OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

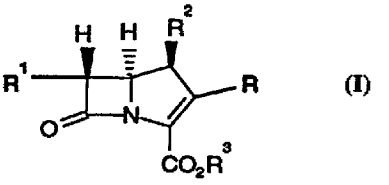
(12) (19) (CA) **Demande-Application**

(21) (A1) **2,217,885**
(86) 1996/05/02
(87) 1996/11/07

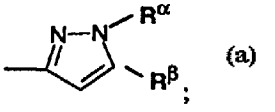
(72) BURTON, George, GB
(72) FELL, Stephen Christopher Martin, GB
(72) EGLINGTON, Alfred John, GB
(72) MOSS, Stephen Frederick, GB
(71) SMITHKLINE BEECHAM PLC, GB

(51) Int.Cl.[6] C07D 477/14, C07F 7/10, A61K 31/415, A61K 31/695
(30) 1995/05/03 (9508960.3) GB
(30) 1995/05/03 (9508964.5) GB
(30) 1995/05/03 (9508959.5) GB

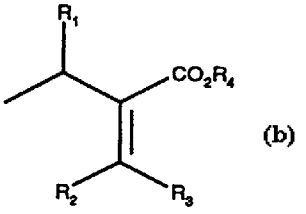
(54) **ESTERS DE CARBAPENEMES**
(54) **ESTERS OF CARBAPENEMS**



(I)



(a)



(b)

(57) L'invention porte sur un composé s'avérant utile pour le traitement d'affections bactériennes de formule générale (I) dans laquelle R est (a) et où R.alpha. est hydrogène, C_{1-6} alkyle facultativement substitué ou aryle facultativement substitué; R.beta. est hydrogène, C_{1-6} alkyle facultativement substitué ou aryle facultativement substitué; R.alpha. et R.beta. forment ensemble un noyau hétérocyclique à 5 ou 6 éléments avec ou sans hétéroatomes additionnels, R^1 est C_{1-6} alkyle substitué ou non par fluoro, un groupe hydroxy

(57) A compound of general formula (I) in which R is (a); wherein R.alpha. is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl; R.beta. is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl; or R.alpha. and R.beta. together form an optionally substituted 5 or 6 membered heterocyclic ring with or without additional heteroatoms; R^1 is (C_{1-6})alkyl which is unsubstituted or substituted by fluoro, a hydroxy group which is optionally protected by a readily removable hydroxy protecting group, or by

OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(21) (A1) **2,217,885**
(86) 1996/05/02
(87) 1996/11/07

facultativement protégé par un groupe protecteur hydroxy facilement retirable ou un groupe amino facultativement protégé par un groupe protecteur amino facilement retirable, R^2 est hydrogène ou méthyle et R^3 est sélectionné:(a) dans un groupe de formule (i) où R_1 est hydrogène ou C_{1-6} alkyle, R_2 est hydrogène, C_{1-6} alkyle facultativement substitué par halogène, C_{1-6} alcényle, C_{1-6} alkoxycarbonyle, aryle ou hétéroaryle, R_3 est hydrogène, C_{1-6} alkyle, C_{1-6} alkoxycarbonyle; et R_4 est un groupe ester pharmacocompatible, et (b): un groupe $CH(R^a)O.CO.R^b$ dans lequel R^a est hydrogène, C_{1-6} alkyle, C_{3-7} cycloalkyle, méthyle ou phényle; et R^b est C_{1-6} alkyle, C_{3-7} cycloalkyloxy ou C_{1-6} alkoxy C_{1-6} alkyle.

an amino group which is optionally protected by a readily removable amino protecting group; R^2 is hydrogen or methyl; and R^3 is selected from the group consisting of (a) a group of formula (i) wherein R_1 is hydrogen or (C_{1-6})alkyl, R_2 is hydrogen, (C_{1-6})alkyl optionally substituted by halogen, (C_{1-6})alkenyl, (C_{1-6})alkoxycarbonyl, aryl, or heteroaryl, R_3 is hydrogen, (C_{1-6})alkyl, or (C_{1-6})alkoxycarbonyl, and R_4 is a pharmaceutically acceptable ester forming group, and (b) a group of formula $CH(R^a)O.CO.R^b$, wherein R^a is hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, methyl, or phenyl; and R^b is (C_{1-6})alkyl(C_{3-7})cycloalkyloxy or (C_{1-6})alkoxy(C_{1-6})alkyl, is useful in the treatment of bacterial infections.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 477/14, 477/08, A61K 31/415 — A1

(11) International Publication Number: WO 96/34869

(43) International Publication Date: 7 November 1996 (07.11.96)

(21) International Application Number: PCT/EP96/01882

(22) International Filing Date: 2 May 1996 (02.05.96)

(30) Priority Data:

9508959.5	3 May 1995 (03.05.95)	GB
9508964.5	3 May 1995 (03.05.95)	GB
9508960.3	3 May 1995 (03.05.95)	GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BURTON, George [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB). FELL, Stephen, Christopher, Martin [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB). EGLINGTON, Alfred, John [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB). MOSS, Stephen, Frederick [GB/GB]; SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ (GB).

(74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

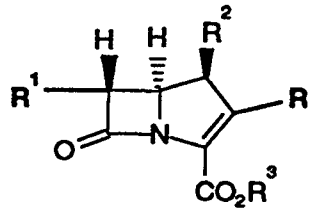
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

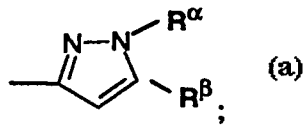
(54) Title: ESTERS OF CARBAPENEMS

(57) Abstract

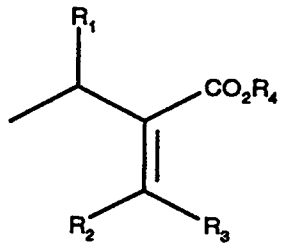
A compound of general formula (I) in which R is (a); wherein R_α is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl; R_β is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl; or R_α and R_β together form an optionally substituted 5 or 6 membered heterocyclic ring with or without additional heteroatoms; R^1 is (C_{1-6})alkyl which is unsubstituted or substituted by fluoro, a hydroxy group which is optionally protected by a readily removable hydroxy protecting group, or by an amino group which is optionally protected by a readily removable amino protecting group; R^2 is hydrogen or methyl; and R^3 is selected from the group consisting of (a) a group of formula (i) wherein R_1 is hydrogen or (C_{1-6})alkyl, R_2 is hydrogen, (C_{1-6})alkyl optionally substituted by halogen, (C_{1-6})alkenyl, (C_{1-6})alkoxycarbonyl, aryl, or heteroaryl, R_3 is hydrogen, (C_{1-6})alkyl, or (C_{1-6})alkoxycarbonyl, and R_4 is a pharmaceutically acceptable ester forming group, and (b) a group of formula $CH(R^a)O.CO.R^b$, wherein R^a is hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, methyl, or phenyl; and R^b is (C_{1-6})alkyl(C_{3-7})cycloalkyloxy or (C_{1-6})alkoxy(C_{1-6})alkyl, is useful in the treatment of bacterial infections.



(I)



(a)



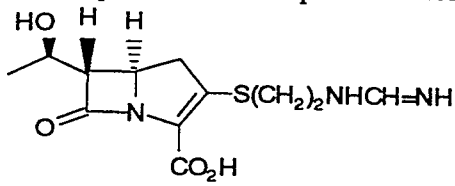
(b)

WO 96/34869 PCT/EP96/01882

ESTERS OF CARBAPENEMS

This invention relates to a class of antibacterial compounds, in particular a class of carbapenems, processes for their preparation, pharmaceutical and veterinary compositions comprising such compounds, intermediates thereof, and their use in antibacterial therapy.

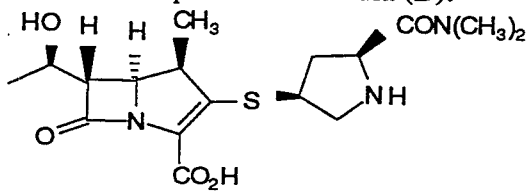
Carbapenems such as imipenem, the compound of formula (A):



(A)

have a potent, broad spectrum of antibacterial activity (see US 3 950 357 and US 4 194 047; Merck and Co). Such carbapenems however tend to be vulnerable to hydrolysis by the enzyme renal dehydropeptidase-1 (DHP-1) and this limits their use in chemotherapy. In the case of imipenem, this problem may be overcome by the co-administration of an inhibitor of DHP-1.

Stability towards DHP-1 may also be imparted by chemical modification of the carbapenem nucleus, for instance by incorporating a 1β-methyl substitutent, as in the compound meropenem, the compound of formula (B):



(B)

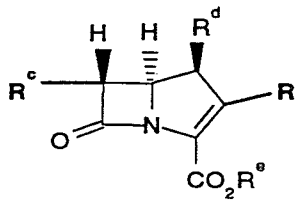
(see Shih D.H. *et al.*, Heterocycles, 1984, **21**, 29 and Sunagawa M. *et al.*, J. Antibiotics, 1990, **43**, 519). More recently, this has been extended to a 1β-aminoalkyl substituent (see EP 0 433 759, Bristol-Meyers Squibb).

An alternative approach to imparting improved stability to DHP-1 utilises 2-carbon substituted carbapenems, for instance, 2-aryl, 2-heteroaryl and 2-heteroaromatic carbapenems (US 4 543 257, US 4 260 627, US 4 962 101, US 4 978 659, EP 0 14 493, EP 0 414 489, EP 0 010 316 and EP 0 030 032 Merck & Co) and 2-(substituted)methyl carbapenems (Schmidt *et al*, J.Antibiotics, **41**, 1988, 780).

UK Patent 1 593 524, Merck & Co. discloses a number of 5-membered heteroaromatic carbapenem derivatives including diazolyl and tetrazolyl compounds. However, in the case of the pyrazolyl derivatives the heterocyclic compound is attached to the carbapenem nucleus through the C-4 position.

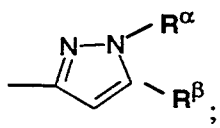
Other structural modifications introduced at position-2 include a substituted vinyl group $-C(R_a)=CHR_b$ in which, for instance, R_a is hydrogen or methyl and R_b is hydrogen or lower alkyl (EP 0 330 108; Fujisawa) or R_a and R_b are selected from hydrogen, lower alkyl, aminocarbonyl, lower alkoxy, cyano, nitro and lower alkoxycarbonyl (EP 0 430 037, Banyu Pharmaceutical Co.). In the absence of a 1β-methyl substituent, such a modification does not however appear to impart DHP-1 stability.

International Patent Application No. PCT/GB94/02347 describes compounds of the general formula (C):



(C)

in which R is:



;

wherein

R^α is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl;

R^β is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl; or

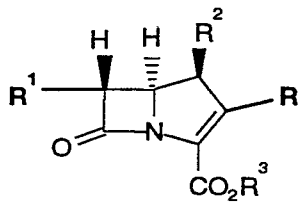
R^α and R^β together form an optionally substituted 5 or 6 membered heterocyclic ring with or without additional heteroatoms;

R^c is (C_{1-6})alkyl which is unsubstituted or substituted by fluoro, a hydroxy group which is optionally protected by a readily removable hydroxy protecting group, or by an amino group which is optionally protected by a readily removable amino protecting group;

R^d is hydrogen or methyl; and

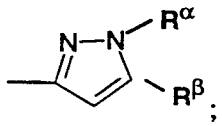
$-CO_2R^e$ is carboxy or a carboxylate anion or the group R^e is a readily removable carboxy protecting group.

The present invention provides a compound of the general formula (I):



(I)

in which R is:



wherein

R^{α} is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl;

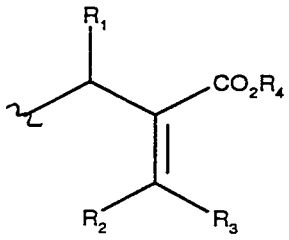
R^{β} is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl; or

R^{α} and R^{β} together form an optionally substituted 5 or 6 membered heterocyclic ring with or without additional heteroatoms;

R^1 is (C_{1-6})alkyl which is unsubstituted or substituted by fluoro, a hydroxy group which is optionally protected by a readily removable hydroxy protecting group, or by an amino group which is optionally protected by a readily removable amino protecting group;

R^2 is hydrogen or methyl; and

R^3 is selected from the group consisting of (a) a group of formula:



wherein;

R_1 is hydrogen or (C_{1-6})alkyl,

R_2 is hydrogen, (C_{1-6})alkyl optionally substituted by halogen, (C_{1-6})alkenyl, (C_{1-6})alkoxycarbonyl, aryl, or heteroaryl,

R_3 is hydrogen, (C_{1-6})alkyl, or (C_{1-6})alkoxycarbonyl, and

R_4 is a pharmaceutically acceptable ester forming group, and (b) a group of formula $CH(R^a)O.CO.R^b$, wherein R^a is hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, methyl, or phenyl; and R^b is (C_{1-6})alkyl(C_{3-7})cycloalkyloxy or (C_{1-6})alkoxy(C_{1-6})alkyl.

Compounds of formula (I) have a broad spectrum of anti-bacterial activity and show good stability towards DHP-1.

Suitable (C_{1-6}) alkyl groups for R^α and R^β include straight and branched chain alkyl groups having from 1 to 6 carbon atoms, for instance methyl, ethyl, *n*-propyl and *iso*-propyl, preferably ethyl and methyl.

Representative examples of R^α and R^β as (C_{1-6})alkyl are when both are methyl or ethyl. A particularly preferred example is when R^α is ethyl and R^β is methyl .

Suitable optional substituents for the (C_{1-6}) alkyl group for R^α and R^β include, for example, halogen, hydroxy, (C_{1-6})alkoxy, carboxy and salt thereof, (C_{1-6})alkoxycarbonyl, carbamoyl, mono- or di(C_{1-6})alkylcarbamoyl, sulphamoyl, mono- and di(C_{1-6})alkylsulphamoyl, amino, mono- and di(C_{1-6})alkylamino, (C_{1-6})acylamino, ureido, (C_{1-6})alkoxycarbonylamino, aminocarbonyloxy and mono- and di(C_{1-6})alkylaminocarbonyloxy, 2,2,2-trichloroethoxycarbonylamino, aryl, heterocyclyl, oxo, acyl, heteroaryl, (C_{1-6})alkylthio, arylthio,heterocyclythio, (C_{1-6})alkane-sulphinyl, arylsulphinyl, (C_{1-6})alkanesulphonyl, arylsulphonyl, (C_{1-6})alkoxyimino, hydroxyimino, hydrazono, benzohydroxyimoyl, and 2-thiophene-carbohydroxyimoyl. Preferred substituents include carbamoyl, aryl, especially phenyl, and heteroaryl.

Suitable (C_{1-6}) alkyl groups for R^1 include straight and branched chain alkyl groups having from 1 to 6 carbon atoms. Preferred alkyl groups include methyl, ethyl, *iso*-propyl, of which ethyl is especially preferred.

Preferably the (C_{1-6}) alkyl group of R^1 has a hydroxy, fluoro or amino substituent which is suitably at position-1 of the alkyl group. Advantageously R^1 is (**R**)-1-hydroxyethyl.

Suitably R^2 is hydrogen.

When used herein, the term "aryl" includes phenyl and naphthyl.

Suitably an aryl group, including phenyl and naphthyl, may be optionally substituted by up to five, preferably up to three, substituents.

A representative example of R^α or R^β being an aryl group is phenyl.

Suitable optional substituents for the aryl group include halogen, (C_{1-6})alkyl, aryl(C_{1-4})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, amino, mono- and di-*N*-(C_{1-6})alkylamino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-*N*-(C_{1-6})alkylcarbamoyl, (C_{1-6})alkoxycarbonyl, (C_{1-6}) alkoxycarboxylate, aryloxycarbonyl,

(C_{1-6})alkoxycarbonyl-(C_{1-6})alkyl aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkyl sulphinyl (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl (C_{1-4})alkyl. In addition, two adjacent ring carbon atoms may be linked by a (C_{3-5})alkylene chain, to form a carbocyclic ring.

When used herein, the term "heteroatom" includes one or more of the elements oxygen, nitrogen and sulphur.

When used herein, the term "heteroaryl" includes aromatic single and fused rings containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three substituents. Each heteroaryl ring suitably has 5 or 6 ring atoms. A fused heteroaryl ring may include carbocyclic rings and need include only one heteroaryl ring.

When used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings ,may be unsubstituted or substituted by, for example, up to three substituents. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

Preferably a substituent for a heteroaryl or a heterocyclyl group is selected from halogen, (C_{1-6})alkyl, aryl(C_{1-4})alkyl(C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl,hydroxy, amino, mono- and di-*N*-(C_{1-6})alkyl-amino, acylamino,carboxy salts,carboxy esters, carbamoyl, mono- and di-*N*-(C_{1-6})alkylcarbonyl, (C1-6) alkoxycarboxylate, aryloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl(C_{1-4})alkyl.

Suitable hydroxy and amino protecting groups for use in R^1 are those well known in the art and which may be removed under conventional conditions and without disrupting the remainder of the molecule. A comprehensive discussion of the ways in which hydroxy and amino groups may be protected and methods for cleaving the resulting protected derivatives is given in for example "Protective Groups in Organic Chemistry" (T.W. Greene, Wiley-Interscience, New York, 2nd edition, 1991). Particularly suitable hydroxy protecting groups include, for example, triorganosilyl groups such as, for instance, trialkylsilyl and also organooxycarbonyl groups such, as for instance, allyloxycarbonyl, trichloroethyloxycarbonyl, 4-methoxybenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl. Particularly suitable

amino protecting groups include alkoxycarbonyl, 4-methoxybenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl.

Since the carbapenem compounds of the present invention are intended for use in pharmaceutical compositions, it will be further understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be present in the crystalline product. This invention includes within its scope stoichiometric hydrates.

The carbapenem antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, according to techniques and procedures *per se* known in the art with reference to other antibiotics, and the invention therefore includes within its scope a pharmaceutical composition comprising an antibiotic compound according to the present invention , together with a pharmaceutically acceptable carrier or excipient. The compositions may be formulated for administration by any suitable route, such as oral, parenteral or topical application, although the oral route is preferred. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form and may contain conventional excipients such as binding agents, for example, syrup acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan

monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters, glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid; and, if desired conventional flavouring or colouring agents. Suppositories will contain conventional suppository base, eg cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, agents such as local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99.5% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 mg to 12 g per day for an average adult patient (body weight 70 kg), for instance 1500 mg per day, depending on the route and frequency of administration. Such dosages correspond to approximately 1.5 to 170 mg/kg per day. Suitably the dosage is from 1 to 6g per day.

The daily dosage is suitably given by administering a compound of the invention several times in a 24-hour period. Typically, 250 mg is administered 4 times a day although, in practice, the dosage and frequency of administration which will be most suitable for an individual patient will vary with the age, weight and response of the patients, and there will be occasions when the physician will choose a higher or lower dosage and a different frequency of administration. Such dosage regimens are within the scope of this invention.

No toxicological effects are indicated when a compound of the invention is administered in the above mentioned dosage range.

The present invention also includes a method of treating bacterial infections in humans and animals which method comprises administering a therapeutically effective amount of an antibiotic compound of the present invention.

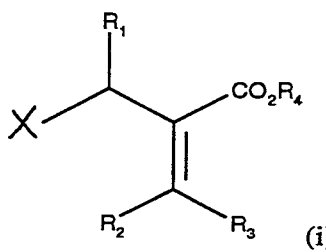
In a further aspect, the present invention also provides for the use of a compound of formula (I) for the manufacture of a medicament for treating bacterial infection.

The compounds of the present invention are active against a broad range of Gram-positive and Gram-negative bacteria, and may be used to treat a wide range of bacterial infections including those in immunocompromised patients.

Amongst many other uses, the compounds of the invention are of value in the treatment of skin, soft tissue, respiratory tract and urinary tract infections in humans and may also be used to treat mastitis in cattle.

A particular advantage of the antibacterially active compounds of this invention is their stability to β-lactamase enzymes and they are therefore effective against β-lactamase producing organisms.

The present invention further provides a process for the preparation of a compound of formula (I) which process comprises treating a corresponding compound of formula (I), wherein R is an alkali metal cation, with a compound of formula (i) or (ii):



(i)

$XCH(R^a)O.CO.R^b$ (ii)

wherein X is a leaving group such as halogen, more particularly bromine or iodine.

The reaction is typically carried out at between 0 and 60 C, for example at ambient temperature, under an inert, for example argon, atmosphere, in a suitable organic solvent , for example, N-methylpyrrolidin-2-one. Other suitable solvent systems include N, N'-dimethylformamide and N, N'-dimethylacetamide.

Compounds of formula (i) can be prepared as described by F. Ameer et al, *J. Chem. Soc.*, (1983), 2293.

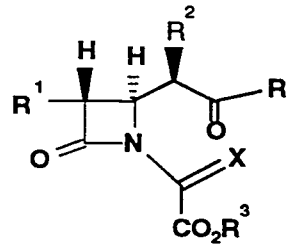
Compounds of formula $ICH(R^a)O.CO.R^b$ can be prepared from the corresponding chloride *via* the Finkelstein reaction, which is well known to those skilled in the art.

Compounds of formula $ClCH(R^a)O.CO.R^b$ can be prepared by esterifying an acid of formula R^bCOOH with chloromethyl chlorosulphate (Binderup et al.,

Synthetic Commun., 14(9), 857-864 (1984)), or by treating a compound of formula $ClCH(R^a)OCOCl$ with a compound of formula HR^b in dichloromethane/pyridine (Yoshimura et al., *J. Antibiot.*, 1987, **40(1)**, 81-90).

Compounds of formula (I) wherein R is an alkali metal cation,, such as sodium, are described in International Patent Application No. PCT/GB94/02347, and hereinbelow in Preparation 1.

A further process for the preparation of a compound of formula (I) comprises subjecting a compound of formula (II):



(II)

in which R, R^1 and R^2 are as hereinbefore defined,
R^3 is a readily removable carboxy protecting group,
X is oxygen or a group $PR^4R^5R^6$,
R^4, R^5 and R^6 may be the same or different and is each an optionally substituted (C_{1-6})alkyl or an optionally substituted aryl group, preferably an *n*-butyl or a phenyl group;
to carbapenem ring forming conditions;
and thereafter, and if necessary, carrying out any or all of the following steps:
removing any protecting group(s);
converting a first group R^1 comprising a hydroxyl substituent into a further group R^1 comprising an amino or fluoro group;
converting the product into a salt; and
esterifying the product as set out above.

Suitable carbapenem ring forming conditions are well known in the art.

When X is oxygen, suitable ring forming conditions include treating the compound of formula (II) with a trivalent organic phosphorus compound of formula (III):

$$PR^7(OR^8)(OR^9) \qquad \text{(III)}$$

in which:
R^7 is (C_{1-4})alkyl, (C_{1-3})alkoxy or phenyl optionally substitued by (C_{1-3})alkyl; and R^8 and R^9 which may be the same or different is each (C_{1-4})alkyl, allyl, benzyl or phenyl optionally substitued by (C_{1-3})alkyl or (C_{1-3})alkoxy; by analogy with the process described in EP 0 476 649-A (Hoechst AG). Suitable reagents of formula (III) include trimethyl phosphite, triethyl phosphite, dimethyl methylphosphonite and

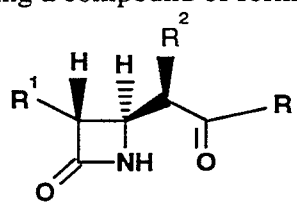
diethyl methylphosphonite. Suitably, the reaction is effected in an organic solvent such as tetrahydrofuran, ethyl acetate, an aromatic solvent such as benzene, toluene, xylene or mesitylene or a halogenated hydrocarbon solvent such as dichloromethane, trichloromethane or 1,1,2-trichloroethane, and at a temperature between 50 and 180° C, preferably between 70 and 165°C.

When X is a group $PR^4R^5R^6$, compounds of formula (I) may be obtained by the well known Wittig cyclisation route to carbapenems (Guthikonda *et al*, J. Med. Chem., 1987, **30**, 871). For instance, when R^4, R^5 and R^6 is each phenyl, the process comprises the ring closing elimination of the elements of triphenylphosphine oxide. The ring closure may be suitably effected by heating the compound of formula (II, X = $PR^4R^5R^6$) at a temperature which is preferably in the range 40 to 145°C, more preferably 80 to 140°C, in an inert solvent such as benzene, toluene or xylene, preferably under dry conditions and under an inert atmosphere and optionally in the presence of a radical scavanger such as hydroquinone. When R^4, R^5 and R^6 is each *n*-butyl, cyclisation may be effected at a lower temperature, for instance above 50°C, by analogy with the process described in WO 92/01695 (Beecham Group, for analogous penems).

In the substituent R^1, a hydroxyl or an amino group, if present, may optionally be protected. Suitable hydroxy protecting groups include organosilyl, for instance a trialkylsilyl group such as trimethylsilyl or t-butyl dimethylsilyl, or trichloroethyloxycarbonyl, 4-nitrobenzyloxy-carbonyl, 4-methoxybenzyloxy carbonyl and allyloxycarbonyl. Suitable amino protecting groups include alloxycarbonyl, 4-methoxybenzyloxy carbonyl and 4-nitrobenzyloxycarbonyl.

Suitable values for the protecting group R^3 include allyl, 4-methoxybenzyl and 4-nitrobenzyl. The conditions necessary for removing the protecting group will, of course, depend upon the precise nature of the protecting group. For instance, when R^3 is 4-methoxybenzyl, aluminium trichloride and anisole in dichloromethane at -30 to -70°C may be used, when R^3 is allyl (prop-2-en-1-yl), a combination of triphenylphosphine, sodium-2-ethylhexanoate in ethyl acetate/MDC and *tetrakis*-(triphenylphosphine)palladium (0) may be used and when R3 is p-nitrobenzyl hydrogenation in the presence of palladium on a carbon catalyst in aqueous solvent eg, aqueous 1,4,dioxan THF ethanol may be used.

Compounds of formula (II) in which X is oxygen may be obtained by a process which comprises reacting a compound of formula (IV):



(IV)

in which R, R^1 and R^2 are as hereinbefore defined, with a compound of formula (V):

$$ClCOCO_2R^3 \quad (V)$$

in which R^3 is a readily removable carboxy protecting group;
under acylating conditions, by analogy with the process described in Tetrahedron Letters, **25**, 1984, 2395.

Compounds of formula (II) in which X is a group $PR^4R^5R^6$ may be obtained from a compound of formula (IV) as hereinbefore defined by the following sequence of steps:

(a) reacting with a suitably protected glyoxylic acid derivative of formula (VI) or a functional equivalent thereof such as the hydrate;

$$(OHC)CO_2R^3 \quad (VI)$$

in which R^3 is a readily removable carboxy protecting group; under dehydrating conditions, for instance azeotropic removal of water;

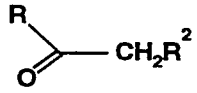
(b) treating the intermediate formed in step (a) with a halogenating agent, for instance thionyl chloride, in the presence of a suitable base such as 2,6-lutidine; and

(c) treating the intermediate formed in step (b) with a phosphorus reagent of the formula (VII):

$$PR^4R^5R^6 \quad (VII)$$

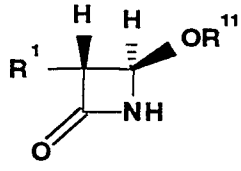
in which R^4, R^5 and R^6 are as hereinbefore defined, in the presence of a suitable base such as 2,6-lutidine.

Compounds of formula (IV) may be prepared by treating a compound of formula (VIII):



(VIII)

in which R and R^2 are as hereinbefore defined;
with a compound of formula (IX)

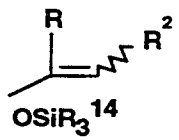


(IX)

in which R^1 is as hereinbefore defined, and

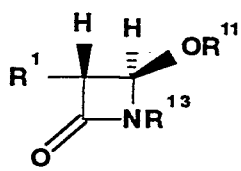
R^{11} is an acyl group, for instance acetyl;
in the presence of a base, such as, for instance, lithium hexamethyldisilazide (LHMDS);
according to the procedures described in Tetrahedron Lett., 1987, **28**, 507, and Can. J. Chem, 1988, **66**, 1537.

Compounds of formula (IV) may also be prepared by treating a compound of formula (VIIIa):



(VIIIa)

in which R and R^2 are as hereinbefore defined and $SiR_3{}^{14}$ is a trialkylsilyl such as trimethylsilyl or t-butyldimethylsilyl,
with a compound of formula (IXa):



(IXa)

in which R^1 and R^{11} are as hereinbefore defined and
R^{13} is either hydrogen or an aminoprotecting group, for instance, a trialkylsilyl group such as trimethylsilyl;
in the presence of a Lewis acid, such as, for instance, zinc chloride or trimethylsilyl trifluoromethane sulphonate, in an inert organic solvent such a halogenated hydrocarbon solvent, for instance dichloromethane at ambient temperature:
Compounds of formula (VIIIa) may be prepared by treating compounds of formula (VIII) with trialkylsilyl chloride or trialkylsilyl triflate, and triethylamine in MDC.

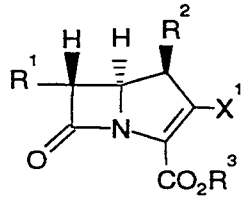
If the aminoprotecting group R^{13} in (IXa) requires subsequent removal, this may be achieved by conventional means, such as mild acid treatment eg, methanol and hydrochloric acid or pyridinium p-toluenesulphonate, where R^{13} is trimethylsilyl.

Compounds of formula (VIII) are well known to those skilled in the art and may be obtained by standard synthetic procedures as described in the following Examples.

Compounds of formula (IX) are well known to those skilled in the art and may be obtained by standard synthetic procedures such as described in, for example, Het., 1982, **17**, 201 (IX, R^1 is 1-hydroxyethyl) and EP 0 234 484 (IX, R^1 is 1-fluoroethyl).

Compounds of formula (I) in which R^1 is an amino-substituted alkyl or cycloalkyl may be conveniently prepared from a corresponding compound of formula (I) in which R^1 includes a hydroxy group by a Mitsunobu-type azide displacement of the hydroxy group thereof, followed by catalytic reduction, according to the procedure described in J Chem Soc, Perkin I, 1982, 3011.

Compounds of formula (I) may also be prepared by a process which comprises reacting a compound of formula (X):



(X)

in which R^1 and R^2 are as hereinbefore defined, R^3 is a readily removable carboxy protecting group and X^1 is a leaving group,
with a compound of formula (XI):

M-R (XI)

in which M is a metallo group and R is as hereinbefore defined;
in a cross-coupling reaction in the presence of a cross-coupling reaction catalyst selected according to the identity of M and thereafter and if necessary removing any protecting group and/or converting the product into a salt and/or esterifying the product as set out hereinabove.

Suitable values for the protecting group R^3 include 4-methoxybenzyl 4-nitrobenzyl.

Examples of suitable leaving groups X^1 include for instance trifluoromethanesulphonyloxy, methanesulphonyloxy, 4-toluene sulphonyloxy, fluorosulphonyloxy, chloro, bromo, iodo and diphenoxyphosphoryloxy.

Suitable metals for use in the metallo group M are well known in the art and include tin, aluminium, zinc, boron, mercury and zirconium.

Preferred examples of the metallo group M include for instance $R^{14}R^{15}R^{16}Sn$, $B(OR)_2$ and ZnCl in which R^{14}, R^{15} and R^{16} may the same or different and are each (C_{1-6}) alkyl. Preferably, the metallo group M is an organostannane $R^{14}R^{15}R^{16}Sn$, and R^{14}=R^{15}=R^{16}= methyl or n-butyl.

Suitable cross-coupling catalysts are well known in the art and include palladium compounds, in particular palladium (0) and palladium (II) compounds, such as those described in "Palladium Reagents in Organic Synthesis", RF Heck, Academic Press Ltd, 1985. Examples thereof include *tris*(dibenzylideneacetone)dipalladium (0), *tetrakis*(triphenylphosphine)palladium (0), *trans* dimethyl *bis*(triphenylphosphine)palladium (II), and palladium (II) acetate, benzyl *bis*(triphenylphosphine)palladium (II) chloride, *bis*(triphenylphosphine)palladium (II) dichloride. Such palladium reagents are preferably used in combination with a halide source such as zinc chloride or lithum chloride and optionally in the presence of a phosphine ligand of palladium, for instance a compound such as a triarylphosphine, for example, *tris*(4-methoxyphenyl)phosphine or *tris*(2,4,6-trimethoxyphenyl) phosphine; a tri-heteroarylphosphine, for example, trifurylphosphine, or a triarylarsine, for example triphenylarsine.

When M is an organostannane R^{14} R^{15} R^{16} Sn-, a preferred catalyst system is *tris*(dibenzylideneacetone)dipalladium (0), in the presence of zinc chloride and a phosphine compound. When M is ZnCl a preferred catalyst is *tris*(dibenzylideneacetone dipalladium (0), in the presence of a phosphine compound.

Suitably the reaction is effected in an inert aprotic polar coordinating solvent such as tetrahydrofuran, diethylether, dioxane, 2-dimethoxyethane, acetonitrile, dimethyl formamide, dimethyl sulphoxide and the like, and under a dry, inert atmosphere such as argon. Suitably, the reaction is effected initially at a low temperature, for instance about -78°C, with the final phase of the reaction then being effected at ambient temperature.

Analogous procedures in which M is organostannane are described in EP 0 444 889 (Merck & Co.) and EP 0 430 037 (Banyu Pharmaceutical Co.).

Compounds of formula (X) are well known in the art and may be obtained according to the procedures described in EP 0 444 889 (Merck & Co.), EP 0 430 037 (Banyu Pharmaceutical Co.) and by Rano *et al,* Tet. Letters, 1990, **31**, 2853.

Compounds of formula (XI) are well known in the art and may be obtained according to the procedure described in Heterocycles, 1992, **33(2)**, 813.

The following Examples illustrate the invention but are not intended to limit the scope in any way.

General Instructions - Solutions were dried using anhydrous magnesium sulphate and solvents were removed by evaporation under reduced pressure using a rotary evaporator. Column chromatography on silica gel used Merck silica gel 60, particle size <0.063mm.

Example 1

2-Ethoxycarbonyl-*E*-but-2-enyl (5*R*,6*S*)-2-(1-Ethyl-5-methyl-1,2-pyrazol-5-yl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate

Sodium (5*R*,6*S*)-2-(1-ethyl-5-methyl-1,2-pyrazol-5-yl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (200mg) in *N*-methylpyrrolidinone (2ml) at room temperature under argon was treated with a solution of ethyl *E*-2-bromomethylbut-2-enoate [F. Ameer et al, *J. Chem. Soc.*, (1983), 2293], (253mg) in *N*-methylpyrrolidinone (1ml).

After 2h the solution was diluted with ethyl acetate, washed with water (3x), dried over anhydrous magnesium sulphate and concentrated. The product was purified by flash silica gel chromatography eluting with 50% ethyl acetate/hexane, then ethyl acetate to give the *title compound* as a pale yellow foam, (153mg, 58%); (Found: M^+, 431.2065, $C_{22}H_{29}N_3O_6$ requires M 431.2056); n_{max} (CH_2Cl_2) 3605(w), 1774, 1712 cm^{-1}; d_H($CDCl_3$) 1.24-1.41 (9H, m), 1.82 (1H, d, *J*4.9Hz), 1.98 (3H, d, *J*7.3Hz), 2.28 (3H, s), 3.16 (1h, dd, *J*2.8,6.6Hz), 3.27 (1H, dd, *J*9.0,18.5Hz), 3.57 (1H, dd, *J*9.9,18.5Hz), 4.07 (2H, q, *J*7.3Hz), 4.17-4.29 (3H, m), 5.03 and 5.11 (2H ABq, *J*11.9Hz), 6.94 (1H, s) and 7.21 (1h, q, *J*7.3Hz).

Example 2

1-Methylcyclohexyloxycarbonyloxymethyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methyl-pyrazol-3-yl)carbapen-2-em-3-carboxylate

(a) Iodomethyl 1-methylcyclohexyl carbonate

1-Methylcyclohexanol (4.57 g) in dichloromethane (40 ml) was cooled in an ice-bath and treated with pyridine (3.24 ml). Chloromethyl chloroformate (3.65 ml) in dichloromethane (10 ml) was added dropwise through a pressure-equalising funnel. The mixture was stirred for 2 h and then washed with water (2 x), dried ($MgSO_4$) and then evaporated to leave a reddish-coloured oil, which was dissolved in dichloromethane and filtered through silica gel (230 - 400 mesh ASTM) to give (after evaporation) chloromethyl 1-methylcyclohexyl carbonate as a colourless oil (8.97 g), υ_{max}(CH_2Cl_2) 2940, 2865, 1763, 1444, 1346, 1292, and 1237 cm^{-1}; δ($CDCl_3$) 1.25 - 1.70 (11H, m), 2.12 -2.18 (2H, m), 5.69 (2H,s) ppm.

Chloromethyl 1-methylcyclohexyl carbonate (2.07 g) in acetone (7.5 ml) was treated with 2,6-lutidine (0.116 ml). Sodium iodide (2.25 g) was then added and the mixture was stirred for 1.5 h. More sodium iodide (1.5 g) was then added and stirring was

continued. After a total of 2.5 h the acetone was removed and CH_2Cl_2 / water were added and the layers separated. The dichloromethane layer was washed with 5% aqueous $Na_2S_2O_3$, dried ($MgSO_4$) and evaporated to leave an oil. This was taken up in hexane (50 ml) and loaded onto a silica gel column, and the column was eluted with 5% ethyl acetate in hexane to give iodomethyl 1-methylcyclohexyl carbonate containing some of the starting chloromethyl compound, $\delta(CDCl_3)$ 1.26 - 1.35 (2H, m), 1.40 - 1.65 (9H, m, including s at δ 1.52), 2.10 -2.20 (2H, m), 5.69 (s) and 5.91 (s) (together 2H, ratio 1 : 5) ppm.

(b) 1-Methylcyclohexyloxycarbonyloxymethyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methyl-pyrazol-3-yl)carbapen-2-em-3-carboxylate

Sodium (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate (200 mg) in *N*-methylpyrrolidinone (2 ml) containing 2,6-lutidine (0.07 ml) was treated with iodomethyl 1-methylcyclohexyl carbonate (363 mg) in tetrahydrofuran (0.5 ml). The mixture was stirred under argon for 20 min. Ethyl acetate (20 ml) was added and washed with water (3 x 25 ml), then with 5% $Na_2S_2O_3$ (20 ml), then with 0.05M HCl, followed by saturated brine. After drying ($MgSO_4$) the ethyl acetate was evaporated to leave a gum which was purified by chromatography on silica gel (230 - 400 mesh ASTM) (2.5 x 12 cm column), loading in CH_2Cl_2 / hexane, and eluting with ethyl acetate / hexane mixtures, followed by ethyl acetate. Fractions containing the product were combined and evaporated and then rechromatographed on silica gel (230 - 400 mesh ASTM) (2 x), eluting with acetone / hexane (1 : 1). Fractions containing the product were combined and evaporated. Hexane was added and evaporated to give 1-methylcyclohexyloxycarbonyloxymethyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate (187 mg) as a solid foam, $\upsilon_{max}(CH_2Cl_2)$ 3678, 3601, 2939, 1773, 1598, 1546, 1450, 1380, 1317, and 1241 cm^{-1}; λ_{max}(EtOH/nm 325 ($\varepsilon/dm^3mol^{-1}cm^{-1}$ 10,924), 213 ($\varepsilon/dm^3mol^{-1}cm^{-1}$ 9,391); $\delta(CDCl_3)$ 1.2 - 1.5 (14H, m, including d, *J* 6.4 at δ 1.35, t, *J* 7.3 Hz at δ 1.39 and s at δ 1.51), 1.93 (1H,d, *J* 4.7 Hz), 2.05 - 2.2 (2H, m), 2.28 (3H, s), 3.18 (1H, dd, *J* 2.7 & 6.5 Hz), 3.29 (1H, dd, *J* 9.1 & 18.7 Hz), 3.64 (1H, dd, *J* 9.9 & 18.8 Hz), 4.08 (2H, q, *J* 7.3 Hz), 4.15 - 4.30 (2H, m), 5.90 (2H, s), 7.05 (1H, s) ppm.

Example 3

2-Methoxyprop-2-ylcarbonyloxymethyl (5*R*,6*S*)-2-(1-ethyl-5-methylpyrazol-3-yl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate

The product from Preparation 1 (200 mg, 0.61 mmol) was dissolved in N-methylpyrrolidin-2-one (2 ml). A solution of 2-methoxyprop-2-ylcarbonyloxymethyl iodide (0.34 g, 1.3 mmol) in N-methylpyrrolidin-2-one (0.5 ml) was added to this solution at room temperature under argon and after 0.5 h the reaction mixture was diluted with ethyl acetate (15 ml) and the solution was washed with water (3 x 15 ml), 5% sodium thiosulfate solution (15 ml) and then saturated brine (15 ml). The organic extract was dried (Na_2SO_4) and concentrated to an oil which was purified by chromatography on silica gel eluting with an acetone/toluene gradient mixture to yield a pale yellow solid which was recrystallised from acetone/diethyl ether to afford the *title compound* as a colourless oil (0.23 g, 87%); (Found: M^+ 435.2007. $C_{21}H_{29}N_3O_7$ requires *M* 435.2006); ν_{max} ($CHCl_3$) 3612, 3016, 2981, 2937, 1771, 1734(sh), 1596 cm^{-1}; δ_H ($CDCl_3$) 1.38-1.45 (12H, m), 1.81 (1H, d, *J*4.9 Hz), 2.29 (3H, s), 3.18 (1H, dd, *J*2.8, 6.6 Hz), 3.30 (1H, dd, *J*9.1, 18.8 Hz), 3.64 (1H, dd, *J*9.9, 18.8 Hz), 4.08 (2H, q, *J*7.3 Hz), 4.16-4.29 (2H, m), 5.96 (1H, d, *J*5.5 Hz), 6.03 (1H, *J*5.5 Hz) and 7.02 (1H, s) ppm.

Preparation 1

Sodium (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate

(a) Ethyl 1-ethyl-5-methylpyrazole-3-carboxylate

N-Ethylhydrazine oxalate (12 g) in glacial acetic acid (100 ml) was cooled in an ice-bath and treated with ethyl 2,4-dioxovalerate (11.24 ml). After addition was complete the mixture was stirred at room temperature; after *ca.* 45 min the mixture was warmed to dissolve insoluble ethylhydrazine oxalate. The mixture was stirred for a further 2 h and then poured into water(*ca.* 300 ml) / ethyl acetate (*ca.* 700 ml) and solid K_2CO_3 was carefully added, with stirring, until the pH was neutral. After separation the aqueous layer was re-extracted with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$), and the solvents removed to leave an oil. Chromatography on silica gel, loading in CH_2Cl_2/hexane and eluting with a gradient elution of ethyl acetate/hexane mixtures (from 2:8 to 1:1) gave ethyl 1-ethyl-5-methylpyrazole-3-carboxylate as an oil (13.2 g); υ_{max} (CH_2Cl_2) 1717, 1446, 1389, and 1219 cm^{-1}; δ($CDCl_3$) 1.38 (3H, t, *J* 7.2 Hz), 1.42 (3H, t, *J* 7.3 Hz), 2.30 (3H, s), 4.17 (2H, q, *J* 7.3 Hz), 4.38 (2H, q, *J* 7.1 Hz), 6.55 (1H, s); (Found *m/z* 182.1055. $C_9H_{14}N_2O_2$ requires *m/z* 182.1055).

(b) 1-Ethyl-5-methylpyrazole-3-carboxylic acid

Ethyl 1-ethyl-5-methylpyrazole-3-carboxylate (10.93 g) in ethanol (70 ml) was treated with KOH (3.69 g), followed by water (30 ml), and the mixture was stirred and heated under reflux for 6 h. The ethanol was removed using a rotary evaporator and ethyl acetate/water were added. The pH of the mixture was adjusted to 3.0 and the layers were separated. The aqueous layer was re-extracted with ethyl acetate. The combined ethyl acetate layers were extracted with excess aqueous $NaHCO_3$. The $NaHCO_3$ extract was poured into excess acid, and the pH was then adjusted to 3, and NaCl was added to the solution. The mixture was then repeatedly extracted with ethyl acetate, and the combined extracts were dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether to give the acid as a solid (5.65 g); υ_{max} (CH_2Cl_2) 2754, 2598, 1698, 1498, 1464, 1387, and 1233 cm^{-1}; $\delta(CDCl_3)$ 1.40 (3H, t, *J* 7.3 Hz), 2.32 (3H,s), 4.19 (2H, q, *J* 7.3 Hz), 6.61 (1H,s) ppm; (Found *m/z* 154.0740. $C_7H_{10}N_2O_2$ requires *m/z* 154.0742).

(c)*N*-Methoxy-*N*-methyl-1-ethyl-5-methylpyrazole-3-carboxamide

1-Ethyl-5-methylpyrazole-3-carboxylic acid (5.25 g) in dry dichloromethane (100 ml) containing *N,N*-dimethylformamide (0.26 ml) was cooled in an ice-bath and treated with a solution of oxalyl chloride (3.27 ml) in dichloromethane (25 ml), added dropwise. The mixture was stirred in the cold for 25 min, and then allowed to warm to room temperature, when evolution of a gas was observed. After 10 min the solvent was removed by evaporation *in vacuo* and toluene was added and removed (x 2) to ensure any residual HCl and oxalyl chloride had been removed. The resultant acid chloride was redissolved in dry dichloromethane and then treated with *N,O*-dimethylhydroxylamine hydrochloride (3.61 g). The mixture was cooled in an ice-bath and treated with pyridine (6.0 ml). the mixture was then allowed to stir at room temperature for 1.5 h and then diluted with ether (100 ml) and washed with brine. The organic layer was then dried ($MgSO_4$) and evaporated to leave an oil. This was the chromatographed on silica gel, loading in dichloromethane, and eluting with ethyl acetate / hexane mixtures to give, after evaporation of requisite fractions, the hydroxamate (5.2 g) as a solid;
$\upsilon_{max}(CH_2Cl_2)$ 2982, 2937, 1641, 1489, 1445, 1379,and 975 cm^{-1}; $\delta(CDCl_3)$ 1.43 (3H, t, *J* 7.3 Hz), 2.29 (3H, s), 3.42 (3H, s), 3.76 (3H, s,), 4.13 (2H, q, *J* 7.3 Hz), 6.49 (1H, s); (Found *m/z* 197.1164. $C_9H_{15}N_3O_2$ requires *m/z* 197.1164).

(d) 3-Acetyl-1-ethyl-5-methylpyrazole

N-Methoxy-*N*-methyl-1-ethyl-5-methylpyrazole-3-carboxamide (3.12 g) in dry tetrahydrofuran (60 ml) was cooled in an ice-bath and treated with a 3.0M solution of methylmagnesium bromide in ether (11.08 ml). After stirring for 1.5 h the mixture was poured into a mixture of methanol (100 ml) and 5M aqueous HCl (10 ml) in an ice-bath. The mixture was then evaporated to lower volume and treated with a mixture of dichloromethane, water and saturated brine. After separation the aqueous layer was re-extracted with dichloromethane. The combined dichloromethane extracts were dried ($MgSO_4$) and evaporated to leave an oil (2.26 g), which solidified on standing; υ_{max} (CH_2Cl_2) 1680, 1446, 1425, 1380, 1324, 1208, and 945 cm^{-1}; δ ($CDCl_3$) 1.44 (3H, t, *J* 7.3 Hz), 2.30 (3H, s), 2.53 (3H, s), 4.13 (2H, q, *J* 7.3 Hz,), 6.51 (1H,s); (Found: *m/z* 152.0949. $C_8H_{12}N_2O$ requires *m/z* 152.090).

(e) (3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]azetidin-2-one

3-Acetyl-1-ethyl-5-methylpyrazole (3.51 g) in dry tetrahydrofuran (THF) (150 ml) under an argon atmosphere was cooled in an acetone / solid carbon dioxide bath and then treated with a 1M solution of lithium bis(trimethylsilyl)amide (50 ml). The mixture was stirred for 45 minutes and then (3*R*,4*R*)-4-acetoxy-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]azetidinone (6.6 g) was added as a solid under a blanket of argon. The mixture was stirred in the cold for 3.5h. Saturated aqueous ammonium chloride was then added, followed by ethyl acetate, and the mixture was allowed to warm to room temperature. A little water was added and the layers were separated and the aqueous layer was re-extracted with ethyl acetate. The combined ethyl acetate extracts were washed with saturated brine, dried and evaporated. Chromatography on silica gel, eluting with ethyl acetate/hexane mixtures gave the title compound (3.65 g), υ_{max} (CH_2Cl_2) 3411, 1761, 1678, 1376, 1151, and 838 cm^{-1}; δ($CDCl_3$) 0.064 (6H, s), 0.86 (9H, s), 1.20 (3H,d, *J* 6.3 Hz), 1.44 (3H, t, *J* 7.3 Hz), 2.31 (3H, s), 2.89 (1H, dd, *J* 1.8 & 4.9 Hz), 3.15 (1H, dd, *J* 10.0 & 17.1 Hz), 3.50 (1H, dd, *J* 3.5 & 17.0 Hz), 4.06 - 4.25 (4H, m), 6.11 (1H, s), 6.53 (1H, s). (Found *m/z* 379.2296. $C_{19}H_{33}N_3O_3Si$ requires *m/z* 379.2291).

(f) Allyl (2*R* and 2*S*)-2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-oxoazetidinyl}-2-hydroxyacetate.

(3*S*,4*R*)-4-[(1-Ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]azetidin-2-one (3.6 g) and allyl glyoxylate hydrate (1.66 g) in toluene (100 ml) were heated under reflux in a Dean and Stark apparatus under an atmosphere of argon for 3.5h. T.l.c. of the reaction mixture showed the reaction had almost prceeded to completion, so more allyl glyoxylate hydrate (190 mg) was added and the mixture was heated under reflux for a further 45 min. The mixture was cooled, the toluene was removed to give crude allyl (2*R* and 2*S*)-2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-oxoazetidinyl}-2-hydroxyacetate, which was used in the next stage; υ_{max} (CH_2Cl_2) 3681, 3518, 1758, 1676, 1448, 1376, 1326, 1209, 1148, 1092, 954, and 836 cm^{-1}; $\delta(CDCl_3)$ *inter alia* 0.035 (s), 0.061 (s) (together 6H,), 0.858 (s), 0.865 (s) (together 9H), 1.21 (d, *J* 6.2 Hz), 1.24 (d, *J* 6.2 Hz), (together 3H), 1.44 (3H, t, *J* 7.2 Hz), 2.31 (3H, s), 2.95 - 3.00 (1H, m), 3.25 - 3.64 (2H, m), 6.53 (s), 6.56 (s) ppm.

(g) Allyl 2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-oxoazetidinyl}-2-(tri-*n*-butylphosphoranylidene)acetate.

Allyl (2*R* and 2*S*)-2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-oxoazetidinyl}-2-hydroxyacetate (crude from the above preparation) in dry THF (125 ml) under argon was cooled to -20°C and treated with 2,6-lutidine (1.98 ml), followed by thionyl chloride (1.24 ml). The mixture was stirred at -20°C for 30 minutes, and then allowed to warm to room temperature and filtered, washing the residue with THF (20 ml). The filtrate was evaporated *in vacuo*, toluene (70ml) was added and removed *in vacuo* and the residual oil was dried *in vacuo*. The oil was then taken up in 1,4-dioxan (40 ml) under an argon atmosphere, and treated with tri-*n*-butylphosphine (3.11 ml). The mixture was stirred for 1 h. 2,6-Lutidine (1.59 ml) was then added and the mixture was stirred for a further 30 minutes. The mixture was diluted with ethyl acetate , washed with water, then with brine, and dried ($MgSO_4$). After removal of the ethyl acetate the crude product was chromatographed on silica gel,

eluting with ethyl acetate/hexane mixtures to give the phosphorane, which was used in the next stage.

(h) Allyl 2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-hydroxyethyl]-2-oxoazetidinyl}-2-(tri-*n*-butylphosphoranylidene)acetate.

The phosphorane prepared above was taken up in 1,4-dioxan (60 ml) and treated with 5M HCl (20 ml). After 1 h the mixture was carefully treated with *ca.* 40 ml saturated aqueous $NaHCO_3$, followed by solid $NaHCO_3$ until the pH was slightly alkaline. Saturated brine was added and the mixture was extracted twice with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with ethyl acetate/hexane mixtures to give the hydroxy compound, (2.60 g), υ_{max} (CH_2Cl_2) 3454, 1741, 1667, 1606, 1448, 1403, 1379, 1155, 1087, 953, and 811 cm^{-1}.

(i) Allyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate

Allyl 2-{(3*S*,4*R*)-4-[(1-ethyl-5-methylpyrazol-3-yl)carbonylmethyl]-3-[(*R*)-1-hydroxyethyl]-2-oxoazetidinyl}-2-(tri-*n*-butylphosphoranylidene)acetate (2.6 g), in toluene (120 ml) containing hydroquinone (20 mg) was heated under reflux in an argon atmosphere for 4 h, allowed to stand for 64 h, and then heated under reflux for a further 2 h. The mixture was cooled and then loaded onto a column (4.5 x 12 cm) of silica gel (particle size 0.040 -0.063 mm), eluting with ethyl acetate/hexane mixtures; 1:1; 6:4; 7:3; 8:2; 9:1 (250 ml of each), followed by ethyl acetate. This gave the carbapenem (436 mg); υ_{max}(CH_2Cl_2) 3604, 2976, 1774, 1716, 1600, 1546, 1311, 1189 cm^{-1}; λ_{max}(EtOH)/nm 321.5 (ε/$dm^3mol^{-1}cm^{-1}$ 14,856), δ($CDCl_3$) 1.36 (d, *J* 6.3 Hz), 1.39 (t, *J* 7.3 Hz) (together 5H), 1.80 (1H, d, *J* 5.0 Hz), 2.28 (3H,s), 3.19 (1H, dd *J* 2.7 & 6.7 Hz), 3.28 (1H, dd, *J* 9.0 & 18.6 Hz), 3.60 (1H, dd, *J* 9.9 & 18.5 Hz), 4.08 (2H, q, *J* 7.3 Hz), 4.16 - 4.30 (2H, m), 4.68 - 4.90 (2H, m), 5.27

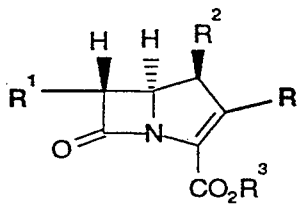
(1H, m, approx d, *J ca.* 12 Hz), 5.46 (m, approx d, *J ca.* 17 Hz), 5.93 - 6.08 (1H, m), 7.00 (1H, s) ppm; [Found *m/z* 345.1693. $C_{18}H_{23}N_3O_4$ requires *m/z* 345.1689].

(j) Sodium (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methyl-pyrazol-3-yl)carbapen-2-em-3-carboxylate

Allyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate (267 mg) in dichloromethane (3ml) and ethyl acetate (3 ml) under argon was treated with sodium 2-ethylhexanoate (183 mg), followed by triphenylphosphine (24 mg), followed by tetrakis(triphenylphosphine)palladium(0) (35 mg) and the mixture was stirred for 45 min. Diethyl ether (100ml) was then added, and after stirring for 90 minutes, the mixture was centrifuged. The residual solid was dried under a stream of argon, and then in a desiccator. The solid was then taken up in water containing sodium chloride and chromatographed on DIAION HP20SS resin, eluting with water, followed by water/THF mixtures; 1%, 2%, and 3%,THF. Fractions were monitored by HPLC, and those containing the product were combined, reduced in volume and freeze-dried to give sodium (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methylpyrazol-3-yl)carbapen-2-em-3-carboxylate as a solid (168 mg); υ_{max}(KBr) 1761, 1608, 1577, 1381, 1225 cm^{-1}; $\lambda_{max}(H_2O)$/nm 298 ($\varepsilon/dm^3mol^{-1}cm^{-1}$ 8,531); $\delta(D_2O)$ 1.26 (d, *J ca.* 6 Hz), 1.27 (d, *J ca.* 7 Hz) (together 5H), 2.23 (3H, s), 3.17 (2H, approx d, *J ca.* 9 Hz), 3.44 (1H, dd, *J* 2.9 & 6.0 Hz), 4.04 (2H, q, *J* 7.3 Hz), 4.15 - 4.25 (2H, m), 6.41 (1H, s) ppm.

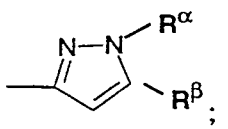
Claims

1. A compound of the general formula (I):



(I)

in which R is:



wherein

R^{α} is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl;

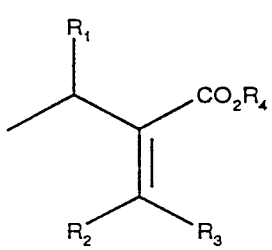
R^{β} is hydrogen, optionally substituted (C_{1-6})alkyl or optionally substituted aryl; or

R^{α} and R^{β} together form an optionally substituted 5 or 6 membered heterocyclic ring with or without additional heteroatoms;

R^1 is (C_{1-6})alkyl which is unsubstituted or substituted by fluoro, a hydroxy group which is optionally protected by a readily removable hydroxy protecting group, or by an amino group which is optionally protected by a readily removable amino protecting group;

R^2 is hydrogen or methyl; and

R^3 is selected from the group consisting of (a) a group of formula:



wherein;

R_1 is hydrogen or (C_{1-6})alkyl,

R_2 is hydrogen, (C_{1-6})alkyl optionally substituted by halogen, (C_{1-6})alkenyl, (C_{1-6})alkoxycarbonyl, aryl, or heteroaryl,

R_3 is hydrogen, (C_{1-6})alkyl, or (C_{1-6})alkoxycarbonyl, and
R_4 is a pharmaceutically acceptable ester forming group, and (b) a group of formula $CH(R^a)O.CO.R^b$, wherein R^a is hydrogen, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, methyl, or phenyl; and R^b is (C_{1-6})alkyl(C_{3-7})cycloalkyloxy or (C_{1-6})alkoxy(C_{1-6})alkyl.

2. 2-Ethoxycarbonyl-*E*-but-2-enyl (5*R*,6*S*)-2-(1-Ethyl-5-methyl-1,2-pyrazol-5-yl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate.

3. 1-Methylcyclohexyloxycarbonyloxymethyl (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-(1-ethyl-5-methyl-pyrazol-3-yl)carbapen-2-em-3-carboxylate.

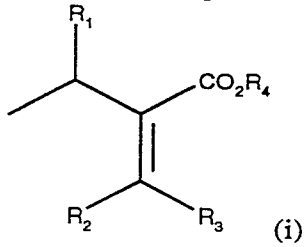
4. 2-Methoxyprop-2-ylcarbonyloxymethyl (5*R*,6*S*)-2-(1-ethyl-5-methylpyrazol-3-yl)-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate.

5. A pharmaceutical composition comprising an antibiotic compound according to any one of the preceding claims, together with a pharmaceutically acceptable carrier or excipient.

6. A method of treating bacterial infections in humans and animals which method comprises administering a therapeutically effective amount of an antibiotic compound according to any one of claims 1 to 4.

7. Use of a compound according to any one of claims 1 to 4 for the manufacture of a medicament for treating bacterial infection.

8. A process for the preparation of a compound of formula (I) in accordance with claim 1, which process comprises treating a corresponding compound of formula (I), wherein R is an alkali metal cation, with a compound of formula (i) or (ii):

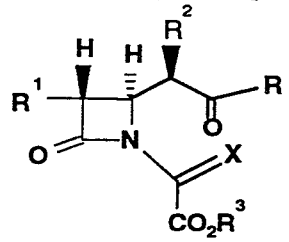


(i)

$XCH(R^a)O.CO.R^b$ (ii)

wherein X is a leaving group.

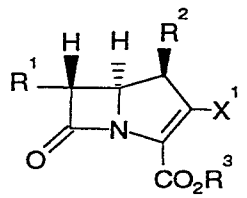
9. A process for the preparation of a compound of formula (I) in accordance with claim 1, which process comprises subjecting a compound of formula (II):



(II)

in which R, R^1 and R^2 are as hereinbefore defined,
R^3 is a readily removable carboxy protecting group,
X is oxygen or a group $PR^4R^5R^6$, and
R^4, R^5 and R^6 may be the same or different and each is an optionally substituted (C_{1-6})alkyl or an optionally substituted aryl group;
to carbapenem ring forming conditions;
and thereafter, and if necessary, carrying out any or all of the following steps:
removing any protecting group(s);
converting a first group R^1 comprising a hydroxyl substituent into a further group R^1 comprising an amino or fluoro group;
converting the product into a salt; and
esterifying the product.

10. A process for the preparation of a compound of formula (I) in accordance with claim 1, which process comprises reacting a compound of formula (X):

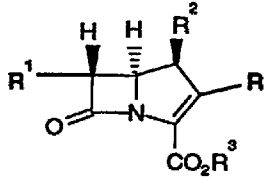


(X)

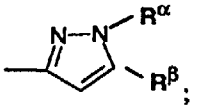
in which R^1 and R^2 are as hereinbefore defined, R^3 is a readily removable carboxy protecting group and X^1 is a leaving group,
with a compound of formula (XI):

M-R (XI)

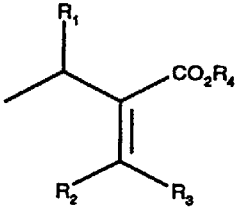
in which M is a metallo group and R is as hereinbefore defined;
in a cross-coupling reaction in the presence of a cross-coupling reaction catalyst selected according to the identity of M and thereafter and if necessary removing any protecting group and/or esterifying the product.



(I)



(a);



(b)