

Title: 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-
DEMETHYL-6-DEOXYTETRACYCLINES

BACKGROUND OF THE INVENTION

1. Field of the Invention

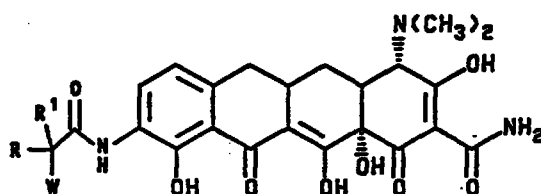
The invention relates to novel [4S-(4alpha, 12aalpha)]-4-(dimethylamino)-9-[[(substituted amino)-substituted]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides herein after called 9-[(substituted glycy)-amido]-6-demethyl-6-deoxytetracyclines, which exhibit antibiotic activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and are useful as antibiotic agents.

The invention also relates to novel 9-[(haloacyl)amido]-6-demethyl-6-deoxytetracycline intermediates useful for making the novel compounds of the present invention and to novel methods for producing the novel compounds and intermediate compounds.

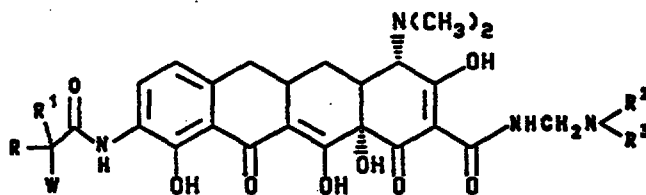
SUMMARY OF THE INVENTION

This invention is concerned with novel 9-[(substituted glycy)amido]-6-demethyl-6-deoxytetracyclines. represented by formula I and II, which have antibacterial activity; with methods of treating infectious diseases in warm blooded animals employing these new compounds; with pharmaceutical preparations containing these compounds; with novel intermediate compounds and processes for the production of these compounds. More particularly, this invention is

concerned with compounds of formula I and II which have enhanced in vitro and in vivo antibacterial activity against tetracycline resistant strains as well as a high level of activity against strains which are normally susceptible to tetracyclines.



I



II

In formula I and II,

R is selected from hydrogen; straight or branched (C₁-C₈)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C₁-C₄)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl; α-hydroxy(C₁-C₄)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl(C₁-C₈)alkyl group; (C₆-C₁₀)aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C₆-C₁₀)aryl group (substitution selected from hydroxy, halogen, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)alkoxycarbonyl, (C₁-C₃)alkylamino and carboxy); (C₇-C₉)aralkyl group

selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted(C_7-C_9)aralkyl group
[substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];
 R^1 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; hydroxylamino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_3-C_8)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_3-C_8)cycloalkyl monosubstituted amino group; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)-methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3-C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl,

2-butenyl (cis or trans), 2-pentenyl, 4-octenyl,
2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl
2-cyclopentenyl and 2-cyclohexenyl; (C₆-C₁₀)aryl
5 monosubstituted amino group substitution selected from
phenyl and naphthyl; (C₇-C₁₀)aralkylamino group
substitution selected from benzyl, 2-phenylethyl,
1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl
and phenylpropyl; substituted (C₆-C₁₀)aryl
10 monosubstituted amino group [substitution selected from
(C₁-C₅)acyl, (C₁-C₅)acylamino, (C₁-C₄)alkyl, mono or
disubstituted (C₁-C₈)alkylamino, (C₁-C₄)alkoxy,
(C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkylsulfonyl, amino,
carboxy, cyano, halogen, hydroxy, nitro and
15 trihalo(C₁-C₃)alkyl]; straight or branched symmetrical
disubstituted (C₂-C₁₄)alkylamino group substitution
selected from dimethyl, diethyl, diisopropyl,
di-n-propyl, di-n-butyl and diisobutyl; symmetrical
disubstituted (C₃-C₁₄)cycloalkylamino group
20 substitution selected from dicyclopropyl, dicyclobutyl,
dicyclopentyl, dicyclohexyl and dicycloheptyl; straight
or branched unsymmetrical disubstituted
(C₃-C₁₄)alkylamino group wherein the total number of
carbons in the substitution is not more than 14;
25 unsymmetrical disubstituted (C₄-C₁₄)cycloalkylamino
group wherein the total number of carbons in the
substitution is not more than 14; (C₂-C₈)azacycloalkyl
and substituted (C₂-C₈)azacycloalkyl group substitution
selected from aziridinyl, azetidiny, pyrrolidinyl,
30 piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl,
cis-3,4-dimethylpyrrolidinyl,
trans-3,4-dimethylpyrrolidinyl,
2-azabicyclo[2.1.1]hex-2-yl,
5-azabicyclo[2.1.1]hex-5-yl,
35 2-azabicyclo[2.2.1]hept-2-yl,
7-azabicyclo[2.2.1]hept-7-yl, and
2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and
enantiomers of said (C₂-C₈)azacycloalkyl and

substituted (C_2-C_8)azacycloalkyl group;
1-aza-oxacycloalkyl group selected from morpholinyl and
1-aza-5-oxocycloheptane; substituted
5 1-aza-oxacycloalkyl group substitution selected from
2- (C_1-C_3) alkylmorpholinyl,
3- (C_1-C_3) alkylisooxazolidinyl, tetrahydrooxazinyl and
3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and
substituted [1,n]-diazacycloalkyl group selected from
10 piperazinyl, 2- (C_1-C_3) alkylpiperazinyl,
4- (C_1-C_3) alkylpiperazinyl, 2,4-dimethylpiperazinyl,
4- (C_1-C_4) alkoxypiperazinyl,
4- (C_6-C_{10}) aryloxypiperazinyl, 4-hydroxypiperazinyl,
2,5-diazabicyclo[2.2.1]hept-2-yl,
15 2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl,
2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, and
2,5-diaza-5,7-dimethylbicyclo[2.2.2]oct-2-yl and
the diastereomers or enantiomers of said
[1,n]-diazacycloalkyl and substituted
20 [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and
substituted 1-azathiacycloalkyl group selected from
thiomorpholinyl, 2- (C_1-C_3) alkylthiomorpholinyl and
3- (C_3-C_6) cycloalkylthiomorpholinyl; N-azolyl and
substituted N-azolyl group selected from 1-imidazolyl,
25 2- (C_1-C_3) alkyl-1-imidazolyl, 3- (C_1-C_3) alkyl-1-imid-
azolyl, 1-pyrrolyl, 2- (C_1-C_3) alkyl-1-pyrrolyl,
3- (C_1-C_3) alkyl-1-pyrrolyl, 1-pyrazolyl, 3- (C_1-C_3) -
alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl),
4- (C_1-C_3) alkyl-1-(1,2,3-triazolyl), 5- (C_1-C_3) alkyl-1-
30 (1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl,
2-tetrazolyl and benzimidazolyl; (heterocycle)amino
group said heterocycle selected from 2- or 3-furanyl,
2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or
5-pyridazinyl, 2-pyrazinyl, 2-(imidazolyl),
35 (benzimidazolyl), and (benzothiazolyl) and substituted
(heterocycle)amino group (substitution selected from
straight or branched (C_1-C_6) alkyl);
(heterocycle)methylamino group selected from 2- or

3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3-
or 4-pyridylmethylamino, 2- or 5-pyridazinylmethyl-
amino, 2-pyrazinylmethylamino, 2-(imidazolyl)methyl-
5 amino, (benzimidazolyl)methylamino, and
(benzothiazolyl)methylamino and substituted
(heterocycle)methylamino group (substitution selected
from straight or branched (C_1-C_6)alkyl);
carboxy(C_2-C_4)alkylamino group selected from
10 aminoacetic acid, α -aminopropionic acid,
 β -aminopropionic acid, α -butyric acid, and
 β -aminobutyric acid and the enantiomers of said
carboxy(C_2-C_4)alkylamino group;
(C_1-C_4)alkoxycarbonylamino group substitution selected
15 from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl,
propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethyl-
ethoxycarbonyl, n-butoxycarbonyl, and
2-methylpropoxycarbonyl; (C_1-C_4)alkoxyamino group
substitution selected from methoxy, ethoxy, n-propoxy,
20 1-methylethoxy, n-butoxy, 2-methylpropoxy, and
1,1-dimethylethoxy; (C_3-C_8)cycloalkoxyamino group
selected from cyclopropoxy, trans-1,2-dimethylcyclo-
propoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy,
cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy,
25 bicyclo[2.2.1]hept-2-yloxy, and bicyclo[2.2.2]oct-2-yl-
oxy and the diastereomers and enantiomers of said
(C_3-C_8)cycloalkoxyamino group; (C_6-C_{10})aryloxyamino
group selected from phenoxyamino, 1-naphthyloxyamino
and 2-naphthyloxyamino; (C_7-C_{11})arylalkoxyamino group
30 substitution selected from benzyloxy, 2-phenylethoxy,
1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)-
methoxy and phenylpropoxy;
 R^2 is selected from hydrogen; straight or branched
(C_1-C_3)alkyl group selected from methyl, ethyl,
35 n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected
from phenyl, α -naphthyl or β -naphthyl; (C_7-C_9)aralkyl
group such as benzyl, 1-phenylethyl, 2-phenylethyl or
phenylpropyl; a heterocycle group selected from a five

membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

5



10

Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrroli-
diny, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl,
furanyl, benzofuranyl, tetrahydrothienyl, thienyl,
benzothienyl or selenazolyl, or a five membered
aromatic ring with two N, O, S or Se heteroatoms
optionally having a benzo or pyrido ring fused thereto:

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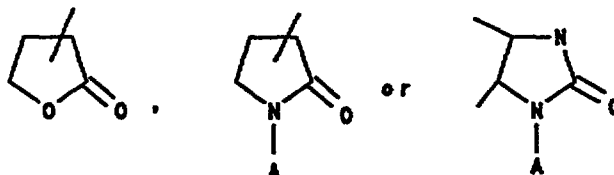
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Z or Z' = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazo-
lyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazol-
yl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimid-
azolyl, or a five membered saturated ring with one or
two N, O, S or Se heteroatoms and an adjacent appended
O heteroatom:

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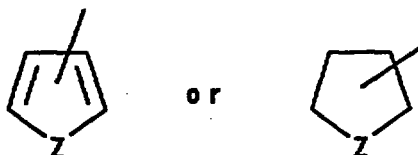


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(A is selected from hydrogen; straight or branched
(C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl
(substitution selected from halo, (C₁-C₄)alkoxy,
trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-
alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-

aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

5 such as γ -butyrolactam, γ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3)
10 alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-
15 2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxo-thiomorpholinyl; or $-(CH_2)_n COOR^4$ where $n=0-4$ and R^4 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl group
20 selected from phenyl, α -naphthyl, or β -naphthyl; R^3 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α -naphthyl or β -naphthyl; (C_7-C_9)aralkyl
25 group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

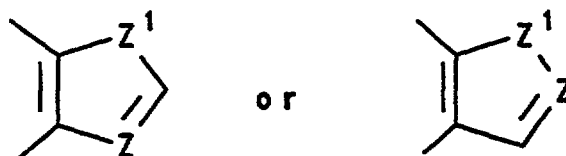


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Z = N, O, S or Se

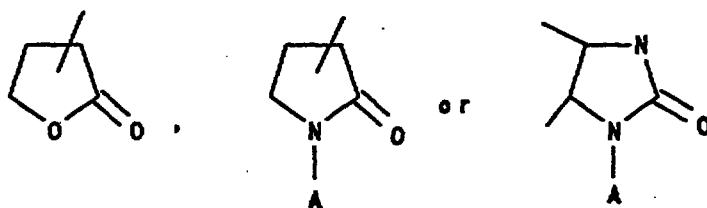
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrroli-

dinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z¹ = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitution selected from halo, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as γ -butyrolactam, γ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six

membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C₁-C₃)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or -(CH₂)_nCOOR⁴ where n=0-4 and R⁴ is selected from hydrogen; straight or branched (C₁-C₃)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C₆-C₁₀)aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R² and R³ cannot both be hydrogen; or R² and R³ taken together are -(CH₂)₂B(CH₂)₂-, wherein B is selected from (CH₂)_n and n=0-1, -NH, -N(C₁-C₃)alkyl [straight or branched], -N(C₁-C₄)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Preferred compounds are compounds according to the above formula I and II wherein:
R is selected from hydrogen; straight or branched (C₁-C₈)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C₁-C₄)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl; α-hydroxy(C₁-C₄)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl(C₁-C₈)alkyl group; (C₆-C₁₀)aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C₇-C₉)aralkyl group selected from benzyl, 1-phenylethyl,

2-phenylethyl and phenylpropyl;

substituted(C₇-C₉)aralkyl group [substitution selected from halo, (C₁-C₄)alkyl, nitro, hydroxy, amino, mono- or di-substituted (C₁-C₄)alkylamino, (C₁-C₄)alkoxy, (C₁-C₄)alkylsulfonyl, cyano and carboxy];

R¹ is selected from hydrogen and (C₁-C₆)alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R does not equal R¹ the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; hydroxylamino; (C₁-C₁₂) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C₃-C₈)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C₃-C₈)cycloalkyl monosubstituted amino group; [(C₄-C₁₀)cycloalkyl]alkyl monosubstituted amino group substitution selected

from(cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C₃-C₁₀)alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl,

4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl
 2-cyclopentenyl and 2-cyclohexenyl; (C_6-C_{10})aryl
 monosubstituted amino group substitution selected from
 5 phenyl and naphthyl; (C_7-C_{11})aralkylamino group
 substitution selected from benzyl, 2-phenylethyl,
 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl
 and phenylpropyl; straight or branched symmetrical
 disubstituted (C_2-C_{14})alkylamino group substitution
 10 selected from dimethyl, diethyl, diisopropyl and
 di-n-propyl; symmetrical disubstituted
 (C_3-C_{14})cycloalkylamino group substitution selected
 from dicyclopropyl, dicyclobutyl, dicyclopentyl,
 dicyclohexyl and dicycloheptyl; straight or branched
 15 unsymmetrical disubstituted (C_3-C_{14})alkylamino group
 wherein the total number of carbons in the substitution
 is not more than 14; unsymmetrical disubstituted
 (C_4-C_{14})cycloalkylamino group wherein the total number
 of carbons in the substitution is not more than 14;
 20 (C_2-C_8)azacycloalkyl and substituted
 (C_2-C_8)azacycloalkyl group selected from aziridinyl,
 azetidiny, pyrrolidinyl, piperidinyl, 4-methylpiperi-
 dinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrroli-
 dinyl, trans-3,4-dimethylpyrrolidinyl,
 25 2-azabicyclo[2.1.1]hex-2-yl,
 5-azabicyclo[2.1.1]hex-5-yl,
 2-azabicyclo[2.2.1]hept-2-yl,
 7-azabicyclo[2.2.1]hept-7-yl, and
 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and
 30 enantiomers of said (C_2-C_8)azacycloalkyl and
 substituted (C_2-C_8)azacycloalkyl group;
 1-aza-oxacycloalkyl group selected from morpholinyl and
 1-aza-5-oxacycloheptane; substituted
 1-aza-oxacycloalkyl group selected from 2-(C_1-C_3)alkyl-
 35 morpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl, tetrahydro-
 oxazinyl and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl
 and substituted [1,n]-diazacycloalkyl group selected
 from piperazinyl, 2-(C_1-C_4)alkylpiperazinyl,

4-(C₁-C₃)alkylpiperazinyl, 2,4-dimethylpiperazinyl,
4-(C₁-C₃)alkoxypiperazinyl, 4-(C₆-C₁₀)-
aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diaza-
5 bicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo-
[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]-
oct-2-yl, and 2,5-diaza-5,7-dimethylbicyclo[2.2.2]oct-
2-yl and the diastereomers or enantiomers of said
[1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group;
10 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C₁-C₃)alkylthiomorpholinyl and 3-(C₃-C₆)cycloalkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C₁-C₃)alkyl-1-imidazolyl, 3-(C₁-C₃)alkyl-1-imidazolyl,
15 1-pyrrolyl, 2-(C₁-C₃)alkyl-1-pyrrolyl, 3-(C₁-C₃)alkyl-1-pyrrolyl, 1-pyrazolyl, 3-(C₁-C₃)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-alkyl-1-(1,2,3-triazolyl), 5-(C₁-C₃)alkyl-1-(1,2,3-triazolyl),
20 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl; (heterocycle)amino group said heterocycle selected from 2- or 3-furanyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 5-pyridazinyl, 2-pyrazinyl, 2-(imidazolyl), (benzimidazolyl), and
25 (benzothiazolyl) and substituted (heterocycle)amino group (substitution selected from straight or branched (C₁-C₆)alkyl); (heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino,
30 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and substituted (heterocycle)methylamino group (substitution selected from straight or branched (C₁-C₆)alkyl);
35 carboxy(C₂-C₄)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, and β-aminobutyric acid and the enantiomers of said

carboxy(C_2-C_4)alkylamino group;

(C_1-C_4)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy; (C_3-C_8)cycloalkoxyamino group substitution selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, and bicyclo[2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group; (C_6-C_{10})aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino; (C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

R^2 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α -naphthyl or β -naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O, S or Se

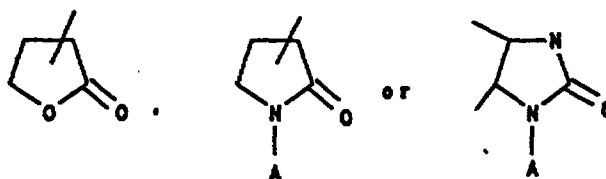
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrroli-

dinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z' - N, O, S or Se

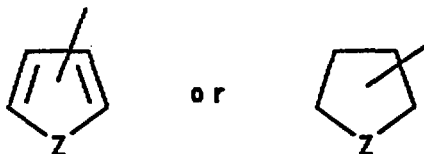
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitution selected from halo, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

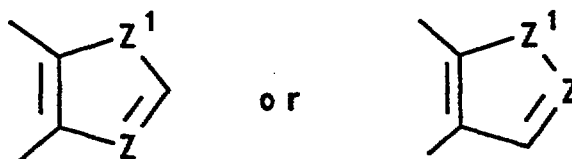
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C₁-C₃)alkylthio-pyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-

piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl,
 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-
 2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxo-
 5 thiomorpholinyl; or $-(CH_2)_n COOR^4$ where $n=0-4$ and R^4 is
 selected from hydrogen; straight or branched
 (C_1-C_3) alkyl group selected from methyl, ethyl,
 n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl group
 selected from phenyl, α -naphthyl, β -naphthyl;
 10 R^3 is selected from hydrogen; straight or branched
 (C_1-C_3) alkyl group selected from methyl, ethyl,
 n-propyl or 1-methylethyl; (C_6-C_{10}) aryl group selected
 from phenyl, α -naphthyl or β -naphthyl; (C_7-C_9) aralkyl
 group such as benzyl, 1-phenylethyl, 2-phenylethyl or
 15 phenylpropyl; a heterocycle group selected from a five
 membered aromatic or saturated ring with one N, O, S or
 Se heteroatom optionally having a benzo or pyrido ring
 fused thereto:



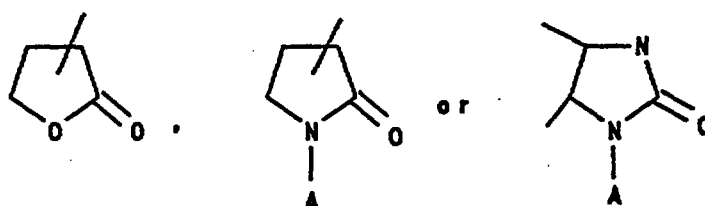
25 $Z = N, O, S \text{ or } Se$

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrroli-
 danyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl,
 furanyl, benzofuranyl, tetrahydrothienyl, thienyl,
 benzothienyl or selenazolyl, or a five membered
 30 aromatic ring with two N, O, S or Se heteroatoms
 optionally having a benzo or pyrido ring fused thereto:



$Z \text{ or } Z^1 = N, O, S \text{ or } Se$

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitution selected from halo, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as γ -butyrolactam, γ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C₁-C₃)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxo-thiomorpholinyl; or -(CH₂)_nCOOR⁴ where n=0-4 and R⁴ is selected from hydrogen; straight or branched (C₁-C₃)alkyl selected from methyl, ethyl, n-propyl or

1-methylethyl; or (C₆-C₁₀)aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R² and R³ cannot both be hydrogen;

5 or R² and R³ taken together are -(CH₂)₂B(CH₂)₂-, wherein B is selected from (CH₂)_n and n=0-1, -NH, -N(C₁-C₃)alkyl [straight or branched], -N(C₁-C₄)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, 10 pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Particularly preferred compounds are compounds according to the above formula I and II 15 wherein:

R is selected from hydrogen; straight or branched (C₁-C₈)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C₁-C₄)alkyl group selected from 20 mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl and α-mercaptopropyl; α-hydroxy-(C₁-C₄)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl and α-hydroxypropyl; carboxyl(C₁-C₈)alkyl group; 25 (C₆-C₁₀)aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C₇-C₉)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; R¹ is selected from hydrogen and (C₁-C₆)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, 30 pentyl and hexyl;

when R does not equal R¹ the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

35 W is selected from amino; (C₁-C₁₂) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethyl-

ethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl,
2,2-dimethylpropyl, 3-methylbutyl, n-hexyl,
1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl,
5 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl,
1-methyl-1-ethylpropyl, heptyl, octyl, nonyl and decyl
and the diastereomers and enantiomers of said branched
alkyl monosubstituted amino group; (C₃-C₈)cycloalkyl
monosubstituted amino group substitution selected from
10 cyclopropyl, trans-1,2-dimethylcyclopropyl,
cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, cycloheptyl and cyclooctyl and the
diastereomers and enantiomers of said (C₃-C₈)cycloalkyl
monosubstituted amino group; [(C₄-C₁₀)cycloalkyl]alkyl
15 monosubstituted amino group substitution selected from
(cyclopropyl)methyl, (cyclopropyl)ethyl and
(cyclobutyl)methyl; (C₃-C₁₀)alkenyl monosubstituted
amino group substitution selected from allyl,
3-butenyl, 2-butenyl (cis or trans), 2-pentenyl,
20 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl
2-cyclopentenyl and 2-cyclohexenyl;
(C₇-C₁₀)aralkylamino group substitution selected from
benzyl, 2-phenylethyl, 1-phenylethyl,
2-(naphthyl)methyl, 1-(naphthyl)methyl and
25 phenylpropyl; straight or branched symmetrical
disubstituted (C₂-C₁₄)alkylamino group substitution
selected from dimethyl, diethyl, diisopropyl and
di-n-propyl; straight or branched unsymmetrical
disubstituted (C₃-C₁₄)alkylamino group wherein the
30 total number of carbons in the substitution is not more
than 14; unsymmetrical disubstituted (C₄-C₁₄)cyclo-
alkylamino group wherein the total number of carbons
in the substitution is not more than 14;
(C₂-C₈)azacycloalkyl and substituted (C₂-C₈)azacyclo-
35 alkyl group selected from aziridinyl, azetidiny,
pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-
methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, and
trans-3,4-dimethylpyrrolidinyl and the diastereomers

and enantiomers of said (C₂-C₈)azacycloalkyl and substituted (C₂-C₈)aza- cycloalkyl group;

5 1-azaoxacycloalkyl group selected from morpholinyl and 1-aza-5-oxacycloheptane; substituted 1-azaoxacycloalkyl group selected from 2-(C₁-C₃)alkylmorpholinyl, 3-(C₁-C₃)alkylisooxazolidinyl and tetrahydrooxazinyl; [1,n]-diazacycloalkyl and substituted

10 [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C₁-C₃)alkylpiperazinyl, 4-(C₁-C₃)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl, and 2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, the diastereomers or enantiomers of

15 said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and 2-(C₁-C₃)alkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C₁-C₃)alkyl-1-imidazolyl, 3-(C₁-C₃)alkyl-1-imidazolyl, 1-pyrrolyl, 2-(C₁-C₃)alkyl-1-pyrrolyl,

20 3-(C₁-C₃)alkyl-1-pyrrolyl, 1-pyrazolyl, 3-(C₁-C₃)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C₁-C₃)alkyl-1-(1,2,3-triazolyl), 5-(C₁-C₃)alkyl-1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl;

25 (heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and substituted (heterocycle)methylamino group (substitution selected from straight or branched (C₁-C₆)alkyl); carboxy(C₂-C₄)alkylamino group selected from aminoacetic acid, α-aminopropionic acid,

30 β-aminopropionic acid, α-butyric acid, and β-aminobutyric acid and the enantiomers of said carboxy(C₂-C₄)alkylamino group;

35 (C₁-C₄)alkoxycarbonylamino group substitution selected

from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C₁-C₄)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy; (C₇-C₁₁)arylalkoxyamino group substitution selected from benzyoxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)-methoxy and phenylpropoxy; R² is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C₆-C₁₀)aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C₇-C₉)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



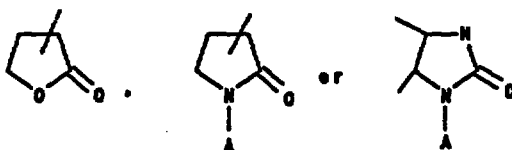
Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z' = N, O, S or Se

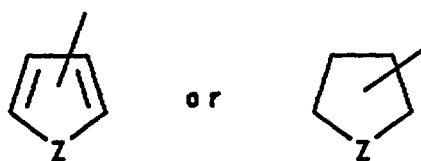
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitution selected from halo, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

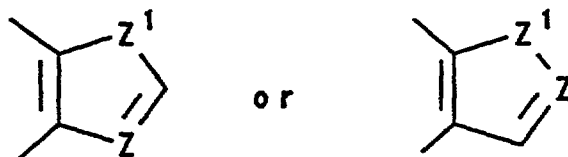
such as γ -butyrolactam, γ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C₁-C₃) alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxo-thiomorpholinyl; or $-(CH_2)_nCOOR^4$ where $n=0-4$ and R^4 is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C₆-C₁₀)aryl group selected from phenyl, α -naphthyl, β -naphthyl; R^3 is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C₆-C₁₀)aryl group selected

from phenyl, α -naphthyl or β -naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



Z = N, O, S or Se

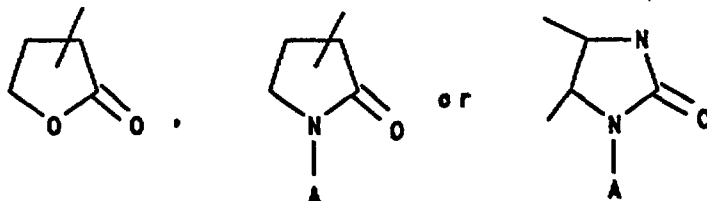
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrroli-
diny, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl,
furanyl, benzofuranyl, tetrahydrothienyl, thienyl,
benzothienyl or selenazolyl, or a five membered
aromatic ring with two N, O, S or Se heteroatoms
optionally having a benzo or pyrido ring fused thereto:



Z or Z¹ = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazo-
lyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazo-
lyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimid-
azolyl, or a five membered saturated ring with one or
two N, O, S or Se heteroatoms and an adjacent appended
O heteroatom:

5



10

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(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitution selected from halo, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

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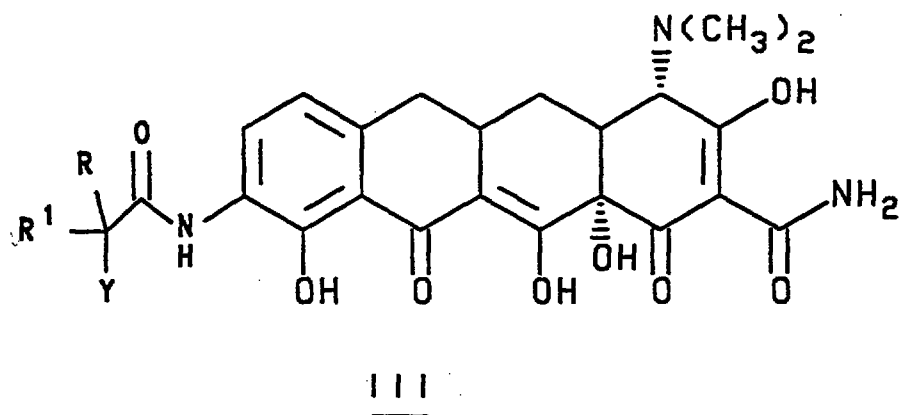
such as γ -butyrolactam, γ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C₁-C₃)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxo-thiomorpholinyl; or -(CH₂)_nCOOR⁴ where n=0-4 and R⁴ is selected from hydrogen; straight or branched (C₁-C₃)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C₆-C₁₀)aryl selected from phenyl, α -naphthyl or β -naphthyl; with the proviso that R² and R³ cannot both be hydrogen; or R² and R³ taken together are -(CH₂)₂B(CH₂)₂-, wherein B is selected from (CH₂)_n and n=0-1, -NH, -N(C₁-C₃)alkyl [straight or branched], -N(C₁-C₄)alkoxy,

oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Compounds of special interest are compounds according to the above formula I and II wherein:
R is selected from hydrogen; straight or branched (C_1-C_2)alkyl group selected from methyl and ethyl;
 R^1 selected from hydrogen or (C_1-C_2)alkyl selected from methyl and ethyl;
when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; (C_1-C_8) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, n-hexyl and n-octyl; (C_3-C_6)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, cyclopentyl and cyclohexyl; [(C_4-C_5)cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl and (cyclopropyl)ethyl; (C_3-C_4)alkenyl monosubstituted amino group substitution selected from allyl and 3-butenyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl and 1-phenylethyl; straight or branched symmetrical disubstituted (C_2-C_4)alkylamino group substitution selected from dimethyl and diethyl; straight or branched unsymmetrical disubstituted (C_3)alkylamino group substitution selected from methyl(ethyl); (C_2-C_5)azacycloalkyl group selected from pyrrolidinyl and piperidinyl; 1-azaoxacycloalkyl group selected from morpholinyl; substituted 1-azaoxacycloalkyl group selected from 2-(C_1-C_3)alkylmorpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacyclo-

alkyl group selected from piperazinyl, 2-(C₁-C₃)alkyl-
piperazinyl, 4-(C₁-C₃)alkylpiperazinyl, and
2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl and
5 the diastereomers and enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group;
1-azathiacycloalkyl and substituted 1-azathiacycloalkyl
group selected from thiomorpholinyl and
2-(C₁-C₃)alkylthiomorpholinyl; N-azolyl group selected
10 from 1-imidazolyl; (heterocycle)methylamino group
selected from 2- or 3-thienylmethylamino and 2-, 3- or
4-pyridylmethylamino; (C₁-C₄)alkoxycarbonylamino group
substitution selected from methoxycarbonyl,
ethoxycarbonyl, and 1,1-dimethylethoxycarbonyl;
15 R² is selected from hydrogen; straight or branched
(C₁-C₃)alkyl group selected from methyl, ethyl,
n-propyl or 1-methylethyl;
R³ is selected from hydrogen; straight or branched
(C₁-C₃)alkyl group selected from methyl, ethyl,
20 n-propyl or 1-methylethyl; with the proviso that R²
and R³ cannot both be hydrogen;
or R² and R³ taken together are -(CH₂)₂B(CH₂)₂-,
wherein B is selected from (CH₂)_n and n=0-1, -NH,
-N(C₁-C₃)alkyl [straight or branched], -N(C₁-C₄)alkoxy,
25 oxygen, sulfur or substituted congeners selected from
(L or D)proline, ethyl(L or D)prolinate, morpholine,
pyrrolidine or piperidine; and the pharmacologically
acceptable organic and inorganic salts or metal
complexes.

30 Also included in the present invention are
compounds useful as intermediates for producing the
above compounds of formula I and II. Such intermediate
include those having the formula III:



wherein:

Y is selected from $(CH_2)_nX$, $n = 0-5$, X is halogen selected from bromine, chlorine, fluorine and iodine; R is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) -alkyl, nitro, amino, cyano, (C_1-C_4) alkoxycarbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group [substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4) alkylamino, (C_1-C_4) alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxy];



R^1 is selected from hydrogen and (C_1-C_6) alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

5 when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal
10 complexes.

Preferred compounds are compounds according to the above formula III wherein:

Y is selected from $(CH_2)_nX$, $n = 0-5$, X is halogen selected from bromine, chlorine, fluorine and iodine;

15 R is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl;
20 α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl;

carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected
25 from phenyl, α -naphthyl and β -naphthyl; (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl;

substituted (C_7-C_9) aralkyl group [substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono-
30 or di-substituted (C_1-C_4) alkylamino, (C_1-C_4) alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxyl];

R^1 is selected from hydrogen and (C_1-C_6) alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

35 when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the



pharmacologically acceptable organic and inorganic salts and metal complexes.

Particularly preferred compounds are compounds according to the above formula III wherein:

Y is selected from $(CH_2)_nX$, $n = 0-5$, X is halogen selected from bromine, chlorine, fluorine and iodine; R is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl and α -mercaptopropyl; α -hydroxy- (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl and α -hydroxypropyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; R^1 is selected from hydrogen and (C_1-C_6) alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal complexes.

Compounds of special interest are compounds according to the above formula III wherein:

Y is selected from $(CH_2)_nX$, $n = 0-5$, X is halogen selected from bromine, chlorine, fluorine and iodine; R is selected from hydrogen; straight or branched (C_1-C_2) alkyl group selected from methyl and ethyl; R^1 is selected from hydrogen and (C_1-C_2) alkyl selected from methyl and ethyl;



when R does not equal R¹ the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal complexes.

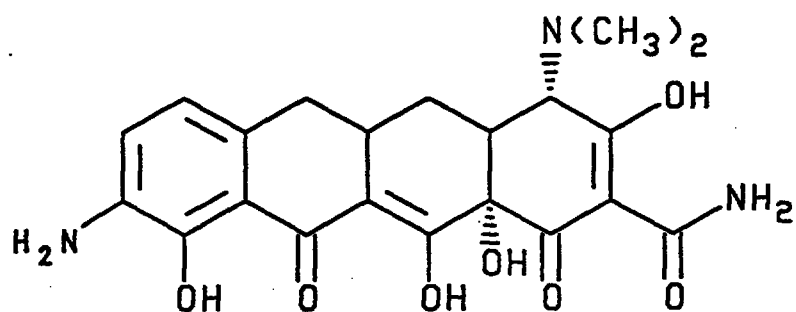
DESCRIPTION OF THE PREFERRED EMBODIMENTS

The novel compounds of the present invention may be readily prepared in accordance with the following schemes.

Scheme I

5

10



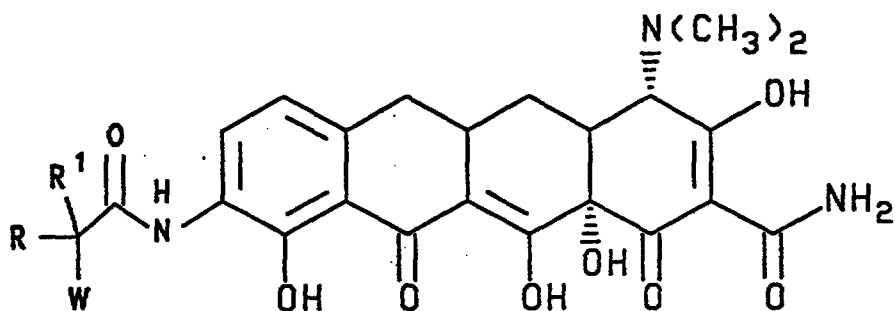
15

1 mineral acid
salt

20



25



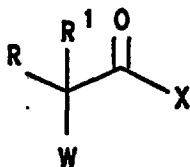
30

3 mineral acid
salt

35

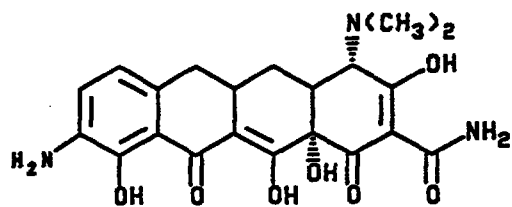


The 9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracyclines, or mineral acid salts, can be made by the procedure described in scheme I. In accordance with scheme I, 9-amino-6-demethyl-6-deoxy-tetracycline or its mineral acid salt, 1, is dissolved in a mixture of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone and acetonitrile. Sodium carbonate is added and the mixture is stirred for 5 minutes. An acid chloride of the formula:

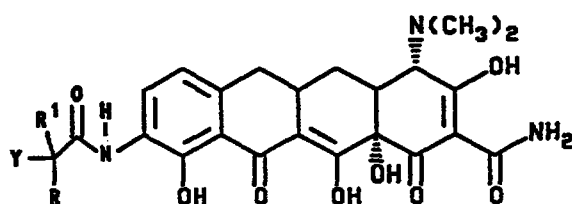
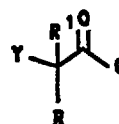


wherein R, R¹, W and X have been described hereinabove is added and the reaction is stirred at room temperature for from 0.5-2 hours to give the corresponding 9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracycline, or its mineral acid salt 3.

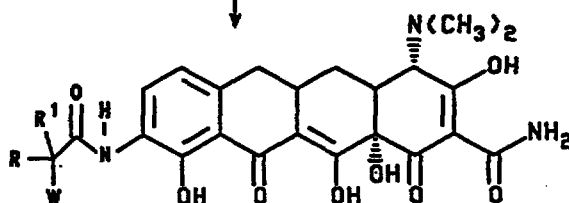
Scheme II



1 mineral acid salt



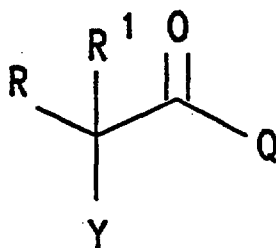
2 mineral acid salt



3 mineral acid salt

The preferred method for producing 9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracyclines or its mineral acid salt 3, is shown in scheme II.

This method uses common intermediates which are easily prepared by reacting commercially available haloacyl halides of the formula:



wherein Y, R and R¹ are as defined hereinabove and Q is halogen selected from bromine, chlorine, iodine and fluorine; with 9-amino-6-demethyl-6-deoxytetracyclines, or its mineral acid salt 1, to give straight or branched 9-[(haloacyloamido]-6-demethyl-6-deoxytetracyclines or its mineral acid salt, 2, in almost quantitative yield. The above intermediates, straight or branched 9-[(haloacyloamido]-6-demethyl-6-deoxytetracyclines or its mineral acid salt 2, react with a wide variety of nucleophiles, especially amines, having the formula WH, wherein W is as defined hereinabove to give the new 9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracyclines or mineral acid salt 3 of the present invention.

In accordance with Scheme II, 9-amino-6-demethyl-6-deoxytetracycline or its mineral acid salt, 1, is mixed with

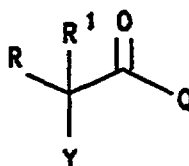
a) a polar-aprotic solvent such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidone, herein after called DMPU, hexamethylphosphoramide herein after called HMPA, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, 1,2-dimethoxyethane or equivalent thereof;



b) an inert solvent such as acetonitrile, methylene chloride, tetrahydrofuran, chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethane, diethyl ether, t-butyl methylether, isopropyl ether or equivalent thereof;

c) a base such as sodium carbonate, sodium bicarbonate, sodium acetate, potassium carbonate, potassium bicarbonate, triethylamine, cesium carbonate, lithium carbonate or bicarbonate equivalents; and

d) a straight or branched haloacyl halide of the formula:



wherein Y, R, R¹ and Q are as defined hereinabove, such as bromoacetyl bromide, chloroacetyl chloride or 2-bromopropionyl bromide or equivalent thereof; the halo, Y, and halide, Q, in the haloacyl halide can be the same or different halogen and is selected from bromine, chlorine, iodine and fluorine; Y is (CH₂)_nX, n= 0-5, X is halogen;

e) for 0.5 to 5 hours at room temperature to the reflux temperature of the reaction; to form the corresponding 9-[(haloacyl)amido]-6-de-methyl-6-deoxy-tetracycline, 2, or its mineral acid salt.

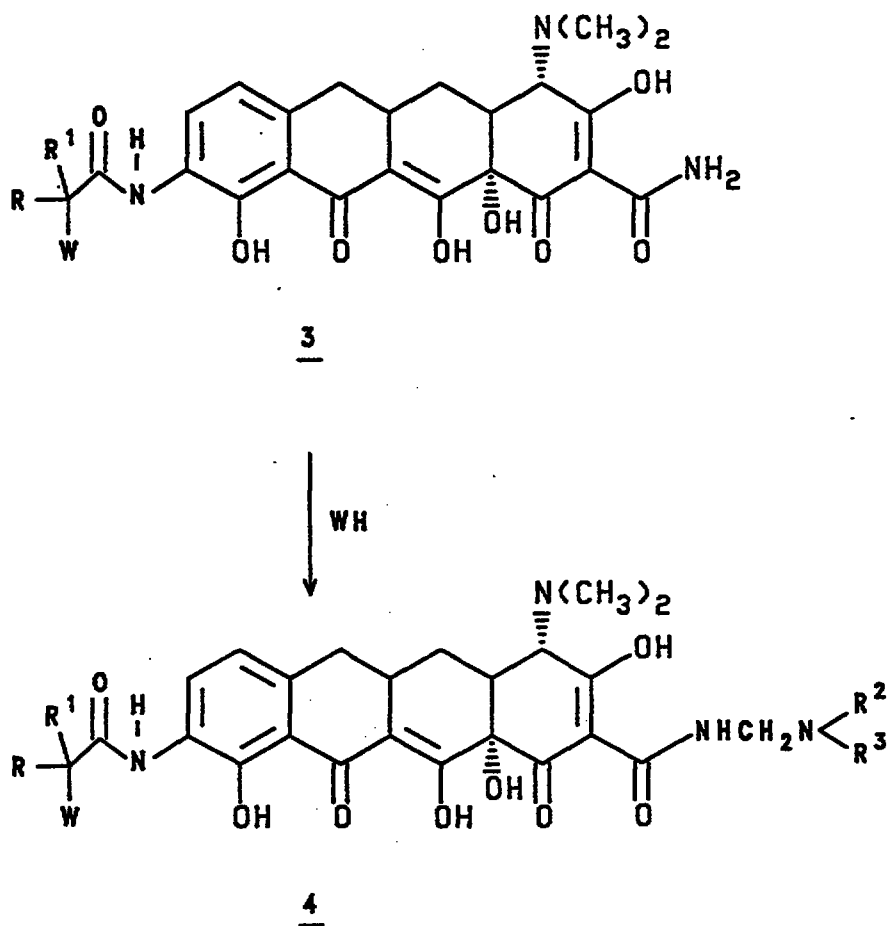
The intermediate, 9-[(haloacyl)amido]-6-de-methyl-6-deoxytetracycline or mineral acid salt 2, is treated, under an inert atmosphere of helium, argon or nitrogen, with

a) a nucleophile WH such as an amine or substituted amine or equivalent for example methylamine, dimethylamine, ethylamine, n-butylamine, propylamine or n-hexylamine;

b) a polar-aprotic solvent such as DMPU, HMPA, dimethylformamide, dimethylacetamide, N-methylpyrrolidone or 1,2-dimethoxyethane;

c) for from 0.5 - 2 hours at room temperature or under reflux temperature to produce the desired 9-[(substituted glycy1)amido]-6-demethyl-6-deoxytetra-cycline, 3, or its mineral acid salt.

Scheme III



In accordance with Scheme III, compounds of formula 3 are N-alkylated in the presence of formaldehyde and either a primary amine such as methylamine, ethylamine, benzylamine, methyl glycinate, (L or D)alanine, (L or D)lysine or their substituted congeners; or a secondary amine such as morpholine, pyrrolidine, piperidine or their substituted congeners to give the corresponding Mannich base adduct, 4.

The 9-[(substituted glycyloxy)amido]-6-demethyl-6-deoxytetracyclines 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). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hygroscopicity and solubility. Preferably, the 9-[(substituted glycyloxy)amido]-6-demethyl-6-deoxytetracyclines are obtained as inorganic salt such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salt such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate. Depending on the stoichiometry of the acids used, the salt formation occurs with the C(4)-dimethylamino group (1 equivalent of acid) or with both the C(4)-dimethylamino group and the W group (2 equivalents of acid). The salts are preferred for oral and parenteral administration.

Some of the compounds of the hereinbefore described Schemes have centers of asymmetry at the carbon bearing the W substituent. The compounds may, therefore, exist in at least two (2) stereoisomeric forms. The present invention encompasses the racemic mixture of stereo isomers as well as all stereoisomers

of the compounds whether free from other stereoisomers or admixed with stereoisomers in any proportion of enantiomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography.

The stereochemistry centers on the tetracycline unit (i.e. C-4, C-4a, C-5a and C-12a) remain intact throughout the reaction sequences.

BIOLOGICAL ACTIVITY

Method for in Vitro Antibacterial Evaluation (Tables I, II and V)

The minimum inhibitory concentration (MIC), the lowest concentration of the antibiotic which inhibits growth to the test organism, is determined by the agar dilution method using Muller-Hinton II agar (Baltimore Biological Laboratories). An inoculum density of $1-5 \times 10^5$ CFU/ml and a range of antibiotic concentrations ($32-0.004 \mu\text{g/ml}$) is used. The plates are incubated for 18 hours at 35°C in a forced air incubator. The test organisms comprise strains that are sensitive to tetracycline and genetically defined strains that are resistant to tetracycline, due to inability to bind to bacterial ribosomes (tetM) or by a tetK encoded membrane protein which confers tetracycline resistance by energy-dependent efflux of the antibiotic from the cell.

E. coli in Vitro Protein Translation System (Table III)

An in vitro, cell free, protein translation system using extracts from E. coli strain MRE600 (tetracycline sensitive) and a derivative of MRE600 containing the tetM determinant has been developed based on literature methods [J.M. Pratt, Coupled Transcription-translation in Prokaryotic Cell-free Systems, Transcription and Translation, a Practical Approach, (B.D. Hames and S.J. Higgins, eds) p. 179-209, IRL Press, Oxford-Washington, 1984].

Using the system described above, the tetracycline compounds of the present invention are tested for their ability to inhibit protein synthesis in vitro. Briefly, each 10 μ l reaction contains S30 extract (a whole extract) made from either tetracycline sensitive cells or an isogenic tetracycline resistant (tetM) strain, low molecular weight components necessary for transcription and translation (i.e. ATP and GTP), a mix of 19 amino acids (no methionine), 35 S labeled methionine, DNA template (either pBR322 or pUC119), and either DMSO (control) or the novel tetracycline compound to be tested ("novel TC") dissolved in DMSO.

The reactions are incubated for 30 minutes at 37°C. Timing is initiated with the addition of the S30 extract, the last component to be added. After 30 minutes, 2.5 μ l of the reaction is removed and mixed with 0.5 ml of 1N NaOH to destroy RNA and tRNA. Two ml of 25% trichloroacetic acid is added and the mixture incubated at room temperature for 15 minutes. The trichloroacetic acid precipitated material is collected on Whatman GF/C filters and washed with a solution of 10% trichloroacetic acid. The filters are dried and the retained radioactivity, representing incorporation of 35 S-methionine into polypeptides, is counted using standard liquid scintillation methods.

The percent inhibition (P.I.) of protein synthesis is determined to be:

$$P.I.=100-\left(\frac{\text{Retained radioactivity of novel TC containing sample}}{\text{Retained radioactivity of the DMSO control reaction}}\right)\times 100$$

In Vivo Antibacterial Evaluation (Table IV)

The therapeutic effects of tetracyclines are determined against an acute lethal infection with Staphylococcus aureus strain Smith (tetracycline sensitive). Female, mice, strain CD-1 (Charles River

Laboratories), 20±2 grams, are challenged by an intraperitoneal injection of sufficient bacteria (suspended in hog mucin) to kill non-treated controls within 24-48 hours. Antibacterial agents, contained in 0.5 ml of 0.2% aqueous agar, are administered subcutaneously or orally 30 minutes after infection. When an oral dosing schedule is used, animals are deprived of food for 5 hours before and 2 hours after infection. Five mice are treated at each dose level. The 7 day survival ratios from 3 separate tests are pooled for calculation of median effective dose (ED₅₀).

Testing Results

The claimed compounds exhibit antibacterial activity against a spectrum of tetracycline sensitive and resistant Gram-positive and Gram-negative bacteria, especially, strains of E. coli and S. aureus containing tetM resistance determinants, and E. coli containing the tetA, tetB, tetC and tetD resistance determinants. Notable is 9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline, CC, as shown in Table I, which demonstrated excellent in vitro activity against tetracycline resistant strains containing the tetM resistance determinant (such as S. aureus UBMS 88-5, S. aureus UBMS 90-1 and 90-2, E. coli UBMS 89-1 and 90-4) and tetracycline resistant strains containing tetB resistance determinants (such as E. coli UBMS 88-1 and E. coli TN10C tetB). 9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline, also has good activity against E. coli strains containing tetA, tetC and tetD resistance determinants. It is as effective as minocycline against susceptible strains and is superior to minocycline against a number of recently isolated bacteria from clinical sources. (Table II)

As shown in Table II, the free base, disulfate, dihydrochloride, monohydrochloride and the Mannich bases of 9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxytetracycline, show comparable in vitro

antibacterial activity.

Minocycline and 9-[(N,N-dimethylglycyl)-
amido]-6-demethyl-6-deoxytetracycline are assayed for
their ability to inhibit protein synthesis taking place
on either wild type or TetM modified ribosomes using a
coupled transcription and translation system. Both
compounds effectively inhibit protein synthesis
occurring on wild type ribosomes, at equivalent levels
of activity. Minocycline is not effective in
inhibiting protein synthesis occurring on tetM modified
ribosomes. In contrast, 9-[(N,N-dimethylglycyl)amido]-
6-demethyl-6-deoxytetracycline is effective at
inhibiting protein synthesis occurring on TetM modified
ribosomes, although a slightly higher concentration is
required to achieve similar levels of inhibition
relative to wild type ribosomes. (Table III)

9-[(N,N-Dimethylglycyl)amido]-6-demethyl-6-
deoxytetracycline binds reversibly to its target (the
ribosome) since bacterial growth resumes when the
compound is removed by washing of the organism.
Therefore, the ability of 9-[(N,N-dimethylglycyl)-
amido]-6-demethyl-6-deoxytetracycline to inhibit
bacterial growth appears to be a direct consequence of
its ability to inhibit protein synthesis at the
ribosome level.

As shown in Table IV, the claimed compounds
AA, BB, DD, CC, H, C, D, G and Q show very good in vivo
activity when tested intravenously against the mino-
cycline sensitive organism, S. aureus Smith. The
claimed compound CC when administered intravenously
exhibits potent activity (ED₅₀ 1.6 mg/kg) against E.
coli UBMS 90-4 (TetM), which is resistant to
minocycline, i.e. (ED₅₀ >32 mg/kg).

As shown in Table V, 9-[(N,N-dimethylglycyl)-
amido]-6-demethyl-6-deoxytetracycline shows potent in
vitro antibacterial activity against a broad spectrum
of recent clinical isolates, including a number from

5 veterinary sources. It was more active than mino-
cycline and tetracycline against the majority of the
isolates tested. The claimed compound is especially
active against E. faecalis, E. faecium including
vancomycin resistant strains. The 9-[(dimethylglycyl)-
amido]-6-demethyl-6-deoxytetracycline also exhibits
potent activity against E. coli, Salmonella spp.,
10 Shigella spp., Salmonella choleraesuis, Proteus
mirabilis, Proteus vulgaris, Morganella morganii,
Neisseria gonorrhoeae, Bacteroides spp., Clastridium
spp. and Streptococcus spp. The activity of the
9-[(N,N-dimethylglycyl)amido]-6-demethyl-6-deoxy-
tetracycline is generally greater than minocycline and
15 tetracycline.

As can be seen from Tables I-V, compounds of
the invention can be used to prevent or control
important mammalian and veterinary diseases such as
diarrhea, urinary tract infections, infections of skin
20 and skin structure, ear, nose and throat infections,
wound infections, mastitis and the like.

Thus, the improved efficacy of 9-[(N,N-di-
methylglycyl)amido]-6-demethyl-6-deoxytetracycline is
demonstrated by the in vitro activity against isogenic
25 strains into which the resistance determinants, such as
tetM, are cloned (Table I); the inhibition of protein
synthesis by TetM modified ribosomes (Table III); and
the in vivo activity against experimental infections
caused by strains resistant to the tetracyclines, due
30 to the presence of resistance determinants, such as tet
M (Table IV).

When the compounds are employed as anti-
bacterials, they can be combined with one or more phar-
maceutically acceptable carriers, for example, sol-
35 vents, diluents and the like, and may be administered
orally in such forms as tablets, capsules, dispersible
powders, granules, or suspensions containing, for exam-
ple, 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 2.0 mg/kg of body weight to 100.0 mg/kg of body weight should 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 pre-

paration 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 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.

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 glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary 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 must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserve 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 thereof, and vegetable oil.

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

COMPOUND LEGEND FOR TABLES

5	A	[7S-(7alpha,10alpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride
10	B	[4S-(4alpha,12alpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
15	C	[4S-(4alpha,12alpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino) acetyl]-amino]-2-naphthacenecarboxamide dihydrochloride
20	D	[7S-(7alpha,10alpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride
25	E	[4S-(4alpha,12alpha)]-4-(Dimethylamino)-9-[[(ethylamino) acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
30	F	[4S-(4alpha,12alpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methylamino) acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
35	G	[4S-(4alpha,12alpha)]-4-(Dimethylamino)-9-[[(hexylamino) acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

- 5 H [4S-(4alpha,12aalpha)]-9-[[(Butylamino)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
- 10 I [7S-(7alpha,10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-1-piperidineacetamide dihydrochloride (331,404)
- 15 J [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(phenylmethyl)-amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
- 20 K [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]-amino]-2-naphthacenecarboxamide monohydrochloride
- 25 L [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(2-thienylmethyl)-amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
- 30 M [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(2-methylpropyl)amino]acetyl]-amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
- 35 N [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(2-pyridinylmethyl)-amino]acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
- O [4S-(4alpha,12aalpha)]-9-[[(Diethylamino)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-

		1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
5	P	[7S-(7alpha,10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-alpha-methyl-1-pyrrolidinecarboxamide
10	Q	[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
15	R	[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride
20	S	[4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
25	T	Tetracycline
	U	Minocycline
	AA	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide disulfate
30	BB	[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

- 5 CC [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-
 [[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,
 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-2-naphthacenecarboxamide dihydro-
 chloride
- 10 DD [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-
 [[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,
 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-2-naphthacenecarboxamide mono-
 hydrochloride
- 15 EE [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-
 [[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,
 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-N-(1-pyrrolidinylmethyl)-2-
 naphthacenecarboxamide

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Table I
ANTIBACTERIAL ACTIVITY OF 9-((SUBSTITUTED GLYCYL)AMIDO)-6-DEETHYL-6-DEOXYTETRACYCLINES
MIC (µg/ml)

Organism	Compound										
	A	B	C	D	E	F	G	H	I	J	K
E. coli UBHS 88-1 Tet B	1	1	0.5	0.25	0.5	1	1	0.25	1	4	1
E. coli J3272 Tet sens	NT	NT	NT	NT	NT	NT	NT	0.12	NT	NT	NT
E. coli MC 4100 Tet sens.	0.25	0.25	0.12	0.12	0.25	0.5	0.12	NT	0.25	0.5	0.5
E. coli PRP1 Tet A	1	2	1	0.25	2	4	1	0.25	1	4	0.5
E. coli MC 4100 TMI0C Tet B	1	0.5	0.5	0.25	1	1	1	0.25	1	4	0.5
E. coli J3272 Tet C	1	1	0.5	0.25	1	4	1	0.12	1	4	0.5
E. coli UBHS 89-1 Tet M	0.25	0.5	0.25	0.12	0.25	0.5	0.25	0.12	0.25	2	0.25
E. coli UBHS 89-2 Tet sens.	0.5	1	0.25	0.25	0.5	1	1	0.12	0.5	4	0.25
E. coli J2175	0.5	1	0.25	0.25	0.5	0.5	1	0.25	0.5	4	0.5
E. coli BAJ9003 IMP MJT	0.12	0.25	0.06	0.06	0.12	0.5	0.12	0.06	0.12	0.5	0.25
E. coli UBHS 90-4 Tet M	0.5	0.5	0.25	0.25	0.25	0.5	0.5	0.12	0.5	4	0.5
E. coli UBHS 90-5	0.5	0.5	0.25	0.25	0.5	0.5	1	0.12	0.5	4	0.5
E. coli #311 (MP)	0.25	0.5	0.5	0.25	0.5	0.5	1	0.12	0.5	4	0.5
E. coli ATCC 25922	0.25	0.5	0.12	0.12	0.25	0.5	1	0.12	0.5	4	0.5
E. coli J3272 Tet D	0.25	0.5	0.12	0.12	0.25	0.5	0.5	0.06	0.5	4	0.5
S. marcescens FPOR 8733	8	8	4	2	4	4	8	2	8	>32	4
X. maltophilia NEMC 87210	0.5	2	4	1	8	16	1	1	0.5	16	1
Ps. aeruginosa ATCC 27853	>32	32	16	16	16	32	32	8	>32	>32	32
S. aureus NEMC 8769	no growth	0.06	0.06	0.06	0.12	0.25	0.12	0.03	0.5	1	0.12

Table 1 (cont'd)
ANTIBACTERIAL ACTIVITY OF 9-((SUBSTITUTED GLYCYL)AMIDO)-6-DE METHYL-6-DEOXYTETRACYCLINES
MIC (μ g/ml)

Organism	Compound										
	A	B	C	D	E	F	G	H	I	J	K
<i>S. aureus</i> UBMS 88-4	0.5	0.25	0.25	0.12	0.5	0.5	0.25	0.06	0.5	1	0.25
<i>S. aureus</i> UBMS 88-5 Tet M	0.5	0.5	0.5	0.12	0.5	1	0.5	0.06	0.5	2	0.5
<i>S. aureus</i> UBMS 88-7 Tet K	1	1	2	0.5	8	16	1	1	0.5	4	2
<i>S. aureus</i> UBMS 90-1 Tet M	1	0.5	0.25	0.25	0.5	0.5	1	0.12	0.5	4	0.5
<i>S. aureus</i> UBMS 90-3	0.5	0.06	0.06	0.12	0.12	0.5	0.25	0.03	0.25	0.5	0.25
<i>S. aureus</i> UBMS 90-2 Tet M	0.5	0.25	0.25	0.25	0.12	0.5	0.25	0.12	0.25	1	0.25
<i>S. aureus</i> IVES 2943	0.5	1	4	1	16	>32	2	1	1	4	2
<i>S. aureus</i> ROSE (MP)	2	4	16	2	>32	>32	4	4	4	8	8
<i>S. aureus</i> SMITH (MP)	0.5	0.25	0.12	0.12	0.25	0.5	0.25	0.12	0.25	0.5	0.25
<i>S. aureus</i> IVES 1 983	1	1	4	1	8	16	1	2	1	4	2
<i>S. aureus</i> ATCC 29213	0.5	0.25	0.25	0.12	0.5	0.5	0.5	0.06	0.5	1	0.5
<i>S. hemolyticus</i> AVIAN 88-3	2	1	0.5	0.25	1	1	2	0.5	2	4	2
<i>Enterococcus</i> 12201	0.5	0.25	0.25	0.12	0.25	0.5	0.25	0.12	0.25	2	0.25
<i>E. faecalis</i> ATCC 29212	0.25	0.25	0.12	0.12	0.25	0.5	0.12	0.12	0.25	0.25	0.25

Table 1 (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEETHYL-6-DEOXYTETRACYCLINES
MIC (μ g/ml)

Organism	Compound											
	L	M	N	O	P	Q	R	S	T	U		
<i>E. coli</i> UBMS 88-1 Tet B	32	1	>32	1	2	0.5	>32	>32	>32	16		
<i>E. coli</i> J3272 Tet sens	NT	NT	NT	NT	NT	NT	32	4	1	1		
<i>E. coli</i> MC 4100 Tet sens.	8	0.25	8	0.5	0.25	0.25	NT	NT	0.25	0.12		
<i>E. coli</i> PRP1 Tet A	16	1	32	4	2	2	>32	>32	16	2		
<i>E. coli</i> MC 4100 TNOIC Tet B	32	1	32	1	2	1	>32	>32	>32	16		
<i>E. coli</i> J3272 Tet C	32	1	>32	1	1	0.5	>32	>32	>32	1		
<i>E. coli</i> UBMS 89-1 Tet M	8	0.5	16	0.5	0.5	0.5	8	>32	32	8		
<i>E. coli</i> UBMS 89-2 Tet sens.	16	1	32	1	1	1	32	16	1	1		
<i>E. coli</i> J2175	16	1	>32	1	1	1	32	16	1	1		
<i>E. coli</i> BAJ9003 INP MUT	4	0.25	2	0.12	0.25	0.25	1	1	0.25	0.03		
<i>E. coli</i> UBMS 90-4 Tet M	8	0.5	16	0.5	1	0.25	32	>32	32	>32		
<i>E. coli</i> UBMS 90-5	16	1	32	1	0.5	0.5	32	8	0.5	1		
<i>E. coli</i> #311 (NP)	16	1	32	1	1	1	16	8	1	0.25		
<i>E. coli</i> ATCC 25922	8	0.5	32	0.5	1	0.5	16	8	0.5	0.25		
<i>E. coli</i> J3272 Tet D	16	0.25	32	0.5	0.5	0.25	>32	>32	>32	8		
<i>S. marcescens</i> FPOR 8733	>32	8	>32	8	16	8	>32	>32	>32	4		
<i>X. maltophilia</i> NEMC 87210	>32	2	>32	1	4	4	16	16	8	0.12		
<i>Ps. aeruginosa</i> ATCC 27853	>32	32	>32	32	>32	16	>32	>32	>32	8		
<i>S. aureus</i> NEMC 8769	8	8	8	1	0.5	0.5	0.25	0.25	0.06	<0.015		

Table 1 (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMID]-6-DEETHYL-6-DEOXYTETRACYCLINES

MIC μ g/ml

Organism	Compound										
	L	M	N	O	P	Q	R	S	T	U	
<i>S. aureus</i> UBHS 88-4	8	0.5	8	0.5	0.5	0.5	0.5	2	0.12	0.03	
<i>S. aureus</i> UBHS 88-5 Tet M	8	0.5	8	0.5	0.5	0.5	2	32	>32	4	
<i>S. aureus</i> UBHS 88-7 Tet K	16	2	>32	0.5	1	8	8	16	>32	0.06	
<i>S. aureus</i> UBHS 90-1 Tet M	8	0.5	8	0.5	0.5	0.5	1	32	>32	8	
<i>S. aureus</i> UBHS 90-3	4	0.25	4	0.25	0.25	0.5	1	2	0.12	<0.015	
<i>S. aureus</i> UBHS 90-2 Tet M	8	0.5	8	0.5	0.5	0.5	2	16	32	2	
<i>S. aureus</i> IVES 2943	16	4	>32	1	2	8	16	32	>32	2	
<i>S. aureus</i> ROSE (NP)	32	8	>32	2	8	16	16	>32	>32	0.25	
<i>S. aureus</i> SMITH (NP)	4	0.5	4	0.25	0.5	0.5	1	1	0.12	0.03	
<i>S. aureus</i> IVES 1983	16	2	>32	0.5	1	4	16	32	>32	4	
<i>S. aureus</i> ATCC 29213	8	0.25	8	0.5	0.5	0.5	1	2	<0.015	<0.015	
<i>S. hemolyticus</i> AVNAH 88-3	8	2	>32	2	4	4	8	8	0.5	0.06	
<i>Enterococcus</i> 12201	8	0.5	8	0.25	0.25	0.5	4	32	32	8	
<i>E. faecalis</i> ATCC 29212	4	0.25	4	0.25	0.25	0.25	2	16	16	2	

Table II

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES
MIC μ g/mL

Organism	Compound						
	AA	BB	CC	DD	EE	Y	U
<i>E. coli</i> UBMS 88-1 Tet B	0.25	0.25	0.25	0.25	0.5	>32	16
<i>E. coli</i> J3272 Tet sens	0.25	0.12	0.12	NT	NT	1	1
<i>E. coli</i> MC 4100 Tet sens.	NT	NT	NT	0.06	0.12	0.25	0.12
<i>E. coli</i> PRP1 Tet A	2	0.5	0.5	1	2	16	2
<i>E. coli</i> MC 4100 TWOC Tet B	0.25	0.25	0.25	0.25	0.5	>32	16
<i>E. coli</i> J3272 Tet C	1	0.25	0.25	1	1	>32	1
<i>E. coli</i> UBMS 89-1 Tet M	0.25	0.12	0.12	0.5	0.25	32	8
<i>E. coli</i> UBMS 89-2 Tet sens.	0.25	0.25	0.25	0.25	0.5	1	1
<i>E. coli</i> J2175	0.25	0.25	0.25	0.25	0.5	1	1
<i>E. coli</i> BAJ9003 IMP MJT	0.06	no growth	no growth	0.06	0.12	0.25	0.03
<i>E. coli</i> UBMS 90-4 Tet M	0.25	0.12	0.12	0.12	0.25	32	>32
<i>E. coli</i> UBMS 90-5	0.25	0.12	0.12	0.25	0.25	0.5	1
<i>E. coli</i> #311 (MP)	0.50	0.12	0.12	0.25	0.5	1	0.25
<i>E. coli</i> ATCC 25922	0.25	0.12	0.12	0.25	0.25	0.5	0.25
<i>E. coli</i> J3272 Tet D	0.12	0.06	0.03	0.25	0.25	>32	8
<i>S. marcescens</i> FPOR 8733	4	2	2	4	4	>32	4
<i>X. maltophilia</i> NEMC 87210	2	1	1	2	2	8	0.12
<i>Ps. aeruginosa</i> ATCC 27853	16	8	4	8	16	8	8
<i>S. aureus</i> NEMC 8769	0.03	<0.015	<0.015	0.03	0.25	0.06	<0.015

Table 11 (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEETHYL-6-DEOXYTETRACYCLINES

MIC 64g/ml)

Organism	Compound						T	U
	AA	BB	CC	DD	EE			
<i>S. aureus</i> UBHS 88-4	0.12	0.06	0.03	0.12	0.25		0.12	0.03
<i>S. aureus</i> UBHS 88-5 Tet M	0.12	0.12	0.03	0.12	0.25		>32	4
<i>S. aureus</i> UBHS 88-7 Tet K	1	0.5	0.5	1	1		>32	0.06
<i>S. aureus</i> UBHS 90-1 Tet M	0.25	0.12	0.06	0.12	0.25		>32	8
<i>S. aureus</i> UBHS 90-3	0.06	0.06	0.03	0.06	0.12		0.12	<0.015
<i>S. aureus</i> UBHS 90-2 Tet M	0.12	0.12	0.06	0.12	0.25		32	2
<i>S. aureus</i> IVES 2943	1	0.5	0.5	1	2		>32	2
<i>S. aureus</i> ROSE (MP)	4	2	1	4	8		>32	0.25
<i>S. aureus</i> SMITH (MP)	0.12	0.06	0.03	0.12	0.25		0.12	0.03
<i>S. aureus</i> IVES 1983	2	0.5	0.5	1	2		>32	4
<i>S. aureus</i> ATCC 29213	<0.015	0.3	<0.015	0.12	0.25		<0.015	<0.015
<i>S. hemolyticus</i> AVIAN 88-3	0.5	0.12	0.12	0.25	0.5		0.5	0.06
<i>Enterococcus</i> 12201	0.12	0.06	0.03	0.12	0.25		32	8
<i>E. faecalis</i> ATCC 29212	0.12	0.06	0.03	0.06	0.12		16	2

NT = not tested

Table III
In Vitro Transcription and Translation
Sensitivity to 9-(Glycylamido)-6-deoxy-6-
demethyltetracycline Derivatives

	<u>Compound</u>	<u>Conc.</u>	<u>% Inhibition</u>	
			<u>Wild Type S30</u>	<u>Tet M S30</u>
10	CC	1.0 mg/ml	99	99
		0.25 mg/ml	98	94
		0.06 mg/ml	91	82
15	H	1.0 mg/ml	99	98
		0.25 mg/ml	91	95
		0.06 mg/ml	86	72
	U	1.0 mg/ml	98	68
20		0.25 mg/ml	89	43
		0.06 mg/ml	78	0

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Table IV
Effects of Glycylcycline Derivatives on Acute Lethal Infections in Mice
(ED₅₀ mg/kg)

Organism	Route of Antibiotic Administration	Antibiotic									
		AA	BB	DD	CC	H	C	D	G	Q	U
<u>S. aureus</u> Smith (Sens)	Oral	>16	8-16	12	>8	>16	>16	>16	>16	>16	0.74
	Intravenous	0.5-1	0.5-1	0.67	0.46	0.5-1	1-2	1-2	>4	NT	0.37
<u>Escherichia coli</u> UBMS 90-4 (Tet M)	Intravenous	NT	NT	NT	1.6	NT	NT	NT	NT	NT	>32

Table V

In Vitro Activity of CC and Comparative Antibiotics vs Recent Clinical
and Veterinary Isolates

Organism	[# Isolates]	CC	MIC (μ g/ml) Range U	T
<u>Staphylococcus aureus</u> , (methicillin-resistant)	[15]	0.12-4	0.06-4	0.25->64
<u>Staphylococcus aureus</u> , (methicillin-susceptible)	[15]	0.06-0.25	0.03-0.12	0.12-1
<u>Staphylococcus</u> Coagulase-negative, (methicillin-resistant)	[16]	0.06-16	0.03-1	0.12->64
<u>Staphylococcus</u> Coagulase-negative, (methicillin-susceptible)	[14]	0.06-4	0.015-0.25	0.12->64
<u>Enterococcus faecalis</u>	[10]	0.03-0.25	0.03-16	0.12-64
<u>Enterococcus faecium</u>	[10]	0.06-0.5	0.03-16	0.12-64
<u>Enterococcus spp.</u> (Vancomycin-resistant)	[8]	0.03-0.12	0.03-16	0.12->64
<u>Streptococcus pyogenes</u>	[10]	0.06-0.12	0.03-2	0.12-16
<u>Streptococcus agalactiae</u>	[10]	0.12-0.25	0.12-16	0.25-64

Table V (cont'd)

In Vitro Activity of CC and Comparative Antibiotics vs Recent Clinical
and Veterinary Isolates

Organism	[# Isolates]	MIC (μ g/ml) Range			T
		CC	U		
<u>Streptococcus pneumoniae</u>	[10]	0.03-0.5	0.06-0.5	0.12-2	
<u>Listeria monocytogenes</u>	[8]	0.06-0.12	0.015-0.03	0.12-0.5	
<u>Escherichia coli</u>	[30]	0.25-4	0.25-32	0.5->64	
<u>Escherichia coli</u> (Veterinary)	[15]	0.25-4	1-16	2->64	
<u>Shigella spp.</u>	[14]	0.12-0.5	0.25-8	0.25->64	
<u>Klebsiella pneumoniae</u>	[10]	0.25-4	0.5-8	0.5->64	
<u>Klebsiella oxytoca</u>	[10]	0.25-1	0.5-4	0.5-1	
<u>Citrobacter freundii</u>	[10]	0.5-8	0.03-32	0.5-16	
<u>Citrobacter diversus</u>	[10]	0.25-1	0.25-4	0.5-4	
<u>Salmonella spp.</u>	[11]	0.25-0.5	0.5-16	0.5->64	
<u>Salmonella choleraesuis</u> (Veterinary)	[15]	0.5-8	2->64	1->64	

Table V (cont'd)

In Vitro Activity of CC and Comparative Antibiotics vs Recent Clinical
and Veterinary Isolates

Organism	[# Isolates]	CC	MIC (μ g/ml) Range		T
			U		
<u>Serratia marcescens</u>	[10]	2-8	1-8		8->64
<u>Enterobacter cloacae</u>	[10]	0.5-1	0.25-4		0.5-2
<u>Enterobacter aerogenes</u>	[10]	0.25-1	0.5-1		0.5-1
<u>Providencia spp.</u>	[13]	1-8	4->64		1->64
<u>Proteus mirabilis</u>	[26]	0.12-2	1-32		0.5-64
<u>Proteus vulgaris</u>	[18]	0.06-1	0.5-16		0.25-64
<u>Morganella morganii</u>	[16]	0.5-1	0.25-32		0.25->64
<u>Pseudomonas aeruginosa</u>	[10]	2-16	1-16		2-32
<u>Xanthomonas maltophilia</u>	[10]	1-8	0.12-1		8-16
<u>Moraxella catarrhalis</u>	[18]	0.06-0.12	0.03-0.12		0.06-0.5
<u>Neisseria gonorrhoeae</u>	[14]	0.5-1	0.5-64		1->64
<u>Haemophilus influenzae</u>	[15]	1-2	0.5-2		1-32

Table V (cont'd)

In Vitro Activity of CC and Comparative Antibiotics vs Recent Clinical
and Veterinary Isolates

Organism	[# Isolates]	MIC (μ g/ml) Range		
		CC	U	T
<u>Pasturella multocida</u> (Veterinary)	[17]	0.03-0.25	0.015-4	0.06-16
<u>Bordetella bronchiseptica</u> (Veterinary)	[10]	0.06-0.12	0.06-0.12	0.12-0.25
<u>Bacteroides fragilis</u>	[11]	0.25-1	<0.008-16	0.25->64
<u>Bacteroides fragilis</u> group	[10]	0.12-2	<0.008-4	0.25-32
<u>Bacteroides</u> spp.	[9]	0.12-0.5	0.03-16	0.25->64
<u>Clostridium difficile</u>	[12]	0.06-0.12	0.015-16	0.12-32
<u>Clostridium perfringens</u>	[16]	0.03-2	<0.008-16	0.015-16
<u>Clostridium</u> spp.	[9]	0.03-0.12	<0.008-16	0.015-64
<u>Anaerobic</u> Gram(+) Cocci	[15]	0.015-0.12	0.05-8	4->64

Example 1

[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
monohydrochloride

and

[4S-(4alpha,12aalpha)]-9-[(Chloroacetyl)amino]-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
monohydrochloride

To a room temperature solution of 1.58 g of 9-amino-6-demethyl-6-deoxytetracycline monosulfate, 20 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidine, hereinafter called DMPU, and 4 ml of acetonitrile is added 0.50 g of sodium carbonate. The mixture is stirred for 5 minutes followed by the addition of 0.942 g of bromoacetyl chloride. The reaction is stirred for 1 hour, filtered, and the filtrate added dropwise to a mixture of 50 ml of isopropanol and 500 ml of diethyl ether. The resulting solid is collected, washed first with the mixed solvent (isopropanol and diethyl ether) followed by diethyl ether, and dried to give 1.62 g of a mixture of the desired products.

MS(FAB): m/z 550 (M+H) and 506 (M+H).

Example 2

[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
5 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
monohydrobromide

The title compound is prepared by the procedure of Example 1 using 1.2 g of bromoacetyl bromide to give 1.49 g of the pure desired product.

10 ^1H NMR(D_6 -DMSO): δ 12.1(s,1H), 9.9(bs,1H), 9.8(s,1H), 9.55(s,1H), 9.05(s,1H), 8.05(d,1H), 6.8(d,1H), 4.3(s,1H), 4.2(s,2H), 2.75(s,6H).

Example 3

[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4-
15 (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
monosulfate

To a room temperature solution of 1.05 g of 9-amino-6-demethyl-6-deoxytetracycline monosulfate, 10 ml of DMPU and 2 ml of acetonitrile is added 0.605 g of bromoacetyl bromide. The mixture is stirred for 30 minutes, then poured slowly into a mixture of 5 ml methyl alcohol, 50 ml isopropyl alcohol and 500 ml of diethyl ether. The resulting yellow solid is collected, washed several times with diethyl ether and dried to give 1.27 g of the desired product.

25 ^1H NMR(D_6 -DMSO): δ 12.1(s,1H), 9.9(bs,1H), 9.8(s,1H), 9.55(s,1H), 9.05(s,1H), 8.05(d,1H), 6.8(d,1H), 4.3(s,1H), 4.2(s,2H), 2.75(s,6H).

30 Example 4

[4S-(4alpha,12aalpha)]-9-[(Chloroacetyl)amino]-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
monohydrochloride

35 To a room temperature solution of 0.0465 g of 9-amino-6-demethyl-6-deoxytetracycline hydrochloride, 1.5 ml of DMPU and 0.5 ml of acetonitrile is added 0.023 g of chloroacetyl chloride. The mixture is

stirred for 30 minutes, then poured into a mixture of 0.5 ml of methyl alcohol, 2 ml of isopropyl alcohol and 20 ml of diethyl ether. The resulting solid is collected, washed with diethyl ether and dried to give 0.042 g of the desired product.

MS(FAB): m/z 506 (M+H).

¹H NMR(D₆-DMSO): δ 12.1(s,1H), 10.4(bs,1H), 9.75(s,1H), 9.55(s,1H), 9.05(s,1H), 8.05(d,1H), 6.8(d,1H), 4.4(s,2H), 4.3(s,1H), 2.8(s,6H).

Example 5

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

The title compound is prepared by the procedure of Example 1, using 2.11 g of 9-amino-4-(dimethylamino)-6-demethyl-6-deoxytetracycline monosulfate, 0.7 g of sodium carbonate, 20 ml of DMPU, 8 ml of acetonitrile and 1.73 g of 2-bromopropionyl bromide. The reaction is stirred for 1 hour to give 1.75 g of the desired product. This reaction works equally well without sodium carbonate.

MS(FAB): m/z 564 (M+H).

Example 6

[4S-(4α,12α)]-4-(Dimethylamino)-9-[[hexylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide dihydrochloride

A mixture of 0.23 g of product from Example 2, 0.80 g of n-hexylamine and 5 ml of DMPU, under argon, is stirred at room temperature for 2 hours. The reaction is concentrated in vacuo and the residue diluted with a small volume of methanol. The diluted reaction solution is added dropwise to a mixture of 10 ml of isopropyl alcohol and 100 ml of diethyl ether. 2M hydrochloric acid in diethyl ether is added until a yellow solid is observed. The resulting solid is

collected, washed with diethyl ether and dried to give 0.14 g of the desired product.

MS(FAB): m/z 571 (M+H).

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Substantially following the methods described in detail herein above in Example 6, the compounds of this invention listed below in Examples 7 - 22 are prepared.

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Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS (FAB): m/z
7	[4S-(4alpha,12alpha)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methylamino)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2	Methylamine (40% in water)	2.5 hrs.	501 (M+H)
8	[4S-(4alpha,12alpha)]-4-(Dimethylamino)-9-[[(ethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2	Ethylamine (70% in water)	0.5 hr.	515 (M+H)
9	[7S-(7alpha,10alpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride	2	Pyrrolidine	0.5 hr.	541 (M+H)
10	[7S-(7alpha,10alpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride	2	4-Methyl- piperidine	1.5 hr.	569 (M+H)
11	[4S-(4alpha,12alpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	2	Propylamine	1 hr.	529 (M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
12	[4S-(4alpha,12aalpha)]-9-[[[Butyl-amino)acetyl]amino]-4-(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	1 or 3	n-Butylamine	2 hr.	543 (M+H)
13	[4S-(4alpha,12aalpha)]-4-(Dimethyl-amino)-9-[[[2-(dimethylamino)-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	5	Dimethylamine	2 hr.	529 (M+H)
14	[4S-(4alpha,12aalpha)]-4-(Dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[pentylamino)acetyl]amino]-2-naphthacenecarboxamide monohydrochloride	1	Amylamine	2 hr.	557 (M+H)
15	[7S-(7alpha,10aalpha)]-N-9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-1-piperidineacetamide dihydrochloride	3	Piperidine	1 hr.	555 (M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS (FAB): m/z
16	[4S-(4alpha,12aalpha)]-4-(Dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octa-hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethyl)amino]-acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	3	Benzylamine	1 hr.	577 (M+H)
17	[4S-(4alpha,12aalpha)]-4-(Dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octa-hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-thienylmethyl)amino]-acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	1	2-Thiophene-methylamine	1 1/2 hr.	583 (M+H)
18	[4S-(4alpha,12aalpha)]-4-(Dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octa-hydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylpropyl)amino]acetyl]-amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	3	Isobutylamine	1 1/2 hr.	543 (M+H)
19	[4S-(4alpha,12aalpha)]-4-(Dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octa-hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl)amino]-acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	3	2-(Aminomethyl)pyridine	1 1/2 hr.	578 (M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
20	[4S-(4alpha,12aalpha)]-9-[[(Diethyl- amino) acetyl]amino]-4-(dimethylamino)- 1,4,4a,5,5a,6,11,12a-octahydro-3,10,- 12,12a-tetrahydroxy-1,11-dioxo-2- naphthacenecarboxamide dihydrochloride	3	Diethylamine	1 1/2 hr.	543 (M+H)
21	[7S-(7alpha,10aalpha)]-N-9-(Aminocar- bonyl)-7-(dimethylamino)-5,5a,6,6a,7,- 10,10a,12-octahydro-1,8,10a,11-tetra- hydroxy-10,12-dioxo-2-naphthacenyl]- alpha-methyl-1-pyrrolidinecarboxamide	5	Pyrrolidine	1 hr.	555 (M+H)
22	[4S-(4alpha,12aalpha)]-9-[[[(Cyclo- propylmethyl)amino]acetyl]amino]-4- (dimethylamino)-1,4,4a,5,5a,6,11,12a- tetrahydroxy-1,11-dioxo-2-naphthacene- carboxamide dihydrochloride	3	(Aminomethyl) cyclopropane	1 hr.	541 (M+H)

Example 23

[4S-(4 α ,12 α)]-4-(Dimethylamino)-9-[[[(dimethyl-
amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,
10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarbox-
amide
sulfate, dihydrochloride, monohydrochloride
or free base

A mixture of 0.264g of 9-amino-6-demethyl-6-deoxytetracycline, obtained by literature procedures, 5 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone, 2 ml of acetonitrile and 0.3 g of sodium carbonate is stirred at room temperature for 5 minutes. To this mixture is added 0.094 g of N,N-dimethylglycyl chloride hydrochloride. The reaction is allowed to stir for 30 minutes at room temperature and then filtered. The filtrate is added dropwise to approximately 300 ml of diethyl ether containing a few drop of either concentrated sulfuric or hydrochloric acid. The resulting precipitate is collected, washed with diethyl ether and dried to yield 0.12 g of the desired product.

The hydrochloride salt is converted, by treatment with ammonium hydroxide, to the free base. MS(FAB): m/z 515 (M+H).

Alternatively, the title compound is prepared by the procedure of Example 3, using 0.2 g of product from Example 1, 2, 3 or 4, 1.25 g of dimethylamine (40% in water) and 5 ml of DMPU to give 0.14 g of the desired product.

Example 24

General Procedure for the Preparation of Mannich Bases.

A mixture of 0.5 mm of product from Example 20 (free base), 3 ml of t-butyl alcohol, 0.55 mm of 37% formaldehyde, and 0.55 mm of pyrrolidine, morpholine or piperidine is stirred at room temperature for 30 minutes followed by heating at 100°C for 15 minutes. The reaction mixture is cooled to room temperature and triturated with diethyl ether and hexane. The solid is

collected, washed with diethyl ether and hexane, and dried to give the desired product.

In this manner the following compound is made:

5 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-pyrrolidinylmethyl)-2-naphthacenecarboxamide

10 Substantially following the method described in Example 6, the compounds of this invention listed below in Examples 25-48 are prepared using the product from Example 3 or 4.

Example 25

15 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methoxyamino)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide

Example 26

20 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethoxy)amino]acetyl]amino]-2-naphthacenecarboxamide

Example 27

25 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-ethyl-1H-pyrazole-1-acetamide

Example 28

30 [4S-(4alpha,12aalpha)]-9-[[(Cyclobutylmethylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Example 29

5 [4S-(4alpha,12aalpha)]-9-[[(2-Butenylamino)acetyl]-
amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octa-
hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphtha-
cenecarboxamide

Example 30

10 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-9-[[(hydroxyamino)acetyl]amino]-1,11-
dioxo-2-naphthacenecarboxamide

Example 31

15 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-9-[[[methyl(phenylmethyl)amino]-
acetyl]amino]-2-naphthacenecarboxamide

Example 32

20 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaceny]-
5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-acetamide

Example 33

25 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaceny]-
3-methyl-4-morpholineacetamide

Example 34

30 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaceny]-
2-azabicyclo[2.2.1]heptane-2-acetamide

Example 35

35 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaceny]-
6-methyl-2-azabicyclo[2.2.2]octane-2-acetamide

Example 36

5 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 4-methyl-1-piperazinecarboxamide

Example 37

10 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 4-hydroxy-1-piperazineacetamide

Example 38

15 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 3-methyl-1-piperazinecarboxamide

Example 39

20 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 3-cyclopropyltetrahydro-4H-thiazine-4-acetamide

Example 40

25 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 3-ethyl-1H-pyrrole-1-acetamide

Example 41

30 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
 hydroxy-9-[[(1H-imidazol-2-ylmethylamino) acetyl]-
 amino]-1,11-dioxo-2-naphthacenecarboxamide

Example 42

35 [7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 amino]-2-oxoethyl]alanine

Example 43

5 [7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 amino]-2-oxoethyl]carbamic acid 1,1-dimethylethyl ester

Example 44

10 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
 hydroxy-9-[[[(2-methylcyclopropyl)oxy]amino]acetyl]-
 amino]-1,11-dioxo-2-naphthacenecarboxamide

Example 45

15 [4S-(4alpha,12aalpha)]-9-[[[(Bicyclo[2.2.2]oct-
 2-yloxy)amino]acetyl]amino]-4-(dimethylamino)-
 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
 hydroxy-1,11-dioxo-2-naphthacenecarboxamide

Example 46

20 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
 hydroxy-9-[[[(3-methyl-2-butenyl)amino]acetyl]amino]-
 1,11-dioxo-2-naphthacenecarboxamide

Example 47

25 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
 hydroxy-9-[[[4-[(2-methyl-1-oxopropyl)amino]phenyl]-
 amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide

Example 48

30 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 3-ethyl-1-pyrrolidineacetamide

35 Substantially following the method described
 in Example 6, the compounds of this invention listed
 below in Examples 49-55 are prepared using the product
 from Example 5.

Example 49

5 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-9-[[2-[(1-methyl-1H-imidazol-2-yl)methyl]-
amino]-1-oxopropyl]amino]-1,11-dioxo-2-naphthacene-
carboxamide

Example 50

10 [4S-(4alpha,12aalpha)]-9-[[2-(Dicyclopropylamino)-
1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-
11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide

Example 51

15 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
4-methoxy- α -methyl-1-piperazinecarboxamide

Example 52

20 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
tetrahydro- α ,2-dimethyl-4H-1,4-thiazine-4-acetamide

Example 53

25 [7S-(7alpha,10aalpha)]-[2-[[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
amino]-2-oxo-1-methylethyl]carbamic acid 2-propenyl
ester

Example 54

30 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
4-(aminomethyl)- α -methyl-1-piperidineacetamide

35

Example 55

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-9-[[2-[[3-(methylsulfonyl)phenyl]amino]-
1-oxopropyl]amino]-1,11-dioxo-2-naphthacenecarboxamide

Substantially following the method, described
in detail herein above in Example 5, the compound of
invention Example 56 is prepared.

Example 56

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-2-methyl-
1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide

Example 57

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-
[[2-methyl-2-(methylamino)-1-oxopropyl]amino]-1,11-
dioxo-2-naphthacenecarboxamide

The titled compound is prepared by the
procedure of Example 6. The reactants are the product
from Example 56 and methylamine.

Example 58

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[2-(dimethylamino)-2-methyl-1-oxopropyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide

The titled compound is prepared by the
procedure of Example 6. The reactants are the product
from Example 56 and dimethylamine.

Substantially following the method, described
in detail herein above in Example 5, the compound of
invention Example 59 is prepared.

Example 59

[4S-(4alpha,12alpha)]-9-[(2-Bromo-1-oxobutyl)amino]-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide hydrobromide

Example 60

[4S-(4alpha,12alpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-
[(3-methylcyclobutyl)oxylamino]-1-oxobutyl]amino]-
1,11-dioxo-2-naphthacenecarboxamide hydrobromide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 59 and methylcyclobutyloxyamine.

Example 61

[4S-(4alpha,12alpha)]-9-[[2-[(1,1-dimethylethyl)-
methylamino]-1-oxobutyl]amino]-4-(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 59 and N-methyl-t-butylamine.

Example 62

[7S-(7alpha,10alpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -ethyl-4-methyl-2-isoxazolidineacetamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 59 and 4-methyl-2-isoxazolidine.

Example 63

[7S-(7alpha,10alpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -ethyl-3-methyl-4H-1,2,4-triazole-4-acetamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 59 and 3-methyl-1,2,4-triazole.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 64 is prepared.

5

Example 64

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopentyl)amino]-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide hydrobromide

10

Example 65

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[2-(dimethylamino)-3,3-dimethyl-1-oxobutyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide

15

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 64 and dimethylamine.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 66 is prepared.

20

Example 66

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxobutyl)amino]-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
hydrobromide

25

Example 67

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[2-(ethylamino)-2-methyl-1-oxobutyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide

30

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 66 and ethylamine.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 68 is prepared.

35

Example 68

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-3-hydroxy-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide

Example 69

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[2-(dimethylamino)-3-hydroxy-1-oxopropyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 68 and dimethylamine.

Example 70

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
alpha-(hydroxymethyl)-4-methyl-1H-imidazole-1-acetamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 68 and 4-methylimidazole.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 71 is prepared.

Example 71

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-3-mercapto-
1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide

Example 72

[4S-(4alpha,12aalpha)]-9-[[2-(Diethylamino)-
3-mercapto-1-oxopropyl]amino]-4-(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 71 and diethylamine.

Example 73

5 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10-12-dioxo-2-naphthacenyl]-
 alpha-(mercaptomethyl)-1-piperazineacetamide

Substantially following the method, described
in detail herein above in Example 5, the compound of
invention Example 74 is prepared.

10

Example 74

[7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10-12-dioxo-2-naphthacenyl]-
 amino]-3-bromo-4-oxobutanoic acid hydrobromide

15

Example 75

[7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 amino]-3-(hexylamino)-4-oxobutanoic acid

20

The titled compound is prepared by the proce-
dure by Example 6. The reactants are the product from
Example 74 and n-hexylamine.

Example 76

25 [7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 amino]tetrahydro-6-(hydroxymethyl)-2H-1,2-isoxazine-
 2-propanoic acid

30

The titled compound is prepared by the proce-
dure of Example 6. The reactants are the product from
Example 74 and 6-(hydroxymethyl)-1,2-isoxazine.

Example 77

35 [7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-
 7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 amino]-3-[ethyl(phenylmethyl)amino]-4-oxobutanoic acid

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 74 and N-ethylbenzylamine.

5 Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 78 is prepared.

Example 78

10 [7S-(7alpha,10alpha)]-5-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaceny]]-amino]-4-bromo-5-oxopentanoic acid hydrobromide

Example 79

15 [7S-(7alpha,10alpha)]-5-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthaceny]]-amino]-4-(cyclopropylamino)-5-oxopentanoic acid

20 The titled compound is prepared by procedure of Example 6. The reactants are the product from Example 78 and cyclopropylamine.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 80 is prepared.

Example 80

25 [4S-(4alpha,12alpha)]-9-[(Bromophenylacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide hydrobromide

Example 81

30 [4S-(4alpha,12alpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-phenylacetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

35 The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 80 and dimethylamine.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 82 is prepared.

Example 82

[4S-(4alpha,12aalpha)]-9-[[Bromo(4-hydroxyphenyl)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

Example 83

[4S-(4alpha,12aalpha)]-9-[[(Butylamino) (4-hydroxyphenyl) acetyl] amino]-4-(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 80 and dimethylamine.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 84 is prepared.

Example 84

[4S-(4alpha,12aalpha)]-9-[[Bromo(4-methoxyphenyl)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

Example 85

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[2-(dimethylamino)-3-(4-methoxyphenyl)-1-oxopropyl]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacenecarboxamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 84 and dimethylamine.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 86 is prepared.

Example 86

[4S-(4alpha,12aalpha)]-9-[[Bromo[4-(trifluoromethyl)-
phenyl]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-
11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide

Example 87

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-
(ethylmethylanino)-3-[4-(trifluoromethyl)phenyl]-
1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide

The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 86 and N-ethylmethylanine.

Substantially following the method, described in detail herein above in Example 5, the compound of invention Example 88 is prepared.

Example 88

[4S-(4alpha,12aalpha)]-9-[[Bromo[4-(dimethylamino)-
phenyl]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-
11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide

Example 89

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[[4-(dimethylamino)phenyl](2-propenylanino)acetyl]-
amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

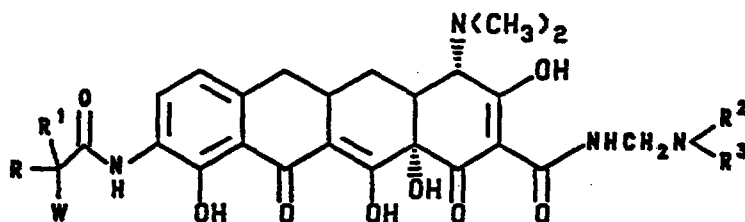
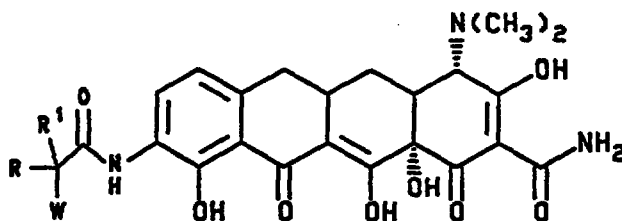
The titled compound is prepared by the procedure of Example 6. The reactants are the product from Example 88 and N-allylanine.



31,925

We Claim:

1. A compound of the formula:



wherein:

R is selected from hydrogen; straight or branched (C₁-C₈)alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C₁-C₄)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl, α-mercaptopropyl and α-mercaptobutyl; α-hydroxy(C₁-C₄)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl, α-hydroxypropyl and α-hydroxybutyl; carboxyl(C₁-C₈)alkyl group; (C₆-C₁₀)aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C₆-C₁₀)aryl group (substitution selected from hydroxy, halogen, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)alkoxycarbonyl, (C₁-C₃)alkylamino and carboxy); (C₇-C₉)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted(C₇-C₉)aralkyl group [substi-

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tution selected from halo, (C₁-C₄)alkyl, nitro, hydroxy, amino, mono- or di-substituted (C₁-C₄)alkyl-amino, (C₁-C₄)alkoxy, (C₁-C₄)alkylsulfonyl, cyano and carboxy];

R¹ is selected from hydrogen and (C₁-C₆)alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R does not equal R¹ the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; hydroxylamino; (C₁-C₁₂) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C₃-C₈)cycloalkyl

monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C₃-C₈)cycloalkyl monosubstituted amino group; [(C₄-C₁₀)cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C₃-C₁₀)alkenyl

monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl



2-cyclopentenyl and 2-cyclohexenyl; (C₆-C₁₀)aryl
monosubstituted amino group substitution selected from
phenyl and naphthyl; (C₇-C₁₀)aralkylamino group
5 substitution selected from benzyl, 2-phenylethyl,
1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl
and phenylpropyl; substituted (C₆-C₁₀)aryl
monosubstituted amino group [substitution selected from
(C₁-C₅)acyl, (C₁-C₅)acylamino, (C₁-C₄)alkyl, mono or
10 disubstituted (C₁-C₈)alkylamino, (C₁-C₄)alkoxy,
(C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkylsulfonyl, amino,
carboxy, cyano, halogen, hydroxy, nitro and trihalo
(C₁-C₃)alkyl]; straight or branched symmetrical
disubstituted (C₂-C₁₄)alkylamino group substitution
15 selected from dimethyl, diethyl, diisopropyl,
di-n-propyl, di-n-butyl and diisobutyl; symmetrical
disubstituted (C₃-C₁₄)cycloalkylamino group
substitution selected from dicyclopropyl, dicyclobutyl,
dicyclopentyl, dicyclohexyl and dicycloheptyl; straight
20 or branched unsymmetrical disubstituted (C₃-C₁₄)alkyl-
amino group wherein the total number of carbons in the
substitution is not more than 14; unsymmetrical
disubstituted (C₄-C₁₄)cycloalkylamino group wherein the
total number of carbons in the substitution is not more
25 than 14; (C₂-C₈)azacycloalkyl and substituted
(C₂-C₈)azacycloalkyl group substitution selected from
aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, 4-
methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-di-
methylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl,
30 2-azabicyclo[2.1.1] hex-2-yl, 5-azabicyclo[2.1.1]hex-
5-yl, 2-azabicyclo [2.2.1]hept-2-yl, 7-azabicyclo-
[2.2.1]hept-7-yl, and 2-azabicyclo[2.2.2]oct-2-yl and
the diastereomers and enantiomers of said (C₂-C₈)aza-
cycloalkyl and substituted (C₂-C₈)azacycloalkyl group;
35 1-aza-oxacycloalkyl group selected from morpholinyl and
1-aza-5-oxocycloheptane; substituted 1-aza-oxacycloalkyl
group substitution selected from 2-(C₁-C₃)alkylmorpho-
linyl, 3-(C₁-C₃)alkylisoxazolidinyl, tetrahydrooxazinyl



and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from

5 piperazinyl, 2-(C₁-C₃)alkylpiperazinyl, 4-(C₁-C₃)alkyl-
piperazinyl, 2,4-dimethylpiperazinyl, 4-(C₁-C₄)alkoxy-
piperazinyl, 4-(C₆-C₁₀)aryloxypiperazinyl, 4-hydroxy-
piperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-di-
aza-5-methylbicyclo[2.2.1]hept-2-yl, 2,3-diaza-3-
methylbicyclo[2.2.2]oct-2-yl, and 2,5-diaza-5,7-di-
10 methylbicyclo[2.2.2]oct-2-yl and the diastereomers or
enantiomers of said [1,n]-diazacycloalkyl and
substituted [1,n]-diazacycloalkyl group;

1-azathiacycloalkyl and substituted 1-azathiacycloalkyl
group selected from thiomorpholinyl, 2-(C₁-C₃)alkyl-
15 thiomorpholinyl and 3-(C₃-C₆)cycloalkylthiomorpholinyl;
N-azolyl and substituted N-azolyl group selected from
1-imidazolyl, 2-(C₁-C₃)alkyl-1-imidazolyl, 3-(C₁-C₃)
alkyl-1-imidazolyl, 1-pyrrolyl, 2-(C₁-C₃)alkyl-1-
pyrrolyl, 3-(C₁-C₃)alkyl-1-pyrrolyl, 1-pyrazolyl,
20 3-(C₁-C₃)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-tria-
zolyl), 4-(C₁-C₃)alkyl-1-(1,2,3-triazolyl), 5-(C₁-C₃)-
alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl,
1-tetrazolyl, 2-tetrazolyl and benzimidazolyl;
(heterocycle)amino group selected from 2- or
25 3-furanylamino, 2- or 3-thienylamino, 2-, 3- or
4-pyridylamino, 2- or 5-pyridazinylamino, 2-pyrazinyl-
amino, 2-(imidazolyl)amido, (benzimidazolyl)amino, and
(benzothiazolyl)amino and substituted (heterocycle)-
amino group as defined above with substitution selected
30 from straight or branched (C₁-C₆)alkyl; (heterocycle)-
methylamino group selected from 2- or 3-furylmethyl-
amino, 2- or 3-thienylmethyl- amino, 2-, 3- or
4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino,
2-pyrazinylmethylamino, 2-(imidazolyl)methylamino,
35 (benzimidazolyl)methylamino, and (benzothiazolyl)
methylamino and substituted (heterocycle)methylamino
group as defined above with substitution selected from
straight or branched (C₁-C₆)alkyl;



carboxy(C_2-C_4)alkylamino group selected from
aminoacetic acid, α -aminopropionic acid,
 β -aminopropionic acid, α -butyric acid, and
5 β -aminobutyric acid and the enantiomers of said
carboxy(C_2-C_4)alkylamino group;

(C_1-C_4)alkoxycarbonylamino group substitution selected
from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl,
propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethyl-
10 ethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxy-
carbonyl; (C_1-C_4)alkoxyamino group substitution
selected from methoxy, ethoxy, n-propoxy, 1-methyl-
ethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethyl

ethoxy; (C_3-C_8)cycloalkoxyamino group selected from
15 cyclopropoxy, trans-1,2-dimethylcyclopropoxy,
cis-1,2-dimethylcyclopropoxy, cyclobutoxy,
cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy,
bicyclo[2.2.1]hept-2-yloxy, and bicyclo[2.2.2]oct-2-
yloxy and the diastereomers and enantiomers of said

(C_3-C_8)cycloalkoxyamino group; (C_6-C_{10})aryloxyamino
20 group selected from phenoxyamino, 1-naphthyloxyamino
and 2-naphthyloxyamino; (C_7-C_{11})arylalkoxyamino group
substitution selected from benzyloxy, 2-phenylethoxy,
1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)
25 methoxy and phenylpropoxy;

R^2 is selected from hydrogen; straight or branched
(C_1-C_3)alkyl group selected from methyl, ethyl,
n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected
from phenyl, α -naphthyl or β -naphthyl; (C_7-C_9)aralkyl
30 group; a heterocycle group selected from a five
membered aromatic or saturated ring with one N, O, S or
Se heteroatom optionally having a benzo or pyrido
ring fused thereto:



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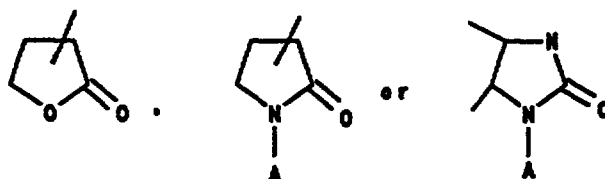
Z - N, O, S or Se

or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z' - N, O, S or Se

or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

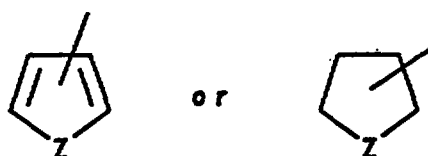


(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitution selected from halo, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

or a six membered aromatic ring with one to three N heteroatoms, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom; or $-(CH_2)_nCOOR^4$ where n=0-4 and R⁴ is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C₆-C₁₀)aryl group selected from phenyl, α -naphthyl, or β -naphthyl;



R^3 is selected from hydrogen; straight or branched
(C_1-C_3)alkyl group selected from methyl, ethyl,
n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected
from phenyl, α -naphthyl or β -naphthyl; (C_7-C_9)aralkyl
group; a heterocycle group selected from a five
membered aromatic or saturated ring with one N, O, S or
Se heteroatom optionally having a benzo or pyrido ring
fused thereto:



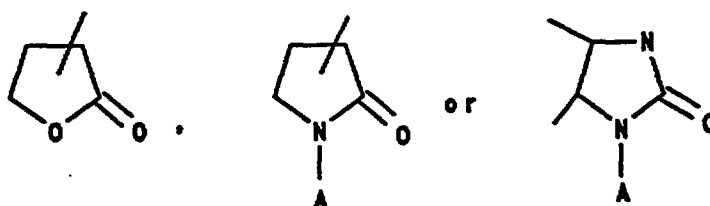
Z = N, O, S, or Se

or a five membered aromatic ring with two N, O, S or Se
heteroatoms optionally having a benzo or pyrido ring
fused thereto:



Z or Z' = N, O, S or Se

or a five membered saturated ring with one or two N, O,
S or Se heteroatoms and an adjacent appended O
heteroatom:





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(A is selected from hydrogen; straight or branched
(C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl
(substitution selected from halo, (C₁-C₄)alkoxy,
5 trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-
alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-
aralkyl group selected from benzyl, 1-phenylethyl,
2-phenylethyl or phenylpropyl)

10 or a six membered aromatic ring with one to three N
heteroatoms, or a six membered saturated ring with one
or two N, O, S or Se heteroatoms and an adjacent
appended O heteroatom; or -(CH₂)_nCOOR⁴ where n=0-4 and
R⁴ is selected from hydrogen; straight or branched
15 (C₁-C₃)alkyl selected from methyl, ethyl, n-propyl or
1-methylethyl; or (C₆-C₁₀)aryl selected from phenyl,
α-naphthyl or β-naphthyl; with the proviso that R² and
R³ cannot both be hydrogen;
or R² and R³ taken together are -(CH₂)₂B(CH₂)₂-,
20 wherein B is selected from (CH₂)_n and n=0-1, -NH,
-N(C₁-C₃)alkyl [straight or branched], -N(C₁-C₄)alkoxy,
oxygen, sulfur or substituted congeners selected from
(L or D)proline, ethyl(L or D)prolinate, morpholine,
pyrrolidine or piperidine; and the pharmacologically
25 acceptable organic and inorganic salts or metal
complexes.

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2. The compound according to Claim 1,
wherein:

R is selected from hydrogen; straight or branched
(C₁-C₂)alkyl group selected from methyl and ethyl;
R¹ selected from hydrogen or (C₁-C₂)alkyl selected from
methyl and ethyl;

25

when R does not equal R¹ the stereochemistry of the
asymmetric carbon (i.e. the carbon bearing the W
substituent) maybe be either the racemate (DL) or the
individual enantiomers (L or D);

30

W is selected from amino; (C₁-C₈) straight or branched
alkyl monosubstituted amino group substitution selected
from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl, n-hexyl and n-octyl;

35

(C₃-C₆)cycloalkyl monosubstituted amino group
substitution selected from cyclopropyl, cyclopentyl and
cyclohexyl; [(C₄-C₅)cycloalkyl]alkyl monosubstituted
amino group substitution selected from (cyclopropyl)-
methyl and (cyclopropyl)ethyl; (C₃-C₄)alkenyl
monosubstituted amino group substitution selected from



allyl and 3-butenyl; (C₇-C₁₀)aralkylamino group
substitution selected from benzyl, 2-phenylethyl and
1-phenylethyl; straight or branched symmetrical
5 disubstituted (C₂-C₄)alkylamino group substitution
selected from dimethyl and diethyl; straight or
branched unsymmetrical disubstituted (C₃)alkylamino
group substitution selected from methyl(ethyl);
(C₂-C₅)azacycloalkyl group selected from pyrrolidinyl
10 and piperidinyl; 1-azaoxacycloalkyl group selected from
morpholinyl; substituted 1-azaoxacycloalkyl group
selected from 2-(C₁-C₃)alkylmorpholinyl; [1,n]-di-
azacycloalkyl and substituted [1,n]-diazacycloalkyl
group selected from piperazinyl, 2-(C₁-C₃)alkyl-
15 piperazinyl, 4-(C₁-C₃)alkylpiperazinyl, and
2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl and
the diastereomers and enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group;
1-azathiacycloalkyl and substituted 1-azathiacycloalkyl
20 group selected from thiomorpholinyl and
2-(C₁-C₃)alkylthiomorpholinyl; N-azolyl group selected
from 1-imidazolyl; (heterocycle)methylamino group
selected from 2- or 3-thienylmethylamino and 2-, 3- or
4-pyridylmethylamino; (C₁-C₄)alkoxycarbonylamino group
25 substitution selected from methoxycarbonyl,
ethoxycarbonyl, and 1,1-dimethylethoxycarbonyl;
R² is selected from hydrogen; straight or branched
(C₁-C₃)alkyl group selected from methyl, ethyl,
n-propyl or 1-methylethyl;
30 R³ is selected from hydrogen; straight or branched
(C₁-C₃)alkyl group selected from methyl, ethyl,
n-propyl or 1-methylethyl; with the proviso that R² and
R³ cannot both be hydrogen;
or R² and R³ taken together are -(CH₂)₂B(CH₂)₂-,
35 wherein B is selected from (CH₂)_n and n=0-1, -NH,
-N(C₁-C₃)alkyl [straight or branched], -N(C₁-C₄)alkoxy,
oxygen, sulfur or substituted congeners selected from
(L or D)proline, ethyl(L or D)prolinate, morpholine,



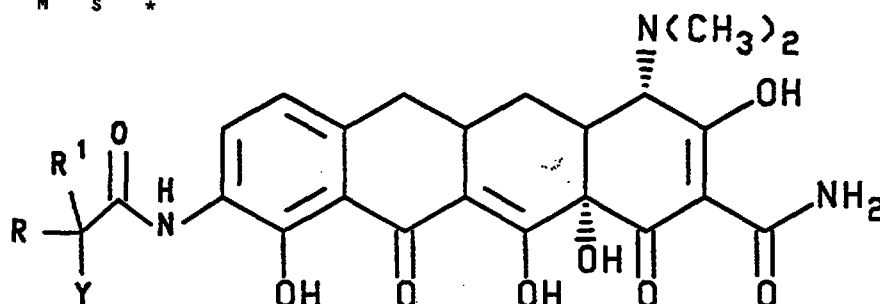
pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

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- 3 - A compound of the formula:



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wherein:

Y is selected from $(CH_2)_nX$, $n = 0-5$, X is halogen selected from bromine, chlorine, fluorine and iodine;

20

R is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-

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methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl;

30

carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl;

substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) alkoxycarbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group

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selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group [substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4) alkyl-



amino, (C₁-C₄)alkoxy, (C₁-C₄)alkylsulfonyl, cyano and carboxy];

R¹ is selected from hydrogen and (C₁-C₆)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R does not equal R¹ the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salt or metal complexes.

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* C L M S *

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4 The compound according to Claim 3,

wherein:

Y is selected from $(CH_2)_nX$, $n = 0-5$, X is halogen
selected from bromine, chlorine, fluorine and iodine;

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R is selected from hydrogen; straight or branched
 (C_1-C_2) alkyl group selected from methyl and ethyl;

R^1 is selected from hydrogen and (C_1-C_2) alkyl selected
from methyl and ethyl;



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when R does not equal R¹ the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the W substituent) may be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salt or metal complexes.

5 The compound according to Claim 1 wherein said salts comprise: hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate,

10 acetate, benzoate, citrate, cysteine or other amino acid, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate, and

15 said metal complexes comprise: aluminum, calcium, iron, magnesium, manganese and complex salts.

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30 6 A compound according to Claim 1, [4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methylamino)acetyl]amino]-1,11-dioxo-2-naphthacene-carboxamide dihydrochloride;

35 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[(ethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octa-





hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenicarboxamide dihydrochloride;

- 5 [7S-(7alpha,10aalpha)]-N-[9-(aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride;
- 10 [7S-(7alpha,10aalpha)]-N-[9-(aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride;
- 15 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino) acetyl] amino]-2-naphthacenecarboxamide dihydrochloride;
- 20 [4S-(4alpha,12aalpha)]-9-[[(butylamino) acetyl] amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;
- 25 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[2-(dimethylamino)-1-oxo-propyl] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;
- 30 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino) acetyl] amino]-2-naphthacene-carboxamide monohydrochloride;
- 35 [7S-(7alpha,10aalpha)]-N-[9-(aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-piperidineacetamide dihydrochloride;



- 5 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[[(phenylmethyl)amino]acetyl]amino]-2-
naphthacenecarboxamide dihydrochloride;
- 10 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[[(2-thienylmethyl)amino]acetyl]amino]-2-
naphthacenecarboxamide dihydrochloride;
- 15 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-
[[[(2-methylpropyl)amino]acetyl]amino]-1,11-dioxo-2-
naphthacenecarboxamide dihydrochloride;
- 20 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[[(2-pyridinylmethyl)amino]acetyl]amino]-2-
naphthacenecarboxamide dihydrochloride;
- 25 [4S-(4alpha,12aalpha)]-9-[[[(dimethylamino)acetyl]-
amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octa-
hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide dihydrochloride;
- 30 [7S-(7alpha,10aalpha)]-N-[9-(aminocarbonyl)-7-(di-
methylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-
10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
alpha-methyl-1-pyrrolidinecarboxamide;
- 35 [4S-(4alpha,12aalpha)]-9-[[[(cyclopropylmethyl)amino]-
acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide di-
hydrochloride;



- 5 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[(dimethyl-
amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,
10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarbox-
amide sulfate;
- 10 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[(dimethyl-
amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,
10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarbox-
amide dihydrochloride;
- 15 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[(dimethyl-
amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,
10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarbox-
amide monohydrochloride;
- 20 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[(dimethyl-
amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,
10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarbox-
amide;
- 25 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[(dimethyl-
amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,
10,12,12a-tetrahydroxy-1,11-dioxo-N-(1-pyrrolidinyl-
methyl)-2-naphthacenecarboxamide;
- 30 [4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[(hexyl-
amino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide dihydrochloride;
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[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-9-[[(methoxyamino) acetyl] amino]-1,11-dioxo-
2-naphthacenecarboxamide;

30

[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-9-[[(phenylmethoxy) amino] acetyl]-
amino]-2-naphthacenecarboxamide;

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[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
4-ethyl-1H-pyrazole-1-acetamide;



- 5 [4S-(4alpha,12aalpha)]-9-[[(Cyclobutylmethylamino)-acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
- 10 [4S-(4alpha,12aalpha)]-9-[[(2-Butenylamino)acetyl]-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
- 15 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(hydroxyamino)acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;
- 20 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[methyl(phenylmethyl)amino]-acetyl]amino]-2-naphthacenecarboxamide;
- 25 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-acetamide;
- 30 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-methyl-4-morpholineacetamide;
- 35 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-2-azabicyclo[2.2.1]heptane-2-acetamide;



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[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-6-methyl-2-azabicyclo[2.2.2]octane-2-acetamide;

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[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperazinecarboxamide;

15

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-hydroxy-1-piperazineacetamide;

20

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-methyl-1-piperazinecarboxamide;

25

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-cyclopropyltetrahydro-4H-thiazine-4-acetamide;

30

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-ethyl-1H-pyrrole-1-acetamide;

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[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(1H-imidazol-2-ylmethylamino) acetyl]-amino]-1,11-dioxo-2-naphthacenecarboxamide;



- 5 [7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]-2-oxoethyl]alanine;
- 10 [7S-(7alpha,10aalpha)]-N-[2-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]-2-oxoethyl]carbamic acid 1,1-dimethylethyl ester;
- 15 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-methylcyclopropyl)oxy]amino]acetyl]-amino]-1,11-dioxo-2-naphthacenecarboxamide;
- 20 [4S-(4alpha,12aalpha)]-9-[[[(Bicyclo[2.2.2]oct-2-yloxy)amino]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
- 25 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methyl-2-butenyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;
- 30 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[4-[(2-methyl-1-oxopropyl)amino]phenyl]-amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;
- 35 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-3-ethyl-1-pyrrolidineacetamide;



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- 5 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-9-[[2-[(1-methyl-1H-imidazol-2-yl)methyl]-
amino]-1-oxopropyl]amino]-1,11-dioxo-2-naphthacene-
carboxamide;
- 10 [4S-(4alpha,12aalpha)]-9-[[2-(Dicyclopropylamino)-
1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-
11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide;
- 15 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
4-methoxy- α -methyl-1-piperazinecarboxamide;
- 20 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
tetrahydro- α ,2-dimethyl-4H-1,4-thiazine-4-acetamide;
- 25 [7S-(7alpha,10aalpha)]-[2-[[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
amino]-2-oxo-1-methylethyl]carbamic acid 2-propenyl
ester;
- 30 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
4-(aminomethyl)- α -methyl-1-piperidineacetamide;

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5 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-9-[[2-[[3-(methylsulfonyl)phenyl]amino]-
1-oxopropyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;

10 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-
[[2-methyl-2-(methylamino)-1-oxopropyl]amino]-1,11-
dioxo-2-naphthacenecarboxamide;

15 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[2-(dimethylamino)-2-methyl-1-oxopropyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide;

20 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[2-
[[3-methylcyclobutyl]oxy]amino]-1-oxobutyl]amino]-
1,11-dioxo-2-naphthacenecarboxamide hydrobromide;

25 [4S-(4alpha,12aalpha)]-9-[[2-[(1,1-dimethylethyl)-
methylamino]-1-oxobutyl]amino]-4-(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide;

30 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -ethyl-4-methyl-2-isoxazolidineacetamide;

35 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -ethyl-3-methyl-4H-1,2,4-triazole-4-acetamide;



- 5 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[2-(dimethylamino)-3,3-dimethyl-1-oxobutyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide;
- 10 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[2-(ethylamino)-2-methyl-1-oxobutyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide;
- 15 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-
9-[[2-(dimethylamino)-3-hydroxy-1-oxopropyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide;
- 20 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -(hydroxymethyl)-4-methyl-1H-imidazole-1-acetamide;
- 25 [4S-(4alpha,12aalpha)]-9-[[2-(Diethylamino)-
3-mercapto-1-oxopropyl]amino]-4-(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
hydroxy-1,11-dioxo-2-naphthacenecarboxamide;
- 30 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -(mercaptomethyl)-1-piperazineacetamide;
- 35 [7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
amino]-3-(hexylamino)-4-oxobutanoic acid;



- 5 [7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a-6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]tetrahydro-6-(hydroxymethyl)-2H-1,2-isoxazine-2-propanoic acid;
- 10 [7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]-3-[ethyl(phenylmethyl)amino]-4-oxobutanoic acid;
- 15 [7S-(7alpha,10aalpha)]-5-[[9-(Aminocarbonyl)-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino]-4-(cyclopropylamino)-5-oxopentanoic acid;
- 20 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(dimethylamino)-2-phenylacetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacenecarboxamide;
- 25 [4S-(4alpha,12aalpha)]-9-[[(Butylamino) (4-hydroxy-phenyl) acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
- 30 [4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[2-(dimethylamino)-3-(4-methoxyphenyl)-1-oxopropyl]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1-11-dioxo-2-naphthacenecarboxamide;
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[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[2-(ethylmethylamino)-3-[4-(trifluoromethyl)phenyl]-1-oxopropyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide; o₂

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[4S-(4alpha,12aalpha)]-4-(Dimethylamino)-9-[[[4-(dimethylamino)phenyl](2-propenylamino)acetyl]-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

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7 A compound according to Claim 3,
[4S-(4alpha,12aalpha)]-9-[(bromoacetyl)amino]-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
30 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
monohydrochloride;

[4S-(4alpha,12aalpha)]-9-[(chloroacetyl)amino]-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
35 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
monohydrochloride;



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[4S-(4alpha,12aalpha)]-9-[(bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide;

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[4S-(4alpha,12aalpha)]-9-[(bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monosulfate;

15

[4S-(4alpha,12aalpha)]-9-[(2-bromo-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide;

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[4S-(4alpha,12aalpha)]-9-[(2-Bromo-2-methyl-1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide;

30

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxobutyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide hydrobromide;

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- 5 [4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopentyl)amino]-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide hydrobromide;
- 10 [4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxobutyl)amino]-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
hydrobromide;
- 15 [4S-(4alpha,12aalpha)]-9-[(2-Bromo-3-hydroxy-1-
oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide;
- 20 [4S-(4alpha,12aalpha)]-9-[(2-Bromo-3-mercapto-
1-oxopropyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide;
- 25 [7S-(7alpha,10aalpha)]-4-[[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10-12-dioxo-2-naphthacenyl]-
amino]-3-bromo-4-oxobutanoic acid hydrobromide;
- 30 [7S-(7alpha,10aalpha)]-5-[[9-(Aminocarbonyl)-
7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a-11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
amino]-4-bromo-5-oxopentanoic acid hydrobromide;
- 35 [4S-(4alpha,12aalpha)]-9-[(Bromophenylacetyl)amino]-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide hydrobromide;



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[4S-(4alpha,12aalpha)]-9-[[Bromo(4-hydroxyphenyl)-
acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide;

10

[4S-(4alpha,12aalpha)]-9-[[Bromo(4-methoxyphenyl)-
acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide;

15

[4S-(4alpha,12aalpha)]-9-[[Bromo[4-(trifluoromethyl)-
phenyl]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-
11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide; OR

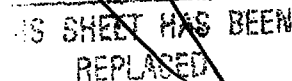
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[4S-(4alpha,12aalpha)]-9-[[Bromo[4-(dimethylamino)-
phenyl]acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,-
11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide hydrobromide.

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NC(=O)C1=C(O)C(=C2C(=C1)C(=O)C3=C(O)C(=C4C(=C2)C(=O)C(=C5C(=C4)C(=O)C(=C(O5)C(=O)N(C)C)C(=O)N(C)C)C(=O)N(C)C)C(=O)N(C)C)C(=O)N(C)C

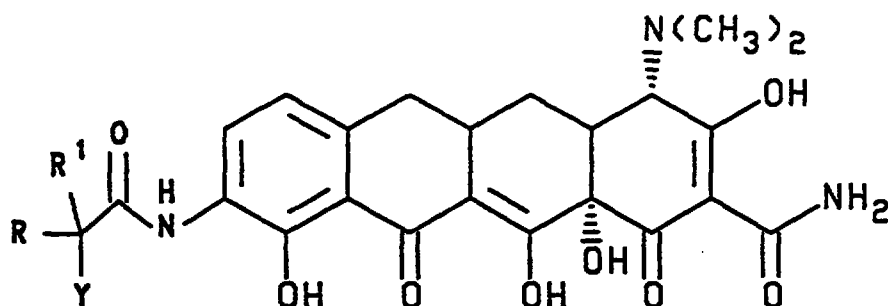
according to Claim 1, which comprises reacting a 9-[(haloacyl)amido]-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:

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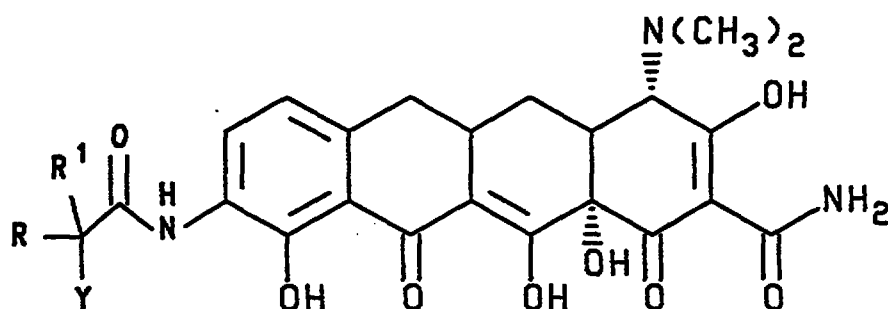


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15 according to Claim 3, with a nucleophile of the formula
WH, wherein W is as defined in Claim 1, in a
polar-aprotic solvent and in an inert atmosphere.

20 9. A method of producing a compound, or
its organic and inorganic salt or metal complex, of the
formula:



35 according to Claim 3, which comprises reacting
9-amino-6-demethyl-6-deoxytetracycline, or its organic
and inorganic salt or metal complex, of the formula:



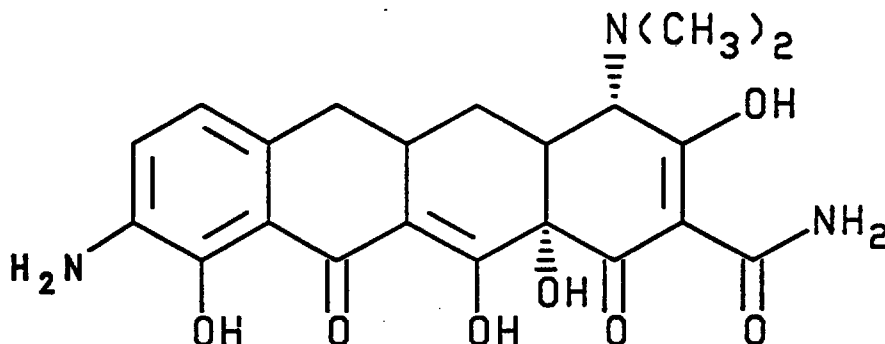


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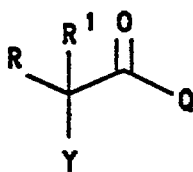
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with a straight or branched haloacyl halide of the
formula:

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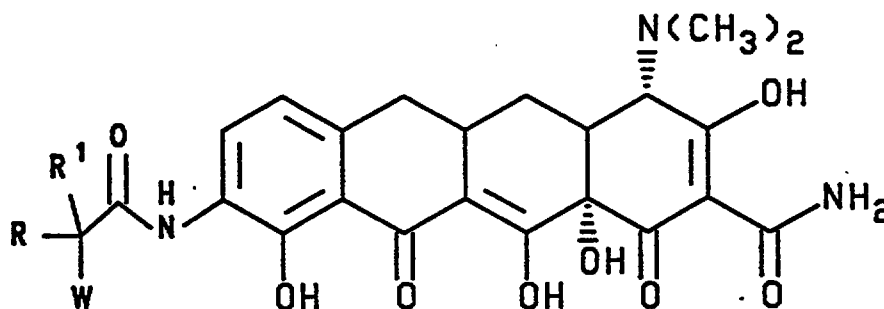
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wherein Y, R and R¹ are as defined in Claim 3 and Q is
halogen selected from bromine, chloride, iodine and
fluorine, in an inert solvent in a polar-aprotic
solvent and in the presence of a base.

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10. A method of producing a compound, or
its organic and inorganic salt or metal complex, of the
formula:

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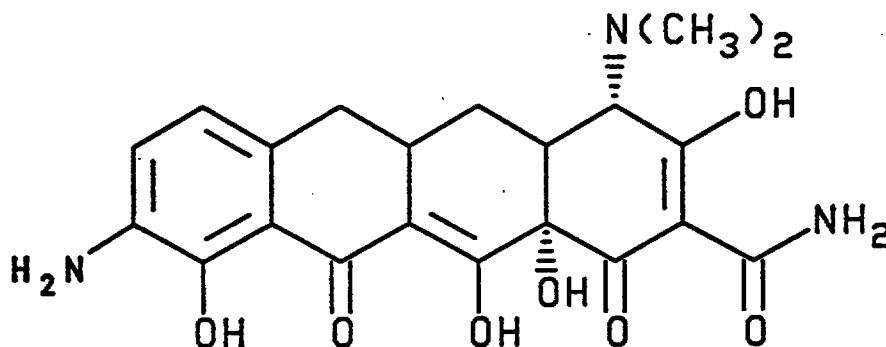


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according to Claim 1, which comprises reacting a
9-amino-6-demethyl-6-deoxytetracycline, or its organic
and inorganic salt or metal complex, of the formula:

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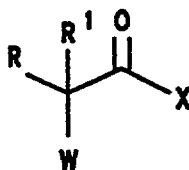
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with an acid chloride of the formula:

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wherein R, R¹, and W are as defined in Claim 1 and X is
halogen selected from bromine, chlorine, iodine and
fluorine, in an inert solvent in a polar-aprotic
solvent and in the presence of a base.

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11. A method for the prevention, 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 Claim 1.

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12. A pharmaceutical composition of matter comprising a pharmacologically effective amount of a compound according to Claim 1 in association with a pharmaceutically acceptable carrier.



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13 A veterinary composition which comprises a pharmacologically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

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14 A method for the prevention, treatment or control of bacterial infections in warm-blooded animals caused by bacteria having the TetM and TetK resistant determinants which comprises administering to said animal a pharmacologically effective amount of a compound according to Claim 1.

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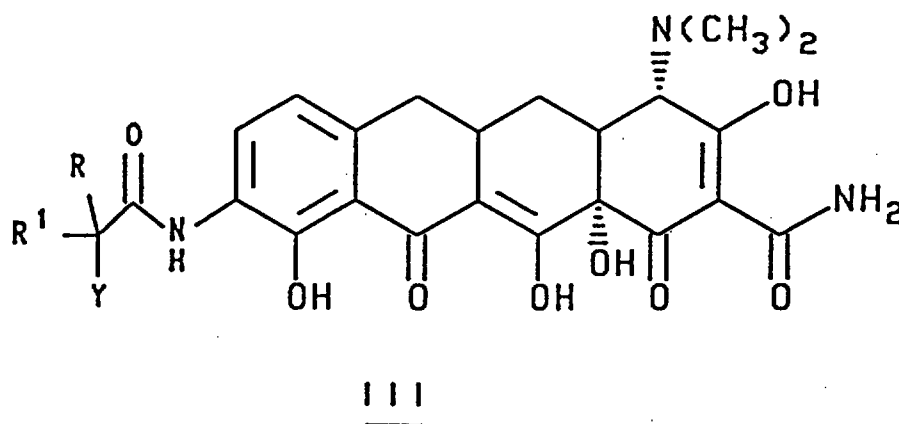


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REPLACEMENT SHEET

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wherein:

Y is selected from $(CH_2)_nX$, $n = 0$, X is halogen selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl;

α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl;

carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl;

substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) -alkyl, nitro, amino, cyano, (C_1-C_4) alkoxycarbonyl,

(C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group

[substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted

(C_1-C_4) alkylamino, (C_1-C_4) alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxy];

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R^1 is selected from hydrogen and (C_1-C_6) alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal complexes.

Preferred compounds are compounds according to the above formula III wherein:

Y is selected from $(CH_2)_nX$, $n = 0$, X is halogen selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl;

carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl;

substituted (C_7-C_9) aralkyl group [substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4) alkylamino, (C_1-C_4) alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxy];

R^1 is selected from hydrogen and (C_1-C_6) alkyl selected from methyl, ethyl propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the

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pharmacologically acceptable organic and inorganic salts and metal complexes.

Particularly preferred compounds are compounds according to the above formula III wherein:

Y is selected from $(CH_2)_nX$, $n = 0$, X is halogen selected from bromine, chlorine, fluorine and iodine; R is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl and α -mercaptopropyl; α -hydroxy- (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl and α -hydroxypropyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; R^1 is selected from hydrogen and (C_1-C_6) alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R does not equal R^1 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts and metal complexes.

Compounds of special interest are compounds according to the above formula III wherein:

Y is selected from $(CH_2)_nX$, $n = 0$, X is halogen selected from bromine, chlorine, fluorine and iodine; R is selected from hydrogen; straight or branched (C_1-C_2) alkyl group selected from methyl and ethyl; R^1 is selected from hydrogen and (C_1-C_2) alkyl selected from methyl and ethyl;

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when R does not equal R^1 the stereochemistry of the
asymmetric carbon (i.e. the carbon bearing the Y
substituent) maybe be either the racemate (DL) or the
individual enantiomers (L or D); and the
pharmacologically acceptable organic and inorganic
salts and metal complexes.

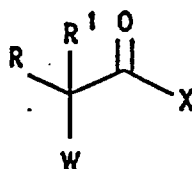
DESCRIPTION OF THE PREFERRED EMBODIMENTS

The novel compounds of the present invention
may be readily prepared in accordance with the
following schemes.

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The 9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracyclines, or mineral acid salts, can be made by the procedure described in scheme I. In accordance with scheme I, 9-amino-6-demethyl-6-deoxytetracycline or its mineral acid salt, 1, is dissolved in a mixture of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone and acetonitrile. Sodium carbonate is added and the mixture is stirred for 5 minutes. An acid halide of the formula:



wherein R, R¹, W and X have been described hereinabove is added and the reaction is stirred at room temperature for from 0.5-2 hours to give the corresponding 9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracycline, or its mineral acid salt 3.

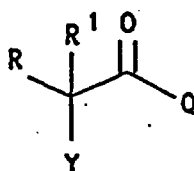
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b) an inert solvent such as acetonitrile, methylene chloride, tetrahydrofuran chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethane, diethyl ether, t-butyl methylether, isopropyl ether or equivalent thereof;

c) a base such as sodium carbonate, sodium bicarbonate, sodium acetate, potassium carbonate, potassium bicarbonate, triethylamine, cesium carbonate, lithium carbonate or bicarbonate equivalents; and

d) a straight or branched haloacyl halide of the formula:



wherein Y, R, R¹ and Q are as defined hereinabove such as bromoacetyl bromide, chloroacetyl chloride or 2-bromopropionyl bromide or equivalent thereof; the halo, Y, and halide, Q, in the haloacyl halide can be the same or different halogen and is selected from bromine, chlorine, iodine and fluorine; Y is (CH₂)_nX, n = 0, X is halogen;

e) for 0.5 to 5 hours at room temperature to the reflux temperature of the reaction; to form the corresponding 9-[(haloacyl)amido]-6-de-methyl-6-deoxy-tetracycline, 2, or its mineral acid salt.

The intermediate, 9-[(haloacyl)amido]-6-de-methyl-6-deoxytetracycline or mineral acid salt 2, is treated, under an inert atmosphere of helium, argon or nitrogen, with

a) a nucleophile WH such as an amine or substituted amine or equivalent for example methylamine, dimethylamine, ethylamine, n-butylamine, propylamine or n-hexylamine;

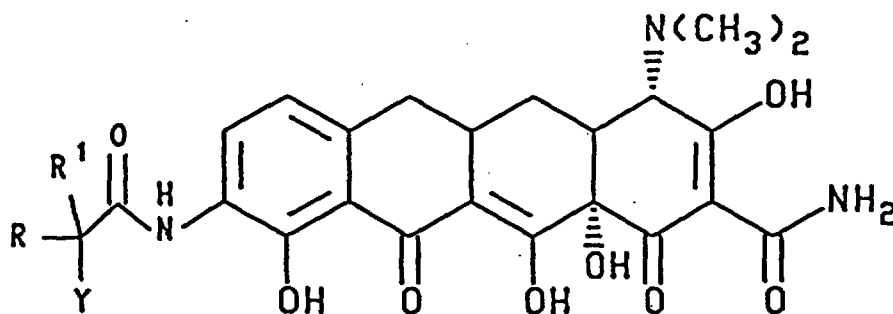


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pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

3. A compound of the formula:



wherein:

Y is selected from $(\text{CH}_2)_n\text{X}$, $n = 0$, X is halogen selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl;

carboxyl (C_1-C_8) alkyl group; $(\text{C}_6-\text{C}_{10})$ aryl group selected from phenyl, α -naphthyl and β -naphthyl;

substituted $(\text{C}_6-\text{C}_{10})$ aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) alkoxycarbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group

selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group [substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4) alkyl-



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amino, (C₁-C₄)alkoxy, (C₁-C₄)alkylsulfonyl, cyano and carboxy];

5 R¹ is selected from hydrogen and (C₁-C₆)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

10 when R does not equal R¹ the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salt or metal complexes.

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REPLACEMENT SHEET

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4. The compound according to Claim 3,
wherein:

Y is selected from $(CH_2)_nX$, $n = 0$, X is halogen
selected from bromine, chlorine, fluorine and iodine;

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R is selected from hydrogen; straight or branched
 (C_1-C_2) alkyl group selected from methyl and ethyl;
 R^1 is selected from hydrogen and (C_1-C_2) alkyl selected
from methyl and ethyl;



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when R does not equal R¹ the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salt or metal complexes.

5. The compound according to Claim 1 wherein said salts comprise: hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate,

acetate, benzoate, citrate, cysteine or other amino acid, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate, and

said metal complexes comprise: aluminum, calcium, iron, magnesium, manganese and complex salts.

6. A compound according to Claim 1, [4S-(4alpha,12aalpha)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(methylamino)acetyl]amino]-1,11-dioxo-2-naphthacene-carboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4-(dimethylamino)-9-[[(ethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octa-

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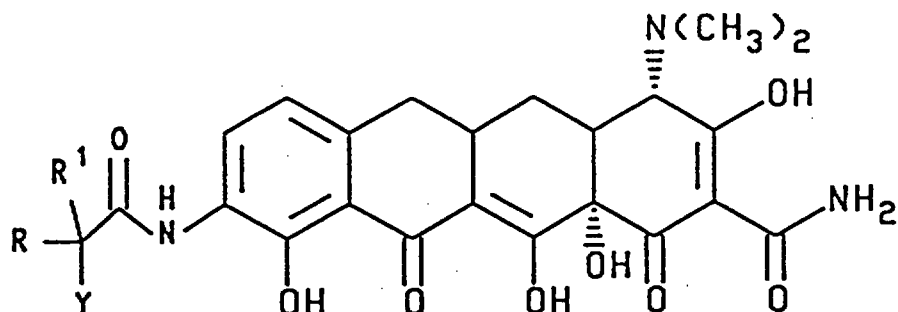
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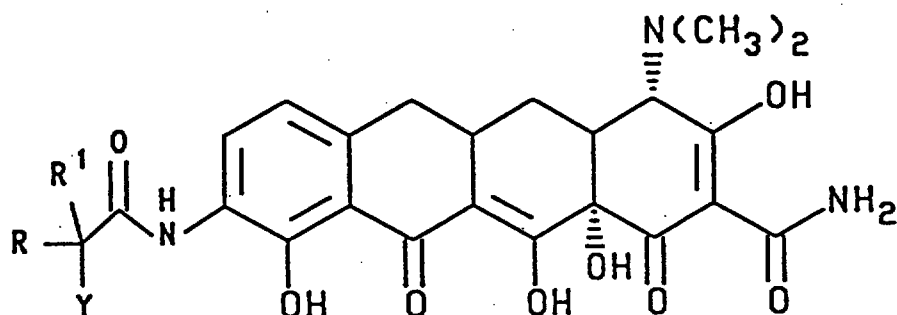
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15 according to Claim 3, with a nucleophile of the formula WH, wherein W is as defined in Claim 1, in a polar-aprotic solvent and in an inert atmosphere.

20 9. A method of producing a compound, or its pharmacologically acceptable organic and inorganic salt or metal complex, of the formula:

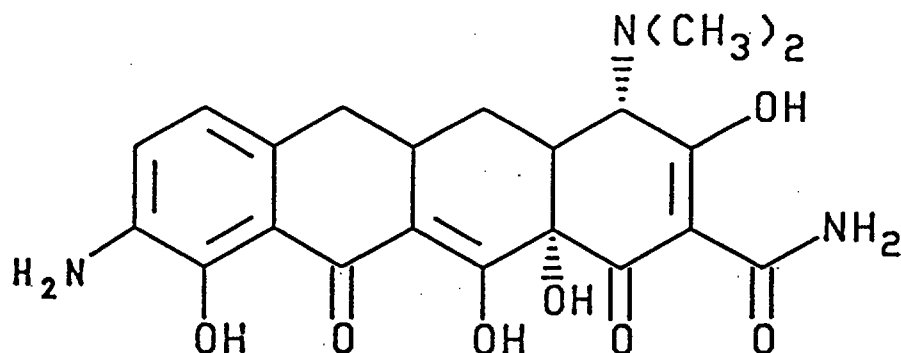


35 according to Claim 3, which comprises reacting 9-amino-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:

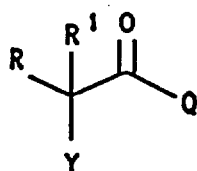


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with a straight or branched haloacyl halide of the formula:

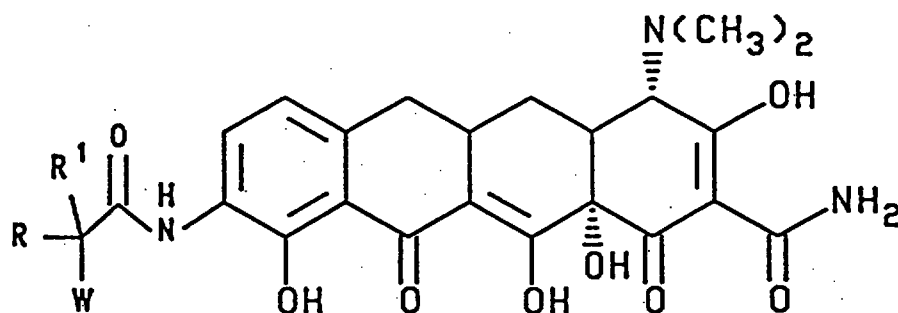


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wherein Y, R and R¹ are as defined in Claim 3 and Q is halogen selected from bromine, chloride, iodine and fluorine, in an inert solvent in a polar-aprotic solvent and in the presence of a base.

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10. A method of producing a compound, or its pharmacologically acceptable organic and inorganic salt or metal complex, of the formula:





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11. A pharmaceutical composition of matter comprising a pharmacologically effective amount of a compound according to Claim 1 in association with a pharmaceutically acceptable carrier.

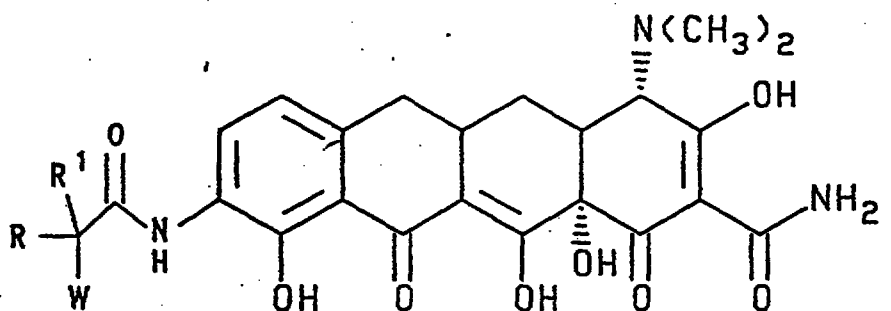
12. A veterinary composition which comprises a pharmacologically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

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9-[(SUBSTITUTED GLYCYL)AMIDO]-6-
DEMETHYL-6-DEOXYTETRACYCLINES

ABSTRACT OF THE INVENTION

The invention provides compounds of the
 formula:



wherein R, R¹ and W are defined in the specification.
 These compounds are useful as antibiotic agents.