

OXAZOLE DERIVATIVES OF TETRACYCLINES

FIELD OF THE INVENTION

5 The present invention relates to novel oxazole derivatives of tetracyclines which are useful as antibiotic agents and exhibit antibacterial activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and other antibiotics. This invention also relates to novel tetracycline intermediates useful for making the novel compounds and novel methods for producing the novel
10 compounds and the intermediate compounds.

BACKGROUND OF THE INVENTION

Since 1947 a variety of tetracycline antibiotics have been synthesized and described
15 for the treatment of infectious diseases in man and animals. Tetracyclines inhibit protein synthesis by binding to the 30S subunit of the bacterial ribosome preventing binding of aminoacyl RNA (Chopra, Handbook of Experimental Pharmacology, Vol. 78, 317-392, Springer-Verlag, 1985). Resistance to tetracyclines has emerged among many clinically important microorganisms which limit the utility of these
20 antibiotics. There are two major mechanisms of bacterial resistance to tetracyclines: a) energy-dependent efflux of the antibiotic mediated by proteins located in the cytoplasmic membrane which prevents intracellular accumulation of tetracycline (S. B. Levy, et al., Antimicrob. Agents Chemotherapy 33, 1373-1374 (1989); and b) ribosomal protection mediated by a cytoplasmic protein which interacts with the
25 ribosome such that tetracycline no longer binds or inhibits protein synthesis (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156, 1990). The efflux mechanism of resistance is encoded by resistance determinants designated tetA-tetL. They are common in many Gram-negative bacteria (resistance genes Class A-E), such as Enterobacteriaceae, Pseudomonas, Haemophilus and
30 Aeromonas, and in Gram-positive bacteria (resistance genes Class K and L), such as Staphylococcus, Bacillus and Streptococcus. The ribosomal protection mechanism of resistance is encoded by resistance determinants designated TetM, N and O, and is common in Staphylococcus, Streptococcus, Campylobacter,

Gardnerella, Haemophilus and Mycoplasma (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156 1990).

A particularly useful tetracycline compound is 7-(dimethylamino)- 6-demethyl-6-deoxytetracycline, known as minocycline (see U.S. Pat. No. 3,148,212, U.S. Pat. No. 5 RE 26,253 and U.S. Pat. No. 3,226,436 discussed below). However, strains harboring the tetB (efflux in gram-negative bacteria) mechanism, but not tetK (efflux in Staphylococcus) are resistant to minocycline. Also, strains carrying tetM (ribosomal protection) are resistant to minocycline. This invention describes the synthesis of novel tetracycline compounds which demonstrate significant in vitro and 10 in vivo activity vs. tetracycline and minocycline susceptible strains and some tetracycline and minocycline resistant strains, that is, those harboring the tetM (ribosomal protection) resistance determinants.

Duggar, U.S. Pat. No. 2,482,055, discloses the preparation of Aureomycin.RTM. by fermentation which have antibacterial activity. Growich et al., U.S. Pat. No. 15 3,007,965, disclose improvements to the fermentation preparation. Beereboom et al., U.S. Pat. No. 3,043,875 discloses tetracycline derivatives Boothe et al., U.S. Pat. No. 3,148,212, reissued as U.S. Pat. No. RE 26,253, and Petisi et al., U.S. Pat. No. 3,226,436, discloses tetracycline derivatives which are useful for treating bacterial infections. Blackwood et al., U.S. Pat. No. 3, 200,149 discloses tetracycline 20 derivatives which possess microbiological activity. Petisi et al., U.S. Pat. No. 3,338,963 discloses tetracycline compounds which have broad-spectrum antibacterial activity. Bitha et al., U.S. Pat. No. 3,341,585 discloses tetracycline compounds which have broad-spectrum antibacterial activity. Shu, U.S. Pat. No. 3,360,557 discloses 9- hydroxytetracyclines which have been found to possess 25 antibacterial activity. Zambrano, U.S. Pat. No. 3,360,561 discloses a process for preparing 9-nitrotetracyclines. Martell et al., U.S. Pat. No. 3,518,306 discloses tetracyclines which possess in vivo antibacterial activity.

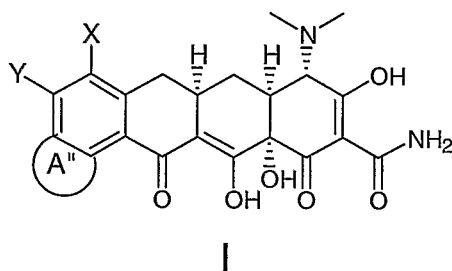
In U.S. Pat. No. 5,021,407 a method of overcoming the resistance of tetracycline resistant bacteria is disclosed. The method involves utilizing a blocking agent 30 compound in conjunction with a tetracycline type antibiotic. This patent does not disclose novel tetracycline compounds which themselves have activity against resistant organisms. Described in U.S. Pat. No. 5,494,903 are 7-substituted-9-

substituted amino-6-demethyl-6-deoxytetracyclines which have broad spectrum antibacterial activity.

In summary, none of the above patents teach or suggest the novel compounds of this application. In addition, none of the above patents teach or suggest novel tetracycline
 5 compounds of the invention having activity against tetracycline and minocycline resistant strains as well as strains which are normally susceptible to tetracyclines.

SUMMARY OF THE INVENTION

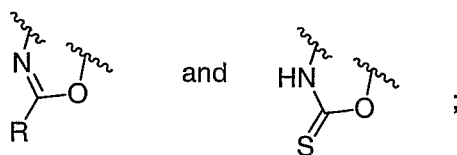
10 In accordance with the present invention, there is provided compounds represented by Formula (I);



15 wherein:

X is selected from hydrogen, amino, $\text{NR}^{11}\text{R}^{12}$, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally
 20 substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

A'' is a moiety selected from the group:



25 R^{11} and R^{12} are each independently H or alkyl of 1 to 12 carbon atoms or

R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

R is selected from alkyl of 1 to 12 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted, $-\text{CH}_2\text{NR}^1\text{R}^2$, aryl of 6, 10 or 14 carbon atoms optionally substituted, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl of 7 to 13 carbon atoms optionally substituted, SR^3 , heteroaryl of 5 or 6 ring atoms optionally substituted, containing 1 to 4 heteroatoms which may be the same or different, independently selected from nitrogen, oxygen and sulfur, and heteroarylcarbonyl of 5 or 6 ring atoms optionally substituted containing 1 to 4 heteroatoms which may be the same or different, independently selected from nitrogen, oxygen and sulfur;

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

R^3 is alkyl of 1 to 12 carbon atoms optionally substituted, $-\text{CH}_2$ -aryl optionally substituted, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl, $-\text{CH}_2(\text{CO})\text{OCH}_2$ aryl optionally substituted, $-\text{CH}_2$ -alkenyl of 2 to 12 carbon atoms optionally substituted, and $-\text{CH}_2$ -alkynyl of 2 to 12 carbon atoms optionally substituted;

with the provisos that when X is NR^1R^2 and R^1 is hydrogen, then R^2 is methyl, ethyl, n-propyl, n-butyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and that when R^1 is methyl or ethyl then R^2 is methyl, ethyl, n-propyl, 1-methylethyl, n-propyl, 1-methylpropyl, or 2-methylpropyl; or a tautomer or pharmaceutically acceptable salts thereof.

5 Definitions

The term alkyl as a group or part of a group means a straight or branched alkyl moiety of 1 to 12 carbon atoms which can be optionally independently substituted with 1 to 3 substituents selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, aryl optionally substituted, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, NH-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, NH-(alkyl of 1 to 12 carbon atoms)-aryl optionally substituted and heterocyclyl of 3 to 8 membered ring. In some embodiments of the invention alkyl is a moiety of 1 to 6 carbon atoms. In other embodiments of the invention alkyl is a moiety of 1 to 3 carbon atoms. In other embodiments alkyl is substituted by heterocyclyl of 4 to 7 ring members (e.g. pyrrolidinyl)

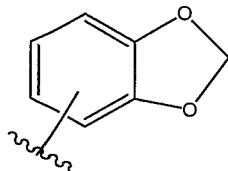
The term alkenyl means a straight or branched carbon chain of 2 to 12 carbon atoms having at least one site of unsaturation optionally independently substituted with 1 to 3 substituents selected from the group optionally substituted aryl, phenyl, heteroaryl, halogen, amino, cyano, alkyl of 1 to 12 carbon atoms, hydroxyl, and alkoxy of 1 to 12 carbon atoms.

The term vinyl means a moiety $\text{CH}_2=\text{CH}-$.

As used herein the term alkoxy as a group or part of a group refers to alkyl-O- wherein alkyl is hereinbefore defined.

As used herein the term aryl as a group or part of a group, e.g., aralkyl, aroyl, means an aromatic moiety having 6, 10 or 14 carbon atoms preferably 6 to 10 carbon atoms, which can be optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, benzyloxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, methylenedioxy and

phenyl. In particular, aryl is phenyl or naphthyl optionally substituted with 1 to 3 substituents. Substituted phenyl may optionally be the moiety



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The term aralkyl as used herein of 7 to 16 carbon atoms means an alkyl substituted with an aryl group in which the aryl and alkyl group are previously defined. Non-limiting exemplary aralkyl groups include benzyl and phenethyl and the like.

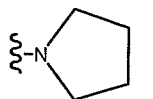
10 Phenyl as used herein refers to a 6-membered carbon aromatic ring.

As used herein the term alkynyl includes both straight chain and branched moieties containing 2 to 12 carbon atoms having at least one carbon to carbon triple bond optionally substituted with 1 to 3 substituents independently selected from the group
15 halogen, amino, cyano, alkyl of 1 to 12 carbon atoms, hydroxyl, and alkoxy of 1 to 12 carbon atoms.

As used herein the term halogen or halo means F, Cl, Br or I.

20 As used herein the term cycloalkyl means a saturated monocyclic ring having from 3 to 6 carbon atoms. Exemplary cycloalkyl rings include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In an embodiment of the invention cycloalkyl is a moiety of 5 or 6 carbon atoms.

25 As used herein, R^1 and R^2 and R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring, where a non-limiting example is pyrrolidinyl,



The term aroyl means an aryl-C(O)- group in which the aryl group is as previously defined. Non-limiting examples include benzoyl and naphthoyl.

- 5 The term heteroaryl means an aromatic heterocyclic, monocyclic ring of 5 or 6 ring atoms containing 1 to 4 heteroatoms independently selected from O, N and S. Heteroaryl rings may optionally be substituted with 1 to 3 substituents selected from the group halogen, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, alkoxy, aryloxy, $-\text{CH}_2\text{OCOCH}_3$ and carboxy. Non-limiting heteroaryl moieties optionally
- 10 substituted include: furanyl, thienyl, pyridyl, tetrazolyl, imidazo, thiazolyl and the like. Further included are benzofuranyl, benzothienyl and quinolinyl.

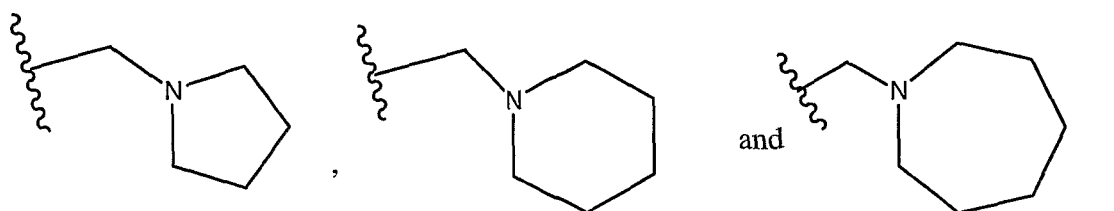
The term heteroarylcarbonyl means a heteroaryl-C(O)- group in which the heteroaryl group is as previously defined.

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The term heterocyclyl as used herein represents a saturated 3 to 8 membered ring containing one to three heteroatoms selected from nitrogen, oxygen and sulfur. Representative examples are pyrrolidyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

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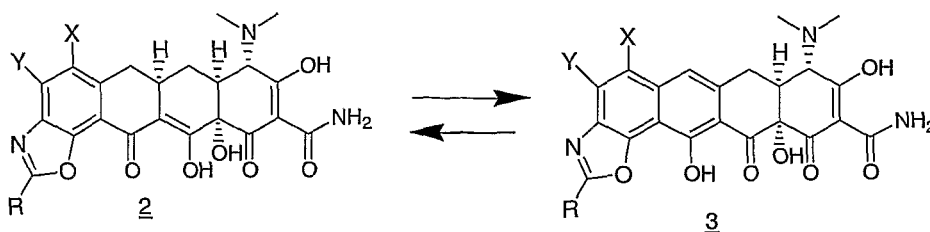
The term alkylheterocyclyl means an alkyl-heterocyclyl group in which the alkyl and heterocyclyl group are previously defined. Non-limiting exemplary alkylheterocyclyl groups include moieties of the formulae:



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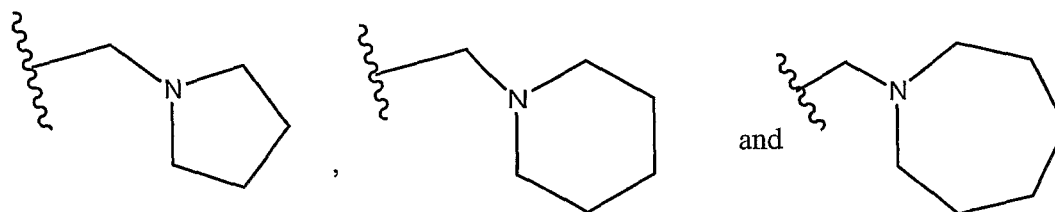
Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be

included within the scope of the present invention. For instance, compounds of formula (I) which exist as tautomers are depicted below:



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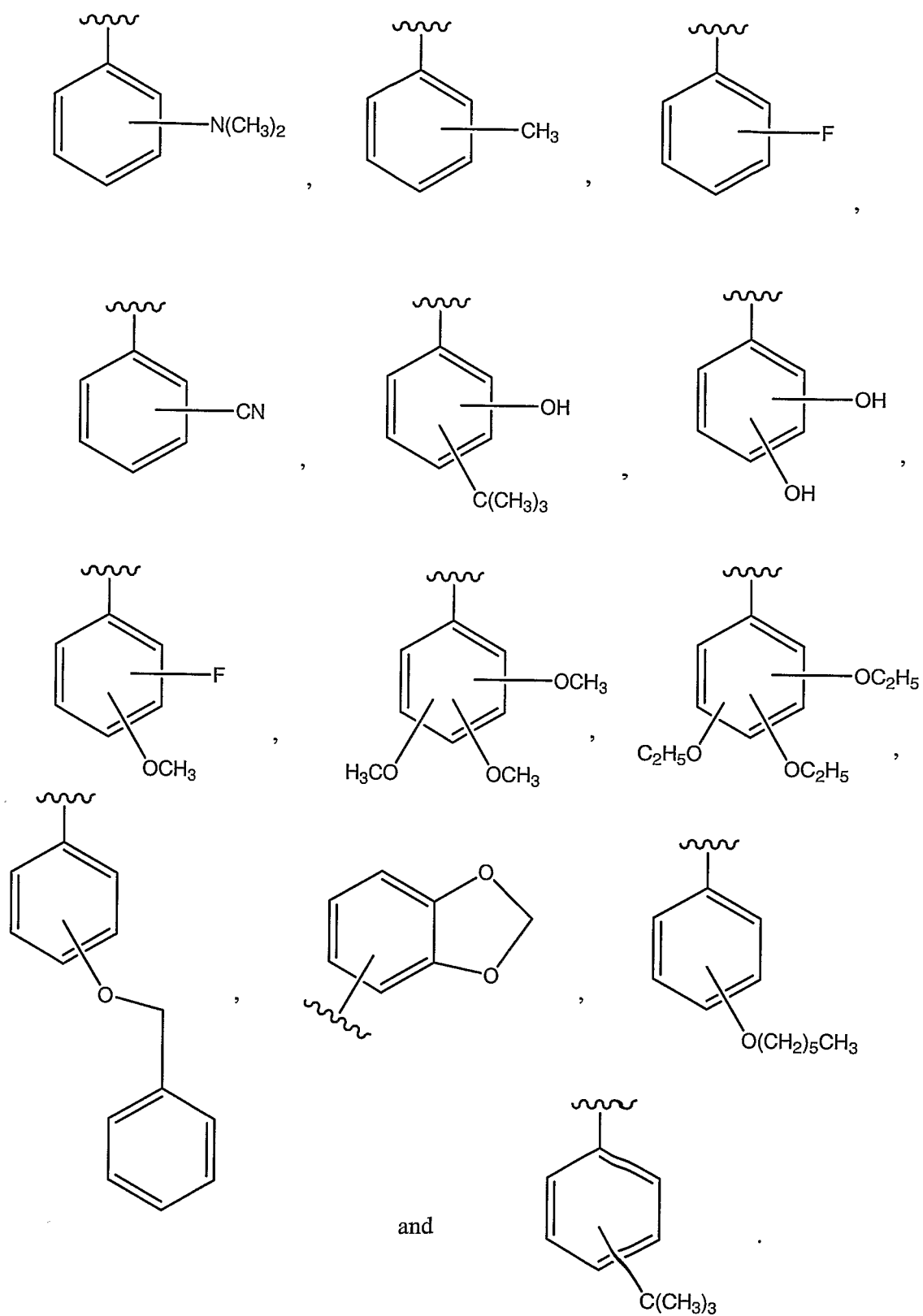
One embodiment of this invention is where R of Formula (I) is selected from the group alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, and alkyl- (heterocyclyl) selected from moieties of the group



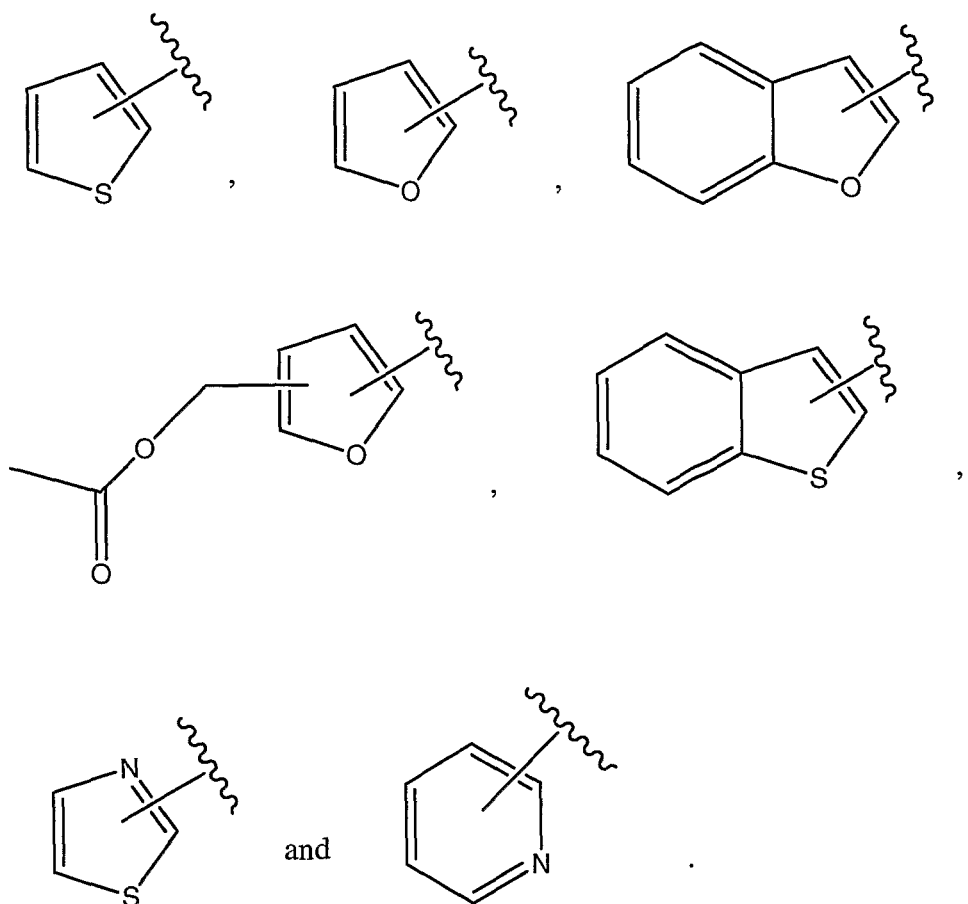
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Another embodiment of the invention is where R of Formula (I) is phenyl optionally substituted with 1 to 3 substituents. In a preferred embodiment R is selected from moieties of the group

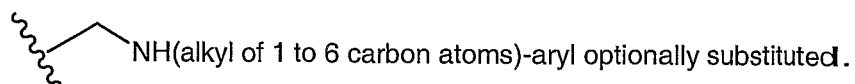
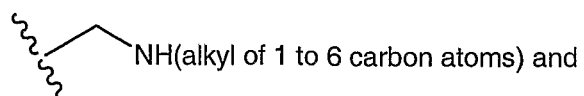
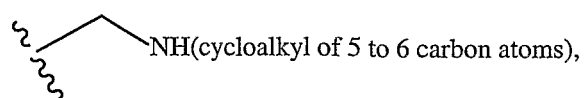
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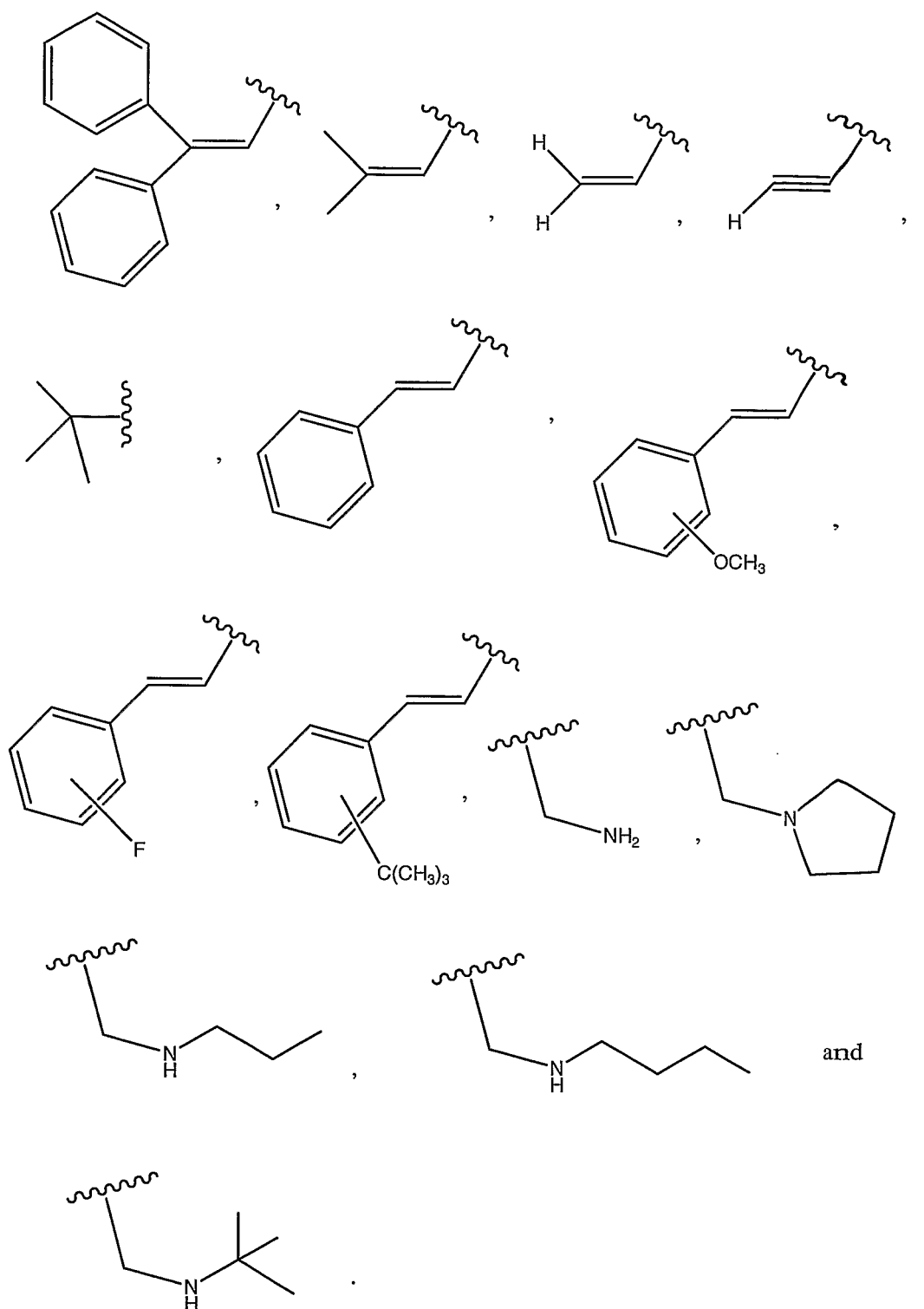
- A further preferred embodiment of the invention is where R is heteroaryl. In a
 5 preferred embodiment R is selected from moieties of the group



- 10 An additional embodiment of the invention is where R is alkyl of 1 to 6 carbon atoms optionally substituted, alkenyl of 2 to 6 carbon atoms optionally substituted,

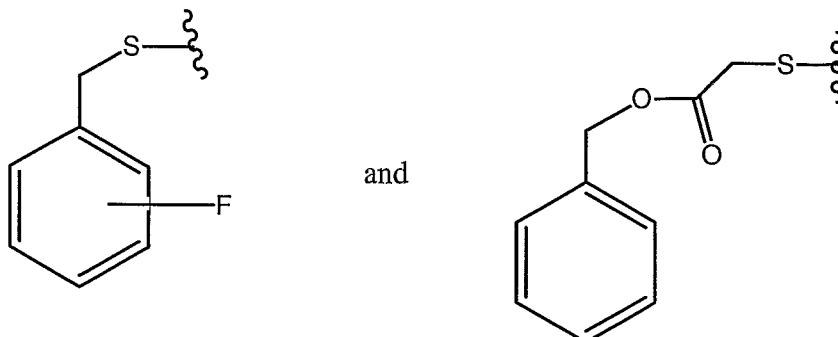


In a preferred embodiment R is selected from moieties of the group



An additional embodiment of the invention is where R of Formula (I) is S-alkyl of 1 to 12 carbon atoms, S-CH₂-aryl optionally substituted and S-CH₂(CO)OCH₂aryl

optionally substituted. In a preferred embodiment R is selected from moieties of the group



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Preferred compounds of the invention include those selected from the group:

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2,2-diphenylvinyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

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(7aS,8S,11aS)-8-(dimethylamino)-9,11a,13-trihydroxy-2-(2-methyl-1-propenyl)-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-carboxamide,

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(6aR,7aS,8S,11aS)-2-*tert*-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(2-furyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

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(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(*E*)-2-phenylethenyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

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- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(4-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(3-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(2-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(E)-2-(4-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(E)-2-(2-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-2-(chloromethyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 25 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(dimethylamino)methyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(pyrrolidin-1-ylmethyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
[(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-2-[(butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-
trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
10 [(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
10-carboxamide and
- (6aR,7aS,8S,11aS)-2-[(*tert*-butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-
trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
15 10-carboxamide.
- Preferred compounds of the invention include those selected from the group:
- (7aS,8S,11aS)-8-(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,13-trihydroxy-
20 11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-
carboxamide,
- (6aR,7aS,8S,11aS)-2-*tert*-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-
dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
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- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(4-methylphenyl)-
11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-
carboxamide,
- 30 (7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluorophenyl)-9,11a,13-trihydroxy-11,12-
dioxo-7,7a,8,11,11a,12-hexahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-2-(4-cyanophenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 10 (6aR,7aS,8S,11aS)-2-(5-*tert*-butyl-2-hydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 15 (6aR,7aS,8S,11aS)-2-[4-(benzyloxy)phenyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 20 (6aR,7aS,8S,11aS)-2-(2,4-dihydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluoro-4-methoxyphenyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 25 (6aR,7aS,8S,11aS)-2-(1,3-benzodioxol-5-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,6-trimethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,5-triethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(1-methyl-1*H*-indol-2-yl)-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 10 (6aR,7aS,8S,11aS)-2-(4-*tert*-butylphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

- 15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(hexyloxy)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide.

Preferred compounds include those selected from the group:

- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thien-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 25 (6aR,7aS,8S,11aS)-2-(1-benzofuran-2-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2-furyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 30 {5-[(6aR,7aS,8S,11aS)-10-(aminocarbonyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazol-2-yl]-2-furyl}methyl acetate,

(6aR,7aS,8S,11aS)-2-(1-benzothien-3-yl)-5,8-bis(dimethylamino)-9,11a,12-

trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

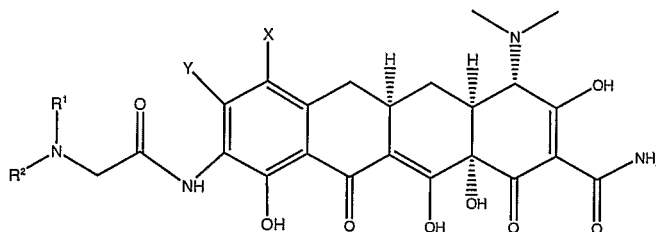
(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(1,3-thiazol-2-yl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-4-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide.

15

An additional embodiment of the invention is a process for the preparation of a compound of the formula



20 or a pharmaceutically acceptable salt thereof

wherein:

X is selected from hydrogen, amino, NR¹R², alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

R¹ and R² are each independently H or alkyl of 1 to 12 carbon atoms or

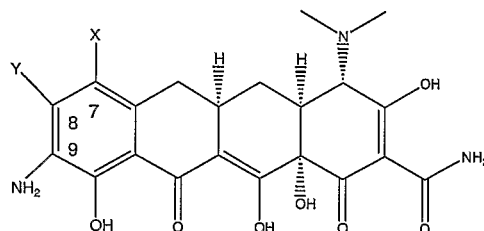
R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

comprising the steps:

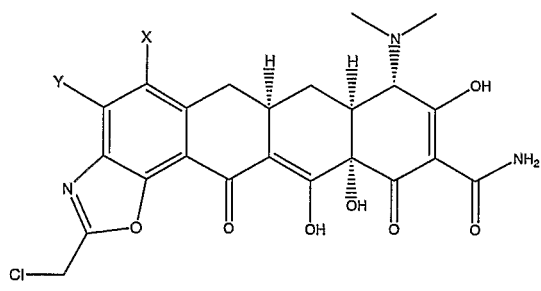
10

a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula

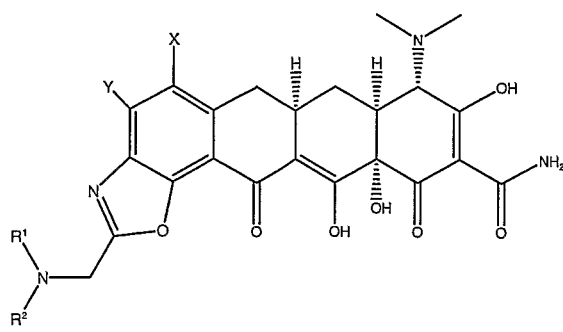


or a pharmaceutically acceptable salt thereof

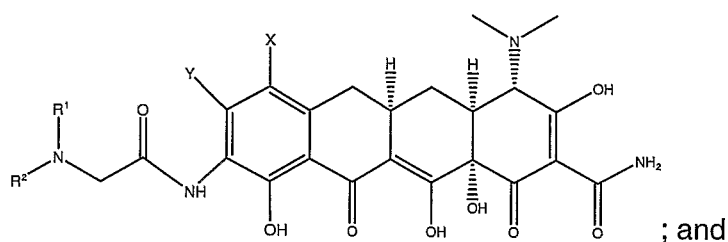
15 with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



20 b. reacting the chloro compound with an amine R^1R^2NH to form a substituted amine of the formula



c. hydrolyzing the substituted amine with acid to give a compound of the formula



5

d. isolating the compound or a pharmaceutically acceptable salt thereof.

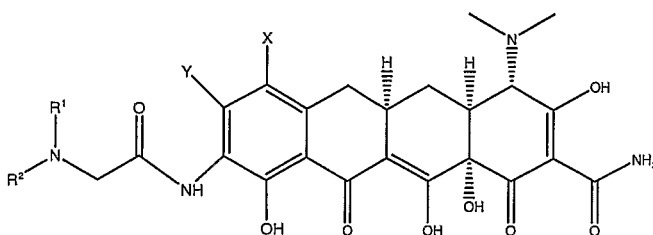
In a preferred embodiment of the process X is $N(CH_3)_2$ and the amine R^1R^2NH is t-butyl amine.

10

In a preferred embodiment of the process the compound [4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof is prepared.

15

A further embodiment of the invention is a process for the preparation of a compound of the formula



20

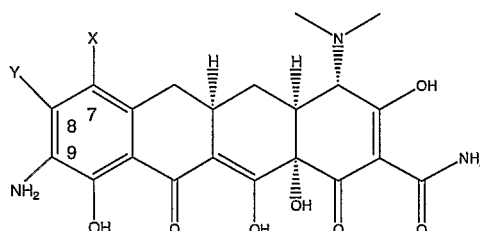
wherein:

X is selected from hydrogen, amino, NR^1R^2 , alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

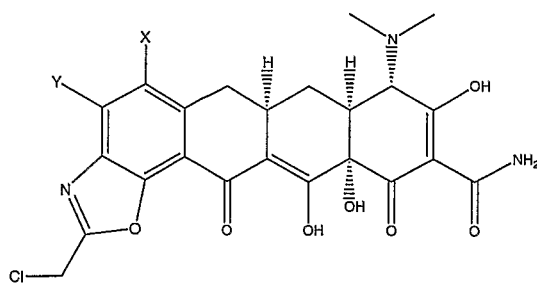
R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;
or a pharmaceutically acceptable salt thereof
comprising the steps:

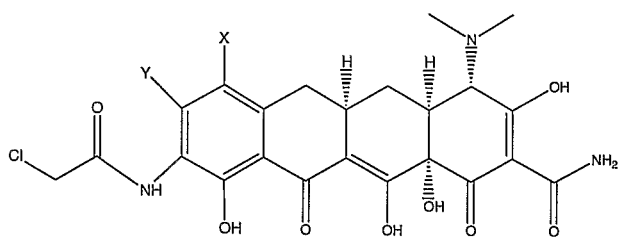
a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula



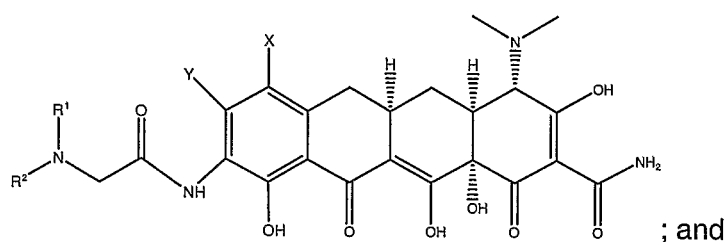
or a pharmaceutically acceptable salt thereof
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



- b. reacting the chloro compound with acid to give 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline of the formula



- c. reacting the 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline with amine R^1R^2NH to give a compound of the formula



- d. isolating the compound or a pharmaceutically acceptable salt thereof.

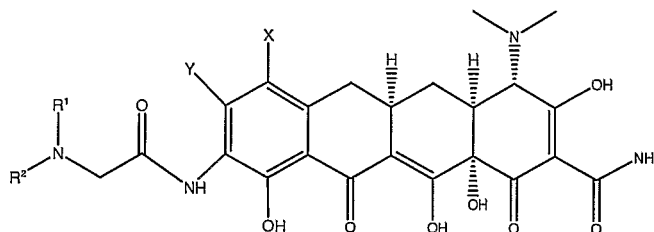
In a preferred embodiment of the process X is $N(CH_3)_2$ and the amine R^1R^2NH is t-butyl amine.

In a preferred embodiment of the process the compound [4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylamino]-

1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof is prepared.

An additional embodiment of the invention is a compound of the formula

5



or a pharmaceutically acceptable salt thereof

wherein:

10

X is selected from hydrogen, amino, NR^1R^2 , alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

15

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

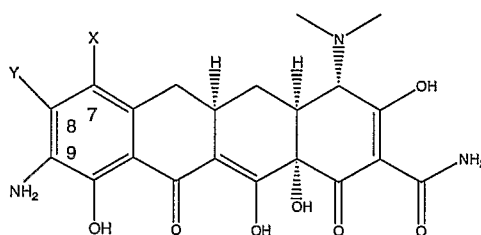
20

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

produced by the process comprising the steps:

25

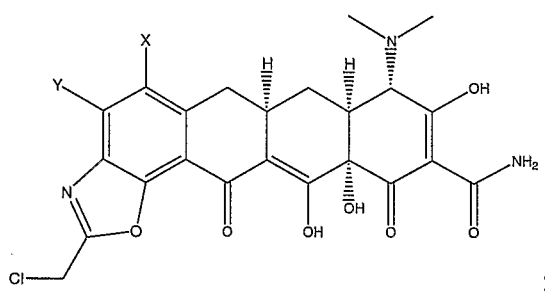
a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula



or a pharmaceutically acceptable salt thereof

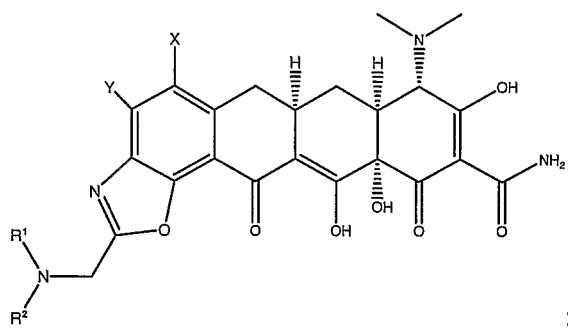
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula

5

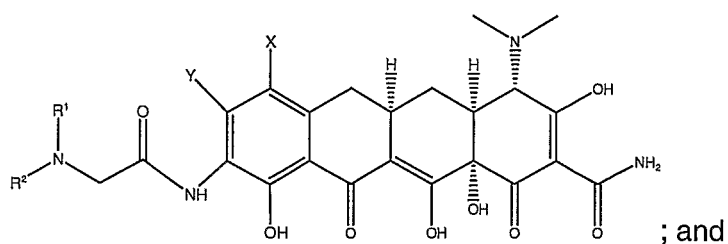


b. reacting the chloro compound with an amine R^1R^2NH to form a substituted amine of the formula

10



c. hydrolyzing the substituted amine with acid to give a compound of the formula



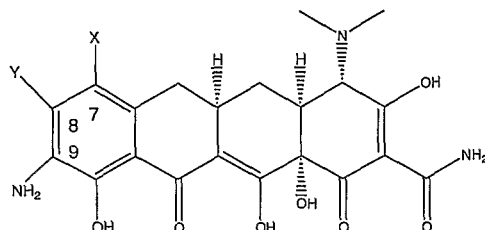
optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

or a pharmaceutically acceptable salt thereof

produced by the process comprising the steps:

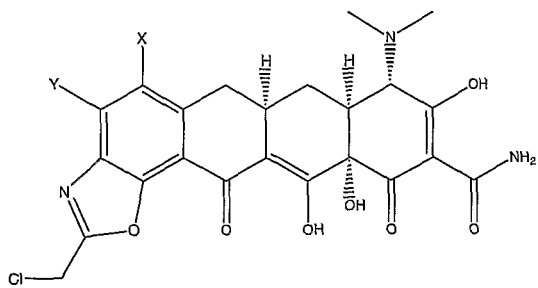
5

a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula

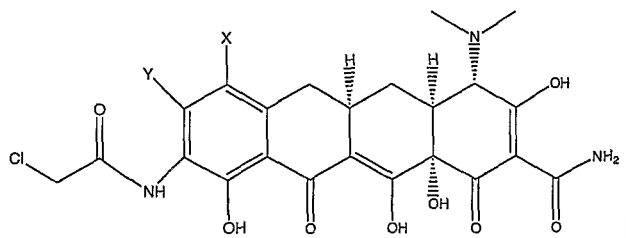


or a pharmaceutically acceptable salt thereof

10 with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula

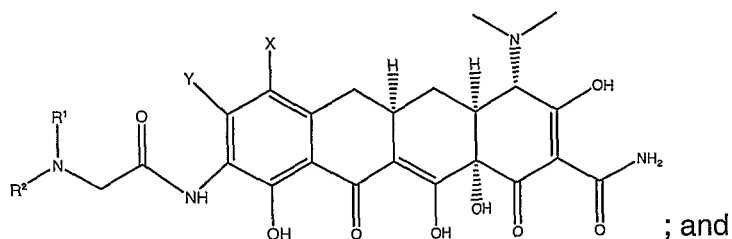


b. reacting the chloro compound with acid to give 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline of the formula



c. reacting the 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline with amine R^1R^2NH to give a compound of the formula

20



- 5 d. isolating the compound or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the process X is $N(CH_3)_2$ and the amine R^1R^2NH is t-butyl amine.

- 10 In a preferred embodiment the compound [4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof is prepared by the process.

15

20

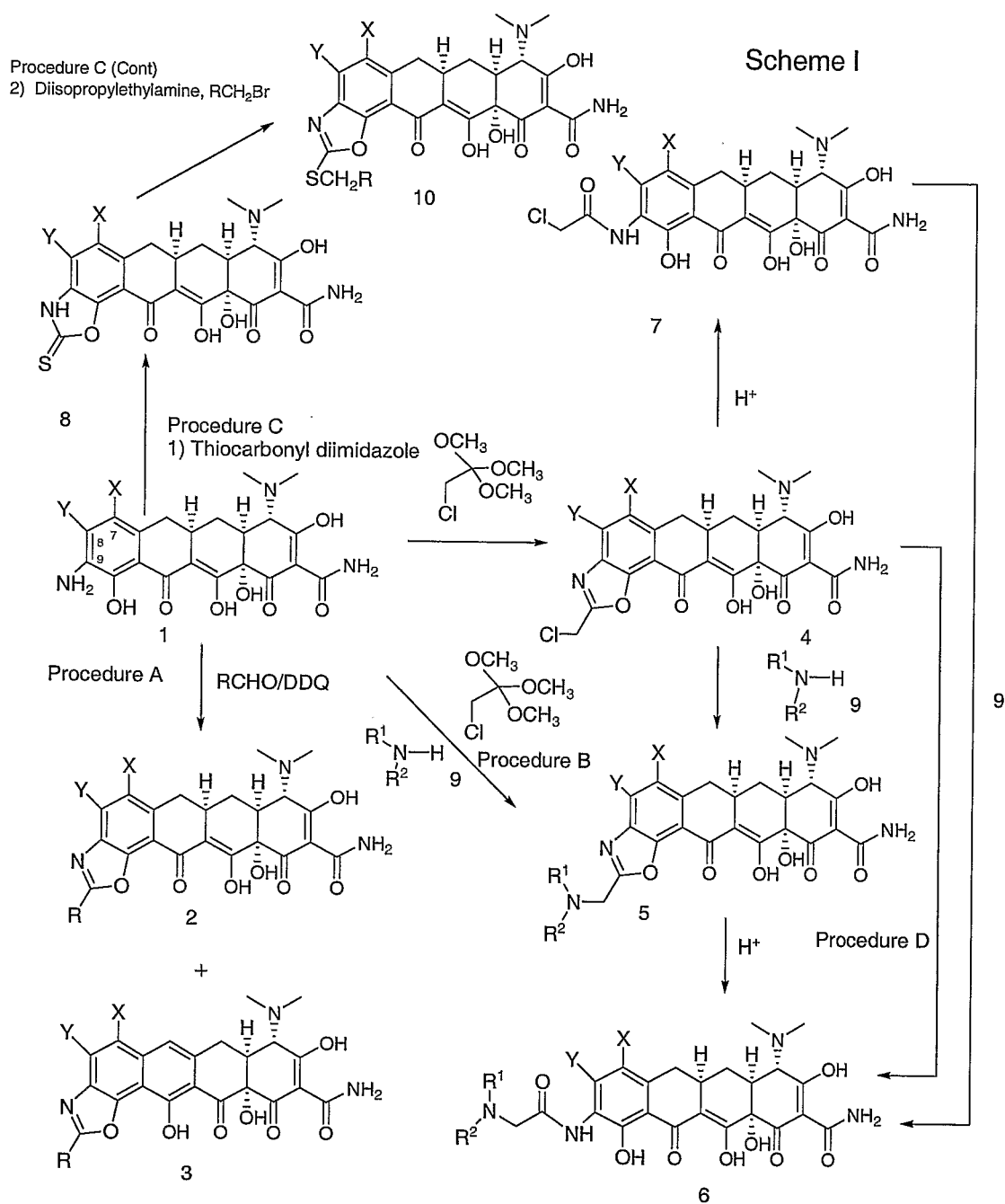
DESCRIPTION OF THE PREFERRED EMBODIMENTS

- 5 The novel compounds of the present invention may be readily prepared in accordance with the following Scheme I.

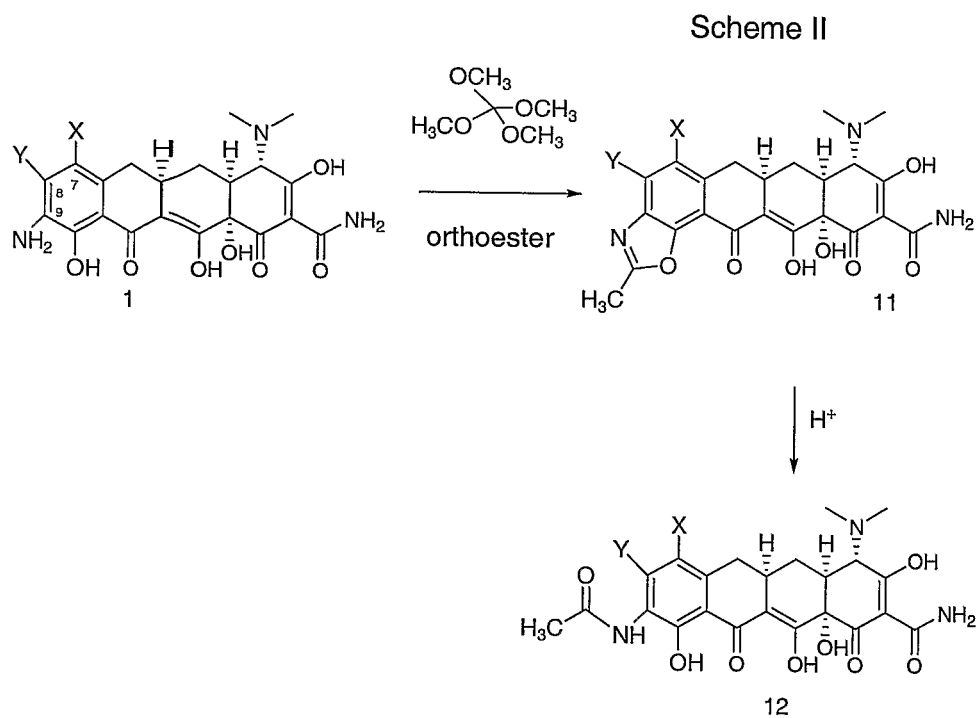
The starting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracyclines 1 or pharmaceutically acceptable salts thereof where X and Y are hereinbefore
10 defined are reacted with aldehyde RCHO in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford benzoxazole 2 and 3 (Procedure A). As further described, reaction of 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracyclines 1 or pharmaceutically acceptable salts thereof where X and Y are hereinbefore defined are reacted with 2-chloro-1,1,1-trimethoxy-ethane in an aprotic
15 solvent such as N,N-dimethylformamide (DMF) to give chloromethyl-benzoxazole 4, optionally isolated, then converted to substituted amine 5 by further reaction with an amine 9 (Procedure B). Hydrolysis of amine 5 affords 9-(2-substituted aminomethyl carbonylamino)substituted-6-dimethyl-6-deoxytetracycline 6 (Procedure D). Hydrolysis of chloromethylbenzoxazole 4 gives 9-(2-chloromethylcarbonyl-
20 amino)substituted-6-demethyl-6-deoxytetracycline 7 which may be further reacted with amine 9 to give 9-(2-substituted aminomethyl carbonylamino)substituted-6-dimethyl-6-deoxytetracycline 6.

25 Additionally, reaction of 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracyclines 1 or pharmaceutically acceptable salts thereof with thiocarbonyldiimidazole provides thio 8 followed by alkylation with RCH_2Br in the presence of an amine which includes N,N-diisopropylethylamine affords oxazole 10 (Procedure C).

30 Preferably, amine 9 in the preparation of 9-(2-substituted aminomethyl carbonylamino)substituted-6-dimethyl-6-deoxytetracycline 6, in Scheme I is t-butylamine.



As shown in Scheme II, the starting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracyclines 1 or pharmaceutically acceptable salts thereof where X and Y are hereinbefore defined are reacted with a methyl orthoester to afford methyl benzoxazole derivative 11. Acid hydrolysis of methyl benzoxazole derivative 11 affords N-acetyl derivative 12.



Reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the various functionalities present on the molecule must be consistent with the chemical transformations proposed. This may necessitate judgement as to the order of synthetic steps, protecting groups, if required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions. Such restrictions to the substituents which are compatible with the reaction conditions will be apparent to one skilled in the art.

Some of the compounds of the hereinbefore described schemes have center of asymmetry. The compounds may, therefore, exist in at least two and often more stereoisomeric forms. The present invention encompasses all stereoisomers of the compounds whether free from other stereoisomers or admixed with other stereoisomers in any proportion and thus includes, for instance, racemic mixture of enantiomers as well as the diastereomeric mixture of isomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography.

Pharmaceutically acceptable salts of the compounds of the invention may be obtained as metal complexes such as aluminum, calcium, iron, magnesium, manganese and complex salts; inorganic and organic salts and corresponding Mannich base adducts using methods known to those skilled in the art (Richard C. Larock, *Comprehensive Organic Transformations*, VCH Publishers, 411-415, 1989). Preferably, the compounds of the invention are obtained as inorganic salts such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salts such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate alkylsulfonate or arylsulfonate. The salt formation preferentially occurs with the C(4)-dimethylamino group when forming inorganic salts. The salts are preferred for oral and parenteral administration.

Standard Pharmacological Test Procedures

5 Methods for in Vitro Antibacterial evaluation

The minimum inhibitory concentration (MIC)

Antimicrobial susceptibility testing. The in vitro activities of the antibiotics are
10 determined by the broth microdilution method as recommended by the National
Committee for Clinical Laboratory Standards (NCCLS) (1). Mueller-Hinton II broth
(MHBII)(BBL Cockeysville, MD) is the medium employed in the testing procedures.
Microtiter plates containing serial dilutions of each antimicrobial agent are inoculated
with each organism to yield the appropriate density (10^5 CFU/ml) in a 100 μ l final
15 volume. The plates are incubated for 18 – 22 hours at 35°C in ambient air. The
minimal inhibitory concentration for all isolates is defined as the lowest concentration
of antimicrobial agent that completely inhibits the growth of the organism as detected
by the unaided eye.

- 20 1. NCCLS. 2000. Methods for Dilution Antimicrobial Susceptibility Tests for
Bacteria That Grow Aerobically; Approved Standards: M7-A5, vol. 20.
National Committee for Clinical Laboratory Standards, Wayne, PA.

TABLE I
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	>64	>64	>64
2 <i>E. coli</i> GC4559 (parent GC4560)	>64	>64	>64	>64	>64	>64
3 <i>E. coli</i> GC4560 (IMP mutant)	32	8	16	16	4	8
4 <i>E. coli</i> GC2203 (ATCC Control)	>64	>64	>64	>64	>64	>64
5 <i>E. coli</i> GC1073 (tet(B))	>64	>64	>64	>64	>64	>64
6 <i>S. aureus</i> GC1131 (Clinical)	16	8	2	16	4	4
7 <i>S. aureus</i> GC6466 (tet(M))	32	8	2	32	4	4
8 <i>S. aureus</i> GC6467 (tet(M)+(K))	32	8	2	32	4	4
9 <i>S. aureus</i> GC1079 (tet(K))	16	8	1	16	4	4
10 <i>S. aureus</i> GC4536 (Smith MP –In Vivo)	16	8	2	32	4	4
11 <i>S. aureus</i> GC2216 (ATCC Control)	16	8	2	32	4	4
12 <i>E. faecalis</i> GC4555 (ATCC Control)	32	8	2	32	4	8
13 <i>E. faecalis</i> GC2267 (tet(L)+(M)+(S))	32	8	2	32	4	4
14 <i>E. faecalis</i> GC2242 (Van-resistant)	16	8	2	32	4	4
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	16	8	2	16	16	16
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	8			32	8	16
17 <i>S. pyogenes</i> * GC4563 (Clinical)	8	8	8	16	16	16
18 <i>M. catarrhalis</i> * GC6907 (Clinical)	>64			16	16	32
19 <i>H. influenzae</i> <> GC6896 (ATCC Control)	>64			>64	>64	>64
20 <i>C. albicans</i> GC3066 ATCC (Control)	>64	>64	>64	>64	>64	>64

TABLE II
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-SUBSTITUTED)-TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 7	Example 8	Example 10	Example 11
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	>64
2 <i>E. coli</i> GC4559 (parent GC4560)	>64	>64	>64	>64
3 <i>E. coli</i> GC4560 (IMP mutant)	8	16	32	>64
4 <i>E. coli</i> GC2203 (ATCC Control)	>64	>64	>64	>64
5 <i>E. coli</i> GC1073 (tet(B))	>64	>64	>64	>64
6 <i>S. aureus</i> GC1131 (Clinical)	8	8	8	32
7 <i>S. aureus</i> GC6466 (tet(M))	8	16	16	64
8 <i>S. aureus</i> GC6467 (tet(M)+(K))	8	8	16	32
9 <i>S. aureus</i> GC1079 (tet(K))	8	16	16	64
10 <i>S. aureus</i> GC4536 (Smith MP –In Vivo)	8	16	16	64
11 <i>S. aureus</i> GC2216 (ATCC Control)	8	8	16	64
12 <i>E. faecalis</i> GC4555 (ATCC Control)	8	32	16	64
13 <i>E. faecalis</i> GC2267 (tet(L)+(M)+(S))	8	16	16	>64
14 <i>E. faecalis</i> GC2242 (Van-resistant)	8	8	8	64
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	8	32	16	32
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	16	16	8	32
17 <i>S. pyogenes</i> * GC4563 (Clinical)	8	16	16	32
18 <i>M. catarrhalis</i> * GC6907 (Clinical)	4	64	>64	32
19 <i>H. influenzae</i> <> GC6896 (ATCC Control)	64	>64	>64	>64
20 <i>C. albicans</i> GC3066 ATCC (Control)	>64	>64	>64	>64

TABLE III
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 12	Example 13	Example 14	Example 15	Example 16
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	>64	>64
2 <i>E. coli</i> GC4559 (parent GC4560)	>64	>64	>64	>64	>64
3 <i>E. coli</i> GC4560 (IMP mutant)	4	4	16	32	16
4 <i>E. coli</i> GC2203 (ATCC Control)	32	>64	>64	>64	>64
5 <i>E. coli</i> GC1073 (tet(B))	>64	>64	>64	>64	>64
6 <i>S. aureus</i> GC1131 (Clinical)	4	4	4	64	16
7 <i>S. aureus</i> GC6466 (tet(M))	8	4	4	64	16
8 <i>S. aureus</i> GC6467 (tet(M)+(K))	8	8	8	64	16
9 <i>S. aureus</i> GC1079 (tet(K))	8	4	4	64	16
10 <i>S. aureus</i> GC4536 (Smith MP –In Vivo)	8	8	4	64	16
11 <i>S. aureus</i> GC2216 (ATCC Control)	4	4	4	64	16
12 <i>E. faecalis</i> GC4555 (ATCC Control)	8	8	8	64	16
13 <i>E. faecalis</i> GC2267 (tet(L)+(M)+(S))	8	8	8	64	16
14 <i>E. faecalis</i> GC2242 (Van-resistant)	8	8	4	64	16
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	8	32	16	>64	>64
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	8	16	16	>64	>64
17 <i>S. pyogenes</i> * GC4563 (Clinical)	4	16	16	>64	64
18 <i>M. catarrhalis</i> * GC6907 (Clinical)	4	16	4	64	>64
19 <i>H. influenzae</i> <> GC6896 (ATCC Control)	16	>64	>64	>64	>64
20 <i>C. albicans</i> GC3066 ATCC (Control)	>64	>64	>64	>64	>64

TABLE IV
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 17	Example 18	Example 19	Example 20	Example 21
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	>64	>64
2 <i>E. coli</i> GC4559 (parent GC4560)	>64	>64	>64	>64	>64
3 <i>E. coli</i> GC4560 (IMP mutant)	4	4	4	32	>64
4 <i>E. coli</i> GC2203 (ATCC Control)	>64	>64	>64	>64	>64
5 <i>E. coli</i> GC1073 (tet(B))	>64	>64	>64	>64	>64
6 <i>S. aureus</i> GC1131 (Clinical)	8	4	4	32	64
7 <i>S. aureus</i> GC6466 (tet(M))	8	4	4	32	32
8 <i>S. aureus</i> GC6467 (tet(M)+(K))	8	4	4	32	32
9 <i>S. aureus</i> GC1079 (tet(K))	8	4	4	32	32
10 <i>S. aureus</i> GC4536 (Smith MP –In Vivo)	8	4	8	64	64
11 <i>S. aureus</i> GC2216 (ATCC Control)	8	4	4	32	32
12 <i>E. faecalis</i> GC4555 (ATCC Control)	8	4	8	64	>64
13 <i>E. faecalis</i> GC2267 (tet(L)+(M)+(S))	16	4	8	64	64
14 <i>E. faecalis</i> GC2242 (Van-resistant)	8	4	4	32	32
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	32	16	4	>64	>64
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	32	16	4	64	>64
17 <i>S. pyogenes</i> * GC4563 (Clinical)	16	16	8	32	>64
18 <i>M. catarrhalis</i> * GC6907 (Clinical)	16	8	16	32	>64
19 <i>H. influenzae</i> <> GC6896 (ATCC Control)	>64	>64	>64	>64	>64
20 <i>C. albicans</i> GC3066 ATCC (Control)	>64	>64	>64	>64	>64

TABLE V

ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 22	Example 24	Example 25	Example 26
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	>64
2 <i>E. coli</i> GC4559 (parent GC4560)	>64	>64	>64	>64
3 <i>E. coli</i> GC4560 (IMP mutant)	8	32	8	32
4 <i>E. coli</i> GC2203 (ATCC Control)	>64	>64	>64	>64
5 <i>E. coli</i> GC1073 (tet(B))	>64	>64	>64	>64
6 <i>S. aureus</i> GC1131 (Clinical)	8	32	8	16
7 <i>S. aureus</i> GC6466 (tet(M))	8	32	4	16
8 <i>S. aureus</i> GC6467 (tet(M)+(K))	8	32	8	16
9 <i>S. aureus</i> GC1079 (tet(K))	8	32	4	32
10 <i>S. aureus</i> GC4536 (Smith MP –In Vivo)	8	32	8	32
11 <i>S. aureus</i> GC2216 (ATCC Control)	8	64	4	16
12 <i>E. faecalis</i> GC4555 (ATCC Control)	8	32	8	32
13 <i>E. faecalis</i> GC2267 (tet(L)+(M)+(S))	8	32	4	16
14 <i>E. faecalis</i> GC2242 (Van-resistant)	8	32	4	16
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	32	64	32	>64
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	32	64	32	>64
17 <i>S. pyogenes</i> * GC4563 (Clinical)	16	32	16	64
18 <i>M. catarrhalis</i> * GC6907 (Clinical)	16	>64	16	>64
19 <i>H. influenzae</i> <> GC6896 (ATCC Control)	>64	>64	>64	>64
20 <i>C. albicans</i> GC3066 ATCC (Control)	>64	>64	>64	>64

TABLE VI
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 27	Example 28	Example 29	Example 30	Example 31
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	>64	>64
2 <i>E. coli</i> GC4559 (parent GC4560)	>64	>64	>64	>64	>64
3 <i>E. coli</i> GC4560 (IMP mutant)	32	16	8	8	4
4 <i>E. coli</i> GC2203 (ATCC Control)	>64	>64	>64	>64	>64
5 <i>E. coli</i> GC1073 (tet(B))	>64	>64	>64	>64	>64
6 <i>S. aureus</i> GC1131 (Clinical)	8	8	8	4	8
7 <i>S. aureus</i> GC6466 (tet(M))	16	8	8	8	4
8 <i>S. aureus</i> GC6467 (tet(M)+(K))	8	8	8	8	8
9 <i>S. aureus</i> GC1079 (tet(K))	8	16	8	8	8
10 <i>S. aureus</i> GC4536 (Smith MP –In Vivo)	16	16	8	8	8
11 <i>S. aureus</i> GC2216 (ATCC Control)	8	8	8	4	8
12 <i>E. faecalis</i> GC4555 (ATCC Control)	16	16	8	8	8
13 <i>E. faecalis</i> GC2267 (tet(L)+(M)+(S))	8	8	8	4	8
14 <i>E. faecalis</i> GC2242 (Van-resistant)	8	8	8	4	8
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	64	32	32	16	8
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	64	64	32	16	8
17 <i>S. pyogenes</i> * GC4563 (Clinical)	64	16	16	16	8
18 <i>M. catarrhalis</i> * GC6907 (Clinical)	>64	64	16	32	16
19 <i>H. influenzae</i> <> GC6896 (ATCC Control)	>64	>64	>64	>64	>64
20 <i>C. albicans</i> GC3066 ATCC (Control)	>64	>64	>64	>64	>64

TABLE VII
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 32	Example 33	Example 34	Example 35	Example 36
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	16	4
2 <i>E. coli</i> GC4559 (parent GC4560)	>64	>64	>64	8	4
3 <i>E. coli</i> GC4560 (IMP mutant)	>64	16	32	0.50	1
4 <i>E. coli</i> GC2203 (ATCC Control)	>64	64	>64	4	2
5 <i>E. coli</i> GC1073 (tet(B))	>64	>64	>64	32	4
6 <i>S. aureus</i> GC1131 (Clinical)	>64	16	32	0.50	4
7 <i>S. aureus</i> GC6466 (tet(M))	>64	32	64	1	4
8 <i>S. aureus</i> GC6467 (tet(M)+(K))	>64	32	64	8	16
9 <i>S. aureus</i> GC1079 (tet(K))	>64	16	32	4	4
10 <i>S. aureus</i> GC4536 (Smith MP –In Vivo)	>64	16	64	1	4
11 <i>S. aureus</i> GC2216 (ATCC Control)	>64	16	32	0.50	2
12 <i>E. faecalis</i> GC4555 (ATCC Control)	64	16	32	1	4
13 <i>E. faecalis</i> GC2267 (tet(L)+(M)+(S))	>64	16	32	4	4
14 <i>E. faecalis</i> GC2242 (Van-resistant)	64	16	32	1	4
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	16	16	32	0.50	1
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	8	32	64	0.25	1
17 <i>S. pyogenes</i> * GC4563 (Clinical)	16	8	32	0.25	1
18 <i>M. catarrhalis</i> * GC6907 (Clinical)	32	8	16	0.50	1
19 <i>H. influenzae</i> <> GC6896 (ATCC Control)	>64	32	>64	2	4
20 <i>C. albicans</i> GC3066 ATCC (Control)	>64	>64	>64	>64	>64

TABLE VIII
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-
TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 37	Example 38	Example 39
1 E. coli GC2270 (tet(M))	4	32	32
2 E. coli GC4559 (parent GC4560)	2	32	32
3 E. coli GC4560 (IMP mutant)	1	8	8
4 E. coli GC2203 (ATCC Control)	2	32	32
5 E. coli GC1073 (tet(B))	2	32	32
6 S. aureus GC1131 (Clinical)	4	32	32
7 S. aureus GC6466 (tet(M))	4	32	32
8 S. aureus GC6467 (tet(M)+(K))	8	>64	>64
9 S. aureus GC1079 (tet(K))	4	64	64
10 S. aureus GC4536 (Smith MP -In Vivo)	4	16	32
11 S. aureus GC2216 (ATCC Control)	4	32	32
12 E. faecalis GC4555 (ATCC Control)	2	16	32
13 E. faecalis GC2267 (tet(L)+(M)+(S))	4	64	64
14 E. faecalis GC2242 (Van-resistant)	2	16	32
15 S. pneumoniae* GC4465 (Clinical)	1	4	8
16 S. pneumoniae* GC1894 (Clinical)	1	4	8
17 S. pyogenes* GC4563 (Clinical)	1	4	8
18 M. catarrhalis* GC6907 (Clinical)	1	4	8
19 H. influenzae<> GC6896 (ATCC Control)	4	64	64
20 C. albicans GC3066 ATCC (Control)	>64	>64	>64

When the compounds of the invention are employed as antibacterials, they can be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

An effective amount of compound from about 2.0 mg/kg of body weight to about 100.0 mg/kg of body weight may be administered one to five times per day via any typical route of administration including but not limited to oral, parenteral (including subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques), topical or rectal, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions of compounds of the invention from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

- 5 These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary
10 conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

- The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and
15 must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures
20 thereof, and vegetable oil.

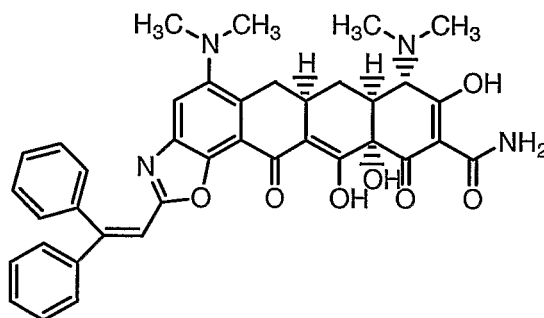
The invention will be more fully described in conjunction with the following specific examples which are not to be construed as limiting the scope of the invention.

5 Example of Procedure A

EXAMPLE 1

(6aR,7aS,8*S*,11a*S*)-5,8-bis(dimethylamino)-2-(2,2-diphenylvinyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

10



15

9-aminomincycline sulfate salt (0.500g, 0.748 mmol) is dissolved in anhydrous DMF and treated with β -phenylcinnamaldehyde (0.779g, 3.74 mmol, 5 equivalents) The solution is then treated with DDQ (0.085 g, 0.374 mmol, 0.5 equivalents) and stirred at room temperature for 5 min. ES+ mass spectrometry showed a 1:1 ratio of product and starting material. A second portion of DDQ (0.068 g, 0.300 mmol, 0.4 equivalents) is added. After approximately 5 minutes, acetonitrile (7.5 mL) is added, and the entire reaction mixture is poured slowly into ether (750 mL.) The pink solid is removed by filtration and washed with fresh ether to yield 0.480g of the crude product. This material is dissolved in water (75 mL) to give a solution at pH 2.2, which is extracted with dichloromethane (2 X 100 mL.) The pH of the aqueous layer is raised to 3.0 with aqueous ammonia, and the solution is again

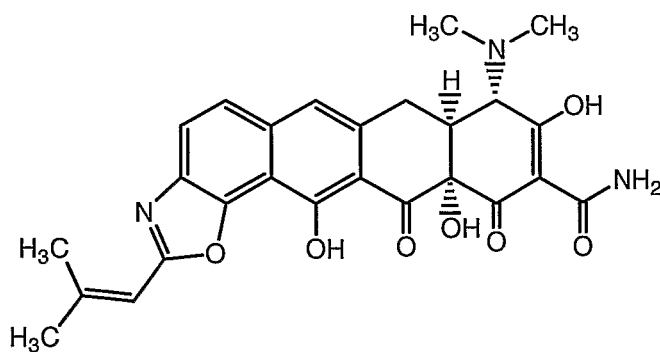
extracted with dichloromethane (2 X 100 mL.) The four organic extracts are dried (Na₂SO₄), filtered and concentrated to a volume of about 2 mL. A small portion of methanol (1 mL) is added, and the concentrated solution is treated dropwise with 1M HCl in ether. The solid precipitate is filtered, washed with fresh ether and dried under vacuum the product as its HCl salt.

Selected ¹H NMR signals: δ 4.26 (s, 1H), 7.13 (s, 1H), 7.26-7.45 (m, 8H), 7.63 (s, 1H), 9.08 (s, 1H), 9.54 (s, 1H).

- 10 The compounds of this invention listed below in Examples 2 to 37 are prepared substantially following the method described in detail hereinabove in Example 1 using procedure A.

EXAMPLE 2

- 15 (7a*S*,8*S*,11a*S*)-8-(dimethylamino)-9,11a,13-trihydroxy-2-(2-methyl-1-propenyl)-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-*d*][1,3]oxazole-10-carboxamide



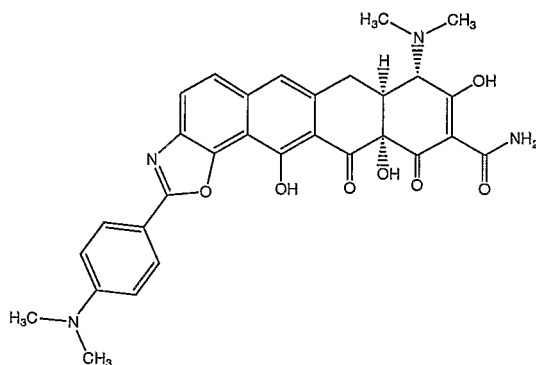
MS *m/z* 492 (M+H)

- 25 HRMS: calcd for C₂₆H₂₆N₃O₇, 491.16925; found (ESI+), 492.1765

EXAMPLE 3

(7a*S*,8*S*,11a*S*)-8-(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,13-trihydroxy-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-*d*][1,3]oxazole-10-carboxamide

5

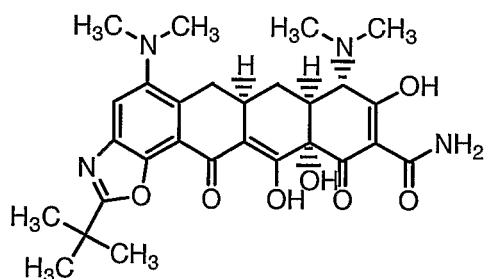


HRMS: calcd for $C_{30}H_{29}N_3O_7$, 566.1958; found (ESI+), 557.2030

10

EXAMPLE 4

(6a*R*,7a*S*,8*S*,11a*S*)-2-*tert*-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-*d*][1,3]oxazole-10-carboxamide



15

MS (ESI) m/z 539.3 ($M+H$);

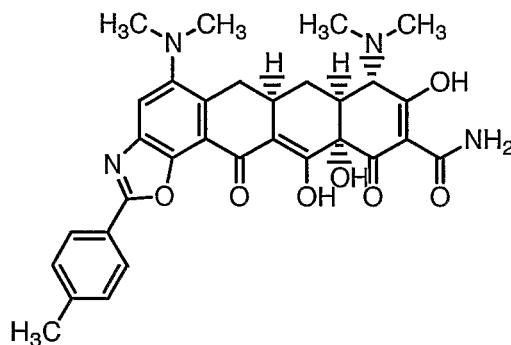
MS (ESI) m/z 270.4 ($M+2H$);

HRMS: calcd for $C_{28}H_{34}N_4O_7 \cdot HCl$, 574.2194; found (ESI-), 537.23462;

20

EXAMPLE 5

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(4-methylphenyl)-
 11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-
 carboxamide



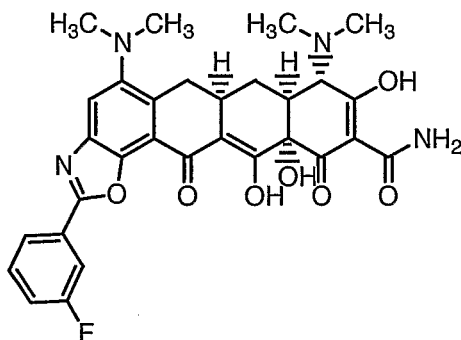
10

MS (ESI) m/z 573.3 (M+H);MS (ESI) m/z 287 (M+2H);HRMS: calcd for $C_{31}H_{32}N_4O_7 \cdot HCl$, 608.2038; found (ESI-), 571.21905;

EXAMPLE 6

15

(7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluorophenyl)-9,11a,13-trihydroxy-11,12-
 dioxo-7,7a,8,11,11a,12-hexahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

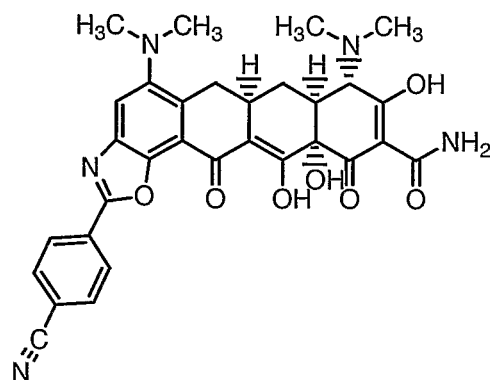


20

EXAMPLE 7

(6aR,7aS,8S,11aS)-2-(4-cyanophenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



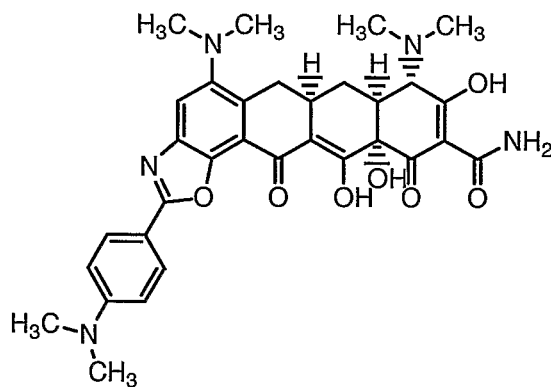
MS (ESI) m/z 584.4 (M+H);

HRMS: calcd for $C_{31}H_{29}N_5O_7 \cdot HCl$, 619.1834; found (ESI-), 582.19817;

10

EXAMPLE 8

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



15

MS (ESI) m/z 602.2 (M+H);

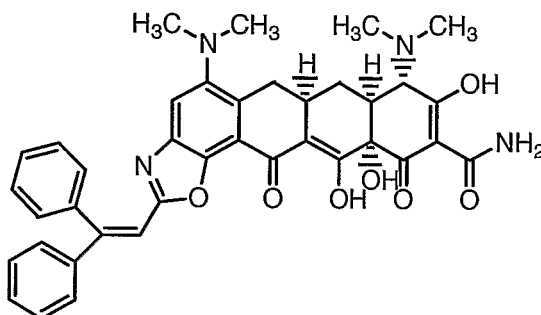
MS (ESI) m/z 301.8 (M+2H);

HRMS: calcd for $C_{32}H_{35}N_5O_7 \cdot HCl$, 637.2303; found (ESI-), 600.24521;

EXAMPLE 9

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2,2-diphenylvinyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 661.3 (M+H);

MS (ESI) m/z 331.3 (M+2H);

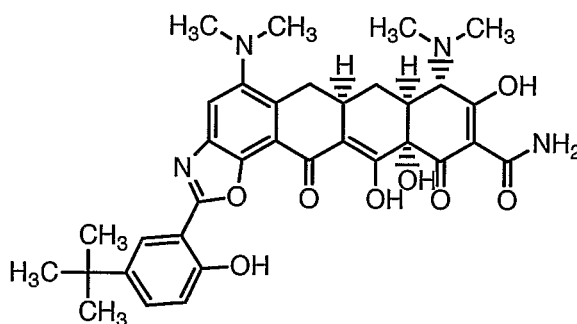
HRMS: calcd for $C_{38}H_{36}N_4O_7 \cdot HCl$, 696.2351; found (ESI-), 659.24957;

10

EXAMPLE 10

(6aR,7aS,8S,11aS)-2-(5-*tert*-butyl-2-hydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



20

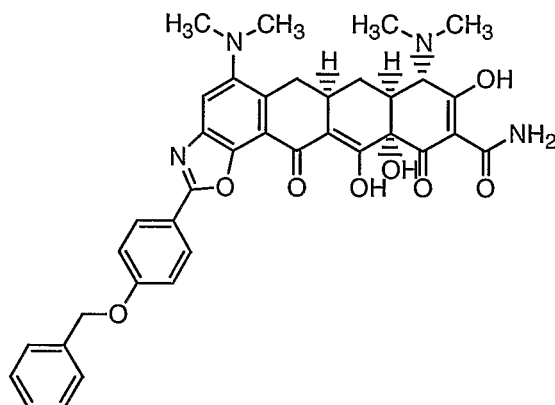
MS (ESI) m/z 631.4 (M+H);

HRMS: calcd for $C_{34}H_{38}N_4O_8 \cdot HCl$, 666.2456; found (ESI+), 631.27753;

EXAMPLE 11

(6aR,7aS,8S,11aS)-2-[4-(benzyloxy)phenyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 665.2 ($M+H$);

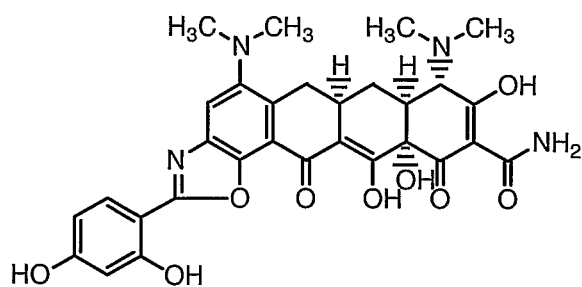
HRMS: calcd for $C_{37}H_{36}N_4O_8 \cdot HCl$, 700.2300; found (ESI+), 665.26096;

10

EXAMPLE 12

(6aR,7aS,8S,11aS)-2-(2,4-dihydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



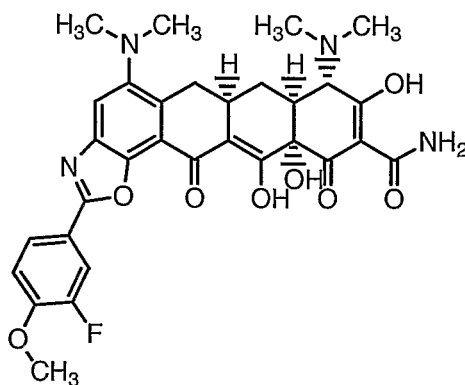
MS (ESI) m/z 591.2 ($M+H$);

HRMS: calcd for $C_{30}H_{30}N_4O_9 \cdot HCl$, 626.1780; found (ESI-), 589.1927;

20

EXAMPLE 13

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluoro-4-methoxyphenyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



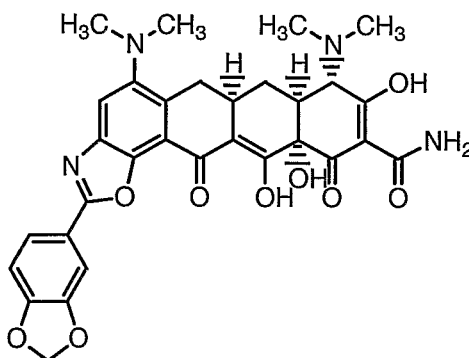
MS (ESI) m/z 607.3 (M+H);

MS (ESI) m/z 304 (M+2H);

HRMS: calcd for $C_{31}H_{31}FN_4O_8 \cdot HCl$, 642.1893; found (ESI-), 605.20519;

EXAMPLE 14

(6aR,7aS,8S,11aS)-2-(1,3-benzodioxol-5-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



MS (ESI) m/z 603.3 (M+H);

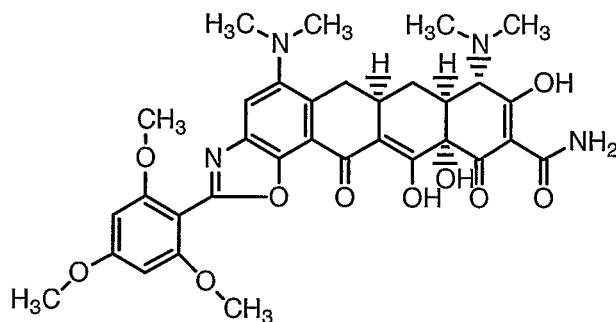
MS (ESI) m/z 302.1 (M+2H);

HRMS: calcd for $C_{31}H_{30}N_4O_9 \cdot HCl$, 638.1780; found (ESI+), 603.20953;

EXAMPLE 15

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,6-trimethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 649.2 (M+H);

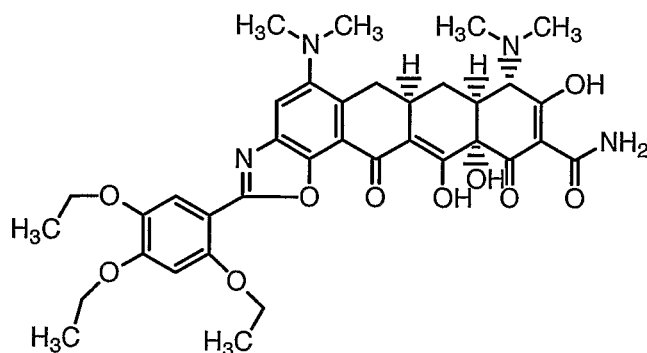
HRMS: calcd for $C_{33}H_{36}N_4O_{10} \cdot HCl$, 684.2198; found (ESI-), 647.23441;

10

EXAMPLE 16

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,5-triethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



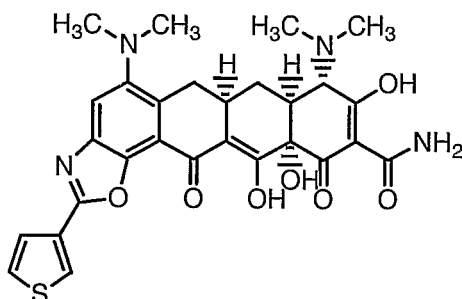
20

MS (ESI) m/z 691.3 (M+H);

HRMS: calcd for $C_{36}H_{42}N_4O_{10} \cdot HCl$, 726.2668; found (ESI+), 691.29817;

EXAMPLE 17

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thien-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



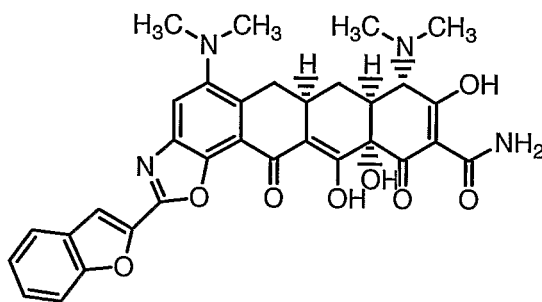
MS (ESI) m/z 565.2 (M+H);

MS (ESI) m/z 283.4 (M+2H);

HRMS: calcd for $C_{28}H_{28}N_4O_7S \cdot HCl$, 600.1445; found (ESI-), 563.15992;

EXAMPLE 18

(6aR,7aS,8S,11aS)-2-(1-benzofuran-2-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



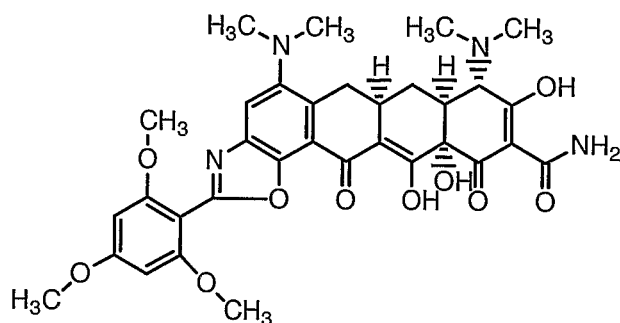
MS (ESI) m/z 599.3 (M+H);

HRMS: calcd for $C_{32}H_{30}N_4O_8 \cdot HCl$, 634.1830; found (ESI-), 597.19811;

EXAMPLE 19

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(1-methyl-1*H*-indol-2-yl)-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



10

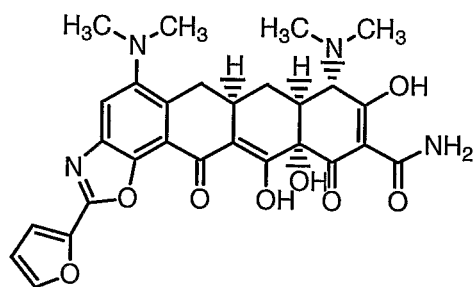
MS (ESI) m/z 612.2 ($M+H$);

HRMS: calcd for $C_{33}H_{33}N_5O_7 \cdot HCl$, 647.2147; found (ESI+), 612.24406;

EXAMPLE 20

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2-furyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



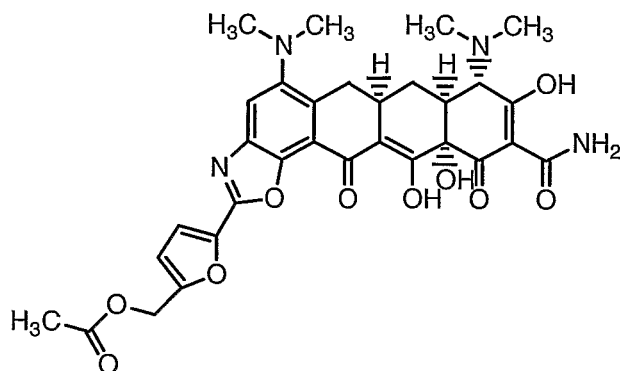
20

MS (ESI) m/z 549.3 ($M+H$);

HRMS: calcd for $C_{28}H_{28}N_4O_8 \cdot HCl$, 584.1674; found (ESI-), 547.1822;

EXAMPLE 21

{5-[(6aR,7aS,8S,11aS)-10-(aminocarbonyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazol-2-yl]-2-furyl}methyl acetate

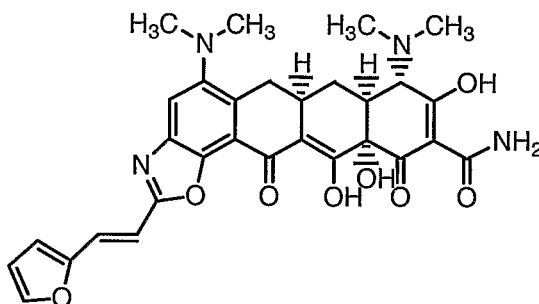


MS (ESI) m/z 621.2 (M+H);

HRMS: calcd for $C_{31}H_{32}N_4O_{10} \cdot HCl$, 656.1885; found (ESI+), 621.21807;

EXAMPLE 22

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(E)-2-(2-furyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



MS (ESI) m/z 575.2 (M+H);

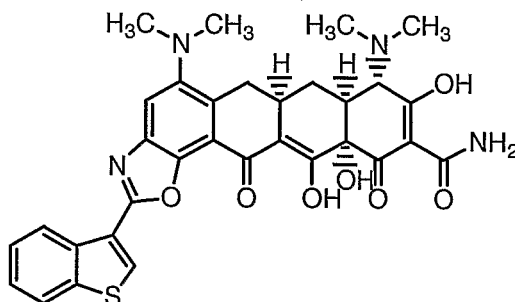
MS (ESI) m/z 288.3 (M+2H);

HRMS: calcd for $C_{30}H_{30}N_4O_8 \cdot HCl$, 610.1830; found (ESI-), 573.1985;

EXAMPLE 23

(6aR,7aS,8S,11aS)-2-(1-benzothien-3-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI+) m/z 615.1 ((M+H)+);

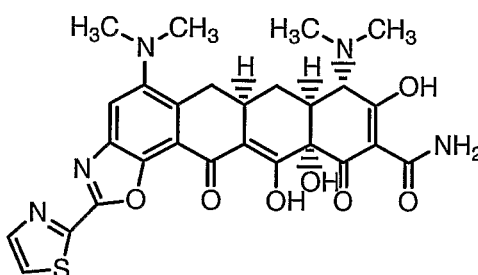
10

HRMS: calcd for $C_{32}H_{30}N_4O_7S \cdot HCl$, 650.1602; found (ESI+), 615.19036;

EXAMPLE 24

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(1,3-thiazol-2-yl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



20

MS (ESI) m/z 566.4 (M+H);

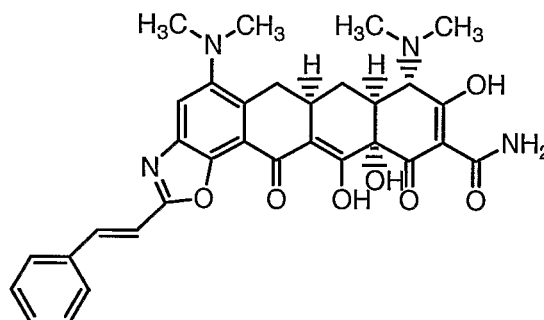
MS (ESI) m/z 283.6 (M+2H);

HRMS: calcd for $C_{27}H_{27}N_5O_7S \cdot HCl$, 601.1398; found (ESI+), 566.16973;

EXAMPLE 25

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(E)-2-phenylethenyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



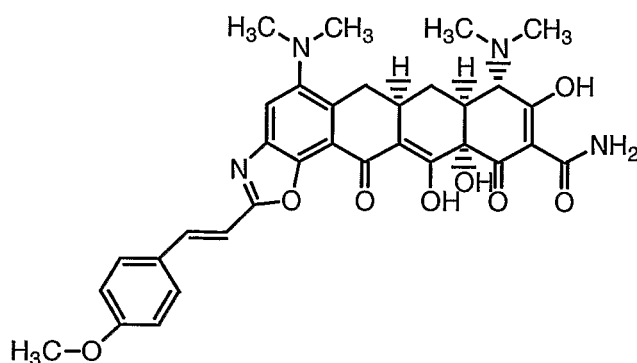
MS (ESI) m/z 585.4 (M+H);

MS (ESI) m/z 293.3 (M+2H);

10 HRMS: calcd for $C_{32}H_{32}N_4O_7 \cdot HCl$, 620.2038; found (ESI+), 585.2329;

EXAMPLE 26

15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(4-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



MS (ESI) m/z 615.3 (M+H);

20

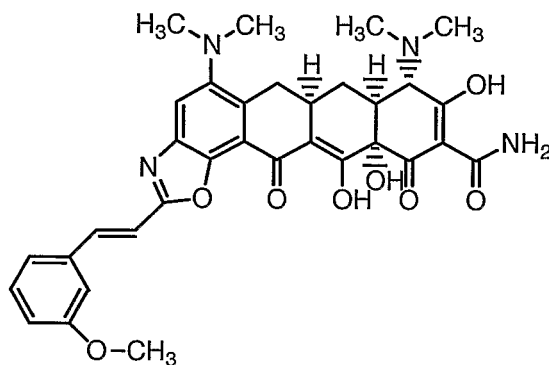
MS (ESI) m/z 308.3 (M+2H);

HRMS: calcd for $C_{33}H_{34}N_4O_8 \cdot HCl$, 650.2143; found (ESI+), 615.24413;

EXAMPLE 27

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(*E*)-2-(3-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 615.4 (M+H);

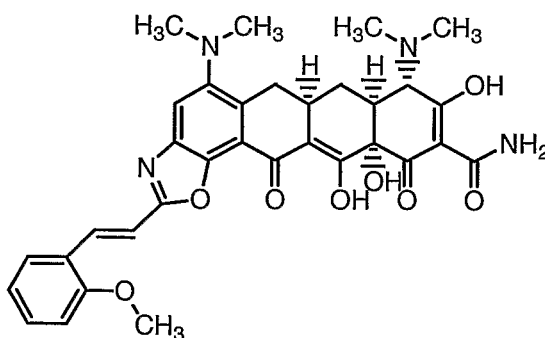
MS (ESI) m/z 308.3 (M+2H);

10 HRMS: calcd for $C_{33}H_{34}N_4O_8 \cdot HCl$, 650.2143; found (ESI+), 615.24419;

EXAMPLE 28

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(*E*)-2-(2-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



MS (ESI) m/z 615.3 (M+H);

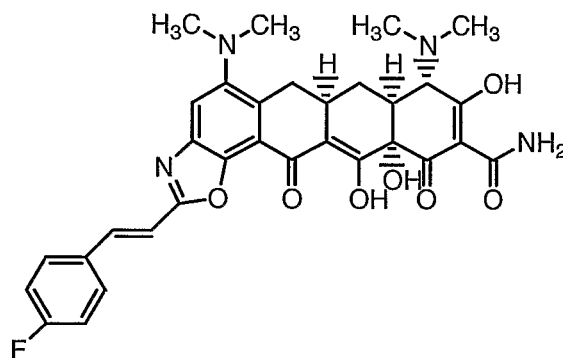
MS (ESI) m/z 308.3 (M+2H);

20 HRMS: calcd for $C_{33}H_{34}N_4O_8 \cdot HCl$, 650.2143; found (ESI+), 615.24408;

EXAMPLE 29

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(4-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 603.3 ($M+H$);

MS (ESI) m/z 302.3 ($M+2H$);

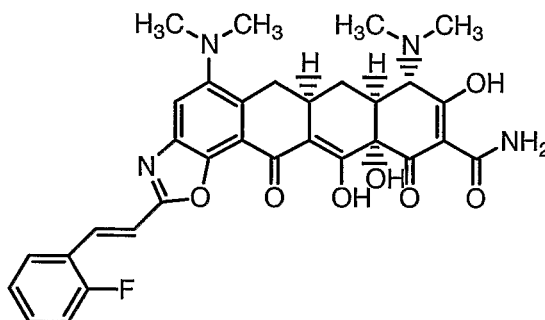
HRMS: calcd for $C_{32}H_{31}FN_4O_7 \cdot HCl$, 638.1944; found (ESI+), 603.22476;

10

EXAMPLE 30

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(2-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



MS (ESI) m/z 603.2 ($M+H$);

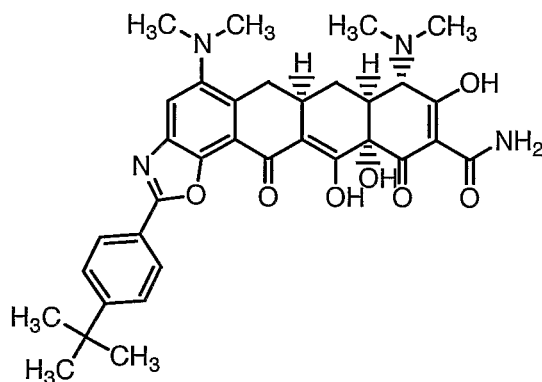
MS (ESI) m/z 302.3 ($M+2H$);

HRMS: calcd for $C_{32}H_{31}FN_4O_7 \cdot HCl$, 638.1944; found (ESI+), 603.22469;

20

EXAMPLE 31

(6aR,7aS,8S,11aS)-2-(4-*tert*-butylphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



MS (ESI) m/z 615.3 (M+H);

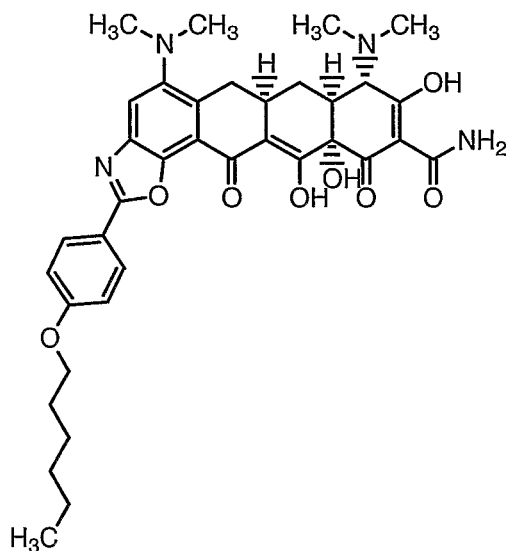
MS (ESI) m/z 308.3 (M+2H);

HRMS: calcd for $C_{34}H_{38}N_4O_7 \cdot HCl$, 650.2507; found (ESI+), 615.28057;

EXAMPLE 32

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(hexyloxy)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 659.4 (M+H);

MS (ESI) m/z 330.4 (M+2H);

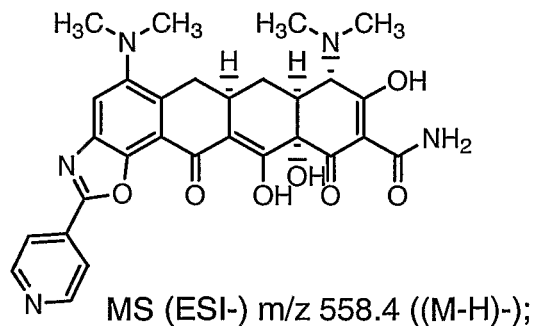
HRMS: calcd for $C_{36}H_{42}N_4O_8 \cdot HCl$, 694.2769; found (ESI+), 659.30693;

10

EXAMPLE 33

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-4-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

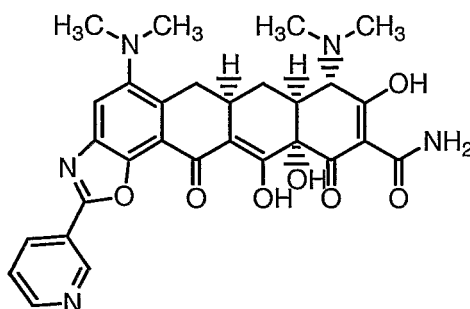
15



EXAMPLE 34

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 560.3 (M+H);

10

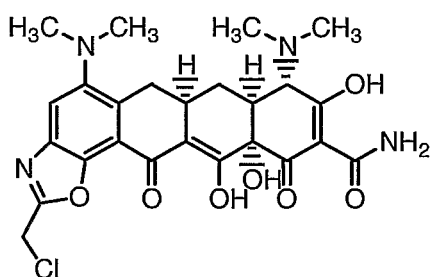
MS (ESI) m/z 280.7 (M+2H);

HRMS: calcd for $C_{29}H_{29}N_5O_7 \cdot HCl$, 595.1834; found (ESI+), 560.21353;

EXAMPLE 35

(6aR,7aS,8S,11aS)-2-(chloromethyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



20

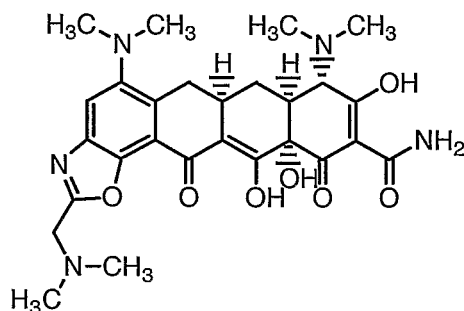
MS (ESI) m/z 531.2 (M+H);

MS (ESI) m/z 266.3 (M+2H);

EXAMPLE 36

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(dimethylamino)methyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 540.4 (M+H);

MS (ESI) m/z 270.7 (M+2H);

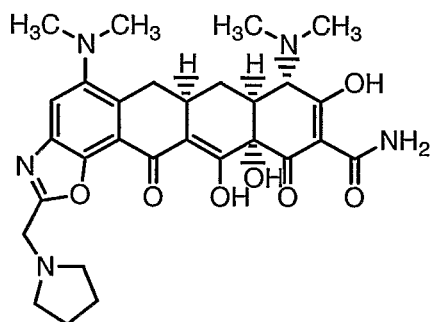
10

HRMS: calcd for $C_{27}H_{33}N_5O_7 \cdot HCl$, 575.2147; found (ESI+), 540.24506;

EXAMPLE 37

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(pyrrolidin-1-ylmethyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



MS (ESI) m/z 566.4 (M+H);

20

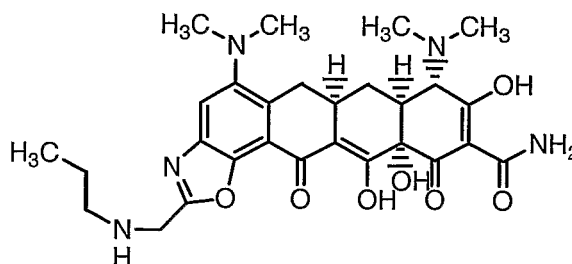
MS (ESI) m/z 283.9 (M+2H);

HRMS: calcd for $C_{29}H_{35}N_5O_7 \cdot HCl$, 601.2303; found (ESI+), 566.26066;

Example of Procedure B

EXAMPLE 38

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
 5 [(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
 10-carboxamide



10

9-aminomincycline sulfate salt (1.0 g, 1.50 mmol) is dissolved in DMF (50 mL) and treated with a solution of 2-chloro-1,1,1-trimethoxyethane (0.463 g, 3.00 mmol, 2 equivalents). The reaction is stirred at room temperature until mass spectrometry
 15 shows conversion to the chloromethylbenzoxazole derivative. The solution is then treated with *n*-propylamine (10 mL, excess) and stirred until mass spectrometry shows conversion to the *n*-propylaminomethyl benzoxazole. The mixture is concentrated under reduced pressure to remove excess *n*-propylamine, and then poured slowly into ether (1 L) and HCl/ether is added to precipitate the salt. The solid
 20 is rinsed with fresh ether and dried under vacuum. The crude solid is dissolved in water (100 mL) giving a solution at pH 2. The pH is raised successively by 0.5 units with aqueous ammonia, and extracted with dichloromethane. The fractions extracted at pH 4-4.5 are combined, dried (Na₂SO₄), filtered and concentrated nearly to dryness. A small volume of methanol is added and the solution is treated with 1M
 25 HCl in ether. The precipitated solid is collected by filtration, washed with fresh ether and dried under vacuum to yield 0.067 g of the product as its HCl salt.

Selected ¹H NMR signals: δ 0.94 (t, 3H), 1.73 (m, 2H), 4.31 (s, 1H), 4.65 (s, 2H), 7.78 (s, 1H), 9.15 (s, 1H), 9.67 (s, 1H).

The compounds of this invention listed below in Examples 39 to 41 are prepared substantially following the method described in detail hereinabove in Example 38 using procedure B.

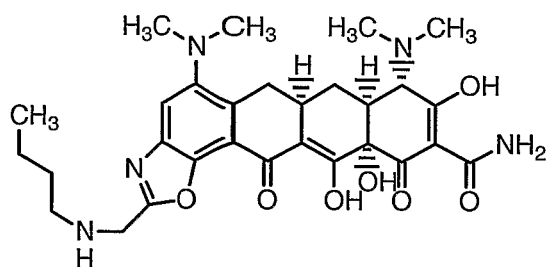
5

(prepared from Procedure B)

EXAMPLE 39

(6aR,7aS,8S,11aS)-2-[(butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

10



15

MS (ESI) m/z 568.3 (M+H);

MS (ESI) m/z 284.8 (M+2H);

MS (ESI) m/z 305.2 (M+ACN+2H);

HRMS: calcd for $C_{29}H_{37}N_5O_7 \cdot HCl$, 603.2460; found (ESI+), 568.27616;

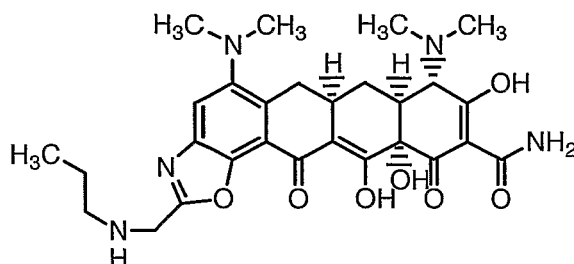
20

25

(Procedure B)

EXAMPLE 40

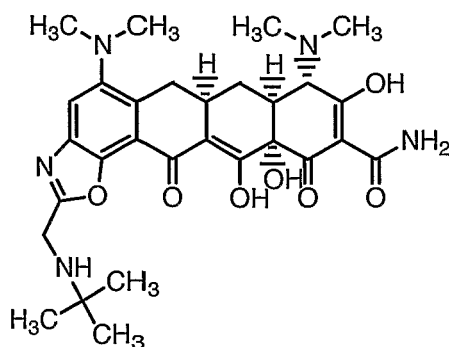
(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
 [(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
 10-carboxamide

MS (ESI) m/z 554.3 (M+H);MS (ESI) m/z 277.7 (M+2H);HRMS: calcd for $C_{28}H_{35}N_5O_7 \cdot HCl$, 589.2303; found (ESI+), 554.2604;

(Procedure B)

EXAMPLE 41

(6aR,7aS,8S,11aS)-2-[(*tert*-butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-
 trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
 10-carboxamide



9-aminomincycline sulfate salt (1.0 g, 1.50 mmol) is dissolved in DMF (20 mL) and treated with a solution of 2-chlorotrimethoxyethane (0.35 g, 2.2 mmol, 1.46 equivalents). The reaction is stirred at room temperature until mass spectrometry showed conversion to the chloromethylbenzoxazole derivative. The solution is then
 5 treated with *t*-butylamine (7.3 mL, excess) and stirred until mass spectrometry showed conversion to the *t*-butylaminomethyl benzoxazole. The mixture is concentrated under reduced pressure to remove excess *t*-butylamine, and then poured slowly into ether (1 L) and HCl/ether is added to precipitate the salt. The solid is rinsed with fresh ether and dried under vacuum. The crude solid is dissolved in
 10 water (100 mL) giving a solution at pH 2. The pH is raised successively by 0.5 units with aqueous ammonia, and extracted with dichloromethane. The fractions extracted at pH 4-4.5 are combined, dried (Na₂SO₄), filtered and concentrated nearly to dryness. A small volume of methanol is added and the solution is treated with 1M HCl in ether. The precipitated solid is collected by filtration, washed with fresh ether
 15 and dried under vacuum to give the product as its HCl salt.

MS (ESI+) *m/z* 568.4 ((M+H)+);

MS (ESI+) *m/z* 284.9 ((M+2H)2+);

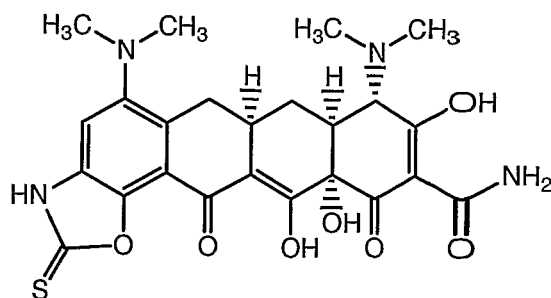
MS (ESI+) *m/z* 146.3 ((M'+H)+);

20 HRMS: calcd for C₂₉H₃₇N₅O₇ · HCl, 603.2460; found (ESI-), 566.26087;

Example of Procedure C

EXAMPLE 42

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thioxo-2,3,6,6a,7,7a,8,11,11a,13-decahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide
 25



To a solution of 9-amino-mino disulfate (0.668 g, 1 mmol) in DMSO (30 mL) is added 2 equivalents of 1,1-thiocarbonyldiimidazole. The reaction is then stirred at room temperature for 2 to 12 hr (followed by MS(ES)). The mixture then triturated with diethyl ether and the solid collected. Material is used in the next step without further purification.

MS (ESI) m/z 515.2 (M+H);

HRMS: calcd for $C_{24}H_{26}N_4O_7S \cdot H_2SO_4$, 612.1196; found (ESI+), 515.15934;

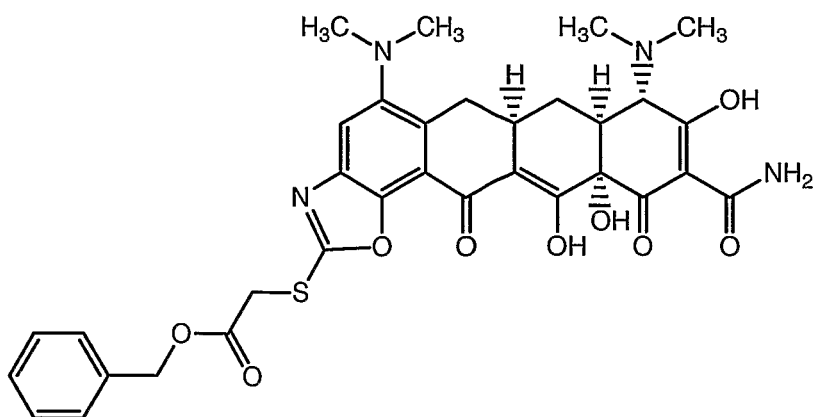
The compounds of this invention listed below in Examples 43 to 44 are prepared substantially following the method described in detail hereinabove in Example 42 using procedure C.

Example of procedure C

(Procedure C)

EXAMPLE 43

benzyl {[(6aR,7aS,8S,11aS)-10-(aminocarbonyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazol-2-yl]thio}acetate



To a solution of (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thioxo-2,3,6,6a,7,7a,8,11,11a,13-decahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide (Example 42) in N,N-dimethylformamide (DMF) is added 2 equivalents of diisopropylethylamine, after stirring for 5 min. 1.2 equivalent of benzyl-2-bromoacetate is added. The reaction mixture is stirred for 1 hr and mixture triturated with diethyl ether and solid is collected. It is purified by extraction.

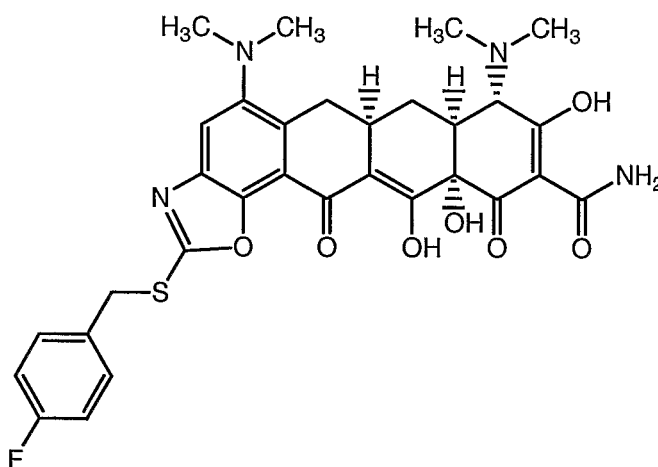
MS (ESI) m/z 663.2 (M+H);

MS (ESI) m/z 332.1 (M+2H);

HRMS: calcd for $C_{33}H_{34}N_4O_9S \cdot HCl$, 698.1813; found (ESI+), 663.2115;

EXAMPLE 44

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(4-fluorobenzyl)thio]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



The compound of the example is prepared using procedure D in Example 43 using 4-fluorobenzylbromide.

MS (ESI) m/z 622.9 (M+H);

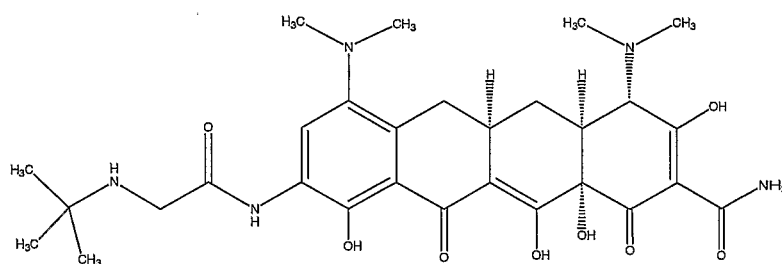
HRMS: calcd for $C_{31}H_{31}FN_4O_7S \cdot HCl$, 658.1664; found (ESI+), 623.19689;

Example of Procedure D (Compound 1 to 4 to 6)

Example 45

5 [4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylaminol-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.
(mono HCl); (free base)

10



9-amininocycline sulfate salt (1.0 g, 1.50 mmol) is dissolved DMF (20 mL) and treated with a solution of 2-chlorotrimethoxyethane (0.35 g, 2.2 mmol, 1.47 equivalents). The reaction is stirred at room temperature until mass spectrometry showed conversion to the chloromethylbenzoxazole derivative. The solution is then treated with *t*-butylamine (7.3 mL, excess) and stirred until mass spectrometry showed conversion to the *t*-butylaminomethyl benzoxazole. The mixture is concentrated under reduced pressure to remove excess *t*-butylamine, and then poured slowly into ether (1 L) and HCl/ether is added to precipitate the salt. The solid is rinsed with fresh ether and dried under vacuum. The crude solid is dissolved in water (100 mL) giving a solution at pH 2. The pH is raised successively by 0.5 units with aqueous ammonia, and extracted with dichloromethane. The fractions extracted at pH 4-4.5 are combined, dried (Na₂SO₄), filtered and concentrated nearly to dryness. A small volume of methanol is added and the solution is treated with 1M HCl in ether. The precipitated solid is collected by filtration, washed with fresh ether and dried under vacuum to give the product as its HCl salt.

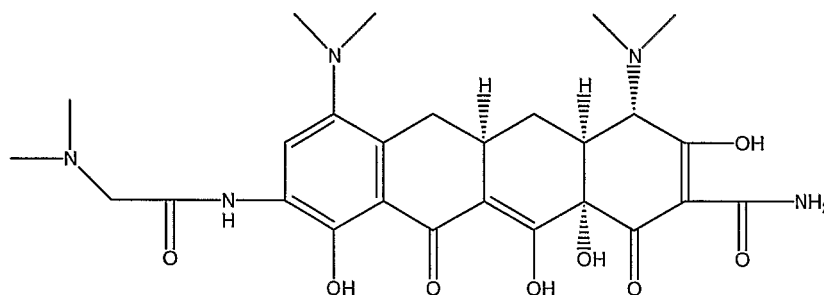
Product from example 41 is treated with aqueous acid for one hour to 24 hour to give mono HCL salt of example 45

MS (ESI+) m/z 586.4 ((M+H)+;

- 5 The following examples are prepared using similar method described in procedure D.

Example 46

[4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[(dimethylamino)acetyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
10 naphthacenecarboxamide.

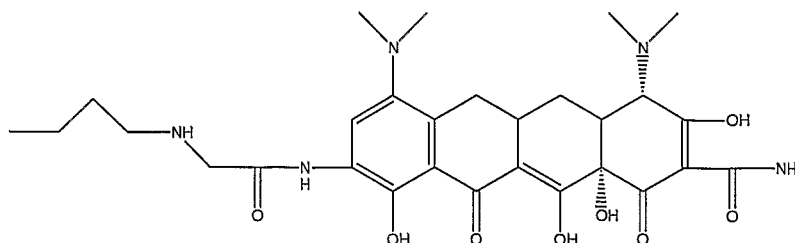


MS (FAB) m/z 558 ((M+H)+;

15

Example 47

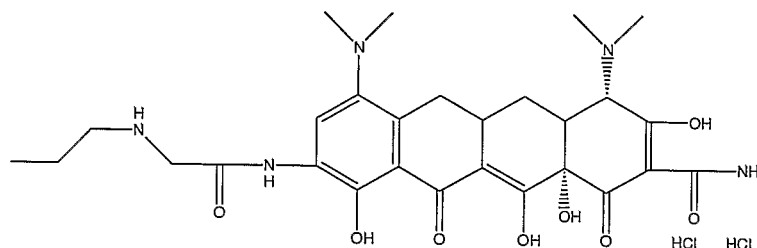
[4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[(n-butylamino)acetyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
20 naphthacenecarboxamide.



MS (FAB) m/z 586 ((M+H)+;

Example 48

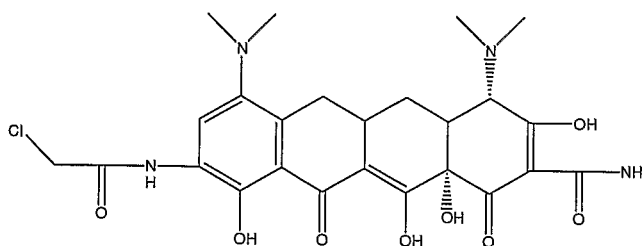
[4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[[propylamino]acetyl]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide



MS (FAB) m/z 572 ((M+H)⁺;

Example 49

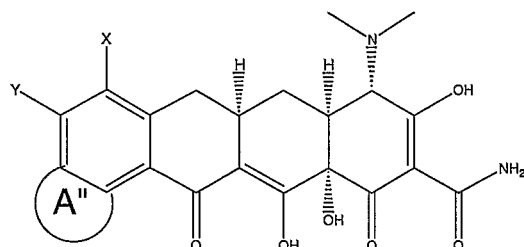
[4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[(chloroacetyl)amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide



MS (FAB) m/z 549 ((M+H)⁺;

WHAT IS CLAIMED IS:

1. A compound of Formula (I);



5

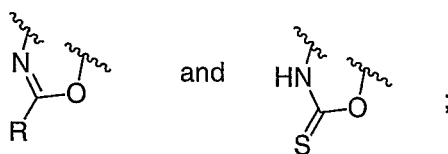
I

wherein:

- X is selected from hydrogen, amino, $\text{NR}^{11}\text{R}^{12}$, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

10

A'' is a moiety selected from the group:



15

R^{11} and R^{12} are each independently H or alkyl of 1 to 12 carbon atoms or R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

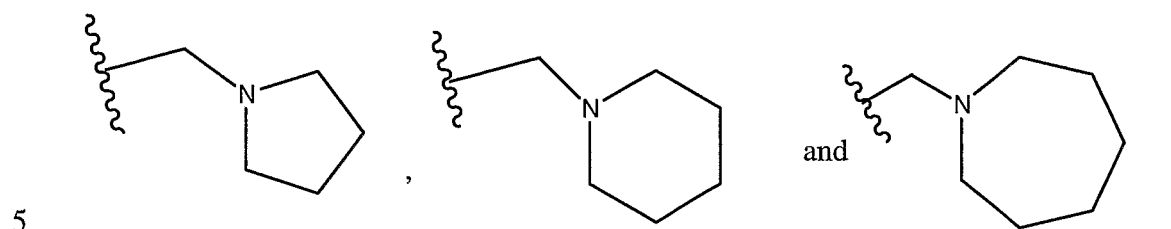
20

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

25

- R is selected from alkyl of 1 to 12 carbon atoms optionally substituted, alkenyl of 2 to 6 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted, $-\text{CH}_2\text{NR}^1\text{R}^2$, aryl of 6, 10 or 14 carbon atoms optionally substituted, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl of 7 to 13 carbon atoms optionally substituted, SR^3 , heteroaryl of 5 or 6 ring atoms optionally substituted, containing 1 to 4 heteroatoms which may be the same or different, independently selected from nitrogen, oxygen and sulfur, and heteroarylcarbonyl of 5 or 6 ring atoms optionally substituted containing 1 to 4 heteroatoms which may be the same or different, independently selected from nitrogen, oxygen and sulfur;
- R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;
- R^3 is alkyl of 1 to 12 carbon atoms optionally substituted, $-\text{CH}_2$ -aryl optionally substituted, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl, $-\text{CH}_2(\text{CO})\text{OCH}_2$ aryl optionally substituted, $-\text{CH}_2$ -alkenyl of 2 to 12 carbon atoms optionally substituted, and $-\text{CH}_2$ -alkynyl of 2 to 12 carbon atoms optionally substituted;
- with the proviso that when X is NR^1R^2 and R^1 is hydrogen, then R^2 is methyl, ethyl, n-propyl, n-butyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and that when R^1 is methyl or ethyl then R^2 is methyl, ethyl, n-propyl, 1-methylethyl, n-propyl, 1-methylpropyl, or 2-methylpropyl;
- or a tautomer or a pharmaceutically acceptable salt thereof.
2. A compound according to claim 1 wherein R is phenyl optionally substituted with 1 to 3 substituents or a pharmaceutically acceptable salt thereof.
3. A compound according to claim 1 wherein R of Formula (I) is selected from the group alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, and alkyl-heterocyclyl or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3 wherein alkyl-heterocyclyl is selected from moieties of the group

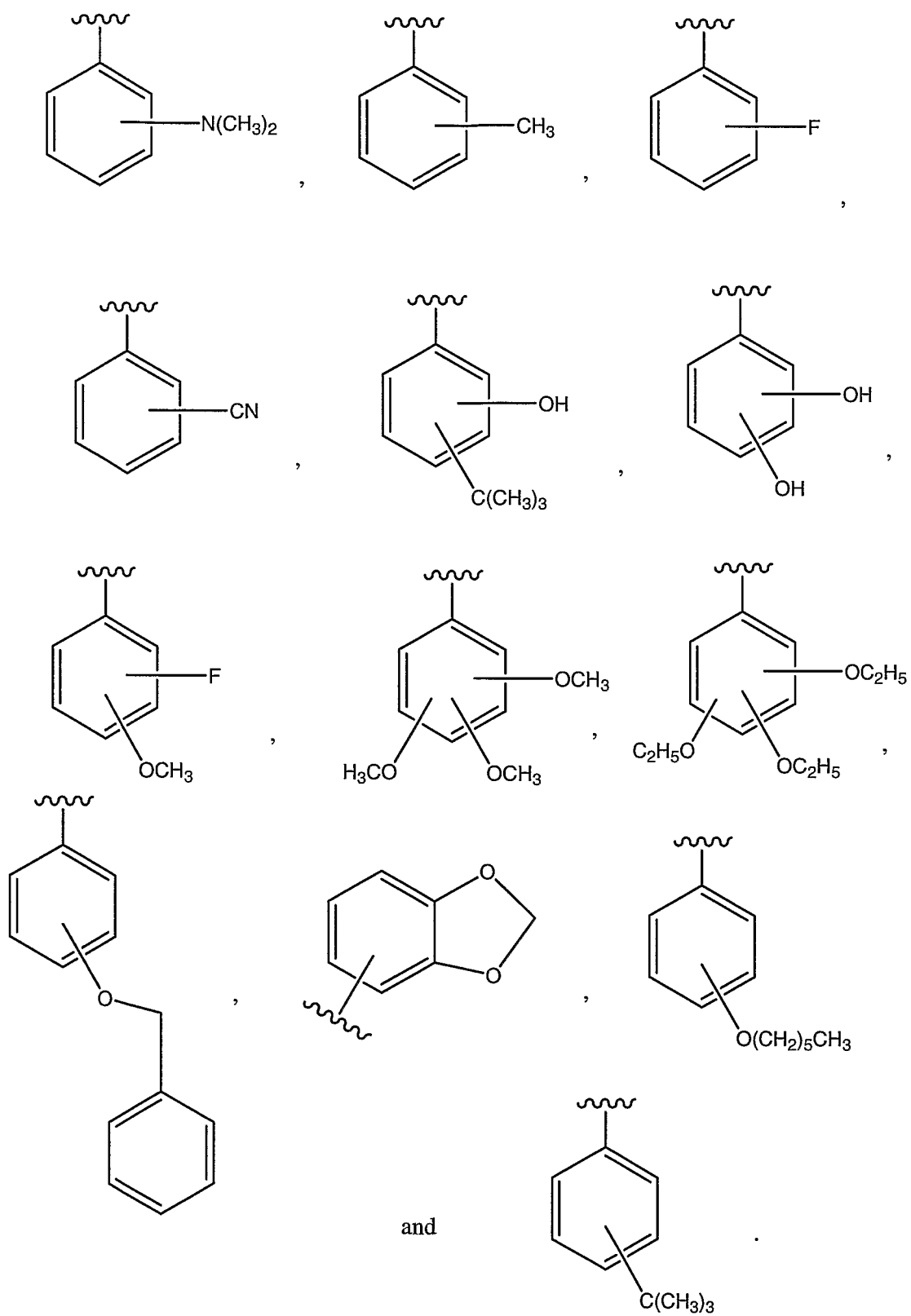


or a pharmaceutically acceptable salt thereof.

10

5. A compound according to claim 2 wherein R is selected from moieties of the group

15

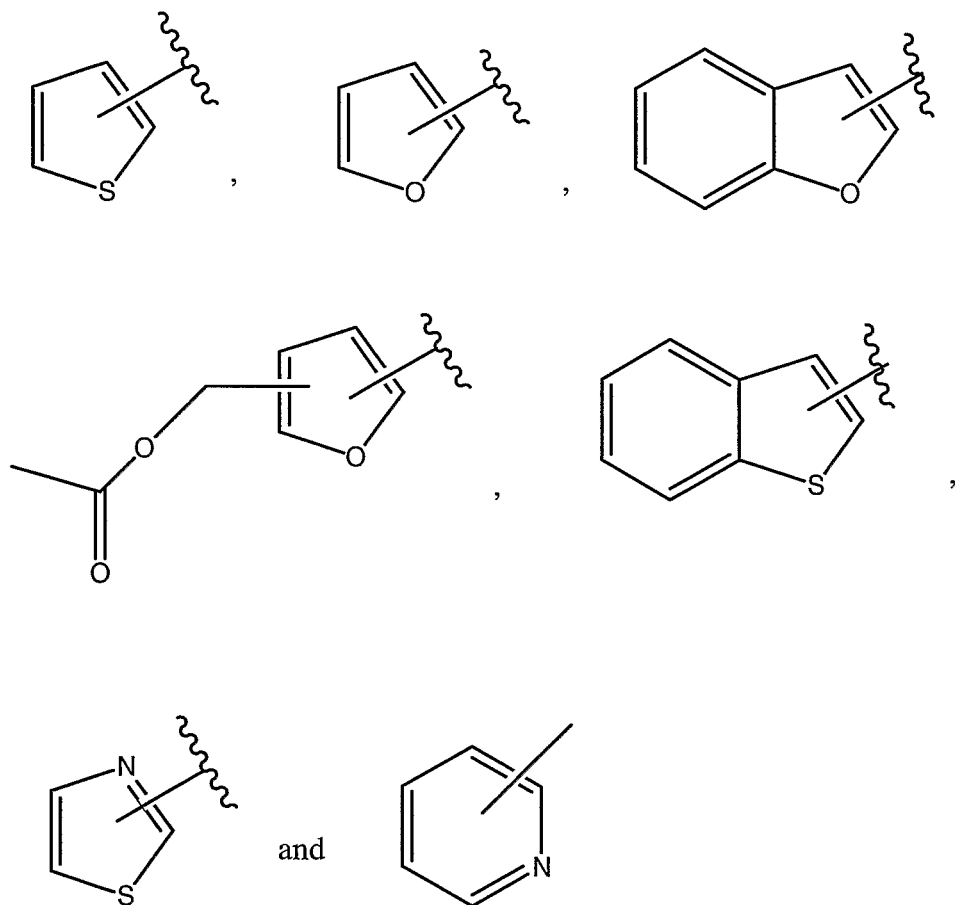


or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1 wherein R is heteroaryl or a
5 pharmaceutically acceptable salt thereof.

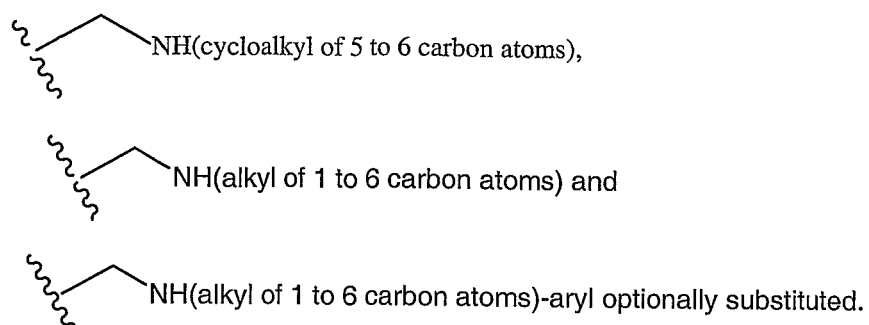
7. A compound according to claim 6 wherein R is selected from moieties
selected from the group

10



or a pharmaceutically acceptable salt thereof.

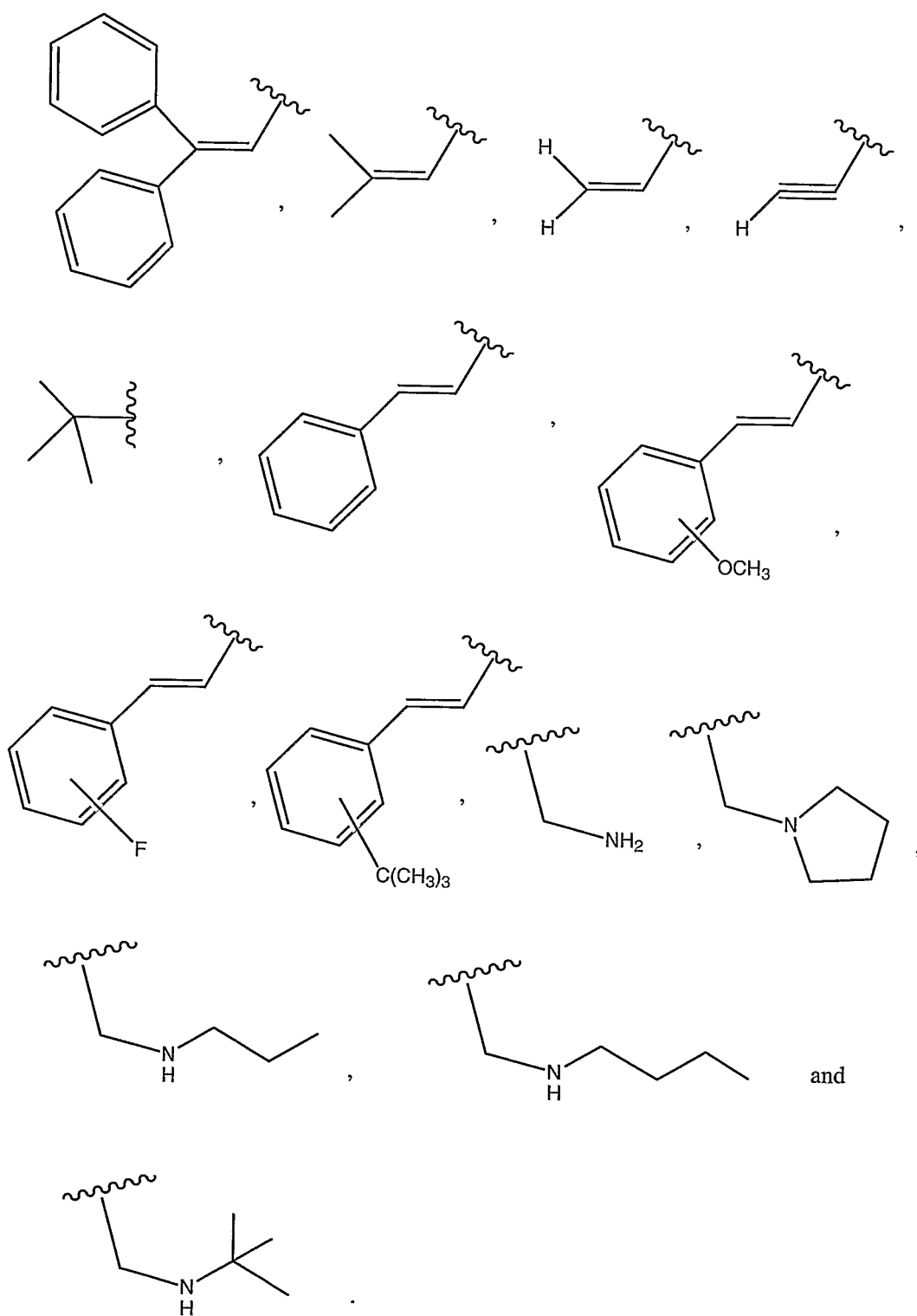
8. A compound according to claim 1 wherein R is alkyl of 1 to 6 carbon atoms
15 optionally substituted, alkenyl of 2 to 6 carbon atoms optionally substituted,



or a pharmaceutically acceptable salt thereof.

5

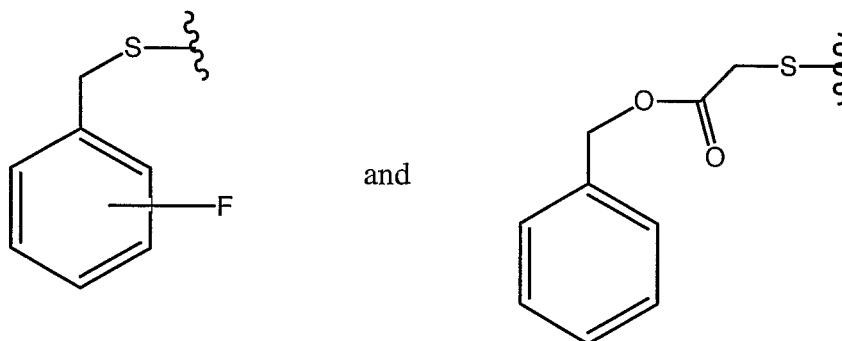
9. A compound according to claim 1 wherein R is selected from moieties



or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 wherein R is S-alkyl of 1 to 12 carbon atoms, S-CH₂-aryl optionally substituted and S-CH₂(CO)OCH₂aryl optionally substituted or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 10 wherein R is selected from moieties of the group



or a pharmaceutically acceptable salt thereof.

12. A compound according to any one of claims 1 to 11 wherein Y is H.
13. A compound according to any one of claims 1 to 12 wherein X is -NMe₂.

14. A compound according to claim 1 selected from the group:

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2,2-diphenylvinyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(7aS,8S,11aS)-8-(dimethylamino)-9,11a,13-trihydroxy-2-(2-methyl-1-propenyl)-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-2-*tert*-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(2-furyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(*E*)-2-phenylethenyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(*E*)-2-(4-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(*E*)-2-(3-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(*E*)-2-(2-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 25 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(4-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(2-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-2-(chloromethyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

5

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(dimethylamino)methyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(pyrrolidin-1-ylmethyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

20 (6aR,7aS,8S,11aS)-2-[(butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

25

(6aR,7aS,8S,11aS)-2-[(*tert*-butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide; or a pharmaceutically acceptable salt thereof.

30 15. A compound according to claim 1 selected from the group:

- (7aS,8S,11aS)-8-(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,13-trihydroxy-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-2-*tert*-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(4-methylphenyl)-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 10 (7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluorophenyl)-9,11a,13-trihydroxy-11,12-dioxo-7,7a,8,11,11a,12-hexahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 15 (6aR,7aS,8S,11aS)-2-(4-cyanophenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 20 (6aR,7aS,8S,11aS)-2-(5-*tert*-butyl-2-hydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 25 (6aR,7aS,8S,11aS)-2-[4-(benzyloxy)phenyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 30

- (6aR,7aS,8S,11aS)-2-(2,4-dihydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluoro-4-methoxyphenyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 10 (6aR,7aS,8S,11aS)-2-(1,3-benzodioxol-5-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,6-trimethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,5-triethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(1-methyl-1*H*-indol-2-yl)-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 25 (6aR,7aS,8S,11aS)-2-(4-*tert*-butylphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and
- 30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(hexyloxy)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide
- or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1 selected from the group:

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thien-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

5

(6aR,7aS,8S,11aS)-2-(1-benzofuran-2-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2-furyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

{5-[(6aR,7aS,8S,11aS)-10-(aminocarbonyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazol-2-yl]-2-furyl}methyl acetate,

15

(6aR,7aS,8S,11aS)-2-(1-benzothien-3-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

20

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(1,3-thiazol-2-yl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

25 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-4-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

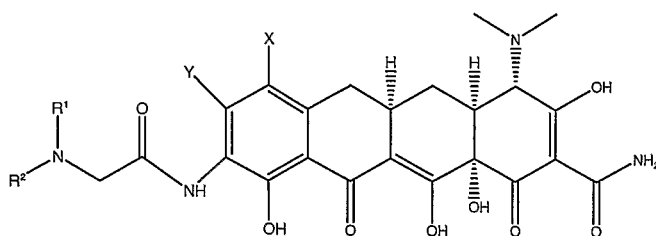
30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.

5 18. A method for the treatment or control of bacterial infections in warm-blooded animals which comprises administering to said animal a pharmacologically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof.

10 19. A process for the preparation of a compound of the formula



or a pharmaceutically acceptable salt thereof

15 wherein:

X is selected from hydrogen, amino, $\text{NR}^{11}\text{R}^{12}$, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

20

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or

R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

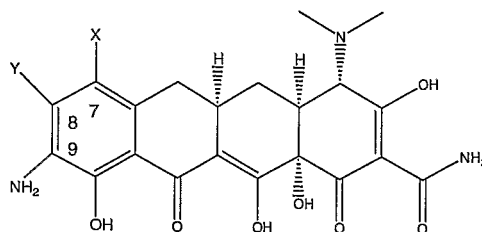
25 R^{11} and R^{12} are each independently H or alkyl of 1 to 12 carbon atoms or

R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

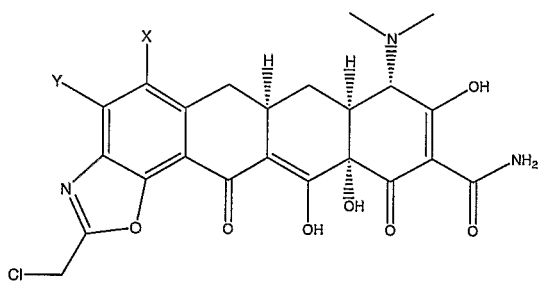
5 comprising the steps:

a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula



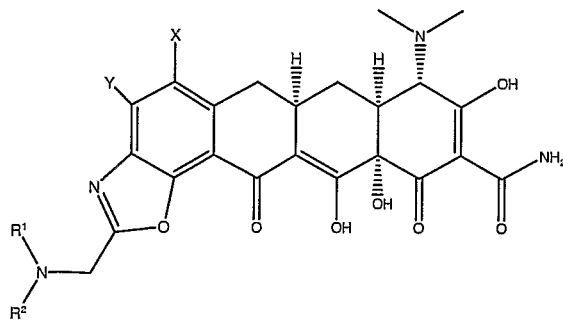
10 or a pharmaceutically acceptable salt thereof

with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula

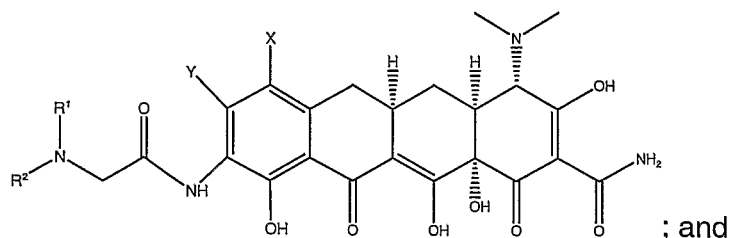


15

b. reacting the chloro compound with an amine R^1R^2NH to form a substituted amine of the formula



- c. hydrolyzing the substituted amine with acid to give a compound of the formula



5

- d. isolating the compound or a pharmaceutically acceptable salt thereof.

20. The process according to claim 19 wherein X is N(CH₃)₂.

10

21. The process according to claim 19 or claim 20 wherein the amine R¹R²NH is t-butyl amine.

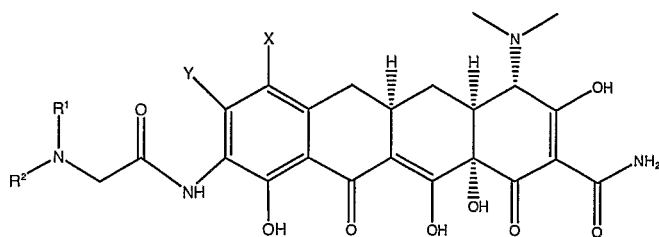
22. The process according to any one of claims 19 to 21 wherein the aprotic solvent is N,N-dimethylformamide.

15

23. The process according to any one of claims 19 to 22 wherein [4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof is prepared.

20

24. A process for the preparation of a compound of the formula



25

wherein:

X is selected from hydrogen, amino, $\text{NR}^{11}\text{R}^{12}$, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

R^{11} and R^{12} are each independently H or alkyl of 1 to 12 carbon atoms or R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

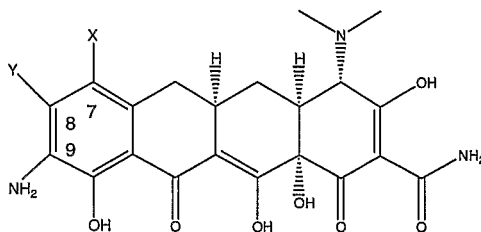
15

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, alkenyl of 2 to 12 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

or a pharmaceutically acceptable salt thereof comprising the steps:

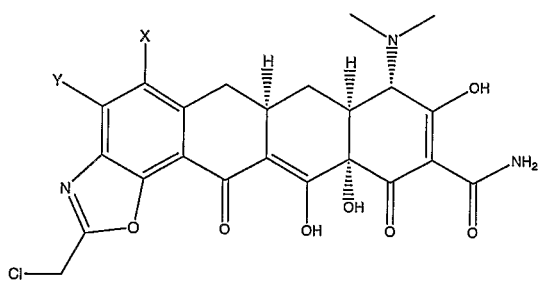
a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula

25

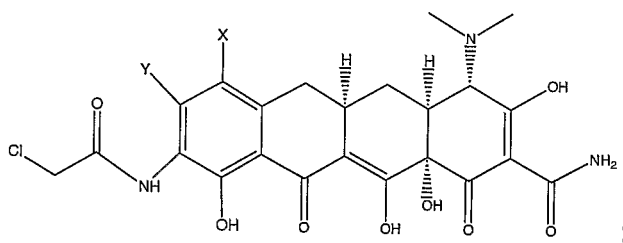


or a pharmaceutically acceptable salt thereof

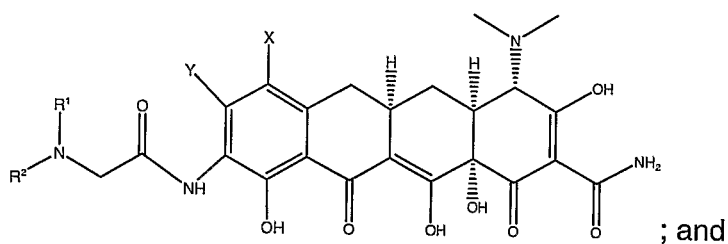
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



- b. reacting the chloro compound with acid to give 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline of the formula



- c. reacting the 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline with amine R^1R^2NH to give a compound of the formula

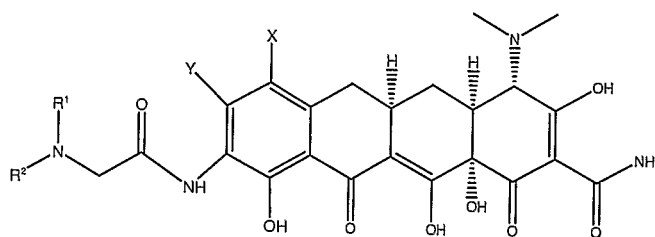


- e. isolating the compound or a pharmaceutically acceptable salt thereof.
25. The process according to claim 24 wherein X is $N(CH_3)_2$.
26. The process according to claim 24 or claim 25 wherein the amine R^1R^2NH is t-butyl amine.

27. The process according to any one of claims 24 to 26 wherein the aprotic solvent is N,N-dimethylformamide.

28. The process according to any one of claim 24 to 27 wherein [4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylaminol-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof is prepared.

29. A compound of the formula



or a pharmaceutically acceptable salt thereof

wherein:

X is selected from hydrogen, amino, NR¹¹R¹², alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

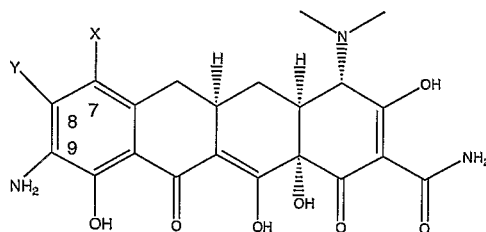
R¹ and R² are each independently H or alkyl of 1 to 12 carbon atoms or R¹ and R² when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

R¹¹ and R¹² are each independently H or alkyl of 1 to 12 carbon atoms or R¹¹ and R¹² when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

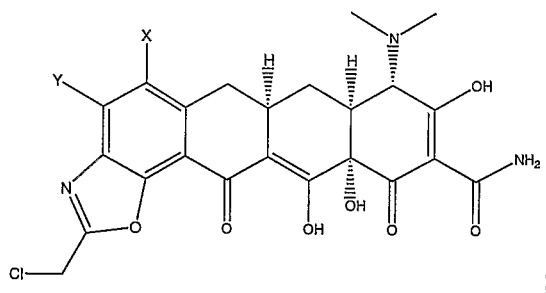
Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

5 produced by the process comprising the steps:

a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula

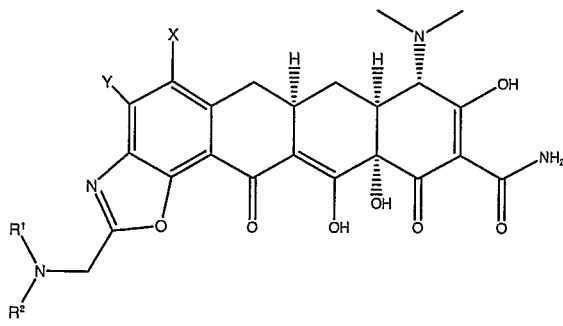


10 or a pharmaceutically acceptable salt thereof
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula

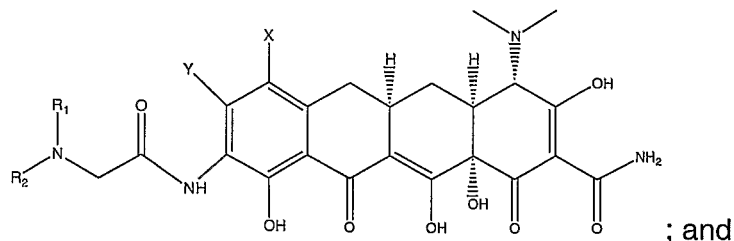


15

b. reacting the chloro compound with an amine R^1R^2NH to form a substituted amine of the formula



- c. hydrolyzing the substituted amine with acid to give a compound of the formula



5

- d. isolating the compound or a pharmaceutically acceptable salt thereof.

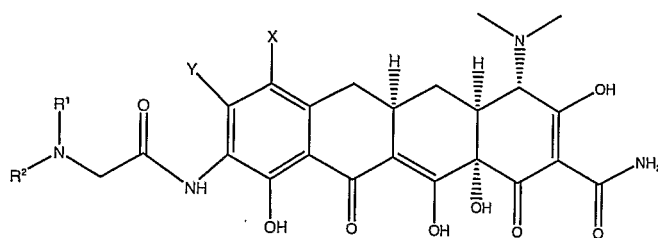
30. The product produced by the process according to claim 29 wherein X is
10 N(CH₃)₂.

31. The product produced by the process according to claim 29 or claim 30
wherein the amine R¹R²NH is t-butyl amine.

- 15 32. The product produced by the process according to any one of claims 29 to 31
wherein the aprotic solvent is N,N-dimethylformamide.

33. The product produced by the process according to any one of claims 29 to 31
which is [4S-(4α,4aα,5aα,12aα)]-4,7-Bis(dimethylamino)-9-[2-(1,1-
20 dimethylethylamino)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically
acceptable salt thereof.

- 25 34. A compound of the formula



wherein:

- 5 X is selected from hydrogen, amino, $\text{NR}^{11}\text{R}^{12}$, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

R¹ and R² are each independently H or alkyl of 1 to 12 carbon atoms or

- 10 R¹ and R² when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

R¹¹ and R¹² are each independently H or alkyl of 1 to 12 carbon atoms or

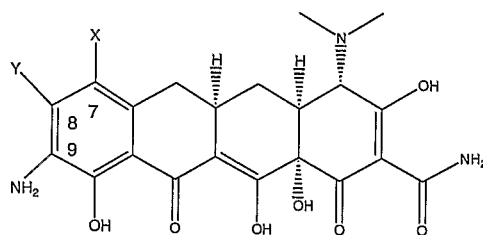
- 15 R¹¹ and R¹² when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

or a pharmaceutically acceptable salt thereof

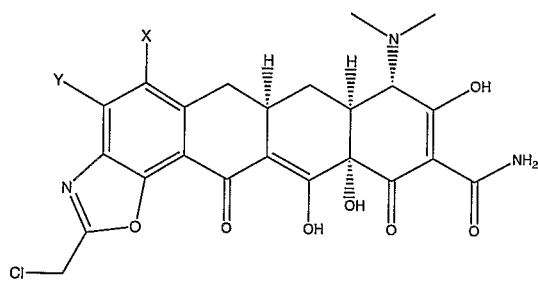
produced by the process comprising the steps:

- 25 a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula



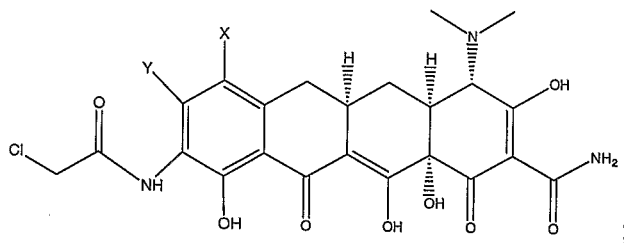
or a pharmaceutically acceptable salt thereof

with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



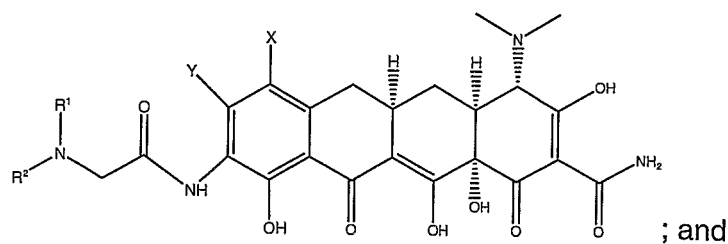
5

b. reacting the chloro compound with acid to give 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline of the formula



10

c. reacting the 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline with amine R^1R^2NH to give a compound of the formula



15

d. isolating the compound or a pharmaceutically acceptable salt thereof.

35. The product prepared by the process according to claim 34 wherein X is
5 $N(CH_3)_2$.

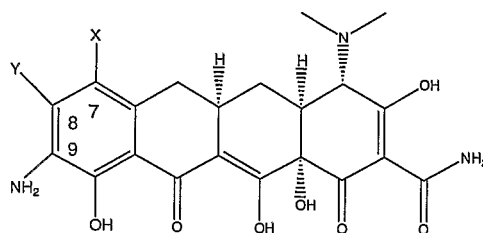
36. The product prepared by the process according to claim 34 or claim 35 wherein the amine R^1R^2NH is t-butyl amine.

10 37. The product prepared by the process according to any one of claims 32 to 36 wherein the aprotic solvent is N,N-dimethylformamide.

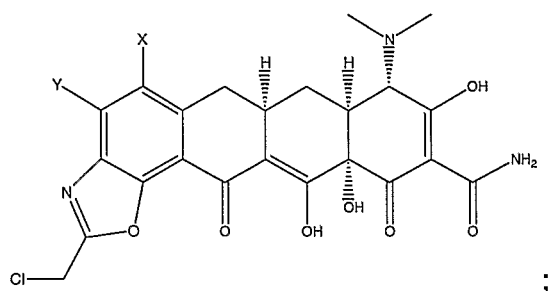
38. The product prepared by the process according to any one of claims 34 to 37 which is [4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-
15 dimethylethylamino)acetylaminol-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof.

39. A process for preparing a compound of formula I according to claim 1 which
20 comprises

a). reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula



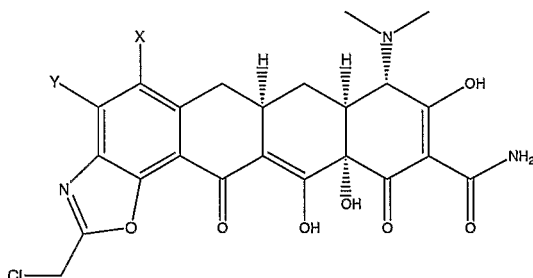
25 or a pharmaceutically acceptable salt thereof with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



wherein the variables are as defined in claim 1;

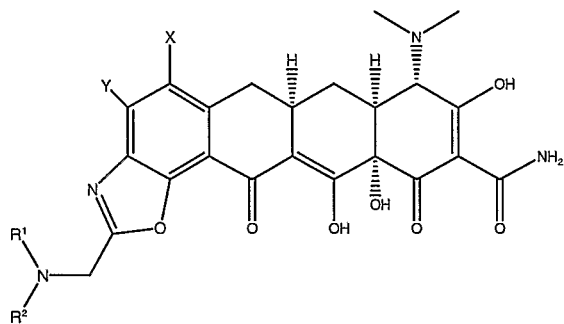
or

- 5 b. reacting a chloro compound of formula



wherein the variables are as defined in claim 1; with an amine R^1R^2NH to form a substituted amine of the formula

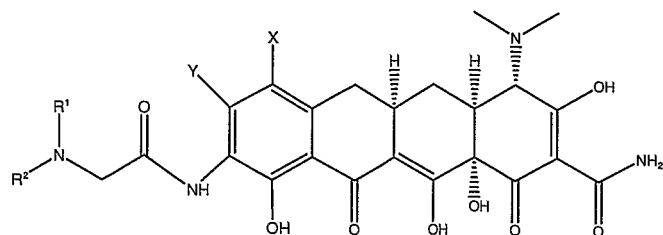
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or

- 15 c) converting a basic compound of formula I as defined in claim 1 to a pharmaceutically acceptable salt thereof or vice versa.

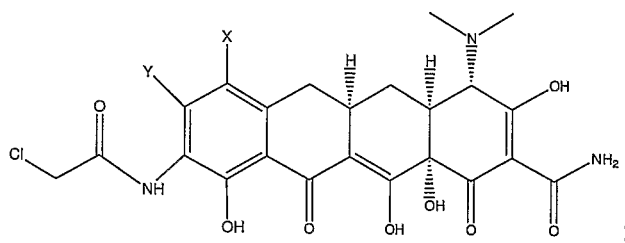
40. A process for preparing a compound of formula:



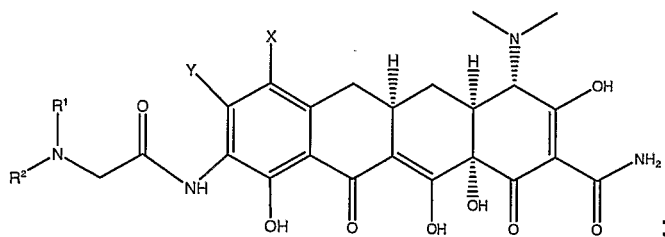
wherein the variables are as defined in claim 34 which comprises:

5

- a) reacting a 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline of the formula



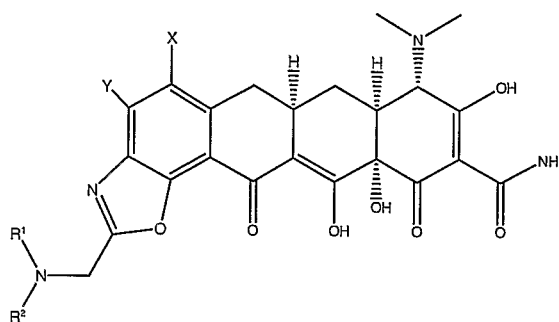
- 10 with an amine R^1R^2NH to give a compound of the formula



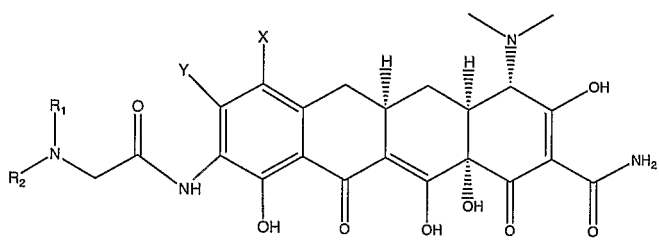
15

or

- b) hydrolyzing a substituted amine of formula



wherein the variables are as defined in claim 29,
with acid to give a compound of the formula



5

and if desired converting the product to a pharmaceutically acceptable salt thereof.

10