AUSTRALIA 647178

Patents Act 1990

NOTICE OF ENTITLEMENT

We, **Glaxo SpA** the applicant in respect of Application No. 84212/91, state the following:-

The Nominated person(s) is/are entitled to the grant of the patent because the Nominated person(s) would, on the grant of a patent for the invention, be entitled to have the patent assigned to him/her/them/it.

The Nominated person(s) is/are entitled to claim priority from the application(s) listed in the declaration under Article 8 of the PCT because the Nominated person made the application(s) listed in the declaration under Article 8 of the PCT.

The application(s) listed under Article 8 of the PCT is/are the first application(s) made in a Convention country in respect of the invention.

Dated this 4th day of January, 1994

(A member of the firm of DAVIES COLLISON CAVE for and on behalf of the applicant)

COMMONWEALTH OF AUSTRALIA

P/00/001
Section 29

The Patents Act 1990

PATENT REQUEST: CONVENTION PATENT

We, GLAXO S.p.A., being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification

Full application details follow:-

Applicant:	GLAXO S.p.A.
Address:	Via A. Fleming 2, 1-37100, Verona, Italy
Nominated Person:	GLAXO S.p.A.
Address:	Via A. Fleming 2, 1-37100, Verona, Italy
Invention Title:	10(1-HYDROXYETHYL)-11-OXO-1-AZATRICYCLO[7.2.0.0.3.8]UNDEC-2-ENE-2-CARBOXYLIC ACID ESTERS AND A PROCESS FOR PREPARING THEREOF
Name(s) of actual Inventor(s):	Alcide PERBONI; Tino ROSSI; Giovanni GAVIRAGHI; Antonella URSINI; Giorgio TARZIA
Address for service in Australia:	CALLINAN LAWRIE, 278 High Street, Kew 3101, Victoria, Australia
Attorney Code:	CL

Convention Details

Application Number	Country	Country Code	Date of Application
9018330.2	United Kingdom	GB	21 August 1990
9104770.4	United Kingdom	GB	7 March 1991

D A T E D this 21st day of April, 1992.

GLAXO S.p.A.
By their Patent Attorneys:
CALLINAN LAWRIE

Jeffrey A. Ryder

AU9184212

(12) PATENT ABRIDGMENT (11) Document No. AU-B-84212/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 647178

(54) Title
10(1-HYDROXYETHYL)-11-OXO-1-AZATRICYCLO(7.2.0.0.3.8)UNDEC-2- ENE-2-CARBOXYLIC ACID ESTERS AND A PROCESS FOR PREPARING THEREOF

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(56) Prior Art Documents
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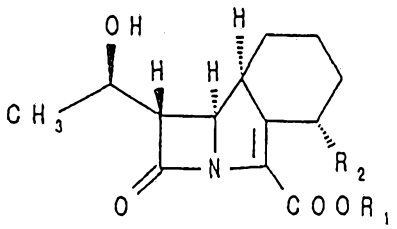
AU 13247/92 C07D 477/00 A61K 031/40
AU 63792/90 C07D 477/00 A61K 031/40

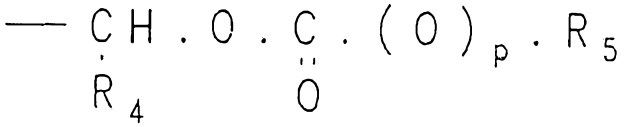
(57) Claim

1. Compounds of general formula (I)



(I)

in which R_1 represents the group



.../2

where R_4 represents a hydrogen atom or a C_{1-4} alkyl group; p is 0 or 1; R_5 is a group selected from C_{1-6} alkyl, C_{5-8} cycloalkyl optionally substituted by a C_{1-3} alkyl group, phenyl and C_{1-4} alkyl substituted by a C_{1-3} alkoxy group; and R_2 is a methoxy group.

8. A method of treatment of a human or non-human body to combat bacterial infections comprising administration to said body of an effective amount of a compound as claimed in any one of claims 1 to 6.

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AOJP DATE 30/04/92 PCT NUMBER PCT/EP91/01589
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(71) Applicant *(for all designated States except US)*: GLAXO S.P.A. [IT/IT]; Via A. Fleming, 2, I-37100 Verona (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : PERBONI, Alcide [IT/IT]; Glaxo S.p.A., Via A. Fleming, 2, I-37100 Verona (IT). ROSSI, Tino [IT/IT]; Glaxo S.p.A, Via A. Fleming, 2, I-37100 Verona (IT). GAVIRAGHI, Giovanni [IT/IT]; URSINI, Antonella [IT/IT]; Glaxo S.p.A., Via A. Fleming, 2, I-37100 Verona (IT). TARZIA, Giorgio [IT/IT]; Glaxa S.p.A., Via A. Fleming, 2, I-37100 Verona (IT).

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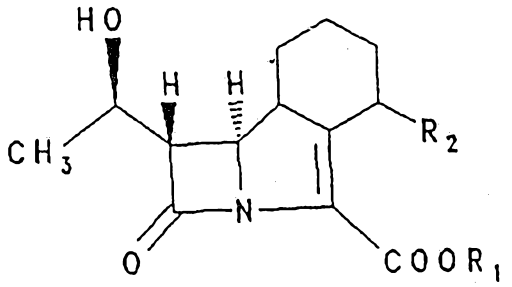
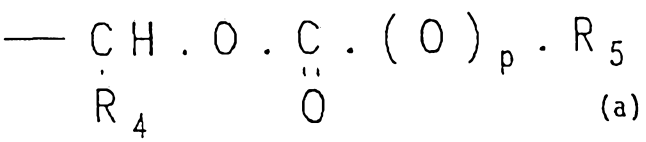
(54) Title: 10(1-HYDROXYETHYL)-11-OXO-1-AZATRICYCLO[7.2.0.0.3.8]UNDEC-2-ENE-2-CARBOXYLIC ACID ESTERS AND A PROCESS FOR PREPARING THEREOF



(I)



(a)

(57) Abstract

Compounds of general formula (I) in which R_1 represents the group (a), where R_4 represents a hydrogen atom or a C_{1-4} alkyl group; p is 0 or 1; R_5 is a group selected from C_{1-6} alkyl, C_{5-8} cycloalkyl optionally substituted by a C_{1-3} alkyl group, phenyl and C_{1-4} alkyl substituted by a C_{1-3} alkoxy group; and R_2 is a group OR_3 where R_3 is a C_{1-5} alkyl group, are orally administrable and exhibit broad spectrum antibacterial activity.

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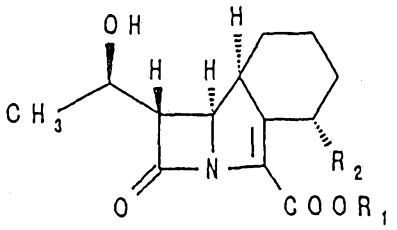
57031/016.570

10-(1-Hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0.^{3,8}] undec-2-ene-2-carboxylic acid esters and a process for preparing thereof

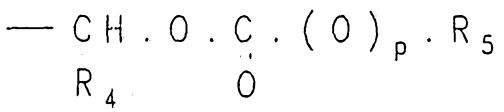
This invention relates to heterocyclic derivatives having antibacterial activity, to processes for their preparation, to compositions containing them and to their use in medicine.

Thus the present invention provides compounds of the general formula (I)



(I)

in which R_1 represents the group



wherein R_4 represents a hydrogen atom or a C_{1-4}alkyl group; p is zero or one; R_5 represents a group selected from C_{1-6}alkyl, C_{5-8}cycloalkyl optionally substituted by a C_{1-3}alkyl group, phenyl, or C_{1-4}alkyl substituted by a C_{1-3}alkoxy group; and R_2 represents a methoxy group.

In addition to the fixed stereochemical arrangement as defined in formula (I) the group R_1 contains at least one asymmetric carbon atom when R_4 is other than hydrogen. It will be appreciated that all stereoisomers including mixtures thereof arising from this asymmetric centre are within the scope of formula (I).

The wedge shaped bonds in formula (I) indicate that the bond is above the plane of the paper. The broken bonds indicate that the bond is below the plane of the paper.

The configuration shown for the carbon atom at the 8-position in formula (I) is hereinafter referred to as the β-configuration.

The configuration shown for the carbon at the 4-position in formula (I) is hereinafter referred to as the α-configuration.

In general, in the specific compounds named below, the β-configuration at the 8-position corresponds to the S isomer and the α-configuration at the 4-position corresponds to the S isomer. The assignment of the S configuration at the 4- and 8-positions has been made according to the rules of Cahn, Ingold and Prelog, Experientia 1956, 12, 81.

The term alkyl as used herein refers to a straight or branched chain alkyl group. When R_4 represents a C_{1-4} alkyl group this may be for example methyl, ethyl, propyl, isopropyl or butyl.

When R_5 represents an alkyl group this may conveniently be a C_{1-4}alkyl group such as methyl, ethyl, isopropyl or t-butyl.

When R_5 represents a C_{1-4}alkyl group substituted by C_{1-3}alkoxy, this may be for example a methyl, ethyl, propyl or isopropyl group substituted by methoxy.

When R_5 represents C_{5-8}cycloalkyl optionally substituted by C_{1-3}alkyl this may be for example a cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl group optionally substituted by a methyl or ethyl group.

A preferred class of compounds of formula (I) are those wherein R_4 represents hydrogen, methyl, propyl or isopropyl, more particularly hydrogen or methyl.

A further preferred class of compounds of formula (I) are those wherein R_5 represents a C_{1-4}alkyl group such as methyl, ethyl, isopropyl or t-butyl; a C_{1-4}alkyl group substituted by methoxy such as 1-methoxy-1-methylethyl; phenyl; or a C_{5-6} cycloalkyl group such as cyclopentyl or cyclohexyl optionally substituted by a methyl or ethyl group e.g. as in ethylcyclohexyl.

A particularly preferred group of esters according to the invention are those wherein R_4 represents a hydrogen atom or a methyl group, p is zero or 1 and R_5 represents C_{1-4} alkyl (e.g. methyl, ethyl, isopropyl or t-butyl), C_{1-4} alkyl substituted by methoxy (e.g. 1-methoxy-1-methylethyl), phenyl, or C_{5-6}cycloalkyl optionally substituted by a C_{1-2}alkyl group (e.g. cyclohexyl or 4-ethylcyclohexyl).

Specific preferred compounds include esters of (4S, 8S, 9R, 10S, 12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.$0^{3,8}$] undec-2-ene-2 carboxylic acid such as the pivaloyloxymethyl, 1-pivaloyloxyethyl, acetoxymethyl, 1-acetoxyethyl, 1-methoxy-1-methylethyl-carbonyloxymethyl, 1-(1-methoxy-1-methylethyl-carbonyloxy)ethyl, 1-benzoyloxyethyl, 1-

isopropoxycarbonyloxyethyl, cyclohexyloxycarbonyloxymethyl, 1-(4-ethylcyclohexyloxycarbonyloxy)ethyl or more particularly 1-cyclohexyloxycarbonyloxyethyl ester.

Compounds according to the invention, when administered orally, exhibit a high level of antibacterial activity against a wide range of pathogenic microorganisms and they have a very high resistance to all ß-lactamases. Compounds of the invention are also relatively stable to renal dehydropeptidase.

Compounds of the invention have been found to exhibit valuable levels of activity against strains of Staphylococcus aureus, Streptococcus faecalis, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Citrobacter freundii, Pseudomonas aeruginosa, Clostridium perfringens, Bacteriodes fragilis and Morganella morganii.

The compounds of the invention may therefore be used for treating a variety of diseases caused by pathogenic bacteria in human beings and animals.

Thus, according to another aspect of the present invention, we provide a compound of formula (I) for use in the therapy or prophylaxis of systemic bacterial infections in a human or animal subject.

According to a further aspect of the invention we provide the use of a compound of formula (I) for the manufacture of a therapeutic agent for the treatment of systemic bacterial infections in human beings and animals.

According to a yet further aspect of the invention we provide a method of treatment of the human or non-human animal body to combat bacterial infections which method comprises administering to the body an effective amount of a compound of formula (I).

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however doses

employed for adult human treatment will typically be in the range of 200-2000mg per day e.g. 1000mg per day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for exmaple as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

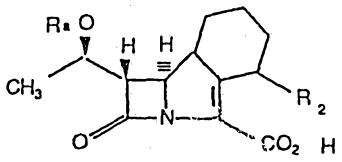
The invention thus further provides a pharmaceutical formulation for oral administration comprising a compound of formula (I) together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical compositions according to the invention may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelantinised maize starch, polyvinyl-pyrrolidone or hydroxypropylmethylcellulose), fillers (e.g. starch, lactose, micro-crystalline cellulose or calcium phosphate), lubricants (e.g. magnesium stearate, hydrogenated vegatable oils, talc, silica, polyethyleneglycols), disintegrants (e.g. potato starch or sodium starch glycolate), or wetting agents (e.g. sodium lauryl sulphate). Flow aids e.g. silicon dioxide may also be used if desired. The tablets may be coated by methods well know in the art.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product either for consitution with water or other suitable vehicle before use for administration as a liquid or for direct administration and then washed down with water or other suitable liquid. Such liquid preparations may be prepared by conventional means with pharmaceutically accepable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats and oils such as hydrogenated castor oil), emulsifying or thickening agents (e.g. lecithin, aluminium stearate

or acacia), non-aqueous vehicles (e.g. almond oil, fractionated coconut oil, oily esters or ethyl alcohol), preservatives (e.g. methyl or butyl p-hydroxybenzoates or sorbic acid) and suitable flavouring and sweetening agents.

Compounds of formula (I) may be prepared by esterification of the carboxylic acid (II)



(II)

in which R_a is hydrogen or a hydroxyl protecting group and R_2 is as defined for formula (I), or a salt or reactive derivative thereof and if required or desired subjecting the resulting compound prior to or subsequent to any separation into its sterochemical isomers, to removal of any protecting group R_a. When R_a represents a hydroxyl protecting group this may be for example a hydrocarbylsilyl group such as trialkylsilyl e.g. trimethylsilyl or t-butyldimethysilyl.

The esterification of a compound of formula (II) or a salt thereof may be carried out by reaction with a compound R_1X in which R_1 has the meanings defined above in formula (I) and X is a leaving group such a halogen atom, e.g. chlorine, bromine or iodine, or an alkyl or aryl sulphonate such as mesylate or tosylate, in the presence of a base. The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include dimethylformamide, dimethylacetamide, or dimethylsulphoxide.

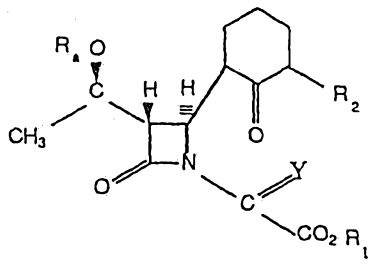
In one embodiment of this process the reaction is conveniently carried out using a salt such as an alkali metal salt e.g. potassium or sodium salt of the carboxylic acid (II) in the presence of a suitable quaternary ammonium salt such as triethyl benzylammonium chloride, trioctyl-methylammonium chloride or tetrabutylammonium bromide and preferably in the presence of a polar aprotic solvent such as dimethylformamide, dimethylacetamide or N-methylpyrrolidinone.

The esterification reaction may be conveniently carried out using a compound of formula (II) in which R_a represents a hydrogen

atom. If the esterfication reaction is carried out on a compound of formula (II) in which R_a represents a hydroxyl protecting group then this group may be removed by conventional procedures. For example when R_a is tert butyldimethylsilyl group this may be removed by treatment with tetrabutylammonium fluoride and acetic acid.

The compounds of formula (II) may be prepared by known methods e.g. as described in EP-A-0416953.

The compounds of formula (I) may also be prepared by the cyclisation of a compound of formula (III)



(III)

in which the groups R_1 and R_2 have the meanings defined for formula (I), R_a is a hydroxyl protecting group and Y is an oxygen atom or a phosphine group, and if required or desired subjecting the resulting compound prior to or subsequent to any separation into its stereochemical isomers, to removal of the protecting group R_a.

The cyclisation of a compound of formula (III) in which Y is oxygen is conveniently carried out by heating in the presence of an organic phosphite. The reaction is preferably carried out in a solvent or mixture of solvents at a temperature within the range 60-200^0. Suitable solvents include hydrocarbons with an appropriate boiling point, for example aromatic hydrocarbons, such as toluene or xylene.

Suitable organic phosphites include acyclic and cyclic trialkylphosphites, triarylphosphites and mixed alkylarylphosphites. Particularly useful organic phosphites are the trialkylphosphites e.g. triethylphosphite or trimethylphosphite.

The cyclisation of a compound of formula (III) in which Y is a phosphine grouping is preferably carried out in a solvent at a temperature between 40-200^{0}C. Suitable solvents include hydrocarbons such as aromatic hydrocarbons, for example xylene or toluene, aliphatic hydrocarbons and halogenated hydrocarbons such as dichloromethane, chloroform and trichloroethane. Examples of

suitable phosphine groups are triarylphosphines e.g. triphenyl phosphine or trialkylphosphines e.g. tri-t-butylphosphine.

The hydroxyl protecting group may be removed by well known standard procedures such as those described in Protective Groups in Organic Chemistry, pages 46-119, Edited by J F W McOmie (Plenum Press, 1973). For example when Ra is a tert butyldimethylsilyl group, this may be removed by treatment with tetrabutyl ammonium fluoride and acetic acid. This process is conveniently carried out in a solvent such as tetrahydrofuran.

Similarly when the R_a is trichloroethoxycarbonyl group this may be removed by treatment with zinc and acetic acid.

The compounds of formula (III) may be prepared by methods analogous to those described in EPA 0416953 for preparing structually related compounds.

In order that the invention may be more fully understood the following examples are given by way of illustration only.

In the Preparations and Examples, unless otherwise stated:

Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. All temperatures refer to ^0C.

Infrared spectra were measured in chloroform-dl solutions on a FT-IR instrument. Proton Magnetic Resonance (1H-NMR) spectra were recorded at 300 MHz as solutions in chloroform-d_1. Chemical shifts are reported in ppm downfield (δ) from Me_4Si, used as an internal standard, and are assigned as singlets (s), doublets (d), doublet of doublets (dd) or multiplets (m).

Column chromatography was carried out over silica gel (Merck AG Darmstadt, Germany).

Solutions were dried over anhydrous sodium sulphate.

"Petrol" refers to petroleum ether, b.p. 40-60^0C.

Methylene chloride was redistilled over calcium hydride; tetrahydrofuran was redistilled over sodium; ethyl ether was redistilled over sodium; xylene was redistilled over phosphorus pentoxide and ethyl acetate was dried over activated molecular sieves.

Intermediate 1

(2-Methoxy-2-methyl) propanoic acid ethenyl ester

To 2-methoxy-2-methylpropanoic acid (1.5g), mercury (II) acetate (0.162g), palladium acetate (0.0285 g), potassium hydroxide (0.067g) and vinyl acetate (1.2g) were added under nitrogen. The resulting solution was heated at 50° C for 4 hrs. To the reaction mixture additional vinyl acetate (2.4g) was then added and the mixture was heated at 50° C for 16 hrs.

After cooling to 20° C, diethyl ether (15ml) was added and the mixture was filtered on a pad of celite. The solution was washed with 10% sodium hydroxide solution (3 x 20ml) and the aqueous phase was filtered on a pad of celite and then extracted with diethyl ether (2 x 70ml). The organic phases were washed with brine (150ml) and dried over anhydrous sodium sulphate to obtain the crude title compound as a pale yellow oil (0.7g); tlc cyclohexane/ethyl acetate 8:2 Rf = 0.7; IR ($CDCl_3$) V_{max} (cm^{-1}): 1749 (C=O ester) 1640 (C=C); 1H-NMR (3oo MH_z; $CDCl_3$) (ppm) 7.30 (m), 4.983(dd), 4.648(dd), 3.297(s), 1.464(s).

Intermediate 2

(2-Methoxy-2-methyl) propanoic acid, 1-chloro ethyl ester

To a solution of the intermediate 1 (2.7g) in ethyl acetate (50ml) anhydrous hydrogen chloride was bubbled for 1 hr at 0° C, then nitrogen was bubbled for 10 minutes. The solvent was evaporated and the residue was purified through kugelrohr distillation (90°C/15 mmHg) to obtain the title compound as a colourless oil (2.1g) Tlc cyclohexane/ethyl aceate 9:1. Rf - 0.9; IR ($CDCl_3$) V_{max} (cm^{-1}): 1755 (C=O ester); 1H-NMR ($CDCl_3$; 300 MH_z) (ppm) 6.58 (q) 3.296(s), 1.837(d), 1.442(s).

Intermediate 3

(1-Chloro-2-methyl)propyl methyl carbonate

A solution of 1-chloro-2-methylpropyl chloroformate (1.71g) in dry dichloromethane (5ml) was added dropwise to a solution of methanol (0.83ml) in dry dichloromethane (5ml) at 0° C, under nitrogen, with stirring.

A solution of pyridine (0.80ml) in dry dichloromethane (10ml) was then added and the reaction mixture was stirred at 20° for 18 hrs.

The mixture was diluted with dichloromethane 950ml), washed with brine (3 x 40ml), dried over anhydrous sodium sulfate and

concentrated under a stream of nitrogen at low temperature, to afford the crude title compound as a colourless oil in quantitative yield.

H-NMR (300 MHZ, $CDCl_3$): 6.18(d), 3.86(s), 2.28-2.12(m), 1.08(d), 1.06(d) ppm.

Intermediate 4

1-Chloroethyl 4-ethylcyclohexyl carbonate

A solution of 1-chloroethyl chloroformate (5.46 g) in dry dichloromethane (20 ml) was added dropwise, under nitrogen at 0°, to a stirred solution of 4-ethylcyclohexanol (5 g) in dry dichloromethane (20ml) in presence of 3A molecular sieves. A solution of pyridine (3 g) in dry dichloromethane (20 ml) was added dropwise to the reaction mixture during 20 min at 0° the mixture was then warmed to 20°, stirred for 20 hours, washed with brine (2x50 ml) and dried. The solvent was removed under vacuum and the residue was distilled to give the title compound as a colourless oil (7.9 g; b.p. 130°/5.2 mbar; t.l.c. cyclohexane/ethyl acetate 9/1 Rf = 0.88; IR (CDCl3), Vmax (cm-1): 1757 (C =O); 1H-NMR (300 MHz, CDCl3): 6.43 (q), 6.42 (q), 4.93 (bs), 4.59 (tt), 2.14-2.01 (bs), 2.00-1.88 (bs), 1.88-1.78 (m), 1.83 (d), 1.82 (d), 1.60-1.50 (m), 1.50-1.32 (m), 1.30-1.15 (m), 1.28-1.18 (m) 1.05-0.95 (m), 0.95-0.85 (m).

Intermediate 5

1-Chloro-2-methylpropyl 2,2-dimethypropionate

2-Methylpropionaldehyde (5.98 g) was added dropwise, during 10 min., to a stirred mixture of zinc chloride (0.11 g) and pivaloyl chloride (10 g), under nitrogen at -20°. The reaction mixture was then warmed to 2[illegible]° and stirred for further 2 hours. The solid was removed by centrifugation and the oily residue was distilled to obtain the title compound as a colourless oil (11.55 g; b.p. 70°/35 mbar; IR (CDCl3), Vmax (cm-1): 1749 (C=O); 1H-NMR (300 MHz, CDCl3): 6.28 (d), 2.16 (m), 1.22 (s), 1.05 (d) ppm)

Intermediate 6

Cyclohexyl chloromethyl carbonate

A stream of chlorine was slowly bubbled into cold (-10/+5°) methyl chloroformate (6 ml) under diffuse light The reaction was monitored

by 1H-NMR and stopped before the dichloromethyl chloroformate concentration became more than 5% molar. Nitrogen was bubbled through the solution until it became co[illegible] less and the residue was distilled to obtain two main fraction[illegible] containing the required intermediate chloromethyl chloroformate; fraction a (2.48 g; molar ratio: methyl chloroformate/chloromethyl chloroformate/dichloromethyl chloroformate 19/77/4), fraction b (1.76 g; molar ratio: methyl chloroformate/chloromethyl chloroformate/ dichloromethyl chloroformate 4/90/6). To an ice cold solution of cyclohexanol (1.37 ml) in dry dichloromethane (5 ml), in presence of 3A molecular sieves and under nitrogen, a solution of the (fraction a) (1.7 g) in dry dichloromethane (5 ml) was added during 5 min. A solution of pyridine (1.06 ml) in dry dichloromethane (5 ml) was then added to the reaction mixture during 30 min. at 0°, and the mixture was slowly warmed to 20-25°. After 5 hours, the solution was filtered, diluted with dichloromethane (30 ml) , washed with water (20 ml), brine (3x30 ml) and dried. The solvent was distilled off and the residue was purified by column chromatography on silic a gel, using cyclohexane/ethyl acetate 9/1 as eluant, to obtain the title compound as a white wax (1.98 g; t.l.c. cyclohexane/ethyl acetate 9/1 Rf=0.44; IR (CDCl3), Vmax (cm-1): 1759 (C=O); 1H-NMR (300 MHz, CDCl3): 5.73 (s), 4.78-4.66 (m), 2.00-1.90 (m), 1.80-1.70 (m), 1.60-1.20 (m)ppm).

Example 1

1-(Cyclohexyloxycarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate

To a solution of potassium (4S,8S,9R,10S,12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo [7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate(hereinafter referred to as "Intermediate A") (0.5g) in dimethylformamide (8ml) tetrabutylammonium bromide (0.5g) and (1-chloroethyl)-cyclohexyl carbonate (0.65g) were added at 22°. The resulting mixture was stirred at 22° for 15 hr, then poured into diethyl ether (60ml), washed with 1% aq HCl (40ml), 5% aq NaHCO3 (2x50ml) and brine (2x50 ml), dried and concentrated. The residue (1g) was dissolved in diethyl ether (2ml) and light petroleum

(20ml) added with vigorous stirring. The precipitate (0.1g) was filtered off and the mother liquors were concentrated to give a residue, which was dissolved in diethyl ether (1ml) and light petroleum (20ml) added under vigorous stirring to give more precipitate (0.14g). The precipitates were combined (0.24g) and further purified by dissolution in diethyl ether (3ml) and precipitation from light petroleum (30ml) under vigorous stirring to obtain the title compound as a white powder (0.160 g; t.l.c. diethyl ether Rf 0.44, m.p. 90-100°).

IR (CDCl3) Vmax (cm-1) 1771, 1632; 1H-NMR (300 MHZ, CDCl3) 6.93-6.85(q+q), 4.92(t), 4.64(m), 4.25-4.05(m), 3.30-3.15(m), 3.25(s), 3.24(s), 2.08(m), 2.0-1.2(m), 1.61(d), 1.59 (d), 1.31(d), 1.30(d).

According the experimental procedures described in the Example 1, the following esters were prepared from Intermediate A.

Example 2

1-(Ethyloxycarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate was obtained as an oil (t.l.c. diethyl ether Rf 0.42). IR (CDCl3) Vmax (cm-1) 1765, 1738, 1600; 1H-NMR (300 MHZ, CDCl3) 6.93-6.87(q+q), 4.933(m), 4.3-1.8(m), 3.26-3.24(s+s), 3.32-3.20(m), 2.08(m), 1.94-1.3(m), 1.62 (d), 1.60(d), 1.36-1.28(m) from Intermediate A and (1-chloroethyl)-ethyl carbonate.

Example 3

1-(Isopropyloxycarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate

IR (CDCl3) Vmax (cm-1) 3614, 1767, 1632; 1H-NMR (300 MHZ, CDCl3) 6.90(q), 6.89(q), 4.95-4.83(m), 4.3-4.2(m), 4.191(dd), 3.35-3.20(m), 3.257(s), 3.243(s), 2.07(m), 1.93-1.75(m), 1.7-1.3 (m), 1.613(d), 1.33-1.29(d+d+d), t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.4 was obtained from Intermediate A and (1-chloroethyl)-isopropyl carbonate.

Example 4

1-(Acetoxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.160 g; t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.4)

IR (CDCl3) Vmax (cm-1) 3605, 1769, 1700; 1H-NMR (300 MHZ, CDCl3) 6.99(q), 6.98(q), 4.93(t), 4.25(m), 4.19(dd), 3.3-3.2(m), 3.25(s), 3.24(s), 2.10(s), 2.07(s), 2.08(m), 1.95-1.3(m), 1.56(d), 1.55(d), 1.31(d), 1.30(d) from Intermediate A and (1-chloroethyl)acetate.

Example 5

1-(Cyclohexylcarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

IR (CDCl3) Vmax (cm-1) 1774, 1750, 1630; 1H-NMR (300 MHZ, CDCl3) 6.997(q), 6.977(q), 4.931(t), 4.913(t), 4.24(m), 4.193(dd), 3.3-3.2(m), 3.25(s), 3.245(s), 2.38-2.24(m), 2.05(m), 1.95-1.2(m), 1.65 (dd), 1.566(d), 1.555(d), 1.326(d), 1.314(d) was obtained from Intermediate A and (1-chloroethyl) cyclohexanecarboxylate.

Example 6

1-(Benzoyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.045 g; t.l.c. cyclohexane, ethyl acetate 1:1 Rf 0.25);

IR (CDCl3) Vmax (cm-1) 1776, 1738, 1640, 1603; 1H-NMR (300 MHZ, CDCl3) 8.1-8.02(m), 7.58(tt), 7.48-7.4(m), 7.27(m), 4.948(t), 4.914(t), 4.3-4.2(m), 4.20(dd), 3.3-3.2(m), 3.23(s), 3.21(s), 2.05(m), 1.9-1.3(m), 1.725 (d), 1.708(d), 1.326(d), 1.302(d) from Intermediate A and (1-chloroethyl)-benzoate.

Example 7

1-[(1,1-Dimethylethyl)carbonyloxy]ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-1'-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.160 g; t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.37);

IR (CDCl3) Vmax (cm-1) 3666, 1776, 1744, 1632; 1H-NMR (300 MHZ, CDCl3) 6.982(q), 6.941(q), 4.94-4.88(m), 4.3-4.16(m), 3.3-3.18(m), 3.238(s), 3.20(s), 2.05(m), 1.9-1.2(m), 1.565(d), 1.554(d),

1.317(d), 1.306(d), 1.207(s), 1.179(s) from Intermediate A and 1-[(1,1-dimethylethyl)carbonyloxy]ethyl chloride.

Example 8

1-[2-Methoxy-2-methyl-propanoyloxy)]ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate, was obtained as an oil (0.130 g; t.l.c. diethyl ether Rf 0.35);
IR (CDCl3) Vmax (cm-1) 1772, 1603; 1H-NMR (300 MHz, CDCl3) 7.028(q), 6.984(q), 4.914(m), 4.3-4.2(m), 4.190(dd), 3.3-3.2(m), 3.260(s), 3.248(s), 3.290(s), 3.226(s), 2.06(m), 1.9-1.35(m), 1.604(m), 1.437(s), 1.429(s), 1.403(s), 1.400(s), 1.315(d) from Intermediate A and 2-methoxy-2-methyl-propanoic acid chloroethyl ester.

Example 9

Acetoxymethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate was obtained as an oil (0.240 g; t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.24);
IR (CDCl3) Vmax (cm-1) 1769, 1730, 1640; 1H-NMR (300 MHz, CDCl3) 4.996(t), 4.802(s), 4.3-4.2(m), 4.23(dd), 3.774(s) 3.36-3.24(m+dd), 3.28(s), 2.1(m), 1.94-1.30(m), 1.769(d), 1.327(d) from Intermediate A and chloromethyl acetate.

Example 10

[(1,1-Dimethyl-ethyl)carbonyloxy]methyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate was obtained as an oil (0.260 g; t.l.c. cyclohexane, ethyl acetate 1:1 Rf 0.26);
IR (CDCl3) Vmax (cm-1) 3569, 1772, 1751, 1600; 1H-NMR (300 MHz, CDCl3) 5.95(d), 5.85(d), 4.88(t), 4.24(m), 4.20(dd), 3.27(m), 3.25(d), 3.23(s), 2.1(m), 2.0(bs), 1.95-1.6(m), 1.5-1.20(m), 1.31(d), 1.21(s) from Intermediate A and [(1,1-dimethylethyl)carbonyloxy]methyl iodide.

Example 11

1-(2-Methoxy-2-methyl-propanoyloxy)methyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.$0^{3,8}$]undec-

2-ene-2-carboxylate was obtained as an oil (0.110 g; t.l.c. diethyl ether Rf 0.33);
IR (CDCl3) Vmax (cm-1) 3600, 1772, 1740, 1640; 1H-NMR (300 MHZ, CDCl3) 5.964(d+d), 4.904(m), 4.242(m), 4.203(dd), 3.984(dd), 3.33-3.22(m+dd), 3.292(s), 3.240(s), 2.1(m), 1.95-1.2(m), 1.441(s), 1.429(s), 1.315(s) from Intermediate A and (2-methoxy-2-methyl)propanoic acid chloromethylester.

Example 12

1-(Methyloxycarbonyloxy)-2-methylpropyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil, (0.040 g; t.l.c. cyclohexane, ethyl acetate 4:6 Rf 0.36);
IR (CDCl3) Vmax (cm-1) 1767, 1734, 1680; 1H-NMR (300 MHZ, CDCl3) 6.661(d), 6.636(d), 4.974(m), 4.936(m), 4.3-4.15(m), 3.824(s), 3.805(s), 3.262(s), 3.242(s), 3.32-3.18(m), 1.327(d), 1.306(d), 1.15-0.95(m), 2.4-1.2(m) from Intermediate A and (1-chloro-2-methyl)propylmethylcarbonate.

Example 13

1-(Acetyloxy)butyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate was obtained as an oil (0.050 g; t.l.c. cyclohexane, ethyl acetate 1:1 Rf 0.33);
IR (CDCl3) Vmax (cm-1) 1769, 1732, 1632; 1H-NMR (300 MHZ, CDCl3) 6.925(q), 4.948(m), 4.28-4.16(m), 3.3-3.2(m), 3.251(s), 3.243(s), 2.105(s), 2.069(s), 2.12-2.04(m), 1.94-1.74(m), 1.74-1.58(m), 1.54-1.349m), 1.318(d), 1.307(d), 0.962(t), 0.957(t) from Intermediate A and 1-bromobutyl acetate.

Example 14

1-[(4-ethylcyclohexyloxy)carbonyloxy]ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroethyl)-11-oxo-1-azatri cyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

To a solution of the Intermediate A (0.3 g) in N,N-dimethylformamide (5ml), tetra-n-butylammonium bromide (0.3 g) and the intermediate 4 (0.47 g) were added under nitrogen and stirring was continued for 16 h at 22°. The reaction mixture was diluted with

diethylether (15 ml), washed with saturated ammonium chloride (2x20 ml), brine (2x20 ml), dried and evaporated in vacuo. The oily residue was chromatographed on silica gel, using cyclohexane/ethyl acetate 7/3 as eluant, to obtain the title compound as a white foam (0.169 g; t.l.c. cyclohexane/ethyl acetate 1/1 Rf = 0.41; IR (CDCl3), Vmax (cm-1): 3640 (OH), 1761 (C=O), 1634 (C=C); 1H-NMR (300 MHz, CDCl3): 6.88 (m), 4.92 (m), 4.91 (m), 4.95-4.85 (m),4.54 (m), 4.28-4.18 (m), 4.18 (dd), 3.30-3.20 (m), 3.24 (s), 3.23 (s), 2.05 (m), 2.00-1.75 (m), 1.70-1.50 (m), 1.60 (m), 1.50-1.09 (m), 1.31 (d), 1.29 (d), 1.25-1.15 (m), 0.86 (m) ppm)

Example 15

(Cyclohexyloxycarbonyloxy)methyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate

To a solution of the Intermediate A (0.22 g) in N,N-dimethylformamide (6.5 ml), in presence of 3A molecular sieves, tetra-n-butylammonium bromide (0.222 g) and the intermediate 6 (0.191 g) were added. The resulting mixture was stirred at 22° for 5 hours, diluted with diethylether (50 ml), washed with water (30 ml), saturated ammonium chloride (2x30 ml), 5% aq sodium hydrogen carbonate (30 ml), brine (2x30 ml), water (30 ml) and dried. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel, using cyclohexane/ethyl acetate 100/0 to 65/35, to obtain the title compound as a white foam (0.1 g; t.l.c. cyclohexane/ethyl acetate 1/1 Rf=0.18; IR (CDCl3), Vmax (cm-1): 3614 (OH), 1772 (C=O β-lactam), 1717 (C=O ester), 1640 (C=C); 1H-NMR (300 MHz, CDCl3): 5.90 (dd), 4.93 (t), 4.67 (m), 4.30-4.20 (m), 4.20 (dd), 3.35-3.25 (m), 3.25 (s), 2.08 (m), 2.00-1.80 (m), 1.80-1.30 (m), 1.32 (d) ppm).

Example 16

1-[(1,1-dimethylethyl)carbonyloxy]-2-methylpropyl (4S,8S,9R,10S,12R)-4-methoxy -10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylate

To a solution of the Intermediate A (0.3 g) in N,N-dimethylformamide (5ml), tetra-n-butylammonium bromide (0.3 g) and the intermediate 5 (0.398 g) were added under nitrogen and stirring

was continued for 16 h at 22°. The reaction mixture was diluted with diethylether (15 ml), washed with saturated ammonium chloride (2x30 ml), brine (2x30 ml), dried, and evaporated in vacuo. The oily residue was chromatographed on silica gel, using cyclohexane/ethyl acetate 7/3 as eluant, to obtain the title compound as a colourless oil (0.057 g; t.l.c. cyclohexane/ethyl acetate 1/1 Rf = 0.45; IR (CDCl3), Vmax (cm-1): 3611 (NH), 1774 (C=O ß-lactam), 1747 (C=O ester), 1632 (C=C); 1H-NMR (300 MHz, CDCl3): 6.76 (d), 6.72 (d), 4.95 (t), 4.92 (t), 4.30-4.16 (m), 3.32-3.19 (m), 3.24 (s), 3.23 (s), 2.10 (m), 2.06 (m), 1.94-1.80 (m), 1.75-1.60 (m), 1.50-1.20 (m), 1.32 (d), 1.31 (d), 1.22 (s), 1.19 (s), 1.06-0.98 (d) ppm)

Example 17

1-(Cyclohexyloxycarbonyloxy)ethyl (4S,8S,9R,10S,12R)-4-methoxy-10-(1'-hydroxyethyl)-11-oxo-1-azatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate

To a solution of sodium (4S,8S,9R,12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo [7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (194mg) in dimethylformamide (8ml) triethylbenzylammonium chloride (146mg) and (1-chloroethyl)-cyclohexyl carbonate (0.142ml) were added at room temperature. THe resulting mixture was stirred at 60^{0} for 97min, diluted with diethyl ether (30ml) and washed with cold water (60ml). The aqueous layer was re-extracted with diethyl ether (30ml) and the combined organic phases were washed with brine (30ml) and dried over sodium sulphate. The organic layer was concentrated under reduced pressure and the resultant white foam (288mg) was crystallised from diethyl ether/petroleum to give the title compound (220mg) as a white solid.

Pharmacy Examples

Tablets

Example A

	mg/tab
Compound of Example 1	320
Lactose	150
Ethyl cellulose	20
Sodium lauryl sulphate	7
Magnesium stearate	3
Tablet core	500mg

The active ingredient and the lactose are blended together and then granulated using water as the granulating fluid. The dried granules are blended with the ethyl cellulose, sodium lauryl sulphate and magnesium stearate and the tablet core formed using an appropriate punch. The tablet may then be coated using conventional techniques and coatings.

Example B

	mg/tab
Compound of Example 1	320
Compressible sugar	170
Sodium lauryl sulphate	7
Magnesium stearate	3
Tablet core	500

The active ingredient and the excipients are blended together and then compressed using an appropriate punch. If required the tablet thus formed may be coated in a conventional manner.

Granules

Example C

	mg/unit dose
Compound of Example 1	320
Starch	100
Cellulose	40
Polymethacrylate	30
Sodium lauryl sulphate	7
Magnesium stearate	3
Flavouring agent	qs

Example D

	mg/unit dose
Compound of Example 1	320
Ethyl cellulose	140
Polymethacrylate	30
Sodium lauryl sulphate	7
Magnesium stearate	3
Flavouring agent	qs

Example E

	mg/unit dose
Compound of Example 1	320
Compressible sugar	140
Polymethacrylate	30
Sodium laurylsulphate	7
Magnesium & stearate	3
Flavouring agent	qs

A solution of the active ingredient in ethanol is sprayed into a suitable fluid bed granulator charged with the major excipients. The granules so formed are dried and screened. If desired the granules may then be coated with a suitable enteric coating and dried. The dried granules are then blended with the remaining excipients including any flavouring agent and coated, for example with an enteric coating. The granules thus obtained may be filled into capsules or the like for a single dose presentation or filled into bottles for subsequent preparation of a multi dose oral liquid presentation.

Activity Data

In conventionally conducted protection tests using mice, orally administered compounds of the invention exhibited very high activity against pathogenic bacteria, as illustrated in the following table, where compounds are compared with the known orally administrable broad spectrum antibiotic cefuroxime axetil:-

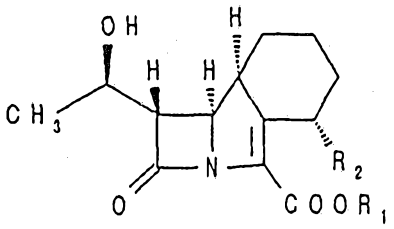
	ED_{50} (mg/kg)	
Compound	Staph. aureus	E. Coli
Example 1	<1	<1
Example 3	<1	<1
Example 10	<1	<1
Cefuroxime axetil	6	26

The compounds of the invention are also essentially non-toxic at therapeutically useful dose levels. For example, no adverse effects were observed when the compound of Example 1 was orally administered to mice at doses up to 1000 mg/kg.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

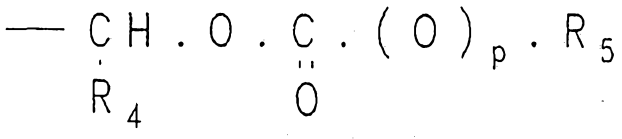
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Compounds of general formula (I)



(I)

in which R_1 represents the group



where R_4 represents a hydrogen atom or a C_{1-4} alkyl group; p is 0 or 1; R_5 is a group selected from C_{1-6} alkyl, C_{5-8} cycloalkyl optionally substituted by a C_{1-3} alkyl group, phenyl and C_{1-4} alkyl substituted by a C_{1-3} alkoxy group; and R_2 is a methoxy group.

2. Compounds as claimed in claim 1 wherein R_4 represents a hydrogen atom or a methyl group.

3. Compounds as claimed in claim 1 or claim 2 wherein R_5 represents a methyl, ethyl, isopropyl, t-butyl, 1-methoxy-1-methylethyl, phenyl, cyclohexyl or 4-ethylcyclohexyl group.

4. Compounds as claimed in claim 1 wherein R_4 represents a hydrogen atom or a methyl group and R_5 is a

group selected from C_{1-4} alkyl, C_{5-6} cycloalkyl optionally substituted by a C_{1-2} alkyl group, phenyl and C_{1-4} alkyl substituted by methoxy.

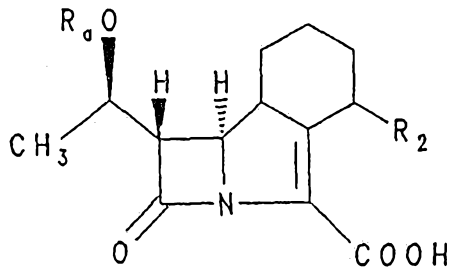
5. The pivaloyloxymethyl, 1-pivaloyloxyethyl, acetoxymethyl, 1-acetoxyethyl, 1-methoxy-1-methylethylcarbonyloxymethyl, 1-(1-methoxy-1-methylethylcarbonyloxy)ethyl, 1-benzoyloxyethyl, 1-isopropoxycarbonyloxyethyl, cyclohexyloxycarbonyloxymethyl and 1-(4-ethylcyclohexyloxycarbonyloxy)ethyl esters of (4S, 8S, 9R, 10S, 12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.$0^{3,8}$]undec-2-ene-2-carboxylic acid.

6. 1-Cyclohexyloxycarbonyloxethyl (4S, 8S, 9R, 10S, 12R)-4-methoxy-10-(1-hydroxyethyl)-11-oxo-1-azatricyclo[7.2.0.0.^{3,8}]undec-2-ene-2-carboxylate.

7. Pharmaceutical compositions comprising a compound as claimed in any one of claims 1 to 6 in admixture with one or more physiologically acceptable carriers or excipients.

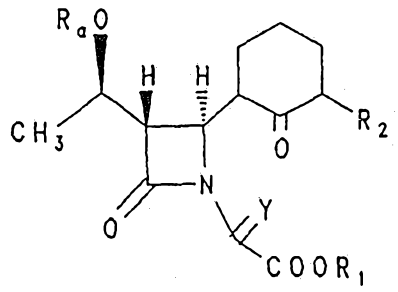
8. A method of treatment of a human or non-human body to combat bacterial infections comprising administration to said body of an effective amount of a compound as claimed in any one of claims 1 to 6.

9. A process for the preparation of compounds of general formula (I) as defined in claim 1 which comprises either (a) reacting a compound of general formula (II)



(II)

(where R_2 is as defined in claim 1 and R_a represents a hydrogen atom or a hydroxyl protecting group) or a salt or reactive derivative thereof with an esterifying agent serving to introduce a group R_1 as defined in claim 1, or (b) cyclising a compound of general formula (III)



(III)

(where R_1 and R_2 are as defined in claim 1, R_a is a hydroxyl protecting group and Y is an oxygen atom or a phosphine group), and thereafter, if necessary or desired, reacting the product to replace a hydroxyl protecting group R_a by a hydrogen atom and/or separating the desired isomer of formula (I) from one or more other isomers thereof.

10. Compounds of general formula (I), processes for their preparation, pharmaceutical compositions containing them or methods of treatment involving them, substantially as hereinbefore described with reference to the Examples.

DATED this 4th day of January, 1994
Glaxo SpA
By Its Patent Attorneys
DAVIES COLLISON CAVE

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01589

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 477/00, A 61 K 31/40

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D; A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP, A2, 0416953 (GLAXO S.P.A.) 13 March 1991, see the whole document --	1-11, 13
Y	DE, A, 2311328 (ASTRA LÄKEMEDEL AB) 18 October 1973, see particularly table 1, pages 9-32, the examples --	1-11
Y	EP, A2, 0422596 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 17 April 1991, see particularly examples 10-11, pages 35-37, example 29, page 51 and example 32, pages 52-53 --	1-11, 13

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5th November 1991	27 NOV 1991
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: MISS I. TAZELAAR

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	DE, A, 2811514 (BEECHAM GROUP LTD.) 21 September 1978, see particularl claims 1, 23, 40, 53, example 14, pages 87-89 and example 27, pages 129-133 --	1-11, 13
A	DE, A, 2311005 (ASTRA LÄKEMEDEL AB) 31 October 1973, see part. page 10-27 --	1-11

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1 [X] Claim numbers 12, because ~~they~~ it relate~~s~~ to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv). Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/EP 91/01589

SA 50401

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 27/09/91
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0416953	13/03/91	EP-A-	0416952	13/03/91
		AU-D-	6226590	14/03/91
DE-A- 2311328	18/10/73	AT-B-	329177	26/04/76
		AT-A-B-	330356	25/06/76
		AU-D-	5320873	12/09/74
		FR-A-	2201871	03/05/74
		GB-A-	1433131	22/04/76
		NL-A-	7303483	17/09/73
		US-A-	3931405	06/01/76
EP-A2- 0422596	17/04/91	AU-D-	6379290	18/04/91
DE-A- 2811514	21/09/78	FR-A-B-	2392996	29/12/78
		GB-A-	1604671	16/12/81
		JP-A-	53119886	19/10/78
		US-A-	4350703	21/09/82
		US-A-	4405637	20/09/83
		US-A-	4431587	14/02/84
		US-A-	4401595	30/08/83
DE-A- 2311005	31/10/73	AT-B-	330955	26/07/76
		AU-D-	5321073	12/09/74
		FR-A-B-	2181813	07/12/73
		GB-A-	1425571	18/02/76
		JP-A-	49024988	05/03/74
		NL-A-	7303484	17/09/73