a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned. The compounds of formulas 1-16 may additionally exist as tautomers. This invention includes all such pure tautomers and mixtures thereof. The invention includes uses of any of the above compounds or mixtures of the compounds.

20

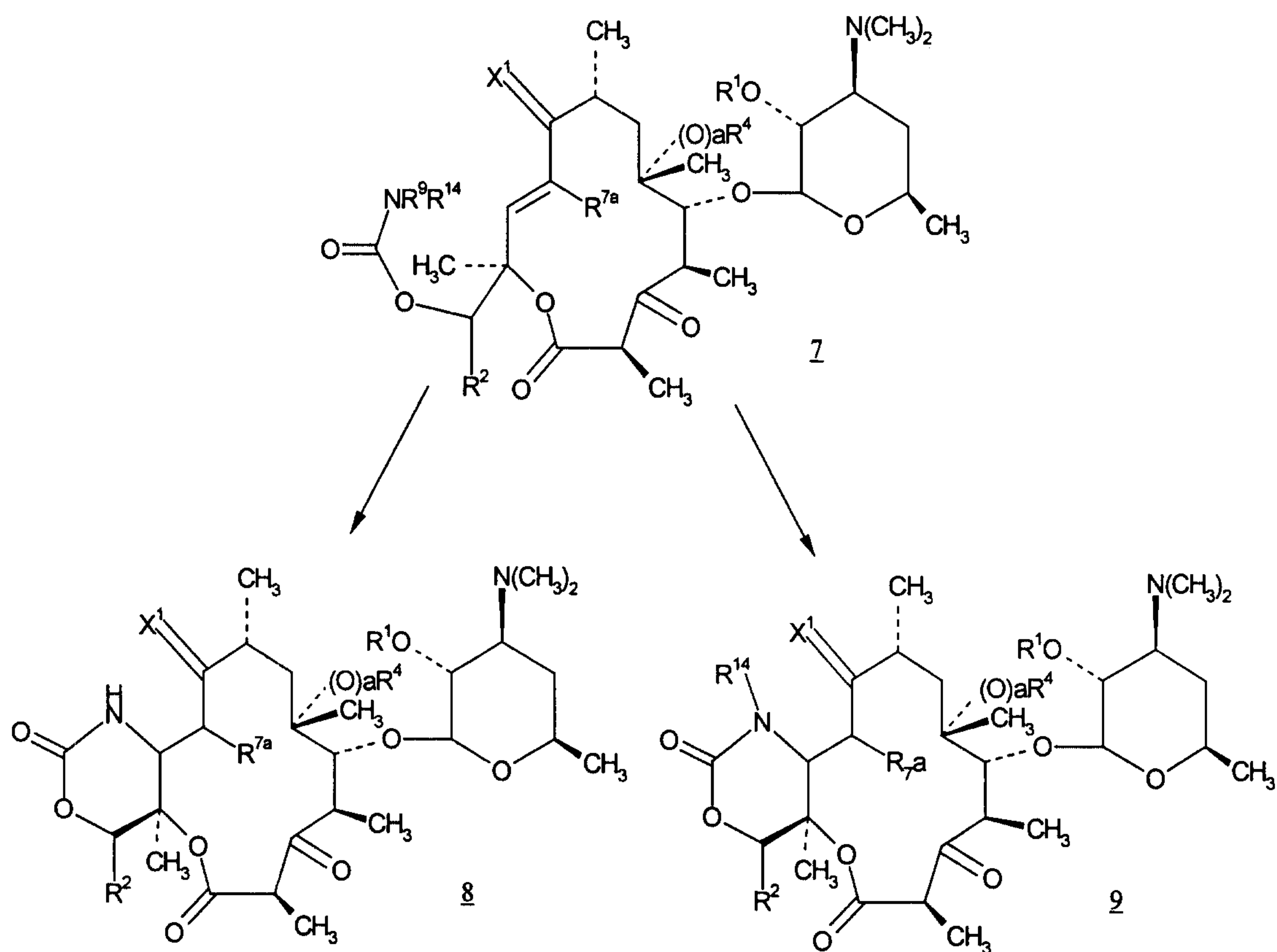
#### Detailed Description of the Invention

The following reaction schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated a,  $R^1$ ,  $R^2$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^{3a}$ ,  $R^{3b}$ ,  $R^4$ ,  $R^6$ ,  $R^{7a}$ ,  $R^{13}$ ,  $R^{13a}$ ,  $X^1$ ,  $X^2$ ,  $Y^a$  and  $Y^{bb}$  are defined as above.

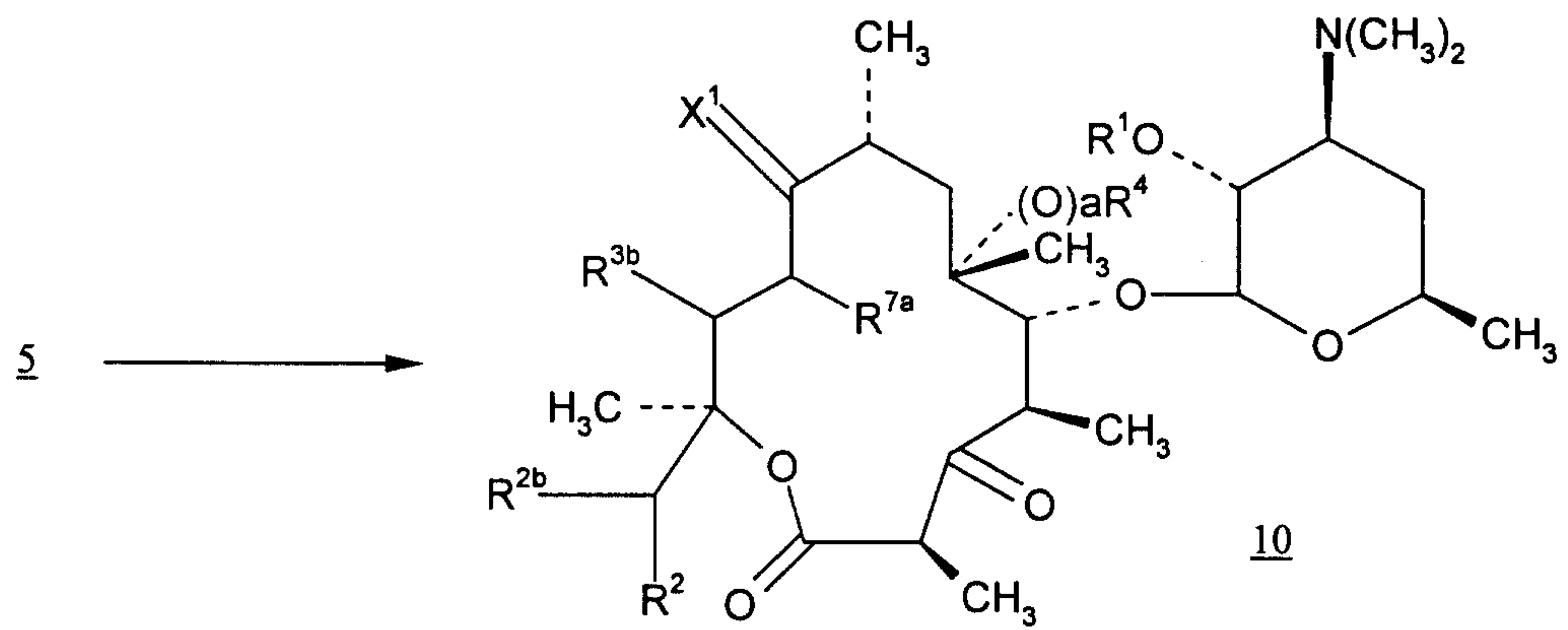
Preparation A

Preparation B



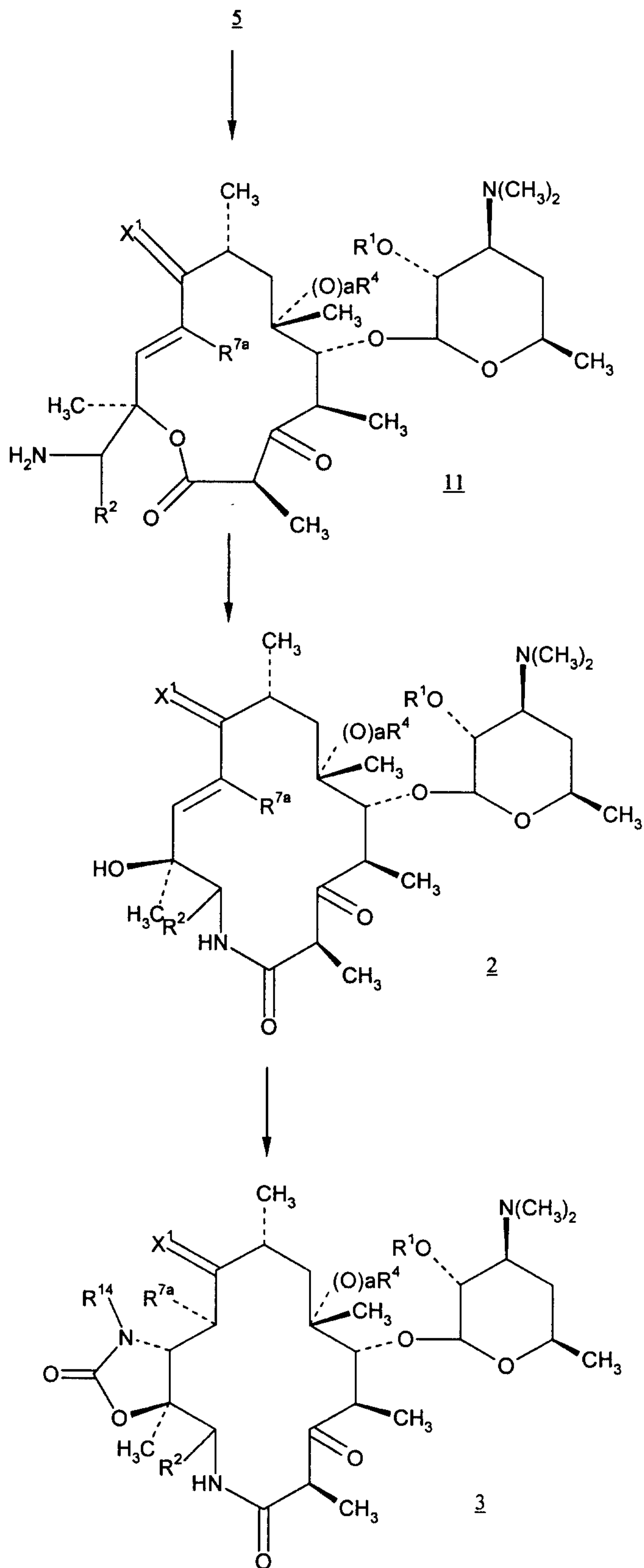
Scheme 25

Scheme 3

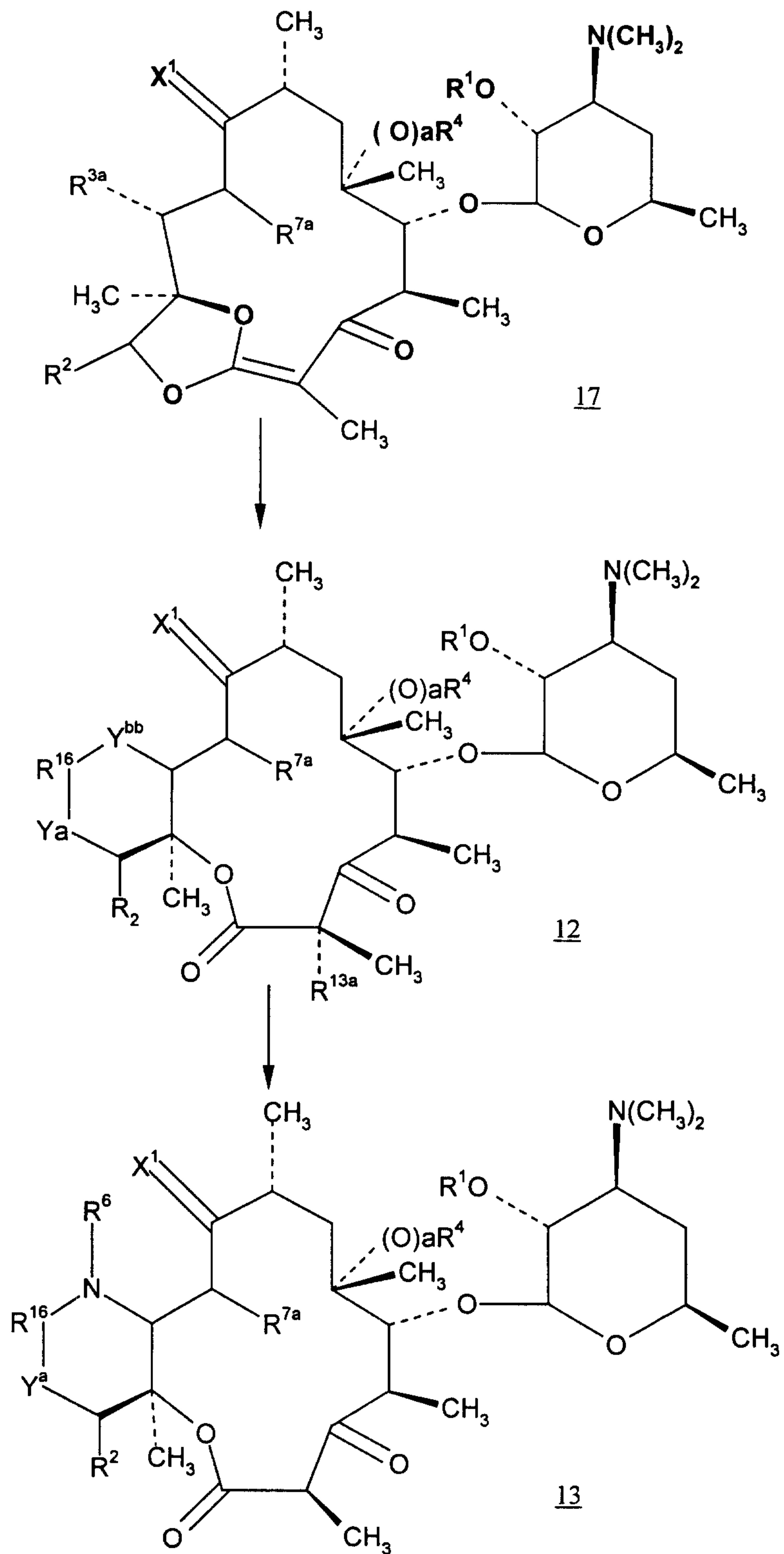




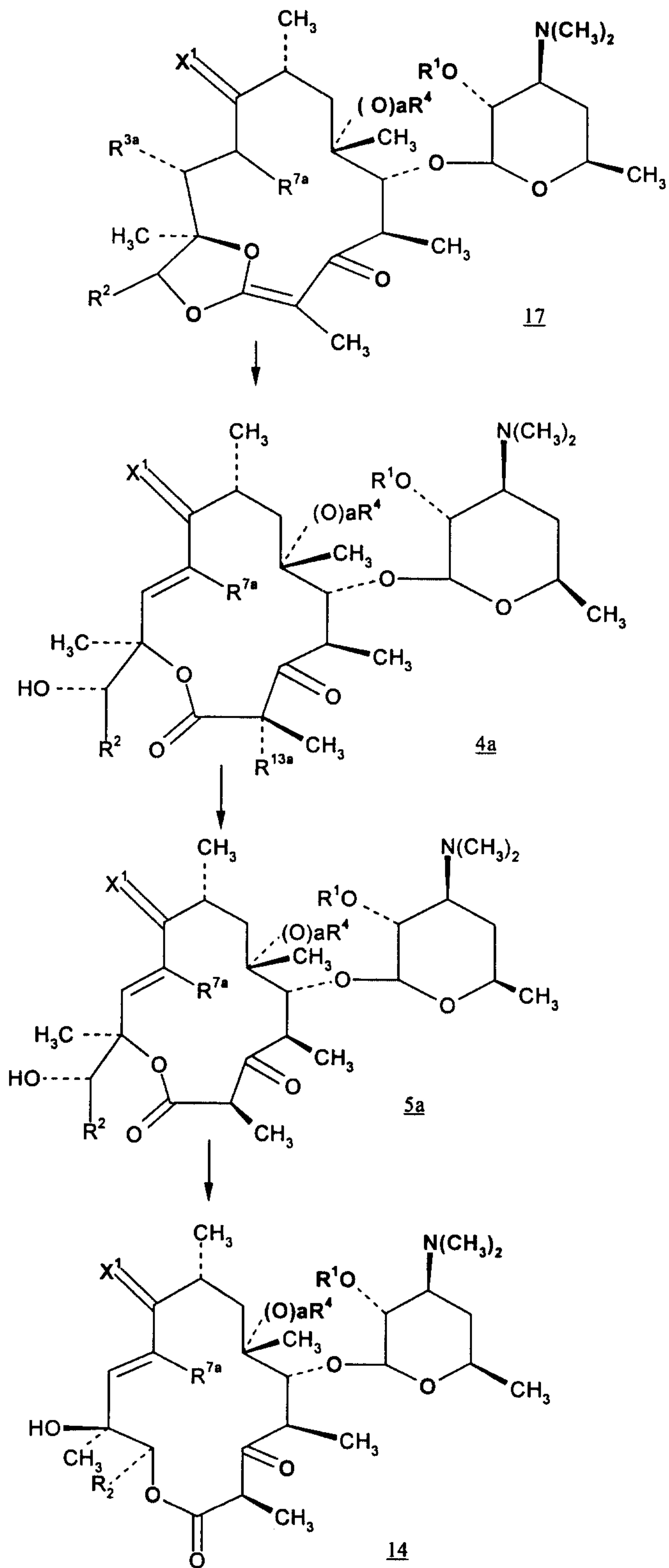
## Scheme 4



Scheme 5

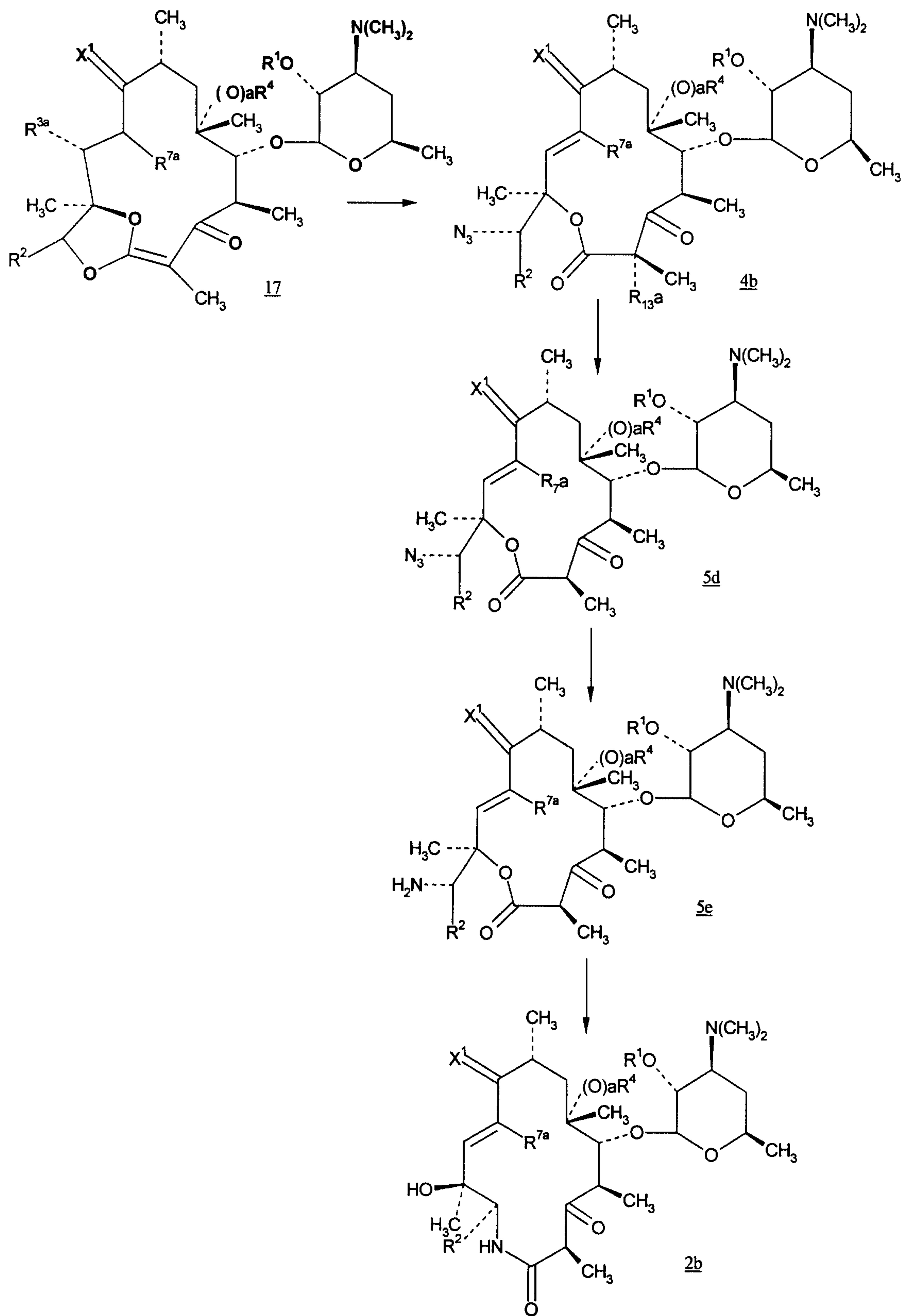


## Scheme 6





## Scheme 8





In the reaction of Preparation A, the compound of formula 19 wherein R<sup>5</sup> is a leaving group, such as (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyloxy, (C<sub>6</sub>-C<sub>10</sub>)arylsulfonyloxy, (C<sub>1</sub>-C<sub>6</sub>)acyloxy or imidizoly carbonyloxy, is converted to the corresponding ketene acetal compound of formula 18 by treating 19 with a base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-  
5 diazabicyclo[4.3.0]non-5-ene, ethyldiisopropylamine, triethylamine, lithium hexamethyldisilazide or potassium hexamethyldisilazide, preferably 1,8-diazabicyclo[5.4.0]undec-7-ene, in the presence of a polar aprotic solvent, such as acetonitrile, dimethylformamide, tetrahydrofuran, preferably acetonitrile. The reaction is stirred at a temperature between about 20°C to about 100°C, preferably about 80°C, for a time period  
10 between about 0.5 hours to about 6 hours, preferably about 2 hours. The starting compound of formula 19 can be prepared as described in United States Patent 5,543,400. The starting compounds of formula 19 where R<sup>4</sup> is various groups can be prepared as described in WO 98/09978.

In the reaction of Preparation B, the conversion of 18 to 17 can be done by mixing  
15 ketene acetal 18 with a nucleophile at room temperature or elevated temperature (up to 100 °C) in an inert solvent such as acetonitrile or trifluoroethanol. The process can be catalyzed by addition of acid such as acetic acid or SNCl<sub>4</sub>. The compound of formula 17 is referred to in United States patent application number 09/432441, filed November 2, 1999, and United States provisional patent application entitled "Novel Antibacterial and Prokinetic Macrolides",  
20 filed December 29, 1999 (attorney docket no. PC 10591).

In Scheme 1, conversion of 18 to 4, in which R<sup>13a</sup> is bromine, may be done by a reaction of N-bromosuccinimide (NBS) or N-bromoacetamide in the presence of a nucleophile at a temperature ranging from 0°C to 50°C in an inert solvent. The bromine atom at C2 can be subsequently removed to give compound 5 by treatment with, for example, zinc and acetic  
25 acid. This reduction may be done at a temperature ranging from 0°C to room temperature for a period of 0.1 hours to about 6 hours, preferably at room temperature for 0.1 hours. Compound 5 can be further derivatized to give compound 6. This may be done by using N-methylmorpholine N-oxide and less than 1 equivalent of OsO<sub>4</sub> in a water-acetone mixture at a temperature ranging from 0°C to room temperature for a period from about 1 hour to 24 hours  
30 to give compound 6, in which both R<sup>3a</sup> and X<sup>2</sup> are hydroxy. It may also be done by first epoxidation of the C10-C11 double bond by treatment with, for example, m-chloroperbenzoic acid or hydrogen peroxide and NaOH, and subsequently treating the resulting epoxide with a nucleophile such as N<sub>3</sub><sup>-</sup>. The m-chloroperbenzoic acid reaction may be done in CH<sub>2</sub>Cl<sub>2</sub> at a temperature ranging from about -25°C to room temperature. The hydrogen acid reaction  
35 may be done in a water-ethanol solution at a temperature ranging from about 0°C to room temperature for a period from 0.1 hours to about 3 hours. In some cases it may be necessary to reduce the N-oxide of desosamine using NaBH<sub>4</sub>, which is a side reaction in those oxidation

reactions. The azide reaction can be carried out by heating the epoxide intermediate with  $\text{NaN}_3$  in methanol at room temperature to  $65^\circ\text{C}$  for about 6 hours to 30 hours. Reduction of the resulting azide will give compound 6 in which  $\text{R}^{3a}$  is  $-\text{NH}_2$  and  $\text{X}^2$  is hydroxy. This reduction can be done using 10-100 psi of hydrogen in the presence of a catalyst, typically  
5 Lindlar's catalyst, in ethanol for a period from about 0.5 hours to about 12 hours. Conversion of compound 18 to 4, in which  $\text{R}^{13a}$  is Cl or I, may be done by a reaction of N-chloro succinimide (NCS) or N-iodo succinimide (NIS), respectively.

In Scheme 2, when  $\text{R}^{2b}$  in compound 5 is hydroxy, compound 5 can be converted to compound 7, in which  $\text{R}^9$  and  $\text{R}^{14}$  are hydrogen, using NaH, carbonyl diimidazole, and  
10 ammonia. This is typically done by reacting the alcohol 5 with NaH and carbonyl diimidazole in THF at  $0^\circ\text{C}$  for 0.5 hours to 6 hours. The resulting imidazole carbonyloxy compound can then be treated with methanolic ammonia at a temperature ranging from  $0^\circ\text{C}$  to room temperature for 0.5 hours to about 6 hours. Compound 7 can then be converted to  
15 compound 8 by heating 7 in the presence of a base such as triethylamine or acid such as acetic acid in an inert solvent such as acetonitrile for 2 hours to 24 hours at a temperature ranging from  $50^\circ\text{C}$  to  $80^\circ\text{C}$ . When substituted amine is used in place of ammonia, compound 5 can be converted to compound 7, in which one or neither of  $\text{R}^9$  and  $\text{R}^{14}$  is hydrogen. When  $\text{R}^9$  is hydrogen, compound 7 upon heating in the presence of a base or acid is converted to  
20 compound 9.

In Scheme 3, compound 5 can be converted to compound 10 by a Michael addition of  
20 a nucleophile to compound 5. This can be done by mixing an appropriate nucleophile with 5 in an inert solvent such as acetonitrile or trifluoroethanol at room temperature or elevated temperature (up to  $100^\circ\text{C}$ ). The process can be catalyzed by addition of an acid such as acetic acid or a base such as triethylamine.

In Scheme 4, when  $\text{R}^{2b}$  in compound 5 is hydroxy, compound 5 can be converted to  
25 compound 11 by a Mitsunobu reaction. This is done in two steps. The first step involves a reaction of 5 with phthalimide, diethyl diazadicarboxylate, and triphenyl phosphine in an inert solvent such as THF at room temperature overnight. The second step involves a reaction of the resulting phthalimide compound with hydrazine in ethanol at its refluxing temperature for  
30 about 1 hour to about 6 hours. The resulting amine, compound 11, can then be converted to compound 2, a lactam, in the presence of an acid such as acetic acid or a base such as ammonium hydroxide in methanol or ethanol at room temperature for 6 to 72 hours. Compound 2 can be further converted to compound 3 under the same conditions described in  
Scheme 2 for the conversion of 5 to 7 to 9.

In Scheme 5, compound 17 can be treated with NBS to give compound 12, in which  
35  $\text{R}^{13a}$  is bromine. The reaction conditions are the same as those described in Scheme 1 for the conversion of 18 to 4. Compound 12 can then be debrominated by treatment with, for



example, zinc and acetic acid. When  $Y^{bb}$  is NH, compound 12 can be further converted to compound 13 by reductive animation with  $R^6$ -CHO. This can be done by mixing 12 with the aldehyde in an inert solvent such as ethanol for 0.5 hours to 24 hours at room temperature and then treating the resulting intermediate with  $NaBH_4$  at a temperature ranging from  $0^\circ C$  to room temperature for 0.5 hours to about 6 hours.

In Scheme 6, compound 17 can be treated with NBS in THF containing a small amount of water to give hydroxylated intermediate compound 4a, in which  $R^{13a}$  is bromine. Compound 4a can then be treated with, for example, zinc dust in acetic acid at a temperature ranging from about  $0^\circ C$  to room temperature to give compound 5b. Compound 5b can then be treated with dilute acid or base to give the 14-membered lactone, compound 14.

In Scheme 7, compound 5a can be reacted with phthalimide, diethyl diazadicarboxylate, and triphenyl phosphine in an inert solvent such as THF at room temperature overnight to give compound 5b. The resulting phthalimide compound can then be reacted with hydrazine in ethanol at its refluxing temperature for 1 hour to 6 hours to give compound 5c. Compound 5c can then be treated with dilute acid or base to give the 14-membered lactam, compound 2a.

In Scheme 8, compound 17 can be treated with NBS and TMS-azide to give C13 azide compound 4b wherein  $R^{13a}$  is bromine. Compound 4b can then be treated with, for example, zinc dust and acetic acid to give compound 5d. The azido group in compound 5d can then be reduced by hydrogenation using a Lindlar catalyst to give compound 5e. Compound 5e can then be treated with a dilute acid or base and converted to the 14-membered lactam, compound 2b.

In Scheme 9, compound 14 can be converted to compound 15 and further converted to compound 16 under the same conditions described in Scheme 2 for the conversion of 5 to 7 to 9.

The amides, carbamates, esters and carbonates of the present invention can be prepared from the amine or alcohol compounds set forth in the Schemes above by standard methods known to those skilled in the art.

The compounds of the present invention may have asymmetric carbon atoms. Such diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. All such isomers, including diastereomeric mixtures and pure enantiomers are considered as part of the invention.

The compounds of formulas 1-16 that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formulas 1-16 from the reaction mixture as a pharmaceutically

unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially  
5 equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

10 Those compounds of formula 1-16 that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts may be prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those  
15 which form non-toxic base salts with the acidic compounds of formulas 1-16. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness,  
20 preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

25 The activity of the compounds of the present invention against bacterial and protozoa pathogens is demonstrated by the compound's ability to inhibit growth of defined strains of human (Assay I) or animal (Assays II and III) pathogens.

#### Assay I

30 Assay I, described below, employs conventional methodology and interpretation criteria and is designed to provide direction for chemical modifications that may lead to compounds that circumvent defined mechanisms of macrolide resistance. In Assay I, a panel of bacterial strains is assembled to include a variety of target pathogenic species, including representatives of macrolide resistance mechanisms that have been characterized. Use of this panel enables the chemical structure/activity relationship to be determined with respect to  
35 potency, spectrum of activity, and structural elements or modifications that may be necessary to obviate resistance mechanisms. Bacterial pathogens that comprise the screening panel are shown in the table below. In many cases, both the macrolide-susceptible parent strain

and the macrolide-resistant strain derived from it are available to provide a more accurate assessment of the compound's ability to circumvent the resistance mechanism. Strains that contain the gene with the designation of *ermA/ermB/ermC* are resistant to macrolides, lincosamides, and streptogramin B antibiotics due to modifications (methylation) of 23S rRNA molecules by an Erm methylase, thereby generally prevent the binding of all three structural classes. Two types of macrolide efflux have been described; *msrA* encodes a component of an efflux system in staphylococci that prevents the entry of macrolides and streptogramins while *mefA/E* encodes a transmembrane protein that appears to efflux only macrolides. Inactivation of macrolide antibiotics can occur and can be mediated by either a phosphorylation of the 2'-hydroxy (*mph*) or by cleavage of the macrocyclic lactone (esterase). The strains may be characterized using conventional polymerase chain reaction (PCR) technology and/or by sequencing the resistance determinant. The use of PCR technology in this application is described in J. Sutcliffe et al., "Detection Of Erythromycin-Resistant Determinants By PCR", *Antimicrobial Agents and Chemotherapy*, 40(11), 2562-2566 (1996). The assay is performed in microtiter trays and interpreted according to Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition; Approved Standard, published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines; the minimum inhibitory concentration (MIC) is used to compare strains. Compounds are initially dissolved in dimethylsulfoxide (DMSO) as 40 mg/ml stock solutions.

Strain Designation	Macrolide Resistance Mechanism(s)
Staphylococcus aureus 1116	susceptible parent
Staphylococcus aureus 1117	ErmB
Staphylococcus aureus 0052	susceptible parent
Staphylococcus aureus 1120	ErmC
Staphylococcus aureus 1032	<i>msrA</i> , <i>mph</i> , esterase
Staphylococcus hemolyticus 1006	<i>msrA</i> , <i>mph</i>
Streptococcus pyogenes 0203	susceptible parent
Streptococcus pyogenes 1079	ErmB
Streptococcus pyogenes 1062	susceptible parent
Streptococcus pyogenes 1061	ErmB
Streptococcus pyogenes 1064	ErmB
Streptococcus agalactiae 1024	susceptible parent
Streptococcus agalactiae 1023	ErmB
Streptococcus pneumoniae 1016	Susceptible
Streptococcus pneumoniae 1046	ErmB
Streptococcus pneumoniae 1095	ErmB

Strain Designation	Macrolide Resistance Mechanism(s)
Streptococcus pneumoniae 1175	MefE
Streptococcus pneumoniae 0085	Susceptible
Haemophilus influenzae 0131	Susceptible
Moraxella catarrhalis 0040	Susceptible
Moraxella catarrhalis 1055	erythromycin intermediate resistance
Escherichia coli 0266	Susceptible

Assay II is utilized to test for activity against *Pasteurella multocida* and Assay III is utilized to test for activity against *Pasteurella haemolytica*.

#### Assay II

5 This assay is based on the liquid dilution method in microliter format. A single colony of *P. multocida* (strain 59A067) is inoculated into 5 ml of brain heart infusion (BHI) broth. The test compounds are prepared by solubilizing 1 mg of the compound in 125  $\mu$ l of dimethylsulfoxide (DMSO). Dilutions of the test compound are prepared using uninoculated BHI broth. The concentrations of the test compound used range from 200  $\mu$ g/ml to 0.098  $\mu$ g/ml by two-fold  
10 serial dilutions. The *P. multocida* inoculated BHI is diluted with uninoculated BHI broth to make a  $10^4$  cell suspension per 200  $\mu$ l. The BHI cell suspensions are mixed with respective serial dilutions of the test compound, and incubated at 37°C for 18 hours. The minimum inhibitory concentration (MIC) is equal to the concentration of the compound exhibiting 100% inhibition of growth of *P. multocida* as determined by comparison with an uninoculated control.

#### Assay III

15 This assay is based on the agar dilution method using a Steers Replicator. Two to five colonies isolated from an agar plate are inoculated into BHI broth and incubated overnight at 37°C with shaking (200 rpm). The next morning, 300  $\mu$ l of the fully grown *P. haemolytica* preculture is inoculated into 3 ml of fresh BHI broth and is incubated at 37°C with shaking (200  
20 rpm). The appropriate amounts of the test compounds are dissolved in ethanol and a series of two-fold serial dilutions are prepared. Two ml of the respective serial dilution is mixed with 18 ml of molten BHI agar and solidified. When the inoculated *P. haemolytica* culture reaches 0.5 McFarland standard density, about 5  $\mu$ l of the *P. haemolytica* culture is inoculated onto BHI agar plates containing the various concentrations of the test compound using a Steers Replicator and  
25 incubated for 18 hours at 37°C. Initial concentrations of the test compound range from 100-200  $\mu$ g/ml. The MIC is equal to the concentration of the test compound exhibiting 100% inhibition of growth of *P. haemolytica* as determined by comparison with an uninoculated control.

The in vivo activity of the compounds of formulas 1-16 can be determined by conventional animal protection studies well known to those skilled in the art, usually carried out in mice.

Mice are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for  
5 a minimum of 48 hours before being used. Animals are inoculated with 0.5 ml of a  $3 \times 10^3$   
CFU/ml bacterial suspension (*P. multocida* strain 59A006) intraperitoneally. Each experiment  
has at least 3 non-medicated control groups including one infected with 0.1X challenge dose  
and two infected with 1X challenge dose; a 10X challenge data group may also be used.  
Generally, all mice in a given study can be challenged within 30-90 minutes, especially if a  
10 repeating syringe (such as a Cornwall® syringe) is used to administer the challenge. Thirty  
minutes after challenging has begun, the first compound treatment is given. It may be  
necessary for a second person to begin compound dosing if all of the animals have not been  
challenged at the end of 30 minutes. The routes of administration are subcutaneous or oral  
doses. Subcutaneous doses are administered into the loose skin in the back of the neck  
15 whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml  
is used per mouse. Compounds are administered 30 minutes, 4 hours, and 24 hours after  
challenge. A control compound of known efficacy administered by the same route is included in  
each test. Animals are observed daily, and the number of survivors in each group is recorded.  
The *P. multocida* model monitoring continues for 96 hours (four days) post challenge.

20 The  $PD_{50}$  is a calculated dose at which the compound tested protects 50% of a group of  
mice from mortality due to the bacterial infection which would be lethal in the absence of drug  
treatment.

The compounds of formulas 1-16, and the pharmaceutically acceptable salts and  
solvates thereof (hereinafter "the active compounds"), may be administered through oral,  
25 parenteral, topical, or rectal routes in the treatment or prevention of bacterial or protozoa  
infections. In general, these compounds are most desirably administered in dosages ranging  
from about 0.2 mg per kg body weight per day (mg/kg/day) to about 200 mg/kg/day in single or  
divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur  
depending upon the species, weight and condition of the subject being treated and the  
30 particular route of administration chosen. However, a dosage level that is in the range of about  
4 mg/kg/day to about 50 mg/kg/day is most desirably employed. Variations may nevertheless  
occur depending upon the species of mammal, fish or bird being treated and its individual  
response to said medicament, as well as on the type of pharmaceutical formulation chosen and  
the time period and interval at which such administration is carried out. In some instances,  
35 dosage levels below the lower limit of the aforesaid range may be more than adequate, while in  
other cases still larger doses may be employed without causing any harmful side effects,

provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the active compounds may be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active compound may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of an active compound in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer the active compounds of the present invention topically and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

For administration to animals other than humans, such as cattle or domestic animals, the active compounds may be administered in the feed of the animals or orally as a drench composition.

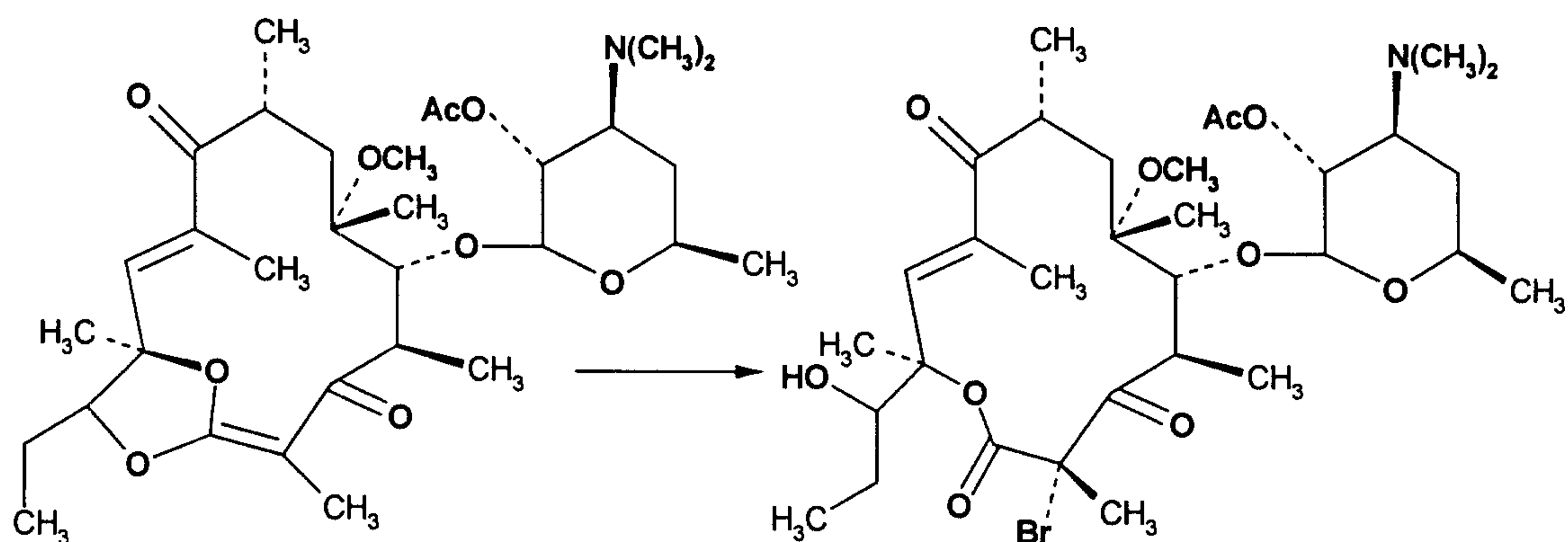
5 The active compounds may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

10 The active compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide phenyl, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoylresidues. Furthermore, the active compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, 15 polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

20 The compounds of this invention may be co-administered with other compounds of this invention or with other prokinetic compounds to increase the effect of therapy. Combination therapies according to this invention may exert an additive or synergistic prokinetic effect, e.g., because each component agent of the combination may act on a different site or through a different mechanism. The use of such combination therapies may also advantageously reduce the dosage of a given conventional prokinetic agent that would be required for a desired therapeutic effect, as compared to when that agent is administered as a monotherapy. Such combinations may reduce or eliminate the side effects of 25 conventional prokinetic therapies, while not interfering with the prokinetic activity of those agents. These combinations reduce the potential of resistance to single agent therapies, while minimizing any associated toxicity. Alternatively, pharmaceutical compositions according to this invention may be comprised of a combination of a compound of this invention and another agent having a different therapeutic or prophylactic effect.

30 The Example(s) provided below illustrate specific embodiments of the invention, but the invention is not limited in scope to the Examples specifically exemplified.

#### Example 1

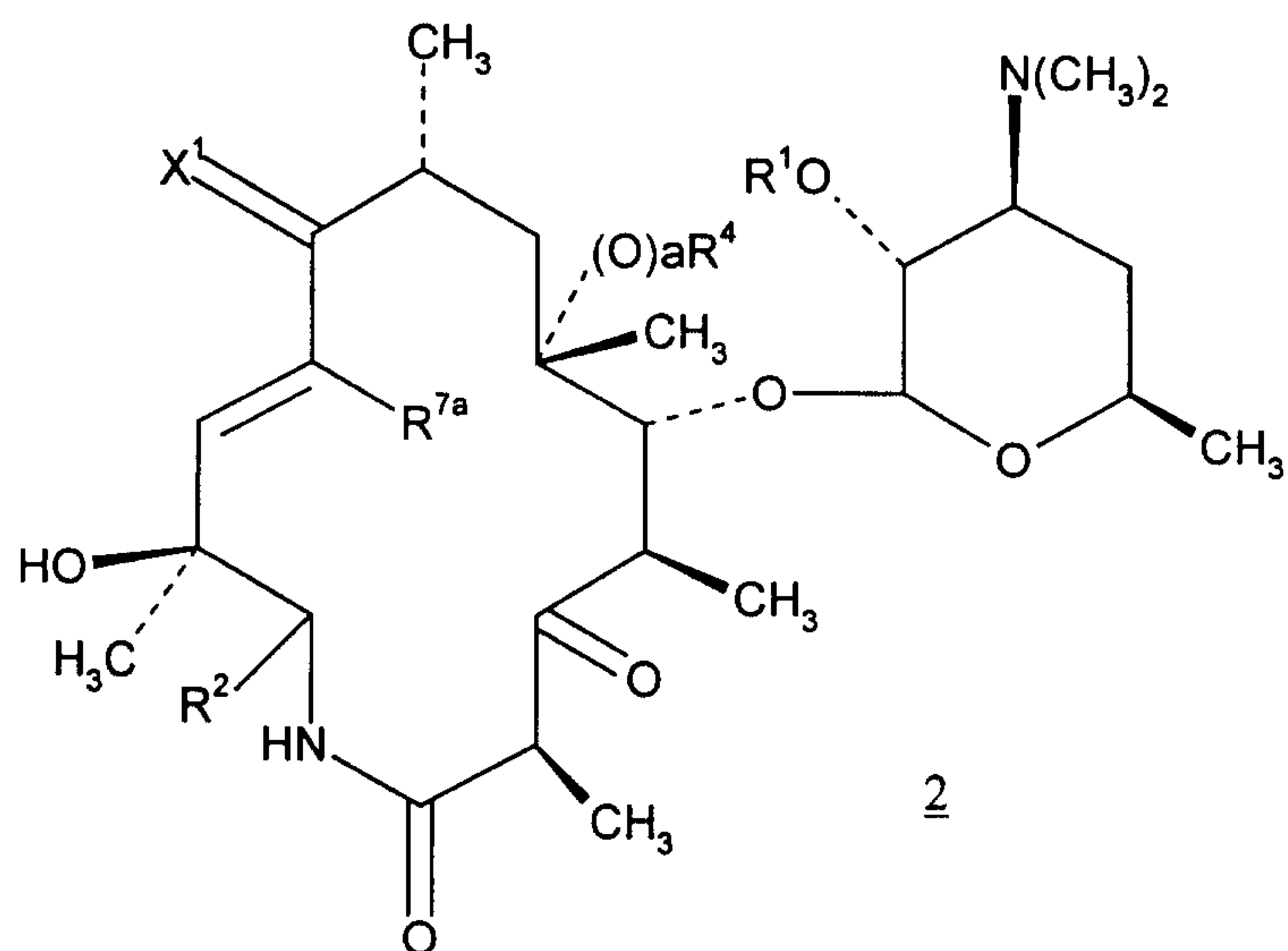


- To a solution of ketene acetal (**18**, 30 mg, 0.05 mmol) in 1 mL of a 1:1 mixture of THF and H<sub>2</sub>O was added N-bromosuccinimide at room temperature. After 2 minutes of stirring the reaction mixture was diluted with 15 ml of ethyl acetate and washed with water and brine.
5. Drying over Na<sub>2</sub>SO<sub>4</sub> and removal of the solvent gave 29 mg of crude product. This material was purified by silica gel chromatography (TLC plate, 5% MeOH-0.5% NH<sub>4</sub>OH-CH<sub>2</sub>Cl<sub>2</sub>) to give 19 mg of the purified product **4**: MS m/e 690 (M+).

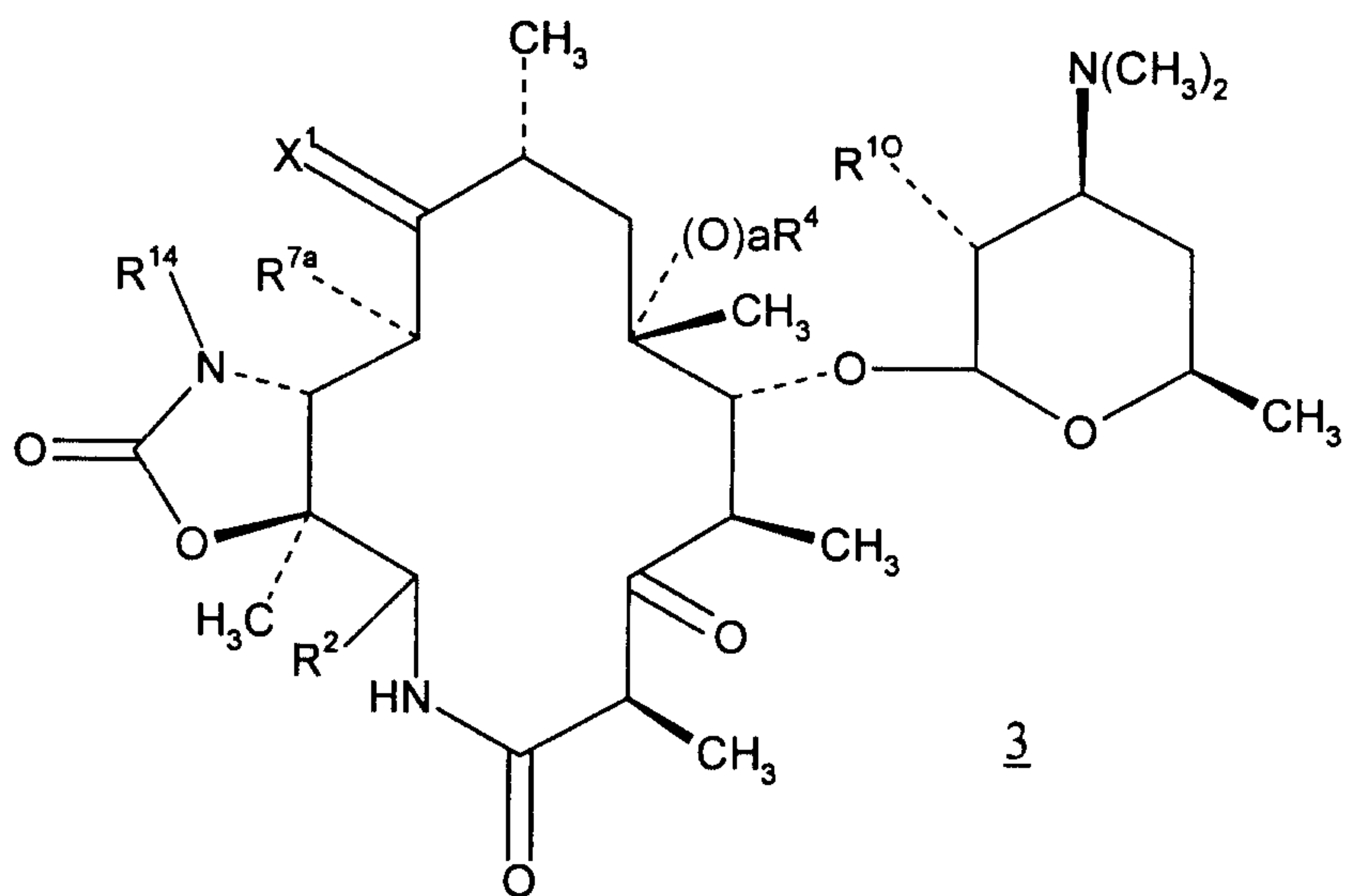


CLAIMS

1. A compound of the formula

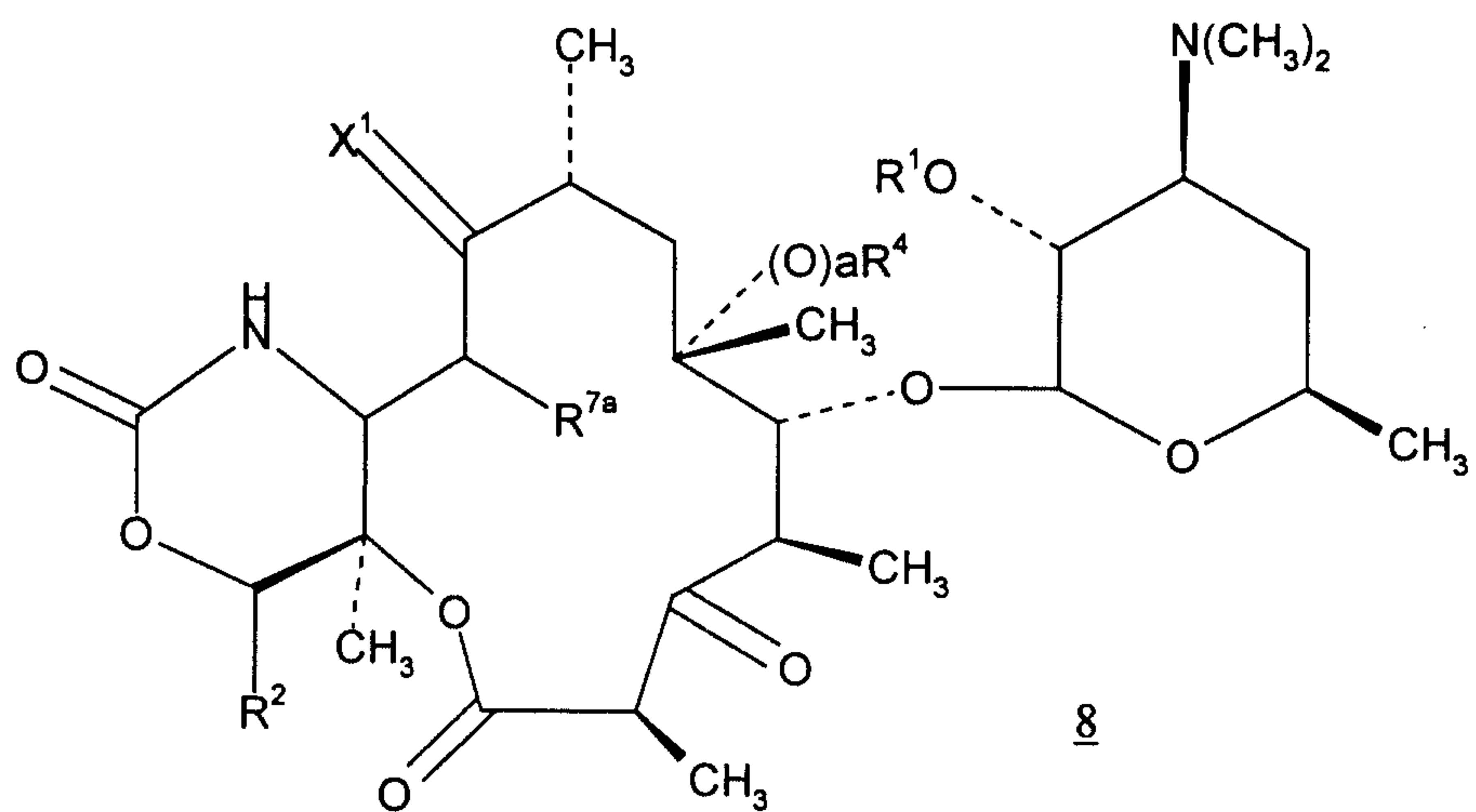


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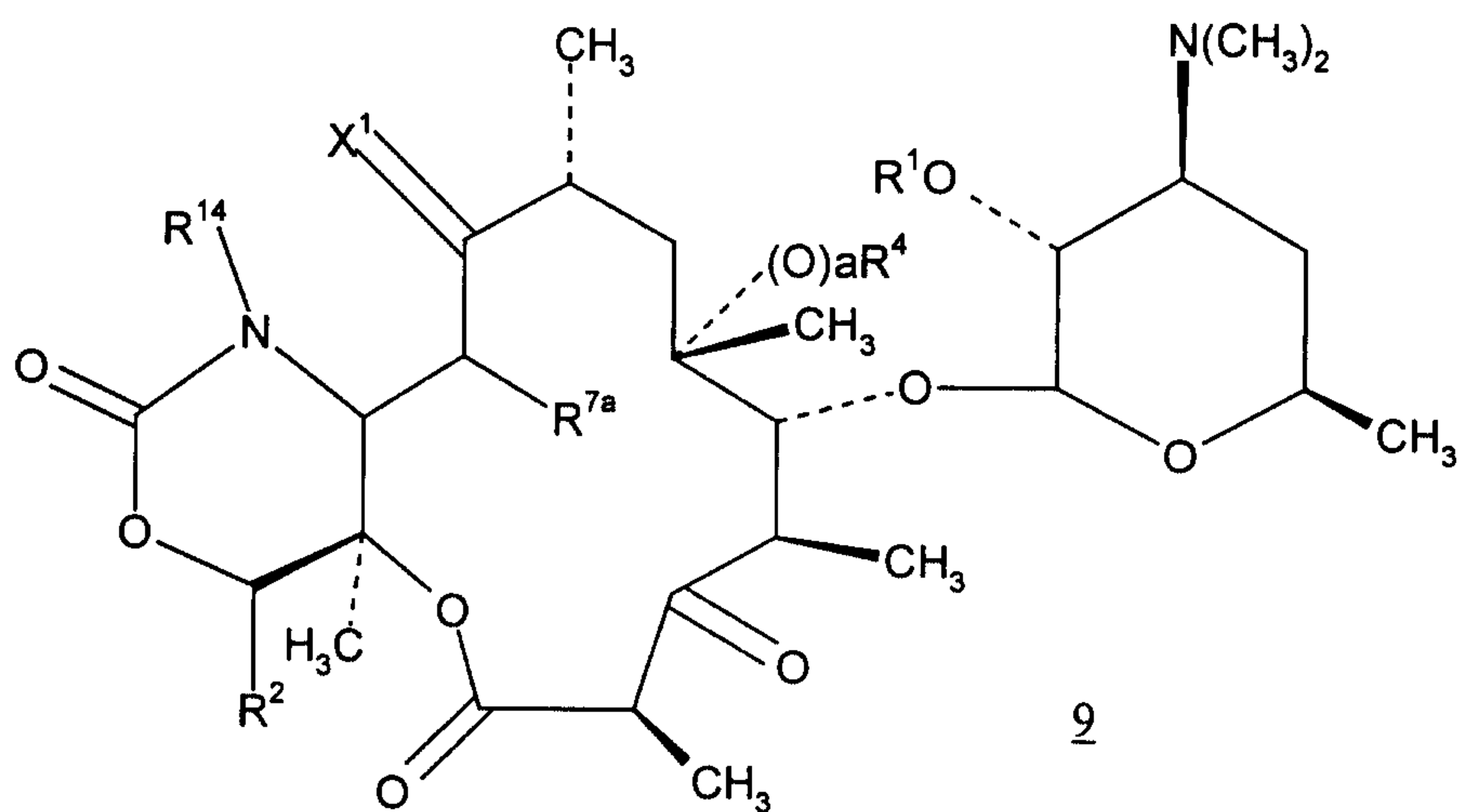


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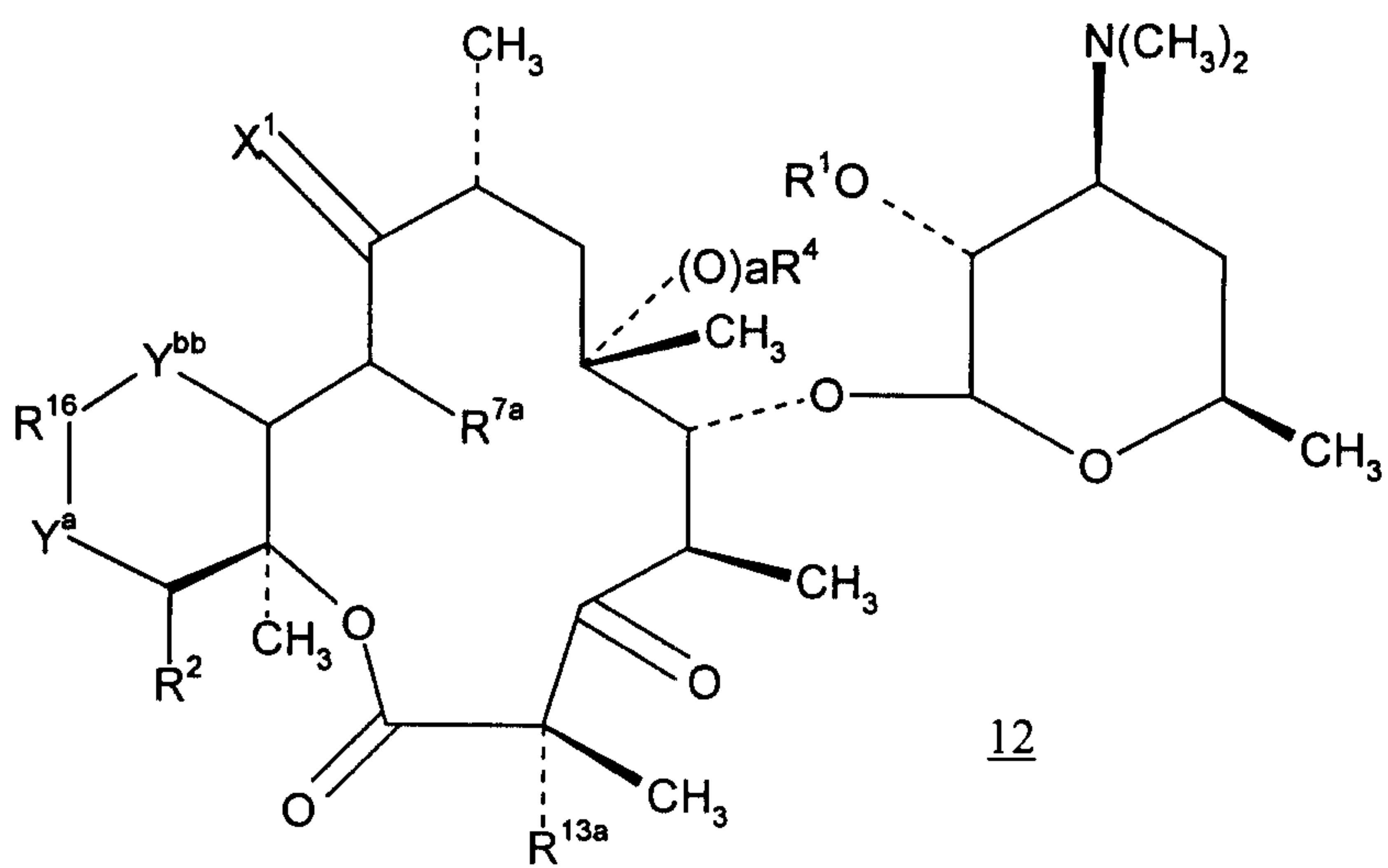
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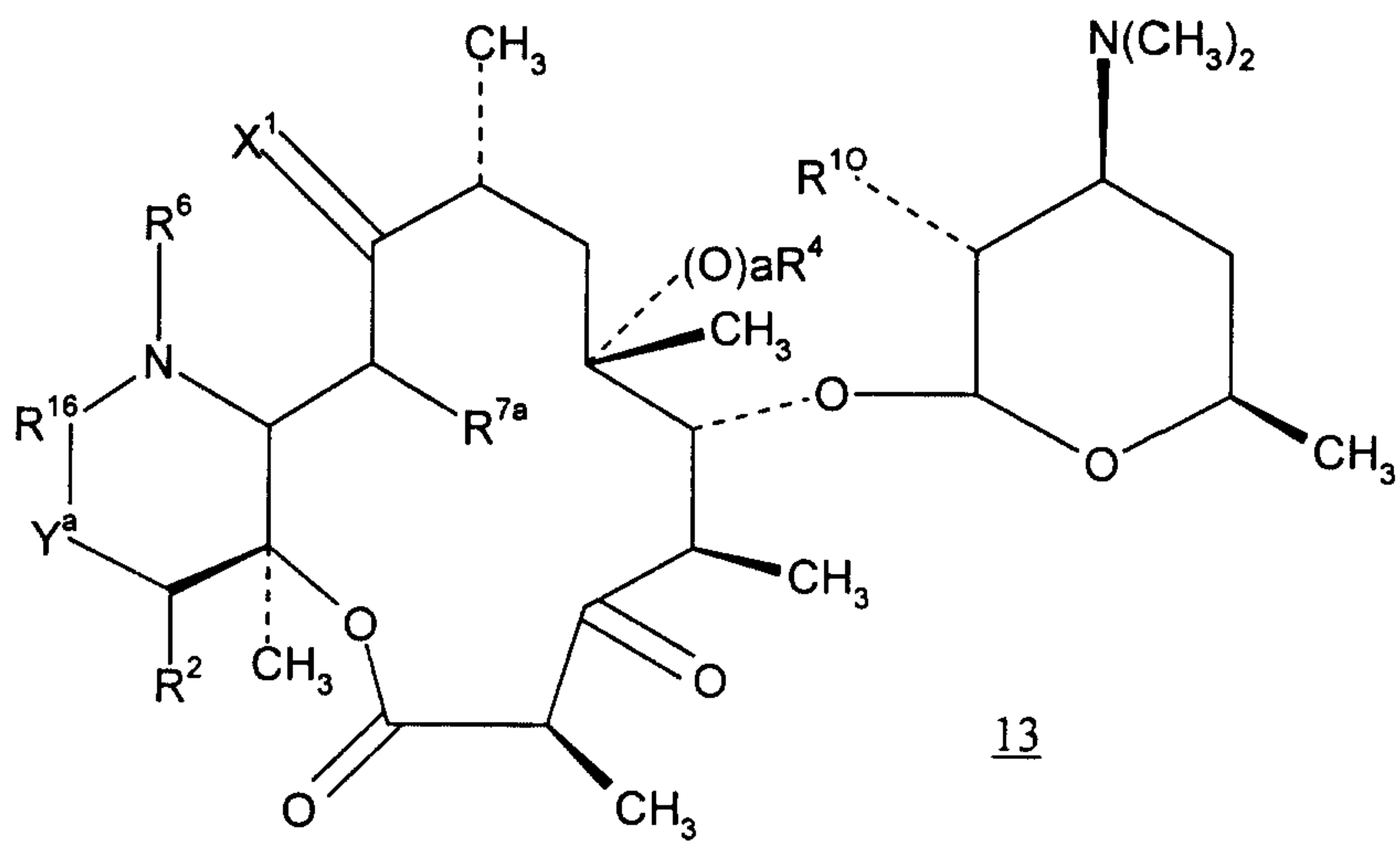
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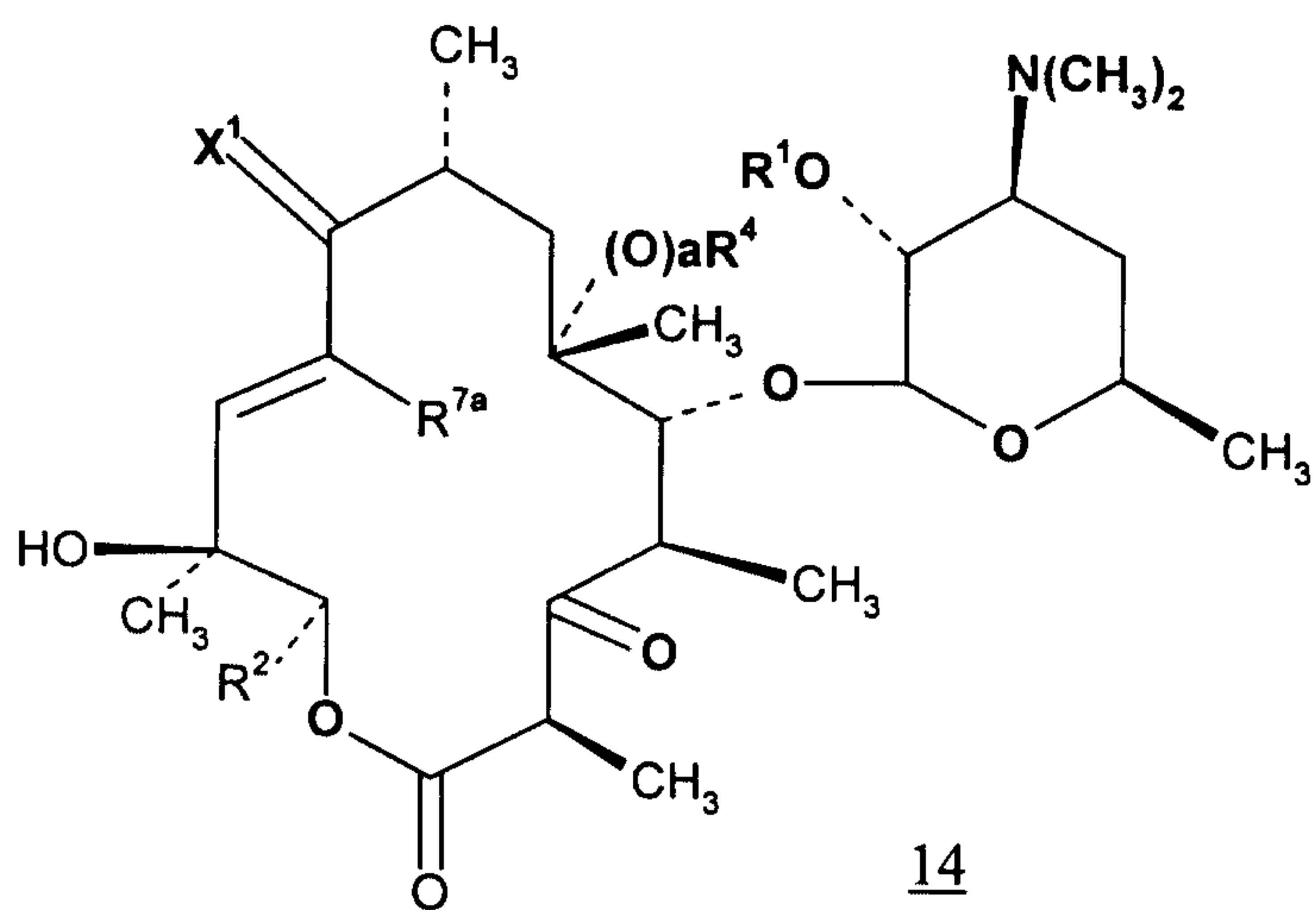
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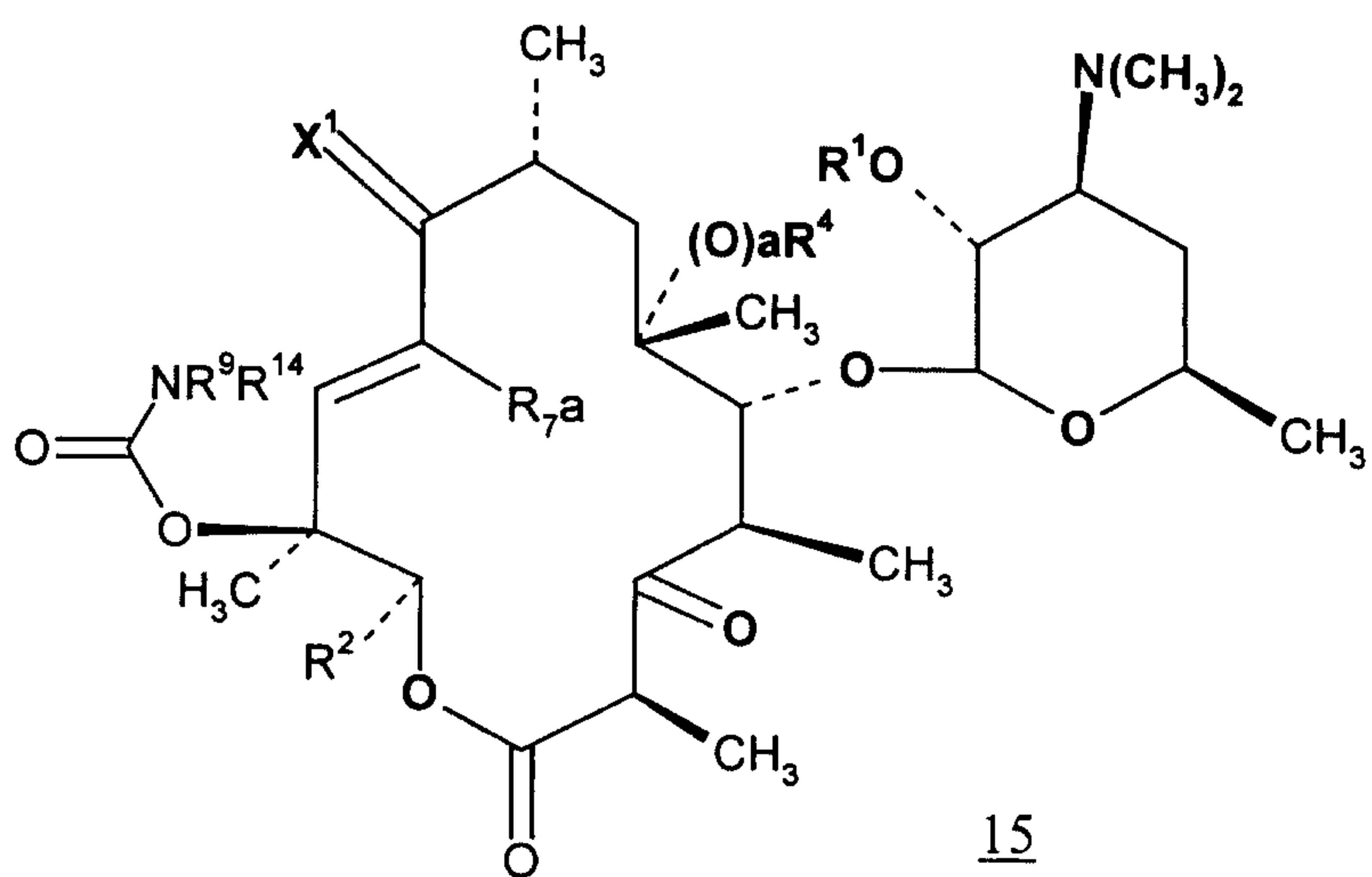
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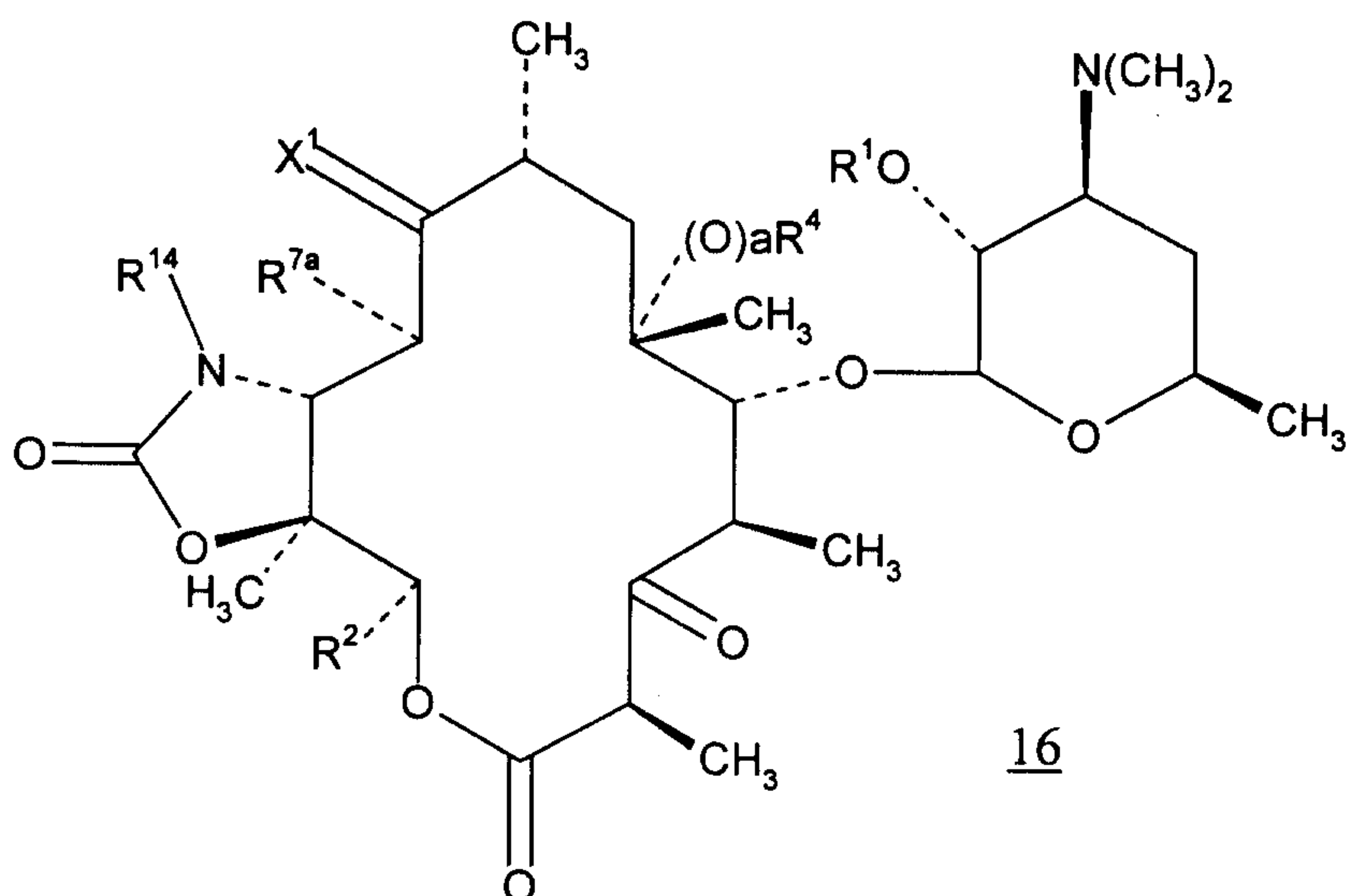


or



5

or



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

a is 0 or 1;

R<sup>1</sup> is hydrogen or a hydroxy protecting group;

5 R<sup>2</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>5</sub>-C<sub>10</sub> cycloalkenyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, (C<sub>1</sub>-C<sub>6</sub> alkoxy)C<sub>1</sub>-C<sub>6</sub> alkyl, (C<sub>1</sub>-C<sub>6</sub> alkylthio)C<sub>1</sub>-C<sub>6</sub> alkyl, -(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), and -(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 6, and the foregoing R<sup>2</sup> groups, except hydrogen, are optionally substituted by one to three R<sup>8</sup> substituents;

10 R<sup>2a</sup> is -NH<sub>2</sub>, -NR<sup>9</sup>R<sup>14</sup>, -NHC(O)R<sup>6</sup>, -NHC(O)OR<sup>6</sup>, -OR<sup>6</sup>, -OC(O)R<sup>6</sup>, -OC(O)NR<sup>9</sup>R<sup>14</sup> or R<sup>2b</sup>;

each R<sup>2b</sup> is hydroxy, azido, cyano, -OCN, -SH or -SCN;

R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted by one or two R<sup>8</sup> groups;

15 each R<sup>6</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>12</sub> alkenyl, C<sub>2</sub>-C<sub>12</sub> alkynyl, (C<sub>3</sub>-C<sub>10</sub> cycloalkyl)C<sub>1</sub>-C<sub>6</sub> alkyl, -(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), and -(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 6; and the foregoing R<sup>6</sup> groups, except hydrogen, are optionally substituted by one to three R<sup>8</sup> substituents;

R<sup>7a</sup> is hydrogen or methyl;

20 each R<sup>8</sup> is independently selected from C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -OR<sup>9</sup>, -C(O)R<sup>9</sup>, -C(O)OR<sup>9</sup>, -NR<sup>10</sup>C(O)OR<sup>12</sup>, -OC(O)R<sup>9</sup>, -NR<sup>10</sup>SO<sub>2</sub>R<sup>12</sup>, -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, -NR<sup>10</sup>C(O)R<sup>9</sup>, -C(O)NR<sup>9</sup>R<sup>10</sup>, -NR<sup>9</sup>R<sup>10</sup>, -S(O)<sub>j</sub>(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), -S(O)<sub>j</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), wherein j is an integer from 0 to 2, -(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), -O(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), -NR<sup>10</sup>(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), and -(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 4; said alkyl, alkenyl and alkynyl groups optionally contain 1 or 2 hetero

25

moieties selected from O,  $-S(O)_j-$  wherein j is an integer from 0 to 2, and  $-N(R^9)-$  with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a triple bond or a non-aromatic double bond; said cycloalkyl, aryl and heterocyclic  $R^2$  groups are optionally fused to a  $C_6-C_{10}$  aryl group, a  $C_5-C_8$  cycloalkyl group, or a 4 to 10 membered heterocyclic group; and said alkyl, cycloalkyl, aryl and heterocyclic  $R^2$  groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido,  $-NR^{10}SO_2R^{12}$ ,  $-SO_2NR^9R^{10}$ ,  $-C(O)R^9$ ,  $-C(O)OR^9$ ,  $-OC(O)R^9$ ,  $-NR^{10}C(O)OR^{12}$ ,  $-NR^{10}C(O)R^9$ ,  $-C(O)NR^9R^{10}$ ,  $-NR^9R^{10}$ ,  $-OR^9$ ,  $C_1-C_{10}$  alkyl,  $-(CR^{10}R^{11})_m(C_6-C_{10}$  aryl), and  $-(CR^{10}R^{11})_m(4$  to 10 membered heterocyclic), wherein each m is independently an integer ranging from 0 to 4;

each  $R^9$  is independently selected from H,  $C_1-C_{10}$  alkyl,  $-(CR^{10}R^{11})_m(C_6-C_{10}$  aryl), and  $-(CR^{10}R^{11})_m(4$  to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 4; said alkyl group optionally includes 1 or 2 hetero moieties selected from O,  $-S(O)_j-$  wherein j is an integer ranging from 0 to 2, and  $-N(R^{10})-$  with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said cycloalkyl, aryl and heterocyclic  $R^9$  groups are optionally fused to a  $C_6-C_{10}$  aryl group, a  $C_5-C_8$  cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing  $R^9$  substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido,  $-C(O)R^{10}$ ,  $-C(O)OR^{10}$ ,  $-OC(O)R^{10}$ ,  $-NR^{10}C(O)R^{11}$ ,  $-C(O)NR^{10}R^{11}$ ,  $-NR^{10}R^{11}$ , hydroxy,  $C_1-C_6$  alkyl, and  $C_1-C_6$  alkoxy, and with the proviso that  $R^9$  must be attached through a carbon atom unless  $R^9$  is H;

each  $R^{10}$  and  $R^{11}$  is independently H or  $C_1-C_6$  alkyl;

each  $R^{12}$  is selected from the substituents provided in the definition of  $R^9$  except  $R^{12}$  is not H;

$R^{13}$  is hydrogen or halogen;

$R^{13a}$  is halogen;

$R^{14}$  is  $-R^6$ ,  $-OR^6$  or  $-NHR^6$ ;

$R^{16}$  is  $(C_2-C_4)$ alkylene wherein the alkylene group is optionally substituted by one to three  $R^8$  substituents;

$X^1$  is  $=O$  or  $=NOR^6$ ;

$Y^a$  is  $-NH-$ ,  $-O-$  or  $-S-$ ;

$Y^{bb}$  is  $-NH-$ ,  $-O-$  or  $-S-$ ; and

with the proviso that when a is zero,  $R^4$  is hydrogen.

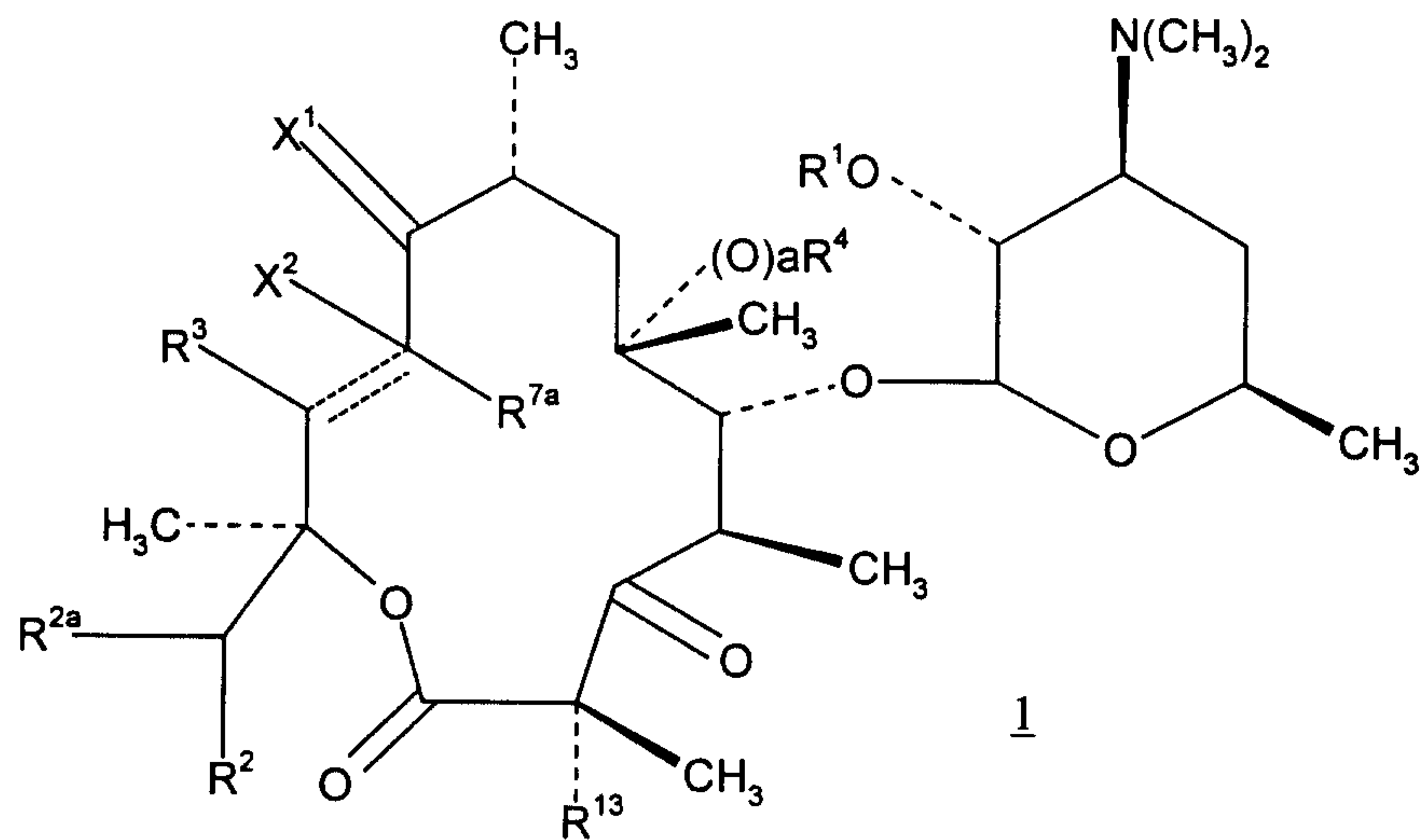
2. A pharmaceutical composition for the treatment of a disorder selected from a bacterial infection, a protozoal infection, and a disorder related to a bacterial infection or

protozoal infection in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

3. A method of treating a disorder selected from a bacterial infection, a protozoal infection, and a disorder related to a bacterial infection or protozoal infection in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound of claim 1.

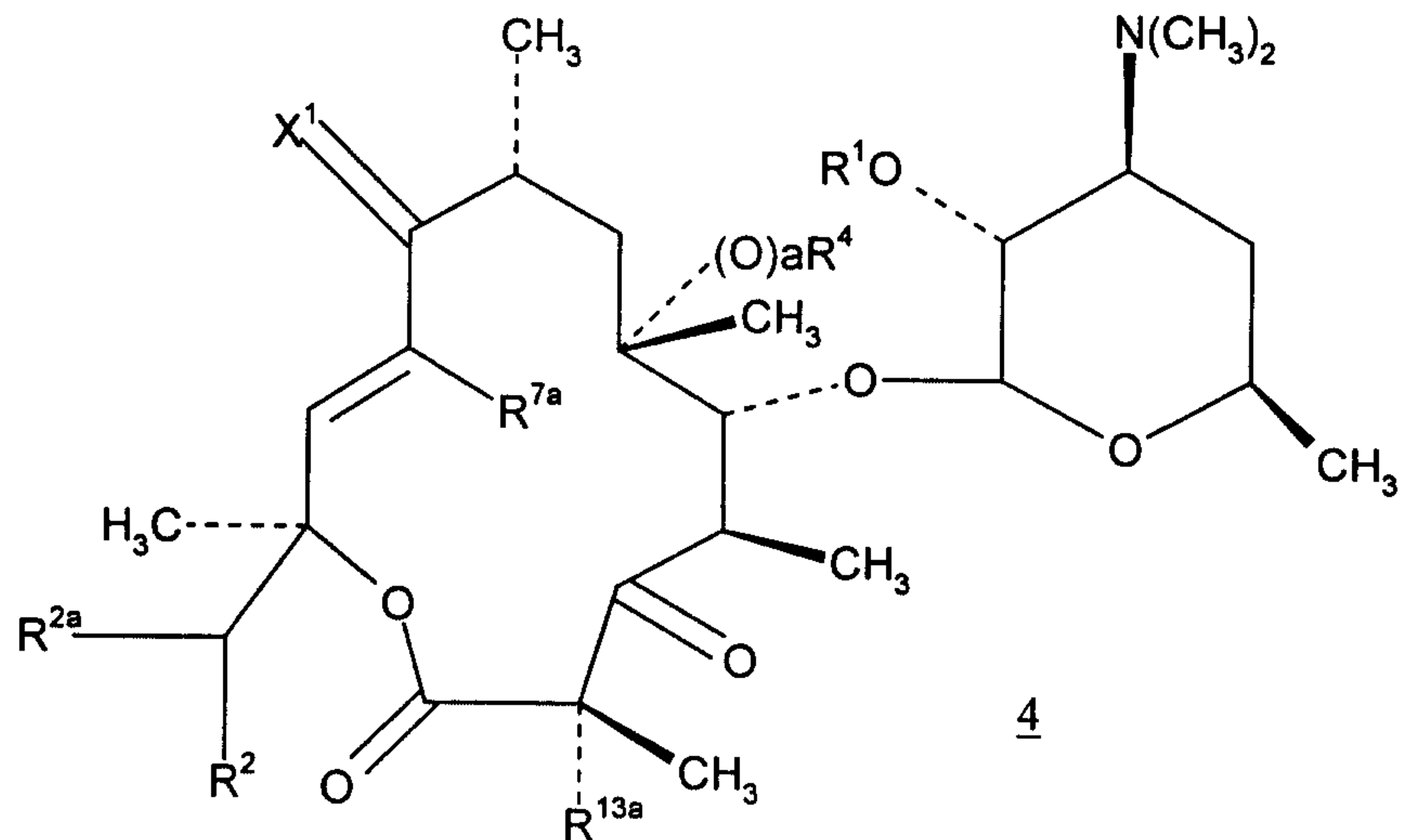
4. A method of treating cancer or atherosclerosis in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of claim 1.

5. A compound of the formula

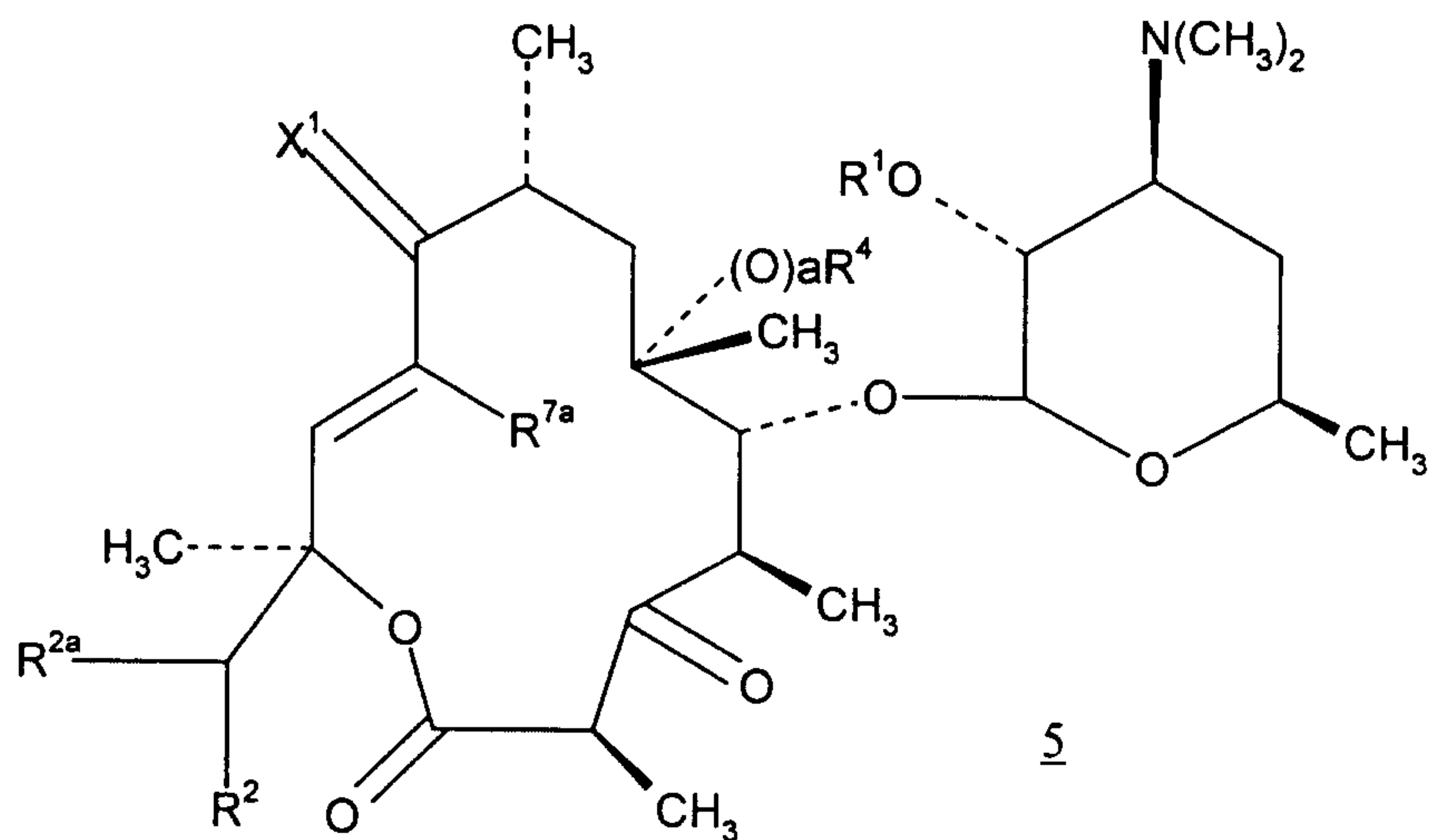


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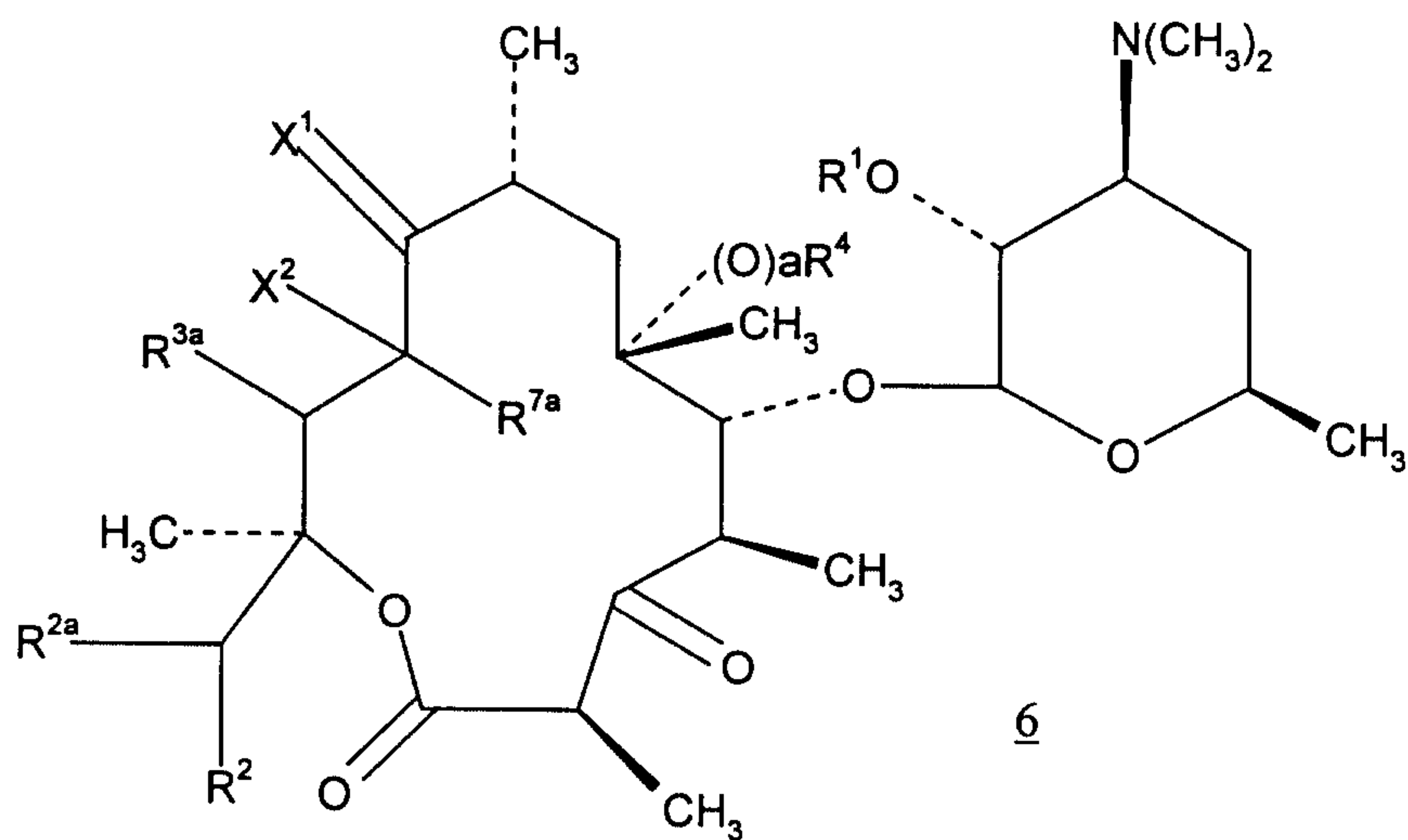
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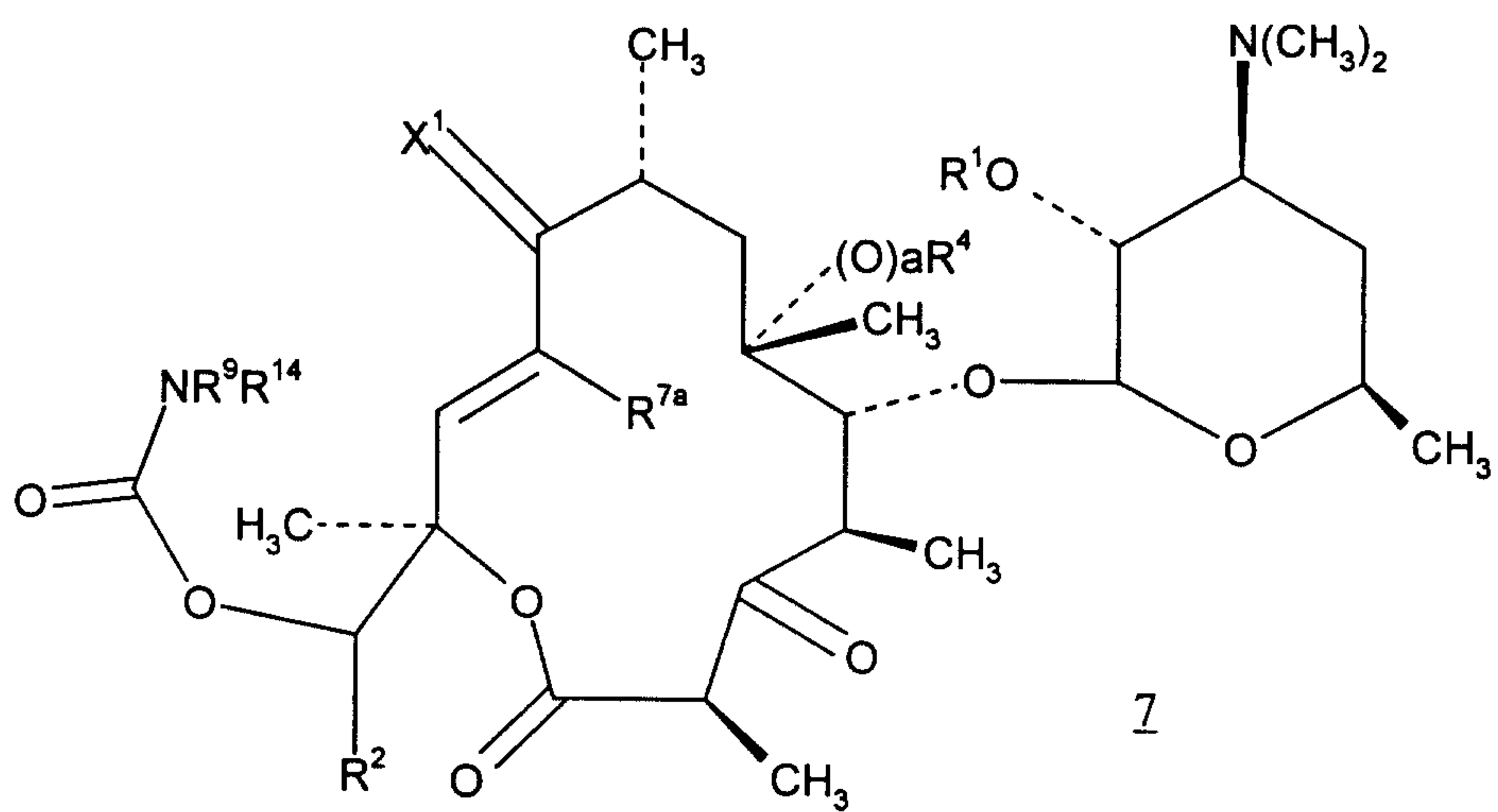
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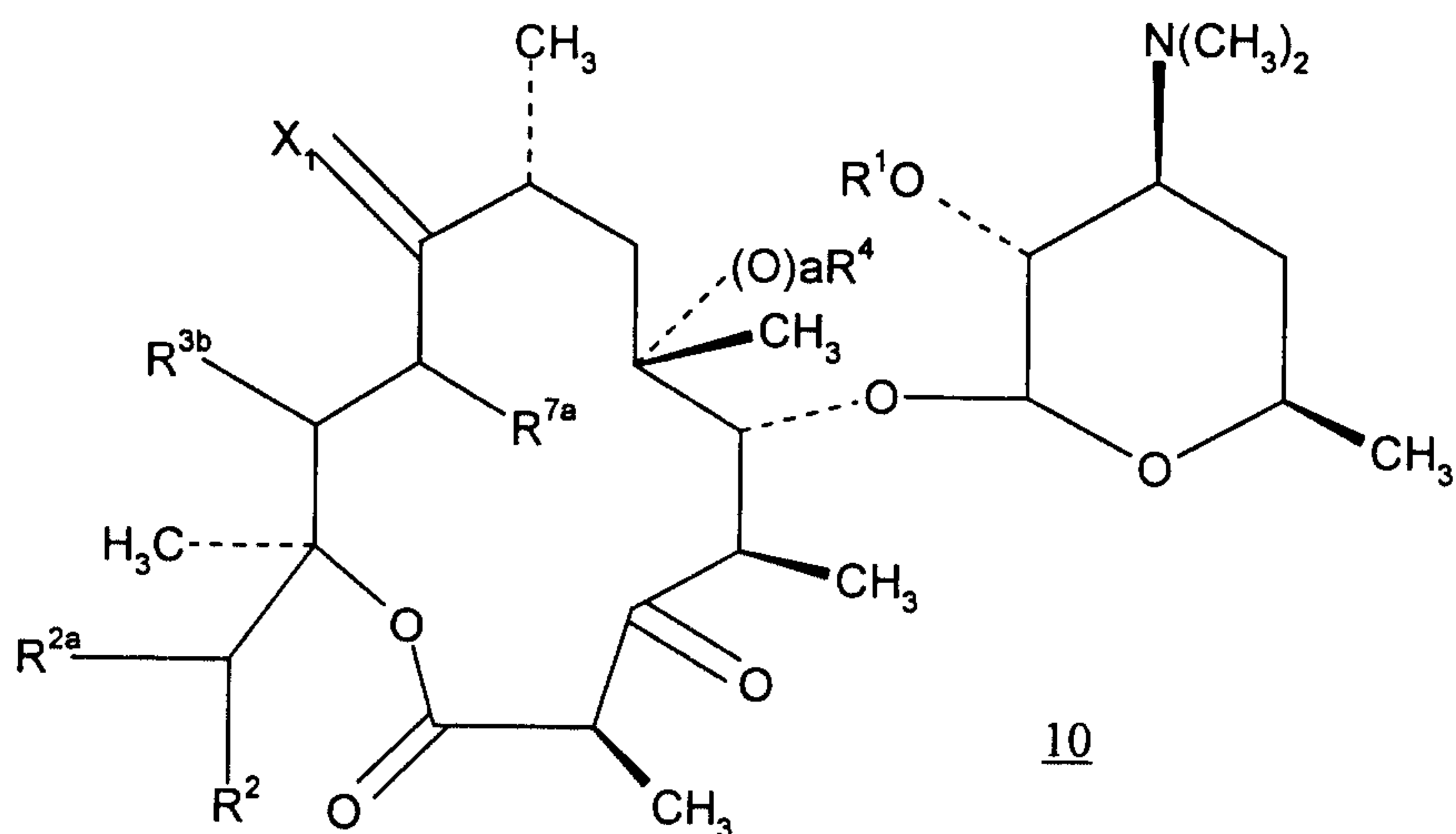


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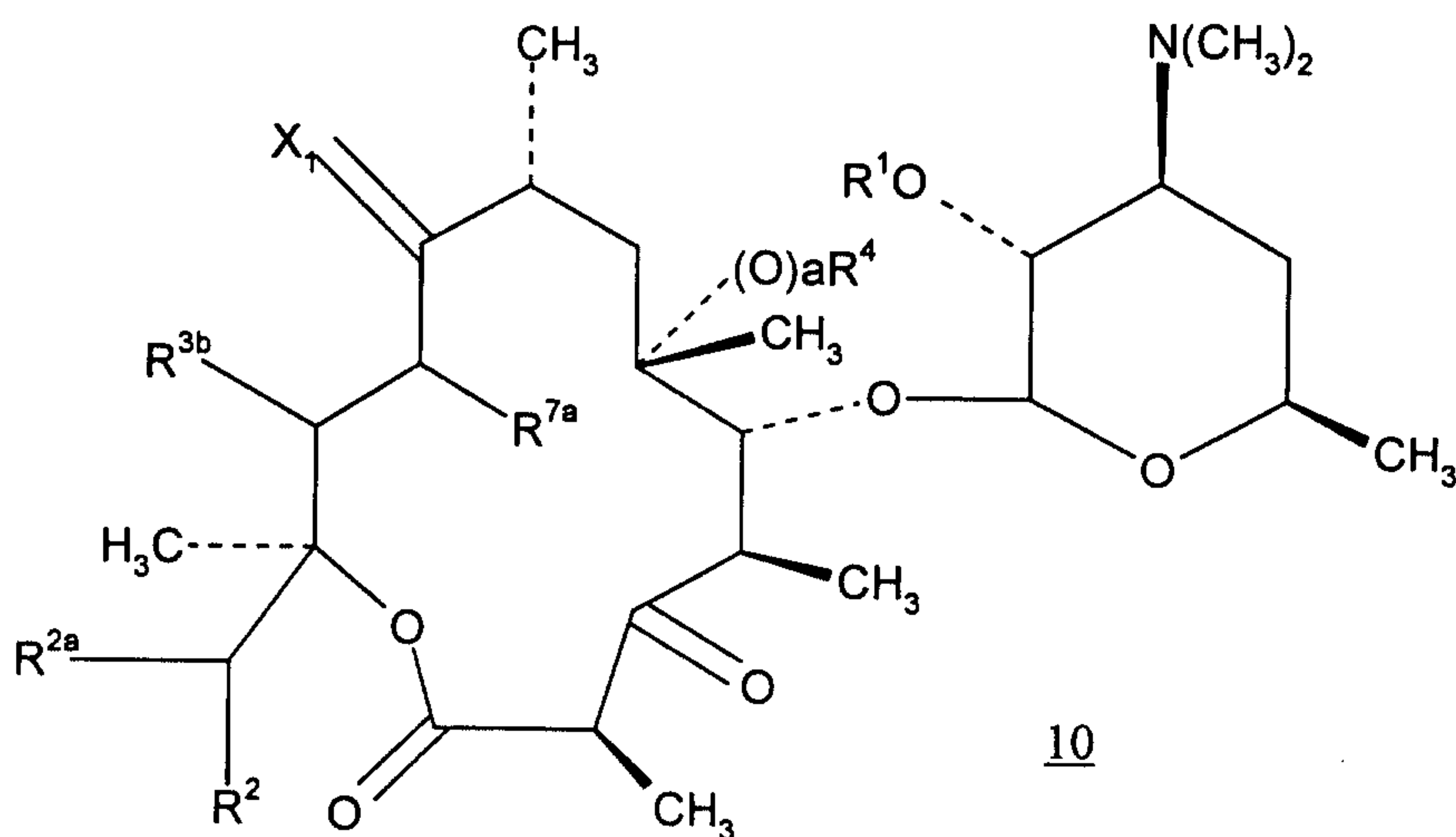


5

or



or



or a salt or solvate thereof, wherein:

- 5           the dashed line between positions 10 and 11 in formula 1 represents an optional double bond;
- a is 0 or 1;
- R<sup>1</sup> is hydrogen or a hydroxy protecting group;
- R<sup>2</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>5</sub>-C<sub>10</sub> cycloalkenyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, (C<sub>1</sub>-C<sub>6</sub> alkoxy)C<sub>1</sub>-C<sub>6</sub> alkyl, (C<sub>1</sub>-C<sub>6</sub> alkylthio)C<sub>1</sub>-C<sub>6</sub> alkyl, -(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(C<sub>6</sub>-C<sub>10</sub> aryl), and -(CR<sup>10</sup>R<sup>11</sup>)<sub>m</sub>(4 to 10 membered heterocyclic), wherein each m is independently an integer from 0 to 6, and the foregoing R<sup>2</sup> groups, except hydrogen, are optionally substituted by one to three R<sup>8</sup> substituents;
- 10           R<sup>2a</sup> is -NH<sub>2</sub>, -NR<sup>9</sup>R<sup>14</sup>, -NHC(O)R<sup>6</sup>, -NHC(O)OR<sup>6</sup>, -OR<sup>6</sup>, -OC(O)R<sup>6</sup>, -OC(O)NR<sup>9</sup>R<sup>14</sup> or
- 15           R<sup>2b</sup>;
- each R<sup>2b</sup> is hydroxy, azido, cyano, -OCN, -SH or -SCN;
- R<sup>3</sup> is hydrogen, hydroxy, amino, -OR<sup>6</sup>, -NHR<sup>6</sup> or -SR<sup>6</sup>;



$R^{3a}$  is hydrogen, hydroxy or amino;

$R^{3b}$  is  $-OR^6$ ,  $-NHR^6$  or  $-SR^6$ ;

$R^4$  is hydrogen or  $C_1$ - $C_{10}$  alkyl optionally substituted by one or two  $R^8$  groups;

each  $R^6$  is independently selected from hydrogen,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_{12}$  alkenyl,  $C_2$ - $C_{12}$  alkynyl,  $(C_3$ - $C_{10}$  cycloalkyl) $C_1$ - $C_6$  alkyl,  $-(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl), and  $-(CR^{10}R^{11})_m$  (4 to 10 membered heterocyclic), wherein each  $m$  is independently an integer from 0 to 6; and the foregoing  $R^6$  groups, except hydrogen, are optionally substituted by one to three  $R^8$  substituents;

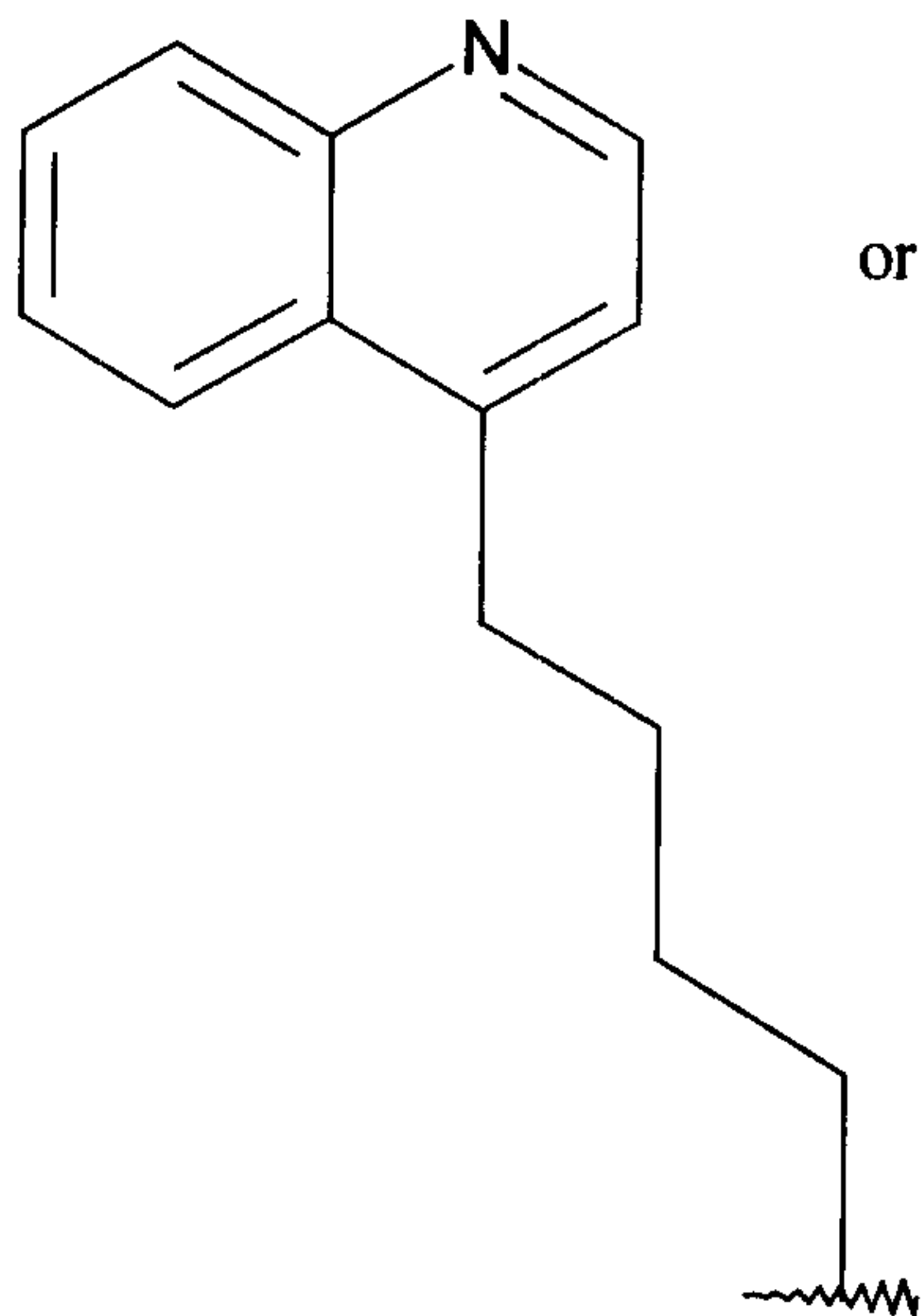
$R^{7a}$  is hydrogen or methyl;

each  $R^8$  is independently selected from  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{10}$  alkynyl, oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido,  $-OR^9$ ,  $-C(O)R^9$ ,  $-C(O)OR^9$ ,  $-NR^{10}C(O)OR^{12}$ ,  $-OC(O)R^9$ ,  $-NR^{10}SO_2R^{12}$ ,  $-SO_2NR^9R^{10}$ ,  $-NR^{10}C(O)R^9$ ,  $-C(O)NR^9R^{10}$ ,  $-NR^9R^{10}$ ,  $-S(O)_j(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl),  $-S(O)_j(C_1$ - $C_6$  alkyl), wherein  $j$  is an integer from 0 to 2,  $-(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl),  $-O(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl),  $-NR^{10}(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl), and  $-(CR^{10}R^{11})_m$  (4 to 10 membered heterocyclic), wherein each  $m$  is independently an integer from 0 to 4; said alkyl, alkenyl and alkynyl groups optionally contain 1 or 2 hetero moieties selected from O,  $-S(O)_j$ - wherein  $j$  is an integer from 0 to 2, and  $-N(R^9)$ - with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other, and the proviso that an O atom, a S atom or a N atom are not attached directly to a triple bond or a non-aromatic double bond; said cycloalkyl, aryl and heterocyclic  $R^2$  groups are optionally fused to a  $C_6$ - $C_{10}$  aryl group, a  $C_5$ - $C_8$  cycloalkyl group, or a 4 to 10 membered heterocyclic group; and said alkyl, cycloalkyl, aryl and heterocyclic  $R^2$  groups are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido,  $-NR^{10}SO_2R^{12}$ ,  $-SO_2NR^9R^{10}$ ,  $-C(O)R^9$ ,  $-C(O)OR^9$ ,  $-OC(O)R^9$ ,  $-NR^{10}C(O)OR^{12}$ ,  $-NR^{10}C(O)R^9$ ,  $-C(O)NR^9R^{10}$ ,  $-NR^9R^{10}$ ,  $-OR^9$ ,  $C_1$ - $C_{10}$  alkyl,  $-(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl), and  $-(CR^{10}R^{11})_m$  (4 to 10 membered heterocyclic), wherein each  $m$  is independently an integer ranging from 0 to 4;

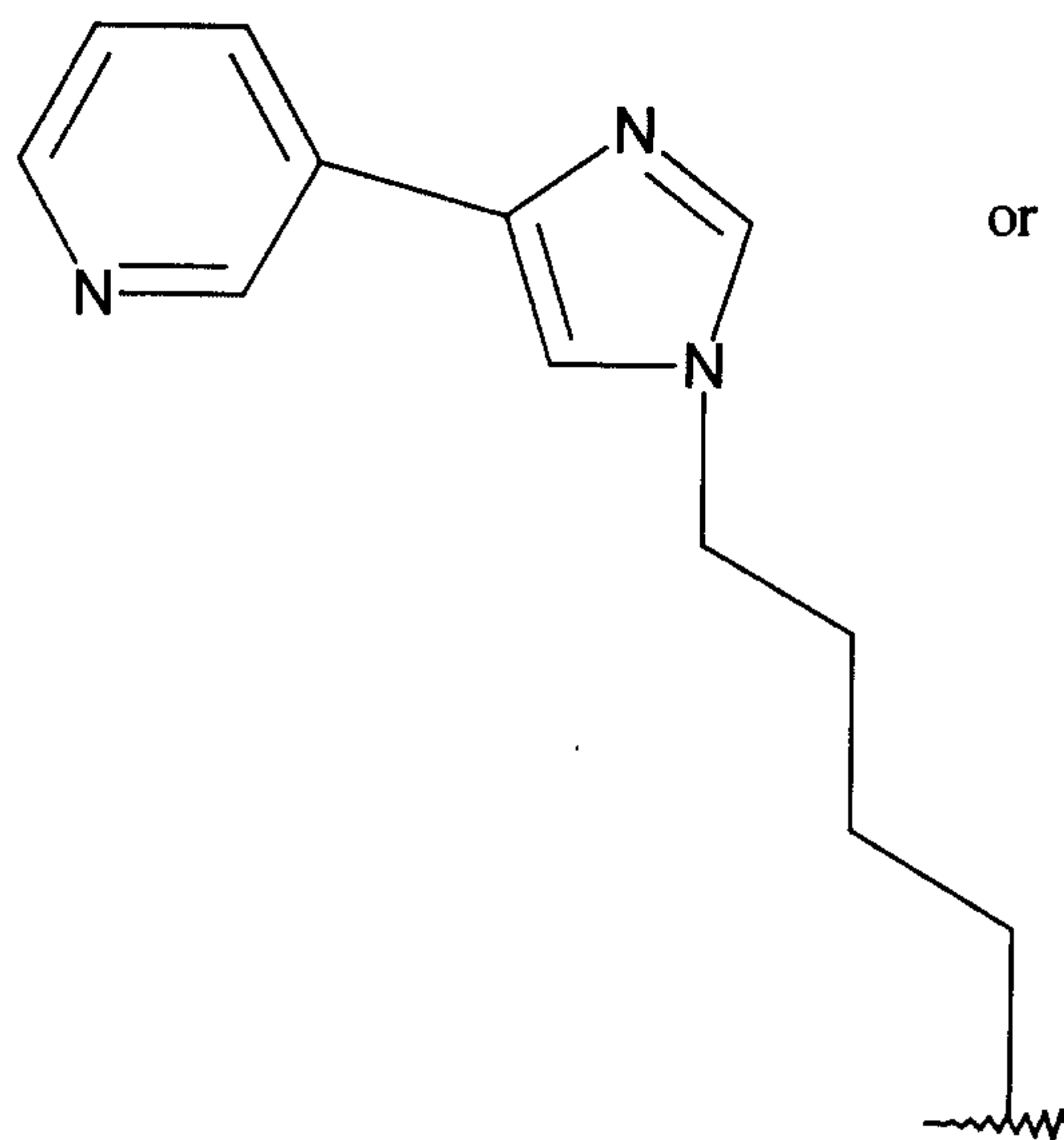
each  $R^9$  is independently selected from H,  $C_1$ - $C_{10}$  alkyl,  $-(CR^{10}R^{11})_m(C_6$ - $C_{10}$  aryl), and  $-(CR^{10}R^{11})_m$  (4 to 10 membered heterocyclic), wherein each  $m$  is independently an integer from 0 to 4; said alkyl group optionally includes 1 or 2 hetero moieties selected from O,  $-S(O)_j$ - wherein  $j$  is an integer ranging from 0 to 2, and  $-N(R^{10})$ - with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; said cycloalkyl, aryl and heterocyclic  $R^9$  groups are optionally fused to a  $C_6$ - $C_{10}$  aryl group, a  $C_5$ - $C_8$  cycloalkyl group, or a 4 to 10 membered heterocyclic group; and the foregoing  $R^9$  substituents, except H, are optionally substituted by 1 to 5 substituents independently selected from oxo, halo, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido,  $-C(O)R^{10}$ ,  $-C(O)OR^{10}$ ,

- OC(O)R<sup>10</sup>, -NR<sup>10</sup>C(O)R<sup>11</sup>, -C(O)NR<sup>10</sup>R<sup>11</sup>, -NR<sup>10</sup>R<sup>11</sup>, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, and C<sub>1</sub>-C<sub>6</sub> alkoxy, and with the proviso that R<sup>9</sup> must be attached through a carbon atom unless R<sup>9</sup> is H;  
 each R<sup>10</sup> and R<sup>11</sup> is independently H or C<sub>1</sub>-C<sub>6</sub> alkyl;  
 each R<sup>12</sup> is selected from the substituents provided in the definition of R<sup>9</sup> except R<sup>12</sup> is not H;
- 5 R<sup>13</sup> is hydrogen or halogen;  
 R<sup>13a</sup> is halogen;  
 R<sup>14</sup> is -R<sup>6</sup>, -OR<sup>6</sup> or -NHR<sup>6</sup>;  
 X<sup>1</sup> is =O or =NOR<sup>6</sup>;
- 10 X<sup>2</sup> is hydrogen or hydroxy;  
 with the proviso that when a is zero, R<sup>4</sup> is hydrogen;  
 and with the proviso that when the dashed line between positions 10 and 11 in formula 1 represents a double bond, X<sup>2</sup> is absent and R<sup>3</sup> is hydrogen.
6. A compound according to claim 5 wherein said compound is a compound of  
 15 formula 4 and a is 1, X<sup>1</sup> is O, R<sup>1</sup> is H, R<sup>2</sup> is CH<sub>2</sub>CH<sub>3</sub> and R<sup>4</sup> is CH<sub>3</sub>.

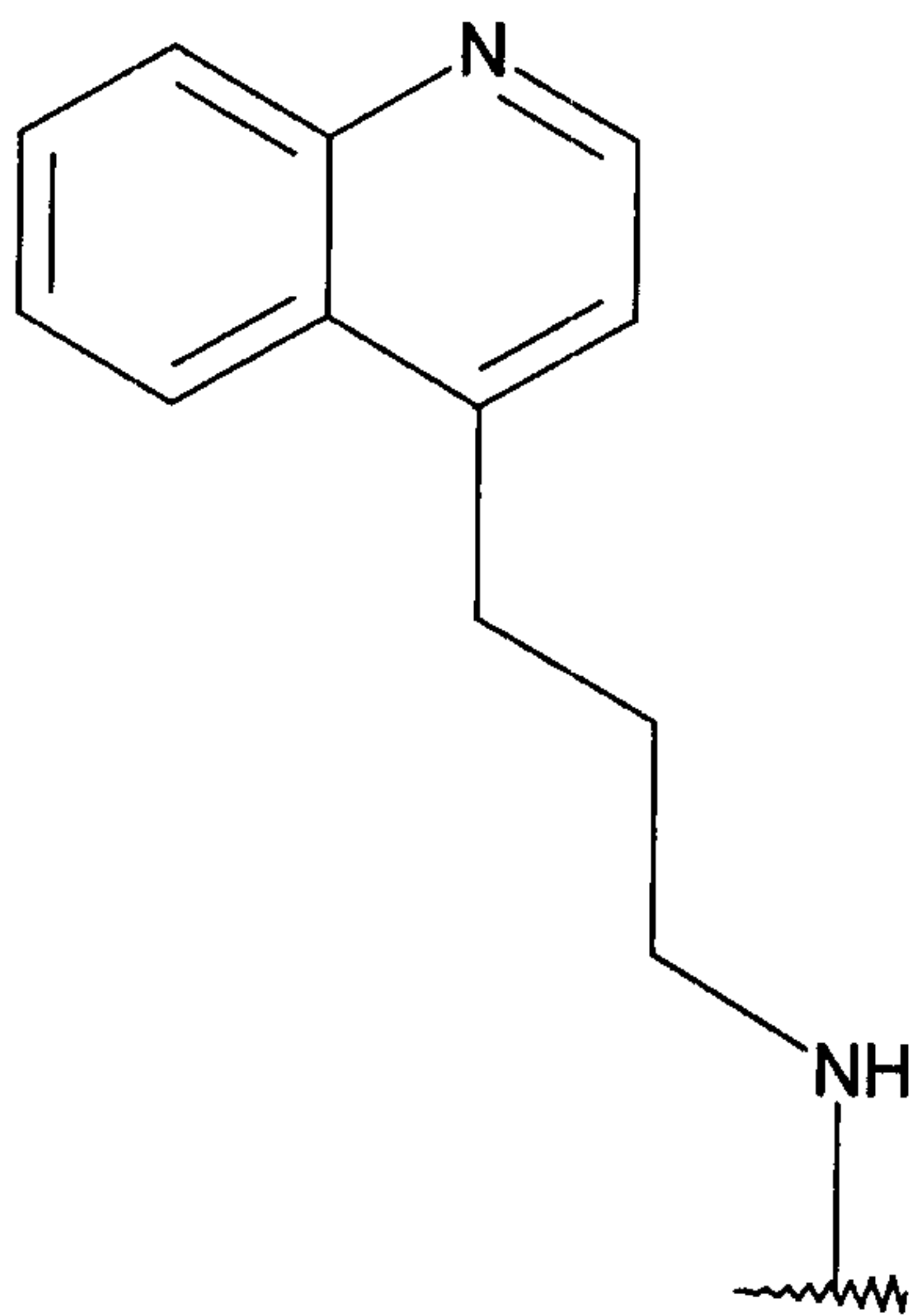
7. A compound according to claim 1 wherein said compound is a compound of formula 9 and a is 1, X<sup>1</sup> is O, R<sup>1</sup> is H, R<sup>2</sup> is CH<sub>2</sub>CH<sub>3</sub>, R<sup>4</sup> is CH<sub>3</sub>, R<sup>7a</sup> is CH<sub>3</sub> and R<sup>14</sup> is a compound of formula



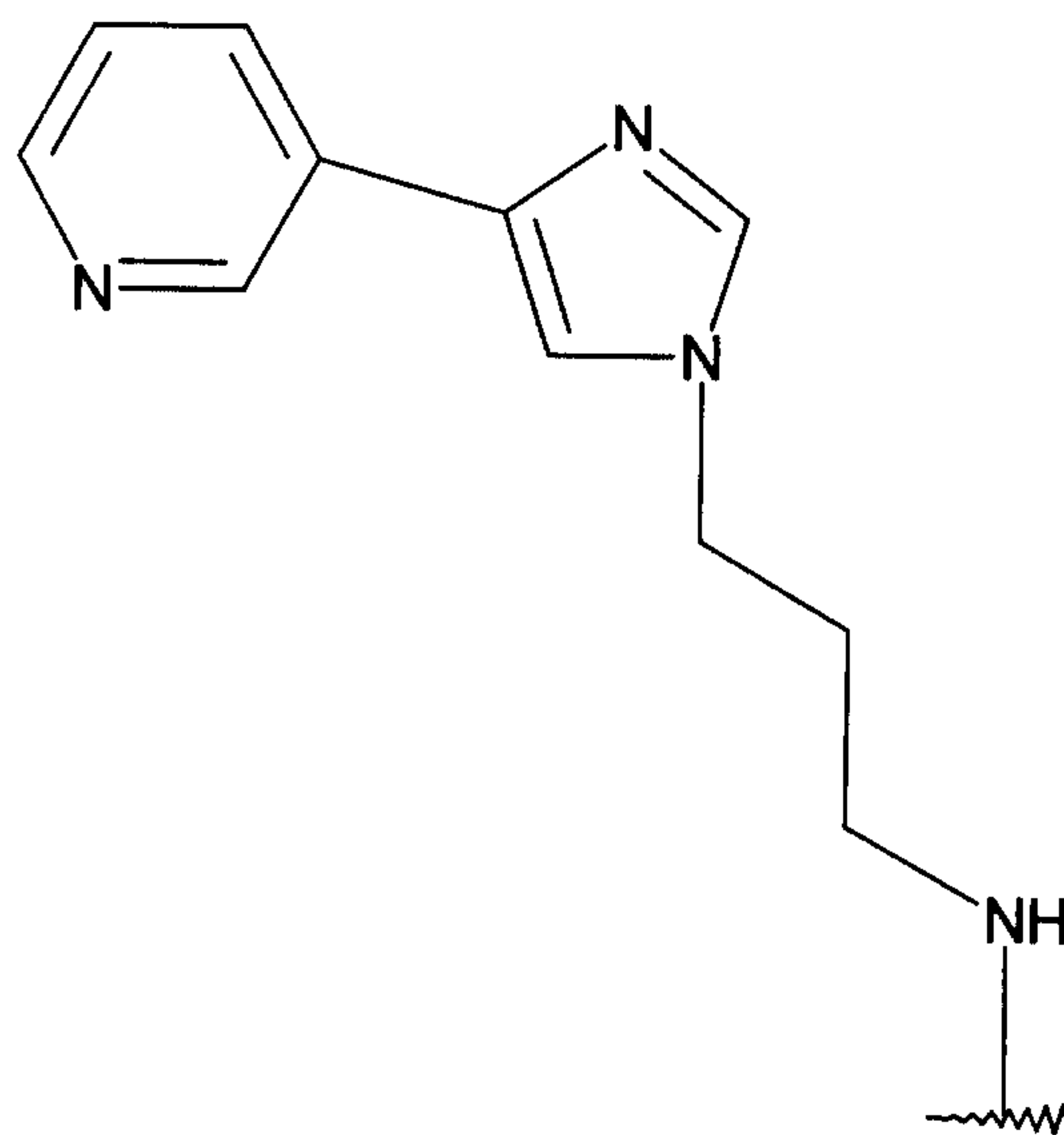
or



or



or



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