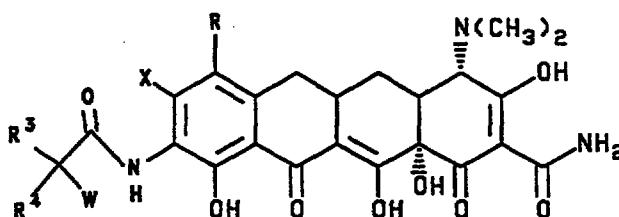


31,926

NOVEL 7-(SUBSTITUTED)-8-
(SUBSTITUTED)-9-[(SUBSTITUTED
GLYCYL)AMIDO]-6-DEMETHYL-6-
DEOXYTETRACYCLINES

ABSTRACT OF THE INVENTION

The invention provides compounds of the formula:



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wherein R, R³, R⁴, X and W are defined in the specification. These compounds are useful as antibiotic agents.

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☒	Description : paged 1 to paged 15	
☒	Claim(s) : paged 16 to paged 20	
☐	Drawing(s) : paged to paged	
☒	Abstract : paged 4 to paged 5	
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Title: NOVEL 7-(SUBSTITUTED)-8-
(SUBSTITUTED)-9-[(SUBSTITUTED
GLYCYL)AMIDO]-6-DEMETHYL-6-
DEOXYTETRACYCLINES

BACKGROUND OF THE INVENTION

1. Field of the Invention

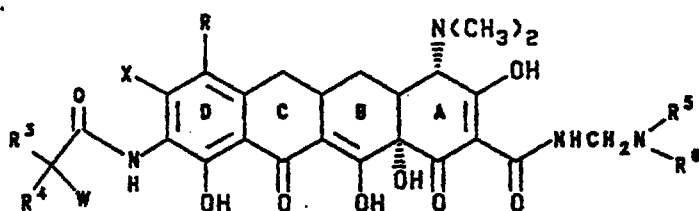
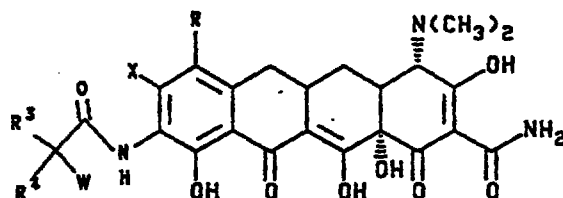
The invention relates to novel [4S-(4alpha,-12aalpha)]-4-(dimethylamino)-7-(substituted)-8-(substituted)-9-[[(substituted amino) substituted] amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides, herein after called 7-(substituted)-8-(substituted)-9-[(substituted glycy) amido]-6-demethyl-6-deoxytetracyclines, which exhibit antibiotic activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and are useful as anti-biotic agents.

The invention also relates to novel 9-[(haloacyl) amido]-7-(substituted)-8-(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)-8-(substituted)-9-[(substituted glycy) amido]-6-demethyl-6-deoxytetracyclines, represented by formula I and II, which have antibacterial activity;

with method of treating infectious diseases in warm
 blooded animals employing these compounds; with pharma-
 ceutical preparations containing these compounds; with
 novel intermediate compounds and processes for the pro-
 duction of these compounds. More particularly, this
 invention is concerned with compounds of formula I and
 II which have enhanced antibiotic activity against
 tetracycline resistant strains as well as a high level
 of activity against strains which are normally
 susceptible to tetracyclines.



In formula I and II,

X is halogen or trifluoromethanesulfonyloxy, the
halogen is selected from bromine, chlorine, fluorine
and iodine;

R is selected from hydrogen; 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_1-C_8)alkyl group selected from methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and
octyl; α -mercapto(C_1-C_4)alkyl group selected from
mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methyl-
ethyl, α -mercaptopropyl and α -mercaptobutyl;

α -hydroxy(C_1-C_4)alkyl group selected from hydroxy-
methyl, α -hydroxyethyl, α -hydroxy-1-methylethyl,

α -hydroxypropyl and α -hydroxybutyl; carboxyl(C_1-C_8)-
alkyl group; (C_6-C_{10})aryl group selected from phenyl,
 α -naphthyl and β -naphthyl; substituted(C_6-C_{10})aryl
group (substitution selected from hydroxy, halogen,

(C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino,
cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and
carboxy); (C_7-C_9)aralkyl group selected from benzyl,

1-phenylethyl, 2-phenylethyl and phenylpropyl; substi-
tuted(C_7-C_9)aralkyl group [substitution selected from



halo, (C₁-C₄)alkyl, nitro, hydroxy, amino, mono- or disubstituted (C₁-C₄)alkylamino, (C₁-C₄)alkoxy, (C₁-C₄)alkylsulfonyl, cyano and carboxy];

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

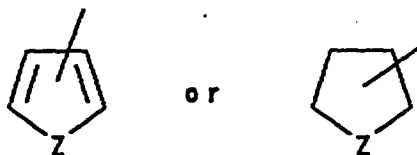
W is selected from amino; hydroxylamino; (C₁-C₁₂) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C₃-C₈)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]-hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C₃-C₈)cycloalkyl monosubstituted amino; [(C₄-C₁₀)cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)-methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C₃-C₁₀)alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl(cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (C₆-C₁₀)aryl

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alkyl group selected from piperazinyl, 2-(C₁-C₃)alkyl-
piperazinyl, 4-(C₁-C₃)alkylpiperazinyl, 2,4-dimethyl-
piperazinyl, 4-(C₁-C₄)alkoxypiperazinyl, 4-(C₆-C₁₀)-
aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diaza-
bicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo-
[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo-
[2.2.2]oct-2-yl, 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 substi-
tuted 1-azathiacycloalkyl group selected from thio-
morpholinyl, 2-(C₁-C₃)alkylthiomorpholinyl and 3-
(C₃-C₆)cycloalkylthiomorpholinyl; N-azolyl and substi-
tuted N-azolyl group selected from 1-imidazolyl, 2-
(C₁-C₃)alkyl-1-imidazolyl, 3-(C₁-C₃)alkyl-1-imidazo-
lyl, 1-pyrrolyl, 2-(C₁-C₃)alkyl-1-pyrrolyl, 3-(C₁-C₃)-
alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-
(C₁-C₃)alkyl-1-(1,2,3-triazolyl), 5-(C₁-C₃)alkyl-1-
(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl,
2-tetrazolyl and benzimidazolyl; (heterocycle)amino
group selected from 2- or 3-furanylamino, 2- or
3-thienylamino, 2-, 3- or 4-pyridylamino, 2- or
5-pyridazinylamino, 2-pyrazinylamino, 2-(imidazolyl)-
amino, (benzimidazolyl)amino, and (benzothiazolyl)amino
and substituted (heterocycle)amino group as defined
above with 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-pyrazinylmethyl-
amino, 2-(imidazolyl)methylamino, (benzimidazolyl)-
methylamino, and (benzothiazolyl)methylamino and
substituted (heterocycle)methylamino group as defined
above with 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, and

β -aminobutyric acid and the enantiomers of said
 carboxy(C_2-C_4)alkylamino group; (C_1-C_4)alkoxy-
 carbonylamino group substitution selected from methoxy-
 5 carbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycar-
 bonyl, isopropoxycarbonyl, 1,1-dimethyl-
 ethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxy-
 carbonyl; (C_1-C_4)alkoxyamino group substitution select-
 10 ed from methoxy, ethoxy, n-propoxy, 1-methylethoxy,
 n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy;
 (C_3-C_8)cycloalkoxyamino group selected from cyclopro-
 poxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethyl-
 cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy,
 15 cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy,
 bicyclo[2.2.2]oct-2-yloxy and the diastereomers and
 enantiomers of said (C_3-C_8)cycloalkoxyamino group;
 (C_6-C_{10})aryloxyamino group selected from phenoxyamino,
 1-naphthyloxyamino and 2-naphthyloxyamino; (C_7-C_{11})-
 arylalkoxyamino group substitution selected from
 20 benzyloxy, 2-phenylethoxy, 1-phenylethoxy,
 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpro-
 poxy;
 R^5 is selected from hydrogen; straight or branched
 (C_1-C_3)alkyl group selected from methyl, ethyl,
 25 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
 30 membered aromatic or saturated ring with one N, O, S or
 Se heteroatom optionally having a benzo or pyrido ring
 fused thereto:

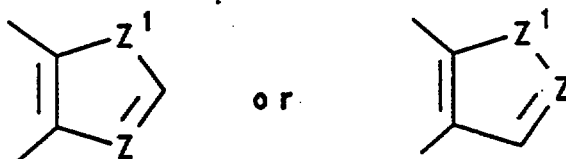


Z = N, O, S or Se



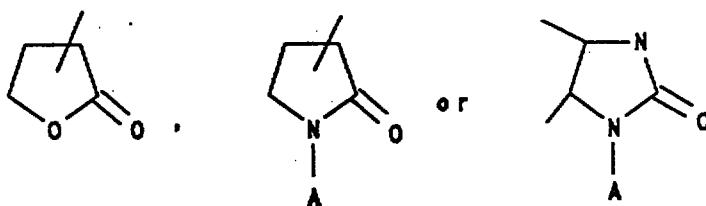


such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrro-
lidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydro-
furanyl, furanyl, benzofuranyl, tetrahydrothienyl,
thienyl, benzothienyl or selenazolyl, or a five mem-
bered aromatic ring with two N, O, S or Se heteroatoms
optionally having a benzo or pyrido ring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



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

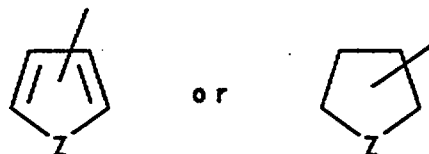
such as imidazolyl, pyrazolyl, benzimidazolyl, oxa-
zolyl, benzoxazolyl, indazolyl, thiazolyl, benzothia-
zolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimi-
dazolyl, or a five membered saturated ring with one or
two N, O, S or Se heteroatoms and an adjacent appended
O heteroatom:



(A is selected from hydrogen; straight or branched
(C_1-C_4)alkyl; C_6 -aryl; substituted C_6 -aryl (substitu-
tion selected from halo, (C_1-C_4)alkoxy, trihalo(C_1-C_3)-
alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl,
(C_1-C_3)alkylamino or carboxy); (C_7-C_9)aralkyl group
selected from benzyl, 1-phenylethyl, 2-phenylethyl or
phenylpropyl)

such as γ -butyrolactam, γ -butyrolactone, imidazo-
lidinone or N-aminoimidazolidinone, or a six membered
aromatic ring with one to three N heteroatoms such as

pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C₁-C₃)alkylthio-pyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiophomorpholinyl; or -(CH₂)_nCOOR⁷ where n=0-4 and R⁷ 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; 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:



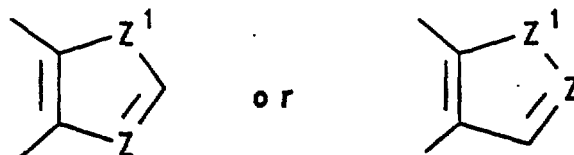
Z = N, O, S or Se

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



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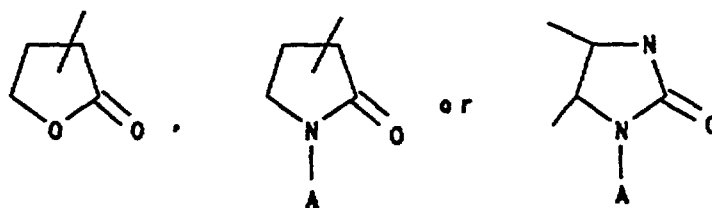


$Z \text{ or } Z' = N, O, S \text{ or } Se$

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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:

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(A is selected from hydrogen; straight or branched (C_1-C_4) alkyl; C_6 -aryl; substituted C_6 -aryl (substitution selected from halo, (C_1-C_4) alkoxy, trihalo (C_1-C_3) -alkyl, nitro, amino, cyano, (C_1-C_4) alkoxycarbonyl, (C_1-C_3) alkylamino or carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

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such as γ -butyrolactam, γ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3) 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-dioxomorpho-
linyl, 2-dioxothiomorpholinyl; or $-(CH_2)_nCOOR^7$ where
5 $n=0-4$ and R^7 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 pro-
viso that R^5 and R^6 cannot both be hydrogen;
or R^5 and R^6 taken together are $-(CH_2)_2B(CH_2)_2-$, where-
10 in 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
15 acceptable organic and inorganic salts or metal com-
plexes.

Preferred compounds are compounds according
to the above formula I and II wherein: X is halogen
or trifluoromethanesulfonyloxy, the halogen is selected
20 from bromine, chlorine, fluorine and iodine; R is
selected from hydrogen; halogen selected from bromine,
chlorine and iodine; or $R = -NR^1R^2$
and when $R = -NR^1R^2$
and $R^1 = \text{hydrogen}$, $R^2 = \text{methyl, ethyl, n-propyl,}$
25 $1\text{-methylethyl, n-butyl, 1-methylpropyl or}$
 2-methylpropyl;
and when $R^1 = \text{methyl or ethyl,}$
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,}$
 $1\text{-methylpropyl or 2-methylpropyl;}$
30 R^3 is selected from hydrogen; straight or branched
 (C_1-C_8) alkyl group selected from methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and
octyl; α -hydroxy (C_1-C_4) alkyl group selected from
hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl,
35 α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) -
alkyl group; (C_6-C_{10}) aryl group selected from phenyl,
 α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl
group (substitution selected from hydroxy, halogen,



(C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, and carboxy);

(C₇-C₉)aralkyl group selected from benzyl,

1-phenylethyl, 2-phenylethyl and phenylpropyl;

substituted(C₇-C₉)aralkyl group [substitution selected from halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-sulfonyl, cyano and carboxy];

R⁴ is selected from hydrogen and (C₁-C₄)alkyl selected from methyl, ethyl propyl, isopropyl, butyl and isobutyl;

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

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

enantiomers of said branched alkyl monosubstituted amino group; (C₃-C₈)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the diastereomers and enantiomers of

said (C₃-C₈)cycloalkyl monosubstituted amino group; [(C₄-C₁₀)cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl and (cis-2-methylcyclobutyl)-

methyl; (C₃-C₁₀)alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-



2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and
2-cyclohexenyl; (C₇-C₁₀)alkylamino group substitution
5 selected from benzyl, 2-phenylethyl, 1-phenylethyl,
2-(naphthyl)methyl, 1-(naphthyl)methyl and phenyl-
propyl; straight or branched symmetrical disubstituted
(C₂-C₁₄)alkylamino group substitution selected from
dimethyl, diethyl, diisopropyl, di-n-propyl, dibutyl
10 and diisobutyl; symmetrical disubstituted (C₃-C₁₄)-
cycloalkylamino group substitution selected from
dicyclopropyl, dicyclobutyl, dicyclopentyl,
dicyclohexyl and dicycloheptyl; straight or branched
unsymmetrical disubstituted (C₃-C₁₄)alkyl amino group
15 wherein the total number of carbons in the substitution
is not more than 14; unsymmetrical disubstituted
(C₄-C₁₄)cycloalkylamino group wherein the total number
of carbons in the substitution is not more than 14;
(C₂-C₈)azacycloalkyl and substituted
(C₂-C₈)azacycloalkyl group substitution selected from
20 aziridinyl, azetidiny, pyrrolidinyl, piperidinyl,
4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-
3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrroli-
diny, 2-azabicyclo[2.1.1]hex-2-yl, 5-azabicyclo-
[2.1.1]hex-5-yl, 2-azabicyclo[2.2.1]hept-2-yl,
25 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)azacyclo-
alkyl group; 1-aza-oxacycloalkyl selected from
morpholinyl and 1-aza-5-oxocycloheptane; substituted
30 1-aza-oxacycloalkyl group substitution selected from
2-(C₁-C₃)alkylmorpholinyl, 3-(C₁-C₃)alkylisoxazo-
lidiny, tetrahydrooxazinyl and 3,4-dihydrooxazinyl;
[1,n]-diazacycloalkyl and substituted [1,n]-diazacyclo-
alkyl group selected from piperazinyl, 2-(C₁-C₃)alkyl-
35 piperazinyl, 4-(C₁-C₃)alkylpiperazinyl, 2,4-dimethyl-
piperazinyl, 4-(C₁-C₄)alkoxy piperazinyl, 2,5-diaza-
bicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo-
[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]-
oct-2-yl, and 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)alkylthiomorpholinyl and
3-(C₃-C₆)cycloalkylthiomorpholinyl; N-azolyl and
substituted N-azolyl group selected from 1-imidazolyl,
2-(C₁-C₃)alkyl-1-imidazolyl, 3-(C₁-C₃)alkyl-1-
imidazolyl, 1-pyrrolyl, 2-(C₁-C₃)alkyl-1-pyrrolyl,
3-(C₁-C₃)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-
triazolyl), 4-(C₁-C₃)alkyl-1-(1,2,3-triazolyl),
5-(C₁-C₃)alkyl-1-(1,2,3-triazolyl) and
4-(1,2,4-triazolyl); (heterocycle)methylamino group
said heterocycle selected from 2- or
3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3-
or 4-pyridylmethylamino, 2- or 5-pyridazinylmethyl-
amino, 2-pyrazinylmethylamino, 2-(imidazolyl)-
methylamino, (benzimidazolyl)methylamino, and
(benzothiazolyl)methylamino and substituted
(heterocycle)amino group as defined above with
substitution selected from straight or branched
(C₁-C₆)alkyl; carboxy(C₂-C₄)alkylamino group selected
from aminoacetic acid, α-aminopropionic acid, β-amino-
propionic acid, α-butyric acid, β-aminobutyric acid and
the enantiomers of said carboxy(C₂-C₄)alkylamino group;
(C₁^{*}-C₄)alkoxycarbonylamino group substitution selected
from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl,
propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethyl-
ethoxycarbonyl, n-butoxycarbonyl, and 2-methylpro-
poxycarbonyl; (C₁-C₄)alkoxyamino group substitution
selected from methoxy, ethoxy, n-propoxy, 1-methyl-
ethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethyl-
ethoxy; (C₃-C₈)cycloalkoxyamino group selected from
cyclopropoxy, trans-1,2-dimethylcyclopropoxy,
cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclo-
pentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy,
bicyclo[2.2.1]hept-2-yloxy, bicyclo[2.2.2]oct-2-yloxy
and the diastereomers and enantiomers of said



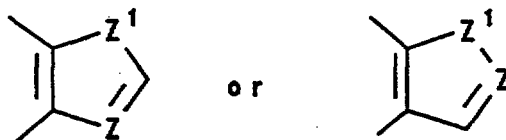
(C₃-C₈)cycloalkoxyamino group; (C₇-C₁₁)arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

R⁵ 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

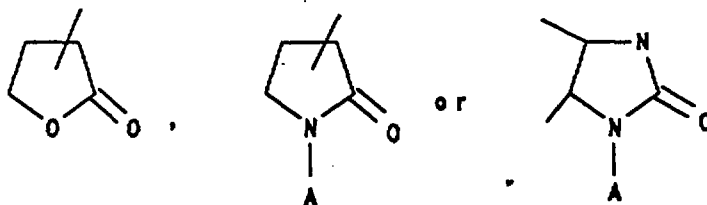
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused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



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

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

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(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)

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such as γ -butyrolactam, γ -butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C₁-C₃)alkylthiopyridazinyl; or -(CH₂)_nCOOR⁷ where n=0-4 and R⁷ 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;

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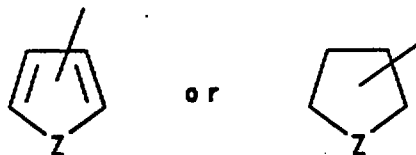
R⁶ is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C₆-C₁₀)aryl group selected from phenyl, α -naphthyl or β -naphthyl; (C₇-C₉)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected 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:

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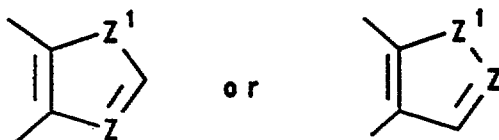


Z = N, O, S or Se

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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 aro-
matic ring with two N, O, S or Se heteroatoms optional-
ly having a benzo or pyrido ring fused thereto:

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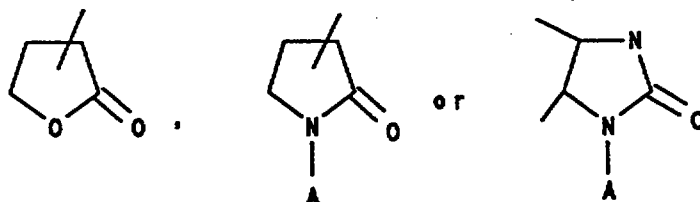


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Z or Z¹ = N, O, S or Se

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

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(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 phenyl-
propyl)

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such as γ -butyrolactam, γ -butyrolactone, imidazo-
lidinone or N-aminoimidazolidinone, or a six membered
aromatic ring with one to three N heteroatoms such as
pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-
triazinyl, pyrimidinyl or (C_1-C_3) alkylthiopyridazinyl;
or $-(CH_2)_nCOOR^7$ where $n=0-4$ and R^7 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^5 and R^6 cannot both
be hydrogen; or R^5 and R^6 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.

Particularly preferred compounds are com-
pounds according to the above formula I and II wherein:
X is halogen or trifluoromethanesulfonyloxy, the
halogen is selected from bromine, chlorine, fluorine
and iodine; R is selected from hydrogen; halogen
selected from bromine, chlorine and iodine;
or $R = -NR^1R^2$
and when $R = -NR^1R^2$ and $R^1 = \text{hydrogen}$,
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,}$
 $1\text{-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;}$
and when $R^1 = \text{methyl or ethyl,}$
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,}$
 $1\text{-methylpropyl or 2-methylpropyl;}$
 R^3 is selected from hydrogen; straight or branched
 (C_1-C_6) alkyl group selected from methyl, ethyl, propyl,
isopropyl, 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;



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

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

W is selected from amino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl,

2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group;

(C_3-C_5)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl and the diastereomers and enantiomers of said (C_3-C_5)cycloalkyl monosubstituted amino group;

[(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl and (cyclobutyl)methyl; (C_3-C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl,

3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (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_2-C_{14})alkyl-

amino group substitution selected from dimethyl, diethyl, diisopropyl, and di-n-propyl; 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
aziridinyl, azetidiny, pyrrolidinyl, piperidinyl,
4-methylpiperidinyl, 2-methylpyrrolidinyl,
cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethyl-
pyrrolidinyl and the diastereomers and enantiomers of
said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)-
azacycloalkyl group; 1-azaioxacycloalkyl selected from
morpholinyl and 1-aza-5-oxocycloheptane; substituted
1-azaioxacycloalkyl group substitution selected from
2- (C_1-C_3) alkylmorpholinyl, 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) alkyl-
piperazinyl, 2,4-dimethylpiperazinyl, 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,
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
and 2- (C_1-C_3) alkylthiomorpholinyl; N-azolyl and
substituted N-azolyl group selected from 1-imidazolyl,
indolyl, 1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl);
(heterocycle)methylamino group selected from 2- or
3-furylmethylamino, 2- or 3-thienylmethylamino and 2-,
3- or 4-pyridylmethylamino; (C_1-C_4)alkoxycarbonylamino
group substitution selected from methoxycarbonyl,
ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl,
isopropoxycarbonyl, 1,1-dimethylethoxycarbonyl,
n-butoxycarbonyl, and 2-methylpropoxycarbonyl;
(C_1-C_4)alkoxyamino group substitution selected from
methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy,
2-methylpropoxy, and 1,1-dimethylethoxy;



(C₇-C₁₁)arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

R⁵ 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 aro-
matic ring with two N, O, S or Se heteroatoms optional-
ly 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 -(CH₂)_nCOOR⁷ where n=0-4 and R⁷ is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;



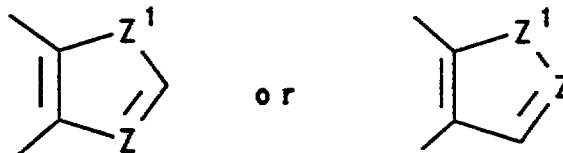
or (C₆-C₁₀)aryl group selected from phenyl, α-naphthyl, or β-naphthyl;

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



Z or 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 pyridyl-imidazolyl; or -(CH₂)_nCOOR⁷ where n=0-4 and R⁷ is selected from hydrogen; straight or branched (C₁-C₃)-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^5 and R^6 cannot both be hydrogen; or R^5 and R^6 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.

Compounds of special interest are compounds according to the above formula I and II wherein: X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is selected from hydrogen; halogen selected from chlorine and iodine; or $R = -NR^1R^2$

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

R^3 is selected from hydrogen; straight or branched (C_1-C_2) alkyl group selected from methyl and ethyl; R^4 is selected from hydrogen and (C_1-C_6) 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 W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

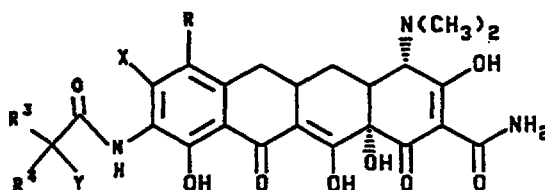
W is selected from amino; (C_1-C_4) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl and 1-methylpropyl; (C_3-C_4) cycloalkyl monosubstituted amino group substitution selected from cyclopropyl and cyclobutyl; (C_2-C_8) azacycloalkyl and substituted (C_2-C_8) azacycloalkyl selected from pyrrolidinyl, piperidinyl and 4-methylpiperidinyl; 1-azaoxacycloalkyl selected from morpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl and 4- (C_1-C_3) alkylpiperazinyl; N-azolyl and substituted

N-azolyyl group selected from 1-imidazolyyl, 2-(C₁-C₃)alkyl-1-imidazolyyl and 3-(C₁-C₃)alkyl-1-imidazolyyl; (heterocycle)methylamino group said heterocycle selected from 2-, 3- or 4-pyridylmethylamino; 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;

R⁵ is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;

R⁶ is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R⁵ and R⁶ cannot both be hydrogen; or R⁵ and R⁶ 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:





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wherein:

Y is selected from $(\text{CH}_2)_n\text{X}'$, $n = 0-5$, X' is halogen selected from bromine, chlorine, fluorine and iodine; X is halogen or trifluoromethanesulfonyl, the halogen is selected from bromine, chlorine, fluorine and iodine. R is selected from hydrogen; halogen selected from bromine, chlorine, fluorine and iodine; or $\text{R} = -\text{NR}^1\text{R}^2$ and when $\text{R} = -\text{NR}^1\text{R}^2$ and $\text{R}^1 = \text{hydrogen}$, $\text{R}^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$; and when $\text{R}^1 = \text{methyl or ethyl}$, $\text{R}^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$; and when $\text{R}^1 = \text{n-propyl}$, $\text{R}^2 = \text{n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$; and when $\text{R}^1 = \text{1-methylethyl}$, $\text{R}^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$; and when $\text{R}^1 = \text{n-butyl}$, $\text{R}^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$; and when $\text{R}^1 = \text{1-methylpropyl}$, $\text{R}^2 = \text{2-methylpropyl}$; R^3 is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; $(\text{C}_6-\text{C}_{10})$ aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted $(\text{C}_6-\text{C}_{10})$ aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo- (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) alkoxy-carbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl,



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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
disubstituted (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 W sub-
stituent) maybe be either the racemate (DL) or the in-
dividual enantiomers (L or D); and the pharmaco logic-
ally 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, flourine and iodine;
X is halogen or trifluoromethanesulfonyloxy, the
halogen is selected from bromine, chlorine, fluorine
and iodine;

R is selected from hydrogen; halogen selected from bro-
mine, chlorine 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 or 2-methylpropyl;

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_1-C_8)alkyl group selected from methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and
octyl; α -hydroxy(C_1-C_4)alkyl group selected from
hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl,
 α -hydroxypropyl and α -hydroxybutyl; carboxyl(C_1-C_8)-
alkyl group; (C_6-C_{10})aryl group selected from phenyl,
 α -naphthyl and β -naphthyl; substituted(C_6-C_{10})aryl



group (substitution selected from hydroxy, halogen,
(C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, and carboxy);
(C₇-C₉)aralkyl group selected from benzyl, 1-phenyl-
ethyl, 2-phenylethyl and phenylpropyl; substituted-
(C₇-C₉)aralkyl group [substitution selected from halo,
(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylsulfonyl,
cyano and carboxy];

R⁴ is selected from hydrogen and (C₁-C₄)alkyl selected
from methyl, ethyl propyl, isopropyl, butyl and iso-
butyl;

when R³ does not equal R⁴ the stereochemistry of the
asymmetric carbon (i.e., the carbon bearing the W sub-
stituent) maybe be either the racemate (DL) or the in-
dividual enantiomers (L or D); and the pharmaco-
logically acceptable organic and inorganic salts or
metal complexes.

Particularly preferred compounds are com-
pounds according to the above formula III wherein:
Y is selected from (CH₂)_nX', n=0-5, X' is halogen
selected from bromine, chlorine, fluorine and iodine;
X is halogen or trifluoromethanesulfonyloxy, the
halogen is selected from bromine, chlorine, fluorine
and iodine;

R is selected from hydrogen; halogen selected from bro-
mine, chlorine and iodine; or R = -NR¹R²

and when R = -NR¹R² and R¹ = hydrogen,

R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R¹ = methyl or ethyl,

R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl or 2-methylpropyl;

R³ is selected from hydrogen; straight or branched

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

(C₆-C₁₀)aryl group selected from phenyl, α-naphthyl and
β-naphthyl; (C₇-C₉)aralkyl group selected from benzyl,
1-phenylethyl, 2-phenylethyl and phenylpropyl;



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

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

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

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

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is selected from hydrogen; halogen selected from chlorine and iodine; or $R = -NR^1R^2$

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

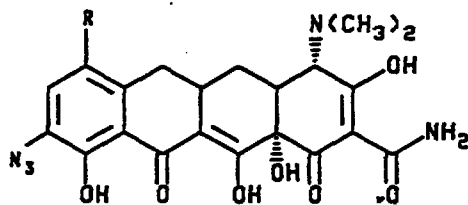
R^3 is selected from hydrogen; straight or branched (C_1-C_2) alkyl group selected from methyl and ethyl;

R^4 is selected from hydrogen and (C_1-C_6) 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 W substituent) 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.

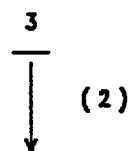
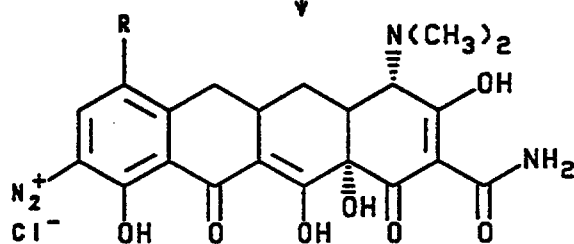
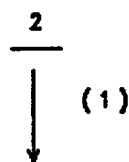
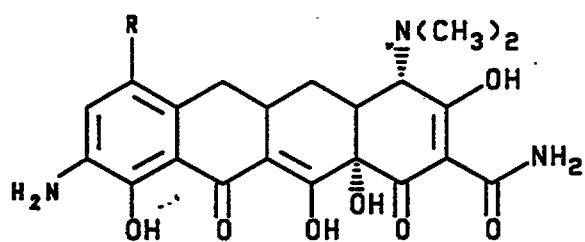


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- 1a. $R = NR^2R^3$, $R^2 = R^3$
- 1b. $R = NR^2R^3$, $R^2 \neq R^3$
- 1c. $R = X$, $X = \text{halogen, hydrogen}$

The starting 9-azido-7-(substituted)-6-de-methyl-6-deoxytetracycline, 1, described in formula 1 is prepared according to Scheme I.

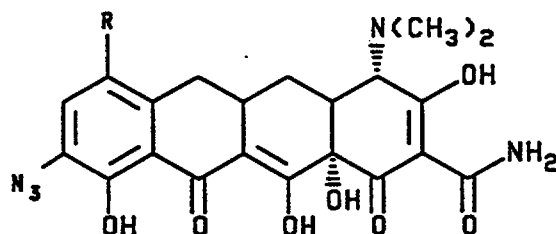
Scheme 1



Reagents.

(1) BuONO_2
0.1N $\text{CH}_3\text{OH}/\text{HCl}$

(2) NaN_3
0.1N $\text{CH}_3\text{OH}/\text{HCl}$



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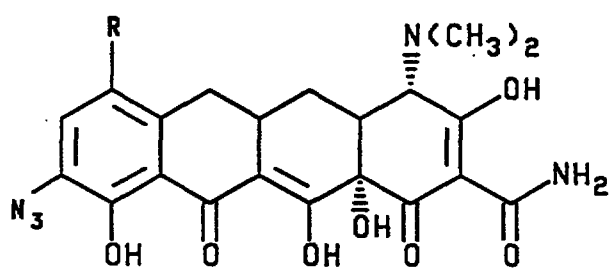
In accordance with Scheme I, 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline 2, or the mineral acid or halide salt, dissolved in 0.1N methanolic hydrogen chloride, is treated for from 5 minutes to 8 hours at from -20°C to $+45^{\circ}\text{C}$ with an excess of n-butyl nitrite to give a 9-diazonium-7-(substituted)-6-demethyl-6-deoxytetracycline, 3, or the mineral acid or halide salt. The formed diazonium compound, 3, or the mineral acid or halide salt, dissolved in 0.1 N methanolic hydrogen chloride, is treated for 5 minutes to 8 hours at from -5°C to $+50^{\circ}\text{C}$ with one equivalent of sodium azide to give the corresponding 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1, or the mineral acid or halide salt.

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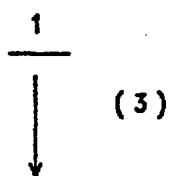
Scheme 2

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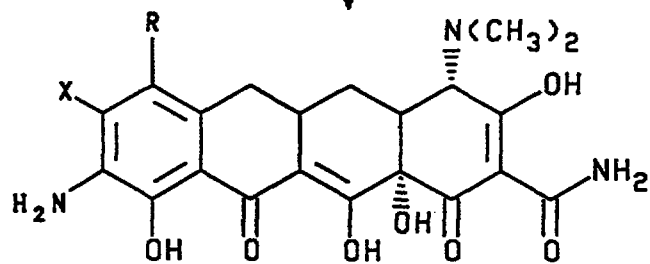
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3. Strong acid
(HCl, H₂SO₄, CF₃SO₃H, CH₃SO₃H,
HI, HF and HBr)

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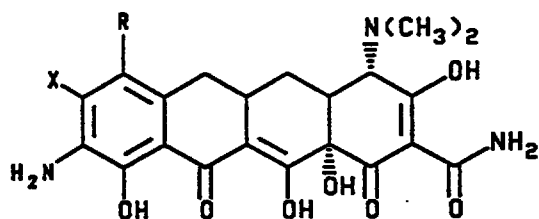
In accordance with Scheme II, a 9-azido-7-(substituted)-6-demethyl-6-deoxytetracycline, 1, or the mineral acid or halide salt, is treated for from 5 minutes to 12 hours at from -5°C to 40°C with a strong acid, such as sulfuric acid, hydrochloric acid, methanesulfonic acid, trifluoromethanesulfonic acid, hydrobromic, hydroiodic, or hydrogen fluoride to produce a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 4, or the mineral acid or halide salt.

The 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 4, or the mineral acid or halide salt, can be further converted as described in Scheme III.

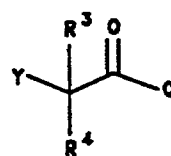
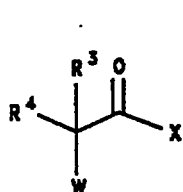
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Scheme 3

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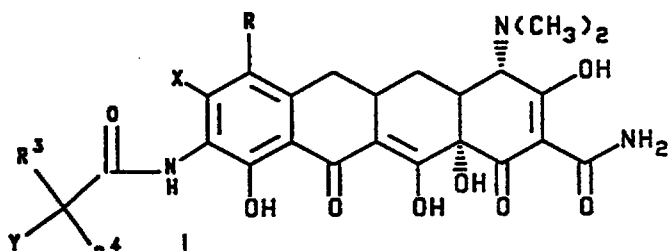


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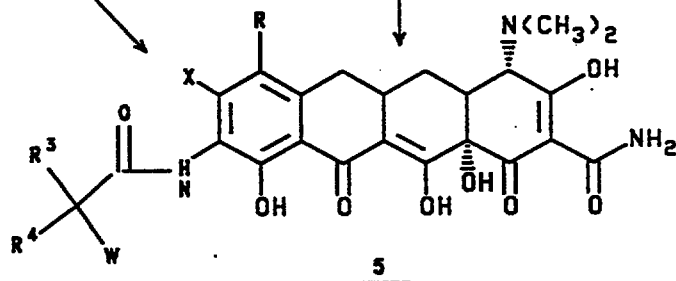


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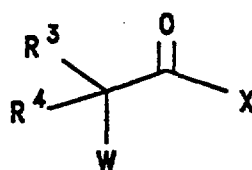


$Y = (CH_2)_n X', \quad n = 0 - 5$

X and Q = Cl, Br, I and F

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In accordance with Scheme III, a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 4, or the mineral acid or halide salt, is treated at room temperature for from 0.5 - 2 hours with an acid chloride of the formula:

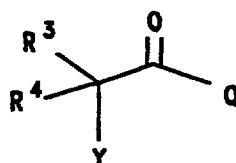


wherein R^3 , R^4 , W and X are defined hereinabove; in the presence of a suitable acid scavenger, in a suitable solvent, to form the corresponding 9-[(substituted glycyloamido)-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 5, or the mineral acid or halide salt.

The acid scavenger is selected from sodium bicarbonate, sodium acetate, pyridine, triethylamine, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, potassium carbonate, a basic ion exchange resin or equivalent thereof.

The solvents are selected from water, tetrahydrofuran, N-methylpyrrolidone, 1,3-dimethyl-2-imidazolidinone, hexamethylphosphoramide, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone, 1,2-dimethoxyethane or equivalent thereof.

Alternatively, in accordance with Scheme III, 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 4, or the mineral acid or halide salt, is treated with a straight or branched chain α -haloacyl halide of the formula:



wherein R^3 , R^4 and Y are defined hereinabove and Q is halogen selected from bromine, chlorine, fluorine and iodine, such as bromoacetyl bromide, chloroacetyl chloride, 2-bromopropionyl bromide or equivalent thereof; in the presence of a suitable acid scavenger, in a suitable solvent, to form the corresponding 9-[(haloacyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 6, or the mineral acid or halide salt.

The halogen, Y, and halide, Q, in the haloacyl halide can be the same or different halogen and are selected from bromine, chlorine, iodine and fluorine; Y is $(CH_2)_n X'$, $n = 0-5$ and X' is a halogen.

The acid scavenger and suitable solvent are as defined hereinabove.

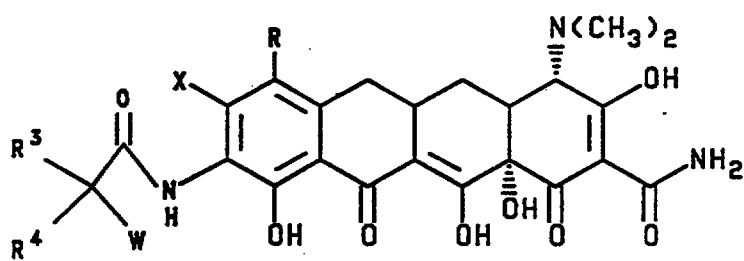
The 9-[(haloacyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 6, or mineral acid or halide salt, is treated, under an inert atmosphere of nitrogen, argon or helium, with nucleophiles of the formula, WH, where W is defined hereinabove, such as amines or substituted amines or equivalents thereof, in a suitable solvent to form the corresponding 9-[(substituted glycyloxy)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, 5, or mineral acid or halide salt.

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Scheme 4

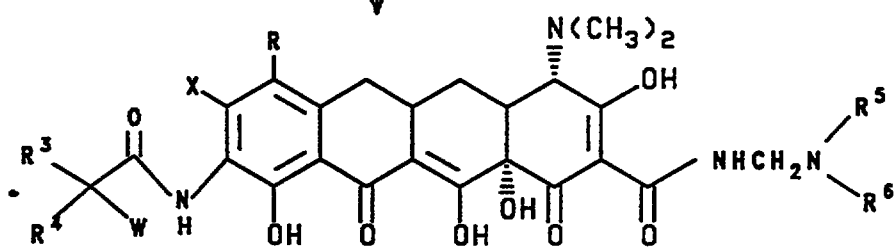
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In accordance with Scheme IV, compound 5 is selectively N-alkylated in the presence of formaldehyde and either a primary amine of the formula R^5NH_2 such as methylamine, ethylamine, benzylamine, methyl glycinate, (L or D)lysine, (L or D)alanine or their substituted congeners; or a secondary amine of the formula R^5R^6NH such as morpholine, pyrrolidine, piperidine or their substituted congeners to give the corresponding Mannich base adduct, 7.

The 9-[(substituted glycyloamido)-7-(substituted)-8-(substituted)-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). Preferably, the 7-(substituted)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxy-tetracyclines are obtained as inorganic salts such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salts such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate. 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 or 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 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 level of $1-5 \times 10^5$ CFU/ml, and a range of antibiotic concentrations (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 genetically defined strains that are sensitive to tetracycline and resistant strains that are insensitive to tetracycline, either by preventing the antibiotic from interacting with bacterial ribosomes (tetM) or by a tetK encoded membrane protein which confers tetracycline resistance by energy-dependent efflux of the antibiotic from the cell.

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 the tetM resistance determinants (Table I). Notable is 8-chloro-9-(N,N-dimethylglycyl-amido)-6-demethyl-6-deoxytetracycline, as shown in Table I, which has good 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 is equally as effective as minocycline against susceptible strains.

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Most importantly, these compounds also exhibit antibacterial activity against bacteria that contain an active efflux resistant mechanism as in tetA, tetB, or tetK (i.e., E. coli UBMS 88-1, E. coli PRPI tetA, E. coli Me4100 TN10-tetB, and S. aureus UBMS 88-7 tetK).

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As can be seen from Table I, compounds of the invention may be used to prevent or control important mammalian and 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.

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COMPOUND LEGEND FOR TABLES

- 5 A [4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4-(dimethylamino)-9-
 [[(dimethylamino) acetyl] amino]-1,4,4a,5,5a,-
 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-2-naphthacenecarboxamide disulfate.
- 10 B [4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4,7-(dimethylamino)-
 9-[[(dimethylamino) acetyl] amino]-1,4,4a,5,5a,6,-
 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
 dioxo-2-naphthacenecarboxamide.
- 15 C [4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4-(dimethylamino)-
 9-[[(dimethylamino) acetyl] amino]-1,4,4a,5,5a,-
 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-2-naphthacenecarboxamide.
- 20 D [4S-(4 α ,12 $\alpha\alpha$)]-9-[[(Butylamino) acetyl] amino]-8-
 chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-
 octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
 2-naphthacenecarboxamide dihydrochloride.
- 25 E [7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-7-
 (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-
 naphthacenyl]-1-pyrrolidineacetamide dihydro-
 chloride.
- 30 F [4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4-(dimethylamino)-1,4,-
 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
 hydroxy-1,11-dioxo-9-[[(propylamino) acetyl] amino]-
 2-naphthacenecarboxamide dihydrochloride.
- 35 G [4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-9-[[(cyclopropylmethyl-
 amino) acetyl] amino]-4-(dimethylamino)-1,4,4a,5,-
 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-2-naphthacenecarboxamide dihydro-

chloride.

- 5 H [4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4-(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
1,11-dioxo-9-[[(pentylamino) acetyl] amino]-2-
naphthacenecarboxamide dihydrochloride.
- 10 I [4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4-(dimethylamino)-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
1,11-dioxo-9-[[(methylamino) acetyl] amino]-2-
naphthacenecarboxamide dihydrochloride.
- 15 J [7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-7-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-
naphthacenyl]-1-piperidineacetamide dihydro-
chloride.
- 20 K [4S-(4 α ,12 $\alpha\alpha$)]-9-[(Chloroacetyl) amino]-8-chloro-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide hydrochloride.
- 25 L Minocycline
- M Tetracycline

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Table I
ANTIBACTERIAL ACTIVITY OF 8-(SUBSTITUED)-9-(SUBSTITUED GLYCYLAMIDO)-6-DEMEHTL-6-DEOXYTETRACYCLINES
MIC (µg/ml)

Organism	Compound															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
E. coli UBMS 88-1 Tet B	2	>32	1	2	1	0.5	1	2	1	4	>32	16	>32	16	NT	NT
E. coli J3272 Tet sens	1	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
E. coli MC 4100 Tet sens.	NT	2	0.25	0.25	0.25	0.12	0.25	0.25	0.25	1	8	0.25	0.5			
E. coli PRP1 Tet A	4	16	8	4	2	4	4	2	16	8	>32	4	32			
E. coli MC 4100 TNOCC Tet B	2	>32	1	1	1	0.5	1	2	1	4	>32	8	>32			
E. coli J3272 Tet C	8	16	8	2	1	1	1	2	16	4	>32	2	>32			
E. coli UBMS 89-1 Tet M	0.5	32	0.25	0.5	0.25	0.5	0.5	0.5	2	1	8	16	32			
E. coli UBMS 89-2 Tet sens.	2	16	1	2	1	1	1	2	2	2	>32	1	2			
E. coli J2175	1	32	1	1	1	1	1	2	1	4	>32	1	2			
E. coli BAJ9003 IMP MUT	0.25	0.12	0.12	0.25	0.12	0.12	0.12	0.25	0.25	0.25	1	0.06	0.5			
E. coli UBMS 90-4 Tet M	1	>32	0.5	1	1	0.5	1	2	1	4	>32	>32	32			
E. coli UBMS 90-5	1	32	1	1	1	0.5	1	2	1	4	>32	1	1			
E. coli #511 (MP)	0.5	4	0.5	1	0.25	0.5	1	2	2	2	16	1	1			
E. coli ATCC 25922	0.5	8	0.5	1	0.25	0.5	1	2	1	2	16	1	1			
E. coli J3272 Tet D	0.5	32	0.5	1	0.25	0.25	1	1	1	2	>32	8	>32			
S. mariescens FPOB 8733	16	>32	8	16	8	8	8	16	16	>32	>32	8	>32			
X. maltophilus NEMC 87210	2	0.5	0.05	4	1	2	4	4	16	4	8	0.25	8			
Ps. aeruginosa ATCC 27853	>32	>32	>32	>32	32	32	32	>32	16	>32	>32	8	16			
S. aureus NEMC 8769	0.06	0.12	0.03	0.5	0.25	0.25	0.5	0.5	0.5	0.5	0.5	0.12	0.25			

Table 1 (cont'd)
 ANTIBACTERIAL ACTIVITY OF 8-(SUBSTITUTED)-9-((SUBSTITUTED GLYCYL)AMIDO)-6-DEMEHTYL-6-DEOXYTETRACYCLINES
 MIC (µg/mL)

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



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

[7S-(7 α , 10 α)]-9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenediazonium chloride sulfate (1:1)

To a 0°C solution of 3.0 g of 9-amino-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate, dissolved in 100 ml of 0.1N methanolic hydrogen chloride is added, dropwise, 6.6 ml of butyl nitrite. The reaction is stirred at 0°C for 1 hour, poured into 400 ml of diethyl ether, collected and dried to give 2.64 g of the desired product.

MS(FAB): m/z 484 (M + H)

Example 2

[4S-(4 α , 12 α)]-9-Azido-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1)

To a room temperature solution of 2.64 g of product from Example 1 dissolved in 84 ml of 0.1N methanolic hydrogen chloride is added 0.353 g of sodium azide. The mixture is stirred at room temperature for 4 hours, poured into 500 ml of diethyl ether and collected to give 2.5 g of the desired product.

IR(KBr): 2080 cm⁻¹.

Example 3

9-Amino-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate

One gram of product from Example 2 is added to 10 ml of 0°C concentrated sulfuric acid. The reaction is stirred at 0°C for 1.5 hours, poured into 500 ml of diethyl ether, collected and dried to give 1.1 g of the desired product.

MS(FAB): m/z 507 (M + H).

Example 4

[4S-(4 α , 12 α)]-9-Amino-4,7-bis(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 3 using the product of Example 2 and liquid hydrogen fluoride.

Example 5

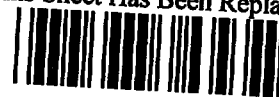
9-Amino-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride (1:1)

To 10 ml of concentrated hydrochloric acid at 0°C is added 0.20 g of 9-azido-6-demethyl-6-deoxy-tetracycline hydrochloride prepared by the procedure described in J. Am. Chem. Soc., 84: 1426-1430. The reaction is stirred at 0°C for 1 1/2 hours and concentrated in vacuo to give 0.195 g of the desired product. MS(FAB): m/z 464 (M + H).

Example 6

[4S-(4 α , 12 α)]-9-Amino-4-(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene carboxamide

The title compound is prepared by the procedure of Example 3 using 9-azido-6-demethyl-6-deoxytetracycline and liquid hydrogen fluoride.

Example 7

[4S-(4 α ,12 α)]-9-Amino-4,7-bis(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-8-[[trifluoromethyl]-
sulfonyl]oxy]-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 3 using 9-azido-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline and trifluoromethanesulfonic acid.

Example 8

[4S-(4 α ,12 α)]-9-Amino-4-(dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a,tetrahydroxy-1,11-
dioxo-8-[[trifluoromethyl)sulfonyl]oxy]-2-
naphthacenecarboxamide

The title compound is prepared by the procedure of Example 3 using 9-azido-4-(dimethylamino)-6-demethyl-6-deoxytetracycline and trifluoromethanesulfonic acid.

Example 9

[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-8-chloro-4,7-
bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide.

A well-stirred cold solution of 1.0 g of product from Example 3, 2 ml of 1,3-dimethyl-2-imidazolidinone and 1.0 g of sodium bicarbonate is treated with 0.30 ml of chloroacetyl chloride. The solution is stirred at 25°C for 30 minutes, filtered and the filtrate added dropwise to 500 ml of diethyl ether to afford 1.0 g of yellow product.

Example 10

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-8-chloro-
4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide.

A well-stirred cold solution of 1.0 g of product from Example 3, 2 ml of 1,3-dimethyl-2-

imidazolidinone and 1.0 g of sodium bicarbonate was treated with 0.36 ml of bromoacetyl bromide. The solution was stirred at 25°C for 30 minutes, filtered and the filtrate added dropwise to 500 ml of diethyl ether to afford 0.7 g of yellow product.

Example 11

[4S-(4 α ,12 α)]-9-[(α -Bromopropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

A well-stirred cold solution of 1.0 g of product from Example 3, 2 ml of 1,3-dimethyl-2-imidazolidinone and 1.0 g of sodium bicarbonate was treated with 0.42 ml of bromopropionyl bromide. The solution was stirred at 25°C for 30 minutes, filtered and the filtrate added dropwise to 500 ml of diethyl ether to afford 1.0 g of yellow product.

Substantially following the method, described in detail herein above in Example 10, the compounds of the invention listed in Examples 12 - 19 are prepared.

Example 12

[4S-(4 α ,12 α)]-9-[(α -Bromocyclobutylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Example 13

[4S-(4 α ,12 α)]-9-[(α -Bromophenylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Example 14

[4S-(4 α ,12 α)]-9-[(α -Bromo- α -cyclopropylpropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Example 15

[4S-(4 α ,12 α)]-9-[(α -Bromo-2,2-dimethylbutyryl)amino]-
8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide

Example 16

[4S-(4 α ,12 α)]-9-[(α -Bromo-(2,4-difluorophenyl)acetyl)-
amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,-
5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
1,11-dioxo-2-naphthacenecarboxamide

Example 17

[4S-(4 α ,12 α)]-9-[(α -Bromo-(2-furyl)propionyl)amino]-
8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide

Example 18

[4S-(4 α ,12 α)]-9-[(α -Bromo-(3-methoxycarbonyl-
propionyl))amino]-8-chloro-4,7-bis(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Example 19

[4S-(4 α ,12 α)]-9-[(α -Bromo-(4-methoxycarbonylbutyryl))
amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,
11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-2-naphthacenecarboxamide

Example 20

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4,7-bis-
(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide

The title compound is prepared by the
procedure of Example 10 using the product from Example
4.

Example 21

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-8-[[trifluoromethyl)-
sulfonyl]oxy]-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 10 and using the product from Example 7.

Example 22

[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-8-chloro-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide hydrochloride

A 25°C solution of 1.247 g of product from Example 5, 12 ml of DMPU and 6 ml of acetonitrile is treated with 0.564 g of chloroacetyl chloride. The mixture is stirred for 45 minutes and added dropwise to a mixture of 80 ml of 2-propanol and 400 ml of diethyl ether. The resultant yellow solid is filtered and washed several times with diethyl ether and dried in vacuo to give 1.25 g of product.

MS (FAB) = m/z 540 (M + H)

Example 23

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-8-chloro-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide hydrobromide

A 25°C solution of 1.247 g of product from Example 5, 12 ml of DMPU and 6 ml of acetonitrile is treated with 0.62 g of bromoacetyl bromide. The mixture is stirred for 45 minutes and added dropwise to a mixture of 80 ml of 2-propanol and 400 ml of diethyl ether. The resultant yellow solid is filtered and washed several times with diethyl ether and dried in vacuo to give 1.35 g of product.

Substantially following the method, described in detail herein above in Example 22 or 23, the



compounds of the invention listed in Examples 24 - 30 are prepared.

Example 24

[4S-(4 α ,12 α)]-9-[(Chloropropionyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

Example 25

[4S-(4 α ,12 α)]-9-[(Chlorobutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride.

Example 26

[4S-(4 α ,12 α)]-9-[[(4-Hydroxyphenyl)- α -chloroacetyl]-amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

Example 27

[4S-(4 α ,12 α)]-9-[[(2-Fluorophenyl)- α -bromoacetyl]-amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

Example 28

[4S-(4 α ,12 α)]-9-[(2-Bromo-4-pentenoyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

Example 29

[4S-(4 α ,12 α)]-9-[(α -Bromophenylbutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

Example 30

[4S-(4 α ,12 α)]-9-[(4-Pyridyl)- α -bromoacetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

Example 31

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4-(dimethyl-
amino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 10 using the product from Example 6.

Example 32

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4-(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-8-[[trifluoromethyl)-
sulfonyl]oxy]-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 10 using the product from Example 8.

Example 33

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-9-
[[dimethylamino)acetyl]amino]-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
1,11-dioxo-2-naphthacenecarboxamide
disulfate

A well stirred solution (25°C) of 0.2805 g of product from Example 5, 10 ml of DMPU, 3 ml of acetonitrile and 0.3 g of sodium carbonate is treated with 0.157g of N,N-dimethylaminoacetyl chloride hydrochloride. After 30 minutes, the reaction is filtered and the filtrate is added dropwise to 300 ml of diethyl ether. Concentrated sulfuric acid is added dropwise and a yellow solid precipitated. The yellow solid is collected, washed well with ether, and dried in vacuo to afford 0.21 g of product:

MS (FAB) = m/z 549 (M + H).

Example 34

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-9-
5 [[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
1,11-dioxo-2-naphthacenecarboxamide

A well stirred solution 25°C of 0.20 g of
product from Example 5, 3 ml of N-methylpyrrolidone, 1
ml of acetonitrile and 0.2 g of sodium bicarbonate is
10 treated with 0.071g of N,N-dimethylaminoacetyl chloride
hydrochloride. After 30 minutes, the reaction is
filtered and the filtrate is added dropwise to 200 ml
of diethyl ether. The yellow solid is collected,
washed well with ether, and dried in vacuo to afford
15 0.15 g of product:

MS (FAB) = m/z 548 (M + H).

Example 35

[4S-(4 α ,12 α)]-8-Chloro-4,7-(dimethylamino)-
9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,-
20 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide

A well stirred solution (25°C) of 0.104 g of
product from Example 3, 1.5 ml of N-methylpyrrolidone,
0.5 ml of acetonitrile and 0.105 g of sodium bicarbon-
25 ate is treated with 0.034g of N,N-dimethylaminoacetyl
chloride hydrochloride. After 1 hr, the reaction is
filtered and the filtrate is added dropwise to 100 ml
of diethyl ether. The yellow solid is collected,
washed well with ether, and dried in vacuo to afford
30 0.085 g of product:

MS (FAB) = m/z 591 (M + H).

Example 36

[4S-(4 α ,12 α)]-9-[[(Butylamino)acetyl]amino]-8-chloro-
4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
35 3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide

A solution of 0.20 g of the product from
Example 10, 2 ml of 1,3-dimethyl-2-imidazolidinone and



0.1 ml of n-butylamine is stirred at room temperature for 1 hr and added dropwise to 50 ml of diethyl ether to afford 0.20 g of yellow color product:

MS (FAB) m/z 620 (M + H)

Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 37 - 45 are prepared.

Example 37

[4S-(4 α , 12 α)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methylcyclobutyl)amino]acetyl]-amino]-1,11-dioxo-2-naphthacenecarboxamide

Example 38

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

Example 39

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

Example 40

[4S-(4 α , 12 α)]-8-Chloro-4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Example 41

[4S-(4 α , 12 α)]-8-Chloro-9-[[[(cyclopropylamino)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

Example 42

[4S-(4 α , 12 α)]-8-Chloro-9-[[[(cyclobutyloxy)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

Example 43

5 [7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide

Example 44

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

Example 45

15 [4S-(4 α ,12 α)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(propylamino)]-acetyl]amino]-2-naphthacenecarboxamide

Example 46

20 [4S-(4 α ,12 α)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo-2-(propylamino)propyl]amino]-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromopropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and n-propylamine.

Example 47

30 [7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -cyclobutyltetrahydro-2H-1,2-isoxazine-2-acetamide

35 The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromocyclobutylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-



12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
and tetrahydro-1,2-oxazine.

Example 48

[4S-(4 α ,12 α)]-8-Chloro-4,7-bis(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-9-[[phenyl[(phenyl-
methyl)amino]acetyl]amino]-2-
naphthacenecarboxamide

The title compound is prepared by the
procedure of Example 36 using [4S-(4 α , 12 α)]-9-[(α -
bromophenylacetyl)amino]-8-chloro-4,7-bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and
benzylamine.

Example 49

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-
10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -cyclopropyl- α -methyl-1-azetidineacetamide

The title compound is prepared by the
procedure of Example 36 using [4S-(4 α ,12 α)]-9-
[(α -bromo- α -cyclopropylpropionyl)amino]-8-chloro-
4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecar-
boxamide and azetidine.

Example 50

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -(1,1-dimethylethyl)-(3-methyl-4-
morpholine)acetamide

The title compound is prepared by the
procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -
bromo-2,2-dimethylbutyryl)amino]-8-chloro-4,7-bis(di-
methylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,-
12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
and 3-methyl-4-morpholine.

Example 51

[4S-(4 α ,12 α)]-8-Chloro-9-[[(2,4-difluorophenyl) [(2-phenylethyl)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

The title compound is prepared by the procedure Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromo-(2,4-difluorophenyl)acetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 2-phenethylamine.

Example 52

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -(methoxyamino)- α -methyl-2-furanacetamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromo-(2-furyl)propionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and methoxyamine.

Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 53 - 54 are prepared from [4S-(4 α ,12 α)]-9-[(α -bromo-(3-methoxycarbonylpropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

Example 53

[7S-(7 α ,10 α)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-amino-3-[(1,1-dimethylethyl)amino]-4-oxobutanoic acid methyl ester



Example 54

[7S-(7 α ,10 α)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenvyl]-amino]-3-(dimethylamino)-4-oxobutanoic acid methyl ester

Example 55

[7S-(7 α ,10 α)]- γ -[[[9-(Aminocarbonyl)-3-chloro-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenvyl]-amino]carbonyl]-1-pyrrolidinebutanoic acid methyl ester

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromo-(4-methoxycarbonylbutyryl))amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and pyrrolidine.

Example 56

[4S-(4 α ,12 α)]-4,7-Bis(Dimethylamino)-9-[[[(dimethylamino)acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(bromoacetyl)amino]-4,7-bis(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and dimethylamine.

Example 57

[4S-(4 α ,12 α)]-9-[[[(Butylamino)acetyl]amino]-8-chloro-4-(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 the product from Example 22, 0.5 g of n-butylamine and 3 ml of DMPU, under argon, is stirred at room temperature for 2 h.

The excess n-butylamine was removed in vacuo and the solids filtered. The filtrate is diluted with a small amount of methanol and the solution added dropwise to a mixture of 10 ml of 2-propanol and 120 ml of diethyl ether. The solution is treated dropwise with 1.0 M hydrogen chloride - diethyl ether solution to afford a yellow solid. The resulting solid is collected and dried in vacuo to afford 0.175 g of product:

MS (FAB) = m/z 576 (M + H)

Substantially following the method described in detail herein above in Example 57, the compounds of the invention listed below in Examples 58 - 66 are prepared.

Example 58

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,-
5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[(propylamino)acetyl]amino]-
2-naphthacenecarboxamide
dihydrochloride

Example 59

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,-
5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[(pentylamino)acetyl]amino]-
2-naphthacenecarboxamide
dihydrochloride

Example 60

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,-
5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-9-[[(methylamino)acetyl]amino]-2-
naphthacenecarboxamide dihydrochloride

Example 61

[4S-(4 α ,12 α)]-8-Chloro-9-[[(cyclopropylmethylamino)-
acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-2-naphthacenecarboxamide dihydrochloride

Example 62

5 [7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
1-pyrrolidineacetamide dihydrochloride

Example 63

10 [7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-
naphthacenyl]-1-piperidineacetamide
dihydrochloride

Example 64

15 7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-
naphthacenyl]-5-azabicyclo[2.1.1]hexane-
5-acetamide dihydrochloride

Example 65

20 [4S-(4 α ,12 α)]-8-Chloro-9-[(cyclobutylamino)acetyl]-
amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-2-naphthacenecarboxamide
dihydrochloride

Example 66

25 [7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-
naphthacenyl]- α -ethyl-1H-imidazole-1-
30 acetamide dihydrochloride

35 Substantially following the method, described
in detail herein above in Example 36, the compounds of
the invention listed in Examples 67 - 68 are prepared
from [4S-(4 α ,12 α)]-9-[(bromopropionyl)amino]-8-chloro-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide.

Example 67

[4S-(4 α ,12 α)]-8-Chloro-9-[[2-(diethylamino)-1-oxo-
propyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide

Example 68

[7S-(7 α ,10 α)]-1-[2-[[9-(Aminocarbonyl)-3-chloro-7-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,
8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
amino]-1-methyl-2-oxoethyl] proline methyl ester

Example 69

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
 α -(4-hydroxyphenyl)-6-methyl-2,6-diazabicyclo-
[2.1.1]heptane-2-acetamide

The title compound is prepared by the
procedure of Example 36 using [4S-(4 α ,12 α)]-9-[[(4-
Hydroxyphenyl)- α -bromoacetyl]amino]-8-chloro-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
and 6-methyl-2,6-diazabicyclo[2.1.1]heptane.

Example 70

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-9-[[(di-
methylamino)(2-fluorophenyl)acetyl]amino]-1,4,4a,5,-
5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-2-naphthacenecarboxamide

The title compound is prepared by the
procedure of Example 36 using [4S-(4 α ,12 α)]-9-[[(2-
fluorophenyl)- α -bromoacetyl]amino]-8-chloro-4-(di-
methylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,-
12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide
and dimethylamine.



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Example 71

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[1-(4-
methoxy-1-piperazinyl)-4-pentenoyl]amino]-1,11-dioxo-
2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(2-bromo-4-pentenoyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 4-methoxypiperazine.

Example 72

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,
5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,-
11-dioxo-9-[[1-oxo-4-phenyl-2-[(phenylmethoxy)-
amino]butyl]amino]-2-naphthacenecarboxamide.

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromophenylbutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and benzyloxyamine.

Example 73

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,
10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -
4-pyridyl-5-azabicyclo[2.1.1]hexan-5-acetamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[[4-pyridyl]- α -bromoacetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 5-azabicyclo[2.1.1]hexane.

Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 74 - 75 are prepared from [4S-(4 α ,12 α)]-9-[(bromoacetyl)amino]-4-(di-

methylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-
carboxamide.

5

Example 74

[4S-(4 α ,12 α)]-4-(Dimethylamino)-9-[[(dimethylamino)-
acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-
dioxo-2-naphthacenecarboxamide

10

Example 75

[4S-(4 α ,12 α)]-4-(Dimethylamino)-8-fluoro-1,4,4a,5,
5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
1,11-dioxo-9-[[(propylamino)acetyl]amino]-
2-naphthacenecarboxamide.

15

Example 76

[4S-(4 α ,12 α)]-4-(Dimethylamino)-9-[[(dimethylamino)-
acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-
12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluoro-
methyl)sulfonyl]oxy]-2-naphthacenecarboxamide

20

The title compound is prepared by the
procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(bromo-
acetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-
[[(trifluoromethyl)sulfonyl]oxy]-2-naphthacene-
carboxamide and dimethylamine.

25

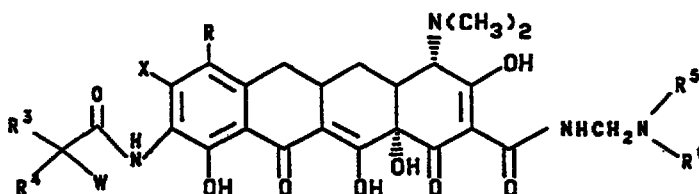
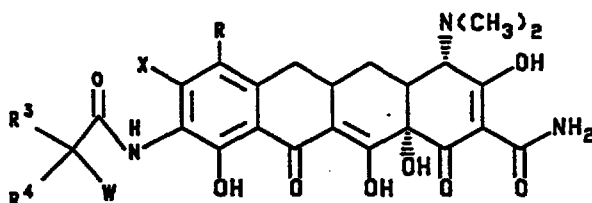
MASS SPECTRAL DATA

	<u>Example #</u>	<u>MS (FAB):m/z</u>
30	59	592 (M + H)
	60	535 (M + H)
	61	575 (M + H)
	63	589 (M + H)

35

We claim:

1. A compound of the formula :



wherein:

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine, and iodine;

R is selected from hydrogen; 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_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methyl-ethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy- (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo- (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) alkoxy-carbonyl, (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 disubstituted (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 W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; hydroxylamino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl-



butyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl mono-substituted amino group; (C_3 - C_8)cycloalkyl mono-substituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_3 - C_8)cycloalkyl monosubstituted amino; [$(C_4$ - $C_{10})$ cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3 - C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (C_6 - C_{10})aryl mono-substituted 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_2 - C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl, di-n-propyl, dibutyl and diisobutyl; symmetrical disubstituted (C_3 - C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, dicyclohexyl and dicycloheptyl; straight or branched unsymmetrical disubstituted (C_3 - C_{14})alkylamino group wherein the



total number of carbons in the substitution is not more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is not more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group substitution selected from aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo[2.1.1]hex-2-yl, 5-azabicyclo[2.1.1]hex-5-yl, 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; 1-azaoxacycloalkyl selected from morpholinyl and 1-aza-5-oxocycloheptane; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkyl- morpholinyl, 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)alkyl- piperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethyl- piperazinyl, 4-(C_1-C_4)alkoxypiperazinyl, 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)alkylthiomorpholinyl 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-pyrazolyl, 2-(C_1-C_3)alkyl-1-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-



triazolyl), 5-(C₁-C₃)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl; (heterocycle)amino group selected from 2- or 3-furanylamino, 2- or 3-thienylamino, 2-, 3- or 4-pyridylamino, 2- or 5-pyridazinylamino, 2-pyrazinylamino, 2-(imidazolyl)amino, (benzimidazolyl)amino, and (benzothiazolyl)amino and substituted (heterocycle)-amino group as defined above with 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 as defined above with 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, and β -aminobutyric acid and the enantiomers of said carboxy-(C₂-C₄)alkylamino group; (C₁-C₄)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C₁-C₄)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy; (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;





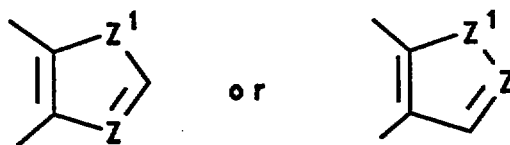
(C₇-C₁₁)arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl) methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

R⁵ 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

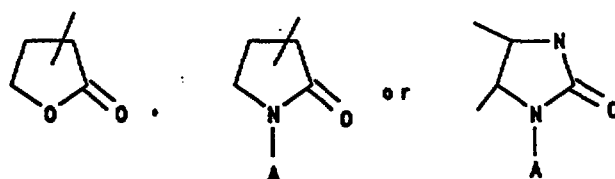
such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrroli-dinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused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





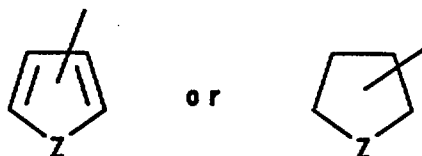
(A is selected from hydrogen; straight or branched (C_1-C_4) alkyl; C_6 -aryl; substituted C_6 -aryl (substitution selected from halo, (C_1-C_4) alkoxy, trihalo (C_1-C_3) -alkyl, nitro, amino, cyano, (C_1-C_4) alkoxycarbonyl, (C_1-C_3) alkylamino or carboxy); (C_7-C_9) aralkyl group selected from benzyl, 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 (C_1-C_3) alkylthio-pyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or $-(CH_2)_n COOR^7$ where $n=0-4$ and R^7 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^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

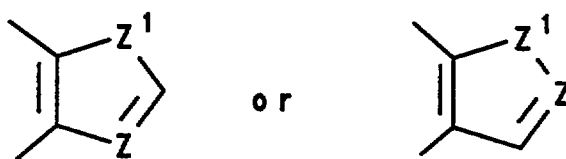


Se heteroatom optionally having a benzo or pyrido ring fused thereto:



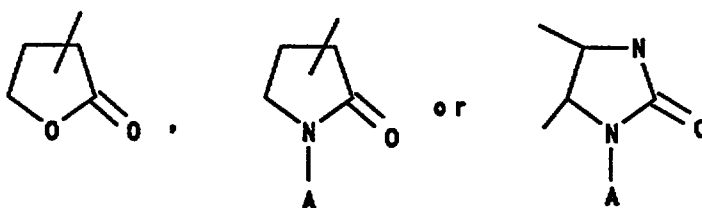
Z = N, O, S or Se

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



Z or Z¹ = N, O, S or Se

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





(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-dioxothiopholinyl; or $-(CH_2)_nCOOR^7$ where $n=0-4$ and R^7 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 R^5 and R^6 cannot both be hydrogen; or R^5 and R^6 taken together are $-(CH_2)_2B(CH_2)_2-$, where in B is selected from $(CH_2)_n$ 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.

2. The compound according to Claim 1, wherein:

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is selected from hydrogen; halogen selected from chlorine and iodine; or $R = -NR^1R^2$ and when $R = -NR^1R^2$ and $R^1 =$ methyl or ethyl,



R^2 = methyl and ethyl;

R^3 is selected from hydrogen; straight or branched (C_1-C_2) alkyl group selected from methyl and ethyl;

R^4 is selected from hydrogen and (C_1-C_6) 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 W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; (C_1-C_4) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl and 1-methylpropyl; (C_3-C_4) cycloalkyl monosubstituted amino group substitution selected from cyclopropyl and cyclobutyl; (C_4-C_5) azacycloalkyl and substituted azacycloalkyl substitution selected from pyrrolidinyl, piperidinyl, 4-methylpiperidinyl; 1-aza-oxacycloalkyl selected from morpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl and 4- (C_1-C_3) alkylpiperazinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2- (C_1-C_3) alkyl-1-imidazolyl and 3- (C_1-C_3) alkyl-1-imidazolyl; (heterocycle)methylamino group said heterocycle selected from 2-, 3- or 4-pyridylmethylamino; carboxy (C_2-C_4) alkylamino group selected from aminoacetic acid, α -aminopropionic acid, β -aminopropionic acid, α -butyric acid, β -aminobutyric acid and the enantiomers of said carboxy (C_2-C_4) alkylamino group; R^5 is selected from hydrogen; straight or branched (C_1-C_3) alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;

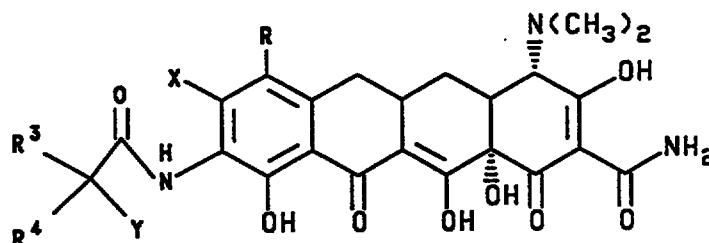
R^6 is selected from hydrogen; straight or branched (C_1-C_3) alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R^5 and R^6 cannot both be hydrogen;

or R^5 and R^6 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.

3. A compound of the formula:



* C L M S *

wherein:

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

R is selected from hydrogen; 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 $R^1 = 1\text{-methylpropyl}$,

$R^2 = 2\text{-methylpropyl}$;

R^3 is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy- (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) -alkoxycarbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group [substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4) alkylamino, (C_1-C_4) alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxy]; R^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 W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

4. The compound according to Claim 3,

wherein:

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

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is



selected from hydrogen; halogen selected from chlorine and iodine; or $R = -NR^1R^2$

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

$R^2 = \text{methyl and ethyl}$;

R^3 is selected from hydrogen; straight or branched

(C_1-C_2) alkyl group selected from methyl and ethyl;

R^4 is selected from hydrogen and (C_1-C_6) 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 W substituent) 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 3 wherein said salts or metal complexes comprise: hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric, sulfate, acetate, benzoate, citrate, cysteine or other amino acid, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate, arylsulfonate, aluminum, calcium, iron, magnesium or manganese.

6. The compound according to Claim 1, $[4S-(4\alpha, 12\alpha)]$ -8-Chloro-4-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide disulfate;

$[4S-(4\alpha, 12\alpha)]$ -8-Chloro-4-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

$[4S-(4\alpha, 12\alpha)]$ -8-Chloro-4,7-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

$[4S-(4\alpha, 12\alpha)]$ -9-[[(Butylamino)acetyl]amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-



3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide;

[4S-(4 α , 12 α)]-8-Chloro-4,7-bis(dimethylamino)-1,4,-4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methylcyclobutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;

[7S-(7 α , 10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-naphthacenyl]-1H-pyrrole-1-acetamide;

[4S-(4 α , 12 α)]-8-Chloro-4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]amino]-1,4,4a,5,-5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α , 12 α)]-8-Chloro-9-[(cyclopropylamino)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;

[4S-(4 α , 12 α)]-8-Chloro-9-[[[(cyclobutyloxy)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;

[7S-(7 α , 10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide;

[7S-(7 α , 10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,9,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-(3-methyl-1-pyrrolidine)acetamide;

[4S-(4 α , 12 α)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[(propylamino)acetyl]amino]-2-naphthacene-carboxamide;

[4S-(4 α , 12 α)]-8-Chloro-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-





dioxo-9-[1-oxo-2-(propylamino)propyl]amino]-2-naphthacenecarboxamide;

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -cyclobutyltetrahydro-2H-1,2-isoxazine-2-acetamide;
[4S-(4 α ,12 α)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[phenyl[(phenylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide;

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -cyclopropyl- α -methyl-1-azetidineacetamide;

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -(1,1-dimethylethyl)-(3-methyl-4-morpholine)acetamide;
[4S-(4 α ,12 α)]-8-Chloro-9-[[2,4-difluorophenyl][(2-phenylethyl)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.

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -(methoxyamino)- α -methyl-2-furanacetamide;

[7S-(7 α ,10 α)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-[(1,1-dimethylethyl)amino]-4-oxobutanoic acid methyl ester;

[7S-(7 α ,10 α)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-(dimethylamino)-4-oxobutanoic acid methyl ester;

[7S-(7 α ,10 α)]- γ -[[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-

10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-carbonyl]-1-pyrrolidinebutanoic acid methyl ester;
[4S-(4 α ,12 $\alpha\alpha$)]-4,7-Bis(Dimethylamino)-9-[[(dimethylamino)acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 $\alpha\alpha$)]-9-[[(Butylamino)acetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino)acetyl]amino]-2-naphthacene-carboxamide dihydrochloride;

[4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(pentylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride;

[4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(methylamino)acetyl]amino]-2-naphthacene-carboxamide dihydrochloride;

[4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-9-[[(cyclopropylmethylamino)acetyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride;

[7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-piperidineacetamide dihydrochloride;

7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-





10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-5-azabicyclo[2.1.1]hexane-5-acetamide dihydrochloride;
[4S-(4 α ,12 α)]-8-Chloro-9-[[(cyclobutylamino) acetyl]-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;
[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,-11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -ethyl-1H-imidazole-1-acetamide dihydrochloride;
[4S-(4 α ,12 α)]-8-Chloro-9-[[2-(diethylamino)-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
[7S-(7 α ,10 α)]-1-[2-[[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-1-methyl-2-oxoethyl] proline methyl ester;
[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -(4-hydroxyphenyl)-6-methyl-2,6-diazabicyclo[2.1.1]-heptane-2-acetamide;
[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-9-[[(dimethylamino) (2-fluorophenyl) acetyl]amino]-1,4,4a,5,-5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[1-(4-methoxy-1-piperazinyl)-4-pentenoyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;
[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,-5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo-4-phenyl-2-[(phenylmethoxy) amino]-butyl]amino]-2-naphthacenecarboxamide;
[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,-



11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -4-pyridyl-5-azabicyclo[2.1.1]hexan-5-acetamide;
[4S-(4 α ,12 α)]-4-(Dimethylamino)-9-[[(dimethylamino)-acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide;

[4S-(4 α ,12 α)]-4-(Dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(propylamino) acetyl]amino]-2-naphthacene-carboxamide; or

[4S-(4 α ,12 α)]-4-(Dimethylamino)-9-[[(dimethylamino)-acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[(trifluoromethyl)-sulfonyl]oxy]-2-naphthacenecarboxamide.

7. The compound according to claim 3,

[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide;

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(α -Bromopropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide;

[4S-(4 α ,12 α)]-9-[(α -Bromocyclobutylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-8-Chloro-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[1-oxo-2-(propylamino)propyl]amino]-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(α -Bromo- α -cyclopropylpropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,-

6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(α -Bromo-2,2-dimethylbutyryl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(α -Bromo-(2,4-difluorophenyl)acetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(α -Bromo-(2-furyl)propionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(α -Bromo-(3-methoxycarbonylpropionyl)amino)-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(α -Bromo-(4-methoxycarbonylbutyryl)amino)-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide;

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[[trifluoromethyl)sulfonyl]oxy]-2-naphthacenecarboxamide;

[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide hydrochloride;

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-



12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide hydrobromide;

[4S-(4 α ,12 α)]-9-[(Chloropropionyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride;

[4S-(4 α ,12 α)]-9-[(Chlorobutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride;

[4S-(4 α ,12 α)]-9-[(4-Hydroxyphenyl)- α -chloroacetyl)-amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride;

[4S-(4 α ,12 α)]-9-[(2-Fluorophenyl)- α -bromoacetyl)-amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide;

[4S-(4 α ,12 α)]-9-[(2-Bromo-4-pentenoyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide;

[4S-(4 α ,12 α)]-9-[(α -Bromophenylbutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide;

[4S-(4 α ,12 α)]-9-[(4-Pyridyl)- α -bromoacetyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide;

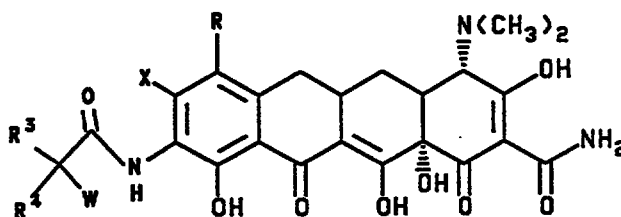
[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4-(dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; or

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-



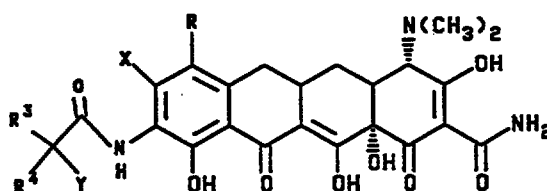
tetrahydroxy-1,11-dioxo-8-[[(trifluoromethyl)sulfonyl]-oxy]-2-naphthacenecarboxamide.

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



I

according to Claim 1, which comprises reacting a 9-[(haloacyl)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:

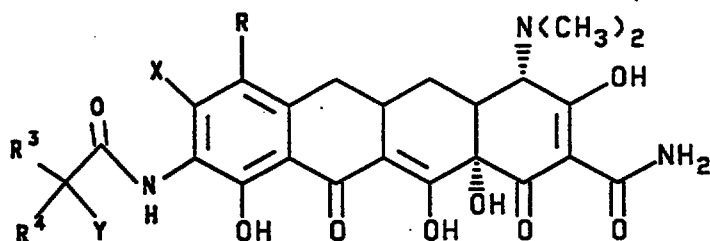


III

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

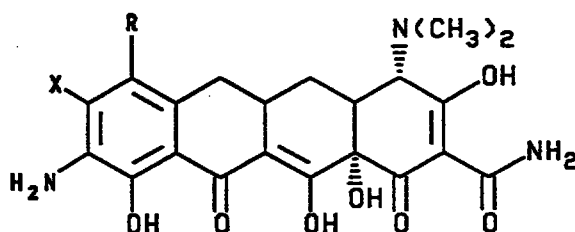
9. A method of producing a compound, or its organic and inorganic salt or metal complex, of the formula:



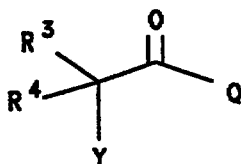


|||

according to Claim 3, which comprises reacting a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:



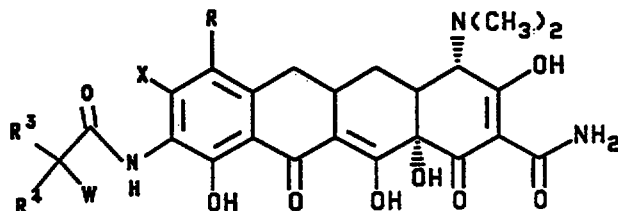
with a straight or branched haloacyl halide of the formula:



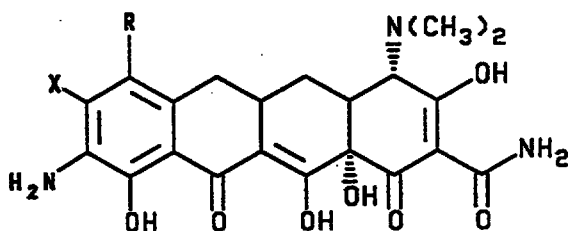
wherein Y, R³ and R⁴ are as defined in Claim 1 and Q is halogen selected from bromine, chlorine, iodine and fluorine, in an inert solvent, in a polar protic solvent and in the presence of a base.

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

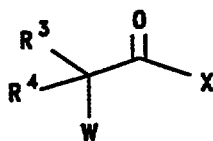




according to Claim 1, which comprises reacting a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:



with a straight or branched acid chloride of the formula:



wherein R^3 , R^4 and W are as defined in Claim 1 and X is halogen selected from bromine, chlorine, iodine and fluorine, in a suitable acid scavenger and suitable solvent.

11. A method of producing a compound of the formula:



11

[illegible]

1

$$\begin{array}{c} R^5 \\ \diagdown \\ R^6 \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array} NH$$

12. 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.

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





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

15. 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.



* C L M S *

REPLACED SHEETS		SG
☒	Description : paged 26-28 to paged 1-5	
☒	Claim(s) : paged 74-75, 87, 141-140 to paged 1-5	
☐	Drawing(s) : paged to paged	
☐	Abstract : paged to paged	
DATE OF RECEIPT		

REPLACEMENT SHEETS		SG
☒	Description : paged 1-5 to paged 26-28	
☒	Claim(s) : paged 1-5 to paged 74-75, 87, 141-140	
☐	Drawing(s) : paged to paged	
☒	Abstract : paged 1-5 to paged 74-75, 87, 141-140	
DATE OF RECEIPT 1/10/91		

Title: NOVEL 7-(SUBSTITUTED)-8-
(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)-8-(substituted)-9-[[(substituted amino)substituted]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides, herein after called 7-(substituted)-8-(substituted)-9-[(substituted glycylyl)amido]-6-demethyl-6-deoxytetracyclines, which exhibit antibiotic activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and are useful as anti-biotic agents.

The invention also relates to novel 9-[(haloacyl)amido]-7-(substituted)-8-(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)-8-(substituted)-9-[(substituted glycylyl)-amido]-6-demethyl-6-deoxytetracyclines, represented by formula I and II, which have antibacterial activity;

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Date: 1 OCT 1996

In formula I and II,

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen; 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 $R^1 = \text{1-methylpropyl}$, $R^2 = \text{2-methylpropyl}$;

R^3 is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl;

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

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

group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) alkoxycarbonyl, (C_1-C_3) alkylamino and

carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group [substitution selected from

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Date: - 1 OCT 1996

halo, (C₁-C₄)alkyl, nitro, hydroxy, amino, mono- or
disubstituted (C₁-C₄)alkylamino, (C₁-C₄)alkoxy,
(C₁-C₄)alkylsulfonyl, cyano and carboxy];
5 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 W sub-
10 stituent) maybe be either the racemate (DL) or the in-
dividual enantiomers (L or D);
W is selected from amino; hydroxylamino; (C₁-C₁₂)
straight or branched alkyl monosubstituted amino group
substitution selected from methyl, ethyl, n-propyl,
15 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,
1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-di-
methylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,
n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl,
2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl,
20 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl,
octyl, nonyl, decyl, undecyl and dodecyl and the
diastereomers and enantiomers of said branched alkyl
monosubstituted amino group; (C₃-C₈)cycloalkyl
monosubstituted amino group substitution selected from
25 cyclopropyl, trans-1,2-dimethylcyclopropyl,
cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]-
hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the
diastereomers and enantiomers of said (C₃-C₈)cycloalkyl
30 monosubstituted amino; [(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
35 monosubstituted amino group substitution selected from
allyl, 3-butenyl, 2-butenyl(cis or trans), 2-pentenyl,
4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl,
2-cyclopentenyl and 2-cyclohexenyl; (C₆-C₁₀)aryl

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alkyl group selected from piperazinyl, 2-(C₁-C₃)alkyl-
 piperazinyl, 4-(C₁-C₃)alkylpiperazinyl, 2,4-dimethyl-
 piperazinyl, 4-(C₁-C₄)alkoxypiperazinyl, 4-(C₆-C₁₀)-
 aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diaza-
 bicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo-
 [2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo-
 [2.2.2]oct-2-yl, 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 substi-
 tuted 1-azathiacycloalkyl group selected from thio-
 morpholinyl, 2-(C₁-C₃)alkylthiomorpholinyl and 3-
 (C₃-C₆)cycloalkylthiomorpholinyl; N-azolyl and substi-
 tuted N-azolyl group selected from 1-imidazolyl, 2-
 (C₁-C₃)alkyl-1-imidazolyl, 3-(C₁-C₃)alkyl-1-imidazo-
 ly, 1-pyrrolyl, 2-(C₁-C₃)alkyl-1-pyrrolyl, 3-(C₁-C₃)-
 alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-
 (C₁-C₃)alkyl-1-(1,2,3-triazolyl), 5-(C₁-C₃)alkyl-1-
 (1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl,
 2-tetrazolyl and benzimidazolyl; (heterocycle)amino
 group selected from 2- or 3-furanylamino, 2- or
 3-thienylamino, 2-, 3- or 4-pyridylamino, 2- or
 5-pyridazinylamino, 2-pyrazinylamino, 2-(imidazolyl)-
 amino, (benzimidazolyl)amino, and (benzothiazolyl)amino
 and substituted (heterocycle)amino group as defined
 above with 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-pyrazinylmethyl-
 amino, 2-(imidazolyl)methylamino, (benzimidazolyl)-
 methylamino, and (benzothiazolyl)methylamino and
 substituted (heterocycle)methylamino group as defined
 above with 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, and

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β -aminobutyric acid and the enantiomers of said
 carboxy(C_2-C_4)alkylamino group; (C_1-C_4)alkoxy-
 carbonylamino group substitution selected from methoxy-
 5 carbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycar-
 bonyl, isopropoxycarbonyl, 1,1-dimethyl-
 ethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxy-
 carbonyl; (C_1-C_4)alkoxyamino group substitution select-
 10 ed from methoxy, ethoxy, n-propoxy, 1-methylethoxy,
 n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy;
 (C_3-C_8)cycloalkoxyamino group selected from cyclopro-
 poxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethyl-
 cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy,
 15 cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy,
 bicyclo[2.2.2]oct-2-yloxy and the diastereomers and
 enantiomers of said (C_3-C_8)cycloalkoxyamino group;
 (C_6-C_{10})aryloxyamino group selected from phenoxyamino,
 1-naphthyloxyamino and 2-naphthyloxyamino; (C_7-C_{11})-
 arylalkoxyamino group substitution selected from
 20 benzyloxy, 2-phenylethoxy, 1-phenylethoxy,
 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpro-
 poxy;
 R^5 is selected from hydrogen; straight or branched
 (C_1-C_3)alkyl group selected from methyl, ethyl,
 25 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
 30 membered aromatic or saturated ring with one N, O, S or
 Se heteroatom optionally having a benzo or pyrido ring
 fused thereto:

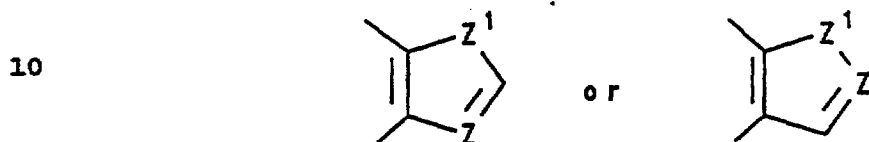


Z = N, O, S or Se

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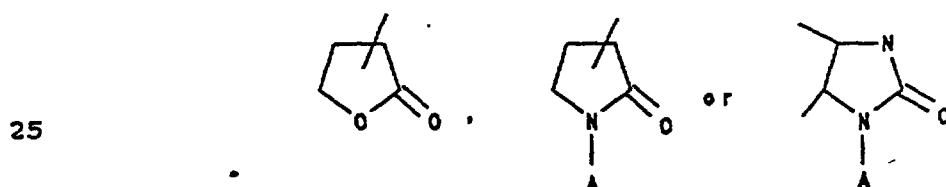
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such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrro-
lidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydro-
furanyl, furanyl, benzofuranyl, tetrahydrothienyl,
thienyl, benzothienyl or selenazolyl, or a five mem-
bered aromatic ring with two N, O, S or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



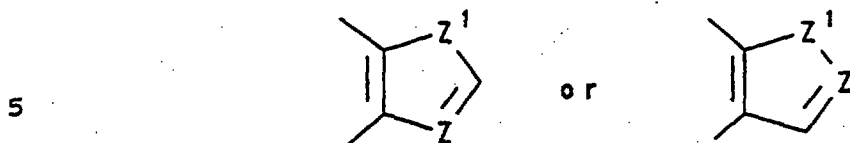
Z or Z' = N, O, S or Se

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



(A is selected from hydrogen; straight or branched
(C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitu-
30 tion 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)

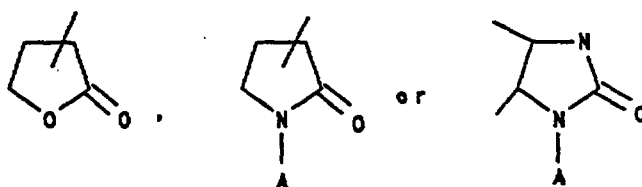
35 such as γ-butyrolactam, γ-butyrolactone, imidazo-
lidinone or N-aminoimidazolidinone, or a six membered
aromatic ring with one to three N heteroatoms such as



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

10 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:

15



25 (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)

30 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,

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4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpho-
 liny, 2-dioxothiomorpholinyl; or $-(CH_2)_nCOOR^7$ where
 5 $n=0-4$ and R^7 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 pro-
 viso that R^5 and R^6 cannot both be hydrogen;
 or R^5 and R^6 taken together are $-(CH_2)_2B(CH_2)_2-$, where-
 10 in 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,
 15 pyrrolidine or piperidine; and the pharmacologically
 acceptable organic and inorganic salts or metal com-
 plexes.

Preferred compounds are compounds according
 to the above formula I and II wherein: X is halogen
 or trifluoromethanesulfonyloxy, the halogen is selected
 20 from bromine, chlorine, fluorine and iodine; R is
 selected from hydrogen; halogen selected from bromine,
 chlorine and iodine; or $R = -NR^1R^2$
 and when $R = -NR^1R^2$
 and $R^1 = \text{hydrogen}$, $R^2 = \text{methyl, ethyl, n-propyl,}$
 25 $1\text{-methylethyl, n-butyl, 1-methylpropyl or}$
 2-methylpropyl;
 and when $R^1 = \text{methyl or ethyl,}$
 $R^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,}$
 $1\text{-methylpropyl or 2-methylpropyl;}$
 30 R^3 is selected from hydrogen; straight or branched
 (C_1-C_8) alkyl group selected from methyl, ethyl, propyl,
 isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and
 octyl; α -hydroxy (C_1-C_4) alkyl group selected from
 hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl,
 35 α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) -
 alkyl group; (C_6-C_{10}) aryl group selected from phenyl,
 α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl
 group (substitution selected from hydroxy, halogen,

(C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, and carboxy);
(C₇-C₉)aralkyl group selected from benzyl,
1-phenylethyl, 2-phenylethyl and phenylpropyl;
5 substituted(C₇-C₉)aralkyl group [substitution selected
from halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkyl-
sulfonyl, cyano and carboxy];
R⁴ is selected from hydrogen and (C₁-C₄)alkyl selected
10 from methyl, ethyl propyl, isopropyl, butyl and
isobutyl;
when R³ does not equal R⁴ the stereochemistry of the
asymmetric carbon (i.e., the carbon bearing the W sub-
stituent) maybe be either the racemate (DL) or the in-
dividual enantiomers (L or D);
15 W is selected from amino; hydroxylamino; (C₁-C₁₂)
straight or branched alkyl monosubstituted amino group
substitution selected from methyl, ethyl, n-propyl,
1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl,
1,1-dimethylethyl, n-pentyl, 2-methylbutyl,
20 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl,
n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl,
2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl,
1,3-dimethylbutyl, 1-methyl-1-ethylpropyl, heptyl,
octyl, nonyl, decyl and the diastereomers and
25 enantiomers of said branched alkyl monosubstituted
amino group; (C₃-C₈)cycloalkyl monosubstituted amino
group substitution selected from cyclopropyl, trans-
1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,
30 cyclooctyl, 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-
35 methylcyclopropyl)methyl and (cis-2-methylcyclobutyl)-
methyl; (C₃-C₁₀)alkenyl monosubstituted amino group
substitution selected from allyl, 3-butenyl, 2-butenyl
(cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-

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

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[1,n]-diazacycloalkyl and substituted
[1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and
substituted 1-azathiacycloalkyl group selected from
5 thiomorpholinyl, 2-(C₁-C₃)alkylthiomorpholinyl and
3-(C₃-C₆)cycloalkylthiomorpholinyl; N-azolyl and
substituted N-azolyl group selected from 1-imidazolyl,
2-(C₁-C₃)alkyl-1-imidazolyl, 3-(C₁-C₃)alkyl-1-
imidazolyl, 1-pyrrolyl, 2-(C₁-C₃)alkyl-1-pyrrolyl,
10 3-(C₁-C₃)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-
triazolyl), 4-(C₁-C₃)alkyl-1-(1,2,3-triazolyl),
5-(C₁-C₃)alkyl-1-(1,2,3-triazolyl) and
4-(1,2,4-triazolyl); (heterocycle)methylamino group
said heterocycle selected from 2- or
15 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3-
or 4-pyridylmethylamino, 2- or 5-pyridazinylmethyl-
amino, 2-pyrazinylmethylamino, 2-(imidazolyl)-
methylamino, (benzimidazolyl)methylamino, and
(benzothiazolyl)methylamino and substituted
20 (heterocycle)amino group as defined above with
substitution selected from straight or branched
(C₁-C₆)alkyl; carboxy(C₂-C₄)alkylamino group selected
from aminoacetic acid, α-aminopropionic acid, β-amino-
propionic acid, α-butyric acid, β-aminobutyric acid and
25 the enantiomers of said carboxy(C₂-C₄)alkylamino group;
(C₁-C₄)alkoxycarbonylamino group substitution selected
from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl,
propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethyl-
ethoxycarbonyl, n-butoxycarbonyl, and 2-methylpro-
30 poxycarbonyl; (C₁-C₄)alkoxyamino group substitution
selected from methoxy, ethoxy, n-propoxy, 1-methyl-
ethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethyl-
ethoxy; (C₃-C₈)cycloalkoxyamino group selected from
cyclopropoxy, trans-1,2-dimethylcyclopropoxy,
35 cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclo-
pentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy,
bicyclo[2.2.1]hept-2-yloxy, bicyclo[2.2.2]oct-2-yloxy
and the diastereomers and enantiomers of said

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(C₃-C₈)cycloalkoxyamino group; (C₇-C₁₁)arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy; R⁵ 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-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



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

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

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such as γ -butyrolactam, γ -butyrolactone, imidazo-
lidinone or N-aminoimidazolidinone, or a six membered
aromatic ring with one to three N heteroatoms such as
pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-
triazinyl, pyrimidinyl or (C_1-C_3) alkylthiopyridazinyl;
or $-(CH_2)_nCOOR^7$ where $n=0-4$ and R^7 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^5 and R^6 cannot both
be hydrogen; or R^5 and R^6 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.

Particularly preferred compounds are com-
pounds according to the above formula I and II wherein:
X is halogen or trifluoromethanesulfonyloxy, the
halogen is selected from bromine, chlorine, fluorine
and iodine; R is selected from hydrogen; halogen
selected from bromine, chlorine 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_1-C_6) alkyl group selected from methyl, ethyl, propyl,
isopropyl, 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;

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

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

W is selected from amino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl,

2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methyl-pentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1-methyl-1-ethylpropyl and the diastereomers and enantiomers of said branched alkyl monosubstituted

amino group; (C_3-C_5) cycloalkyl monosubstituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl and the diastereomers and enantiomers of said (C_3-C_5) cycloalkyl monosubstituted amino group;

$[(C_4-C_{10})$ cycloalkyl] alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl and (cyclobutyl)methyl; (C_3-C_{10}) -alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl,

3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (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_2-C_{14}) alkyl-amino group substitution selected from dimethyl, diethyl, diisopropyl, and di-n-propyl; straight or branched unsymmetrical disubstituted (C_3-C_{14}) alkylamino group wherein the total number of carbons in the

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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
5 than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)-
azacycloalkyl group substitution selected from
aziridinyl, azetidiny, pyrrolidinyl, piperidinyl,
4-methylpiperidinyl, 2-methylpyrrolidinyl,
10 cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethyl-
pyrrolidinyl and the diastereomers and enantiomers of
said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)-
azacycloalkyl group; 1-aza-oxacycloalkyl selected from
morpholinyl and 1-aza-5-oxocycloheptane; substituted
15 1-aza-oxacycloalkyl group substitution selected from
2- (C_1-C_3) alkylmorpholinyl, 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) alkyl-
20 piperazinyl, 2,4-dimethylpiperazinyl, 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,
and the diastereomers or enantiomers of said
[1,n]-diazacycloalkyl and substituted [1,n]-diaza-
cycloalkyl group; 1-azathiacycloalkyl and substituted
25 1-azathiacycloalkyl group selected from thiomorpholinyl
and 2- (C_1-C_3) alkylthiomorpholinyl; N-azolyl and
substituted N-azolyl group selected from 1-imidazolyl,
indolyl, 1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl);
(heterocycle)methylamino group selected from 2- or
30 3-furylmethylamino, 2- or 3-thienylmethylamino and 2-,
3- or 4-pyridylmethylamino; (C_1-C_4)alkoxycarbonylamino
group substitution selected from methoxycarbonyl,
ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl,
isopropoxycarbonyl, 1,1-dimethylethoxycarbonyl,
35 n-butoxycarbonyl, and 2-methylpropoxycarbonyl;
(C_1-C_4)alkoxyamino group substitution selected from
methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy,
2-methylpropoxy, and 1,1-dimethylethoxy;

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(C₇-C₁₁)arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

R⁵ 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-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



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

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl; or -(CH₂)_nCOOR⁷ where n=0-4 and R⁷ is selected from hydrogen; straight or branched (C₁-C₃)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;

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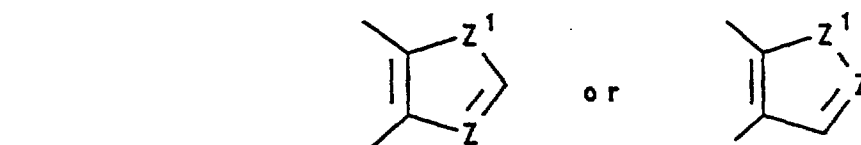
or (C₆-C₁₀)aryl group selected from phenyl, α-naphthyl, or β-naphthyl;

5 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
10 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

20 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 aro-
25 matic ring with two N, O, S or Se heteroatoms optional-
ly having a benzo or pyrido ring fused thereto:



Z or Z¹ = N, O, S or Se

35 such as imidazolyl, pyrazolyl, benzimidazolyl, oxazo-
lyl, benzoxazolyl, indazolyl, thiazolyl, benzothia-
zolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridyl-
imidazolyl; or -(CH₂)_nCOOR⁷ where n=0-4 and R⁷ is se-
lected from hydrogen; straight or branched (C₁-C₃)-
alkyl selected from methyl, ethyl, n-propyl or

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5 1-methylethyl; or (C₆-C₁₀)aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R⁵ and R⁶ cannot both be hydrogen; or R⁵ and R⁶ taken together
10 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
15 the pharmacologically acceptable organic and inorganic salts or metal complexes.

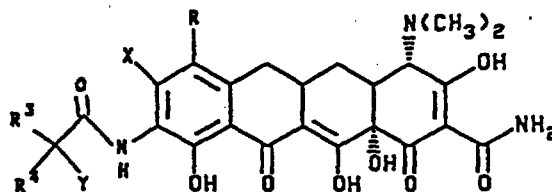
Compounds of special interest are compounds according to the above formula I and II wherein: X is
15 halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is selected from hydrogen; halogen selected from chlorine and iodine; or R = -NR¹R²
and when R = -NR¹R² and R¹ = methyl or ethyl, R² = methyl and ethyl;
20 R³ is selected from hydrogen; straight or branched (C₁-C₂)alkyl group selected from methyl and ethyl; R⁴ is selected from hydrogen and (C₁-C₆)alkyl selected from methyl and ethyl;
when R³ does not equal R⁴ the stereochemistry of the
25 asymmetric carbon (i.e., the carbon bearing the W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from amino; (C₁-C₄)straight or branched alkyl monosubstituted amino group substitution selected
30 from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl and 1-methylpropyl; (C₃-C₄)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl and cyclobutyl; (C₂-C₈)azacycloalkyl and substituted (C₂-C₈)azacycloalkyl selected from pyrrolidinyl,
35 piperidinyl and 4-methylpiperidinyl; 1-azaoxacycloalkyl selected from morpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl and 4-(C₁-C₃)alkylpiperazinyl; N-azolyl and substituted

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N-azolyl group selected from 1-imidazolyl,
 2-(C₁-C₃)alkyl-1-imidazolyl and 3-(C₁-C₃)alkyl-
 1-imidazolyl; (heterocycle)methylamino group said
 heterocycle selected from 2-, 3- or
 4-pyridylmethylamino; 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;
 R⁵ is selected from hydrogen; straight or branched
 (C₁-C₃)alkyl group selected from methyl, ethyl,
 n-propyl or 1-methylethyl;
 R⁶ is selected from hydrogen; straight or branched
 (C₁-C₃)alkyl group selected from methyl, ethyl,
 n-propyl or 1-methylethyl; with the proviso that R⁵
 and R⁶ cannot both be hydrogen; or R⁵ and R⁶ 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 organ-
 ic 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 inter-
 mediates include those having the formula III:



wherein:

Y is selected from $(\text{CH}_2)_n\text{X}'$, $n = 0-5$, X' is halogen selected from bromine, chlorine, fluorine and iodine; X is halogen or trifluoromethanesulfonyl, the halogen is selected from bromine, chlorine, fluorine and iodine. R is selected from hydrogen; halogen selected from bromine, chlorine, fluorine and iodine; or $\text{R} = -\text{NR}^1\text{R}^2$ and when $\text{R} = -\text{NR}^1\text{R}^2$ and $\text{R}^1 = \text{hydrogen}$, $\text{R}^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl}$; and when $\text{R}^1 = \text{methyl or ethyl}$, $\text{R}^2 = \text{methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$; and when $\text{R}^1 = \text{n-propyl}$, $\text{R}^2 = \text{n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl}$; and when $\text{R}^1 = \text{1-methylethyl}$, $\text{R}^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$; and when $\text{R}^1 = \text{n-butyl}$, $\text{R}^2 = \text{n-butyl, 1-methylpropyl or 2-methylpropyl}$; and when $\text{R}^1 = \text{1-methylpropyl}$, $\text{R}^2 = \text{2-methylpropyl}$; R^3 is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; $(\text{C}_6-\text{C}_{10})$ aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted $(\text{C}_6-\text{C}_{10})$ aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) alkoxy-carbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl,

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2-phenylethyl and phenylpropyl; substituted(C_7-C_9)-
 aralkyl group [substitution selected from halo,
 5 (C_1-C_4)alkyl, nitro, hydroxy, amino, mono- or
 disubstituted (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,
 10 pentyl and hexyl;
 when R^3 does not equal R^4 the stereochemistry of the
 asymmetric carbon (i.e., the carbon bearing the W sub-
 stituent) maybe be either the racemate (DL) or the in-
 dividual enantiomers (L or D); and the pharmaco logic-
 15 ally acceptable organic and inorganic salts or metal
 complexes.

Preferred compounds are compounds according
 to the above formula III wherein:
 Y is selected from $(CH_2)_n X'$, $n=0-5$, X' is halogen
 selected from bromine, chlorine, flourine and iodine;
 20 X is halogen or trifluoromethanesulfonyloxy, the
 halogen is selected from bromine, chlorine, fluorine
 and iodine;
 R is selected from hydrogen; halogen selected from bro-
 mine, chlorine and iodine; or $R = -NR^1R^2$
 25 and when $R = -NR^1R^2$ and $R^1 =$ hydrogen,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
 1-methylpropyl or 2-methylpropyl;
 and when $R^1 =$ methyl or ethyl,
 $R^2 =$ methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
 30 1-methylpropyl or 2-methylpropyl;
 R^3 is selected from hydrogen; straight or branched
 (C_1-C_8)alkyl group selected from methyl, ethyl, propyl,
 isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and
 octyl; α -hydroxy(C_1-C_4)alkyl group selected from
 35 hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl,
 α -hydroxypropyl and α -hydroxybutyl; carboxyl(C_1-C_8)-
 alkyl group; (C_6-C_{10})aryl group selected from phenyl,
 α -naphthyl and β -naphthyl; substituted(C_6-C_{10})aryl



5 group (substitution selected from hydroxy, halogen,
 (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, and carboxy);
 (C₇-C₉)aralkyl group selected from benzyl, 1-phenyl-
 ethyl, 2-phenylethyl and phenylpropyl; substituted-
 (C₇-C₉)aralkyl group [substitution selected from halo,
 (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylsulfonyl,
 cyano and carboxy];
 10 R⁴ is selected from hydrogen and (C₁-C₄)alkyl selected
 from methyl, ethyl propyl, isopropyl, butyl and iso-
 butyl;
 when R³ does not equal R⁴ the stereochemistry of the
 asymmetric carbon (i.e., the carbon bearing the W sub-
 15 stituent) maybe be either the racemate (DL) or the in-
 dividual enantiomers (L or D); and the pharmaco-
 logically acceptable organic and inorganic salts or
 metal complexes.

Particularly preferred compounds are com-
 pounds according to the above formula III wherein:
 20 Y is selected from (CH₂)_nX', n=0-5, X' is halogen
 selected from bromine, chlorine, fluorine and iodine;
 X is halogen or trifluoromethanesulfonyloxy, the
 halogen is selected from bromine, chlorine, fluorine
 and iodine;
 25 R is selected from hydrogen; halogen selected from bro-
 mine, chlorine and iodine; or R = -NR¹R²
 and when R = -NR¹R² and R¹ = hydrogen,
 R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
 30 and when R¹ = methyl or ethyl,
 R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
 1-methylpropyl or 2-methylpropyl;
 R³ is selected from hydrogen; straight or branched
 (C₁-C₆)alkyl group selected from methyl, ethyl, propyl,
 35 isopropyl, butyl, isobutyl, pentyl and hexyl;
 (C₆-C₁₀)aryl group selected from phenyl, α-naphthyl and
 β-naphthyl; (C₇-C₉)aralkyl group selected from benzyl,
 1-phenylethyl, 2-phenylethyl and phenylpropyl;

In accordance with Scheme IV, compound 5 is selectively N-alkylated in the presence of formaldehyde and either a primary amine of the formula R^5NH_2 such as methylamine, ethylamine, benzylamine, methylglycinate, (L or D)lysine, (L or D)alanine or their substituted congeners; or a secondary amine of the formula R^5R^6NH such as morpholine, pyrrolidine, piperidine or their substituted congeners to give the corresponding Mannich base adduct, 7.

The 9-[(substituted glycyloxy)amido]-7-(substituted)-8-(substituted)-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). Preferably, the 7-(substituted)-8-(substituted)-9-(substituted)-6-demethyl-6-deoxytetracyclines are obtained as inorganic salts such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salts such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate or arylsulfonate. 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 or 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 all stereoisomers of the compounds whether free from other stereoisomers or admixed with stereoisomers in any

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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 level of $1-5 \times 10^5$ CFU/ml, and a range of antibiotic concentrations (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 genetically defined strains that are sensitive to tetracycline and resistant strains that are insensitive to tetracycline, either by preventing the antibiotic from interacting with bacterial ribosomes (tetM) or by a tetK encoded membrane protein which confers tetracycline resistance by energy-dependent efflux of the antibiotic from the cell.

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 the tetM resistance determinants (Table I). Notable is 8-chloro-9-(N,N-dimethylglycyl-amido)-6-demethyl-6-deoxytetracycline, as shown in Table I, which has good in vitro activity against tetracycline resistant strains containing the tetM resistance determinant (such as S. aureus UBMS 88-5,

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COMPOUND LEGEND FOR TABLES

- 5 A [4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-9-
 [[(dimethylamino) acetyl] amino]-1,4,4a,5,5a,-
 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-2-naphthacenecarboxamide disulfate.
- 10 B [4S-(4 α ,12 α)]-8-Chloro-4,7-(dimethylamino)-
 9-[[(dimethylamino) acetyl] amino]-1,4,4a,5,5a,6,-
 11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
 dioxo-2-naphthacenecarboxamide.
- 15 C [4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-
 9-[[(dimethylamino) acetyl] amino]-1,4,4a,5,5a,-
 6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-2-naphthacenecarboxamide.
- 20 D [4S-(4 α ,12 α)]-9-[[(Butylamino) acetyl] amino]-8-
 chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-
 octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
 2-naphthacenecarboxamide dihydrochloride.
- 25 E [7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-
 (dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
 1,8,10a,11-tetrahydroxy-10,12-dioxo-2-
 naphthacenyl]-1-pyrrolidineacetamide dihydro-
 chloride.
- 30 F [4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,-
 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetra-
 hydroxy-1,11-dioxo-9-[[(propylamino) acetyl] amino]-
 2-naphthacenecarboxamide dihydrochloride.
- 35 G [4S-(4 α ,12 α)]-8-Chloro-9-[[(cyclopropylmethyl-
 amino) acetyl] amino]-4-(dimethylamino)-1,4,4a,5,-
 5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
 1,11-dioxo-2-naphthacenecarboxamide dihydro-

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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,

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Example 7

[4S-(4 α ,12 α)]-9-Amino-4,7-bis(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-8-[[trifluoromethyl]-
sulfonyl]oxy]-2-naphthacenecarboxamide

The title compound is prepared by the
procedure of Example 3 using 9-azido-4,7-bis(dimethyl-
amino)-6-demethyl-6-deoxytetracycline and trifluoro-
methanesulfonic acid.

Example 8

[4S-(4 α ,12 α)]-9-Amino-4-(dimethylamino)-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a,tetrahydroxy-1,11-
dioxo-8-[[trifluoromethyl)sulfonyl]oxy]-2-
naphthacenecarboxamide

The title compound is prepared by the
procedure of Example 3 using 9-azido-4-(dimethylamino)-
6-demethyl-6-deoxytetracycline and trifluoromethane-
sulfonic acid.

Example 9

[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-8-chloro-4,7-
bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide.

A well-stirred cold solution of 1.0 g of
product from Example 3, 2 ml of 1,3-dimethyl-2-
imidazolidinone and 1.0 g of sodium bicarbonate is
treated with 0.30 ml of chloroacetyl chloride. The
solution is stirred at 25°C for 30 minutes, filtered
and the filtrate added dropwise to 500 ml of diethyl
ether to afford 1.0 g of yellow product.

Example 10

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-8-chloro-
4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide.

A well-stirred cold solution of 1.0 g of
product from Example 3, 2 ml of 1,3-dimethyl-2-

Example 21

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethyl-
amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-8-[[trifluoromethyl)-
sulfonyl]oxy]-2-naphthacenecarboxamide

The title compound is prepared by the
procedure of Example 10 and using the product from
Example 7.

Example 22

[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-8-chloro-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide hydrochloride

A 25°C solution of 1.247 g of product from
Example 5, 12 ml of DMPU and 6 ml of acetonitrile is
treated with 0.564 g of chloroacetyl chloride. The
mixture is stirred for 45 minutes and added dropwise to
a mixture of 80 ml of 2-propanol and 400 ml of diethyl
ether. The resultant yellow solid is filtered and
washed several times with diethyl ether and dried in
vacuo to give 1.25 g of product.

MS (FAB) = m/z 540 (M + H)

Example 23

[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-8-chloro-4-
(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide hydrobromide

A 25°C solution of 1.247 g of product from
Example 5, 12 ml of DMPU and 6 ml of acetonitrile is
treated with 0.62 g of bromoacetyl bromide. The
mixture is stirred for 45 minutes and added dropwise to
a mixture of 80 ml of 2-propanol and 400 ml of diethyl
ether. The resultant yellow solid is filtered and
washed several times with diethyl ether and dried in
vacuo to give 1.35 g of product.

Substantially following the method, described
in detail herein above in Example 22 or 23, the

compounds of the invention listed in Examples 24 - 30 are prepared.

5

Example 24

[4S-(4 α ,12 α)]-9-[(Chloropropionyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

10

Example 25

[4S-(4 α ,12 α)]-9-[(Chlorobutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride.

15

Example 26

[4S-(4 α ,12 α)]-9-[[(4-Hydroxyphenyl)- α -chloroacetyl]-amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrochloride

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Example 27

[4S-(4 α ,12 α)]-9-[[(2-Fluorophenyl)- α -bromoacetyl]-amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

25

Example 28

[4S-(4 α ,12 α)]-9-[(2-Bromo-4-pentenoyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

30

Example 29

[4S-(4 α ,12 α)]-9-[(α -Bromophenylbutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

35

Example 30

[4S-(4 α ,12 α)]-9-[[(4-Pyridyl)- α -bromoacetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide hydrobromide

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Example 34

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-9-
[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-
6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-
1,11-dioxo-2-naphthacenecarboxamide

A well stirred solution 25°C of 0.20 g of product from Example 5, 3 ml of N-methylpyrrolidone, 1 ml of acetonitrile and 0.2 g of sodium bicarbonate is treated with 0.071g of N,N-dimethylaminoacetyl chloride hydrochloride. After 30 minutes, the reaction is filtered and the filtrate is added dropwise to 200 ml of diethyl ether. The yellow solid is collected, washed well with ether, and dried in vacuo to afford 0.15 g of product:
MS (FAB) = m/z 548 (M + H).

Example 35

[4S-(4 α ,12 α)]-8-Chloro-4,7-(dimethylamino)-
9-[[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,-
12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide

A well stirred solution (25°C) of 0.104 g of product from Example 3, 1.5 ml of N-methylpyrrolidone, 0.5 ml of acetonitrile and 0.105 g of sodium bicarbonate is treated with 0.034g of N,N-dimethylaminoacetyl chloride hydrochloride. After 1 hr, the reaction is filtered and the filtrate is added dropwise to 100 ml of diethyl ether. The yellow solid is collected, washed well with ether, and dried in vacuo to afford 0.085 g of product:
MS (FAB) = m/z 591 (M + H).

Example 36

[4S-(4 α ,12 α)]-9-[[[(Butylamino)acetyl]amino]-8-chloro-
4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide

A solution of 0.20 g of the product from Example 10, 2 ml of 1,3-dimethyl-2-imidazolidinone and

0.1 ml of n-butylamine is stirred at room temperature for 1 hr and added dropwise to 50 ml of diethyl ether to afford 0.20 g of yellow color product:

MS (FAB) m/z 620 (M + H)

Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 37 - 45 are prepared.

Example 37

[4S-(4 α , 12 α)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methylcyclobutyl)amino]acetyl]-amino]-1,11-dioxo-2-naphthacenecarboxamide

Example 38

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

Example 39

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

Example 40

[4S-(4 α , 12 α)]-8-Chloro-4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide

Example 41

[4S-(4 α , 12 α)]-8-Chloro-9-[[[(cyclopropylamino)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

Example 42

[4S-(4 α , 12 α)]-8-Chloro-9-[[[(cyclobutyloxy)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

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12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and tetrahydro-1,2-oxazine.

Example 48

[4S-(4 α ,12 α)]-8-Chloro-4,7-bis(dimethylamino)-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-9-[[phenyl[(phenyl-
methyl)amino]acetyl]amino]-2-
naphthacenecarboxamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α , 12 α)]-9-[(α -bromophenylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and benzylamine.

Example 49

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-
10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenvyl]-
 α -cyclopropyl- α -methyl-1-azetidineacetamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromo- α -cyclopropylpropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and azetidine.

Example 50

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-
(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenvyl]-
 α -(1,1-dimethylethyl)-(3-methyl-4-
morpholine)acetamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromo-2,2-dimethylbutyryl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 3-methyl-4-morpholine.

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Example 54

5 [7S-(7 α ,10 α)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-
bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
amino]-3-(dimethylamino)-4-oxobutanoic acid
methyl ester

Example 55

10 [7S-(7 α ,10 α)]-7-[[9-(Aminocarbonyl)-3-chloro-4,7-
bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-
1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-
amino]carbonyl]-1-pyrrolidinebutanoic acid
methyl ester

15 The title compound is prepared by the
procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -
bromo-(4-methoxycarbonylbutyryl))amino]-8-chloro-4,7-
bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,-
10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxa-
20 mide and pyrrolidine.

Example 56

[4S-(4 α ,12 α)]-4,7-Bis(Dimethylamino)-9-[[(dimethyl-
amino)acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-
octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide

5 The title compound is prepared by the
procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(bromo-
acetyl)amino]-4,7-bis(dimethylamino)-8-fluoro-1,4,4a,-
5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-
30 dioxo-2-naphthacenecarboxamide and dimethylamine.

Example 57

[4S-(4 α ,12 α)]-9-[[(Butylamino)acetyl]amino]-8-chloro-
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
3,10,12,12a-tetrahydroxy-1,11-dioxo-
2-naphthacenecarboxamide
35 dihydrochloride

A mixture of 0.20 g of the product from
Example 22, 0.5 g of n-butylamine and 3 ml of DMPU,
under argon, is stirred at room temperature for 2 h.

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Example 62

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-pyrrolidineacetamide dihydrochloride

Example 63

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-piperidineacetamide dihydrochloride

Example 64

7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-5-azabicyclo[2.1.1]hexane-5-acetamide dihydrochloride

Example 65

[4S-(4 α ,12 α)]-8-Chloro-9-[[cyclobutylamino)acetyl]-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

Example 66

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

Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 67 - 68 are prepared from [4S-(4 α ,12 α)]-9-[(bromopropionyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide.

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Example 71

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[1-(4-methoxy-1-piperazinyl)-4-pentenoyl]amino]-1,11-dioxo-2-naphthacenecarboxamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(2-bromo-4-pentenoyl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 4-methoxypiperazine.

Example 72

[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo-4-phenyl-2-[(phenylmethoxy)aminobutyl]amino]-2-naphthacenecarboxamide.

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[(α -bromophenylbutyryl)amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and benzyloxyamine.

Example 73

[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -4-pyridyl-5-azabicyclo[2.1.1]hexan-5-acetamide

The title compound is prepared by the procedure of Example 36 using [4S-(4 α ,12 α)]-9-[[4-pyridyl]- α -bromoacetyl]amino]-8-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide and 5-azabicyclo[2.1.1]hexane.

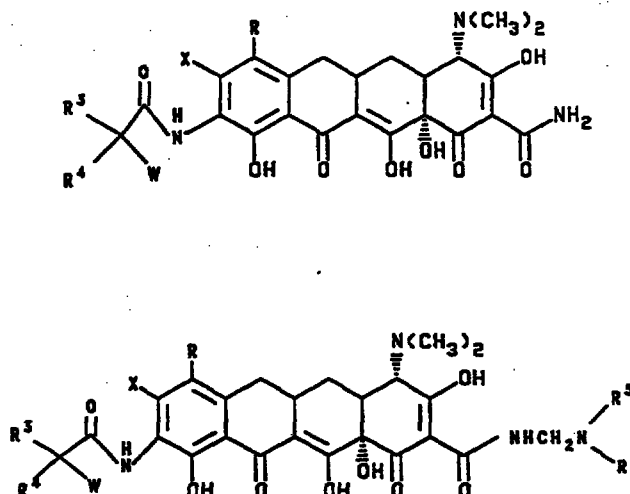
Substantially following the method, described in detail herein above in Example 36, the compounds of the invention listed in Examples 74 - 75 are prepared from [4S-(4 α ,12 α)]-9-[(bromoacetyl)amino]-4-(di-

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We claim:

1. A compound of the formula :



wherein:

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine, and iodine;

R is selected from hydrogen; 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 $R^1 = \text{n-butyl}$,

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



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and when $R^1 = 1\text{-methylpropyl}$,
 $R^2 = 2\text{-methylpropyl}$;
 R^3 is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methyl-ethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy- (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo- (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) alkoxy-carbonyl, (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 disubstituted (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 W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; hydroxylamino; (C_1-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 2-methylbutyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethyl-



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butyl, 1-methyl-1-ethylpropyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl and the diastereomers and enantiomers of said branched alkyl mono-substituted amino group; (C_3 - C_8)cycloalkyl mono-substituted amino group substitution selected from cyclopropyl, trans-1,2-dimethylcyclopropyl, cis-1,2-dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_3 - C_8)cycloalkyl monosubstituted amino; [(C_4 - C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3 - C_{10})alkenyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (C_6 - C_{10})aryl mono-substituted 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_2 - C_{14})alkylamino group substitution selected from dimethyl, diethyl, diisopropyl, di-n-propyl, dibutyl and diisobutyl; symmetrical disubstituted (C_3 - C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, dicyclohexyl and dicycloheptyl; straight or branched unsymmetrical disubstituted (C_3 - C_{14})alkylamino group wherein the



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total number of carbons in the substitution is not more than 14; unsymmetrical disubstituted (C_4-C_{14}) cycloalkylamino group wherein the total number of carbons in the substitution is not more than 14; (C_2-C_8) azacycloalkyl and substituted (C_2-C_8) azacycloalkyl group substitution selected from aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, 4-methylpiperidinyl, 2-methylpyrrolidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo[2.1.1]hex-2-yl, 5-azabicyclo[2.1.1]hex-5-yl, 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; 1-aza-oxacycloalkyl selected from morpholinyl and 1-aza-5-oxocycloheptane; substituted 1-aza-oxacycloalkyl group substitution selected from 2-(C_1-C_3)alkyl-morpholinyl, 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)alkyl-piperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethyl-piperazinyl, 4-(C_1-C_4)alkoxy-piperazinyl, 4-(C_6-C_{10})-aryloxy-piperazinyl, 4-hydroxy-piperazinyl, 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)alkylthiomorpholinyl 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-pyrazolyl, 2-(C_1-C_3)alkyl-1-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-



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triazolyl), 5-(C₁-C₃)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl; (heterocycle)amino group selected from 2- or 3-furanylamino, 2- or 3-thienylamino, 2-, 3- or 4-pyridylamino, 2- or 5-pyridazinylamino, 2-pyrazinylamino, 2-(imidazolyl)amino, (benzimidazolyl)amino, and (benzothiazolyl)amino and substituted (heterocycle)-amino group as defined above with 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 as defined above with 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, and β -aminobutyric acid and the enantiomers of said carboxy-(C₂-C₄)alkylamino group; (C₁-C₄)alkoxycarbonylamino group substitution selected from methoxycarbonyl, ethoxycarbonyl, allyloxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, 1,1-dimethylethoxycarbonyl, n-butoxycarbonyl, and 2-methylpropoxycarbonyl; (C₁-C₄)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy, and 1,1-dimethylethoxy; (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;



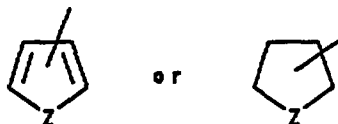
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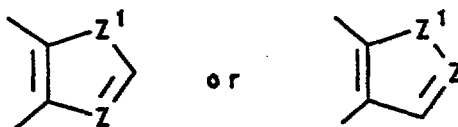
(C₇-C₁₁)arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl) methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

R⁵ 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-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



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

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



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(A is selected from hydrogen; straight or branched (C₁-C₄)alkyl; C₆-aryl; substituted C₆-aryl (substitution selected from halo, (C₁-C₄)alkoxy, trihalo(C₁-C₃)-alkyl, nitro, amino, cyano, (C₁-C₄)alkoxycarbonyl, (C₁-C₃)alkylamino or carboxy); (C₇-C₉)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl) 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-dioxo-morpholinyl, 2-dioxothiopholinyl; or -(CH₂)_nCOOR⁷ where n=0-4 and R⁷ 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 R⁵ and R⁶ cannot both be hydrogen; or R⁵ and R⁶ taken together are -(CH₂)₂B(CH₂)₂-, where in 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.

2. The compound according to Claim 1, wherein:
X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is selected from hydrogen; halogen selected from chlorine and iodine; or R = -NR¹R² and when R = -NR¹R² and R¹ = methyl or ethyl,



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R^2 = methyl and ethyl;

R^3 is selected from hydrogen; straight or branched (C_1-C_2)alkyl group selected from methyl and ethyl;

R^4 is selected from hydrogen and (C_1-C_6)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 W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from amino; (C_1-C_4) straight or branched alkyl monosubstituted amino group substitution selected from methyl, ethyl, n-propyl, 1-methylethyl, n-butyl and 1-methylpropyl; (C_3-C_4)cycloalkyl monosubstituted amino group substitution selected from cyclopropyl and cyclobutyl; (C_4-C_5)azacycloalkyl and substituted azacycloalkyl substitution selected from pyrrolidinyl, piperidinyl, 4-methylpiperidinyl; 1-azaoxacycloalkyl selected from morpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl and 4-(C_1-C_3)alkylpiperazinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl and 3-(C_1-C_3)alkyl-1-imidazolyl; (heterocycle)methylamino group said heterocycle selected from 2-, 3- or 4-pyridylmethylamino; carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α -aminopropionic acid, β -aminopropionic acid, α -butyric acid, β -aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group;

R^5 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;

R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R^5 and R^6 cannot both be hydrogen;

or R^5 and R^6 taken together are $-(CH_2)_2B(CH_2)_2-$, wherein B is selected from $(CH_2)_n$ and $n=0-1$, $-NH$, $-N(C_1-C_3)-$



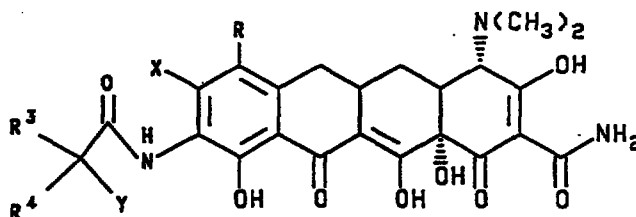
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alkyl [straight or branched], $-N(C_1-C_4)$ alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

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 and iodine; X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen; 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;



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and when $R^1 = 1\text{-methylpropyl}$,
 $R^2 = 2\text{-methylpropyl}$;
 R^3 is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy- (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) -alkoxycarbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group [substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4) alkylamino, (C_1-C_4) alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxy];
 R^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 W substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

4. The compound according to Claim 3, wherein:

Y is selected from $(CH_2)_n X'$, $n = 0-5$, X' is halogen selected from bromine, chlorine, fluorine and iodine;
 X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is



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dioxo-9-[[1-oxo-2-(propylamino)propyl]amino]-2-naphthacenecarboxamide;

[7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -cyclobutyltetrahydro-2H-1,2-isoxazine-2-acetamide;

[4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-4,7-bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[phenyl[(phenylmethyl)amino]acetyl]amino]-2-naphthacenecarboxamide;

[7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -cyclopropyl- α -methyl-1-azetidineacetamide;

[7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -(1,1-dimethylethyl)-(3-methyl-4-morpholine)acetamide;

[4S-(4 α ,12 $\alpha\alpha$)]-8-Chloro-9-[[[(2,4-difluorophenyl)[(2-phenylethyl)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.

[7S-(7 α ,10 $\alpha\alpha$)]-N-[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -(methoxyamino)- α -methyl-2-furanacetamide;

[7S-(7 α ,10 $\alpha\alpha$)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-[(1,1-dimethylethyl)amino]-4-oxobutanoic acid methyl ester;

[7S-(7 α ,10 $\alpha\alpha$)]-4-[[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-3-(dimethylamino)-4-oxobutanoic acid methyl ester;

[7S-(7 α ,10 $\alpha\alpha$)]-7-[[[9-(Aminocarbonyl)-3-chloro-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-



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10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-5-azabicyclo[2.1.1]hexane-5-acetamide dihydrochloride;
[4S-(4 α ,12 α)]-8-Chloro-9-[[(cyclobutylamino) acetyl]-amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;
[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -ethyl-1H-imidazole-1-acetamide dihydrochloride;
[4S-(4 α ,12 α)]-8-Chloro-9-[[2-(diethylamino)-1-oxopropyl]amino]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
[7S-(7 α ,10 α)]-1-[2-[[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]amino]-1-methyl-2-oxoethyl] proline methyl ester;
[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -(4-hydroxyphenyl)-6-methyl-2,6-diazabicyclo[2.1.1]heptane-2-acetamide;
[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-9-[[(dimethylamino) (2-fluorophenyl) acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[1-(4-methoxy-1-piperazinyl)-4-pentenoyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;
[4S-(4 α ,12 α)]-8-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo-4-phenyl-2-[(phenylmethoxy) amino]butyl]amino]-2-naphthacenecarboxamide;
[7S-(7 α ,10 α)]-N-[9-(Aminocarbonyl)-3-chloro-7-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,-



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11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]- α -4-pyridyl-5-azabicyclo[2.1.1]hexan-5-acetamide;
[4S-(4 α ,12 α)]-4-(Dimethylamino)-9-[(dimethylamino)-acetyl]amino]-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide;
[4S-(4 α ,12 α)]-4-(Dimethylamino)-8-fluoro-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[(propylamino)acetyl]amino]-2-naphthacene-carboxamide; or
[4S-(4 α ,12 α)]-4-(Dimethylamino)-9-[(dimethylamino)-acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-8-[(trifluoromethyl)sulfonyl]oxy]-2-naphthacenecarboxamide.

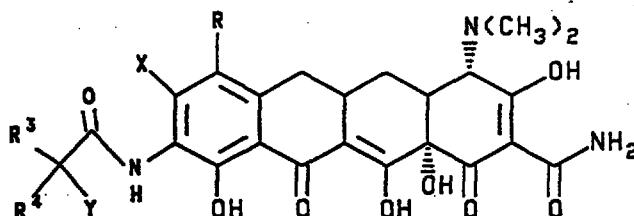
7. The compound according to claim 3,
[4S-(4 α ,12 α)]-9-[(Chloroacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide;
[4S-(4 α ,12 α)]-9-[(Bromoacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
[4S-(4 α ,12 α)]-9-[(α -Bromopropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide;
[4S-(4 α ,12 α)]-9-[(α -Bromocyclobutylacetyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide;
[4S-(4 α ,12 α)]-8-Chloro-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[1-oxo-2-(propylamino)propyl]amino]-2-naphthacenecarboxamide;
[4S-(4 α ,12 α)]-9-[(α -Bromo- α -cyclopropylpropionyl)amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,-

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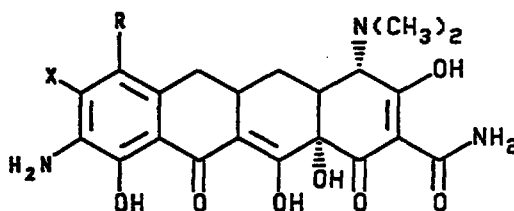
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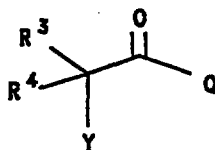


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according to Claim 3, which comprises reacting a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:



with a straight or branched haloacyl halide of the formula:



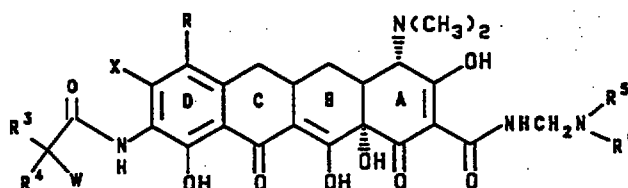
wherein Y, R³ and R⁴ are as defined in Claim 1 and Q is halogen selected from bromine, chlorine, iodine and fluorine, in an inert solvent, in a polar protic solvent and in the presence of a base.

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



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$$\begin{array}{c} \text{R}^5 \\ \diagdown \\ \text{N} \\ \diagup \\ \text{R}^6 \end{array}$$

12. 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.

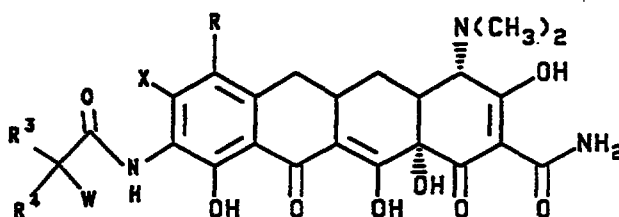
13. A pharmaceutical composition of matter comprising a pharmacologically effective amount of a compound according to Claim 1 in association with a pharmaceutically acceptable carrier.

31,926

NOVEL 7-(SUBSTITUTED)-8-
(SUBSTITUTED)-9-[(SUBSTITUTED
GLYCYL)AMIDO]-6-DEMETHYL-6-
DEOXYTETRACYCLINES

ABSTRACT OF THE INVENTION

The invention provides compounds of the formula:



I

wherein R , R^3 , R^4 , X and W are defined in the specification. These compounds are useful as antibiotic agents.

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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
disubstituted (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 Y sub-
stituent) maybe be either the racemate (DL) or the in-
dividual enantiomers (L or D); and the pharmaco logic-
ally acceptable organic and inorganic salts or metal
complexes.

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

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

X is halogen or trifluoromethanesulfonyloxy, the
halogen is selected from bromine, chlorine, fluorine
and iodine;

R is selected from hydrogen; halogen selected from bro-
mine, chlorine 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 or 2-methylpropyl;

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_1-C_8)alkyl group selected from methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and

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

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

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☒ Claim(s) : paged ~~mm~~ to paged ~~mm~~
☐ Drawing(s) : paged to paged
☐ Abstract : paged to paged

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group (substitution selected from hydroxy, halogen,
(C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, and carboxy);
(C₇-C₉)aralkyl group selected from benzyl, 1-phenyl-
ethyl, 2-phenylethyl and phenylpropyl; substituted-
(C₇-C₉)aralkyl group [substitution selected from halo,
(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylsulfonyl,
cyano and carboxy];

R⁴ is selected from hydrogen and (C₁-C₄)alkyl selected
from methyl, ethyl propyl, isopropyl, butyl and iso-
butyl;

when R³ does not equal R⁴ the stereochemistry of the
asymmetric carbon (i.e., the carbon bearing the Y sub-
stituent) maybe be either the racemate (DL) or the in-
dividual enantiomers (L or D); and the pharmaco-
logically acceptable organic and inorganic salts or
metal complexes.

Particularly preferred compounds are com-
pounds according to the above formula III wherein:
Y is selected from (CH₂)_nX', n=0-5, X' is halogen
selected from bromine, chlorine, fluorine and iodine;
X is halogen or trifluoromethanesulfonyloxy, the
halogen is selected from bromine, chlorine, fluorine
and iodine;

R is selected from hydrogen; halogen selected from bro-
mine, chlorine and iodine; or R = -NR¹R²

and when R = -NR¹R² and R¹ = hydrogen,
R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R¹ = methyl or ethyl,
R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl,
1-methylpropyl or 2-methylpropyl;

R³ is selected from hydrogen; straight or branched
(C₁-C₆)alkyl group selected from methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, pentyl and hexyl;

(C₆-C₁₀)aryl group selected from phenyl, α-naphthyl and
β-naphthyl; (C₇-C₉)aralkyl group selected from benzyl,
1-phenylethyl, 2-phenylethyl and phenylpropyl;

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

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

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

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

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is selected from hydrogen; halogen selected from chlorine and iodine; or $R = -NR^1R^2$

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

R^3 is selected from hydrogen; straight or branched (C_1-C_2) alkyl group selected from methyl and ethyl;

R^4 is selected from hydrogen and (C_1-C_6) 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 Y substituent) 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.



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

$R^2 = 2\text{-methylpropyl}$;

R^3 is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) -alkoxycarbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group [substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4) alkylamino, (C_1-C_4) alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxy]; R^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 Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

4. The compound according to Claim 3,

wherein:

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

X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from chlorine and fluorine; R is



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selected from hydrogen; halogen selected from chlorine and iodine; or $R = -NR^1R^2$ and when $R = -NR^1R^2$ and $R^1 = \text{methyl or ethyl}$, $R^2 = \text{methyl and ethyl}$; R^3 is selected from hydrogen; straight or branched (C_1-C_2) alkyl group selected from methyl and ethyl; R^4 is selected from hydrogen and (C_1-C_6) 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 Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

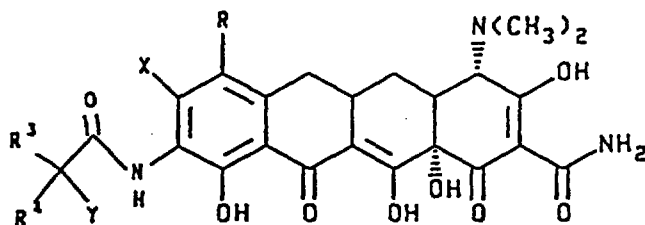
5. The compound according to Claims 1 or 3 wherein said salts or metal complexes comprise: hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric, sulfate, acetate, benzoate, citrate, cysteine or other amino acid, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate, arylsulfonate, aluminum, calcium, iron, magnesium or manganese.

6. The compound according to Claim 1, [4S-(4 α , 12 α)]-8-Chloro-4-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide disulfate; [4S-(4 α , 12 α)]-8-Chloro-4-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,-6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4 α , 12 α)]-8-Chloro-4,7-(dimethylamino)-9-[[(dimethylamino)acetyl]amino]-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide; [4S-(4 α , 12 α)]-9-[[(Butylamino)acetyl]amino]-8-chloro-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-

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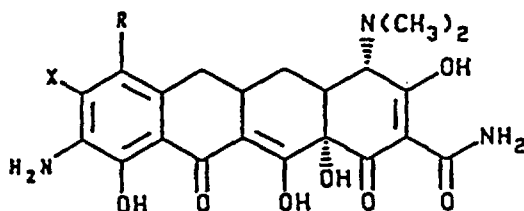


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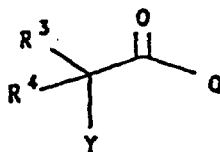


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according to Claim 3, which comprises reacting a 9-amino-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline, or its organic and inorganic salt or metal complex, of the formula:



with a straight or branched haloacyl halide of the formula:



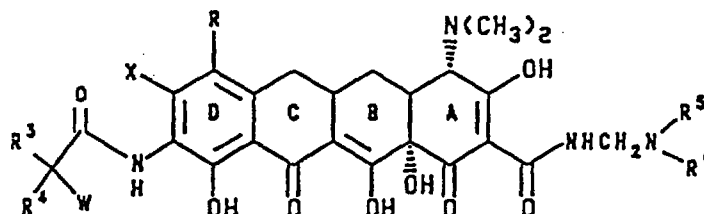
wherein Y, R³ and R⁴ are as defined in Claim 3 and Q is halogen selected from bromine, chlorine, iodine and fluorine, in an inert solvent, in a polar protic solvent and in the presence of a base.

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



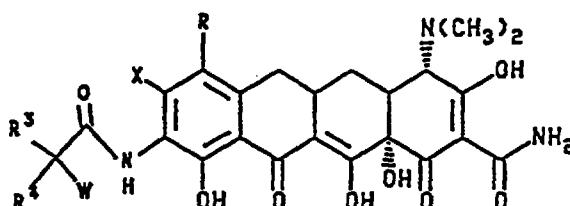
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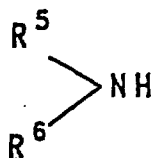
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according to Claim 1, which comprises reacting a 9-[(substituted glycy)amido]-7-(substituted)-8-(substituted)-6-demethyl-6-deoxytetracycline of the formula:



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according to Claim 1 with a primary amine of the formula R^5NH_2 or a secondary amine of the formula



in the presence of formaldehyde.

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



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

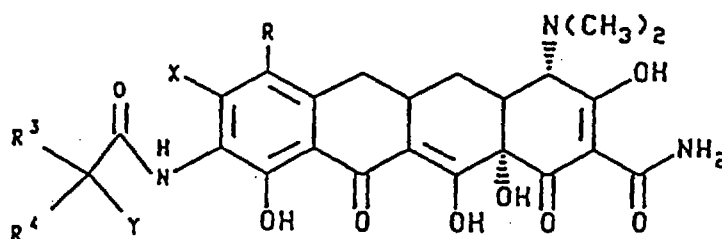


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alkyl [straight or branched], -N(C₁-C₄)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

3. A compound of the formula:



wherein:

Y is selected from bromine, chlorine, fluorine and iodine;
X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine, fluorine and iodine;

R is selected from hydrogen; halogen selected from bromine, chlorine, fluorine and iodine; or R = -NR¹R²

and when R = -NR¹R² and R¹ = hydrogen,

R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R¹ = methyl or ethyl,

R² = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R¹ = n-propyl,

R² = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R¹ = 1-methylethyl,

R² = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R¹ = n-butyl,

R² = n-butyl, 1-methylpropyl or 2-methylpropyl;



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

$R^2 = 2\text{-methylpropyl}$:

R^3 is selected from hydrogen; straight or branched (C_1-C_8) alkyl group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α -mercapto (C_1-C_4) alkyl group selected from mercaptomethyl, α -mercaptoethyl, α -mercapto-1-methylethyl, α -mercaptopropyl and α -mercaptobutyl; α -hydroxy- (C_1-C_4) alkyl group selected from hydroxymethyl, α -hydroxyethyl, α -hydroxy-1-methylethyl, α -hydroxypropyl and α -hydroxybutyl; carboxyl (C_1-C_8) alkyl group; (C_6-C_{10}) aryl group selected from phenyl, α -naphthyl and β -naphthyl; substituted (C_6-C_{10}) aryl group (substitution selected from hydroxy, halogen, (C_1-C_4) alkoxy, trihalo (C_1-C_3) alkyl, nitro, amino, cyano, (C_1-C_4) -alkoxycarbonyl, (C_1-C_3) alkylamino and carboxy); (C_7-C_9) aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9) aralkyl group (substitution selected from halo, (C_1-C_4) alkyl, nitro, hydroxy, amino, mono- or di-substituted (C_1-C_4) alkylamino, (C_1-C_4) alkoxy, (C_1-C_4) alkylsulfonyl, cyano and carboxy); R^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 Y substituent) maybe be either the racemate (DL) or the individual enantiomers (L or D); with the proviso that CR^3R^4 is not $-\text{CH}_2-$, $-\text{CHCH}_3-$, $-\text{CH}(\text{CH}_2\text{CH}_3)-$ or $-\text{C}(\text{CH}_3)_2-$; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

4. The compound according to Claim 3,
wherein:

Y is selected from bromine, chlorine, fluorine and iodine; X is halogen or trifluoromethanesulfonyloxy, the halogen is selected from bromine, chlorine and fluorine; R is



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14. A veterinary composition which comprises a veterinarily effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

15. 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 veterinarily effective amount of a compound according to Claim 1.

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