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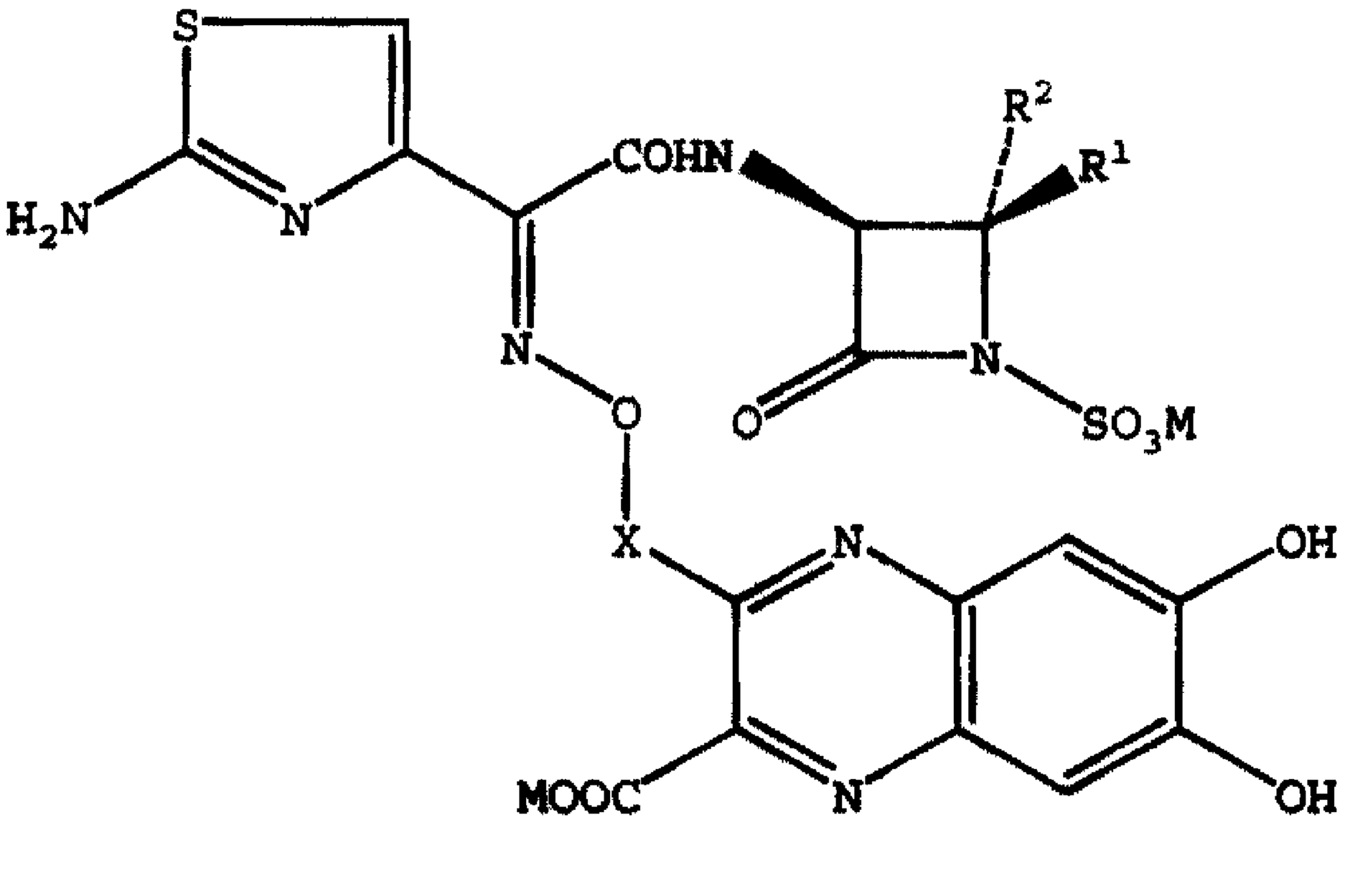
(54) Titre : DERIVES HETEROAROYLE D'ANTIBIOTIQUES DU TYPE BETA-LACTAM MONOCYCLIQUE
(54) Title: HETEROAROYL DERIVATIVES OF MONOCYCLIC BETA-LACTAM ANTIBIOTICS



(57) Abrégé/Abstract:
Antibacterial activity is exhibited by novel compounds having the formula (see formula I).

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Abstract

Heteroaroyl Derivatives of Monocyclic Beta-Lactam Antibiotics

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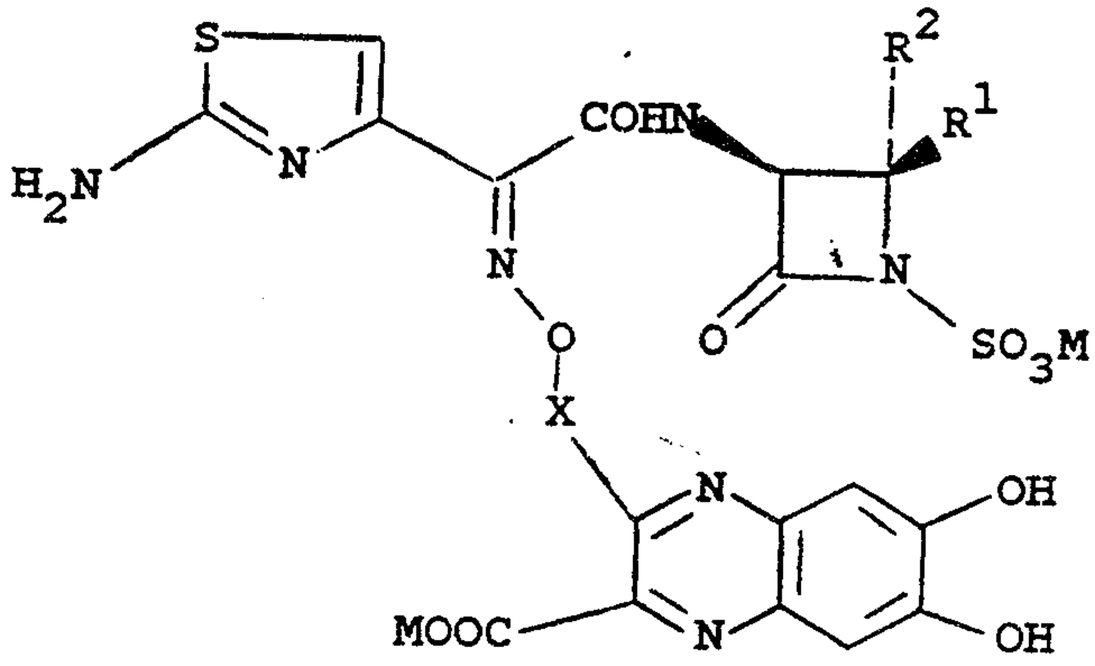

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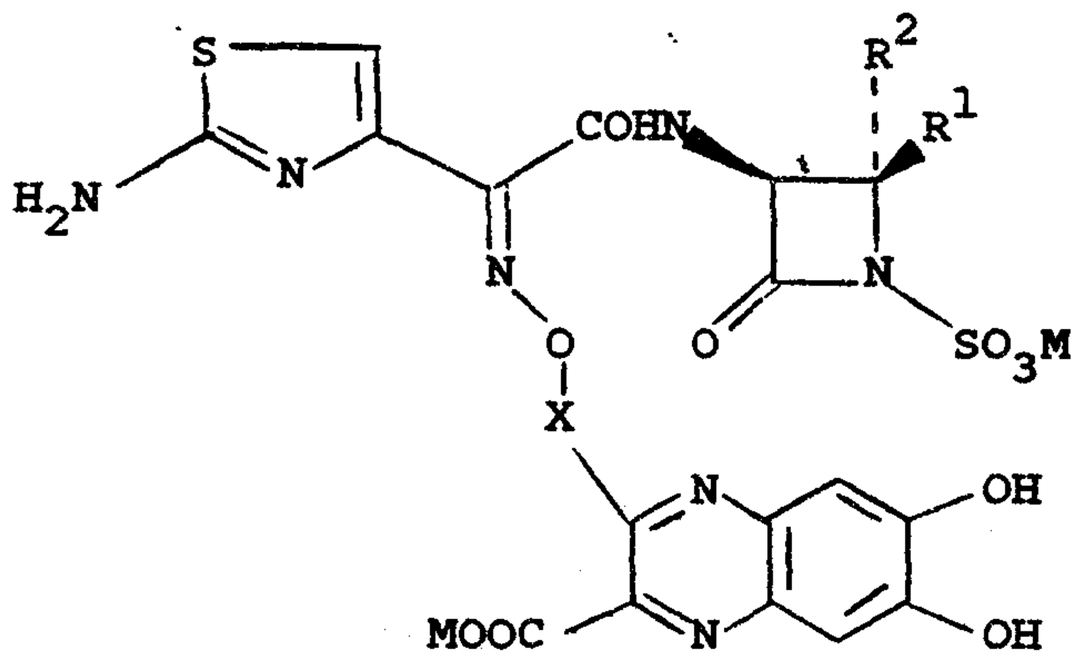
Heteroaroyl Derivatives of Monocyclic Beta-Lactam Antibiotics

Compounds having the formula



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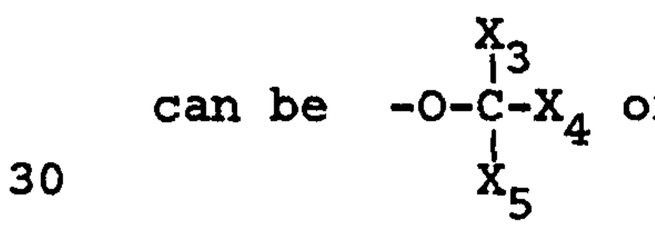
having antibacterial activity are described herein. In formula 1, and throughout the specification, the symbols are as defined below.

R_1 and R_2 are the same or different and each is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, substituted phenyl or a 4, 5, 6 or 7-membered heterocycle (hereinafter referred to as R_a), or one of R_1 and R_2 is hydrogen and the other is azido, halomethyl, dihalomethyl, trihalomethyl, alkoxycarbonyl, phenylethyl, 2-phenylethenyl, 2-phenylethynyl, carboxyl, $-CH_2X_1$ [wherein X_1 is azido, amino, hydroxy, carboxyl, alkoxycarbonyl, alkanoylamino, phenylcarbonylamino, (substituted phenyl)carbonylamino, alkylsulfonyloxy, phenylsulfonyloxy, (substituted phenyl)sulfonyloxy, phenyl, substituted

phenyl, cyano, $-A-C(=O)-NH_6X_7$, $-S-X_2$, or $-O-X_2$ wherein A, X_2, X_6 and X_7 are as hereinafter defined], $-S-X_2$ or $-O-X_2$ [wherein X_2, is alkyl, substituted alkyl, phenyl, substituted phenyl, phenylalkyl, (substituted phenyl) alkyl, formyl, alkanoyl, substituted alkanoyl, phenylalkanoyl, substituted phenylalkanoyl, phenylcarbonyl, substituted phenylcarbonyl, heteroaryl, heteroarylalkyl, heteroarylalkanoyl or heteroarylcarbonyl, and in the case of when X_1 is $O-X_2$ then X_2 can also be alkylideneamino, alkanoylamino, carboxyalkylideneamino, alkylsulphonylamino, alkoxycarbonyl, alkylsulphonylamino or N,N-cyclodialkanoylamino]. In addition R_1 and R_2 can be



[wherein one of X_3 and X_4 is hydrogen and the other is hydrogen or alkyl, or X_3 and X_4 when taken together with the carbon atom to which they are attached form a cycloalkyl group; and X_5 is formyl, alkanoyl,

phenylcarbonyl, substituted phenylcarbonyl, phenylalkylcarbonyl, substituted phenylalkylcarbonyl, carboxyl, alkoxycarbonyl, aminocarbonyl, substituted aminocarbonyl, or cyano] or $-A-\overset{O}{\overset{\|}{C}}-NX_6X_7$ [wherein A is $-CH=CH-$, $-(CH_2)_m-$, $-(CH_2)_m-O-$, $-(CH_2)_m-NH-$, or $-CH_2-S-CH_2-$, m is 0, 1 or 2, and X_6 and X_7 are the same or different and each is hydrogen, alkyl, phenyl or substituted phenyl, or X_6 is hydrogen an X_7 is amino, substituted amino, alkanoylamino or alkoxy, or X_6 and X_7 when taken together with the nitrogen atom to which they are attached form a 4, 5, 6 or 7-membered heterocycle];

X is $(CH_2)_n$ wherein n is 0, 1, 2, 3 or 4 or CR_3R_4 wherein R_3 and R_4 are the same or different and each is hydrogen, CH_3 or C_2H_5 or R_3 and R_4 taken together with the carbon atom to which they are attached form a 3, 4, 5, 6 or 7-membered cycloalkyl ring; M is hydrogen, tetraalkylammonium, sodium, potassium or any other cation capable of forming a pharmaceutically acceptable salt. Preferred compounds are when X is CH_2. The preferred compound is illustrated in Examples eleven and twenty. The compounds of this invention are pictured as acids or salts. They can also exist, however, as zwitterions (internal or inner salts), and these are also included within the language "pharmaceutically acceptable salts" and the scope of this invention.

Listed below are definitions of various terms used to describe the β-lactams of this invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The terms "alkyl" and "alkoxy" refer to both straight and branched chain groups. Those groups having 1 to 10 carbon atoms are preferred.

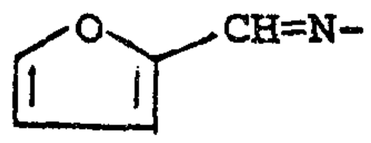
The term "cycloalkyl" refers to cycloalkyl groups having 3, 4, 5, 6 or 7 carbon atoms.

The term "substituted alkyl" refers to alkyl groups substituted with one or more (preferably 1, 2 or 3) azido, amino ($-NH_2$), halogen, hydroxy, carboxy, cyano, alkoxycarbonyl, aminocarbonyl, alkanoyloxy, alkoxy, phenyloxy, (substituted phenyl)oxy, R_a-oxy, mercapto, alkylthio, phenylthio, (substituted phenyl) thio, alkylsulfinyl, or alkylsulfonyl groups.

The terms "alkanoyl", "alkenyl", and "alkynyl" refer to both straight and branched chain groups. Those groups having 2 to 10 carbon atoms are preferred.

The term "substituted alkanoyl" refers to alkanoyl groups substituted with one or more (preferably 1, 2 or 3) azido, amino ($-NH_2$), halogen, hydroxy, carboxy, cyano, alkoxycarbonyl, aminocarbonyl, alkanoyloxy, alkoxy, phenyloxy, (substituted phenyl)oxy, mercapto, alkylthio, phenylthio, (substituted phenyl)thio, alkylsufinyl or alkylsulfonyl groups.

The term "substituted phenyl" refers to a phenyl group substituted with 1, 2 or 3 amino ($-NH_2$), halogen, hydroxyl, trifluoromethyl, alkyl (of 1 to 4 carbon atoms), alkoxy (of 1 to 4 carbon atoms), alkanoyloxy, aminocarbonyl, or carboxy groups.

The expression "a 4, 5, 6 or 7-membered heterocycle" (referred to as "R_a") refers to substituted and unsubstituted, aromatic and non-aromatic groups containing one or more (preferably 1, 2 or 3) nitrogen, oxygen or sulfur atoms. Exemplary substituents are oxo (=O), halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbons, alkoxy or 1 to 4 carbons, alkylsulfony, phenyl, substitued phenyl, 2-furfurylideneamino (), benzylideneamino and substituted alkyl groups (wherein the alkyl group has 1 to 4 carbons). One type of "4, 5, 6 or 7-membered heterocycle" is the heteroaryl" group. The term "heteroaryl" refers to those 4, 5, 6 or 7-membered heterocycles which are aromatic. Exemplary heteroaryl groups are substitued and unsubstituted pyridinyl, furanyl, pyrrolyl, thienyl, 1, 2, 3-triazolyl, 1,2,4-triazolyl, imidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, oxazolyl, triazinyl and tetrazolyl.

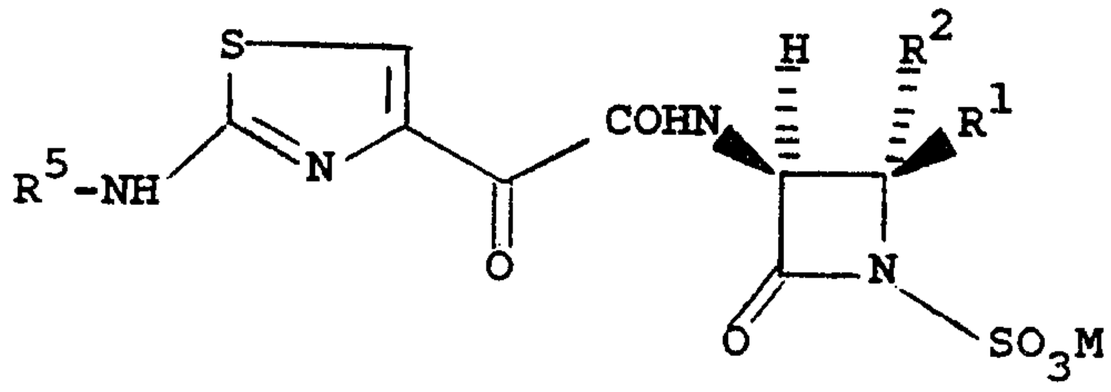
Exemplary nonaromatic heterocycles (i.e., fully or partially saturated heterocyclic groups) are substituted and unsubstituted azetidinyl, oxetanyl, thietanyl, piperidinyl, piperazinyl, imidazolidinyl, oxazolidinyl, pyrrolidinyl, tetrahydropyrimidinyl, dihydrothiazolyl and hexahydroazepinyl. Exemplary of the substituted 4, 5, 6 or 7-membered heterocycles are 1-alkyl-3-azetidinyl, 2-oxo-1-imidazolidinyl, 3-alkylsulfonyl-2-oxo-1-imidazolidinyl, 3-benzylideneamino-2-oxo-1-imidazolidinyl, 3-alkyl-2-oxo-1-imidazolidinyl, 3-phenyl (or substituted phenyl)-2-oxo-1-imidazolidinyl, 3-benzyl-2-oxo-1-imidazolidinyl, 3-(2-aminoethyl)-2-oxo-1-imidazolidinyl, 3-amino-2-oxo-1-imidazolidinyl, 3-[alkoxycarbonyl)amino]-2-oxo-1-imidazolidinyl, 3-[2-[(alkoxycarbonyl)-amino]ethyl]-2-oxo-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2-oxo-3-oxazolidinyl, 4-hydroxy-6-methyl-2-pyrimidinyl, 2-oxo-1-hexahydroazepinyl, 2-oxo-3-pyrrolidinyl, 2-oxo-3-tetrahydrofuranyl, 2,3-dioxo-1-piperazinyl, 2,5-dioxo-1-piperazinyl, 4-alkyl-2,3-dioxo-1-piperazinyl, and 4-phenyl-2, 3-dioxo-1-piperazinyl.

The term "substituted amino" refers to a group having the formula $-NX_8X_9$ wherein X_8 is hydrogen, alkyl, phenyl, substituted phenyl, phenylalkyl or (substituted phenyl)alkyl, and X_9 is alkyl, phenyl, substituted phenyl, phenylalkyl, (substituted phenyl)alkyl, hydroxy, cyano, alkoxy, phenylalkoxy or amino.

The β-lactams of formula 1 have activity against gram-positive and gram-negative organisms. Of particular interest is the good activity against gram negative organisms *in vitro* and *in vivo* exhibited by the compounds of this invention. The compound of this invention can be used as agents to combat bacterial infections (including urinary tract infections and respiratory infections) in mammalian species, such as domesticated animals (e.g., dogs, cats, cows, horses, and the like) and humans.

For combating bacterial infections in mammals, a compound of this invention can be administered to a mammal in need thereof in an amount of about 1.4 mg/kg/day to about 350 mg/kg/day, preferably about 14 mg/kg/day to about 100 mg/kg/day. All modes of administration which have been used in the past to deliver penicillins and cephalosporins to the site of the infection are also contemplated for use with β-lactams of this invention. Such methods of administration include oral, intravenous, intramuscular, and as a suppository.

The compounds of this invention can be prepared by coupling a compound having the formula



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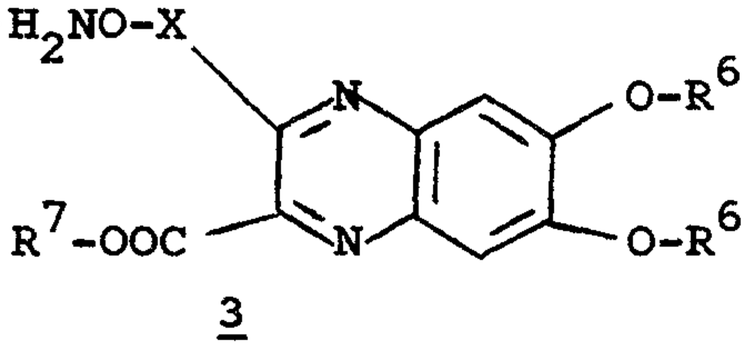
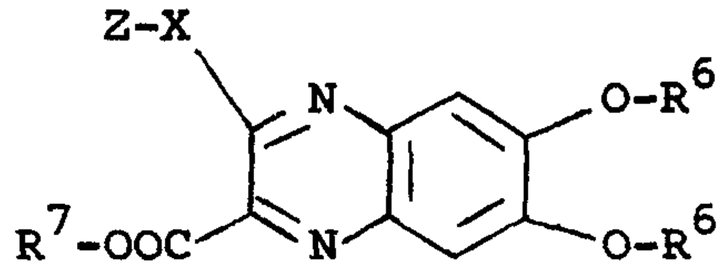
wherein R^5 is hydrogen or a suitable protecting group such as formyl or trityl with a compound of the formula



3

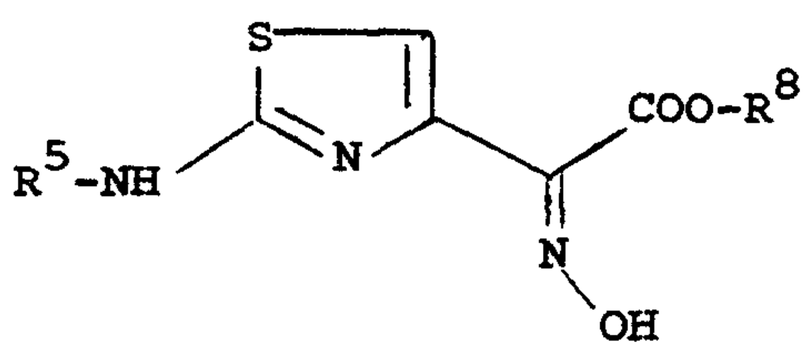
wherein R^6 is hydrogen or a suitable phenol-protecting group or R^6/R^6 is a catechol protecting group such as Si(t-butyl)$_2$, R^7 is hydrogen or a suitable protecting group such as t-butyl or diphenylmethyl and HY is a mineral acid, sulfonic acid or another non-nucleophilic acid capable of forming a stable hydroxylamine salt and m is 0, 1, or 2 or fractions of 1 or 2. All synthesis of compounds using intermediates carrying protecting groups such as R^5, R^6, and R^7 in formulae 2, 3 and 6 provide protected derivatives of 1 which must be finally deprotected.

Alternatively, the compounds of formula 1 can be prepared by reacting a compound of the formula



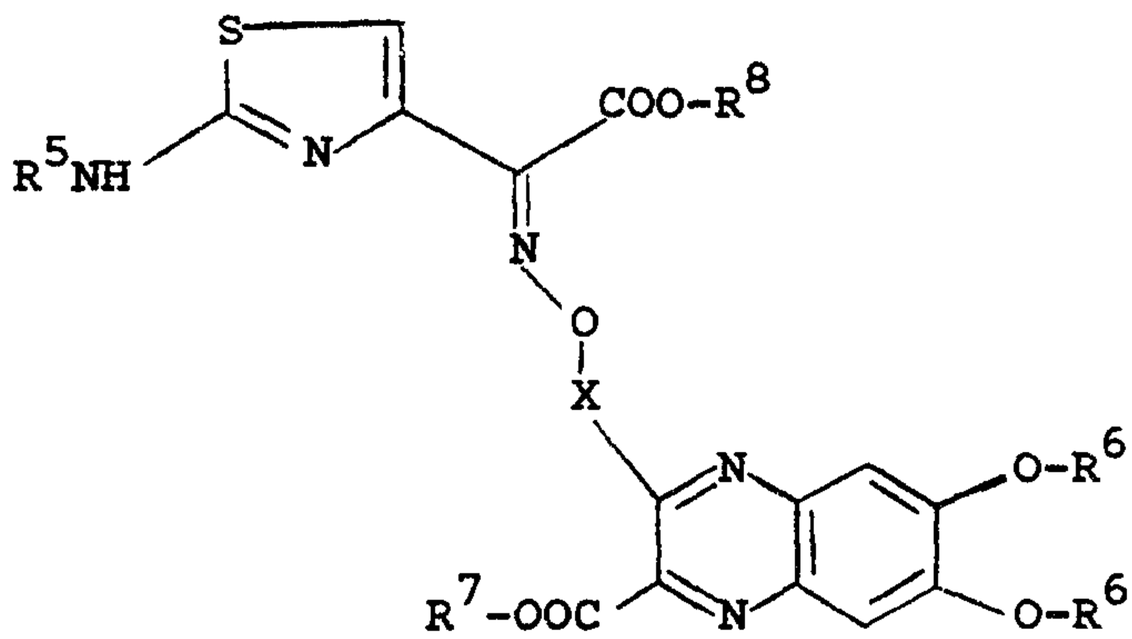
4

wherein Z is a leaving group such as halogen, trifluoroacetate, alkylsulfonate, arylsulfonate or other activated esters of alcohols; wherein R^6 is the same as above with the proviso that if R^5 is trityl then R^6 may also be benzyl or another protecting group which can be removed by catalytic hydrogenation and R^7 is the same as above with the proviso that in compound 4 R^7 may also be allyl, trimethylsilylethyl or other non-sterically crowded carboxyl protecting group with a compound of the formula



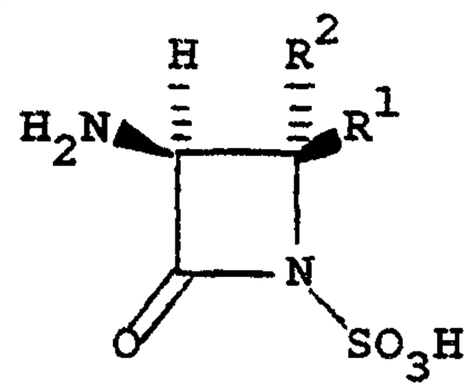
5

wherein R^5 is a defined above and R^8 is hydrogen or a carboxyl protecting group which can be removed under conditions wherein R^7 remains inert. If R^5 is trityl then R_8 may also be p-nitrobenzyl to form a compound of the formula



6

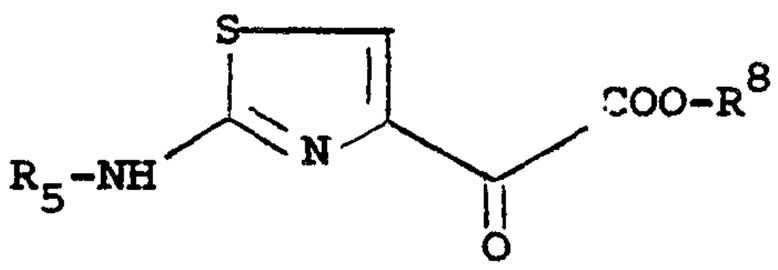
wherein R^5, R^6, R^7 and R^8 have hereinbefore been defined. Compound 6 is then reacted with a compound of the formula



7

to form compounds of the invention represented by formula 1.

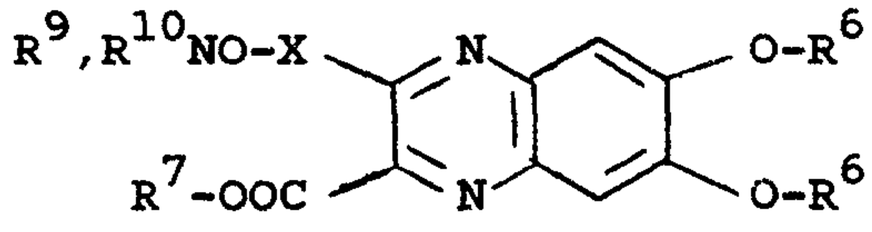
Compound 6 can also be formed by reacting compound 3 with a compound of the formula



8

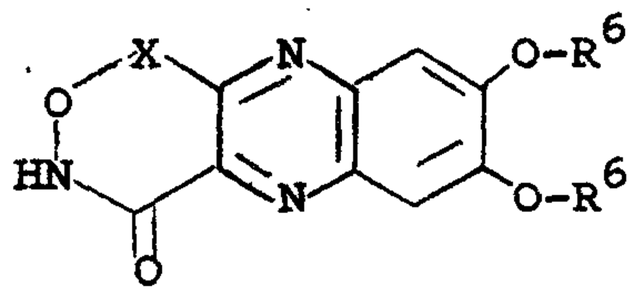
wherein R^5 and R^8 are as hereinbefore defined.

Compound 3 can be prepared from compound 9 by total or partial removal of the protecting groups R^6, R^7, R^9, R^{10}.



9

Also, the cyclic hydroxamic acids of formula 10 can be hydrolyzed (HCl conc., ca 80°) to form the hydroxylamines of formula 3.



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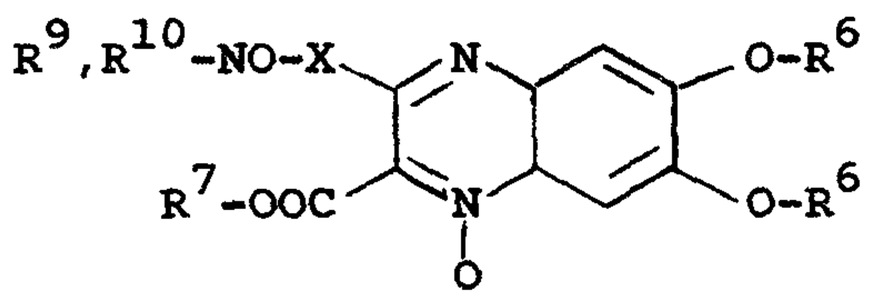
Alternatively, compound 3 can be prepared from compound 11 by desoxygenation and total or partial removal of the protecting group R^6, R^7, R^9, R^{10}.



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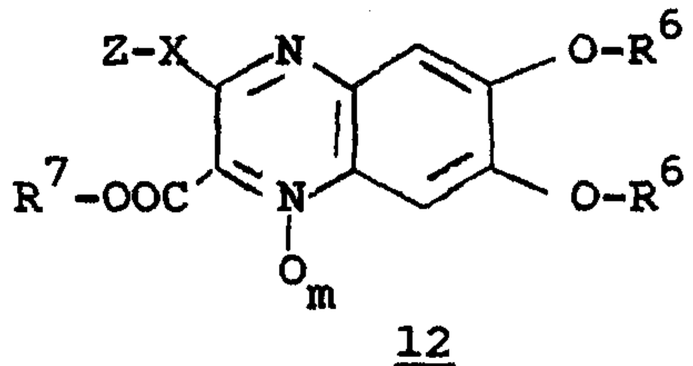
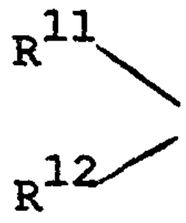
Compounds 9 and 11 can be prepared by reacting a compound of formula 12, with a N-protected derivative of hydroxylamine of the formula 13 in an organic solvent and in the presence of a base such as K_2CO_3 or triethylamine.



12

m = 0 or 1

In the case of m = 0 formula 12 is identical with formula 4. Hence, all definitions of R^6, R^7, X and Z are specified as in formula 4. Instead of activated esters of alcohols as leaving groups Z, the alcohols themselves (Z = OH) can be used if the alcohols are preactivated by using e.g. Mitsunobu conditions (PPh_3/DEAD/THF).



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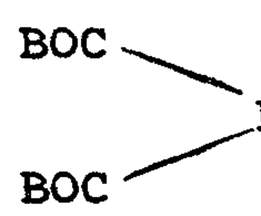
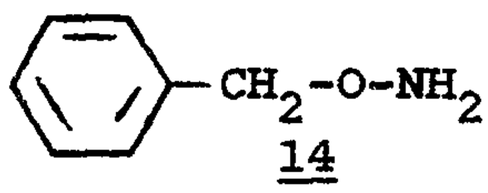


13a

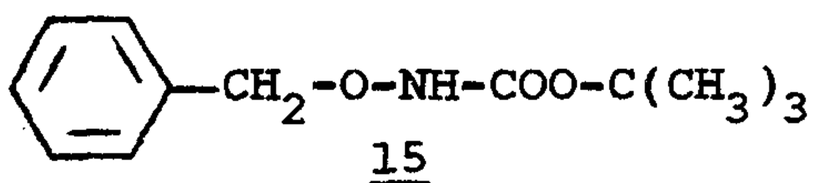
In formula 13 R^{11} and R^{12} are combinations of suitable protecting groups such as H, t-butyl-oxy-carbonyl (BOC), benzyloxy-carbonyl or R^{11} and R^{12} taken together form a divalent, cyclic protective group such as isopropylidene group $(CH_3)_2C$ or a phthalyl group. In the case of R^{11} = R^{12} = BOC ($(BOC)_2NOH$) compound 13a is novel and forms an integral part of this invention. In formula 9 and 11, R^9 and R^{10} are equivalent to R^{11} and R^{12} in formula 13.

Compound 13a is made by reacting a compound of the formula 14



14

with di-t-butyldicarbonate in a mixture of water, tetrahydrofuran (THF) and NaOH to form a compound of the formula 15. Intermediate 15 is also reported in the literature: R. Sulsky and J.P. Demers, Tetrahedron Letters, 30, (1989), 31-34.



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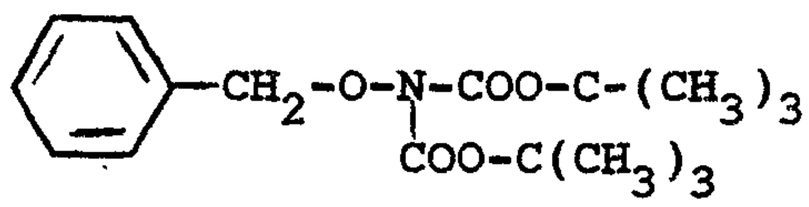
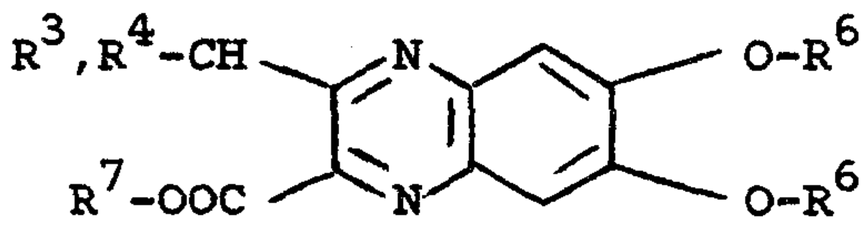
Compound 15 is reacted with di-t-butyldicarbonate in tetrahydrofuran and 4-dimethylaminopyridine to form a compound of the formula 16.



16

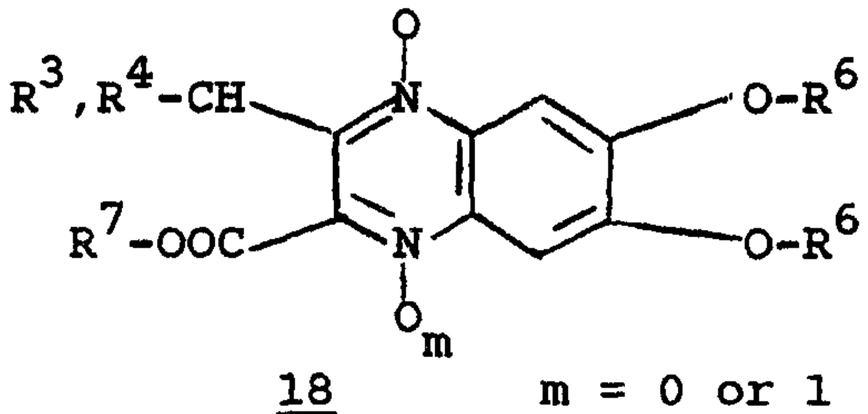
Compound 16 is hydrogenated in the presence of palladium on activated carbon to form compound 13a.

Compound 12 can be prepared by halogenation (e.g. NBS) of the corresponding alkyl substituted compound 17.



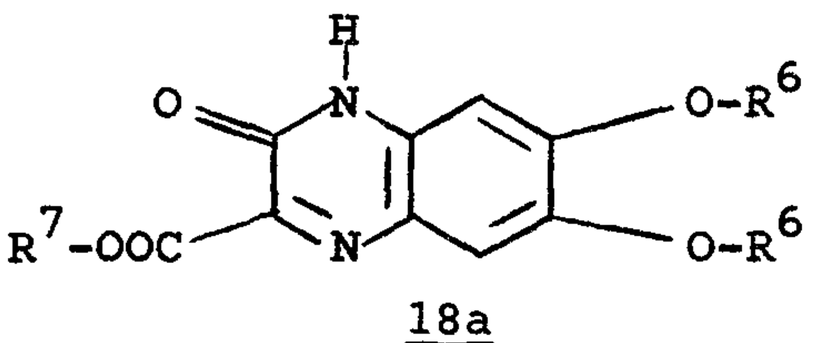
17

wherein R^3, R^4 is defined previously or by conversion of the correponding N-oxides of the formula 18 with acetylchloride or trifluoroacetic anhydride. The acetate group introduced in this manner is subsequently displaced by halide ion and in the case when m is one in formula 18 the remaining N-oxide moiety is deoxygenated to afford a compound of formula 12.



18 m = 0 or 1

In order to prepare compounds of formula 1 when n is zero, compounds of formula 4 wherein Z is halogen and X is a single bond are prepared by reacting compounds of the formula

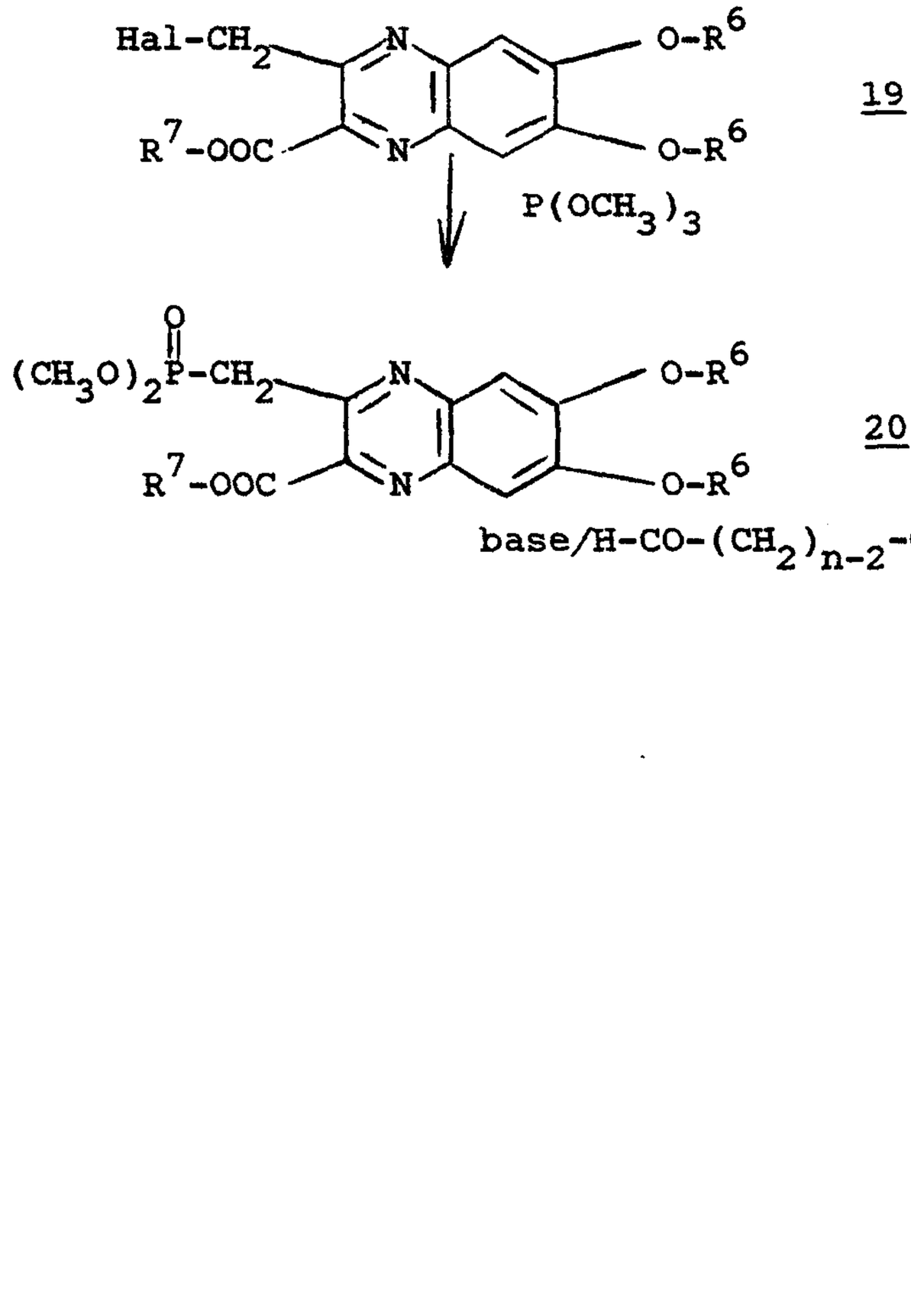


18a

with $POCl_3$. A compound of formula 18a is equivalent to a compound of formula 4 when Z is OH and n is zero.

Alternatively, compound 12 can be prepared by conversion of the Z - X group in 12 to a modified Z' - X' group as exemplified in the following Scheme 1 and Scheme 2. Formula 19 is identical with formula 12 if Z = Hal, X = CH_2 and m = 0; formula 19 is also identical with formula 4 if Z = Hal and X = CH_2.

Scheme 1



19

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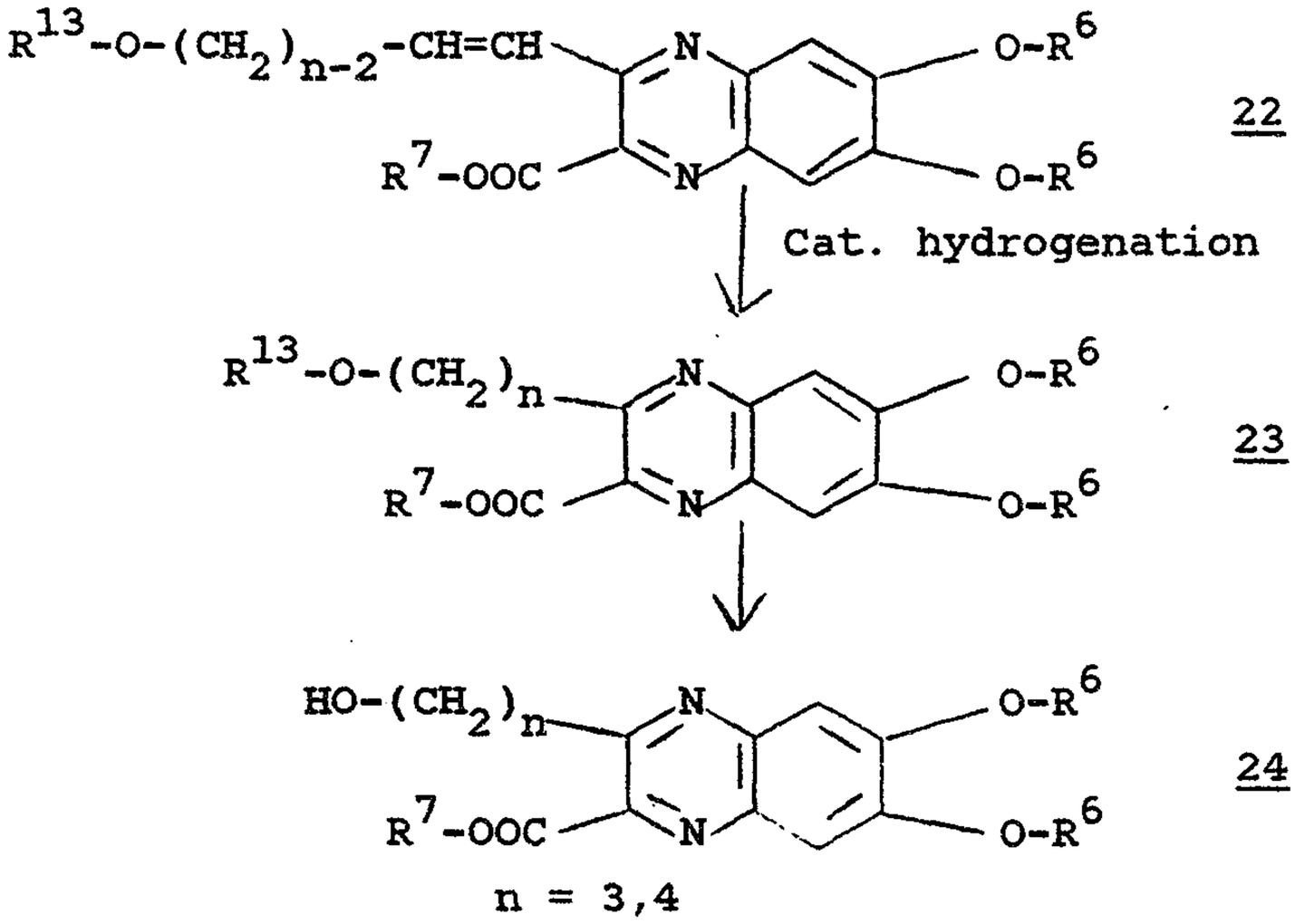
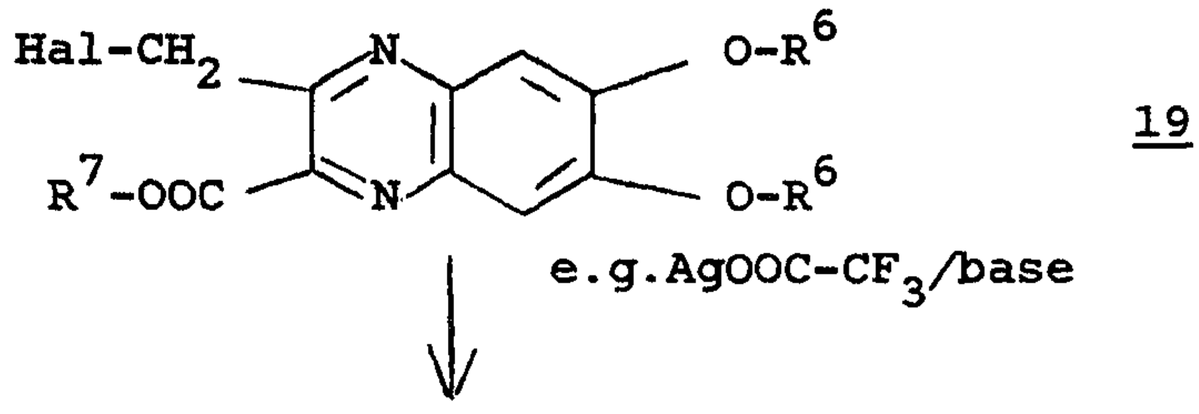
21

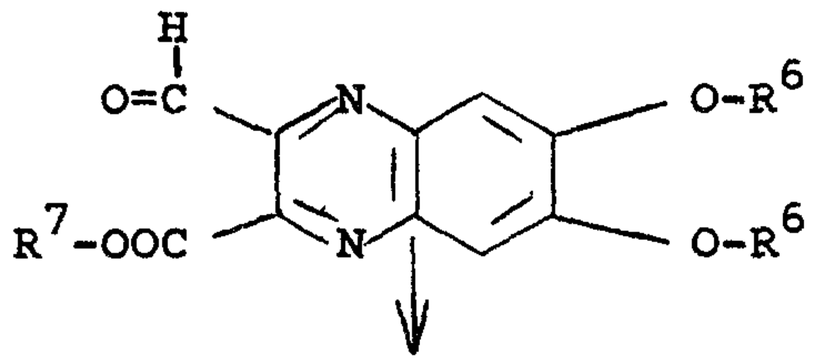


Formula 24 is identical with formula 4 if Z = OH and X = $(CH_2)_n$.

Aldehydes 21 (n = 3,4) with suitable protective groups R^{13} such as acetate, benzyl etc. are known from the literature. Alternatively, compound 22 can be prepared via the following scheme 2.

Scheme 2





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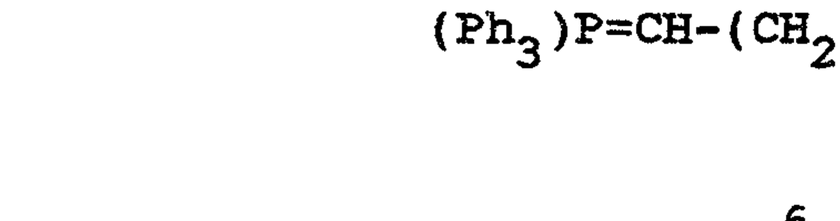

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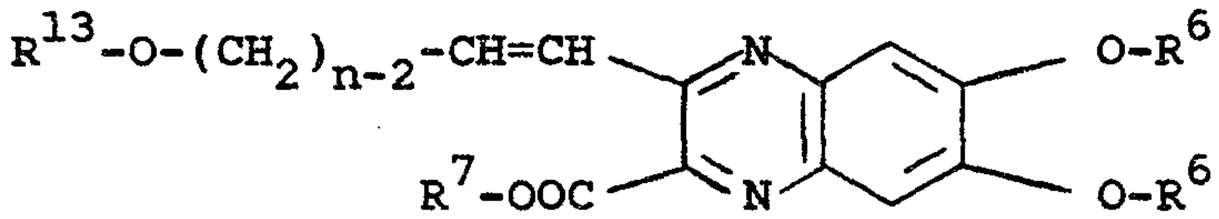
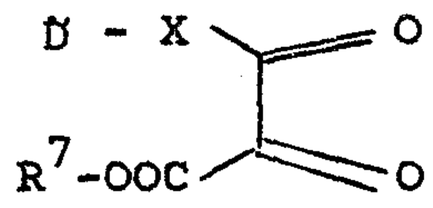


22

n = 4

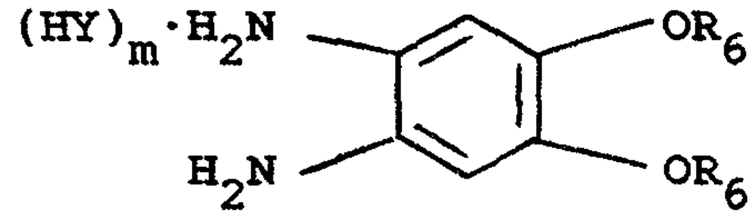
The necessary Wittig reagent 26 (n = 4) with a suitable protective group R^{13}, such as benzyl, is known from the literature.

Alternatively, compound of formula 12 with m = 0 and D = OR^{13} or H can be prepared by reacting a compound of formula 27 wherein X is CR^3R^4 or $(CH_2)_n$; n = 1,2,3,4 (as defined previously) and Z is hydrogen or a suitable protected hydroxy group (as defined previously) with



27

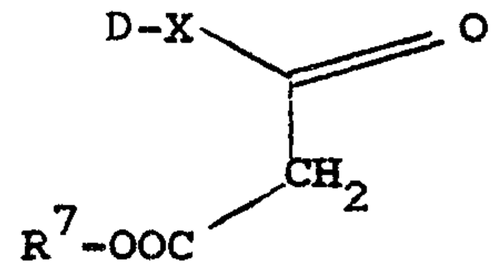
a compound of formula 28 wherein R^6 is a suitable phenol-protecting group (as defined previously) or R^6/R^6 is a catechol protecting group (as defined previously).



28

m = 0,1,2 or fractions of 1 and 2

Instead of compound of the formula 27, derivatives thereof such as hydrates or bisulfite adducts can be used. Compound of formula 27 can be prepared from compounds of the formula 29 by direct oxidation (e.g. by means of SeO_2) or by indirect oxidation (e.g. nitrosation followed by treatment with N_2O_4 or condensation with dimethoxy dimethylamino methane followed by ozonolysis).



29

X = CR^3, R^4; $(CH_2)_n$; n = 1,2,3,4

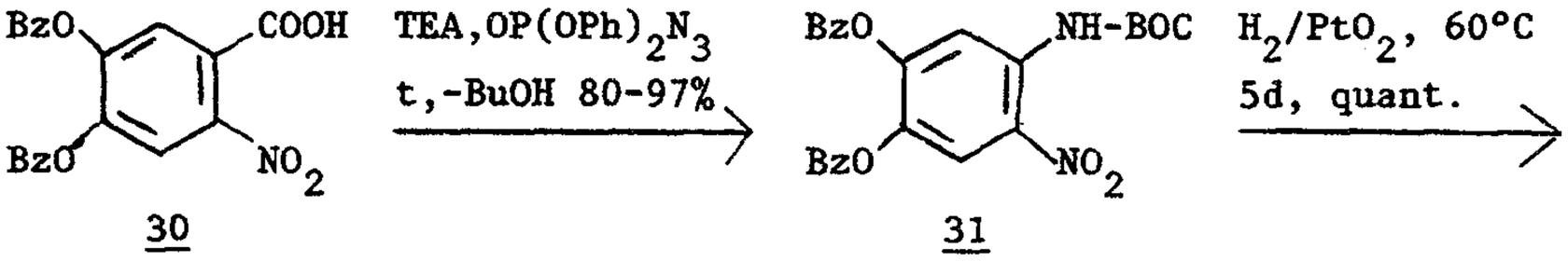
D = H, OR^{13}

R^7 = as defined previously

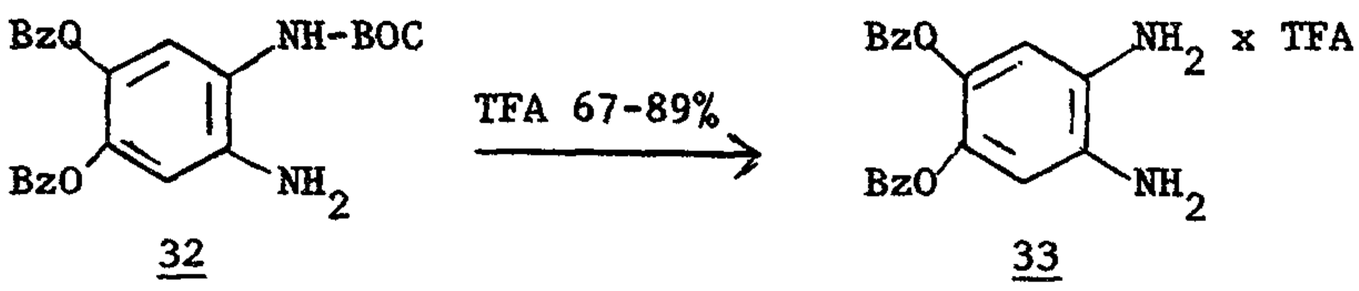
Compounds of formula 28 can be prepared by reduction of corresponding dinitro compounds as exemplified for the isopropylidene-protected derivative 28 (R^6/R^6 = $C(CH_3)_2$) in U.S. 4,904,757, Example 3D.

Alternatively, compound 28 can be prepared by reduction of a protected amino-nitro-catechol as exemplified for the dibenzyl protected derivative 33 (24, $R^6 = CH_2-C_6H_5$) in scheme 3.

Scheme 3



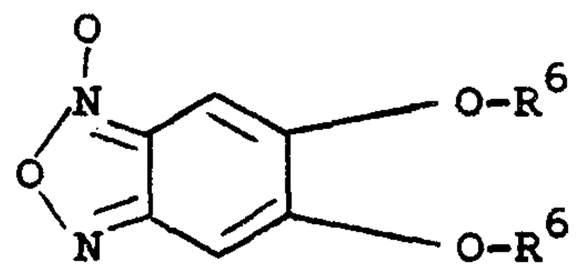
30 31



32 33

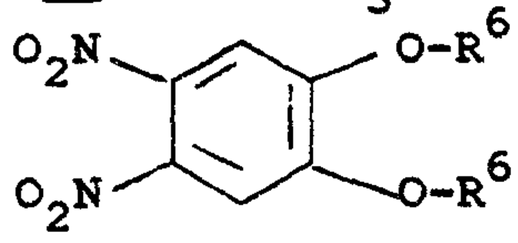
The dibenzyl compound 33 is novel and forms an integral part of this invention.

Compound 18 with m = 1 can be prepared by oxidation of compound 17 by means of peroxy acids or by reacting a compound of formula 34 (wherein R^6 is defined as previously) with a compound of formula 29 (wherein X and D are defined as previously).



34

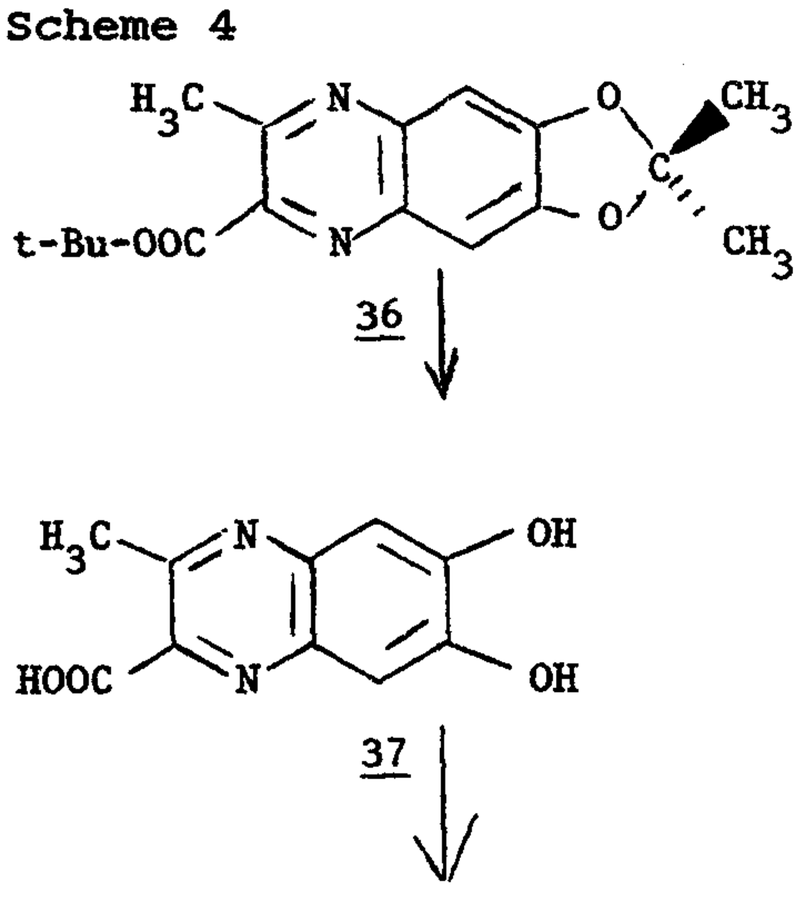
Compound 34 can be prepared by reacting compound 35 with NaN_3 in dimethyl sulfoxide.

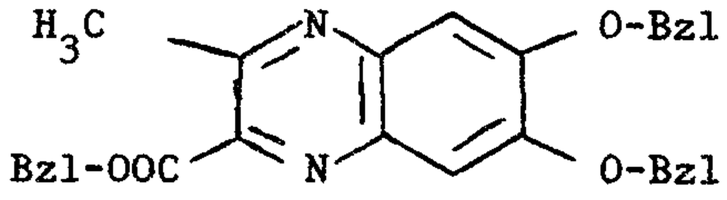


35

The isopropylidene-protected derivative 35 ($R^6/R^6 = C(CH_3)_2$) is disclosed in U.S. 4,904,775. Replacement of the isopropylidene protecting group by other protecting groups can be achieved by hydrolysis removal (HCl conc./80°C) of the isopropylidene group and subsequent protection of 4,5-dinitrocatechol with another phenol/or catechol-protecting group. Obviously, such a replacement of a protective group by another protective group R^6 can also be performed on a later stage of the synthesis as exemplified by the following scheme 4.

Scheme 4





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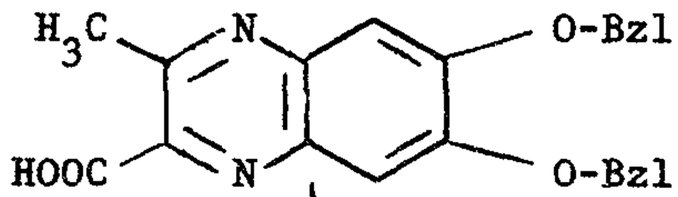
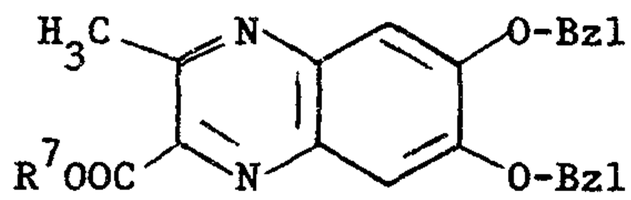


39



40

The preferred method of preparation for the preferred compound of Example 20 involves the following sequence.

Examples 20A → 20B → 21 → 3 → 8 → 9 → 20H → 20I.

The compounds of formula 1 contain at least one chiral center - the carbon atom (in the 3-position of the β-lactam nucleus) to which the acylamino substituent is attached. This invention is directed to those β-lactams which have been described above, wherein the stereochemistry at the chiral center in the 3-position of the β-lactam nucleus is the same as the configuration at the

carbon atom in the 6-position of naturally occurring penicillins (e.g., penicillin G) and as the configuration at the carbon atom in the 7-position of naturally occurring cephalosporins (e.g., cephalosporin C).

The compounds of formula 1 have the imino substituent $-\overset{\|}{\underset{N}{C}}-$ and can, therefore, exist as the syn or anti isomer or as a mixture of isomers. All of these isomeric forms are within the scope of this invention. In general, however, the syn isomer of a compound of formula 1 has the greatest activity.

The following examples are specific embodiments of this invention.

Example 1
t-butyl-2,3-dioxobutyrate

The above compound was prepared accordingly to the procedure described by H. Dahn, H. Cowal and H. P. Schlunke, Helv. Chim. Acta. 53, 1598 (1970) by oxidation (N_2O_4) of t-butyl-2-oximino-3-oxo-butyrate. M.P. 62 - 66°C

Example 2
2,2,7-Trimethyl-1,3-dioxolo-[4,5-g]-quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

[5,6-diamino-2,2-dimethyl-1,3-benzodioxole; dihydrochloride salt] (U.S. 4,904,775, Example 3D) (6.8 g, 0.02 mmol) was dissolved in a mixture of 25 ml water and 10 ml tetrahydrofuran and the pH of the solution was adjusted to 5.5 by the addition of 2N NaOH. After addition of the compound from Example 1 (3.8 g; 0.02 mol) the mixture was refluxed for 2 hours, concentrated *in vacuo* to remove the organic solvent tetrahydrofuran and then extracted with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4) and then evaporated *in vacuo* to leave an

oil which crystallized by the addition of petroleum ether. M.P. 104 - 105°C; yield 5.2 g (82%).

$C_{17}H_{20}N_2O_4$ %C calc. 64.54%, found 64.40%
%H calc. 6.37%, found 6.41%
%N calc. 8.85%, found 8.86%

IR(KBr): 1710 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 1.65 (s, 9H); 1.81 (s, 6H); 2.73 (s, 3H) 7.34 (s, 1H); 7.42 (s, 1H) ppm; ^{13}C-NMR (DMSO-d_6): δ = 21.95 (q); 25.28 (q); 27.46 (q); 82.22 (s); 102.94 (d); 103.50 (d); 120.43 (s); 137.24 (s); 140.28 (s); 142.50 (s); 147.94 (s); 150.16 (s); 151.43 (s), 164.61 (s)

Example 3

7-Bromomethyl-2,2-dimethyl-1,3-dioxolo-[4,5-g]-quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

To a solution of the compound from Example 2 (7.8 g, 24.6 mmol) in 150 ml dry tetrachloromethane, N-bromosuccinimide (4.38 g, 24.6 mmol) and a trace of azobisisobutylronitrile (AiBN) were added and the suspension was refluxed for 3 hours. Over this period of time, small additional quantities of the catalyst (AiBN) were added. After cooling, the formed succinimide was filtered off (2.1 g) and the filtrate was evaporated *in vacuo* to leave an oil which was chromatographed on silicagel eluting with ethylacetate/toluene (1:6). Evaporation of the relevant fractions yielded the corresponding dibromo derivative (0.8 g; 7%) as side product, the

desired monobromo compound (6.5 g, 67%) as main product and recovered starting material (1.8g; 23%). Recrystallization of the monobromo compound from petroleum ether (bp 60 - 80°C) containing a trace of ethyl acetate afforded a pure sample of title compound; m.p. 130.5°C - 131.5°C; yield 4.85 g (50%).

IR(KBr): 1728 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 1.63 (s, 9H); 1.81 (s, 6H); 4.97 (s, 2H) 7.41 (s, 1H); 7.48 (s, 1H) ppm; ^{13}C-NMR (DMSO-d_6): δ = 24.16 (q); 27.43 (q); 31.82 (t); 82.91 (s); 103.14 (d); 103.63 (d); 121.18 (s); 138.62 (s); 140.13 (s); 141.53 (s); 146.98 (s); 151.59 (s); 152.24 (s), 163.53 (s) ppm

Example 4

t-Butyl-N-benzyloxycarbamate

To a stirred solution of O-benzylhydroxyl-amine (16.0 g; 0.13 mol) and di-t-butyldicarbonate (28.4 g; 0.13 mol) in a mixture of water (150 ml) and tetrahydrofuran (150 ml) 2N NaOH solution was added dropwise to adjust the pH to 8 - 9 and this pH was maintained for an additional 2 hours by occasional addition of 2N NaOH. After extraction with ethylacetate the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to leave an oil which was used in the next example without any further purification; yield 29 g (100%).

Example 5

(Phenylmethoxy)imidodicarbonic acid, bis(1,1-dimethylethyl) ester

To a stirred solution of the compound of Example 4 (29 g; 0.13 mol) triethylamine (27.9 ml; 0.2 mol) and 4-dimethylamino-pyridine (trace) in dry tetrahydrofuran (200 ml) a solution of di-t-butyl dicarbonate (39.7 g; 0.18 mol) in 20 ml dry tetrahydrofuran was added dropwise at a rate that the temperature did not exceed 40°C. Stirring was continued at this temperature (40°C) for additional 30 minutes and then at room temperature overnight. The mixture was taken up in ether, washed with buffer solution pH = 4 (citrate) and brine, dried ($MgSO_4$) and evaporated *in vacuo*. From the oily residue (still containing few ml of ether) the title compound was crystallized by cooling to 0°C; m.p. 77.5 - 78.5°C; yield 70.4%; an analytical sample was recrystallized from petroleum ether (bp 40 - 60°C); m.p. 77.5 - 78.5°C.

$C_{17}H_{25}NO_5$	%C calc.	63.14%,	found 63.14%
	%H calc.	7.79%,	found 7.82%
	%N calc.	4.33%,	found 4.35%

IR(KBr): 1755 1730cm^{-1}:

^{1}H-NMR (DMSO-d6): δ = 1.49 (s, 18H); 4.88 (s, 2H), 7.42 (s, 5H) ppm

Example 6

Hydroxyimidodicarbonic acid, bis(1,1-dimethylethyl)ester

A solution of the compound of Example 5 (8.09 g, 0.025 mol) in ethanol (150 ml) was hydrogenated in the presence of palladium (10%) on activated carbon (3.5 g). After 15 minutes the hydrogenation was completed (monitored by thin layer chromatography), the catalyst was removed by suction and the filtrate was evaporated *in vacuo*. The oily residue solidified by stirring with pentane; m.p. 88.5 - 89.5°C, yield 71.2%; an analytical sample was recrystallized from petroleum ether (60 - 70°C); m.p. sint 88.7°C, 91 - 92°C

$C_{10}H_{19}NO_5$	%C calc.	51.49%, found 51.48%
	%H calc.	8.21%, found 8.21%
	%N calc.	6.00%, found 6.02%

IR(KBr): 1775 1752, 1685cm^{-1}

^{1}H-NMR (DMSO-d6): δ = 1.48 (s, 18H); 9.95 (s, 1H)

Example 7

(2R-cis)-3-[[[2-(Formylamino)-4-thiazolyl]-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid, N,N,N-tributyl-1-butanammonium salt

To a suspension of (2R-cis)-3-[[[2-(Formyl-amino)-4-thiazolyl]-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid, monopotassium

salt as described in Example 16A (10.0 g; 0.025 mol) in water (250 ml) tetrabutylammonium-hydrogensulfate (9.33 g; 0.027 mol) was added and the pH was adjusted to 5.5 - 6.0 by the addition of 2N KOH. The mixture was extracted thrice with chloroform (100 ml, 60 ml, 60 ml) and the combined organic layers were washed with few ml water, dried ($MgSO_4$) and evaporated *in vacuo* to leave a viscous foam which solidified by stirring with petroleum ether (bp 60 - 80°C); the solid was collected by suction and dried *in vacuo* over P_2O_5; mp = 82 - 88.5°C dec; yield 11.6 g (77%). $C_{26}H_{45}N_5O_7S_2$ %C calc. 51.72%, found 50.96%

%H calc. 7.51%, found 7.61%

%N calc. 11.60%, found 11.30%

%N calc. 10.62% found 10.40%

IR(KBr): 1760 cm^{-1};

^{1}H-NMR (DMSO-d_6): δ = 0.89 (t, 12H); 1.22 (d, 3H; J = 7Hz); 1.15 - 1.75 (m, 16H); 3.00 - 3.25 (m, 8H); 4.02 (quin(ps), 1H, J' = 6Hz); 5.05 (d,d, 1H, J' = 6Hz, J" = 8.5 Hz); 8.41 (s, 1H); 8.54 (s, 1H); 9.60 (d, 1H, J" = 8.5 Hz); 12.68 (s, 1H)

Example 8

7-[[[Bis[1,1-dimethylethoxy)carbonyl]amino-oxy]methyl]-2,2-dimethyl-1,3-dioxolo[4,5g]-quinoxaline-6-carboxylic acid, 1,1-dimethyl-ethyl ester

Finely ground potassium carbonate (2.71 g; 19.6 mmol), N,N-diBOC-hydroxylamine (title compound

of Example 6) (1.43 g; 6.13 mmol) and a trace of sodium iodide were added to a suspension of the compound of Example 3 (1.94 g; 4.9 mmol) and stirring was continued for 3 hours at room temperature. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate, washed twice with buffer solution pH 3 (citrate) and, dried (Na_2SO_4). Evaporation of the solvent *in vacuo* yielded an oil (4.4 g) which was purified chromatographically on silicagel eluting with ethyl acetate/toluene (1:3). The relevant fractions were combined, evaporated *in vacuo* to leave the title compound as an oil, which was used in the next step without any additional purification. yield 2.21 g (92%); mp = 91 - 94°C (from hexane).
IR(film): 1790, 1750 - 1710 cm^{-1}
^{1}H-NMR (DMSO-d_6): δ = 1.27 (s, 18H); 1.60 (s, 6H); 1.79 (s, 3H); 5.32 (s, 2H); 7.43 (s, 1H); 7.50 (s, 1H) ppm

Example 9

3-[(Aminooxy)methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid, hydrochloride

A suspension of the compound of Example 8 (4.1 g; 7.5 mmol) in 60 ml conc. HCl was heated at 80 - 85°C for 90 minutes. Over this period of time the starting material of Example 8 was dissolved to form finally a new precipitate.

After cooling to 0°C the precipitate was collected by suction, washed with few ml conc. HCl and dried *in vacuo* over P_2O_5; yield 1.9 g (88%)

$C_{10}H_9N_3O5 \cdot 1.6$ HCl. 0.5 H_2O

%C calc.	37.71%,	found 38.64%
%H calc.	3.67%,	found 3.48%
%N calc.	13.19%,	found 12.80%
%Cl calc.	17.81%	found 17.70%

IR(KBr): 1720 cm^{-1};

^{1}H-NMR (D_2O): δ = 5.32 (s 2H); 6.53 (s, 1H); 6.63 (s, 1H) ppm

Example 10

[2R-[2α,3α(Z)]]-3-[[[[1-[2-(Formylamino)-4-thiazolyl]-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]-amino]oxy]methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid, disodium salt

The compound of Example 7 (9.6 g; 0.015 mol) was dissolved in water (80 ml) and the pH of the filtered solution was lowered to 2.0 by the addition of 2N HCl. Then the hydrochloride salt of Example 9 (1.44 g; 5.0 mmol) was added in small portions while the pH of the solution was corrected constantly to 2.0 by addition of 2N NaOH. Stirring at this pH (2.0) was continued for additional 4.5 hours, then the pH of the suspenion was adjusted to 5.5 - 6.0 by addition of 2N NaOH and the nearly clear solution was filtered and

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freeze-dried. The obtained powder was redissolved in water (75 ml), filtered again and passed through a column with Dowex™ 50 W x 8.20 - 50 mesh (Na^+ - form). Freeze-drying of the relevant fractions yielded 5.6 g of an orange, crude material which was chromatographed (MPLC) on XAD-2 resin eluting with water to remove inter alia recovered sodium salt of the starting material of Example 7. Fractions containing the title compound with an HI ≧ 85% by HPLC (yield 15%) were rechromatographed on XAD-2 resin eluting with water to yield after freeze-drying an yellowish powder with an HI = 95.1 % by HPLC.

IR (KBr): 1755 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ = 1.14 (d, 3H; J = 7 Hz), 4.00 (quin (ps), 1H; J = 7 Hz; J' = 6Hz); 5.15 (dd, 1H J' = 6Hz; J" = 9Hz); 5.55 (d, 1H; J = 14 Hz); 5.70 (d, 1H; J = 14 Hz); 6.76 (s, 1H); 6.98 (s, 1H); 7.38 (s, 1H); 7.38 (s, 1H); 8.46 (s, 1H); 9.97 (d, 1H; J" = 9 Hz) ppm

Example 11

[2R-[2α,3α(Z)]]-3-[[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

To a solution of 228 mg (0.36 mmol) of the compound of Example 10 (HI = 95% by HPLC) in 90 ml water, 27 ml tetrahydrofuran were added and then

the pH of the solution was lowered to pH = 0.8 - 1.0 by the addition of 2N hydrochloric acid. The mixture was stirred at room temperature for 20 hours to deformylate ca. 90% of the starting material Example 10, (proven by HPLC). The precipitated yellowish zwitterion title compound was collected by suction, washed with water and purified by redissolving in 10 ml water at pH 5.5 - 6.0 (addition of 0.5N NaOH) and reprecipitation at pH 1.0 (addition of 2N HCl). After stirring for additional 30 minutes the precipitate was collected by suction, washed with few ml water and dried *in vacuo* over P_2O_5 to yield 90 mg title compound with an HI of 97%; mp > 200° decomposes.
IR(KBr): 1740 cm^{-1}
^{1}H-NMR (DMSO-d_6): δ = 1.02(d, 3H; J = 7 Hz); 3.97 (quin (ps), 1H; J = 7Hz; J' = 6Hz); 5.06 (dd, 1H, J' = 6 Hz, J" = 8 Hz); 5.63 (d, 1H, J = 14 Hz); 5.70 (d, 1H; J = 14 Hz) 6.91 (s, 1H); 7.28 (s, 1H); 7.30 (s, 1H); 9.42 (d, 1H; J" = 8Hz)ppm

Example 12

(2S-trans)-3-[[[2-(Formylamino)-4-thiazolyl]-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid, tetrabutylammonium (1:1) salt

To a suspension of (2S-trans)-3-[[[2-(Formylamino)-4-thiazolyl]-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid, mono-potassium salt (10.0 g; 0.025 mol) in water (250 ml), tetrabutylammonium - hydrogensulfate

(10.32 g; 0.030 mol) was added and the pH was adjusted to 5.5 - 6.0 by the addition of 2N KOH. The mixture was extracted three times with chloroform (100 ml, 70 ml, 70 ml) and the combined organic layers were washed with a few ml water, dried ($MgSO_4$) and evaporated *in vacuo* to leave a viscous foam which solidified by stirring with petroleum ether (bp 60 - 80°C); the solid was collected by suction and dried *in vacuo* over P_2O_5; mp = 82°C (sint), 120. 5°C dec; yield: 13.23 g (87%).

$C_{26}H_{45}N_5O_7S_2$	%C calc.	51.72%,	found 51.03%
	%H calc.	7.51%,	found 7.51%
	%N calc.	11.60%,	found 11.60%

IR(KBr): 1770, 1670 cm^{-1};

^{1}H-NMR (DMSO-d_6): δ = 0.91 (t, 12H); 1.43 (d, 3H); J = 7Hz); 1.10 - 1.80 (m, 16H); 3.00 - 3.30 (m, 8H); 3.82 (dq), 1H; J = 7Hz, J' = 3 Hz); 4.46 (dd, 1H, J' = 3 Hz, J" = 8 Hz); 8.54 (s, 1H); 8.57 (s, 1H); 9.78 (d, 1H, J" = 8Hz); 12.68 (s, broad, 1H)

Example 13

[2S-[2α,3β(Z)]]-3-[[[[1-[2-Formylamino)-4-thiazolyl]-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]-amino]oxy]methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid, disodium salt

The compound of Example 12 (4.53 g; 7.5 mmol) was dissolved in water (40 ml) and the pH of the filtered solution was lowered to 2.0 by the

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addition of 2N HCl. Then the hydrochloride salt of Example 9 (1.44 g; 5.0 mmol) was added in small portions while the pH of the solution was corrected constantly to 2.0 by addition of 2N NaOH. Stirring at this pH (2.0) was continued for additional 4.5 hours, then the pH of the suspension was adjusted to 5.5 - 6.0 by addition of 2N NaOH and the nearly clear solution was filtered and freeze-dried. To replace the tetrabutylammonium cation by the Na-cation the so obtained powder was redissolved in water (40 ml), filtered again and passed through a column with Dowex™ 50W x 8, 20 - 50 mesh (Na^+-form). Freeze-drying of the relevant fractions yielded 5.0 g of an orange, crude material which was chromatographed (MPLC) on XAD-2 resin eluting with water to remove recovered sodium salt of the starting material of Example 12.

Fractions containing the title compound with an HI ≧ 88% by HPLC (yield 14%) were rechromatographed on XAD-2 resin eluting with water to yield after freeze-drying a yellowish powder with an HI = 95.6% by HPLC: yield 140 mg (4.4%).
IR(KBr): 1760 cm^{-1};
^{1}H-NMR (DMSO-d_6 - TFA) δ = 1.39 (d, 3H; J = 7 Hz), 3.77 (dq), 1H; J = 7 Hz), 4.44 (d), 1H; J' = 3 Hz); 5.60 (d, 1H; J = 14 Hz); 5.68 (d, 1H; J = 14 Hz); 7.32 (s, 1H); 7.33 (s, 1H); 7.38 (s, 1H); 8.46 (s, 1H) ppm

Example 14

[2S-[2α,3β(Z)]]-3-[[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

To a solution of 120 mg (0.19 mmol) (HI = 93 - 95% by HPLC) in water (45 ml) tetrahydrofuran (13.5 ml) was added and then the pH of the solution was lowered to pH = 0.8 - 1.0 by the addition of 2N hydrochloric acid. The mixture was stirred at room temperature for 27 hours to deformylate ca. 90% of the starting material (proven by HPLC). The still clear solution was concentrated *in vacuo* to half of its volume and the pH was adjusted to 1.0 by the addition of 0.5 N NaOH. After cooling to 5°C the precipitated yellowish zwitterion title compound was collected by suction, washed with ice water and purified by redissolving in 7 ml water at pH 5 (addition of 0.5 N NaOH) and reprecipitation at pH 1.0 (addition of 2N HCl). After stirring for additional 30 minutes at 10°C the precipitate was collected by suction, washed with a few ml ice water and dried *in vacuo* over P_2O_5 to yield 70 mg (65%) title compound.

IR(KBr): 1760 cm^{-1}; M.P. = >178°C decomposes

^{1}H-NMR (DMSO-d_6): δ = 1.37 (d, 3H; J = 7 Hz); 3.72 (dq, 1H; J = 7 Hz; J' = 3 Hz); 4.42 (dd, 1H, J' = 3 Hz, J" = 8 Hz); 5.66 (s, 2H); 6.89 (s, 1H); 7.28 (s, 1H); 7.30 (s, 1H); 9.47 (d, 1H; J" = 8 Hz)ppm

Example 15

[2R-[2α,3α(Z)]]-3-[2-[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]ethyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

Example 15A

3-oxo-5-(phenylmethoxy)pentanoic acid, 1,1-dimethylethyl ester

Analogous to the procedure described by Brooks, D.W., Kellogg, R.P. and Cooper, C.S., J. Org. Chem. 52 192, (1987) t-butyl acetate (33 ml; 0.20 mol) and benzyl chloromethylether (50 ml; 0.22 mol) were reacted. Chromatographic purification on silica gel eluting with petroleum ether/ethyl acetate (5:1) afforded the title compound as a viscous oil still containing ca 10% (by NMR) of t-butyl acetoacetate. This material was used in the next step without any additional purification. Yield 3.41 g (61 %).
IR(film): 1738, 1712 cm^{-1}; ^{1}H-NMR(DMSO-d_6):δ = 1.34 (s, 9H); 2.72 (t, 2H; J = 7Hz); 3.43 (s, 2H); 3.60 (t, 2H; J = 7 Hz); 4.39 (s, 2H); 7.27 (s(ps), 5 H) ppm.

Example 15B

2-(Hydroxyimino)-3-oxo-5-(phenylmethoxy)-pentanoic acid, (1,1-dimethylethyl) ester

With stirring and cooling (0°C) a solution of sodium nitrite (1.5 g; 22 mmol) in water (5 ml)

was dropped within 10 minutes into a solution of compound of Example 15A (5.56 g; 20 mmol) in acetic acid (3.0 g; 50 mmol) and stirring was continued at 0°C for additional 10 minutes and at room temperature for 30 minutes. The reaction product was extracted with ether and the combined ether phases were washed with aqueous sodiumbicarbonate solution and brine. After drying ($CaSO_4$) the solvent was removed *in vacuo* to leave a residue (5.7 g) which solidified by treatment with petroleum ether (bp 60 - 70°C). Yield: 3.65 g (59.5%) mp: 98-100°C (mp: 100 - 101°C after recrystallization from ether-petroleum ether). IR(KBr):1730, 1679 cm^{-1}; ^{1}H-NMR(DMSO-d_6):δ = 1.46(s, 9H); 3.02(t, 2H; J = 7 Hz); 3.70(t, 2H; J = 7 Hz); 4.45(s, 2H); 7.31 (s(ps), 5H); 13.10(s(broad), 1H) ppm.

Example 15c

2-3-dioxo-3-(phenylmethoxy)butanoic acid 1,1-dimethylethyl ester, hydrate

Anhydrous sodium sulfate (10.0 g) was added to a solution of the compound of Example 15B (28.8 g; 94 mmol) in chloroform (250 ml) at -25°C followed by a solution of dinitrogen tetroxide (4.4 g; 48.0 mmol) in dry chloroform (60 ml). After stirring at -25°C for 5 hours the mixture was allowed to warm to room temperature within 4 days.

After filtration (Na_2SO_4) and removal of the solvent *in vacuo* the residual oil (30 g) was dissolved in ethyl acetate, washed with aqueous $NaHCO_3$ solution (10%) and brine. Drying ($CaSO_4$) and removal of the solvent on a rotary evaporator yielded an oil, which was used in the next step without any further purification: yield: 27.5 g (94%).

Example 15D

2,2-Dimethyl-7-[2-(phenylmethoxy)ethyl]-1,3-dioxolo]4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

The freshly prepared, crude compound, 5,6-diamino-2,2-dimethyl)-1,3-benzodioxole, (16.4g; 91 mmol) was taken up in a mixture of water (180 ml) and tetrahydrofuran (90 ml) and then the crude compound of Example 15c (27.5 g; ca 90 mmol) was added with stirring. The mixture was refluxed for 60 minutes at 80 - 85°C and then evaporated *in vacuo* to leave a residue which was partitioned between ethyl acetate (350 ml) and water (150 ml). After extraction of the aqueous phase with ethyl acetate the combined organic phases were washed with brine and dried (Na_2SO_4). emoval of the solvent *in vacuo* gave an oily esidue which was purified by chromatography on

silica gel eluting with ethyl acetate/petroleum ether (bp 60 - 70°C). Yield: 20.2 g (51%). IR(film): 1735, 1720 (sh) cm^{-1}; ^{1}H-NMR(DMSO-d_6)δ = 1.56(s, 9H); 1.77 (s, 6H); 3.31 (t, 2H; J = 7 Hz); 3.81 (t, 2H)7; J = 7 Hz); 4.44 (s, 2H); 7.23(s(ps), 5H); 7.30(s, 1H); 7.38 (s, 1H) ppm.

Example 15E

7-(2-Hydroxyethyl)-2,2-dimethyl-1,3-dioxolo-[4,5g]quinoxaline-6-carboxylic acid, (1,1-dimethylethyl) ester

The compound of Example 15D (10.5g; 24.0 mmol) was dissolved in dimethylformamide (200 ml) and hydrogenated for 15 minutes in the presence of palladium (10%) on carbon (3.0 g). The catalyst was removed by filtration and the solvent was distilled off *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to leave a residual oil (8.1 g) which was chromatographically purified on silica gel eluting with ethyl acetate/-petroleum ether (45:55). Yield 6.2 g (75%); mp 88-90°C (90-92° from petroleum ether).

$C_{18}H_{22}N_2O_5$

Elemental analysis (%)	Calc.	Found
C	62.41	62.27
H	6.40	6.37
N	8.09	8.19

IR(KBr): 1735 cm^{-1}; ^{1}H-NMR(DMSO-d_6):δ = 1.60(s, 9H); 1.79 (s, 6H); 3.18 (t, 2H; J = 7 Hz); 3.78(q(ps), 2H; J = 7 Hz; J' = 7 Hz); 4.76(t, 1H); J' = 7 Hz); 7.33 (s, 1H); 7.40(s, 1H) ppm.

Example 15F

7-[2-[[Bis[(1,1-dimethylethoxy)carbonyl]-amino]oxy]ethyl-2,2-dimethyl-1,3-dioxolo]4,5g]-quinoxaline-6-carboxylic acid,1,1-dimethylethyl ester

A solution of diethyl azodicarboxylate (5.0 g; 28.6 mmol) in dry tetrahydrofuran (40 ml) was dropped at room temperature into a mixture of the compound of Example 15E (9.9 g; 28.6 mmol), triphenylphosphine (7.5 g; 28.6 mmol) and Hydroxy-imidodicarbonic acid, bis(1,1-dimethylethyl)ester (6.1 g; 26 mmol) in dry tetrahydrofuran (100 ml) and stirring was continued for 5.5 hours at room temperature. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel eluting with petroleum ether/ethyl acetate (gradient 20 - 30%); first fractions contained the corresponding vinyl-compound (de-hydrated starting material; yield 4.5 g; 53%), late fractions the desired titled compound; yield: 4.8 g (33%); viscous oil.

IR (film): 1785, 1750, 1720 cm^{-1}; ^1H-NMR (DMSO-d_6: δ = 1.35(s, 18 H); 1.59(s, 9H); 1.78 (s, 6H); 3.37 (t, 2H); 7.33(s, 1H); 7.41(s, 1H) ppm.

Example 15G

3-[2-(Aminooxy)ethyl]-6,7-dihydroxy-2-quinoxaline-2-carboxylic acid ·HCl

In a simple vacuum distillation apparatus a mixture of the compound of Example 15F (1.8g; 3.3 mmol) and conc. HCl (70 ml) was heated at 85 - 90°C and ca 700 mbar to distill off the generated acetone. After 90 minutes, the mixture was evaporated *in vacuo* to leave a yellow solid (1.0 g) which still contained ca 20% of the corresponding acetone-oxime of the title compound. Rehydrolysis of this solid with conc. HCl (40 ml) using the same conditions (85 - 90°C; 700 mbar) afforded after cooling (0°C) a precipitate, which was collected by suction, washed with few ml conc. HCl and dried *in vacuo* over P_2O_5: yield 0.4 g (40%); mp:>300°C; Hl=96% (by HPLC).

IR(KBr): 1750 cm^{-1}; ^1H-NMR (DMSO-d_6/trifluoro-acetic acid 1:1):δ = 3.56(t, 2H); 4.42(t, 2H); 7.32(s, 1H); 7.38(s, 1H) ppm.

Example 15H

[2R-[2α,3α(Z)]]-3-[2-[[[1-[2-(Formylamino)-4-thiazolyl]-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-ethyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid, tetrabutylammonium (1:2) salt

The tetrabutylammonium salt of Example 7 (0.78 g; 1.30 mmol) was dissolved in water (35 ml)

and the pH of the filtered solution was lowered to 1.9 by the addition of tetrabutylammonium hydrogen sulfate (0.21 g). Then the hydrochloride salt of Example 15G (0.39 g; 1.30 mmol) was added in small portions while the pH of the solution was corrected constantly to 2.0 by addition of a solution of tetrabutylammonium hydroxide in water (20%). Stirring at this pH (2.0) was continued for additional 4.0 hours, then the pH of the suspension was adjusted to 5.8 by addition of tetrabutylammonium hydroxide and the clear solution was freeze-dried to yield 2.5 g of an orange, crude material which was chromatographed (MPLC) on XAD-2 resin eluting with water-acetonitrile (15%).

The E-isomer was isolated from the first fractions (yield: 240 mg, 17%) whereas late fractions contained the pure isomer of the title compound yield: 355 mg (25%); mp: 110°sint, 134-136°C; Hl=97.7% by HPLC.

IR(KBr): 1765 cm^{-1}; 200 MHz-^{1}H-NMR (DMSO-d_6-TFA):δ = 0.90(t, 24H); 1.15 -1.42 (m, 16H) overlapped by 1.28 (d, 3H, J = 7 Hz); 1.42 - 1.75 (m, 16H); 3.0 - 3.3 (m, 18H); 3.57 (t, 2H; J" = 7 Hz); 4.00(quin(ps), 1H, J = 7 Hz, J' = 6 Hz); 4.55 (t, 2H, J"' = 7 Hz); 5.09 (d, 1H, J' = 6 Hz); 7.26 (s, 1H); 7.32 (s, 1H); 7.35 (s, 1H); 8.48 (s, 1H) ppm.

Example 15I

[2R-[2α,3α(Z)]]-3-[2-[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]ethyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

To a solution of the tetrabutylammonium salt of Example 15H (317 mg, 0.29 mmol) purity = 98% by HPLC) in water (72 ml) was added tetrahydrofuran (22 ml) and then the pH of the solution was lowered to a pH of 0.6 by the addition of 2N hydrochloride acid (15 ml). The mixture was stirred at room temperature for 18 hours and the precipitated yellowish zwitterion title compound was collected by suction, washed with a few ml ice-water and dried *in vacuo* over P_2O_5: yield: 105 mg (62.5%); mp:>300°C; purity:98.6% (by HPLC).

$C_{20}H_{19}N_7O_{10}S_2 \cdot 2.5\ H_2O$

Elemental analysis	Calc.	Found
C	38.33	38.28
H	3.86	3.95
N	15.65	15.40

IR(KBr): 1740 cm^{-1}; ^{1}H-NMR (DMSO-d_6/trifluoroacetic acid):δ = 1.07(d, 3H, J = 7 Hz); 3.65 (t, 2H); 3.98 (quintett(ps), 1H), J = 7 Hz, J" = 6 Hz); 4.68 (t, 2H); 5.02 (d, 1H, J' 6 Hz); 6.89 (s, 1H); 7.28 (s, 1H); 7.40 (s, 1H); ppm.

Example 16

Alternate Method for Preparation of [2R-[2α,3α(Z)]]-3-[2-[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]ethyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

Example 16A

(2R-cis)-3-[[[2-Formylamino)-4-thiazolyl]-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid, monopotassium salt

1,8-Diazobicyclo[5.4.0]undec-7-ene (DBU) (16.5 ml; 0.11 mol) was dropped into a suspension of the zwitterion (2R-cis)-3-Amino-2-methyl-4-oxo-1-azetidine-sulfonic acid, inner salt (18.02 g; 0.10 mol) in dry dichloromethane (180 ml) at 10°C and stirring was continued at this temperature for an additional hour. Then the solution was cooled to -30°C (solution A). Formylamino-thiazolylglyoxylic acid (22.22 g; 0.111 mol) was suspended in dry dichloromethane (360 ml) and then dissolved by addition of triethylamine (17.0 ml; 0.122 mol). After being stirred for 1 additional hour insoluble material was filtered off and the filtrate was cooled to -30°C (solution B).

Into solution B was added dropwise at -30°C pyridine (0.62 ml) followed by trimethylacetyl chloride (13.38 g; 0.111 mol) and then by solution A. The mixture was stirred at -25° to -30°C for 1

hour and then allowed to come to ambient temperature. After evaporation *in vacuo* the residue was taken up in ethanol (600 ml) and treated dropwise with a solution of potassium acetate (28 g; 0.285 mol) in ethanol (180 ml). After being stirred for 1 hour the precipitate was collected by suction, washed with ethanol, dried *in vacuo* and purified by recrystallization from hot water (270 ml). Yield 28.4 g (70%); mp >230°C. IR (KBr) 1755, 1670 cm^{-1}; ^1H-NMR (DMSO-d_6):δ = 1.22 (d, 3H); J = 7 Hz); 4.07(quin(ps), 1H; J = 7 Hz; J' = 6 Hz); 5.11 (dd, 1H; J' = 6 Hz; J" = 8.5 Hz); 8.45 (s, 1H); 8.56 (s, 1H); 9.40 (d, 1H; J" = 8.5 Hz); 12.70 (s, 1H) ppm

Example 16B

(2R-cis)-3-[[(2-Amino-4-thiazolyl)-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid

The compound from Example 16A (20 g, 55.2 mmol) was suspended in 270 ml water. The pH was brought to 0.5 with 3N hydrochloric acid and the resulting solution was stirred for two days at room temperature. On taking a sample for tlc analysis, the title compound precipitated. It

was filtered off with suction, washed with water and dried *in vacuo*. Yield 12.6 g (68.4%) m.p. >300°C

IR(KBr): 1710, 1760 cm^{-1} (CO).

^{1}H-NMR (DMSO-d_6): δ = 1.20 (d, 3H), 4.03 (dq, 1H), 5.02 (dd, 1H), 8.19 (s, 1H), 8.35 (s, broad, NH_2, SO_3H and water), 9.70 (d, 1H); ppm

Example 16C

[2R-[2α,3α(Z)]]-3-[2-[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]ethyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

The compound from Example 16B (0.33 g, 1.0 mmol) was suspended in water (15 ml) and the pH was adjusted to 5.5 - 6.0 by addition of a solution of tetrabutylammonium hydroxide in water (20%) to obtain a clear solution. The pH of this solution was lowered to 2.0 by the addition of tetrabutylammonium hydrogen sulfate (0.14 g). Then the hydrochloride salt of 3-[2-Aminooxy)-ethyl]-6,7-dihydroxy-2-quinoxaline-2-carboxylic acid (0.5 g; ca 1.0 mmol; Hl by HPLC: 64%) (Example 15G) was added in small portions while the solution was corrected constantly to 2.0 by addition of a solution of tetrabutylammonium hydroxide in water (20%). Stirring at this pH (2.0) was

continued for additional 4.5 hours, then the pH of the suspension was adjusted to 5.8 by addition of tetrabutylammonium hydroxide and the solution was freeze-dried to yield 1.7 g of an orange, crude material which was chromatographed (MPLC) on XAD-2 resin eluting with water-acetonitrile (gradient 10 - 15%). Freeze-drying of the appropriate fractions yielded 0.18 g (17%) of the di-tetrabutylammonium-salt [2R-[2α,3α(Z)]]-3-[2-(Formylamino)-4-thiazolyl]-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]-ethyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid, from which the title compound was obtained by dissolving in water (15 ml) and precipitation at pH 2.0 (addition of 2N HCl). Yield: 50 mg (54%); mp: >dec. 198°C.

Example 17

[2R-[2α,3α(Z)]]-3-[3-[[[1-(2-Amino-4-thiazolyl-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]propyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

Example 17a

7-[(Dimethoxyphosphinyl)methyl]-2,2-dimethyl-1,3-dioxolo[4,5-g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

A mixture of the compound of Example 3 (3.95g; 10.0 mmol) and trimethyl phosphite (3.5 ml; 30.0 mmol) was heated in an oil bath at 140°C for

30 minutes and the volatile components were distilled off during this period. On cooling, the residue was taken up in petroleum ether and evaporated *in vacuo* to leave a viscous oil (5g), which was purified chromatographically on silica gel eluting with ethyl acetate. Evaporation of the appropriate fractions *in vacuo* afforded a colorless oil, which solidified by stirring with a few ml petroleum ether. Yield 2.77 g (65%); mp = 86.3 - 87.9°C (from petroleum ether).

$C_{19}H_{25}N_2O_7P$

	Calc.(%)	Found(%)
C	53.77	53.45
H	5.94	6.08
N	6.60	6.92

IR(KBr): 1720 cm^{-1}; 200 MHz-^{1}H-NMR (DMSO-d_6): δ = 1.57 (s, 9H); 1.75 (s, 6H); 3.58 (d, 6H, J(^{31}P-^{1}H) = 11.0 Hz); 3.92 (d, 2H, J(^{31}P-^{1}H) = 22.4 Hz); 7.36 (s, 1H); 7.42 (s, 1H) ppm.

Example 17b

7-[3-Acetyloxy)-1-propenyl]-2,2-dimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

A solution (2.5 M) of n-butyllithium (12 ml; 30.1 mmol) was treated dropwise with a solution of diisopropylamine (4.2 ml; 30.0 mmol) in dry tetrahydrofuran (40 ml) with stirring at 0°C. The mixture was held at 0°C for 30 minutes and then cooled to -30°C. A solution of the phosphonate of

Example 17a (12.7 g; 30.0 mmol) in dry tetrahydrofuran (80 ml) was added dropwise and after being stirred at -30°C for another 30 minutes, a solution of 2-acetoxy-acetaldehyde (3.06 g; 30.0 mmol) in dry tetrahydrofuran (60 ml) was added slowly. The mixture was allowed to come to ambient temperature and stirring was continued for an additional 2 hours at this temperature. The solvent was removed on a rotary evaporator and the residue was taken up in ethyl acetate and water and the pH was adjusted to 3 by the addition of 2N HCl. The organic layer was separated, washed with brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo* the oily residue (14.9 g) was purified by chromatography on silica gel eluting with ethyl acetate petroleum ether (1.3) to give the title compound as a mixture of stereoisomers. Yield: 7.2 g (60%).

Example 17c

7-(3-Hydroxypropyl)-2,2-dimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid 1,1-dimethylethyl ester

The mixture of isomers from Example 17b (3.82 g; 9.5 mmol) was dissolved in dry methanol (270 ml) and hydrogenated for 12 minutes (monitored by tlc) in the presence of palladium (10%) on carbon (2 g). After removal of the catalyst by

filtration and evaporation of the filtrate *in vacuo* an oily residue was obtained (10.4 g) containing ca 70% (by NMR) of the desired 7-(3-Acetyloxy)propyl)-2,2-dimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester and ca 30% (by NMR) of a propyl side product. This crude residue was used in the next step without any purification.

To a stirred solution of the so obtained residue (3.62 g) in methanol (100 ml) was added a solution of potassium hydroxide (1.51 g; 27 mmol) in water (7 ml) and stirring was continued at room temperature for 30 minutes. The solvent was removed on a rotary evaporator and the residue was taken up in ethyl acetate and water. The pH of the mixture was brought to 3 by addition of 2N HCl and then the mixture was extracted with ethyl acetate.

The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to leave a residue which was chromatographed on silica gel eluting with petroleum ether/ethyl acetate (3:1). The propyl-compund was eluted first (yield: 0.61 g; mp: 91.7 - 93.1°C) then the desired alcohol yield: 0.99 g (30%); mp: 97.6 - 98.1°C (from petroleum ether bp 60 - 70°C). Using only 1 equivalent potassium hydroxide the yield of the

desired alcohol can be raised up to 70%.

$C_{19}H_{24}N_2O_5$ (360.4)

Elemental analysis (%)		Calc.	Found
	C	63.32	63.04
	H	6.71	6.74
	N	7.77	7.85

IR(KBr): 1725 cm^{-1}; ^{1}H-NMR(DMSO-d_6): δ = 1.60(s, 9H); 1.7 - 2.0 (m, 8H; overlapped by singulett δ = 1.77); 3.02(t, 2H); 3.48(q(ps), 2 H); 4.57(t, 1H); 7.32(s, 1H); 7.37(s, 1H) ppm.

Example 17D

7-[3-[[Bis[(1,1-dimethylethoxy)carbonyl]amino]-oxy]propyl]-2,2-dimethyl-1,3-dioxolo[4,5g]-quinoxaline-6-carboxylic acid, 1,1-dimethyl-ethyl ester

A solution of diethyl azodicarboxylate (0.35 ml; 2.2 mmol) in dry tetrahydrofuran (3 ml) was dropped at room temperature to a mixture of the compound of Example 17D (0.80 g; 2.2 mmol), tri-phenylphosphine (0.58 g; 2.2 mmol) and Hydroxyimi-dodicarbonic acid, bis(1,1-dimethylethyl)ester (0.47g; 2.0 mmol) in dry tetrahydrofuran (13 ml) and stirring was continued for 4 to 5 hours at room temperature. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel eluting with petroleum ether/ethyl

acetate (gradient 20 - 30%); yield: 0.55 g (48%); viscous oil.
IR (film): 1792, 1751, 1720 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=1.33 (s, 18 H); 1.49 (s, 9H); 1.68 (s, 6H); 1.90 (m_c, 2H); 3.00 (t, 2H); 3.89 (t, 2H); 7.20(s, 1H); 7.29 (s, 1H) ppm.

Example 17E

3-[3-(Aminooxy)propyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid, hydrochloride

A mixture of the compound of Example 17D (0.50 g; 0.87 mmol) and conc. HCl (5 ml) was heated at 85 - 90°C for 90 minutes. After cooling to 0°C the precipitate was collected by suction, washed with a few ml conc. HCl and dried *in vacuo* over P_2O_5; yield: 0.22 g (80%); mp: dec >170°C; purity by HPLC: 93%.
IR(KBr): 1710 cm^{-1}; ^{1}H-NMR (DMSO-d_6/trifluoro-acetic acid 1:1): δ = 2.0 - 2.35 (m, 2H); 3.43 (t, 2H)j 4.14 (t, 2H); 7.51 (s, 1H); 7.56 (s, 1H) ppm.

Example 17F

[2R-[2α,3α(Z)]]-3-[3-[[[1-[2-(Formylamino)-4-thiazolyl]-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]-oxy]propyl]-6,7-dihydroxy-2-quinoxaline-carboxylic acid, tetrabutylammonium (1:2) salt

(2R-cis)-3-[[[2-(Formylamino)-4-thiazolyl]-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid, N,N,N-tributyl-1-butanammonium salt

(Example 7) (0.38 g; 0.63 mmol) was dissolved in water (12.5 ml) and the pH of the filtered solution was lowered to 2.0 by the addition of 2N HCl. Then the hydrochloride salt of Example 17E (0.18 g; 0.57 mmol) was added in small portions while the pH of the solution was corrected constantly to 2.0 by addition of a solution of tetrabutylammonium hydroxide in water (40%). Stirring at this pH (2.0) was continued for an additional 4.0 hours, then the pH of the suspension was adjusted to 5.5 - 6.0 by addition of tetrabutylammonium hydroxide and the nearly clear solution was filtered and freeze-dried to yield 1.0 g of an orange, crude material which was chromatographed (MPLC) on XAD-2 resin eluting with water-acetonitrile (10 - 20% gradient). The E-isomer was isolated from the first fractions (yield: 70 mg, 11%) whereas late fractions contained the pure Z-isomer of the title compound yield: 230 mg (36%); Purity = 97% by HPLC.

IR(KBr): 1765 cm^{-1}; 200 MHz-^{1}H-NMR (DMSO):δ = 0.92 (t, 24H); 1.17 - 1.42 (m, 16 H) overlapped by 1.28 (d, 3H, J = 7 Hz); 1.42 - 1.65 (m, 16H); 2.05 (m, 2H); 2.93 (t, 2H), J = 7 Hz); 3.05 - 3.25 (m, 16H); 3.98 (quin(ps), 1H, J = 7 Hz, J = 6 Hz); 4.13 (t, 2H, J = 7 Hz); 5.05 (dd, 1H, J = 6 Hz, J = 9 Hz); 7.02 (s, 1H); 7.06 (s, 1H); 7.37 (s, 1H); 8.48 (s, 1H); 9.65 (d, 1H, J = 9 Hz) ppm.

Example 17G

[2R-[2α,3α(Z)]]-3-[3-[[[1-(2-Amino-4-thiazolyl-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]propyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

To a solution of the tetrabutylammonium salt of Example 17F (220 mg, 0.20 mmol) (purity = 98% by HPLC) in water (48 ml) was added tetrahydrofuran (14.5 ml) and then the pH of the solution was lowered to 0.6 by the addition of 2N hydrochloride acid (10 ml). The mixture was stirred at room temperature for 72 hours and the precipitated yellowish zwitterion of the compound was collected by suction, washed with a few ml ice-water and dried *in vacuo* over P_2O_5: yield 80 mg (67%); M.P. dec. >203°C; purity of 97.0% by HPLC.
IR(KBr): 1740 cm^{-1}; ^{1}H-NMR (DMSO-d_6-trifluoro-acetic acid): δ = 1.22(d, 3H, J = 7 Hz); 2.17(quintett(ps), 2H); 3.21 (t, 2H); 4.04(quintett(ps), 1H, J = 7 Hz, J"=6 Hz); 4.28 (t, 2H); 5.08 (d, 1H, J' = 6 Hz); 6.97 (s, 1H); 7.26(s, 1H); 7.32 (s, 1H); ppm.

Example 18

[2R-[2α,3α(Z)]]-3-[4-[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]butyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

Example 18A

(E)-7-[4-(Acetyloxy)-1-butenyl]-2,2-dimethyl-1,3-dioxolo[4,5g]-quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

A solution (2.5 M) of n-butyllithium (12 ml; 30.0 mmol) in hexane was treated dropwise with a solution of diisopropylamine (4.2 ml; 30.0 mmol) in dry tetrahydrofuran (50 ml) with stirring at -5°C. The mixture was held at 0°C for 30 minutes, and then cooled to -30°C. A solution of the phosphonate of Example 15A was added dropwise and after being stirred at -30°C for a further 30 minutes a solution of 3-Acetyloxy-propanal prepared accordingly to a literature procedure: Hofstraat, R.G., Lange, J., Scheeren, H.W. and Nivard, R.J.F., J. Chem. Soc. Perkin Trans 1, 1988, 2315, (3.48 g; 30.0 mmol) in dry tetrahydrofuran (70 ml) was added slowly. The mixture was allowed to come to ambient temperature and stirring was continued for an additional 2 hours at this temperature. The solvent was removed on a rotary evaporator and the residue was taken up in ethyl acetate and water and the pH was adjusted to 3 by the addition of 2N HCl. The organic layer was separated, washed with brine, and dried ($MgSO_4$). After removal of the solvent *in vacuo* the oily residue (15.9 g) was purified by chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:3) to give the title

compound as a mixture of stereoisomers (E/Z).
Yield: 6.5 g (52.6%).
Stirring off the mixture of stereoisomers (E/Z) with petroleum ether afforded the pure crystalline E-isomer, yield: 4.02 g (34%); mp: 90.7 - 91.2°C.

$C_{22}H_{26}N_2O_6$(414.5)

Elemental analysis (%)	Calc.	Found
C	63.76	63.11
H	6.32	6.39
N	6.76	6.71

IR(KBr): 1735, 1722 cm^{-1}; ^{1}H-NMR(DMSO-d_6):δ = 1.60 (s, 9H); 1.78 (s, 6H); 2.01 (s, 3H); 2.62 (q, 2H; J = 6 Hz, J' = 6 Hz); 4.19 (t, 2H, J = 6 Hz); 6.82 (d, 1H, J" = 16 Hz); 7.03 (dd, 1H, J' = 6 Hz; J" = 16 Hz); 7.30 (s, 1H); 7.38 (s, 1H) ppm

Example 18B

7-[4-Acetyloxy)]butyl]-2,2-dimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

The E-isomer from Example 18A (3.60 g; 8.7 mmol) was dissolved in dry methanol (70 ml) and hydrogenated for 4 minutes (monitored by tlc) in the presence of palladium (10%) on carbon (0.5 g). After removal of the catalyst by filtration and evaporation of the filtrate *in vacuo* an oily residue was obtained containing the acetate and a trace of a butyl side product. This crude residue was used in the next step without any purification. Yield 3.58 g (99%).

Example 18C

7-(4-Hydroxybutyl)-2,2-dimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

To a stirred solution of the so obtained residue of Example 18B (3.54 g; 8.5 mmol) in methanol (95 ml) was added a solution of potassium hydroxide (0.52 g; 9.35 mmol) in water (6.5 ml) and stirring was continued at room temperature for 25 minutes. The solvent was removed on a rotary evaporator and the residue was taken up in ethyl acetate and water. The pH of the mixture was brought to 3 by addtion of 2N HCl and then the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to leave a residue which was chromatographed on silica eluting with petroleum ether/ethyl (acetate (3:1). A trace of the butyl compound was eluated first then the desired alcohol, yield: 2.94 g (92.5%).

Alternate method for preparing the title compound of Example 18C

Example 18D

7-Formyl-2,2-dimethyl-1,3-dioxolo]4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

Under argon the bromide of Example 3 (3.95, 10.0 mmol) was added to a solution of silver tetra-

fluoroborate (2.14 g; 11.0 mmol) in dry dimethyl sulfoxide (100 ml) and the mixture was stirred over night at room temperature. After the addition of N,N-diisopropylethylamine (2.6 ml; 15.0 mmol) stirring was continued at room temperature for 24 hours and then the mixture was poured in ice-water (500 ml). The solution was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to leave a residue (3.5 g) which separated yellowish needles when treated with few ml ethyl acetate/toluene (1:3). Yield: 1.30g (39%); mp: sint. 193°C, 194 - 195°C dec.

Chromatography of the mother liquor on silica gel eluting with ethyl acetate/toluene (1:3) afforded an additional quantity of the desired title compound (0.65g) besides the corresponding alcohol. Overall yield of the aldehyde title compound 1.95 g (59%).

$C_{17}H_{18}N_2O_5$

	Calc. (%)	Found (%)
C	61.81	61.80
H	5.49	5.54
N	8.48	8.50

IR(KBr): 1735, 1705 cm^{-1}, 100 MHz-^{1}H-NMR (DMSO-d_6): δ = 1.61 (s, 9H); 1.84 (s, 6H); 7.60 (s, 1H); 7.62 (s, 1H); 10.15 (s, 1H) ppm.

Example 18E

2,2-Dimethyl-7-[4-(phenylmethoxy)-1-butenyl]-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

To a stirred suspension of 3-(Benzyloxy)-propyl)-triphenylphosphonium bromide prepared accordingly to the literature procedure: F. E. Ziegler, I.K. Scott, K.P. Uttam and W. Tein-Fu, J. Amer. Chem. Soc. 107, 2730 (1985) (10.3 g; 21.0 mmol) in dry tetrahydrofuran (500 ml) at 0°C was added a 2.5 M solution of n-butyllithium in hexane (8 ml; 20.0 mmol) over 30 minutes. Then a solution of the compound of Example 18D (6.9 g; 21.0 mmol) in dry tetrahydrofuran (230 ml) was added dropwise over 45 minutes at 0°C. After being stirred for 3 hours at room temperature the reaction mixture was filtered, the filtrate was evaporated *in vacuo* and the residue was taken up in ethyl acetate and water. The pH of the mixture was brought to 3 by addition of 2N HCl and then the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel eluting with ethyl acetate/toluene (1:3) to yield the desired olefin title compound as a mixture of stereoisomers (E/Z); yield: 6.28 g (68%); oil.

Example 18F

7-(4-Hydroxybutyl)-2,2-dimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

The olefin of Example 18E (mixture of stereoisomers) (3.01 g; 6.5 mmol) was dissolved in dry methanol (40 ml) and hydrogenated for 15 minutes (monitored by tlc) in the presence of palladium (10%) on carbon (0.5 g). After removal of the catalyst by filtration and evaporation of the filtrate *in vacuo* an oily residue of the still benzyl protected title compound was obtained which was used in the next step without any further purification Yield: 2.6 g (87%).

The crude benzyl-compound of above (2.53 g; 5.4 mmol) was dissolved in dry dimethyl formamide (30 ml) and then hydrogenated for 4 minutes in the presence of palladium (10%) on carbon (0.4 g). After the usual work-up the residue was chromatographed on silica gel eluting with petroleum ether/ethyl acetate (gradient) to afford recovered benzyl compound and the desired title compound. Rehydrogenation of the recovered benzyl-compound afforded after chromatographic purification the desired alcohol in an overall yield of 81% mp:

80.5 - 81.5°C (from ether/petroleum ether).

$C_{20}H_{26}N_2O_5$ (374.4)

Elemental analysis (%)		Calc.	Found
	C	64.15	64.04
	H	7.00	6.99
	N	7.48	7.48

IR(KBr): 3350 cm^{-1} (OH); 1727 cm^{-1} (CO);

^{1}H-NMR(DMSO-d_6): δ = 1.3 - 1.9 (m, 4H; overlapped by 1.58 (s, 9H) and 1.76 (s, 6H); 2.98 (t, 2H; J = 7 Hz); 3.40(q(ps), 2H; J' = 7 Hz); 4.40 (t, 1H; J" = 7 Hz); 7.32 (s, 1H); 7.38 (s, 1H) ppm.

Example 18G

7-[4-[[Bis[(1,1-dimethylethoxy)carbonyl]-amino]oxy]butyl]-2,2-dimethyl-1,3-dioxolo-[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

A solution of diethyl azodicarboxylate (1.62 ml; 10.3 mmol) in dry tetrahydrofuran (15 ml) was dropped at room temperature to a mixture of the compound of Example 18C or 18F (3.85 g; 10.3 mmol) triphenylphosphine (2.70 g; 10.3 mmol) and the title compound of Example 6 (2.19 g; 9.4 mmol) in dry tetrahydrofuran (70 ml) and stirring was continued for 3.5 hours at room temperature. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel eluting with petroleum

ether/ethyl acetate (gradient 20 - 30 %); yield 4.32 g (71%), viscous oil.
IR (film): 1792, 1751, 1720 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ = 1.43 (s, 18 H); 1.50 - 1.95 (m, 4H) overlapped by 1.49 (s, 9H) and 1.76 (s, 6H)) 3.01 (t, 2H); 3.87 (t, 2H); 7.31 (s, 1H); 7.39 (s, 1H) ppm.

Example 18H

3-[4-(Aminooxy)butyl]-6,7-dihydroxy-2-quinoxaline-2-carboxylic acid, hydrochloride

In a simple vacuum distillation apparatus a mixture of the compound of Example 18G (2.68 g; 4.54 mmol) and conc. HCl (100 ml) was heated at 85 - 90°C and ca 700 mbar to distill off the generated acetone. After 2 hours the mixture was evaporated *in vacuo* to leave a yellow solid which was dissolved in few ml water and then freeze dried (1.78 g; purity = 88.2% by HPLC). Rehydrolysis of this material with conc. HCl (70 ml) using similar conditions (80 - 85°; 600 mbar) did not improve the purity of the desired compound.
Yield: 1.58 g (quant.); purity = 76.7 % (by HPLC).
This material was used in the next step without any additional purification.
IR(KBr): 1750 cm^{-1}; ^{1}H-NMR (DMSO-d_6/TFA 1:1): δ = 1.7(m_c, 4H); 3.35(m_c, 2H); 4.05(m_c, 2H); 6.96 (s, 1H); 7.56(s, 1H) ppm.

Example 18I

[2R-[2α,3α(Z)]]-3-[4-[[[1-[2-(Formylamino)-4-thiazolyl]-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]]-amino]oxy]butyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid, tetrabutylammonium (1:2) salt

(2R-cis)-3-[[[2-(Formylamino)-4-thiazolyl]-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid, N,N,N-tributyl-1-butanamminium salt (Example 7) (1.21 g; 2.0 mmol) was dissolved in water (40 ml) and the pH of the filtered solution was lowered to 2.0 by the addition of tetrabutylammonium hydrogen sulfate (0.17 g). Then the hydrochloride salt of Example 18H (0.82 g; ca 2.0 mmol; purity by HPLC: 77%) was added in small portions while the pH of the solution was corrected constantly to 2.0 by addition of a solution of tetrabutylammonium hydroxide (TBA-OH) water (20%). Stirring at this pH (2.0) was continued for an additional 3.0 hours, then the pH of the suspension was adjusted to 5.8 by addition of tetrabutylammonium hydroxide and the solution was freeze-dried to yield 4.66 g of an orange, crude material which was chromatographed (MPLC) on XAD-2 resin eluting with water-acetonitrile (15%). Freeze-drying of the appropriate fractions yielded 0.43 g (19%) of a material with a purity (by HPLC) of 77 - 86% and 0.51 g (22.8%) of an additional crop with a

purity by HPLC) of 95.4 - 97.4%; overall yield: ca 37%; mp: 97°sint, dec. >100°C.
IR(KBr): 1762 cm^{-1}; 200 MHz-^{1}H-NMR (DMSO-d_6): δ = 0.90 (t, 24 H); 1.10 - 1.40 (m, 16H) overlapped by 1.28 (d, 3H, J = 7 Hz); 1.40 - 1.85 (m, 20H); 2.88 (t, 2H); J" = 7 Hz); 3.25 (m, 16H); 3.97 (quin(ps), 1H, J = 7 Hz, J' = 6 Hz); 4.27 (t, 2H, J" = 7 Hz); 5.06 (dd, 1H, J' = 6 Hz; J"' = 9 Hz); 7.01 (s, 1H); 7.15 (s, 1H); 7.32 (s, 1H); 8.48 (s, 1H); 9.46 (d, 1H; J"' = 9Hz) ppm.

Example 18J

[2R-[2α,3α(Z)]-3-[4-[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]butyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

To a solution of the tetrabutylammonium salt of Example 18I (336 mg, 0.3 mmol) purity = 97.4% by HPLC) in water (75 ml) was added tetrahydrofuran (25 ml) and then the pH of the solution was lowered to 0.6 by the addition of 2N hydrochloride acid (16 ml). The mixture was stirred at room temperature for 70 hours and the precipitated yellowish zwitterion title compound was collected by suction, washed with few ml ice-water and dried *in vacuo* over P_2O_5. Yield 160 mg (87.4%); mp: dec >217°C; purity

98.8% (by HPLC).

$C_{22}H_{23}N_7O_{10}S_2.2.6\ H_2O$

	Calc.	Found
C	40.25	40.01
H	4.33	4.28
N	14.94	15.00

IR(KBr): 1745 cm^{-1}; ^{1}H-NMR (DMSO-d_6-TFA): δ = 1.18 (d, 3H, J = 7 Hz); 1.80 (m_c, 4H); 3.30 (t, 2H); 4.05(quintett(ps), 1H, J = 7 Hz, J" = 6 Hz); 4.20 (, 2H); 5.07 (d, 1H, J' = 6 Hz); 6.89 (s, 1H); 7.40 (s, 1H); 7.48 (s, 1H) ppm.

Example 19

Alternate Preparation of [2R-[2α,3α(Z)]]-3-[4-[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]butyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

The compound of Example 17B (2S-cis)-3-[[[(2-Amino-4-thiazolyl)-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid (0.50 g, 1.5 mmol) was suspended in water (30 ml) and the pH was adjusted to 5.5 - 6.0 by addition of a solution of tetrabutylammonium hydroxide in water (20%) to obtain a clear solution. The pH of this solution was lowered to 2.0 by the addition of tetrabutylammonium hydrogen sulfate (0.14 g).

Then the hydrochloride of Example 18H 3-[4-(Aminooxy)butyl]-6,7-dihydroxy-2-quinoxaline-2-carboxylic acid, monohydrochloride (0.62 g; ca 1.5 mmol); purity by HPLC; 77%) was added in small portions while the pH of the soltuion was corrected constantly to 2.0 by addition of a solution of tetrabutylammonium hydroxide in water (20 %). Stirring at this pH (2.0) was continued for additional 3.0 hours, then the pH of the suspension was adjusted to 5.8 by addition of tetrabutylammonium hydroxide and the solution was freeze-dried to yield 3.12 g of an orange, crude material which was chromatographed (MPLC) on XAD-2 resin eluting with water-acetonitrile (12%). Freeze-drying of the appropriate fractions yielded 0.11 g (6.7%) of the di-TBA-salt from which the title compound was obtained by dissolving in water (10 ml) and precipitation at pH 2.0 (addition of 2N HCl). Yield: 30 mg (4%); mp: dec. 198°C.

Example 20

Alternate Preparation of [2R-[2α,3α(Z)]]-3-[[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

Example 20A

6,6-Dimethyl[1,3]dioxolo[4,5-f]-2,1,3-benzoxadiazole, 1-oxide

133 g of 2,2-Dimethyl-5,6-dinitro-1,3-benzodioxole was dissolved in 1200 ml dimethylsulfoxide and 39.9 g sodium azide was added and the mixture was stirred at 85 - 90°C for 4 hours. After cooling down to room temperature, the dark solution was poured into 3 L ice water. A precipitate of the title compound was immediately formed. It was isolated by filtration, washed with ice water, redissolved in ethyl acetate (5 L) and dried over Na_2SO_4. After removal of the solvent *in vacuo* 115.7 g of title compound were recovered as yellow needles. M.P. 185 - 187°C.
^{1}H-NMR (DMSO-d_6)δ = 1.71 (s, 6H); 6.79 (s, 1H); 7.04 (s, 1H) ppm.

Example 20B

2,2,7-Trimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester, 5,8-dioxide

To 32 g of the compound of Example 20A and 4.75 g of tert-butyl acetoacetate in 750 ml ethanol were added slowly 155 ml of a 1N solution of NaOH (solid) in ethanol (abs.). The temperature of the reaction mixture rose from room temperature to ~40°C. After complete addition of the NaOH the temperature was kept at 50 - 60°C with heating

for 45 minutes. A yellow precipitate was formed. After cooling with ice the precipitate was isolated by filtration and washed with ice water. Drying over P_2O_5 gave pure title compound 43.6 g yellow needles.

M.P. 205 - 207°C. (from toluene).

^{1}H-NMR(DMSO-d_6):δ = 1.55 (s, 9H); 1.76 (s, 6H); 2.31 (s, 3H); 7.65 (s, 1H); 7.73 (s, 1H) ppm.

IR(KBr):1740 cm^{-1} (COO+)

Example 20C

7-[(Trifluoroacetyloxy)methyl]-2,2-dimethyl-1,3-dioxolo-[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethyl ethyl ester, 5-oxide

To 20 g of the compound of Example 20B suspended in 60 ml dichloromethane was added at -20°C a solution of 100 ml trifluoroacetic acid anhydride in 40 ml dichloromethane. While stirring, an orange colored solution was obtained after 30 minutes. The solution was then stirred at 0°C for one hour. The color turned to a dark green. The solvent, excess trifluoroacetic acid-anhydride and formed trifluoroacetic acid was then distilled of *in vacuo* at room temperature. After evaporation with an oil-vacuo for additional one hour a beige foam was obtained. This was stirred with 150 ml ether and cooled to -20°C. A dark red suspension was obtained. After filtration and washing with ether and hexane the title compound was obtained as a beige solid (20.4 g). The compound is unstable and must be immediately used for further transformation.

Example 20D

7-(Bromomethyl)-2,2-dimethyl-1,3-dioxolo-[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester,5-oxide

16 g of crude 7-[(Trifluoroacetyloxy)methyl]-2,2-dimethyl-1,3-dioxolo-[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethyl ethyl ester, 5-oxide and 7 g lithium bromide was stirred at 50°C for 3 hours in 750 ml acetone. After continued stirring at room temperature overnight, the solvent was distilled off and the residue suspended in toluene/ethyl acetate (6:1) and after filtration the filtrate passed through a column with 500 g silica gel. Toluene/ethyl acetate (6:1) as an eluent. From the relevant fractions 14.7 g pure title compound was obtained after evaporation as a white crystalline solid.
M.P. = 196 - 198°.
IR(KBr): 1735 cm^{-1} (COO+)
^{1}H-NMR(DMSO-d_6):δ = 1.62 (s, 9H); 1.77 (s, 6H); 4.60 (s, 2H); 7.21 (s, 1H); 7.77 (s, 1H) ppm.

Example 20E

7-[[[Bis[(1,1-dimethylethoxy)carbonyl]amino]oxy]-methyl]-2,2-dimethyl-1,3-dioxolo[4,5g]-quinoxaline-6-carboxylic acid, 1,1-dimethyl-ethyl ester, 5-oxide

A mixture of the title compound of Example 20D (2.05 g), and the title compound of Example 6 (1.4 g) and potassium carbonate (powder) (7.1 g)

and acetone (100 ml) was stirred for 3 hours at room temperature. The solvent was distilled off and the residue was taken up in a mixture of water and ethyl acetate. The washed organic phase was concentrated and purified by chromatography on silica gel eluting with toluene/ethyl acetate (3:1). Fractions containing the title compound were collected and evaporated. Yield 2.60 g; m.p. = 122 - 124°C (light yellowish solid).
^{1}H-NMR(DMSO-d_6):δ = 1.29 (s, 18H); 1.50 (s, 9H); 1.81 (s, 6H); 4.93 (s, 2H); 7.40 (s, 1H) ppm.

Example 20F

7-[(Aminooxy)methyl]-2,2-dimethyl-1,3-dioxolo-[4,5g]-quinoxaline-6-carboxylic acid,1,1-dimethylethyl ester, hydrobromide

The title compound of Example 20E (0.563 g) was dissolved in dry dichloromethane (20 ml) and at -70°C boron tribromide (2 ml) was added. Stirring was continued for 2 hours at -70°C and at room temperature overnight. After evaporation *in vacuo* the brown honey like residue was dissolved in 25 ml ethyl acetate/methanol at -80°C, stirred for 10 minutes and again evaporated. The residue was stirred with warm n-hexane. The yellow solid was used in the next step without further purification. Yield: 0.32 g.

Example 20G

3-[(Aminooxy)methyl]-6,7-dihydroxy-2-quinoxaline-6-carboxylic acid, hydrochloride

The compound from Example 20F (0.3 g) was stirred with hydrochloric acid conc. (3 ml) at 65 - 70°C for 1 hour. A yellow precipitate of the title compound was formed. It was isolated by filtration and dried over P_2O_5 *in vacuo* for 8 hours. Yield: 0.25 g.

Example 20H

Alternate method for preparing the title compound of Example 11

[2R-[2α,3α(Z)]]-3-[[[[1-(2-Formylamino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]oxy]-methyl]-6,7-dihydroxy-2-quinoxaline-carboxylic acid, tetrabutylammonium salt (1:2)

2.1 g of (2R-cis)-3-[[[2-(Formylamino)-4-thiazolyl]-oxoacetyl]amino]-2-methyl-4-oxo-1-azetidine-sulfonic acid, N,N,N-tributyl-1-butanammonium salt (Example 7) were stirred in 80 ml water until complete solution (~1 h). 0.55 g tetrabutylammoniumhydrogensulfate were added and the pH of the solution was adjusted to pH 2.0 (1n HCL). 1.2 g of the compound of Example 9 were divided in 6 portions. Every 20 minutes one

portion was added slowly to the solution and after each addition the pH was readjusted to 2.0 (TBA^+OH^-). The reaction solution was stirred for two additinal hours after the last addition of the compound of Example 9 and the pH was controlled every 20 minutes and readjusted to 2.0 if necessary. The reaction was stopped by adjusting the pH to 6.5 (TBA^+OH^-) and the remaining solution freeze dried. 12-13 g solid material of the crude title compound was obtained which was purified by column chromatography.

Example 20I

[2R-[2α,3α(Z)]]-3-[[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid

8.7 of the purified compound of Example 20H freeze-dried material were stirred for one hour in 400 ml ethyl acetate to get a uniform crystalline material. This material was dissolved in 1 L water and 470 tetrahydrofuran and stirred to complete solution. The pH was then adjusted to 0.5 with concentrated hydrochloric acid and the solution stirred for 3 days at room temperature. After ~8 hours crystals of the title compound were formed. On the third day the formed title compound was isolated by filtration and washed with tetrahydrofuran/water (1:10) containing a few drops of 1n hydrochloric acid. After drying over

P_2O_5 *in vacuo* a solid mass of title compound was obtained. This was stirred with 100 ml tetrahydrofuran containing 3 drops water for one hour. After filtration 4.2 g of the title compound light yellowish needles were obtained (drying over silica gel for 6 hours).
Purity 99.5% (by HPLC)
M.P. dec >208°C.

Example 21

Alternate Method for Preparing

2,2,7-Trimethyl-1,3-dioxolo]4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester

To 38 g of the compound of Example 20B dissolved in 100 ml $CHCl_3$ (abs.) was added 75 g PCl_3 dropwise. During adding, the temperature rose to 40°C (about 40 minutes). Stirring was then continued overnight at room temperature. Formed $POCl_3$, solvent and excess PCl_3 were then distilled off *in vacuo*. The oily residue was dissolved in 250 ml ethyl acetate and stirred with ice water for 30 minutes while the pH was adjusted with sodium bicarbonate between 6 - 7. The separated organic phase was then washed with water, dried and the solvent distilled off. 33 g pure title compound was obtained as white crystal solid.

Example 22

Alternate Preparation of 2,2,7-Trimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester, 5,8-dioxide

To a solution of 2,2,7-Trimethyl-1,3-dioxolo[4,5g]quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester (1.26g, 4.0 mmol) in 20 ml chloroform was added 2.53 g (8.8 mmol) m-chloroperoxybenzoic acid. After stirring overnight at room temperature a solid was filtered off and the solvent was distilled off *in vacuo*. The residue was partitioned between water and ethyl acetate. The phases were separated and the organic phase washed with saturated sodium hydrogencarbonate solution and with brine. After drying over sodium sulfate and evaporation 1.41 (quant.) of a mixture of the title compound and 2,2,7-Trimethyl-1,3-dioxolo-[4,5g]-quinoxaline-6-carboxylic acid, 1,1-dimethyl ester, 8-oxide was obtained. The mixture was chromatographed on silica gel with ethyl acetate/petroleum ether 1:2 as eluent to give 0.41 g (30.8%) mono-N-oxide and 0.82 g (58.9%) di-N-oxide. M.P.: 181.9°C

IR (KBr): 1735 cm^{-1} (CO)

^{1}H-NMR (DMSO-d_6):δ = 1.59 (s, 9H); 1.80 (s, 6H); 2.40 (s, 3H); 7.68 (s, 1H); 7.73 (s, 1H); ppm

Using the procedure above with four equivalents of MCPBA afforded the di-N-oxide in 70% yield.

Example 23

7-Bromomethyl-2,2-dimethyl-1,3-dioxolo-[4,5g]-quinoxaline-6-carboxylic acid, 1,1-dimethylethyl ester, 5,8,-dioxide

To a solution of the title compound of Example 22 (3.48 g, 10.0 mmol) in 20 ml carbon tetrachloride were added 1.78 g (10.0 mmol) N-bromo succinimide. The mixture was heated to reflux and 10 portions of catalytical amounts of azobisisobutyronitrile were added within 8 hours. The mixture was heated overnight and after cooling the solid filtered off with suction. The filtrate was evaporated and the residue (3.7 g, 87%) chromatographed on silica gel with ethyl acetate/petroleum ether 1:1 as eluent to give 1.87 g (43.6%) of the title compound. M.P.: 150,9°C
IR(KBr): 1740 cm^{-1} (CO)
^{1}H-NMR (DMSO-d_6):δ = 1.60 (s, 9H); 1.81 (s, 6H); 4.62 (s, 2H); 7.73 (s, 1H); 7.79 (s, 1H); ppm

Example 24

7-[[[Bis[1,1-dimethylethoxy)carbonyl]amino-oxy]methyl]-2,2-dimethyl-1,3-dioxolo[4,5g]-quinoxaline-6-carboxylic acid, 1,1-dimethyl-ethyl ester,5,8-dioxide

To a solution of the title compound of Example 23 (1.81 g, 4.25 mmol) in 30 ml acetone were added 2.35 g (17.0 mmol) potassium carbonate, the title compound of Example 6 (0.97g, 4.16 mmol)

and a catalytical amount of sodium iodide. The mixture was stirred for 60 hours at room temperature. The resulting solid was filtered off with suction, washed with acetone, dissolved in ethyl acetate and washed with water, dil. citric acid and again water. After drying and evaporation of the solvent the residue was dissolved in 10 ml ether and an equal amount of petroleum ether was added. After one night in the refrigerator the resulting precipitate was filtered off, washed with petroleum ether and dried to give 2.1 g (85.1%) of the title compound.

M.P.: 75.5°C

IR (KBr): 1740, 1790 cm^{-1} (CO)

^{1}H-NMR (DMSO-d_6): δ = 1.29 (s, 18H), 1.55 (s, 9H); 1.81 (s, 6H); 5.06 (s, 2H); 7.78 (s, 1H); 7.80 (s, 1H); ppm.

Example 25

5,6-Bis(phenylmethoxy)benzofurazan, 1-oxide

To a solution of 4,5-dibenzyloxy-1,2-dinitrobenzene, (1.9 g, 5.0 mmol) in 25 ml dimethylsulfoxide were added 1.16 g (17.8 mmol) sodium azide and the mixture was stirred at 85°C for 4 hours. The mixture was then poured into water and the resulting precipitate filtered off with suction, washed with water and dried *in vacuo*. Yield of title compound 1.49 g (85.5%)

M.P.: 206 - 208°C (dec.)

^{1}H-NMR (DMSO-d_6:δ = 5.28 (s, 4H), 7.2 - 7.6 (m, 12 H); ppm.

Example 26

3-Methyl-6,7-bis(phenylmethoxy)-2-quinoxalinecarboxylic acid, ethyl ester, 1,4-dioxide

To a suspension of the title compound of Example 25 (1.04 g, 3.0 mmol) in 20 ml ethanol were added at 60°C ethyl acetoacetate (0.78 g, 6.0 mmol) and sodium hydroxide (0.12 g, 3.0 mmol) in 4 ml ethanol. The mixture was stirred at 60°C for 8 hours and another 10 hours at room temperature. The resulting precipitate was filtered off with suction, washed with water and dried *in vacuo* to give 0.62 g of crude product. The crude material was chromatographed on silical gel with ethyl acetate/petroleum ether 2:1 as eluent and yielded 0.38 g (27.5 %) of the title compound.

M.P.: 175 - 177°C (dec.)

IR(KBr): 1740 cm^{-1}(CO)

^{1}H-NMR (DMSO-d_6): δ = 1.34 (t,3H); 2.40 (s, 3H); 4.48 (q, 2H); 5.42 (s, 4H); 7.3 - 7.6 (m, 10H); 7.82 (s, 1H); 7.91 (s, 1H); ppm

Example 27

3-Methyl-6,7-bis(phenylmethoxy)quinoxaline-2-carboxylic acid

Example 27A

3-Methyl-6,7-bis(phenylmethoxy)quinoxaline-2-carboxylic acid, phenylmethyl ester

The compound from Example 2 (6.3 g; 20.0 mmol) was treated with concentrated hydrochloric acid (170 ml) at 75°C for 90 minutes and the formed precipitate was collected from the cold suspension by suction. After drying *in vacuo* over P_2O_5 and subsequent washing with acetonitrile, ether and n-pentane, this crude hydrochloride salt (4.0g; mp 201 - 202°C) was suspended in dry dimethylformamide (50 ml) and then potassium carbonate (12.4 g; 0.09 mol) was added slowly (evolution of CO_2) followed by the addition of benzylbromide (15.4 g; 0.09 mol). After being stirred at 75°C for 4 hours the mixture was cooled, filtered and the filtrate was evaporated *in vacuo*. The resulting residue was washed with few ml ether and then taken up in ethyl acetate and water and the pH of the mixture was adjusted to 2 by the addition of diluted hydrochloric acid. The organic layer was separated, washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue which was crystallized from ethylacetate and petroleum ether, yield: 3.8 g (39 %) mp 137 - 139°C. IR(KBr): 1715, 1703 cm^{-1}; ^{1}H-NMR (DMSO-d_6):δ = 2.78 (s, 3H); 3.33 (s, 2H); 5.37 (s, 2H); 5.43 (s, 2H); 7.25 - 7.65 (m, 17H) ppm.

Example 27B
3-Methyl-6,7-bis(phenylmethoxy)quinoxaline-2-carboxylic acid

The compound of Example 27A (4.9 g, 10.0 mmol) was added to a solution of potassium hydroxide (2.2 g, 40.0 mmol) in ethanol/water (80 ml/16 ml) and the mixture was stirred at 80°C for 20 hours and then cooled (5°C). The precipitate was collected by suction, washed with ether (4.3 g) and then suspended in water (100 ml). After correction of the pH of this suspension to 2 by the addition of 2N HCl stirring was continued at room temperature for 20 minutes and the crystallized title compound was isolated by suction, washed with water and dried *in vacuo* over P_2O_5. Yield: 3.4 g (85%); mp 198 - 200°C.

$C_{24}H_{20}N_2O_4 \cdot 0.1\ H_2O$

	calc. (%)	found (%)
C	71.67	71.50
H	5.06	5.03
N	6.96	7.14

IR(KBr): 1752, 1717 cm^{-1}; ^{1}H-NMR (DMSO-d_6):δ = 2.78 (s, 3H); 4.39 (s, 4H); 7.25 - 7.70 (m, 12H); COOH too broad, not registered.

Example 28
4-Bis(phenylmethoxy)-1,2-benzenediamine, trifluoroacetate (1:1) salt

Example 28A

2,2-Dimethyl-N-[2-nitro-4,5-bis(phenylmethoxy)phenyl]propanamide

To a suspension of 2-nitro-4,5-dibenzyloxybenzoic acid (1.89, 5.0 mmol) in 30 ml tert.-butanol were added diphenylphosphoryl azide (1.65 g, 6.0 mmol) and triethylamine (0.61 g, 6.0 mmol). The mixture was heated to reflux overnight. After cooling the resulting precipitate was filtered off, washed with ether and dried *in vacuo*.

Yield of title compound: 1.74 g (84%)

m.p.: 145 - 149°C

IR(KBr): 1715 cm^{-1}(CO).

^{1}H-NMR (DMSO-d_6):δ = 1.47 (s, 9H); 5.19 (s,2H); 5.22 (s, 2H); 7.40 (mc, 10H); 7.70 (s, 1H); 7.73 (s, 1H); 9.65 (s, 1H); ppm

Example 28B

N-[2-Amino-4,5-bis(phenylmethoxy)phenyl]-2,2-dimethylpropanamide

Under nitrogen, the title compound of Example 28A (15.77 g, 35.0 mmol) was dissolved in 350 ml dimethylformamide. 500 mg platinum (IV) oxide were added, the mixture was heated to 60°C and hydrogenated by monitoring with thin layer chromatography until the end of the reaction (1 - 5 days). The hydrogen was replaced with nitrogen, the catalyst was filtered off and the filtrate

evaporated (all operations under nitrogen, otherwise the product has a deep blue color). The residue was triturated with degassed water to remove residual dimethylformamide.

Yield after drying of title compound: 14.1 g (96%)

m.p. 115°C

IR(KBr): 1680 cm^{-1} (CO).

^{1}H-NMR (DMSO-d_6): δ = 1.45 (s, 1H); 4.60 (s, broad, 2H); 4.91 (s, 2H); 5.00 (s, 2H); 6.50 (s, 1H); 6.94 (s, 1H); 7.40 (mc, 10H); 8.20 (s, 1H);ppm

Example 28C

4-Bis(phenylmethoxy)-1,2-benzenediamine, trifluoroacetate (1:1) salt

A mixture of the title compound of Example 28B (1.0 g, 2.38 mmol) and 20 ml of trifluoroacetic acid was stirred at 0°C for one hour. Trifluoroacetic acid was distilled off and the residue triturated with ether. The title compound was filtered off, washed with water and dried *in vacuo*.

Yield 0.78 g (74%)

M.P.: 122.5°C

$C_{20}H_{20}N_2O_2$ · 1:1 CF_3COOH

Calculated	(%)	Found (%)
C	60.31	59.94
H	4.82	4.83
N	6.37	6.53
F	13.60	13.60

IR(KBr): 1675cm^{-1}(CO).

^{1}H-NMR (DMSO-d_6): δ = 5.03 (s, 4H); 6.79 (s, 2H); 7.41 (mc, 10 H); ppm

Example 29

3-Methyl-6,7-bis(phenylmethoxy)-2-quinoxaline-carboxylic acid, 1,1-dimethylethyl ester

4,5-Bis(phenylmethoxy)-1,2-benzenediamine, trifluoroacetate (1:1) salt (5.48 g, 12.62 mmol) was dissolved in 45 ml water/tetrahydrofuran (2:1) and the pH was brought to 5 with 2N sodium hydroxide solution. t-Butyl 2,3-dioxobutynate (3.44 g, 20.0 mmol) was added and the mixture was heated to reflux for 80 minutes. Tetrahydrofuran was distilled off and the residue was extracted with ethyl acetate. The organic phase was washed with water, dried and stirred with activated carbon. After filtration and evaporation a resin was obtained which crystallized. This material was chromatographed on silica gel with ethyl acetate/petroleum ether (1:2) as eluent. The sample containing fractions were collected to give after evaporation and trituration with petroleum ether 3.33 g (58%) of the title compound.

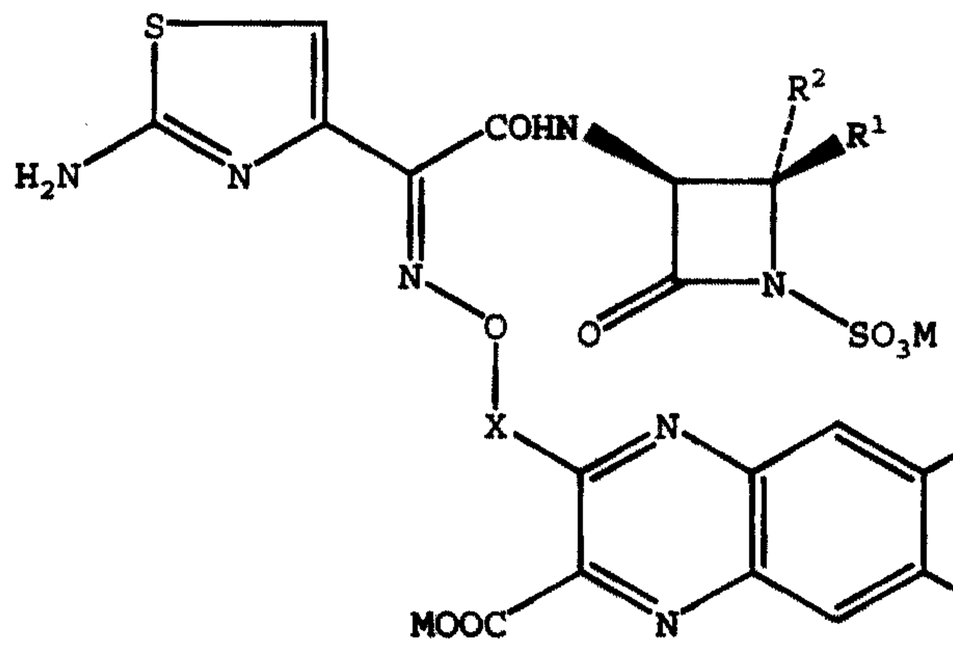
M.P.: 111°C

IR (KBr): 1725 cm^{-1} (CO).

^{1}H-NMR (DMSO-d_6):δ = 1.45 (s, 9H); 2.67 (s, 3H); 5.32 (s, 4H); 7.2 - 7.6 (m, 12 H); ppm

What we claim is:

1. Compounds having the formula



1

wherein

R^1 and R^2 are the same, or different and each is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, substituted phenyl or a 4, 5, 6 or 7-membered heterocycle, or one of R^1 and R^2 is hydrogen and the other is azido, halomethyl, dihalomethyl, trihalomethyl, alkoxycarbonyl, phenylethyl, 2-phenylethenyl, 2-phenylethynyl, carboxyl, $-CH_2X_1$;

wherein X_1 is azido, amino, hydroxy, carboxyl, alkoxycarbonyl, alkanoylamino, phenylcarbonylamino, (substituted phenyl)carbonylamino, alkylsulfonyloxy, phenylsulfonyloxy, (substituted phenyl) sulfonyloxy, phenyl, substituted phenyl, cyano, $-A-\overset{O}{\overset{\|}{C}}-NH_6X_7$, $-S-X_2$, or $-O-X_2$ wherein A, X_2, X_6 and X_7 are as hereinafter defined; $-S-X_2$ or $-O-X_2$, wherein X_2 is alkyl, substituted alkyl, phenyl, substituted phenyl, phenylalkyl, (substituted phenyl) alkyl,

formyl, alkanoyl, substituted alkanoyl, phenylalkanoyl, substituted phenylalkanoyl, phenylcarbonyl, substituted phenylcarbonyl, heteroaryl, heteroarylalkyl, heteroarylalkanoyl or heteroarylcarbonyl, and in the case of when X_1 is O-X_2 then X_2 can also be alkylideneamino, alkanoylamino, carboxyalkylideneamino, alkylsulphonylamino, alkoxycarbonyl, alkylsulphonylamino or N,N-cyclodialkanoylamino;

and R^1 and R^2 can also be $-O-\overset{X_3}{\underset{X_5}{C}}-X_4$ or $-S-\overset{X_3}{\underset{X_5}{C}}-X_4$;

wherein one of X_3 and X_4 is hydrogen and the other is hydrogen or alkyl, or X_3 and X_4 when taken together with the carbon atom to which they are attached form a cycloalkyl group; and X_5 is formyl, alkanoyl, phenylcarbonyl, substituted phenylcarbonyl, phenylalkylcarbonyl, substituted phenylalkylcarbonyl, carboxyl, alkoxycarbonyl, aminocarbonyl, substituted aminocarbonyl, or cyano;

or $-A-\overset{O}{\overset{\|}{C}}-NX_6X_7$

wherein A is -CH=CH-, $(CH_2)_m$-, $-(CH_2)_m$-O-, $-(CH_2)_m$ -NH-, or $-CH_2-S-CH_2-$, m is 0, 1 or 2, and X_6 and X_7 are the same or different and each is hydrogen, alkyl, phenyl or substituted phenyl, or X_6 is hydrogen an X_7 is amino, substituted amino, alkanoylamino or

alkoxy, or X_6 and X_7 when taken together with the nitrogen atom to which they are attached form a 4, 5, 6 or 7 membered heterocycle;

X is $(CH_2)_n$ wherein n is 0, 1, 2, 3 or 4 or CR_3R_4 wherein R_3 and R_4 are the same or different and each is hydrogen, CH_3 or C_2H_5 or R_3 and R_4 taken together with the carbon atom to which they are attached form a 3, 4, 5, 6 or 7-membered cycloalkyl ring;

M is hydrogen or a cation capable of forming a pharmaceutically acceptable salt,

wherein alkyl refers to a C_1 - C_{10} straight or branched alkyl group, alkoxy refers to a C_1 - C_{10} straight or branched alkoxy group, cycloalkyl refers to a C_3 - C_7 cycloalkyl group, alkanoyl refers to a C_2 - C_{10} straight or branched alkanoyl group, alkenyl refers to a C_2 - C_{10} straight or branched alkenyl group, alkynyl refers to a C_2 - C_{10} straight or branched alkynyl group, heterocycle refers to a C_4 - C_7 cyclic group containing one or more nitrogen, oxygen, or sulfur atoms and heteroaryl refers to a C_4 - C_7 aromatic heterocyclic group.

2. A compound according to Claim 1 wherein R^1 is hydrogen and R^2 is methyl.

3. A compound according to Claim 1 wherein R^1 is methyl and R^2 is hydrogen.

4. A compound according to Claim 1 wherein R^1 and R^2 are hydrogen.

5. A compound according to Claim 1 wherein X is $(CH_2)_n$ and n is one.

6. A compound according to Claim 1 wherein n is two.

7. A compound according to Claim 1 wherein n is three.

8. A compound according to Claim 1 wherein n is four.

9. A compound according to Claim 1 wherein M is hydrogen.

10. A compound according to Claim 1 wherein M is selected from the group consisting of tetraalkylammonium, sodium and potassium.

11. A compound according to Claim 1 wherein X is $(CH_2)_n$; wherein n is zero or an integer from one to four and one of R^1 or R^2 is methyl and the other is hydrogen.

12. A compound according to Claim 1, [2R-[2α,3α(Z)]]-3-[[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxo-ethylidene]amino]oxy]methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid.

13. A compound according to Claim 1, [2S-[2α,3β(Z)]]-3-[[[[1-(2-Amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxo-

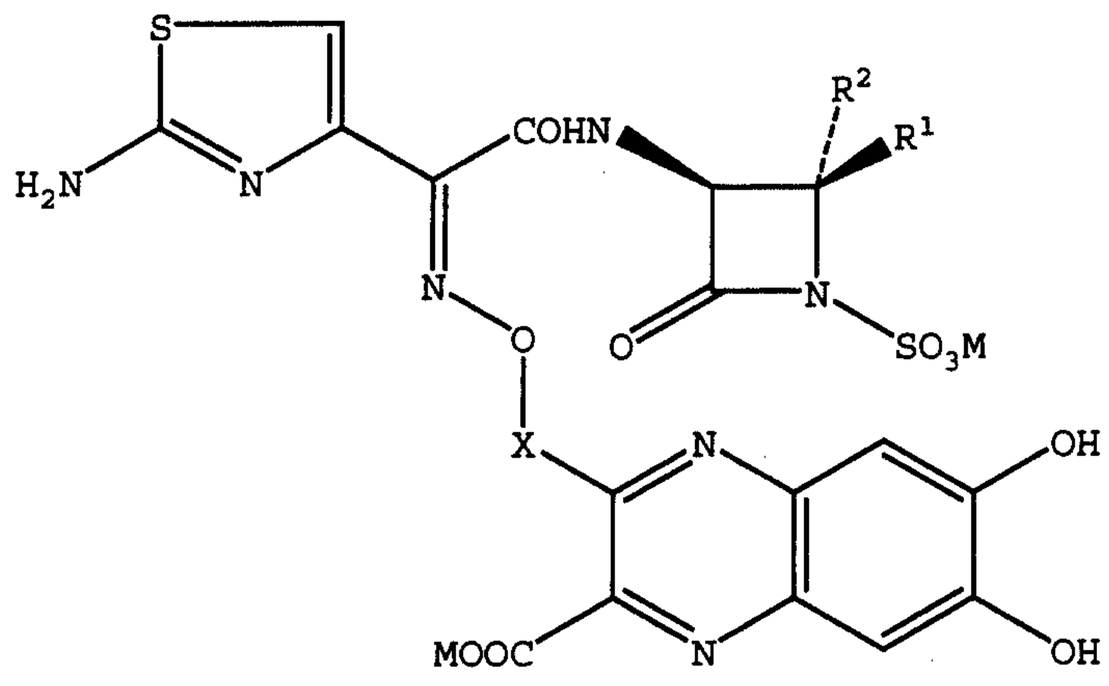
ethylidene]amino]oxy]methyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid.

14. A compound according to claim 1, [2R-[2α,3α(Z)]]-3-[2-[[[1-(2-Amino-4-thiaz-olyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]ethyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid.

15. A compound according to claim 1, [2R-[2α,3α(Z)]]-3-[3-[[[1-(2-Amino-4-thiazolyl-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]propyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid.

16. A compound according to claim 1, [2R-[2α,3α(Z)]]-3-[4-[[[1-(2-Amino-4-thia-zolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)-amino]-2-oxoethylidene]amino]oxy]butyl]-6,7-dihydroxy-2-quinoxalinecarboxylic acid.

17. A process for forming a compound of the formula



1

wherein

R^1 and R^2 are the same, or different and each is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, substituted phenyl or a 4, 5, 6 or 7-membered heterocycle, or one of R^1 and R^2 is hydrogen and the other is azido, halomethyl, dihalomethyl, trihalomethyl, alkoxycarbonyl, phenylethyl, 2-phenylethenyl, 2-phenylethynyl, carboxyl, $-CH_2X_1$;

wherein X_1 is azido, amino, hydroxy, carboxyl, alkoxycarbonyl, alkanoylamino, phenylcarbonylamino, (substituted phenyl)carbonylamino, alkylsulfonyloxy, phenylsulfonyloxy, (substituted phenyl) sulfonyloxy, phenyl, substituted phenyl,

cyano, -A-C-NH_6X_7, -S-X_2, or -O-X_2 wherein A, X_2, X_6 and X_7 are as hereinafter defined; -S-X_2 or -O-X_2, wherein X_2 is alkyl, substituted alkyl, phenyl, substituted phenyl, phenylalkyl, (substituted phenyl) alkyl, formyl, alkanoyl, substituted alkanoyl, phenylalkanoyl, substituted phenylalkanoyl, phenylcarbonyl, substituted phenylcarbonyl, heteroaryl, heteroarylalkyl, heteroarylalkanoyl or heteroarylcarbonyl, and in the case of when X_1 is O-X_2 then X_2 can also be alkylideneamino, alkanoylamino, carboxyalkylideneamino, alkylsulphonylamino, alkoxycarbonyl, alkylsulphonylamino or N,N-cyclodialkanoylamino;

and R^1 and R^2 can also be $-O-\overset{\displaystyle X_3}{\underset{\displaystyle X_5}{\overset{|}{\underset{|}{C}}}}-X_4$ or $-S-\overset{\displaystyle X_3}{\underset{\displaystyle X_5}{\overset{|}{\underset{|}{C}}}}-X_4$;

wherein one of X_3 and X_4 is hydrogen and the other is hydrogen or alkyl, or X_3 and X_4 when taken together with the carbon atom to which they are attached form a cycloalkyl group; and X_5 is formyl, alkanoyl, phenylcarbonyl, substituted phenylcarbonyl, phenylalkylcarbonyl, substituted phenylalkylcarbonyl, carboxyl, alkoxycarbonyl, aminocarbonyl, substituted aminocarbonyl, or cyano;

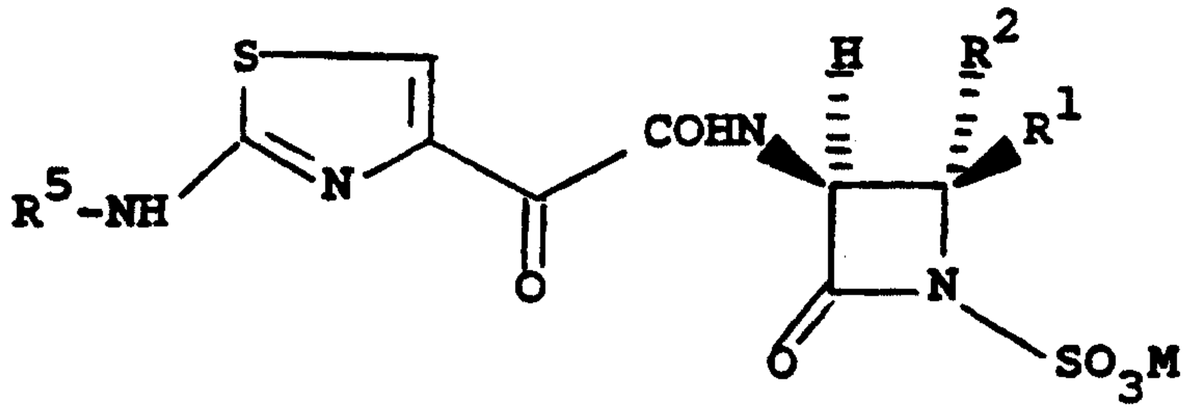
or $-A-\overset{\displaystyle O}{\overset{\|}{C}}-NX_6X_7$

wherein A is $-CH=CH-$, $(CH_2)_m-$, $-(CH_2)_m-O-$, $-(CH_2)_m-NH-$, or $-CH_2-S-CH_2-$, m is 0, 1 or 2, and X_6 and X_7 are the same or different and each is hydrogen, alkyl, phenyl or substituted phenyl, or X_6 is hydrogen an X_7 is amino, substituted amino, alkanoylamino or alkoxy, or X_6 and X_7 when taken together with the nitrogen atom to which they are attached form a 4, 5, 6 or 7 membered heterocycle;

X is $(CH_2)_n$ wherein n is 0, 1, 2, 3 or 4 or CR_3R_4 wherein R_3 and R_4 are the same or different and each is hydrogen, CH_3 or C_2H_5 or R_3 and R_4 taken together with the carbon atom to which they are attached form a 3, 4, 5, 6 or 7-membered cycloalkyl ring;

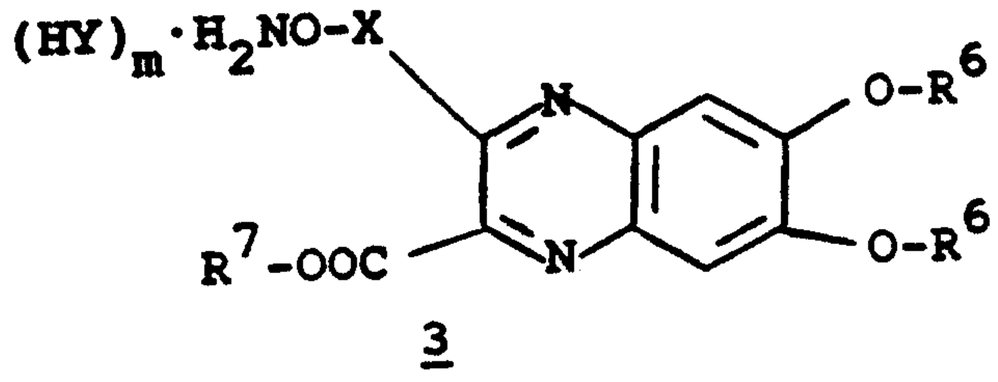
M is hydrogen or a cation capable of forming a pharmaceutically acceptable salt,
wherein alkyl refers to a C_1 - C_{10} straight or branched alkyl group, alkoxy refers to a C_1 - C_{10} straight or branched alkoxy group, cycloalkyl refers to a C_3 - C_7 cycloalkyl group, alkanoyl refers to a C_2 - C_{10} straight or branched alkanoyl group, alkenyl refers to a C_2 - C_{10} straight or branched alkenyl group, alkynyl refers to a C_2 - C_{10} straight or branched alkynyl group, heterocycle refers to a C_4 - C_7 cyclic group containing one or more nitrogen, oxygen, or sulfur atoms and heteroaryl refers to a C_4 - C_7 aromatic heterocyclic group,

characterized in that a compound of formula



2

where R^5 is H or a protecting group
is reacted with a compound of formula

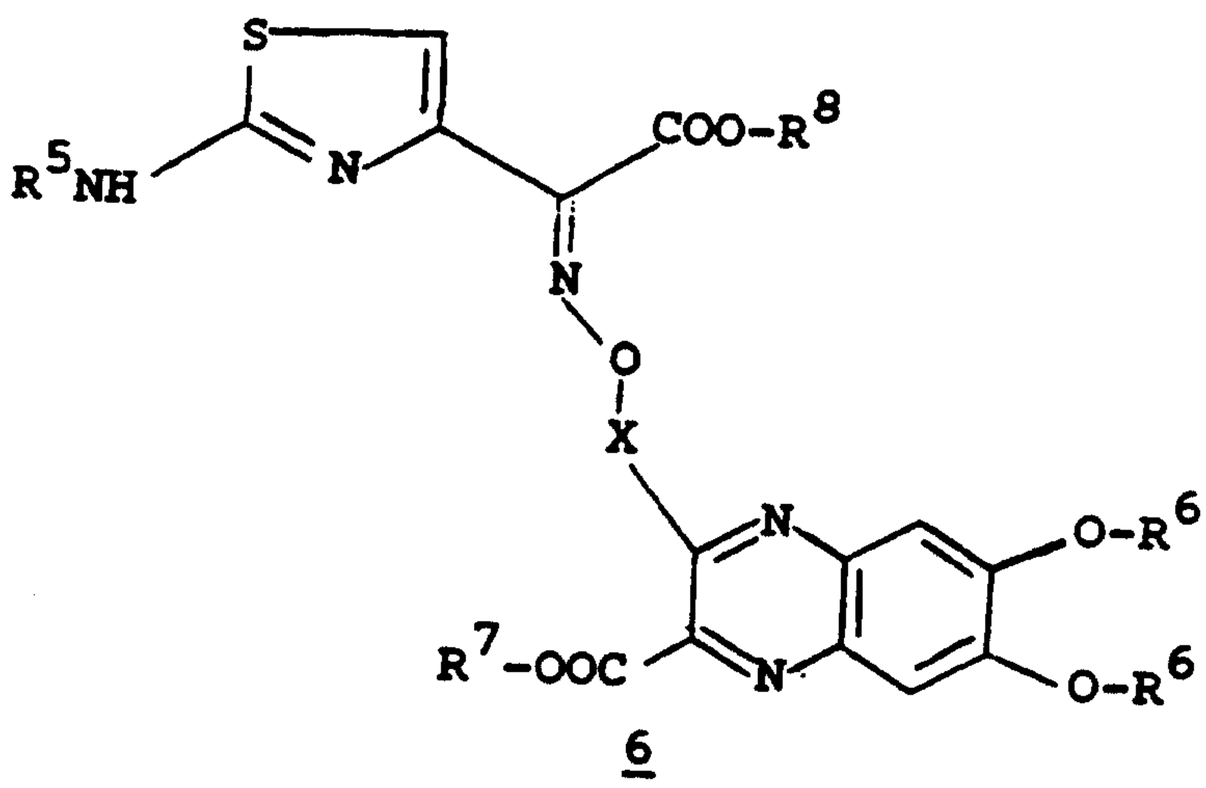


3

where X is as defined above, and
wherein R^6 is hydrogen or a suitable phenol-protecting group or R^6/R^6 is a catechol protecting

group; R^7 is hydrogen or a suitable protecting group; HY is a mineral acid, sulfonic acid or a non-nucleophilic acid capable of forming a stable hydroxylamine salt; m is 0, 1, or 2 or fractions of 1 or 2 and X is $(CH_2)_n$ wherein n is 0, 1, 2, 3 or 4 or CR_3R_4 wherein R_3 and R_4 are the same or different and each is hydrogen, CH_3 or C_2H_5 or R_3 and R_4 taken together with the carbon atom to which they are attached form a 3, 4, 5, 6 or 7—membered cycloalkyl ring;

or a compound of formula



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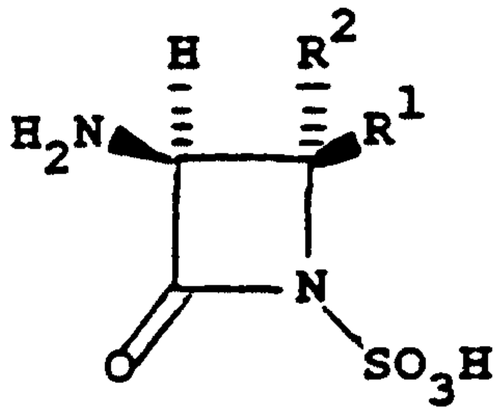
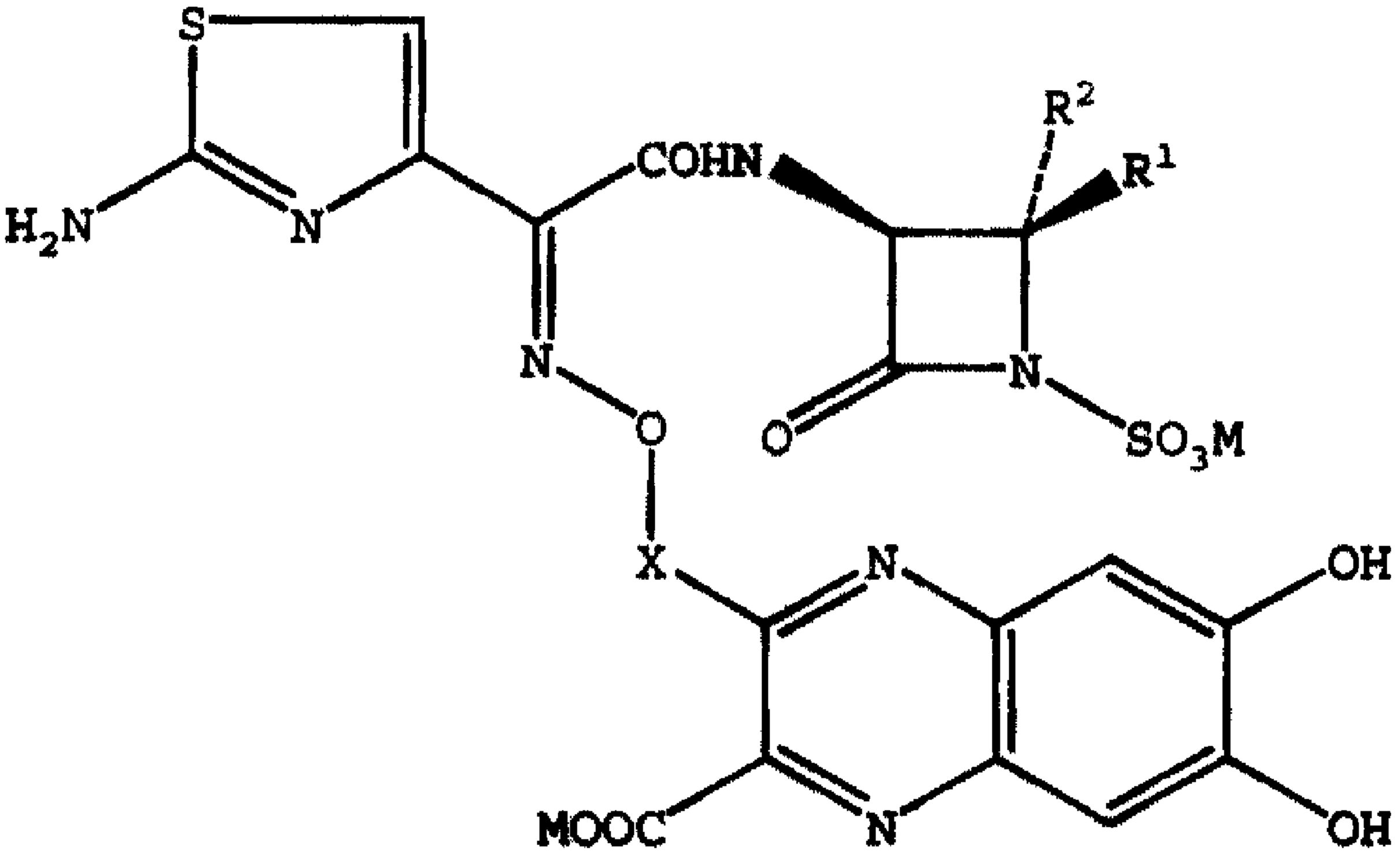
where R^8 is hydrogen or a carboxyl protecting group and R^5, R^6 and R^7 and X are as defined above is reacted with a compound of formula



where R^1 and R^2 are as defined above.


S
H_2N
N
COHN
R^2
R^1
N
O
O
N
SO_3M
X
N
OH
MOOC
N
OH