



Title: 7-(SUBSTITUTED)-9-[(SUBSTITUTED
GLYCYL)AMIDO]-6-DEMETHYL-6-
DEOXYTETRACYCLINES

BACKGROUND OF THE INVENTION

1. Field of the Invention

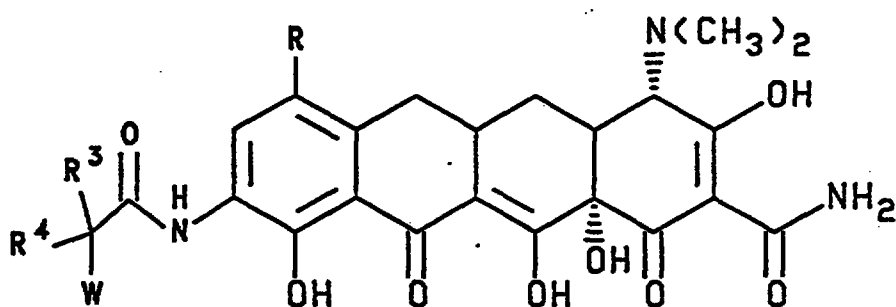
The invention relates to novel [4S-(4alpha, 12aalpha)]-4-(dimethylamino)-7-(substituted)-9-[(substituted glycyloxy)amido]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides herein after called 7-(substituted)-9-[(substituted glycyloxy)amido]-6-demethyl-6-deoxytetracyclines, which exhibit antibiotic activity againsts 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-[(haloacyloxy)amido]-7-(substituted)-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.

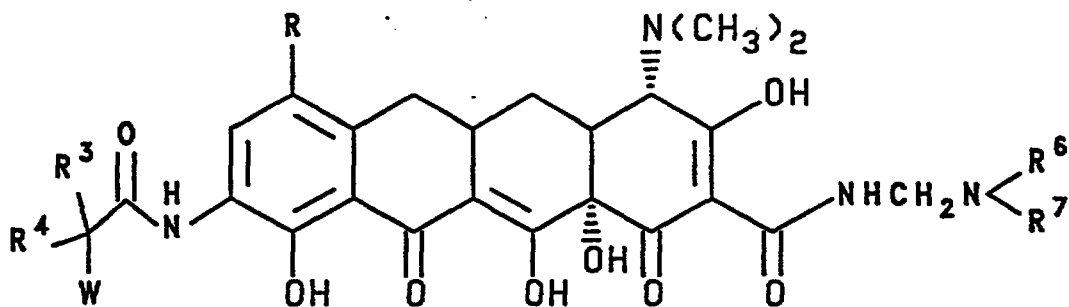
SUMMARY OF THE INVENTION

This invention is concerned with novel 7-(substituted)-9-[(substituted glycyloxy)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 intermediates 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 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 a halogen selected from bromine, chlorine,
fluorine and iodine; or $R = -NR^1R^2$ and when $R = -NR^1R^2$
and $R^1 =$ hydrogen,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when $R^1 =$ methyl or ethyl,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl or 2-methylpropyl;

and when $R^1 =$ n-propyl,

$R^2 =$ n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl
or 2-methylpropyl;

and when $R^1 =$ 1-methylethyl,

$R^2 =$ n-butyl, 1-methylpropyl or 2-methylpropyl;

and when $R^1 =$ n-butyl,

$R^2 =$ n-butyl, 1-methylpropyl or 2-methylpropyl;

and when $R^1 =$ 1-methylpropyl,

$R^2 =$ 2-methylpropyl;

R^3 is selected from hydrogen; straight or branched
(C_4-C_8)alkyl group selected from 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; 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, (C₁-C₄)alkyl, nitro, hydroxy, amino, mono-
or di-substituted (C₁-C₄)alkylamino, (C₁-C₄)alkoxy,
(C₁-C₄)alkylsulfonyl, cyano and carboxyl];

R⁴ is selected from hydrogen and (C₁-C₆)alkyl selected
from methyl, ethyl, propyl, isopropyl, butyl, isobutyl,
pentyl and hexyl;

when R³ does not equal R⁴ the stereochemistry of the
asymmetric carbon (i.e. the carbon bearing the
substituent W) maybe be either the racemate (DL) or the
individual enantiomers (L or D);

W is selected from hydroxylamino; (C₇-C₁₂) straight or
branched alkyl monosubstituted amino group substitution
selected from heptyl, octyl, nonyl, decyl, undecyl,
dodecyl and the diastereomers and enantiomers of said
branched alkyl monosubstituted amino group;

(C₁-C₄) straight or branched fluoroalkylamino group
selected from trifluoromethyl, 2,2,2-trifluoroethyl,
3,3,3-trifluoropropyl, 3,3,3,2,2-pentafluoropropyl,
2,2-difluoropropyl, 4,4,4-trifluorobutyl and 3,3-di-
fluorobutyl; (C₃-C₈)cycloalkyl monosubstituted amino
group substitution selected from cyclopropyl,
trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclo-
propyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, cyclooctyl, bicyclo[2.2.1]hept-2-yl,
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 and
alkynyl monosubstituted amino group substitution
selected from allyl, 3-butenyl, 2-butenyl (cis or
trans), 2-pentenyl, propynyl, 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 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 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 (C₆-C₁₄)alkylamino group substitution

selected from dibutyl, diisobutyl, di-sec-butyl,

dipentyl, diisopentyl, di-sec-pentyl, dihexyl, diiso-

hexyl and di-sec-hexyl; symmetrical disubstituted

(C₆-C₁₄)cycloalkylamino group substitution selected

from dicyclopropyl, dicyclobutyl, dicyclopentyl,

di(dicyclopropyl)methyl, dicyclohexyl and

dicycloheptyl; straight or branched unsymmetrical

disubstituted (C₃-C₁₄)alkylamino group wherein the

total number of carbons in the substitution is no more

than 14; unsymmetrical disubstituted

(C₄-C₁₄)cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14;

(C₂-C₈)azacycloalkyl and substituted (C₂-C₈)azacycloalkyl group substitution selected from 4-methylpiperidine, 4-hydroxypiperidine, 4-(hydroxymethyl)piperidine,

4-(aminomethyl)piperidine, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 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, 2-azabicyclo[2.2.2]oct-2-yl and the

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

substituted 1-azaoxacycloalkyl group substitution

selected from 2-(C₁-C₃)alkylmorpholinyl,

3-(C₁-C₃)alkylisoxazolidinyl, tetrahydrooxazinyl and

3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and

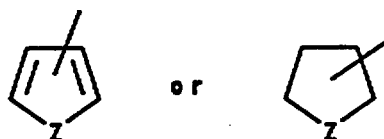


substituted [1,n]-diazacycloalkyl group selected from
 piperazinyl, 2-(C₁-C₃)alkylpiperazinyl, 4-(C₁-C₃)alkyl-
 piperazinyl, 2,4-dimethylpiperazinyl, 4-(C₁-C₄)alkoxy-
 piperazinyl, 4-(C₆-C₁₀)aryloxypiperazinyl,
 4-hydroxypiperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl,
 2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl, 2,3-diaza-3-
 methylbicyclo[2.2.2]oct-2-yl, 2,5-diaza-5,7-dimethyl-
 bicyclo[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-
 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, 3-(C₁-C₃)alkyl-1-pyrazolyl, indolyl,
 1-(1,2,3-triazolyl), 4-(C₁-C₃)alkyl-1-(1,2,3-tri-
 azolyl), 5-(C₁-C₃)alkyl-1-(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), (benzimidazolyl), and
 (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-thienylmethyl-
 amino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyrida-
 zinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazol-
 yl)methylamino, (benzimidazolyl)methylamino, and
 (benzothiazolyl)methylamino and substituted (hetero-
 cycle)methylamino group (substitution selected from
 straight or branched (C₁-C₆)alkyl); carboxy(C₂-C₄)-
 alkylamino group selected from aminoacetic acid,
 α-aminopropionic acid, β-aminopropionic acid, α-butyric

acid, β -aminobutyric acid and the enantiomers of said
 carboxy(C₂-C₄)alkylamino group; 1,1-disubstituted
 hydrazino group selected from 1,1-dimethylhydrazino,
 5 N-aminopiperidinyl, 1,1-diethylhydrazino, and
 N-aminopyrrolidinyl; (C₁-C₄)alkoxyamino group
 substitution selected from methoxy, ethoxy, n-propoxy,
 1-methylethoxy, n-butoxy, 2-methylpropoxy and
 1,1-dimethylethoxy; (C₃-C₈)cycloalkoxyamino group
 10 selected from cyclopropoxy,
 trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethyl-
 cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy,
 cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy,
 bicyclo[2.2.2]oct-2-yloxy and the diastereomers and
 15 enantiomers of said (C₃-C₈)cycloalkoxyamino group;
 (C₆-C₁₀)aryloxyamino group selected from phenoxyamino,
 1-naphthyloxyamino and 2-naphthyloxyamino;
 (C₇-C₁₁)arylalkoxyamino group substitution selected
 from benzyloxy, 2-phenylethoxy, 1-phenylethoxy,
 20 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and
 phenylpropoxy;
 [β or γ -(C₁-C₃)acylamido]alkylamino group substitution
 selected from 2-(formamido)ethyl, 2-(acetamido)ethyl,
 2-(propionylamido)ethyl, 2-(acetamido)propyl,
 25 2-(formamido)propyl and the enantiomers of said [β or
 γ -(C₁-C₃)acylamido]alkylamino group; β or
 γ -(C₁-C₃)alkoxyalkylamino group substitution selected
 from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl,
 2-methoxypropyl, 3-methoxypropyl, 3-ethoxypropyl,
 30 3,3-diethoxypropyl and the enantiomers of said β or
 γ -(C₁-C₃)alkoxyalkylamino group; β , γ , or δ
 (C₂-C₄)hydroxyalkylamino group substitution selected
 from 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl
 and 4-hydroxybutyl;
 35 or R³ and W taken together are selected from
 -(CH₂)_n(R⁵)N-, n= 3 - 4, and -CH₂CH(OH)CH₂(R⁵)N-
 wherein R⁵ is selected from hydrogen and (C₁-C₃)acyl,
 the acyl selected from formyl, acetyl, propionyl and

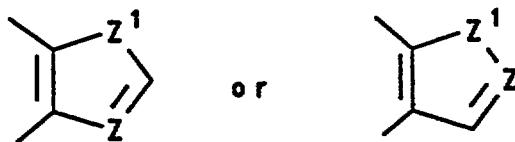
(C₂-C₃)haloacyl selected from chloroacetyl, bromoacetyl, trifluoroacetyl, 3,3,3-trifluoropropionyl and 2,3,3-trifluoropropionyl;

R⁶ 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 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:



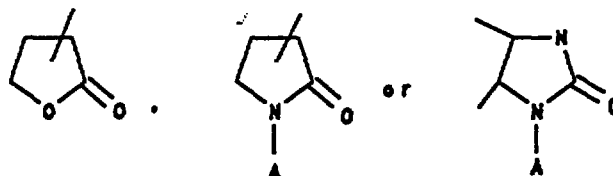
Z = N, O, S or Se

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 Z' = 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:

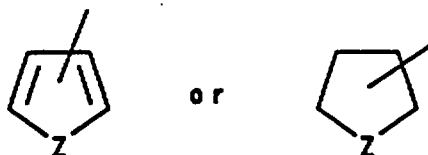


(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitution selected from halo, (C₁-C₄)alkoxy, trihalo(C₁-C₃)alkyl, nitro, amino, cyano, (C₁-C₄)-alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl 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)_nCOOR⁸ where n=0-4 and R⁸ 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; R⁷ 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 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

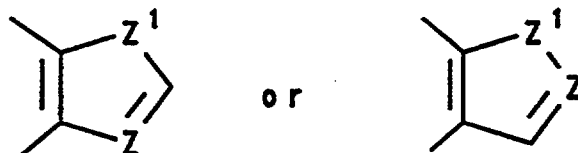


Z = N, O, S or Se

10

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

15



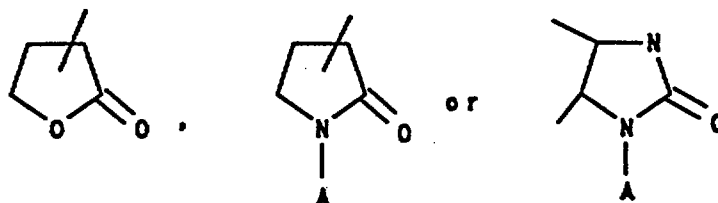
20

Z or Z¹ = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazo-
lyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolo-
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:

25

30



35

(A is selected from hydrogen; straight or branched



-11-

(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)alkylthiopyrida-
zinyl, 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-dioxothiophomorpholinyl; or
-(CH₂)_nCOOR⁸ where n=0-4 and R⁸ 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 R⁶ and R⁷ cannot both
be hydrogen;
or R⁶ and R⁷ 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 a halogen selected from bromine, chlorine,
fluorine and iodine; or R = -NR¹R² and when R = -NR¹R²
and R¹ = hydrogen,



R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R^1 = methyl or ethyl,

5 R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

R^3 is selected from hydrogen; straight or branched (C_4 - C_8)alkyl group selected from butyl, isobutyl, pentyl, hexyl, heptyl and octyl;

10 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;

15 substituted (C_6 - C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1 - C_4)alkoxy, (C_1 - C_4)alkoxycarbonyl 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, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl-sulfonyl, cyano and carboxy];

20 R^4 is selected from hydrogen and (C_1 - C_4)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl and isobutyl;

25 when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D);

30 W is selected from hydroxylamino; (C_7 - C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group;

35 (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, and the diastereomers and



-13-

enantiomers of said (C_3 - C_8)cycloalkyl monosubstituted amino group; (C_1 - C_4) straight or branched fluoroalkyl-amino group selected from 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 2,2-difluoropropyl and 3,3-difluorobutyl, [$(C_4$ - $C_{10})$ 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 and alkynyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, propynyl, 4-octenyl, 2,3-dimethyl-2-butenyl and 3-methyl-2-butenyl; (C_6 - C_{10})aryl monosubstituted amino group substitution selected from phenyl and naphthyl; (C_7 - C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; straight or branched symmetrical disubstituted (C_6 - C_{14})alkylamino group substitution selected from dibutyl, diisobutyl, di-s-butyl, dipentyl, diisopentyl and di-s-pentyl; symmetrical disubstituted (C_6 - C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl and di(dicyclopropyl)methyl; straight or branched unsymmetrical disubstituted (C_3 - C_{14})alkylamino group wherein the total number of carbons in the substitution is no more than 14; unsymmetrical disubstituted (C_4 - C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14; (C_2 - C_8)azacycloalkyl and substituted (C_2 - C_8)azacycloalkyl group substitution selected from 4-methylpiperidine, 4-hydroxypiperidine, 4-(hydroxymethyl)piperidine, 4-(aminomethyl)piperidine, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo [2.2.1]hept-2-yl, 7-azabicyclo [2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2 - C_8)azacyclo-

alkyl and substituted (C_2-C_8)azacycloalkyl group;
substituted 1-azaoxacycloalkyl group substitution
selected from 2- (C_1-C_3) alkylmorpholinyl,
5 3- (C_1-C_3) alkylisoxazolidinyl and tetrahydrooxazinyl;
[1,n]-diazacycloalkyl and substituted
[1,n]-diazacycloalkyl group selected from piperazinyl,
2- (C_1-C_3) alkylpiperazinyl, 4- (C_1-C_3) -alkylpiperazinyl,
2,4-dimethylpiperazinyl, 4- (C_1-C_4) -alkoxy piperazinyl,
10 4- (C_6-C_{10}) aryloxy piperazinyl, 4-hydroxypiperazinyl,
2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, 2,5-diaza-
5,7-dimethylbicyclo[2.2.2]oct-2-yl and the
diastereomers or enantiomers of said [1,n]-diazacyclo-
alkyl and substituted [1,n]-di- azacycloalkyl group;
15 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl
group selected from thiomorpholinyl, 2- (C_1-C_3) alkyl-
thiomorpholinyl and 3- (C_3-C_6) cycloalkylthiomorpholinyl;
N-azolyl and substituted N-azolyl group selected from
1-imidazolyl, 1-pyrrolyl, 1-pyrazolyl, 3- (C_1-C_3) alkyl-
20 pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(1,2,4-tri-
azolyl), 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl;
(heterocycle)methylamino group selected from 2- or
3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3-
or 4-pyridylmethylamino, 2- or 5-pyridazinylmethyl-
25 amino, 2-pyrazinylmethylamino, 2-(imidazolyl)methyl-
amino, (benzimidazolyl)methylamino, and (benzothiazol-
yl)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
30 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; 1,1-disubstituted
hydrazino group selected from 1,1-dimethylhydrazino,
35 N-aminopiperidinyl and 1,1-diethylhydrazino;
 (C_1-C_4) alkoxyamino group substitution selected from
methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy,
2-methylpropoxy and 1,1-dimethylethoxy;

(C₃-C₈)cycloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, and the diastereomers and enantiomers of said (C₃-C₈)-cycloalkoxyamino group;

(C₆-C₁₀)aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino;

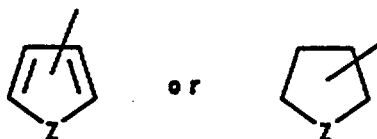
(C₇-C₁₁)arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy; [β or γ -(C₁-C₃)acylamido]alkylamino group substitution selected from 2-(formamido)ethyl, 2-(acetamido)ethyl, 2-(propionylamido)ethyl, 2-(acetamido)propyl, 2-(formamido)propyl and the enantiomers of said [β or γ -(C₁-C₃)acylamido]-alkylamino group; β or γ -(C₁-C₃)alkoxyalkylamino group substitution selected from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl, 2-methoxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3,3-diethoxypropyl and the enantiomers of said β or γ -(C₁-C₃)alkoxyalkylamino group; β , γ or δ (C₂-C₄) hydroxyalkylamino group substitution selected from 2-hydroxyethyl, 3-hydroxypropyl, and 4-hydroxybutyl;

or R³ and W taken together are selected from -(CH₂)_n(R⁵)N-, n= 3 - 4, and -CH₂CH(OH)CH₂(R⁵)N- wherein R⁵ is selected from hydrogen and (C₁-C₃)acyl, the acyl selected from formyl, acetyl, propionyl and (C₂-C₃)-haloacyl selected from chloroacetyl, bromoacetyl, trifluoroacetyl, 3,3,3-trifluoropropionyl and 2,3,3-trifluoropropionyl;

R⁶ 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 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

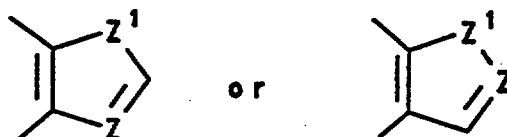


Z = N, O, S or Se

10

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

15



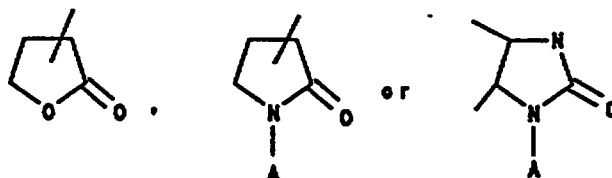
20

Z or Z' = 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:

25

30



(A is selected from hydrogen; straight or branched
(C₁-C₄)alkyl; C₆-aryl; (C₇-C₉)aralkyl group selected
from benzyl, 1-phenylethyl, 2-phenylethyl or
phenylpropyl)

35

such as γ -butyrolactam, γ -butyrolactone,

imidazolidinone or N-aminoimidazolidinone; or
 $-(CH_2)_nCOOR^8$ where $n=0-4$ and R^8 is selected from
hydrogen; straight or branched (C_1-C_3) alkyl group
5 selected from methyl, ethyl, n-propyl or 1-methylethyl;
or (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl,
or β -naphthyl;

R^7 is selected from hydrogen; straight or branched
 (C_1-C_3) alkyl group selected from methyl, ethyl,
10 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
15 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

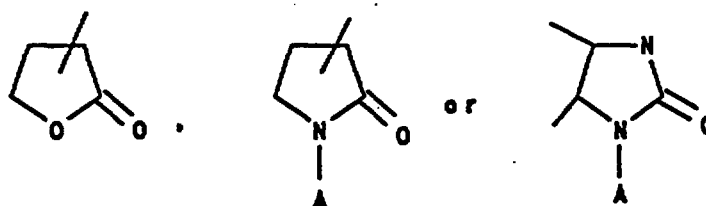
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrroli-
25 dinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl,
furanyl, benzofuranyl, tetrahydrothienyl, thienyl,
benzothienyl or selenazolyl, or a five membered
aromatic ring with two N, O, S or Se heteroatoms
optionally having a benzo or pyrido ring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



Z or Z^1 = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazo-
35 yl, 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:



(A is selected from hydrogen; straight or branched
(C₁-C₄)alkyl; C₆-aryl; (C₇-C₉)aralkyl group selected
from benzyl, 1-phenylethyl, 2-phenylethyl or
phenylpropyl)

such as γ -butyrolactam, γ -butyrolactone,
imidazolidinone or N-aminoimidazolidinone; or
-(CH₂)_nCOOR⁸ where n=0-4 and R⁸ 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 R⁶ and R⁷ cannot both
be hydrogen;
or R⁶ and R⁷ 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.

Particularly preferred compounds are
compounds according to formula I and II wherein:
R is a halogen selected from bromine, chlorine,



-19-

fluorine and iodine; or $R = -NR^1R^2$ and when $R = -NR^1R^2$
and $R^1 =$ hydrogen,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when $R^1 =$ methyl or ethyl,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl or 2-methylpropyl;

R^3 is selected from hydrogen; straight or branched

(C_4-C_6)alkyl group selected from butyl, isobutyl,
pentyl and hexyl; (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^4 is selected from hydrogen and (C_1-C_3)alkyl selected
from methyl, ethyl, propyl and isopropyl;

when R^3 does not equal R^4 the stereochemistry of the
asymmetric carbon (i.e. the carbon bearing the

substituent W) maybe be either the racemate (DL) or the
individual enantiomers (L or D);

W is selected from (C_7-C_{12}) straight or branched alkyl
monosubstituted amino group substitution selected from
heptyl, octyl, nonyl, decyl, undecyl, dodecyl

and the diastereomers and enantiomers of said branched
alkyl monosubstituted amino group; (C_1-C_4) straight or

branched fluoroalkylamino group selected from 2,2,2-
trifluoroethyl, 3,3,3-trifluoropropyl and 2,2-di-

fluoropropyl; (C_3-C_8)cycloalkyl monosubstituted amino
group substitution selected from cyclopropyl, trans-

1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl 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, (cyclo-

propyl)ethyl and (cyclobutyl)methyl; (C_3-C_{10})alkenyl
and alkynyl monosubstituted amino group substitution

selected from allyl, propynyl, 3-butenyl, 2-butenyl



(cis or trans) and 2-pentenyl; (C_7-C_{10}) aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; straight or branched symmetrical disubstituted (C_6-C_{14}) alkylamino group substitution selected from dibutyl, diisobutyl, di-s-butyl, and dipentyl; symmetrical disubstituted (C_6-C_{14}) cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl and dicyclopropylmethyl; straight or branched unsymmetrical disubstituted (C_3-C_{14}) alkylamino group wherein the total number of carbons in the substitution is no more than 14; unsymmetrical disubstituted (C_4-C_{14}) cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14;

(C_2-C_8) azacycloalkyl and substituted (C_2-C_8) azacycloalkyl group substitution selected from 4-methylpiperidine, 4-hydroxypiperidine, 4-(hydroxymethyl)piperidine, 4-(aminomethyl)piperidine, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, and the diastereomers and enantiomers of said (C_2-C_8) azacycloalkyl and substituted (C_2-C_8) azacycloalkyl group;

substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3) alkylmorpholinyl and 3-(C_1-C_3) alkylisoxazolidinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3) alkylpiperazinyl, 4-(C_1-C_3) alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-hydroxypiperazinyl, and the enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group;

1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and 2-(C_1-C_3) alkylthiomorpholinyl;

(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-
 amino and the substituted (heterocycle)methylamino
 group (substitution selected from straight or branched
 5 (C₁-C₆)alkyl); 1,1-disubstituted hydrazino group
 selected from 1,1-dimethylhydrazino, N-aminopiperidinyl
 and 1,1-diethylhydrazino;
 (C₁-C₄)alkoxyamino group substitution selected from
 methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy,
 10 2-methylpropoxy and 1,1-dimethylethoxy;
 (C₇-C₁₁)arylalkoxyamino group substitution selected
 from benzyloxy, 2-phenylethoxy, 1-phenylethoxy,
 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and
 phenylpropoxy;
 15 [β or γ-(C₁-C₃)acylamido]alkylamino group substitution
 selected from 2-(formamido)ethyl, 2-(acetamido)ethyl,
 2-(propionylamido)ethyl, 2-(acetamido)propyl and
 2-(formamido)propyl and the enantiomers of said [β or
 γ-(C₁-C₃)acylamido]alkylamino group;
 20 β or γ-(C₁-C₃)alkoxyalkylamino group
 substitution selected from 2-methoxyethyl, 2-ethoxy-
 ethyl, 2,2-diethoxyethyl, 2-methoxypropyl, 3-methoxy-
 propyl, 3-ethoxypropyl and 3,3-diethoxypropyl and the
 enantiomers of said β or γ-(C₁-C₃)alkoxyalkyl- amino
 25 group; β, γ, or δ (C₂-C₄) hydroxyalkylamino group
 selected from 3-hydroxypropyl and 4-hydroxybutyl;
 or R³ and W taken together are selected from
 -(CH₂)_n(R⁵)N-, n= 3 - 4, and -CH₂CH(OH)CH₂(R⁵)N-
 wherein R⁵ is selected from hydrogen and (C₁-C₃)acyl,
 30 the acyl selected from formyl, acetyl, propionyl and
 (C₂-C₃)haloacyl selected from trifluoroacetyl,
 3,3,3-trifluoropropionyl and 2,3,3-trifluoropropionyl;
 R⁶ is selected from hydrogen; straight or branched
 (C₁-C₃)alkyl group selected from methyl, ethyl,
 35 n-propyl or 1-methylethyl; (C₆-C₁₀)aryl group selected
 from phenyl, α-naphthyl or β-naphthyl; (C₇-C₉)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

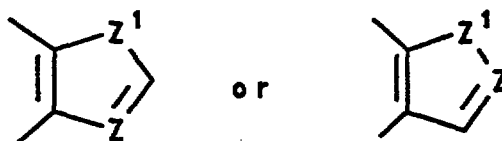


10

Z = N, O, S or Se

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

15



20

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 $-(CH_2)_n COOR^8$ where $n=0-4$ and R^8 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,
or β -naphthyl;

25

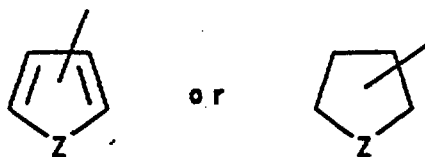
30

R^7 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
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

35

fused thereto:

5

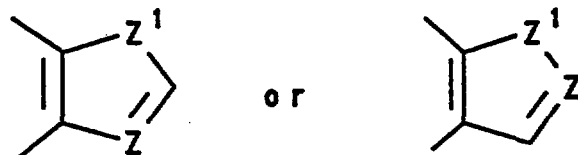


Z = N, O, S or Se

10

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

15



20

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 $-(CH_2)_nCOOR^8$ where $n=0-4$ and R^8 is selected
from hydrogen; straight or branched (C_1-C_3) alkyl
selected from methyl, ethyl, n-propyl or 1-methylethyl;
or (C_6-C_{10}) aryl selected from phenyl, α -naphthyl or
 β -naphthyl; with the proviso that R^6 and R^7 cannot both
be hydrogen;

25

30

or R^6 and R^7 taken together are $-(CH_2)_2B(CH_2)_2-$,
wherein B is selected from $(CH_2)_n$ and $n=0-1$, $-NH$,
 $-N(C_1-C_3)$ alkyl [straight or branched], $-N(C_1-C_4)$ 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

35



complexes.

Compounds of special interest are compound according to formula I and II wherein:

5 R is a halogen selected from bromine, chlorine and iodine; or $R = -NR^1R^2$

and when $R = -NR^1R^2$ and $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl or ethyl}$,

R^3 is selected from hydrogen;

10 R^4 is selected from hydrogen and (C_1-C_2) alkyl selected from methyl and ethyl;

when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D);

15 W is selected from (C_7-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_2) fluoroalkylamino group selected from 2,2,2-trifluoroethyl and 3,3,3-trifluoropropyl;

20 (C_3-C_8) cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the diastereomers and enantiomers of said (C_3-C_8) cycloalkyl monosubstituted amino group; $[(C_4-C_5)$ cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)-methyl and (cyclopropyl)ethyl; (C_3-C_4) alkenyl and

25 alkynyl monosubstituted amino group substitution selected from allyl and propynyl; (C_2-C_7) azacycloalkyl and substituted (C_2-C_7) azacycloalkyl group substitution selected from 4-methylpiperidine, 4-hydroxypiperidine and 4-(hydroxymethyl)piperidine; substituted

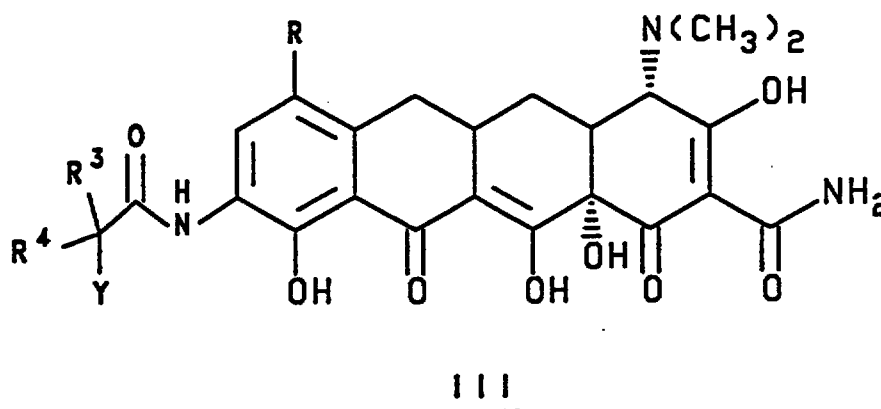
30 1-azaoxacycloalkyl group substitution selected from 2- (C_1-C_3) alkylmorpholinyl; $[1,n]$ -diazacycloalkyl and substituted $[1,n]$ -diazacycloalkyl group selected from piperazinyl and 4- (C_1-C_3) alkylpiperazinyl;

35

1-azathiacycloalkyl and substituted 1-azathiacycloalkyl
group selected from thiomorpholinyl and
2-(C₁-C₃)alkylthiomorpholinyl; (heterocycle)methylamino
group selected from 2- or 3-thienylmethylamino and 2-,
3- or 4-pyridylmethylamino; 1,1-disubstituted hydrazino
group selected from 1,1-dimethylhydrazino and N-amino-
piperidiny1. [β or γ -(C₁-C₃)acylamido]alkylamino group
substitution selected from 2-(acetamido)ethyl; β or
 γ -(C₁-C₃)alkoxyalkylamino group substitution selected
from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl,
2-methoxypropyl and 3-methoxypropyl; β , γ or δ
(C₂-C₄)hydroxyalkylamino selected from 4-hydroxybutyl
and 3-hydroxypropyl; or R³ and W taken together are
selected from -(CH₂)_n(R⁵)N-, n= 3, and R⁵ is selected
from hydrogen and trifluoroacetyl;
R⁶ is selected from hydrogen; straight or branched
(C₁-C₃)alkyl group selected from methyl, ethyl,
n-propyl or 1-methylethyl;
R⁷ is selected from hydrogen; straight or branched
(C₁-C₃)alkyl group selected from methyl, ethyl,
n-propyl or 1-methylethyl; with the proviso that R⁶
and R⁷ cannot both be hydrogen;
or R⁶ and R⁷ 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.

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







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; 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^4 is selected from hydrogen and (C_1 - C_6)alkyl selected

from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the

substituent W) maybe be either the racemate (DL) or the

individual enantiomers (L or D); and the

pharmacologically acceptable organic and inorganic salts or metal 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 or iodine;

R is a halogen selected from bromine, chlorine,

fluorine and iodine; or $R = -NR^1R^2$ and when $R = -NR^1R^2$

and $R^1 =$ hydrogen,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,

1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when $R^1 =$ methyl or ethyl,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,



1-methylpropyl or 2-methylpropyl;

R^3 is selected from hydrogen; straight or branched

(C_4-C_8)alkyl group selected from butyl, isobutyl,

5 pentyl, hexyl, heptyl and octyl;

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

10 from phenyl, α -naphthyl and β -naphthyl;

substituted(C_6-C_{10})aryl group (substitution selected

from hydroxy, halogen, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy-

carbonyl and carboxy); (C_7-C_9)aralkyl group selected

from benzyl, 1-phenylethyl, 2-phenylethyl and phenyl-

15 propyl; substituted (C_7-C_9)aralkyl group [substitution

selected from halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy,

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

R^4 is selected from hydrogen and (C_1-C_4)alkyl selected

from methyl, ethyl, propyl, isopropyl, butyl and

20 isobutyl;

when R^3 does not equal R^4 the stereochemistry of the

asymmetric carbon (i.e. the carbon bearing the

substituent W) maybe be either the racemate (DL) or the

individual enantiomers (L or D); and the

25 pharmacologically acceptable organic and inorganic

salts or metal complexes.

Particularly preferred compounds are

compounds according to formula III wherein:

Y is selected from $(CH_2)_nX$, $n=0-5$, X is halogen

30 selected from bromine, chlorine, fluorine or iodine;

R is a halogen selected from bromine, chlorine,

fluorine and iodine; or $R = -NR^1R^2$ and when $R = -NR^1R^2$

and $R^1 =$ hydrogen,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,

35 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when $R^1 =$ methyl or ethyl,

$R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,

1-methylpropyl or 2-methylpropyl;



R^3 is selected from hydrogen; straight or branched (C_4-C_6)alkyl group selected from butyl, isobutyl, pentyl and hexyl; (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^4 is selected from hydrogen and (C_1-C_3)alkyl selected from methyl, ethyl, propyl and isopropyl;

when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Compounds of special interest are compound according to formula III wherein:

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

R is a halogen selected from bromine, chlorine and iodine; or $R = -NR^1R^2$

and when $R = -NR^1R^2$ and $R^1 =$ methyl or ethyl, $R^2 =$ methyl or ethyl,

R^3 is selected from hydrogen;

R^4 is selected from hydrogen and (C_1-C_2)alkyl selected from methyl and ethyl;

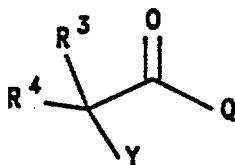
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

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

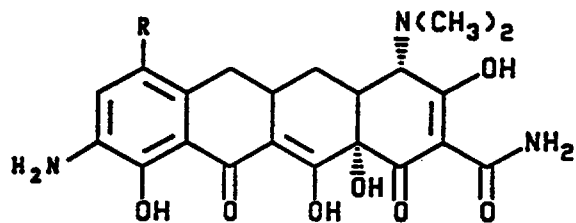
The preferred method for producing 7-(substituted)-9-[(substituted glycyloamido]-6-de-

methy1-6-deoxytetracyclines or the mineral acid salts,
3, is shown in scheme I. This method uses common
intermediates which are easily prepared by reacting
commercially available haloacyl halides of the formula:

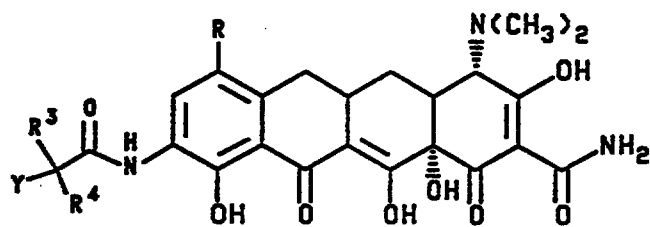
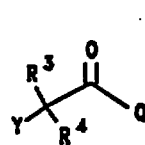


wherein Y, R^3 and R^4 are as defined hereinabove and Q
is halogen selected from bromine, chlorine, iodine and
fluorine; with 9-amino-7-(substituted)-6-demethyl-6-
deoxytetracycline or its mineral acid salt, 1, to give
straight or branched 9-[(haloacyl)amido]-7-(substi-
tuted)-6-demethyl-6-deoxytetracyclines or mineral acid
salts, 2, in almost quantitative yield. The above
intermediates, straight or branched 9-[(haloacyl)-
amido]-7-(substituted)-6-demethyl-6-deoxytetracyclines
or mineral acid salts, 2, react with a wide variety of
nucleophiles, especially amines, having the formula WH,
wherein W is as defined hereinabove, to give a new
7-(substituted)-9-[(substituted glycy1)amido]-7-(sub-
stituted)-6-demethyl-6-deoxytetracyclines or the
mineral acid salts, 3 of the present invention.

Scheme I

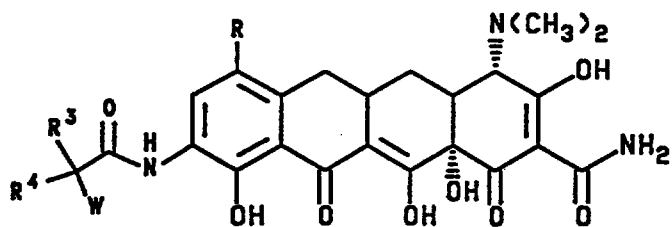


1 • mineral acid salt



2 • mineral acid salt

WH



3 • mineral acid salt



-32-

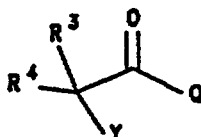
In accordance with scheme I, 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline or its mineral acid salt, 1, is mixed with

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 methyl ether, 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, R³, R⁴ and Q are as hereinabove defined, such as bromoacetyl bromide, chloroacetyl chloride, 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 from room temperature to the reflux temperature of the reaction; to form the corresponding 9-[(haloacyl)amido-7-(substituted)-6-demethyl-6-deoxytetracycline, 2 , or its mineral acid salt.

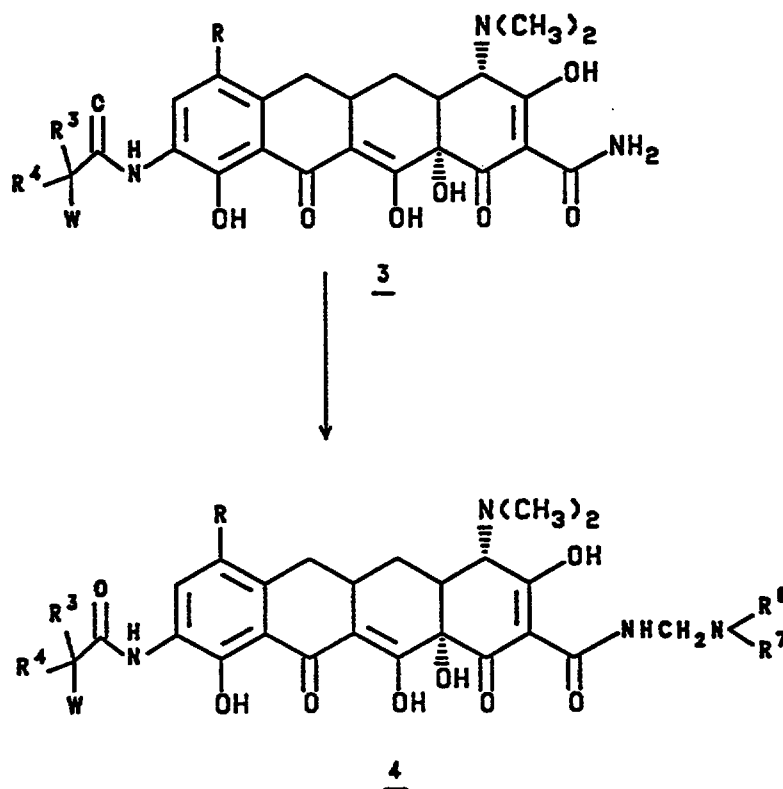
The intermediate, 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline or its mineral acid salt, 2, is treated, under an inert atmosphere of helium, argon or nitrogen, with

a) a nucleophile WH such as an amine, substituted amine or equivalent thereof 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 7-(substituted)-9-[(substituted glycy)amido]-6-demethyl-6-deoxytetracycline, 3, or its mineral acid salt.

Scheme II



In accordance with Scheme II, 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 7-(substituted)-9-[(substituted glycylyl)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 7-(substituted)-9-[(substituted glycylyl)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 stereoisomers 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

Methods for in Vitro antibacterial evaluation (Table I)

The minimum inhibitory concentration (MIC), the lowest concentration of the antibiotic which inhibits growth of the test organism, is determined by the agar dilution method using 0.1 ml Muller-Hinton II agar (Baltimore Biological Laboratories) per well. An inoculum density of $1-5 \times 10^5$ CFU/ml, and an antibiotic concentrations range of 32-0.004 microgram/ml is used. MIC is determined after 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 bacterial ribosomes (tetM).

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

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 microliter reaction contains S30 extract (a whole extract) made from either tetracycline sensitive cells or an isogenic tetracycline resistant (tet^M) strain, low molecular weight components necessary for transcription and translation (i.e. ATP and GTP), a mix of 19 amino acids (no methionine), ³⁵S 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 µl 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 ³⁵S-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

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*, *S. aureus* and *E. faecalis*, containing *tetM* and *tetD* resistance determinants; and *E. coli* containing the *tetB* and *tetD* resistance determinants. Notable are compounds D, G, and K, 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*). These compounds also have good activity against *E. coli tetA*, *E. coli tetC* and *E. coli tetD* and are equally as effective as minocycline against susceptible strains and are superior to that of minocycline against a number of recently isolated bacteria from clinical sources (Table I).

Minocycline and compounds B, C, D, G and H are assayed *in vitro* for their ability to inhibit protein synthesis taking place on either wild type or *tetM* protected ribosomes using a coupled transcription

and translation system. All compounds are found to effectively inhibit protein synthesis occurring on wild type ribosomes, having equivalent levels of activity. Minocycline is unable to inhibit protein synthesis occurring on tetM protected ribosomes. In contrast, compounds B, C, D, G and H are effective at inhibiting protein synthesis occurring on tetM protected ribosomes (Table II).

Compounds B, C, D, G and H bind reversibly to its target (the ribosome) since bacterial growth resumes when the compound is removed from the cultures by washing of the organism. Therefore, the ability of these compounds to inhibit bacterial growth appears to be a direct consequence of its ability to inhibit protein synthesis at the ribosome level.

The activity of compound G against tetracycline susceptible organisms is also demonstrated in vivo in animals infected with S. aureus Smith with ED₅₀'s between 1-2 mg/kg when administered intravenously, and ED₅₀'s of 4-8 mg/kg when given orally.

The improved efficacy of compounds D, G and K is demonstrated by the in vitro activity against isogenic strains into which the resistance determinants, such as tetM and tetB, were cloned (Table I); and the inhibition of protein synthesis by tetM ribosomes (Table II).

As can be seen from Table I and II, compounds of the invention may also be used to prevent or control important veterinary diseases such as diarrhea, urinary tract infections, infections of skin and skin structure, ear, nose and throat infections, wound infections, mastitis and the like.

COMPOUND LEGEND FOR TABLES

5	A	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-(trifluoroacetyl)-2-pyrrolidinecarboxamide dihydrochloride
10	B	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-(methoxyethyl)-amino)acetyl]amino]-1,11-dioxo-2-naphthacene-carboxamide dihydrochloride
15	C	[4S-(4alpha,12aalpha)]-9-[[[(2,2-Diethoxyethyl)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide dihydrochloride
20	D	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-propenylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride
25	E	[4S-(4alpha,12aalpha)]-4,7-bis(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
30	F	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-thiomorpholineacetamide dihydrochloride
35	G	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidine-acetamide dihydrochloride

5	H	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methoxypropyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacene-carboxamide dihydrochloride
10	I	7[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperazine-acetamide dihydrochloride
15	J	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-9-[[(heptylamino) acetyl] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
20	K	[4S-(4alpha,12aalpha)]-9-[[(Cyclopropyl-methyl) amino] acetyl] amino]-4,7-bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide dihydrochloride
25	L	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(undecyl-amino) acetyl] amino]-2-naphthacenecarboxamide dihydrochloride
30	M	[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)-amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride
	N	Tetracycline
	O	Minocycline

- 5 P [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)-
amino]acetyl]amino]-1,11-dioxo-2-naphthacene-
carboxamide monohydrochloride
- 10 Q [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)-
methylamino]acetyl]amino]-1,11-dioxo-2-
naphthacenecarboxamide
- 15 R [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-4-
amino-1-amino)-1,4,4a,5,5a,6,11,12a-octa-
hydro-3,10,12,12a-tetrahydroxy-9-[[[(4-
(hydroxybutyl)amino]acetyl]amino]-1,11-dioxo-
2-naphthacenecarboxamide
- 20 S [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-9-[[[2,2,2-
trifluoroethyl)amino]acetyl]amino-2-naphtha-
cenecarboxamide
- 25 T [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-
amino)-9-[[[(2-fluoroethyl)amino]acetyl]-
amino]-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide
- 30 U [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-9-
[[[[2-(1-piperidinyl)ethyl]amino]acetyl]-
amino]-2-naphthacenecarboxamide
- 35 V [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-9-[[[methyl-2-propynyl-
amino]acetyl]amino]-1,11-dioxo-2-naphtha-
cenecarboxamide

his Sheet Has Been ReplacedT



W [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-hydroxy-1,11-dioxo-9-
5 [[(1-piperidinylamino)acetyl]amino]-2-
naphthacenecarboxamide

X [4S-(4-alpha,12aalpha)]-4,7-Bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenyl-
10 methoxy)amino]acetyl]amino]-2-naphthacene-
carboxamide

15

20

25

30

35

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

Organism	Compound														
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
<i>E. coli</i> UBMS 88-1 Tet B	8	2	16	1	16	>32	2	2	8	2	0.5	32	>32	>32	16
<i>E. coli</i> J3272 Tet sens.	8	2	8	0.5	NT	>32	1	1	NT	NT	NT	NT	16	0.5	0.5
<i>E. coli</i> MC 4100 Tet sens.	NT	NT	NT	NT	2	NT	NT	NT	1	1	0.12	2	NT	NT	NT
<i>E. coli</i> PRP1 Tet A	>32	8	>32	8	32	>32	2	4	16	2	4	32	>32	32	4
<i>E. coli</i> MC 4100 TNOIC Tet B	8	2	8	1	NT	>32	2	2	NT	NT	NT	NT	>32	>32	8
<i>E. coli</i> J3272 Tet C	8	4	16	1	16	>32	1	1	8	2	0.5	32	>32	>32	2
<i>E. coli</i> UBMS 89-1 Tet M	8	2	4	0.5	8	>32	0.5	2	8	0.5	0.5	16	4	8	8
<i>E. coli</i> UBMS 89-2 Tet sens.	8	2	8	0.5	16	>32	2	1	8	2	0.5	16	32	1	0.5
<i>E. coli</i> J2175	8	2	8	0.5	16	>32	1	1	8	2	0.5	16	32	1	0.5
<i>E. coli</i> BAJ9003 IMP MJT	1	0.25	0.5	0.12	1	0.5	0.12	0.12	0.5	0.25	0.12	1	0.25	0.25	0.03
<i>E. coli</i> UBMS 90-4 Tet M	NT	2	4	0.5	8	>32	1	1	8	2	0.5	32	NT	16	>32
<i>E. coli</i> UBMS 90-5	4	2	8	0.5	16	>32	2	1	8	2	0.5	16	16	1	0.5
<i>E. coli</i> #311 (MP)	8	2	8	0.5	8	>32	1	1	8	2	0.5	8	8	1	0.25
<i>E. coli</i> ATCC 25922	8	2	8	0.5	8	32	1	1	8	2	0.5	8	16	0.5	0.5
<i>E. coli</i> J3272 Tet D	2	1	4	0.25	8	16	0.25	0.5	4	2	0.25	32	32	>32	8
<i>S. mariescens</i> FPOR 8733	>32	>32	>32	8	>32	>32	16	16	>32	16	8	>32	>32	32	2
<i>X. maltophilia</i> NEMC 87210															
<i>Ps. aeruginosa</i> ATCC 27853	>32	>32	>32	16	>32	>32	32	32	>32	>32	16	>32	>32	8	8
<i>S. aureus</i> NEMC 8769	1	0.5	0.25	0.12	8	0.25	0.12	0.25	0.5	no growth	1	0.5	0.12	0.03	<0.015

Table I (cont'd)

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

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

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

Organism	Compound									
	P	Q	R	S	T	U	V	W	X	
E. coli UBMS 88-1 Tet B	>32	32	>32	32	16	>32	>32	>32	>32	
E. coli J3272 Tet sens.	NT	NT	NT	NT	NT	NT	NT	NT	NT	
E. coli MC 4100 Tet sens.	4	4	8	16	2	4	32	32	4	
E. coli PRP1 Tet A	>32	>32	>32	>32	>32	>32	>32	>32	>32	
E. coli MC 4100 TNIOC Tet B	>32	>32	>32	>32	16	32	>32	>32	>32	
E. coli J3272 Tet C	>32	>32	>32	>32	>32	16	>32	>32	>32	
E. coli UBMS 89-1 Tet M	>32	32	32	32	8	16	>32	>32	16	
E. coli UBMS 89-2 Tet sens.	>32	32	32	>32	16	32	>32	>32	>32	
E. coli J2175	32	32	32	>32	16	32	>32	>32	>32	
E. coli BAJ9003 IMP MUT	2	2	4	1	1	2	4	16	1	
E. coli UBMS 90-4 Tet M	32	16	32	>32	8	16	>32	>32	>32	
E. coli UBMS 90-5	32	32	32	>32	16	16	>32	>32	>32	
E. coli #311 (MP)	16	32	32	>32	16	16	>32	>32	16	
E. coli ATCC 25922	16	32	32	>32	8	16	>32	>32	16	
E. coli J3272 Tet D	16	32	8	>32	8	8	>32	>32	16	
S. mariescens FPOR 8733	>32	16	8	>32	>32	>32	>32	>32	>32	
X. maltophilia NEMC 87210	>32	8	8	16	16	16	32	>32	16	
Ps. aeruginosa ATCC 27853	>32	>32	>32	>32	>32	>32	>32	>32	>32	
S. aureus NEMC 8769	4	8	8	4	4	8	4	>32	1	

Table 1 (cont'd)

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

MIC (μ g/ml)

Organism	Compound									
	P	Q	R	S	T	U	V	W	X	
<i>S. aureus</i> UBMS 88-4	8	8	8	4	4	8	4	>32	1	
<i>S. aureus</i> UBMS 88-5 Tet H	32	16	32	8	4	16	8	>32	2	
<i>S. aureus</i> UBMS 88-7 Tet K	32	32	32	32	>32	16	32	>32	4	
<i>S. aureus</i> UBMS 90-1 Tet H	32	32	32	16	4	32	16	>32	2	
<i>S. aureus</i> UBMS 90-3	8	8	8	4	2	8	4	16	1	
<i>S. aureus</i> UBMS 90-2 Tet H	16	16	16	4	4	8	8	>32	2	
<i>S. aureus</i> IVES 2943	>32	>32	>32	>32	>32	>32	>32	>32	8	
<i>S. aureus</i> ROSE (MP)	>32	>32	>32	>32	>32	>32	>32	>32	16	
<i>S. aureus</i> SMITH (MP)	4	8	8	1	1	8	4	16	0.5	
<i>S. aureus</i> IVES 1 983	>32	>32	>32	>32	>32	>32	>32	>32	8	
<i>S. aureus</i> ATCC 29213	8	16	16	4	4	8	4	32	1	
<i>S. hemolyticus</i> AVHAH 88-3	32	16	32	16	8	32	32	>32	4	
<i>Enterococcus</i> 12201	8	4	8	4	2	8	8	>32	4	
<i>E. faecalis</i> ATCC 29212	4	4	8	2	1	8	4	>32	1	

NT = Not tested

his Sheet Has Been Replaced T



Table II
In Vitro Transcription and Translation
Sensitivity to Tetracycline Compounds

5

Compound	Conc.	% Inhibition	
		Wild Type S30	TetM S30
B	1.0 mg/ml	98	97
	0.25 mg/ml	96	95
	0.06 mg/ml	92	91
C	1.0 mg/ml	98	96
	0.25 mg/ml	95	84
	0.06 mg/ml	88	65
D	1.0 mg/ml	99	98
	0.25 mg/ml	98	96
	0.06 mg/ml	93	83
G	1.0 mg/ml	99	99
	0.25 mg/ml	97	92
	0.06 mg/ml	90	83
H	1.0 mg/ml	99	98
	0.25 mg/ml	96	94
	0.06 mg/ml	88	85
O	1.0 mg/ml	98	68
	0.25 mg/ml	89	43
	0.06 mg/ml	78	0

10

15

20

25

30

35

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

An effective amount of compound from 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 preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions 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.

Example 1

[4S-(4alpha,12aalpha)]-9-[(Chloroacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

To a room temperature solution of 0.334 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 6 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, hereinafter called DMPU, and 2 ml of acetonitrile is added 0.318 g of sodium carbonate. The mixture is stirred for 5 minutes followed by the addition of 0.068 g of chloroacetyl chloride. The reaction is stirred for 30 minutes, filtered, and the filtrate added dropwise to 100 ml of diethyl ether, containing 1 ml of 1M hydrochloric acid in diethyl ether. The resulting solid is collected and dried to give 0.340 g of the desired intermediate.
MS(FAB): m/z 549 (M+H).

Example 2

[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4,7-bis(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 6.68 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 50 ml of DMPU, 30 ml of acetonitrile, 6.68 g of sodium carbonate and 0.215 g of bromoacetyl bromide. 5.72 g of the desired intermediate is obtained.
MS(FAB): m/z 593 (M+H).

Example 3

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopropyl)amino]-
4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide sulfate

The title compound is prepared by the procedure of Example 1, using 1.00 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 1.0 g of sodium carbonate and 0.648 g of 2-bromopropionyl bromide to give 0.981 g of the desired product.

MS(FAB): m/z 607 (M+H).

Example 4

[4S-(4alpha,12aalpha)]-9-[(4-Bromo-1-oxobutyl)amino]-
4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide dihydrochloride

The title compound is prepared by the procedure of Example 1, using 1.34 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 1.3 of sodium carbonate, 24 ml of DMPU, 8 ml of acetonitrile and 0.389 g of 4-bromobutyryl chloride to give 1.45 g of the desired product.

Example 5

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(di-
methylamino)-5,5a,6,7,10,10a,12-octahydro-1,8,10a,11-
tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-trifluoro-
acetyl)-2-pyrrolidinecarboxamide dihydrochloride

The title compound is prepared by the procedure of Example 1, using 0.334 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 10 ml of DMPU, 2 ml of acetonitrile, 0.34 g of sodium carbonate and 7.5 ml of 0.1M (S)-(-)-N-(trifluoroacetyl)proyl chloride to give 0.292 g of the desired product.

MS(FAB): m/z 666 (M+H).

Example 6

[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]-
acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide dihydrochloride

A mixture of 0.20 g of product from Example 2, 0.50 g of (aminomethyl)cyclopropane and 5 ml of DMPU, under Argon, is stirred at room temperature for 1 hour. The excess amine is removed in vacuo and the residue diluted with a small volume of methyl alcohol. The diluted reaction solution is added dropwise to a mixture of diethyl ether and 5 ml of 2-propanol. 1M Hydrochloric acid in diethyl ether is added until a solid is formed. The resulting solid is collected and dried to give 0.175 g of the desired product.

MS(FAB): m/z 584 (M+H).

Substantially following the methods described in detail herein above in Example 6, the compounds of this invention listed below in Examples 7 - 16 are prepared.

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS (FAB): m/z
7	[4S-(4alpha,12aalpha)]-9-[[[(2,2-Diethoxyethyl)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2or1	2,2-Diethoxyethylamine	3 hrs.	646 (M+H)
8	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[2-(methoxyethyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2or1	2-Methoxyethylamine	2 hr.	588 (M+H)
9	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[2-(propenylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	2or1	Allylamine	2 hr.	570 (M+H)
10	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[3-methoxypropyl]amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2or1	3-Methoxypropylamine	2 hr.	602 (M+H)
11	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-thiomorpholineacetamide dihydrochloride	2	Thiomorpholine	3 hr.	616 (M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
12	[7S-(7alpha,10aalpha)]-N-[9-(Amino-carbonyl)-4,7-bis(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-Methylpiperidine	2 hrs.	612(M+H)
13	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,-6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperazineacetamide dihydrochloride	2	4-Methyl-1-piperazine	0.75 hr.	613(M+H)
14	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(heptylamino) acetyl] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2	N-Heptylamine	2 hr.	628(M+H)
15	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(undecylamino) acetyl] amino]-2-naphthacenecarboxamide dihydrochloride	2	Undecylamine	3.5 hr.	684(M+H)
16	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl) amino] acetyl] amido]-2-naphthacenecarboxamide dihydrochloride	2	2-(Aminomethyl) pyridine	1.5 hr.	621(M+H)

Example 17

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

To a solution of 0.10 g of product from
Example 7A in 2 ml of 1,3-dimethyl-2-imidazolidinone is
added 0.70 ml of 2-amino-1-ethanol. The solution is
stirred at room temperature for 20 minutes, added to
100 ml of diethyl ether and the resulting precipitate
collected to give 0.055 g of the desired product.
MS(FAB):m/z 574 (M+H).

Substantially following the method described
in detail hereinabove in Example 17, the compounds of
this invention listed below in Examples 18-24 are
prepared.

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
18	[4S-(4alpha,12aalpha)]-4,7-Bis(di-methylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)methylamino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide	7A	4-methylamino-1-butanol	0.5 hrs.	588 (M+H)
19	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(4-(hydroxybutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide	7A	4-amino-1-butanol	0.5 hr.	602 (M+H)
20	[4S-(4alpha,12aalpha)]-4,7-Bis(di-methylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[2,2,2-trifluoroethyl)amino]-acetyl]-2-naphthacenecarboxamide	7A	2,2,2-tri-fluoromethyl-amine	2 hr.	612 (M+H)
21	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-9-[[[(2-fluoroethyl)amino]acetyl]-amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide	7A	2-fluoro-ethylamine	2 hr.	576 (M+H)
22	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[2-(1-piperidinyl)ethyl]amino]acetyl]-amino]-2-naphthacenecarboxamide	7A	1-(2-amino-ethyl)pyrrolidine	2 hr.	627 (M+H)

his Sheet Has Been Replaced

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
23	[4S-(4alpha,12aalpha)]-4,7-Bis(di-methylamino)-1,4,4a,5,5a,6,11,12a-octa-hydro-3,10,12,12a-tetrahydroxy-9-[[[methyl-2-propynylamino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide	7A	N-methylpropargylamine	2 hrs.	581 (M+H)
24	[4S-(4alpha,12aalpha)]-4,7-Bis(di-methylamino)-1,4,4a,5,5a,6,11,12a-octa-hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[(1-piperidinylamino)acetyl]amino]-2-naphthacenecarboxamide	7A	1-amino-piperidine	2 hrs.	613 (M+H)

his Sheet Has Been Replaced


Example 25

[4S-(4- α ,12 α)]-4,7-Bis(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

To 0.50 g of O-benzylhydroxylamine and 2.5 ml of 1,3-dimethyl-2-imidazolidinone is added 0.80 g of sodium bicarbonate. The mixture is stirred at room temperature for 2 hours, filtered and the filtrate added to 0.10 g of product from 7A. The reaction solution is stirred at room temperature for 2 hours and then added to 100 ml of diethyl ether. The resulting precipitate is collected and dried to give 0.90 g of the desired product.

MS(FAB): m/z 636 (M+H).

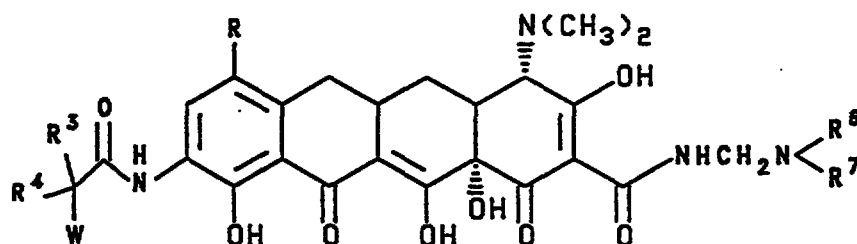
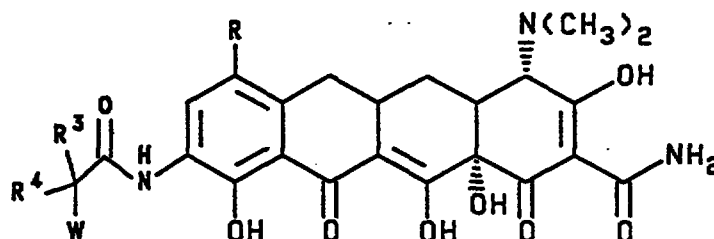
this Sheet Has Been ReplacedT





We claim:

1. A compound of the formula:



wherein:

R is a halogen selected from bromine, chlorine, fluorine and iodine; or $R = -NR^1R^2$ and when $R = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$;

and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-propyl}$,

$R^2 = \text{n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{1-methylethyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-butyl}$,

$R^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$;





and when $R^1 = 1\text{-methylpropyl}$,
 $R^2 = 2\text{-methylpropyl}$;
 R^3 is selected from hydrogen; straight or branched
 (C_4-C_8) alkyl group selected from 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; 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; substi-
 tuted (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^4 is selected from hydrogen and (C_1-C_6) alkyl selected
 from methyl, ethyl, propyl, isopropyl, butyl, isobutyl,
 pentyl and hexyl;
 when R^3 does not equal R^4 the stereochemistry of the
 asymmetric carbon (i.e. the carbon bearing the
 substituent W) maybe be either the racemate (DL) or the
 individual enantiomers (L or D);
 W is selected from hydroxylamino; (C_7-C_{12}) straight or
 branched alkyl monosubstituted amino group substitution
 selected from heptyl, octyl, nonyl, decyl, undecyl,
 dodecyl and the diastereomers and enantiomers of said
 branched alkyl monosubstituted amino group; (C_1-C_4)
 straight or branched fluoroalkylamino group selected
 from trifluoromethyl, 2,2,2-trifluoroethyl,
 3,3,3-trifluoropropyl, 3,3,3,2,2-pentafluoropropyl,
 2,2-difluoropropyl, 4,4,4-trifluorobutyl and 3,3-di-





fluorobutyl; (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, 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 and alkynyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, propynyl, 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 phenyl and naphthyl; (C_7 - C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; substituted (C_6 - C_{10})aryl monosubstituted amino group [substitution selected from (C_1 - C_5)acyl, (C_1 - C_5)acylamino, (C_1 - C_4)alkyl, mono or disubstituted (C_1 - C_8)alkylamino, (C_1 - C_4)alkoxy, (C_1 - C_4)alkoxycarbonyl, (C_1 - C_4)alkylsulfonyl, amino, carboxy, cyano, halogen, hydroxy, nitro and trihalo(C_1 - C_3)alkyl]; straight or branched symmetrical disubstituted (C_6 - C_{14})alkylamino group substitution selected from dibutyl, diisobutyl, di-s-butyl, dipentyl, diisopentyl, di-s-pentyl, dihexyl, diisohexyl and di-s-hexyl; symmetrical disubstituted (C_6 - C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, di(dicyclopropyl)methyl, dicyclohexyl and dicycloheptyl; straight or branched unsymmetrical disubstituted (C_3 - C_{14})alkylamino group wherein the





total number of carbons in the substitution is more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group substitution selected from 4-methylpiperidine, 4-hydroxypiperidine, 4-(hydroxymethyl)piperidine, 4-(aminomethyl)piperidine, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 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, 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_4)alkoxy-piperazinyl, 4-(C_6-C_{10})aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo[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, 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; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3)alkyl-thiomorpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imidazolyl, 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-tri-





azolyl), 5-(C₁-C₃)alkyl-1-(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), (benzimidazolyl), and (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, 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, β-aminopropionic acid, α-butyric acid, β-aminobutyric acid and the enantiomers of said carboxy(C₂-C₄)alkylamino group; 1,1-disubstituted hydrazino group selected from 1,1-dimethylhydrazino, N-aminopiperidinyl, 1,1-diethylhydrazino, and N-aminopyrrolidinyl; (C₁-C₄)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy and 1,1-dimethylethoxy; (C₃-C₈)cycloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, bicyclo[2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C₃-C₈)cycloalkoxyamino group; (C₆-C₁₀)aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino; (C₇-C₁₁)arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)-methoxy and phenylpropoxy;





$[\beta$ or γ -(C_1 - C_3)acylamido]alkylamino group substitution selected from 2-(formamido)ethyl, 2-(acetamido)ethyl, 2-(propionylamido)ethyl, 2-(acetamido)propyl, 2-(formamido)propyl and the enantiomers of said $[\beta$ or γ -(C_1 - C_3)acylamido]alkylamino group; β or γ -(C_1 - C_3)alkoxyalkylamino group substitution selected from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl, 2-methoxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3,3-diethoxypropyl and the enantiomers of said β or γ -(C_1 - C_3)alkoxyalkylamino group; β , γ , or δ (C_2 - C_4)hydroxyalkylamino group substitution selected from 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl and 4-hydroxybutyl; or R^3 and W taken together are selected from $-(CH_2)_n(R^5)N-$, $n = 3 - 4$, and $-CH_2CH(OH)CH_2(R^5)N-$ wherein R^5 is selected from hydrogen and (C_1 - C_3)acyl, the acyl selected from formyl, acetyl, propionyl and (C_2 - C_3)haloacyl selected from chloroacetyl, bromoacetyl, trifluoroacetyl, 3,3,3-trifluoropropionyl and 2,3,3-trifluoropropionyl; R^6 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 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-



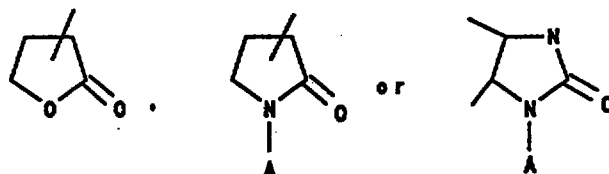


dinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



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) 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-piperaziny1, 4-ethyl-2,3-dioxo-1-piperaziny1, 4-methyl-2,3-dioxo-1-piperaziny1, 4-cyclopropyl-2-dioxo-1-piperaziny1, 2-dioxomorpholinyl, 2-dioxo-thiomorpholinyl; or $-(CH_2)_nCOOR^8$ where $n=0-4$ and R^8 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, or β -naphthyl; R^7 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 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:



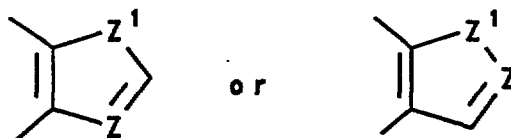
Z = N, O, S or Se

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:



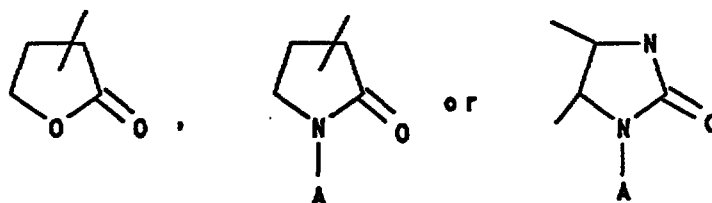


-67-



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 $-(CH_2)_nCOOR^8$ where $n=0-4$ and R^8 is selected from hydrogen; straight or branched (C_1-C_3) alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10}) aryl selected from phenyl, α -naphthyl or β -naphthyl; with the proviso that R^6 and R^7 cannot both be hydrogen; or R^6 and R^7 taken together are $-(CH_2)_2B(CH_2)_2-$, wherein B is selected from $(CH_2)_n$ and $n=0-1$, $-NH$, $-N(C_1-C_3)$ alkyl [straight or branched], $-N(C_1-C_4)$ 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.

2. The compound according to Claim 1, wherein:

R is a halogen selected from bromine, chlorine and iodine; or $R = -NR^1R^2$

and when $R = -NR^1R^2$ and $R^1 =$ methyl or ethyl,

$R^2 =$ methyl or ethyl,

R^3 is selected from hydrogen;

R^4 is selected from hydrogen and (C_1-C_2) alkyl selected from methyl and ethyl;

when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) may be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from (C_7-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group;

(C_2) fluoroalkyl-amino group selected from 2,2,2-trifluoroethyl and 3,3,3-trifluoropropyl;





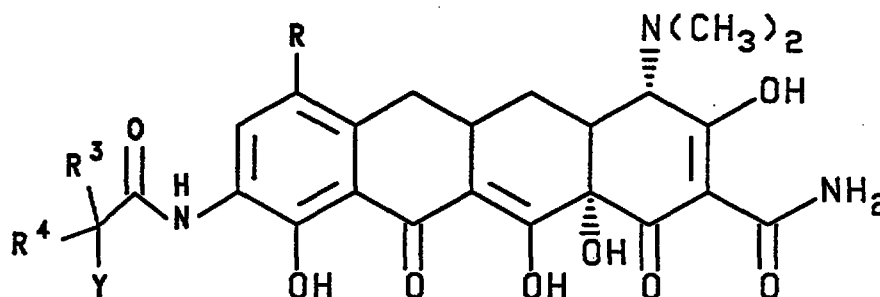
(C₃-C₈)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the diastereomers and enantiomers of said (C₃-C₈)cycloalkyl monosubstituted amino group; [(C₄-C₅)cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)-methyl and (cyclopropyl)ethyl; (C₃-C₄)alkenyl and alkynyl monosubstituted amino group substitution selected from allyl and propynyl; (C₂-C₇)azacycloalkyl and substituted (C₂-C₇)azacycloalkyl group substitution selected from 4-methylpiperidine, 4-hydroxypiperidine and 4-(hydroxymethyl)piperidine; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C₁-C₃)alkylmorpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl and 4-(C₁-C₃)alkylpiperazinyl; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and 2-(C₁-C₃)alkylthiomorpholinyl; (heterocycle)methylamino group selected from 2- or 3-thienylmethylamino and 2-, 3- or 4-pyridylmethylamino; 1,1-disubstituted hydrazino group selected from 1,1-dimethylhydrazino and N-amino-piperidiny. [β or γ -(C₁-C₃)acylamido]alkylamino group substitution selected from 2-(acetamido)ethyl; β or γ -(C₁-C₃)alkoxyalkyl- amino group substitution selected from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl, 2-methoxypropyl and 3-methoxypropyl; β , γ or δ (C₂-C₄)hydroxyalkylamino selected from 4-hydroxybutyl and 3-hydroxypropyl; or R³ and W taken together are selected from -(CH₂)_n(R⁵)N-, n= 3, and R⁵ is selected from hydrogen and trifluoroacetyl; R⁶ is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; R⁷ is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl,





n-propyl or 1-methylethyl; with the proviso that R^6 and R^7 cannot both be hydrogen; or R^6 and R^7 taken together are $-(CH_2)_2B(CH_2)_2-$, wherein B is selected from $(CH_2)_n$ and $n=0-1$, $-NH$, $-N(C_1-C_3)\text{alkyl}$ [straight or branched], $-N(C_1-C_4)\text{alkoxy}$, 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.

3. A compound of the formula:



wherein:

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

R is a halogen selected from bromine, chlorine, fluorine and iodine; or $R = -NR^1R^2$ and when $R = -NR^1R^2$ and $R^1 = \text{hydrogen}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$; and when $R^1 = \text{methyl or ethyl}$,

$R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$;

and when $R^1 = \text{n-propyl}$,





-71-

R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = 1-methylethyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = n-butyl,
 R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = 1-methylpropyl,
 R^2 = 2-methylpropyl;
 R^3 is selected from hydrogen; straight or branched (C_4 - C_8)alkyl group selected from 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; 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^4 is selected from hydrogen and (C_1 - C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.





-72-

4. The compound according to Claim 3, where-
in:

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

R is a halogen selected from bromine, chlorine and iodine; or $R = -NR^1R^2$.

and when $R = -NR^1R^2$ and $R^1 =$ methyl or ethyl,

$R^2 =$ methyl or ethyl,

R^3 is selected from hydrogen;

R^4 is selected from hydrogen and (C_1-C_2) alkyl selected from methyl and ethyl;

when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

5. The compound according to Claims 1 or 2 wherein said salts or complexes comprise: hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric, sulfate, acetate, benzoate, citrate, cysteine, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate, arylsulfonate, aluminum, calcium, iron, magnesium or manganese.

6. The compound according to Claim 1,
[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]-acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;



* C L H S *



-73-

[4S-(4alpha,12aalpha)]-9-[[[(2,2-diethoxyethyl)amino]-acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[2-(methoxyethyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-propenylamino)acetyl]amino]-2-naphthacene-carboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methoxypropyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

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

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis-(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;

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

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[[(heptylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(undecylamino)acetyl]amino]-2-naphthacene-carboxamide dihydrochloride;



* C L M S *



[4S-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[[(2-pyridinylmethyl)amino]acetyl]amido]-2-
naphthacenecarboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-9-[[[(2-hydroxyethyl)amino]acetyl]-
amino]-1,11-dioxo-2-naphthacenecarboxamide
monohydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-
[[[(2-hydroxyethyl)methylamino]acetyl]amino]-1,11-dioxo-
2-naphthacenecarboxamide;

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

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[[2,2,2-trifluoroethyl)amino]-2-naphthacene-
carboxamide;

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

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[[2-(1-piperidinyl)ethyl]amino]acetyl]amino]-
2-naphthacenecarboxamide;

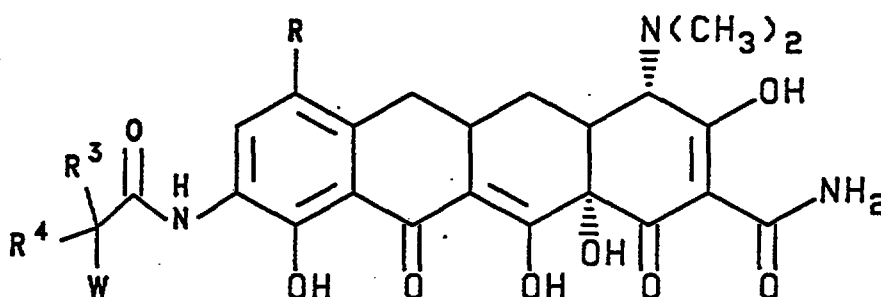
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-
[[[methyl-2-propynylamino]acetyl]amino]-1,11-dioxo-2-
naphthacenecarboxamide;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
hydroxy-1,11-dioxo-9-[[[(1-piperidinylamino)acetyl]-
amine]-2-naphthacenecarboxamide; or

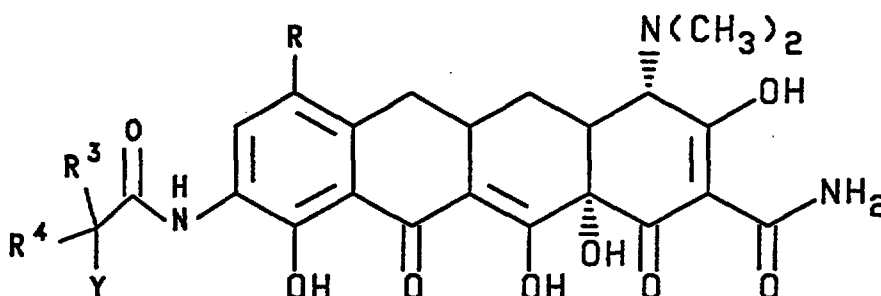


[4S-(4- α ,12 α)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethoxy)-amino]acetyl]amino]-2-naphthacenecarboxamide.

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



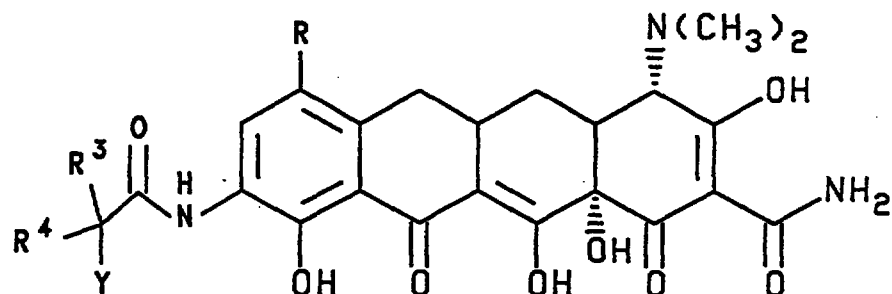
according to Claim 1, which comprises reacting a 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxy-tetracycline, or its organic and inorganic salt or metal complex, of the formula:



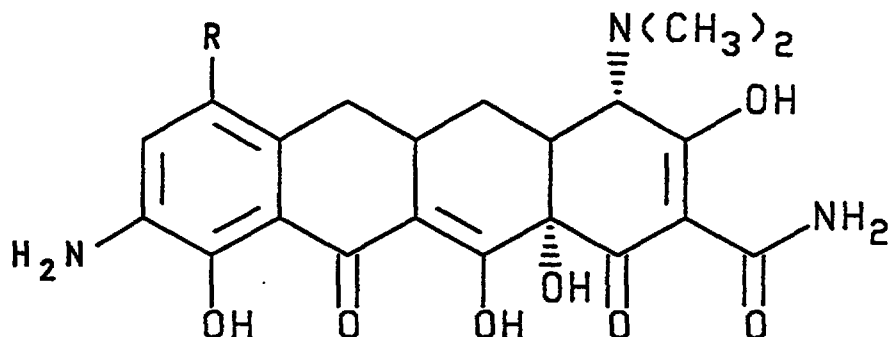
according to Claim 3, with a nucleophile of the formula WH, wherein W is as defined in Claim 1, in a polar-aprotic solvent and in an inert atmosphere.

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

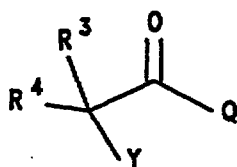




according to Claim 3, which comprises reacting a 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:



with a straight or branched haloacyl halide of the formula:



wherein Y, R³ and R⁴ are as defined in Claim 1 and Q 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.

9. 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.

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

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

12. 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.

This Sheet Has Been Replaced

